UNIVERSITÀ VITA-SALUTE SAN RAFFAELE

CORSO DI DOTTORATO DI RICERCA

IN NEUROSCIENZE COGNITIVE

Parkinson's disease and dementia in the α-synuclein spectrum: the role of cognitive assessment and *in vivo* neuroimaging biomarkers

DoS: Prof. Daniela Perani

Second Supervisor: Prof. Maja Trošt

Tesi di DOTTORATO di RICERCA di Giulia Carli

matr. 013875

Ciclo di dottorato XXXIV

M-PSI/02

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CONSULTAZIONE TESI DI DOTTORATO DI RICERCA

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DECLARATION

This thesis has been composed by myself and has not been used in any previous application for a degree. Throughout the text I use both 'I' and 'We' interchangeably.

All the results presented here were obtained by myself, except for:

1) ***Polysomnographic scoring and variables analyses in iRBD patients (Study III).***
   The polysomnographic scores and relationship with neuropsychological variables (Study III) was assessed by Dr Galbiati Andrea, IRCCS San Raffaele Scientific Institute, Department of Clinical Neurosciences, Neurology – Sleep Disorders Centre, Milan, Italy

2) ***Brain metabolic connectivity analyses (Study VI).***
   The brain metabolic connectivity analyses (Study VI) were performed in collaboration by Ms Boccalini Cecilia, In Vivo Human Molecular and Structural Neuroimaging Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy.

3) ***[123I]FP-CIT-SPECT SUVr and molecular connectivity analyses (Study VII).***
   [123I]FP-CIT-SPECT SUVr and molecular connectivity analyses (Study VII) were performed in collaboration by Ms Boccalini Cecilia, In Vivo Human Molecular and Structural Neuroimaging Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy.

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Abstract

World Health Organization defines neurological disorders as the main source of disability in the world. Parkinson's disease (PD) is a neurological disorder that showed the fastest growth in the last twenty years. The prevalence of PD is more than doubled from 1990 to 2015; in 2018, about 6.2 million individuals had PD. According to the Global Burden of Disease study, PD may exponentially grow to reach 12.9 million affected patients by 2040 since the disease incidence is age-related and the world's population is getting older. The occurrence of frank dementia in PD (PDD) is an essential aspect because it strongly affects patient mortality and quality of life. Accurate early diagnosis is the first step for effective prevention strategies. There is an urgent need for accurate and standardized biomarkers to diagnose dementia, especially in the preclinical/prodromal phase. Identifying and modifying dementia risks have the potential for great benefits; the personal and social welfare take advantage of any delay in the dementia beginning. Providing precise indications regarding the risk factors for dementia and guidelines for using biomarkers or cognitive assessment in PD dementia profiling might increase the chances of effective prevention and future treatments. Risk factors, biomarkers and cognitive markers are crucial to understanding intersubjective clinical variability and getting closer to proper precision medicine.

The studies included in this dissertation contributed to identifying risk factors, biomarkers, cognitive features, and sources of clinical variability of dementia in Lewy Bodies disorders (LBD), starting from the preclinical phases, namely isolated REM sleep Behaviour Disorder. With multiple methodological approaches to neuroimaging data, the studies investigated neurobiological mechanisms that characterize PD patients with a severe clinical phenotype – developing cognitive deterioration – since the preclinical phases. Moreover, the cognitive picture of the LBD clinical spectrum has been explored by combining cross-sectional and longitudinal approaches. This dissertation provides new evidence on modifiable and non-modifiable risk factors that influence the development of severe phenotypes within LBD and those acting on the timing of dementia

symptoms onset. Moreover, we identify valuable biomarker and cognitive marker candidates for dementia risk profiling since early preclinical stages.

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LIST OF STUDIES

Studies Published/Accepted:

1. **Carli, G.,** Caminiti, S. P., Galbiati, A., Marelli, S., Casoni, F., Padovani, A., ... & Perani, D. (2020). In-vivo signatures of neurodegeneration in isolated rapid eye movement sleep behaviour disorder. European journal of neurology, 27(7), 1285-1295. DOI: https://doi.org/10.1111/ene.14215. (Impact factor: 6.089) - **Original Article** - (Study I).

2. **Carli, G.,** Caminiti, S. P., Sala, A., Galbiati, A., Pilotto, A., Ferini-Strambi, L., ... & Perani, D. (2020). Impaired metabolic brain networks associated with neurotransmission systems in the α-synuclein spectrum. Parkinsonism & related disorders, 81, 113-122. DOI: https://doi.org/10.1016/j.parkreldis.2020.10.036 (Impact factor: 4.891) - **Original Article** - (Study II)

3. Galbiati, A., **Carli, G**., Fasiello. E., Casoni, F., Zucconi, Z., De Gennaro, L., Perani, D., & Ferini-Strambi, L. Exploring the functional role and neural correlates of K-complexes in isolated rapid eye movement sleep behavior disorder. (2021) Cortex in Press DOI: https://doi.org/10.1016/j.cortex.2021.08.012 (Impact factor: 4.027). - **Original Article** - (Study III).

4. Caminiti, S. P.*, **Carli***, G., Avenali, M., Blandini, F., & Perani, D. (2021). Clinical and Dopamine Transporter Imaging Trajectories in a Cohort of Parkinson's Disease Patients with GBA Mutations. Movement Disorders. * These authors contributed equally to work. DOI: https://doi.org/10.1002/mds.28818 (Impact factor: 10.338). - **Original Article** - (Study IV).

5. Beretta, L., **Carli**, G., Caffarra, P., & Perani, D. (2021). Distinct brain dysfunctions underlying visuo-constructive deficit in DLB and AD. Brain Imaging and Behavior, 1-6. Brain Imaging and Behaviour. DOI: https://doi.org/10.1007/s11682-021-00515-7 (Impact factor: 3.978). **- Short communication** - (Study V).

6. Boccalini, C., **Carli**, G., Pilotto, A., Padovani, A., & Perani, D. (2021). Gender-Related Vulnerability of Dopaminergic Neural Networks in Parkinson's Disease. Brain Connectivity, 11(1), 3-11. DOI: https://doi.org/10.1089/brain.2020.0781. (Impact factor: 2.262). **- Short communication** - (Study VI).

7. **Carli, G**., Boccalini, C., Vanoli, G., Filippi, M., Iannaccone, S., Magnani, G., & Perani, D. (2020). Specific occupational profiles as proxies of cognitive reserve induce neuroprotection in dementia with Lewy bodies. Brain Imaging and Behavior, 1-11. DOI: https://doi.org/10.1007/s11682-020-00342-2 (Impact factor: 3.978). - **Original Article** - (Study VIII).

8. **Carli**, G. *, Tondo, G.*, Boccalini, C.*, & Perani, D. (2021). Brain Molecular Connectivity in Neurodegenerative Conditions. Brain Sciences, 11(4), 433. DOI:

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Studies published/submitted but not included in this dissertation:

1. Perani, D., Caminiti, S. P., **Carli, G.,** & Tondo, G. (2021). PET neuroimaging in dementia conditions. PET and SPECT in Neurology, 211-282. DOI: https://doi.org/10.1007/978-3-030-53168-3_9 **- Chapter Book -**

2. Tondo, G., **Carli**, G., Santangelo, R., Mattoli, M. V., Presotto, L., Filippi, M., ... & Alzheimer's Disease Neuroimaging Initiative. (2021). Biomarker-based stability in limbic-predominant amnestic mild cognitive impairment. European Journal of Neurology, 28(4), 1123-1133. * These authors contributed equally to work. DOI: https://doi.org/10.1111/ene.14639 (Impact factor: 6.089). - **Original Article** -

3. Boccalini, C., *, **Carli, G.** *, Tondo, G., Polito, C., Berti, V., Bessi, V., Sorbi, A., Iannaccone, S., and Perani, D. Brain metabolic connectivity reconfiguration in the semantic variant of primary progressive aphasia. Submitted to Cortex. (Impact factor: 5.26). - **Original Article** -

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ACRONYMS AND ABBREVIATION

Abbreviation	Full-lenght Word
AAL	Automated Anatomical Labeling
AASM	American Academy of Sleep Medicine
ACC	Anterior Cingulate Cortex
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ADMN	Anterior Default Mode Network
AI	Asymmetry index
AIC	Akaike Information Criterion
ATN	Attentional Network
ATP	Adenosine Triphosphate
BM	Brain Maintenance
BR	Brain Reserve
CBD	Corticobasal Degeneration
CBDRP	CBD related pattern
CBS	Corticobasal Syndrome
CNS	Central Nervous System
CR	Cognitive Reserve
DA	Dopamine
DAT	DA Transporter
DLB	Dementia with Lewy Bodies
DLPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
ECN	Executive Control Network
EEG	Elettroencelography
EMG	Electromyography
ET	Essential Tremor
FWE	Family Wise Error
GBA	Glucosylceramidase Beta
GCase	Glucocerebrosidase
GCI	Glial Cytoplasmic Inclusions
GDS	Geriatric Depression Scale
GI	Gini Index
GWAS	Genome-wide association studies
H/M	Heart-to-mediastinum
HC	Healty Controls
HLVT-R	Hopkins Verbal Learning Test-Revised
HVN	High Visual Network
i	Idiopathic

ICSD-3	3rd edition of the international classification of sleep disorders
ImCalc	Image Calculator
IQ	Intelligence Quotient
iRBD	Isolated RBD
iRBD+MCI	iRBD with MCI
iRBD-MCI	iRBD without MCI
IRCA	Interregional Correlation Analysis
JOLO	Benton Judgment of Line Orientation
JSC	Jaccard similarity coefficient
KC	K-complex
LB	Lewy Bodies
LBD	Lewy Bodies disorders
LC	Locus Coeruleus
LEDD	Levodopa Equivalent Daily Dose
LN	Lewy neurites
LNS	Letter-Number Sequencing
LREM	REM Sleep Latency
LRRK2	The leucine-rich repeat kinase 2
MCC	Middle Cingulate Cortex
MCI	Mild Cognitive Impairment
MCP	Middle Cerebellar Peduncles
MDS	Movement Disorder Society
MMSE	Mini-Mental State Examination
MSA	Multiple System Atrophy
MSA-C	MSA with predominant cerebellar ataxia
MSA-P	MSA with predominant parkinsonism
MSARP	MSA related pattern
N1	Sleep Stage 1
N2	Sleep Stage 2
NACP	Non-amyloid-β Component Precursor
NAWK	Numbers of Awakenings
NBM	Nucleus Basalis of Meynert
NE	Norepinephrine
NFS	N-ethylmaleimide-sensitive factor
NMSs	Non-motor symptoms
O*net	Occupational Information Network
OH	Orthostatic Hypotension
OSA	Obstructive Sleep Apnoea
PAF	Pure Autonomic Failure
PCs	Principal Components
PD	Parkinson's Disease
PD+MCI	PD with MCI
PD+RBD	PD patients with RBD

PDD	Parkinson disease with dementia
PD-MCI	PD without MCI
PDMN	Posterior Default Mode Network
PD-RBD	PD patients without RBD
PD-RBD	PD patients without RBD
PDRPR	PD related pattern
PET	Positron Emission Tomography
PIGD	Postural Instability Gait Difficulty
PNS	Periphery Nervous System
PPMI	Parkinson's Progression Markers Initiative
PSG	Polysomnography
PSP	Progressive Supranuclear Palsy
PSPSRB	PSP related pattern
PVN	Primary Visual Network
QSPT	Qualitative Scoring of Pentagon Test
QUIP	Questionnaire for Impulsive-Compulsive Disorders
RAVLT	Rey Auditory Verbal Learning Test
RBD	REM Sleep Behavuoir Disorder
RBD-CI	RBD with congnitive impaorment
RBD-NC	RBD with normal cognition
RBDQ	RBD Questionnaire
RBDRP	RBD related pattern
RBE	REM-sleep-related behavioural events
REM	Rapid Eye Movement
ROCF	Rey–Osterrieth Complex Figure
ROIs	Regions Of Interest
RSWA	REM sleep without atonia
SCOPA-AUT	Scale for Outcomes for Parkinson’s Disease—autonomic function
SD	Standard Deviation
SDMT	Symbol-Digit Modalities Test
SE	Sleep Efficiency
SL	Sleep Latency
SMA	Supplementary Motor Area
SN	Substantia Nigra
SNARE	Soluble NSF Attachment Protein Receptor
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SSM/PCA	Scaled Subprofile Model/Principal Component Analysis
STAI	State-Trait Anxiety Inventory
SUVr	Specific Uptake Value ratio
SWS	Slow Wave Sleep
TFCE	Threshold-free Cluster Enhancement

TST	Total Sleep Time
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT	40- item University of Pennsylvania Smell Identification Test
VAMP2	Synaptobrevin-2
VBM	Voxel-Based Morphometry
VMAT2	Vesicular Monoamine Transporter 2
VTA	Ventral Tegmental Area
WASO	Wake After Sleep Onset
wDC	Weighted Dice Coefficient
[123I]MIBG	123I-metaiodobenzylguanidine
[18F]FDG	18fluorodeoxyglucose
[I]	Iodine

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1. Introduction

Prolonged human life is a great credit of modern medicine. Since the 1950s, with advances in disease prevention and treatment and social changes, life expectancy in different parts of the world has increased by about 10 to 20 years (Word Health Organization 2015). However, the ageing and growth of the population determined a considerable increase of older people with physical disabilities, which manifest difficulties in daily living. In 2010, there were a total of 101 million older adults in the world who were dependent on others, that is, severely disabled, and these numbers are expected to increase nearly three times reaching 277 million in 2050 (Prince et al. 2015). The main sources of disability in the old population are cognitive decline and dementia (Prince et al. 2015); thus, counteracting the insurgence of dementia is recognised as a priority by the World Health Organization (Word Health Organization 2015).

Parkinson's disease (PD) is the neurological disease with the fastest growing rate (Dorsey and Bloem 2018); 1% of the world population over 60 years have a PD diagnosis (De Lau and Breteler 2006). PD presents a complex and heterogenous clinical picture during the disease course, and dementia represents the most severe condition, with a mean prevalence of 31.5% (Janvin et al. 2006). The onset of frank dementia in PD (PDD) has a distinctive pattern of rapid cognitive decline, characterized by visuoperceptual, memory and psychiatric deficits related to a posterior-cortical impairment (Kehagia et al. 2013). PDD represents an essential aspect of clinical heterogeneity because it affects PD patients mortality and quality of life (Levy et al. 2002). The primary risk factors for dementia development are advanced age, advanced disease stage, akinetic-rigid PD motor subtype, cognitive deficits, dysautonomia and isolated rapid eye movement (REM) sleep behaviour disorder (iRBD) (Y. Xu, Yang, and Shang 2016). Identifying and modifying risks for dementia in PD could greatly benefit individuals; personal and social welfare might benefit from any delay in dementia development (Livingston et al. 2017; Orgeta et al. 2019; Livingston et al. 2020).

Over the past two decades, the clinical research framework has gradually gone from exclusively clinical diagnosis to a biomarker-supported diagnostic process (Perani et al. 2020). Neuroimaging advance has crucially contributed in the research and

diagnosis of dementia (McKhann et al. 2011; Gorno-Tempini et al. 2011; Armstrong et al. 2013; Sperling et al. 2011; Albert et al. 2011; McKeith et al. 2017; Rascovsky et al. 2011). The main applications of biomarkers are prediction, screening, diagnosis, staging, prognostic evaluation and therapy. Multimodal neuroimaging holds an essential role in studying the structural and functional brain changes of pathological conditions and can identify disease-specific features (Saeed et al. 2017). These disease-specific features can work as effective biomarkers to increase the sensitivity and specificity of clinical diagnosis (Saeed et al. 2017). Taking into account the increasing number of PD patients, the overlap of their clinical manifestations with other α-synucleinopathies, and the overall heterogeneity of PD manifestations and prognosis, the validation of PD prognostic and diagnostic biomarkers have become more and more critical since its earliest preclinical phases (i.e. iRBD) (Perani et al. 2020). Identifying specific PD biomarkers can clarify the neuroanatomical and pathophysiological basis of this disease and predict the clinical trajectory, thereby achieving a more accurate diagnosis and effective therapeutic intervention (Saeed et al. 2017).

This doctoral dissertation dives into valuable biomarker and cognitive marker candidates for PD dementia risk profiling since early preclinical stages. Neurobiological mechanisms, clinical and cognitive aspects of PD patients with a severe clinical phenotype have been assessed since the preclinical phases. The studies here discussed contributed to identifying risk factors, biomarkers, cognitive features, and sources of clinical variability of dementia in Lewy Bodies disorders (LBD). New evidence emerged on modifiable and non-modifiable risk factors that influence the development of severe phenotypes in LBD, also influencing the timing of dementia symptoms onset.

1.1. A-synucleinopathies related neurodegeneration

Aggregations of misfolded α-synuclein are the pathological hallmarks of the α-synucleinopathies spectrum, encompassing PD, Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA) (Spillantini, Crowther, Jakes, Hasegawa, et al. 1998; Spillantini 1999). The iRBD is considered a full-fledged part of α-synucleinopathies. Indeed, the association of RBD with the α-synuclein related neurodegeneration was

strongly substantiated by clinical-neuropathological studies and cases series (Schenck 2019).

A-synuclein protein misfolds and aggregates into multiple soluble oligomeric species and insoluble amorphous or fibrillar amyloid-like assemblies, namely the filaments. In particular, the formation of filaments is associated with neurodegeneration (Spillantini and Goedert 2016). Synaptic α-synuclein aggregates seem to crucially contribute to the pathogenesis and dysfunctions characterising the neurodegenerative process of α-synucleinopathies (Calo et al. 2016). In this section, the physiological functions of α-synuclein and its role in α-synucleinopathies will be addressed.

1.1.1. The physiological function of α-synuclein

Synucleins are proteins physiologically present in the brain, and they include three principal members: α-synuclein, β-synuclein and γ-synuclein (Goedert 2001). The first synuclein sequence was described in 1988 in a species of electric ray (Torpedo californica[1]) (Maroteaux, Campanelli, and Scheller 1988). This protein has been called synuclein because it is located in the presynaptic nerve terminals and nuclear membrane. Subsequent studies confirmed synuclein in nerve terminals but failed to confirm nuclear localisation (Goedert 2001). However, due to historical reasons, the original name survived. At the beginning of the Nineties, two amino-acid sequences have been described in animal and human brains. An amino-acid sequence of a protein called phosphoneuroprotein-14 was reported in the rat brain (Tobe et al. 1992). In the meantime, in brains of patients with Alzheimer's disease (AD) was found the amino-acid sequence of a protein, called 'non-amyloid-β component precursor' (NACP) as a result of the localisation of a segment of this protein – the peptide NAC – in amyloid plaques (Uéda et al. 1993). Despite that, a succeeding study has not confirmed the same findings (Bayer et al. 1999). In 1994, Michel Goedert and colleagues put the last piece together. They found the amino-acid sequences of two proteins in the human brain, one indistinguishable to NACP, and the other figuring as the human homologue of phosphoneuroprotein-14 of rat. The authors observed that these proteins resembled the synuclein from Torpedo

[1] Torpedo californica (or Pacific electric ray) is a species of electric ray in the family Torpedinidae, endemic to the coastal waters of the north-eastern Pacific Ocean from Baja California to British Columbia.

californica, naming them α- and β-synuclein, respectively. Instead, the last member (third) of the synuclein family has been independently described by two laboratories (Ji et al. 1997; Buchman et al. 1998), at first under the name of persyn, but now commonly called γ-synuclein. A- and β-synuclein are mainly located in nerve terminals (Clayton and George 1999). At a micro-scale level, they are found in nerve terminals near synaptic vesicles. On the contrary, γ-synuclein seems detectable all over nerve cells (Clayton and George 1999).

All synuclein proteins are present in the healthy brain; however, their physiological functioning is not thoroughly described. The synucleins structure ranges from 127 to 140 amino acid–long, with 55 to 62% identical sequences with similar domain organisation (Goedert 2001) (Figure 1).

Figure 1. The sequence of human synucleins (Open Access Source).

The amino acid identities between at least two of the three sequences are depicted in blue. The familial PD (A30P and A53T) mutations are reported in red in the α-synuclein. The amino-terminal half of synuclein includes 11 amino acid repeats with consensus sequence KTKEGV. A-Synuclein is assembled into filaments through these repetitions. Despite the similar repetitive sequences, β-synuclein and γ-synuclein show poor ability to assemble into filaments. The figure was adapted from (Calo et al. 2016).

The amino-terminal half of each protein comprises imperfect 11-amino-acid repeats, including KTKEGV – consensus sequence – (1-60), and interacts with acidic lipid membranes. The α helix structural conformation characterizes this sequence, like

apolipoproteins[2]-binding domains (Clayton and George 1998). The point mutations of the SNCA[3] gene usually occur within this terminal (Figure 1). After the repetition stands the hydrophobic middle region (61-95) and then the negatively charged carboxyl-terminal domain (95-140); α- and β-synuclein have the same carboxyl terminal. In the α-synuclein, the central hydrophobic region includes the NAC region that seems involved in protein aggregation (Uchihara & Giasson 2016; Uéda et al. 1993). Indeed, β-synuclein and γ-synuclein show poor assembly into filaments (Goedert 2001).

In a healthy adult brain, α-synuclein is colocalised together with presynaptic proteins. The expression and localisation of α-synuclein are developmentally regulated. During human foetal development, α-synuclein is expressed in various peripheral tissues (lung, liver, kidney, heart, adrenal gland and testis), whereas it is mainly present in the adult nervous system (Barbour et al. 2008). In neurons, the expression of α-synuclein is delayed compared to other presynaptic proteins, and the first sites where this protein can be detected are body and neuronal processes. Nonetheless, it ends up mainly at the presynaptic terminal of the brain after birth (D. D. Murphy et al. 2000).

In a physiological scenario, the α-synuclein contained in neurons can assume two structural forms – cytosolic and membrane-bound states – reaching an equilibrium (Calo et al. 2016). In its cytosolic state, α-synuclein appears unfolded, whereas in the membrane-bound state shows the α-helical multimeric conformation. Specifically, an α-synuclein folding pathway has been hypothesised, ranging from a monomeric unfolded form in the cytosol to a multimeric membrane-bound structure. Of note, the α-synuclein plays a physiological role in synaptic functioning once it reaches its membrane-bound multimeric state (Burré et al. 2010). This unstable conformational mixture is why α-synuclein is prone to pathological aggregation and fibrillation (Devine et al. 2011; Sharon et al. 2003). However, the membrane-bound multimeric forms are thought to protect against aggregation (Dettmer et al. 2015; Burré et al. 2010).

A-synuclein has a role in synaptic functions, regulating a) fusion and clustering of synaptic vesicles, b) dopamine homeostasis, b) synaptic plasticity, and c) essential cellular functions. Firstly, α-synuclein seems to regulate the fusion and clustering of

[2] Apolipoproteins are proteins that bind lipids to form lipoproteins, whose primary function is to transport hydrophobic lipid molecules
[3] SNCA is the gene coding for α-synuclein (Goedert 2001).

vesicles (Figure 1A). *In vitro* and *in vivo* evidence revealed that α-synuclein acts to promote soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE) complex assembly. SNAREs proteins are a family of fusion proteins that include two forms: v-SNAREs (referring to vesicle membrane) and t-SNAREs (referring to target-membrane), and together they form the "SNARE complex" (Kandel et al. 2013). In this context, α-synuclein binds to the synaptic plasma membrane, granting the assembly of the SNARE complex (Kandel et al. 2013). In this way, α-synuclein allows the fusion to occur, avoiding possible assembly deficit (Calo et al. 2016). Most studies converge on the hypothesis that α-synuclein modulates fusion through its ability to affect the lipid bilayer's vesicle membrane curvature (Calo et al. 2016). With this mechanism, the α-synuclein should act on the SNARE-complex by altering or disrupting the SNARE-driven fusion of synaptic vesicles (DeWitt & Rhoades, 2013), thus regulating the neurotransmission. Multiple studies on animal models show a decrease in the level of neurotransmitter release upon overexpression of α-synuclein (Larsen et al. 2006; Lundblad et al. 2012; Nemani et al. 2010), and an increase in the rate of induced dopamine (DA) release is found in mice lacking α-synuclein (Anwar et al. 2011). Indeed, α-synuclein seems to be a general modulator of DA homeostasis (Calo et al. 2016). Precisely, it seems to interacts with the vesicular monoamine transporter 2 (VMAT2) and the reuptake of DA via the DA transporter (DAT) (Calo et al. 2016). In general, α-synuclein appears to regulate the size and release features of the synaptic vesicle circulation and reserve pool in neurotransmission mechanisms (Figure 2B) (Nemani et al. 2010; Scott & Roy 2012; Wang et al. 2014).

When α-synuclein overexpression occurs, vesicles in release and reserve pools decrease as the consequence of the synaptic re-clustering inhibition after endocytosis (Nemani et al. 2010; Mori et al. 2020).

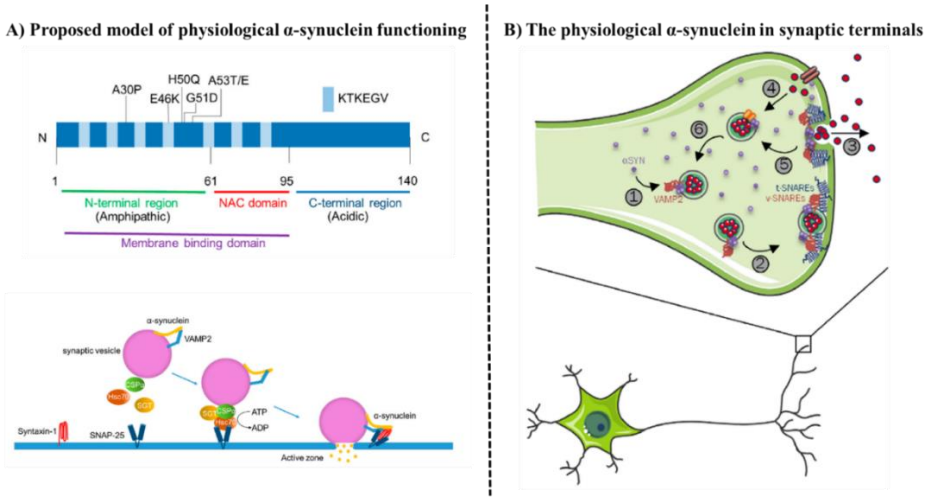

Figure 2. The physiological function of α-synuclein in neurons (Open Access Source).

Panel A) shows that the C-terminal region of α-synuclein links synaptobrevin-2 (VAMP2) on the synaptic vesicle, promoting the SNARE complex (under physiological conditions). Panel B) depicts the physiological role of α-synuclein at the synapse. A-synuclein regulates the neurotransmitter release (3) by modulating (1) vesicle fusion to the presynaptic plasma membrane. Moreover, this protein acts on neurotransmitter reuptake and vesicle filling by modulating neurotransmitter transporters (4). Finally, it plays a role in also in vesicle recycling (5) and trafficking (6). Figure adapted from (Mori et al. 2020) *(Panel A) and* (Calo et al. 2016) *(Panel B).*

The role of α-synuclein in synaptic plasticity has also been explored (Weihe et al. 1996; Calo et al. 2016; Cheng et al. 2011). Specifically, it has been suggested that α-synuclein participates in the short-term and long-term synaptic plasticity modulation (Cheng et al. 2011). The regulatory mechanism in synaptic plasticity seems to be related to the altered release probability of neurotransmitters due to the α-synuclein-related regulation of synaptic vesicles or the transport from the reserve to the release pool (Cheng et al. 2011). Some studies have shown that α-synuclein has a negative effect in mobilising synaptic vesicles from the reserve pool to the easy-release pool, which is accompanied by a decrease in neurotransmitter release (Abeliovich et al. 2000; Steidl et al. 2003; Yavich et al. 2004; Yavich et al. 2006; Larsen et al. 2006; Watson et al. 2009). Other evidence supports a positive role that promotes neurotransmitters' release, increasing vesicle availability for release (Steidl et al. 2003; Liu et al. 2004; 2007; Gureviciene et al. 2007; 2009). This evidence reveals different effects of α-synuclein on the release probability of neurotransmitters, suggesting that it may have differential regulation mechanisms on synaptic plasticity in different conditions.

Finally, the tendency of α-synuclein to associate with cell membranes and endoplasmic reticulum has led to several studies that support a more general role of α-synuclein within basic cell functions (Calo et al. 2016). For example, α-synuclein seems to have a role in the so-called "ATP-ubiquitin-proteasome" pathway, a mechanism for the selective and regulated proteolysis (degradation) of proteins that operates in the cytosol of all regions of the neuron (Calo et al. 2016).

In conclusion, a considerable amount of evidence supports the participation of α-synuclein in several synaptic mechanisms. Abnormal aggregation of α-synuclein may alter α-synuclein normal functions initiating the pathological processes related to α-synucleinopathies (*see paragraph below*). Complete identification of α-synuclein's functions in neurotransmission and synaptic plasticity regulation will shed light on the mechanisms underlying its pathological roles.

1.1.2. A-synuclein pathology: α-synucleinopathies

Among synucleins, only α-synuclein is related to the filamentous inclusions that form the neuropathological lesions in α-synucleinopathies – i.e. PD, DLB, MSA and RBD. Specifically, these neuropathological lesions are characterised by the formation of intracellular inclusions of filamentous aggregated protein in susceptible neuronal soma (Lewy bodies [LB]), neural dendrites (Lewy neurites [LN]) and glial populations (glial cytoplasmic inclusion [GCI])(Calo et al. 2016). Specific antibodies demonstrate that β- and γ-synucleins are not detectable in those inclusions (Spillantini et al. 1998; Spillantini 1999).

Sometimes, two unfolded monomers of the α-synuclein couple up into a dimer. Specifically, α-synuclein forms two types of dimers; one type does not propagate (anti-parallel dimers), meanwhile and the other one can propagate (parallel dimers) (Lashuel et al. 2013). As a result, α-synuclein tends to misfold and aggregate into multiple species, like oligomers or fibrils, increasing numbers of α-synuclein molecules. The addition of unfolded monomers can produce oligomers (Lashuel et al. 2013), and further addition of molecules can lead to the development of small amyloid fibrils, ultimately forming the intracellular inclusions, namely LB and LN (Arnaoutoglou et al. 2019) (Figure 3).

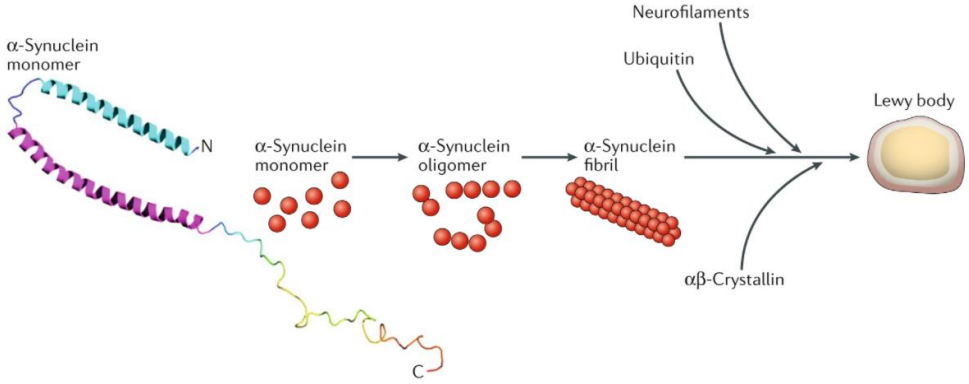

Figure 3. A-synuclein and formation of Lewy bodies (Open Access Source).

The figure depicts monomers' progression to α-synuclein fibrils that combine with other proteinaceous components to comprise the LB, a pathogenic hallmark of PD and DLB. Figure from (Arnaoutoglou et al. 2019).

The synaptic pathology has a central role in the pathogenesis of α-synucleinopathies since synapses are the primary site of α-synuclein localisation. Although LB and LN are the most significant α-synuclein pathological species, some other forms of α-synuclein aggregates – e.g. oligomers, small aggregates, or protofibrils – may be involved in the pathogenesis of α-synucleinopathy (Calo et al. 2016). Small aggregates are particularly abundant in synapses; they can be found early in the disease, usually before the formation of LB and LN, representing the first sign of degeneration in vulnerable neurons (Orimo et al. 2008; Tanji et al. 2010). Essential evidence shows that intermediated species (e.g. pre-fibrillar species) are more toxic to the cells than LB and LN, strongly supporting their involvement in the neurodegeneration process (Winner et al. 2011; Karpinar et al. 2009). The data regarding impairment of neurotransmission represents additional proof that synapses are the primary site of α-synuclein localisation. Synaptic neurotransmitter deficiency can be reproduced by overexpression of α-synuclein *in vitro* (Scott et al. 2010; Larsen et al. 2006) and *in vivo* models (Gaugler et al. 2012; Garcia-Reitböck et al. 2010; Lundblad et al. 2012). This synapse defect has been shown to precede cell death in the disease process. It was shown that, in PD, the dysfunction of dopaminergic cells might precede the development of LB pathology (Milber et al. 2012). Moreover, at the PD diagnosis, the damage of striatal dopaminergic neurotransmission and neurite degeneration is significantly greater than the loss of substantia nigra (SN) dopaminergic neurons (German et al. 1989; Kish et al. 1988; Nikolaus et al. 2009). In line

with this evidence, different subsequent imaging studies demonstrated a higher dopaminergic impairment of the striatum than the SN (Caminiti et al. 2017; Fazio et al. 2015; Hsiao et al. 2014), providing an *in vivo* support of axonal degeneration as the first event in PD (Figure 4).

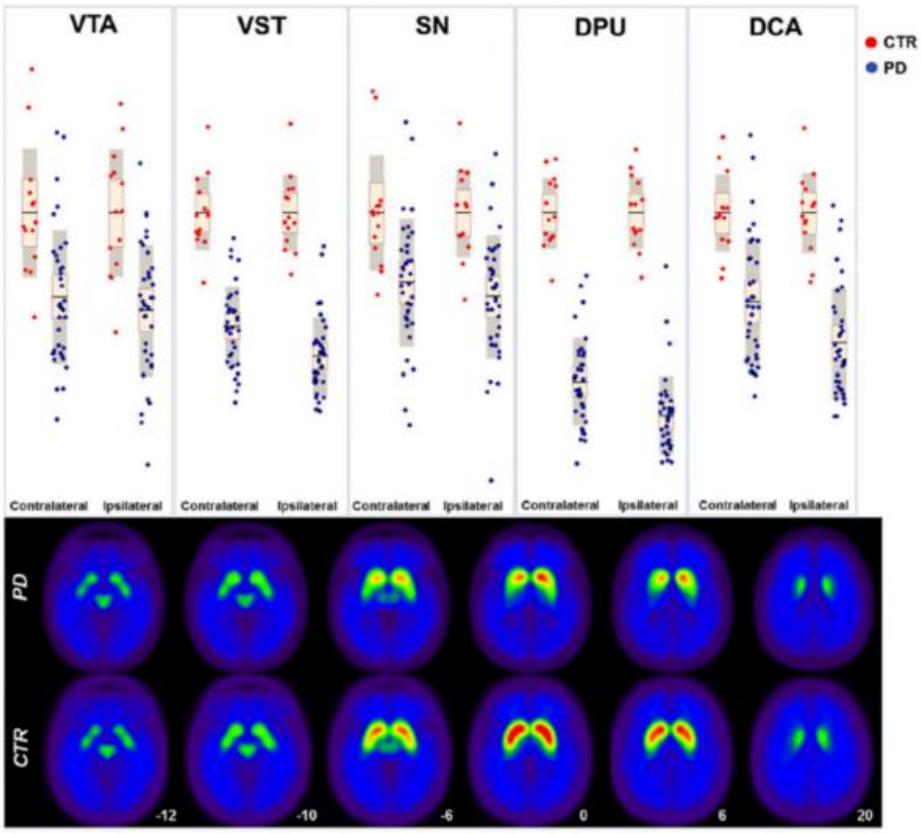

Figure 4. Axonal damage in Parkinson's disease (Open Access Source).

The figure shows a more severe dopaminergic impairment of the dorsal striatum than the SN in PD patients, obtained with [11C]FeCIT PET radiotracer measuring presynaptic DAT. The dorsal striatum receives the projection of substantia nigra forming the nigrostriatal pathway. Therefore, the higher impairment of dorsal putamen than SN might indicate protein aggregations in presynaptic terminals of SN projection neurons, resulting in axonal damage before the cell death. Abbreviation: VTA: ventral tegmental area, VST: ventral striatum; SN: Substantia Nigra; DPU: dorsal putamen, DCA: the dorsal caudate nucleus. Figure from (Caminiti et al. 2017).

All the above leads to postulate a central hypothesis underlying the pathogenesis of α-synucleinopathies asserting that protein aggregation in presynaptic terminals results in axonal damage, preceding the cell death (Calo et al. 2016). This assumption is consistent with a "retrograde progression of pathology", namely a retrograde transfer of degeneration from synapse to the cell body (Calo et al. 2016). Several studies suggest the existence of a "dying-back" pattern of neurodegeneration involving firstly axonal

degenerative changes and resulting from synaptic dysfunction, with just secondary involvement of cell bodies (Calo et al. 2016; Caminiti et al. 2017; Chu et al. 2012; Stoica et al. 2012).

There is increasing evidence that α-synucleinopathy spreads between cells and tissues in a prion-like manner (Goedert et al. 2017; Calo et al. 2016). The insoluble filamentous inclusions seem to be transmitted from cell to cell through interconnected neuronal pathways rather than anatomical proximity, suggesting a transsynaptic transfer (Goedert et al. 2017; Braak et al. 2003). This spread requires the release of α-synuclein aggregates into the extracellular space, the uptake by connected cells and further aggregation of soluble protein (Goedert et al. 2017). The contribution of synapses is plausible in the propagation of misfolded α-synuclein (Calo et al. 2016); however, the detailed cellular mechanisms underlying this pathological processes have not yet been fully clarified. The distribution of α-synuclein in the brain involves only a few vulnerable and axonally interconnected projection neurons within the human nervous system (Braak et al. 2004). Some neuronal populations are more prone to α-synuclein pathology (Lewy-prone systems); hyperbranched of long projection axons innervating several brain areas represents the shared structural feature characterizing these systems (Uchihara & Giasson 2016). This structural template increases the possibility of α-synuclein aggregation at axon terminals, further exacerbating metabolic burden and oxidative stress. Centripetal (retrograde) progression of the axonal lesion may represent a common process in these Lewy-prone systems (Uchihara & Giasson 2016). Accordingly, long and thin hyperbranched axons characterise nigrostriatal dopaminergic projections. Lewy pathology is not limited to the nigrostriatal system, also affecting several systems with similar structural features but with different neurotransmitters – i.e. noradrenergic, cholinergic and serotoninergic systems.

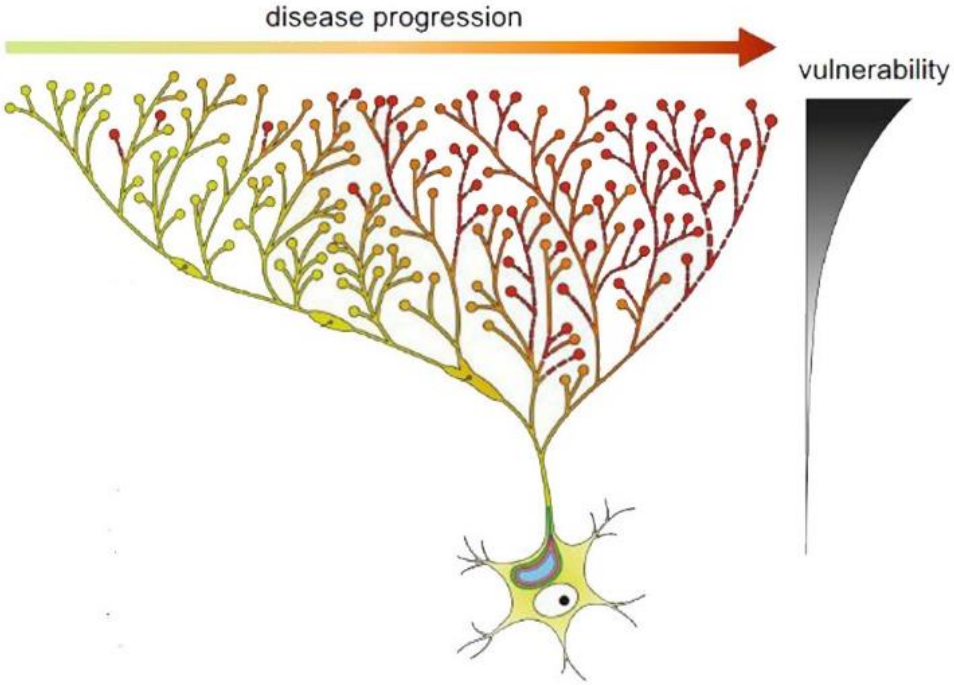

Figure 5. Lewy prone neuron cell and progression of pathology from synapses to neuronal soma (Open Access Source).

In Lewy-prone systems, the vulnerability is enhanced by the length of axons and the extension of the synaptic terminal, exponentially increasing the energy burden, specifically at the distal *components. It is not yet clear how this mechanism is related to α-synuclein deposition. Adapted from* (Uchihara & Giasson 2016).

Following the proposed prion-like behaviour of α-synuclein aggregation, in 2003, Braak and colleagues proposed that α-synuclein pathology progresses in predictable stages to readily recognisable locations in the brain (Braak et al. 2003). They developed a staging model of α-synuclein spreading, identifying six stages of α-synuclein deposition and spread in PD (Braak et al. 2003; Braak & Del Tredici 2009) (Figure 4A). The first α-synuclein pathological aggregates in the brain appear in the olfactory bulb and/or the dorsal motor nucleus of the glossopharyngeal nerve and the vagus nerve (stage 1). The medulla oblongata and pontine tegmentum were affected in stage II, and the amygdala and SN in stage 3. The typical motor symptoms of PD (bradykinesia, rigidity, rest tremor and gait disturbance) appear during this stage. Then, the pathology worsens, and the α-synuclein inclusions reach the temporal cortex (stage 4). Last, LB and LN reach the neocortex in stages 5 and 6, leading to cognitive impairments related to advanced stages of PD. Later in 2016, Braak and colleagues have mastered the first staging model, arguing

that the disease progression may originate in the enteric and peripheral nervous system (Figure 4B). The pathology reaches the dorsal motor nucleus of the vagal nerve in the lower brainstem (stage 1) (Del Tredici & Braak 2016). The occurrence of α-synuclein accumulation in the enteric and peripheral nervous system (PNS) as starting-point of pathology in PD is consistent with the early manifestation of non-motor features, i.e. autonomic involvement, hyposmia and RBD (Goedert et al. 2013).

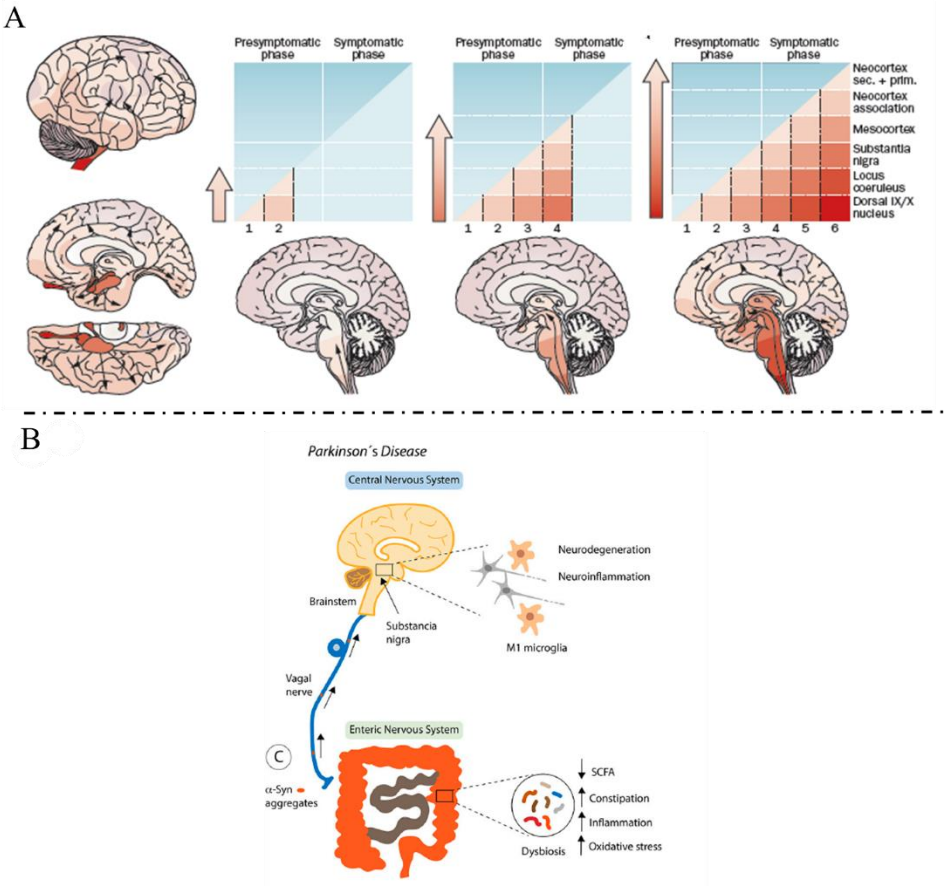

Figure 6. Model of α-synuclein pathology propagation (Open Access Source).

Panel A depicted the six stages of PD pathology according to Braak's model. (Del Tredici & Braak 2016). *Panel B of the figure showed the introduction of the enteric and peripheral nervous systems as the starting point of the pathology. Figures adapted from* (Goedert et al. 2013) *(Panel A) and* (Troncoso-Escudero et al. 2018) *(Panel B).*

The predictability of α-synuclein pathology progression only though Braak's model is still debated. Indeed, Braak himself reported that 6% of cases showed a divergence from the expected caudo-rostral spreading of pathology, suggesting that such divergence was due to the presence of concomitant AD. Moreover, independent research groups found that although Braak staging is accurate for most cases, this propagation

pattern has not been confirmed in a portion of patients – ranging from 10% to 20%. For this reason, new variants have been introduced, including an amygdala plus olfactory variant (Halliday et al. 2012) and an amygdala variant (Uchikado et al. 2006). Borghammer's research group recently proposed a more comprehensive picture (Borghammer & Van Den Berge 2019), suggesting that LBD (PD and DLB) comprise two different starting-point: (1) a PNS-first and (2) a central nervous system (CNS)-first. In the first case, patients should show significant damage to the autonomic PNS before damaging higher Braak stage structures, including the SN. In the latter case, patients exhibit severe damage to the SN before a detectable impairment of the autonomic PNS (Figure 6). This proposal provides a new hypothesis generation framework for hereafter research on the pathogenesis of LBD, and it seems to be able to explain the discrepancies related to neuropathology findings.

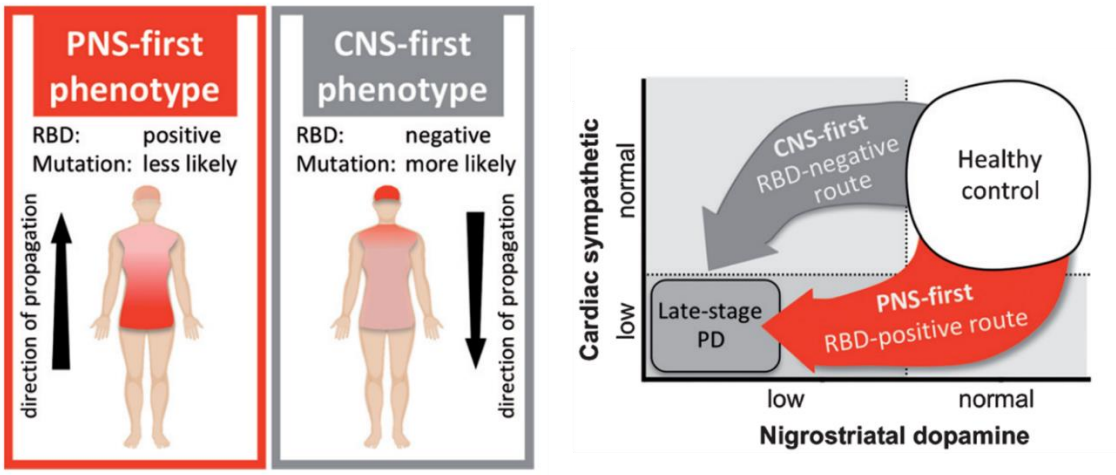

Figure 7. Two theoretical starting points of Lewy body disorder (Open Access Source).

In the PNS-first route (red), α-synuclein pathology propagates with a caudo-rostral direction throughout autonomic connections to the medulla and brainstem. In that case, early damage to the autonomic PNS characterises patients' phenotype (e.g. cardiac sympathetic denervation), which often presents RBD during the prodromal phase. In the CNS-first route (grey), α-synuclein aggregates propagate anterogradely from the CNS to the PNS. In this case, the patients' phenotype derived from the damage of CNS structures –including the SN–, while the autonomic PNS is initially not affected. Of note, these patients did not present a history of RBD during the preclinical phases. Figure adapted from (Borghammer & Van Den Berge 2019).

A-synuclein aggregates constitute LB and LN; however, they can also result in GCIs, which are the neuropathological hallmark of MSA. Specifically, GCIs are

pathological aggregation composed of fibrillary α-synuclein, ubiquitin[4], tau (in a phosphorylated form different from AD and other tauopathies) and several multifunctional proteins (Jellinger 2014). GCI is primarily located in oligodendrocytes and astrocytes, specifically in the cytoplasm and, to a lesser extent, in the oligodendrocytes/astrocytes nucleus. The α-synuclein form present in GCI differs from the insoluble form found in LB and LN, suggesting different processing of α-synuclein in neurons and oligodendrocytes (Campbell et al. 2001). However, mature human oligodendrocytes lightly express α-synuclein, and in oligodendrocytes of patients with MSA does not occur an increased expression of α-synuclein (Yoon et al. 2021). Therefore, since oligodendrocytes do not express large amounts of α-synuclein, how α-synuclein accumulates in the GCI of these cells remains unclear. One possible explanation is the "transmission" hypothesis of α-synuclein, which suggests a transfer of this protein from neurons to oligodendrocytes (Yoon et al. 2021; Jellinger 2014). The accumulation of GCI leads to demyelination and neuronal death in MSA (Figure 8).

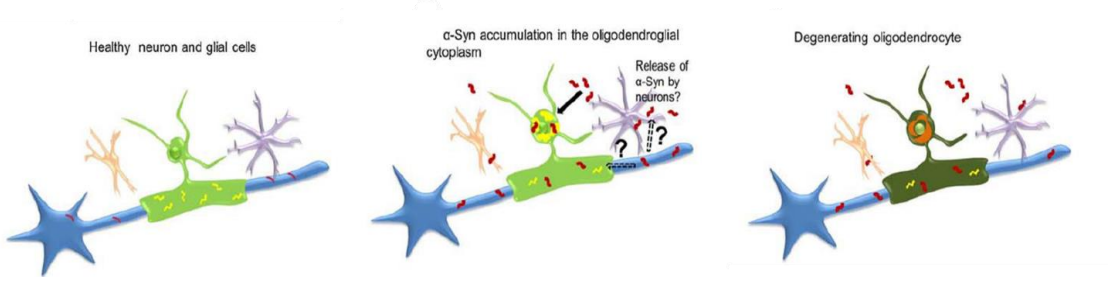

Figure 8. Pathological a-synuclein related oligodendroglial neurodegeneration (Open Access Source).

The figure shows healthy neurons, oligodendrocytes, microglia, astrocyte, and the subsequent neurodegeneration caused by pathological α-synuclein positive GCI (left to right). The GCI is positive for α-synuclein in oligodendrocytes and astrocytes, concomitant with demyelination of axons and neuronal degeneration in MSA. Figure adapted from (Jellinger 2014).

In MSA, GCI affects the SN, striatum, locus coeruleus (LC), pontine nuclei, inferior olives, cerebellum, and spinal cord (Jellinger 2014; Halliday et al. 2011). Moreover, MSA patients can present LBs in several brain components, encompassing the brainstem (Ozawa et al. 2004; Jellinger 2007). These findings suggest that α-synuclein inclusions can be detected within the nuclei of oligodendrocytes and within the cytoplasm and nuclei of neurons in MSA (Papp & Lantos 1992; Nishie et al. 2004;; Jellinger and

[4] Ubiquitin is a small protein found in all eukaryotic cells. It performs its countless functions by binding to multiple target proteins

Lantos 2010). MSA is characterized by high neuropathological variability – neuronal loss and GCI density – causing a parallel clinical heterogeneity that originates a spectrum of diseases (Halliday et al. 2011).

1.2. REM sleep behaviour disorder (RBD)

RBD is a sleep parasomnia characterized by vocalizations, jerks and motor behaviours during REM sleep, often associated with aggressive dream-enacting behaviours that cause repeated injury to patients and/or their bed partner (Högl et al. 2018). RBD has substantial ethical and medical implications compared with other sleep disorders because the majority of iRBD eventually develop a neurodegenerative disease (Pérez-Carbonell and Iranzo 2019). When the occurrence of RBD follows other neurological diseases (usually an α-synucleinopathy), it is defined as secondary (Ferini-Strambi et al. 2019). Differently, when it occurs in the absence of any other disorder, RBD may be classified as primary (or idiopathic/isolated) (iRBD) (Högl et al. 2018). Even in this isolated form, RBD often precedes the development of neurodegenerative diseases. Specifically, 31.95% of iRBD cases may evolve in overt neurodegeneration after a mean follow-up of 5 years, with particular attention to α-synuclein spectrum: PD (43%), DLB (25%), and MSA (5%) (Galbiati et al. 2019). The risk of conversion reaches even 97% after 14 years of disease duration (Galbiati et al. 2019). A significant positive correlation exists between the percentage of conversion and follow-up duration, demonstrating that the risk of conversion increases over the years after iRBD diagnosis (Galbiati et al. 2019). Longitudinal studies, pathological evidence, and neurodegenerative biomarker data defined iRBD as a prodromal stage of α-synucleinopathies (Ferini-Strambi et al. 2019). Early identification of individuals with iRBD is decisive since it may represent a window into the future health of the brain. Patients with iRBD are ideal candidates to test new neuroprotective methods and better understand the neurodegenerative mechanisms underlying α-synucleinopathies from the presymptomatic stage.

This paragraph covers the clinical features of iRBD and its role as an early diagnostic and prognostic biomarker within the α-synuclein spectrum.

1.2.1. Epidemiology

Knowing the prevalence of RBD in the general population can have significant implications in developing strategies for diagnosing and managing affected patients. Despite this, the occurrence of iRBD in the general population is still uncertain. Prevalence data available to date come from two approaches: video-polysomnography (PSG)-based and questionnaires-based studies (Pérez-Carbonell and Iranzo 2019). In PSG-based studies, the prevalence of iRBD in subjects over 60 years ranges from 0.3 to 1.5% (Chiu et al. 2000; Kang et al. 2013; Pujol et al. 2017; Haba-Rubio et al. 2018). On the other hand, the questionnaire-based findings reveal a higher prevalence than the previous one, ranging from 4.6% to 7.7% in the elderly population (Boot et al. 2012; Mahlknecht et al. 2015). The questionnaire-based prevalence data might overestimate the occurrence of this condition because of the risk of false-positive cases, namely those conditions that can mimic iRBD (e.g. severe obstructive sleep apnea, sleepwalking, sleep terrors, the periodic limb movement disorder in sleep) (Iranzo et al. 2016; Pujol et al. 2017) (see *1.2.3.Differential clinical diagnosis*). In the 3rd edition of the international classification of sleep disorders (ICSD-3) the PSG recording is mandatory to diagnose iRBD (Medicine 2014).

iRBD is frequently diagnosed in people over 50 years old (Schenck et al. 1993; Olson et al. 2000; Fernández-Arcos et al. 2016; Li et al. 2017; Barber et al. 2017; Sforza et al. 1997). However, earlier onset has been described in some cases (without PSG confirmed diagnosis), identifying 30 to 40% of iRBD studied cohorts younger than 50 years (Bonakis et al. 2009; Teman et al. 2009; Claassen et al. 2010).

Most patients with iRBD diagnosis are men (Postuma et al. 2009; Iranzo et al. 2005). Specifically, males' prevalence has been reported to reach the 90%, with a male to female ratio ranging from 5:1 to 8:1 (Schenck et al. 1993; Sforza et al. 1997; Olson et al. 2000; Iranzo et al. 2006; Okura et al. 2007; Wing et al. 2008). However, in the last decade, studies failed to report similar epidemiological gender differences (Wong et al. 2016; Frauscher et al. 2010), identifying an overall male to female ratio of iRBD diagnosis closer to 2:1 (Yo El Ju et al. 2009). Together with the absence of sex hormones abnormalities in patients with iRBD (Iranzo et al., 2007), these last findings have led to postulate that iRBD could be under-recognized in women (Bodkin and Schenck 2009). Indeed, female iRBD patients usually have less aggressive dream-enhanced behaviours

(Fernández-Arcos et al. 2016); therefore, sleep-related injuries are uncommon in female patients (Bjørnarå et al. 2013; Zhou et al. 2015; Mahale et al. 2016): it is easy to understand how iRBD females less frequently reach clinical attention. The greater awareness of this issue among clinicians allowed increasing the proportion of iRBD females diagnosed during the last decade (around 20% more diagnosis) (Fernández-Arcos et al. 2016). Of note, the risk of phenoconversion to a neurodegenerative disease seems to be similar in men and women (Fernández-Arcos et al. 2016).

Genetic factors may have a role in the neuropathological mechanisms of iRBD, even if the family gathering is still a controversial issue in this condition (Gan-Or and Rouleau 2019). Although iRBD is considered the preclinical stage of α-synucleinopathies, the scientific research community recently started investigating the associated genetic factors. For a while, the GBA mutations have been identified as the strongest genetic factor associated with iRBD (Gan-Or et al. 2015). Specifically, it has been demonstrated that carriers of GBA mutations show a high risk to develop iRBD (Odd ratio of 6.24) (Gan-Or et al. 2015); furthermore, the association between GBA mutations and iRBD seems to be higher than in PD (Odd ratio of 1.87) (Noreau et al. 2011). A longitudinal study demonstrated that GBA mutation-positive patients develop RBD, depression, autonomic dysfunction, cognitive function, and parkinsonian motor signs over two years of follow-up (Beavan et al. 2015). All the above may suggest that the RBD subtype of PD is more likely associated with GBA mutation. Indeed, PD patients with GBA mutation (GBA-PD) and RBD-associated PD share multiple clinical manifestations, such as faster motor progression (Fereshtehnejad et al. 2015; Brockmann et al. 2011), postural-instability-gait-dysfunction phenotype (Gan-Or et al. 2010; Postuma et al. 2008; Kumar et al. 2013), cognitive decline and progression to dementia (Brockmann et al. 2011; Anang et al. 2014; Cilia at al. 2016; Liu et al. 2016; Alcalay et al. 2012). LRRK2-related PD appears to have a less severe course and slower cognitive decline than GBA-PD. So, mutations in LRRK2 have nothing to relate with iRBD or PD patients who may have iRBD (questionnaires-based). This evidence further supports GBA mutation as an essential genetic factor in RBD.

Few studies also reveal that mutation of the C9orf72 gene and different genetic loci (SCARB2 and MAPT) in iRBD patients are more frequent than in controls subjects (Dagan et al. 2015; Gan-Or et al. 2015). At last, few data suggest that genetic factors may

be related to the conversion rate from iRBD to PD, DLB or MSA (Gan-Or et al. 2015). However, this hypothesis needs support by research conducted in larger cohorts.

1.2.2. Clinical features

The core symptoms of iRBD include abnormal behaviour during REM sleep, unpleasant dreams with the absence of any waking movement and cognitive discomfort, and no neurological disease detection (Pérez-Carbonell and Iranzo 2019). A good portion of iRBD are unconscious of their abnormal sleep behaviours (Fernández-Arcos et al. 2016), so the report of their bed partners are crucial to receiving a comprehensive picture of RBD episodes.

To make the diagnosis of iRBD, a collection of clinical history and video-PSG are mandatory. According to ICSD-3, the current diagnostic criteria are the following: (1) repeated episodes of behaviour or vocalization that must occur during the REM phase, documented by PSG or reports of dream enactment, and (2) evidence of REM sleep without atonia (RSWA) on PSG (according to scoring manual). When RSWA does not occur during the video-PSG recording, the diagnosis may be given provisionally if the other clinical criteria are met (Medicine 2014) (Figure 9).

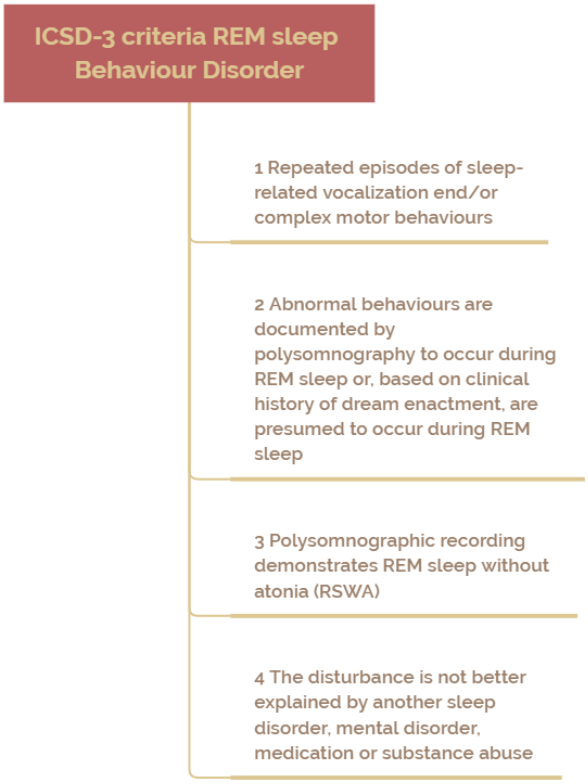

Figure 9. Clinical criteria for iRBD diagnosis.

The onset of iRBD seems to be associated with stressful life experiences like quarrelling with a relative, being a victim of fraud, receiving a severe illness diagnosis, or going through a traumatic event (Schenck and Mahowald 2002; Fernández-Arcos et al. 2016). Of note, some patients reported that a specific scenario (e.g. watching a thriller before going to bed) might activate an RBD episode during the night (Fernández-Arcos et al. 2016).

Abnormal sleep behaviours in iRBD patients mainly manifest as motor actions and vocalizations; they occur unexpectedly – enduring from seconds to few minutes – and usually start and finish in the bed (Pérez-Carbonell and Iranzo 2019). Motor behaviours feature a broad degree of severity and complexity, ranging from simple jerks to highly elaborated movements. Body and limb jerks are the most frequent expression of iRBD. These simple movements have been suggested to represent an abrupt startle rather than a dream (Revonsuo 2000). Furthermore, aggressive dream-enacting actions are ordinary, like punching, kicking, hitting the nightstand, biting, and assaulting the bed partner. Of note, it is common for iRBD patients to experience falling off the bed, causing sleep-related injuries. Patients familiar with such incidents usually apply protective

measures, such as placing pillows on the floor next to their bedside. Although aggressive dream-enacting actions are the most frequent abnormal sleep behaviours, nonviolent behaviours can also occur (Oudiette et al. 2009). For example, iRBD patients can experience elaborate behaviours such as eating, reaching something, speaking, singing, clapping, or dancing (Oudiette et al. 2009; Oudiette et al. 2012).

The above-described behaviours correspond to enacted dreams, experienced as unpleasant, vivid, and intense. Dreams recurring themes include fighting, arguing, being chased by animals or/and strangers (Fernández-Arcos et al. 2016). Patients are frequently personally involved in the dream, protecting themselves and their relatives from a physical attack or humiliation. The clinical manifestation of iRBD differs between men and women (Fernández-Arcos et al. 2016). Men act more aggressive behaviours and vocalisations, combined with more violent and action-filled dreams; on the contrary, women have more frequently depression, and the content of their dream is mainly related to children in life-threatening situations (Fernández-Arcos et al. 2016). Surprisingly, a study of 203 consecutive iRBD patients demonstrated that 44% of patients were unaware of their actions, 70% even reported sleeping properly (Fernández-Arcos et al. 2016).

Additional clinical features can be found in iRBD subjects. Signs or symptoms typical of an overt α-synucleinopathy (i.e. PD, DLB, and MSA) can occur in these patients, suggesting a latent neurodegenerative process (Iranzo et al. 2017). Such clinical manifestations are olfactory loss, depression, altered colour vision, dysautonomia, subtle parkinsonisms, and mild cognitive dysfunction (see *1.2.4.The risk of neurodegeneration in iRBD*) (Iranzo et al. 2017; Pérez-Carbonell and Iranzo 2019).

As for the medication treatment, melatonin and clonazepam before bedtime can reduce the recurrence and severity of abnormal behaviours and unpleasant dreams in iRBD. Still, these therapies do not reduce neurodegenerative symptomatology, thus not preventing synucleinopathies' progression (Pérez-Carbonell and Iranzo 2019).

The presence of subtle signs and symptoms of ongoing neurodegenerative processes makes iRBD an early clinical stage of α-synucleinopathies instead of a prodromal stage. Indeed in the last five years, the concept of a prodromal phase of iRBD has emerged (Sixel-Döring et al. 2016). The term prodromal iRBD defines a stage in which symptoms and signs of iRBD can occur without fully meeting the diagnostic criteria (Sixel-Döring et al. 2016). REM-sleep-related behavioural events (RBE) are

defined as motor behaviours and vocalizations in REM sleep with a seemingly purposeful component that does not reach the quantitative video-polysomnography cut-off scores needed for iRBD diagnosis (Figure 10) (Högl et al. 2018). RBE seems to be a precursor of RBD and is called "prodromal RBD". Accordingly, a longitudinal study demonstrated that 38% of patients with RBE develop overt RBD after two years of follow-up (Sixel-Döring et al. 2016).

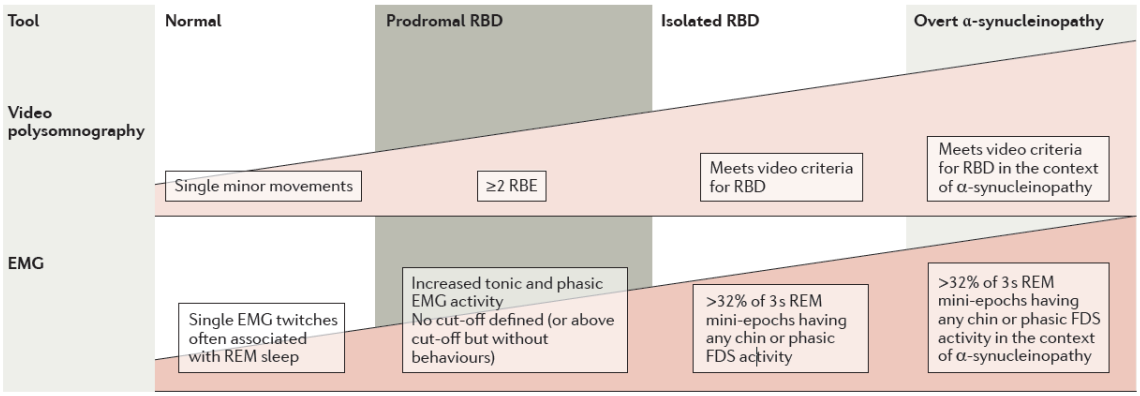

Figure 10. Progression from normal condition to overt RBD (Open Access Source).

The figure depicts how video-PSG, EMG, and behavioural features progress from an initially normal condition to a prodromal stage of RBD, reaching the condition of overt RBD. Figure from (Högl et al. 2018).

These observations indicate that RBD is not a disease with an apparent cut-off onset but instead has insidious episodes, increased EMG activity and minor behavioural events related to REM sleep until the appearance of clinical manifestations of RBD (Högl et al. 2018).

1.2.3. Differential clinical diagnosis

Numerous studies reveal that awareness of iRBD among medical doctors is still poor (Boeve et al. 2013; Fernández-Arcos et al. 2016; Frauscher et al. 2010). Accurate diagnosis of iRBD is challenging, as the disease could be easily confounded with other pathology as obstructive sleep apnoea (OSA) (Iranzo and Santamaria 2005), non-REM parasomnia, periodic limb movement disorder (Gaig et al. 2017), epilepsy or nocturnal

wandering. These misdiagnoses can occur specifically if the patient's history is the only accounted factor in the diagnostic procedure (Fernández-Arcos et al. 2016).

As iRBD, OSA is a men-predominant disease, with onset around the sixties, self-injury, and dream-enacting behaviours (Iranzo and Santamaria 2005). However, the two disorders differ in the underlying mechanisms and pharmacological treatment effects. iRBD is characterized by the impairment of brainstem structures involved in REM sleep and clonazepam-based therapy; in contrast, OSA is based on repetitive sleep obstruction of the upper airway, and clonazepam treatment is detrimental because of apnoea worsening (Iranzo and Santamaria 2005). The video-PSG recording can distinguish between two different sleep disorders, demonstrating that the abnormal sleep behaviours in OSA patients occur only during apnoea-induced arousals (Iranzo and Santamaria 2005). iRBD presents clinical similarities and differences with sleepwalking and sleep terrors that are non-REM sleep parasomnias (Iranzo et al. 2016). Specifically, these parasomnias and iRBD overlap in unpleasant dreams, dream-enacting behaviours (Oudiette et al. 2009), and clonazepam treatment effectiveness (Iranzo et al. 2016). Unlike iRBD, patients with sleepwalking and sleep terrors frequently leave the bed in extended episodes, often with eyes opened. Moreover, in non-REM sleep parasomnias, abnormal sleep behaviours are usually triggered by sleep deprivation, physical contact, and noise during sleep (Iranzo et al. 2016). Unlike iRBD, family history and onset during childhood or adolescence are frequent in non-REM sleep parasomnias (Iranzo et al. 2016). Non-REM parasomnias occur during sleep stages N3 and N2 but not during the REM sleep phase (Irfan et al. 2017). The video-PSG recording can accurately determine when the abnormal behaviour occurs, leading to a diagnosis of iRBD.

Furthermore, nocturnal frontal lobe epilepsy shares with iRBD the same abnormal behaviours, such as screaming, body jerking, kicking, and violent semi-purposeful movements. Contrary to iRBD, it typically occurs during childhood and adolescence, and unpleasant dreams are infrequent. Moreover, REM sleep atonia is preserved (Derry, 2011; Iranzo et al., 2016). Normal REM sleep atonia is present also in periodic limb movements disorder, where, as iRBD, patients experience unpleasant dreams and dream-enacting behaviours (Gaig et al. 2017). Similar to iRBD, men are mainly involved, and the diagnosis is usually during the fifties. However, periodic leg movements occur during NREM sleep (Iranzo et al., 2016).

All these data highlight the crucial role of video-PSG in RBD diagnosis, which can exclude possible disorders mimicking the symptoms of iRBD.

1.2.4. The risk of neurodegeneration in iRBD

According to longitudinal data, 90% of patients with iRBD develop PD, DLB or, in rare cases, MSA after fifteen years of disease duration (Galbiati et al. 2019). Neuropathological findings in iRBD documented α-synuclein accumulation in the autonomic and CNS (Iranzo et al. 2014; Boeve et al. 2013; Uchiyama et al. 1995; Boeve et al. 2007). Similar findings have also been reported in living iRBD subjects using a biopsy approach, showing α-synuclein aggregates in the colon, salivary glands, and skin (Sprenger et al. 2015; Vilas et al. 2016; Iranzo et al. 2017; Doppler et al. 2017; Antelmi et al. 2017). This evidence showed that in iRBD, the neurodegenerative process goes beyond the nuclei that regulate REM sleep, already reaching additional brain structures. Therefore, iRBD constitutes a specific clinical entity, representing an α-synucleinopathy itself (Iranzo et al. 2013).

Clinical markers of neurodegeneration are already present in iRBD patients, encompassing olfactory loss, depression, autonomic dysfunction, and neuropsychological impairments (Högl et al. 2018; Pérez-Carbonell and Iranzo 2019). The occurrence of olfactory loss is more frequent in iRBD than in controls, ranging from 36% to 97% and 3 to 17 %, respectively (Miyamoto et al. 2010; Rossi et al. 2015; Postuma et al. 2006; Postuma et al. 2009). iRBD patients show significant odour identification/ discrimination deficits and overall olfactory dysfunction (Lyu et al. 2021). The presence of olfactory dysfunction seems to precede about five years the development of an overt α-synucleinopathy (Postuma, Desjardins, and Montplaisir 2011; Iranzo et al. 2021). Indeed, hyposmia is considered a short-term risk factor for conversion toward α-synucleinopathies, even if it cannot predict which type of α-synucleinopathy will be developed (Iranzo et al. 2021). Moreover, olfactory deficits do not worsen over time in iRBD, not representing a useful outcome measure in future clinical trials (Iranzo et al. 2013).

Psychiatric symptoms – frequent clinical features in PD and DLB (Chaudhuri et al. 2006) – can also occur in iRBD (Rolinski et al. 2014). 25 to 30% of iRBD subjects experience depression and 18 to 23% anxiety (Postuma et al. 2019). Of note, mood

symptoms seem to be greater in iRBD than in patients with early and untreated PD or healthy adults (Barber et al. 2017). Such severity may explain why iRBD patients have a similarly impaired quality of life to early PD patients (Barber et al. 2017). Treating mood disturbances in patients with iRBD can be challenging, as antidepressants can worse symptoms; thus, alternative treatments are needed for these mood disturbances (Iranzo et al. 2016). There are different theories about the meaning of psychiatric symptoms in iRBD.

On the one hand, the presence of depression, together with other non-motor symptoms (e.g. autonomic dysfunction), could reflect underlying neurodegeneration in multiple regions (Pérez-Carbonell and Iranzo 2019). iRBD patients with depressive symptoms show abnormalities in the LC and dorsal raphe nucleus (Vilas et al. 2015; Bourgouin et al. 2009). However, it has been demonstrated that depression and anxiety do not predict the progression from iRBD to overt α-synucleinopathy (Postuma et al. 2019). Thus, it is also possible that the interplay of other comorbid motor/non-motor features contributes to enhancing this symptomatology. Accordingly, a recent study demonstrated that the presence/severity of motor, sleep and cognitive symptoms could help predict depression (Chiu et al. 2021). Anxiety is predicted by the severity of sleep-related, cognitive and autonomic symptoms instead (Chiu et al. 2021). This perspective leads to reorient the clinical management of depression and anxiety in iRBD patients through non-pharmacological treatments (such as exercise, diet, and sleep hygiene) instead of prescribing antidepressants and anti-anxiety drugs that may exacerbate dreaming behaviour.

iRBD patients show dysautonomia (Postuma et al. 2006; Postuma et al. 2009; Claassen et al. 2010), gastrointestinal, urinary and cardiovascular dysfunctions (Ferini-Strambi et al. 2014). Specifically, gastrointestinal symptoms correlate with the duration of the disease (Ferini-Strambi et al. 2014). Of note, the presence of peripheral cardiovascular denervation in iRBD seems to be the pathological substrate of autonomic cardiovascular dysfunctions (Borghammer & Van Den Berge 2019). Indeed, as measured by uptake of 123I-metaiodobenzylguanidine ([123I]MIBG), cardiac sympathetic denervation is consistently reported by literature in iRBD (Miyamoto et al. 2006). The severity of cardiac sympathetic denervation is like those observed in PD or DLB (Miyamoto et al. 2008; Knudsen et al. 2018). Thus, iRBD patients already have fully

developed peripheral autonomic nervous system pathology, comparable to overt α-synucleinopathies (Knudsen et al. 2018). The presence of autonomic dysfunction strongly supports the caudorostral gradient of dysfunction in iRBD, starting in the peripheral autonomic system and then spreads rostrally to the brainstem, becoming an overt α-synucleinopathy (Borghammer & Van Den Berge 2019).

Regarding neuropsychological impairments, deficits in executive functions, verbal and nonverbal memory, attention, and visuospatial abilities have been reported in iRBD (Ferini-Strambi et al. 2019). Some studies showed that visuospatial and visuoperceptive impairments in iRBD patients are related to α-synucleinopathies development (Ferini–Strambi et al. 2004; Plomhause et al. 2014; Li et al. 2016). However, other studies did not report significant differences between patients and control subjects in this domain (Gagnon et al. 2009; Terzaghi et al. 2008; Massicotte-Marquez et al. 2008). Notably, abnormalities in attention, executive functions and visuospatial impairments are predictors for conversion, especially toward DLB (Ferini-Strambi et al. 2019). A recent longitudinally study investigated a cohort of iRBD for six years. According to the phenoconversion after the follow-up period, the authors classified the iRBD as PD, DLB or still isolated. Then they studied the progression of cognitive decline (Génier Marchand et al. 2018), demonstrating that deficits in attention and executive functions occurred six years before dementia diagnosis, characterizing patients who developed DLB. In contrast, verbal episodic learning and memory impairments started later, becoming clinically significant one to two years before the diagnosis (Génier Marchand et al. 2018).

Of note, iRBD seems to be a significant risk factor for MCI and essential for cognitive impairment in PD (Gagnon et al. 2009). Indeed, MCI was found in 50% of iRBD patients and 73% of PD patients with RBD compared to only 11% and 8% of PD patients without RBD and control subjects, respectively (Gagnon et al. 2009). In light of this evidence, iRBD is increasingly considered a risk factor for dementia development in PD (Gagnon et al. 2009) and DLB conversion (Massicotte-Marquez et al. 2008), stressing its role in predating worse conditions within the α-synucleinopathies spectrum. A recent study showed that iRBD patients reported more frequent pareidolic responses in the pareidolia test than controls (Sasai-Sakuma et al. 2017). This performance was associated with the presence of a cognitive decline in iRBD, suggesting the role of pareidolias in predicting future DLB occurrence, especially in cases of early visual hallucinations

(Sasai-Sakuma et al. 2017). However, this hypothesis needs more evidence, particularly addressing clinical manifestations of visual hallucinations.

Although iRBD is considered the most potent predictor of neurodegenerative synucleinopathies, reaching 90% of converting patients, a minority of iRBD patients who remain disease-free for many years exist called longstanding iRBD (Högl et al. 2018). Despite evaluating long survivors may provide a chance to determine whether a 'benign' subtype of iRBD exists, these patients are understudied. In 2018, the Montreal sleep research group described 11 longstanding iRBD (Yao et al. 2018). They found that most long-term survivors showed signs of neurodegeneration, which progressed over time, and eventually met the criteria for pre-PD, indicating that cases of "non-synucleinopathy" are rare. This study emphasizes the variability of the rate of progress, indicating that there may be subtypes with slower progress, perhaps related to age, environment, or genetic factors.

1.3. Parkinson's disease (PD)

James Parkinson described PD for the first time in 1817 when he published his report "An Essay on the Shaking Palsy" (Parkinson 1817). Years later, Jean-Martin Charcot coined the term "Parkinson's disease" to replace "shaking palsy" or "paralysis agitans" terminology, highlighting that this type of patient was not markedly weak or did not necessarily show tremor (Charcot 1877). Since its original description, the clinical diagnosis of PD is based on a defined motor syndrome (Postuma et al. 2015). However, many non-motor symptoms (NMSs) may occur, and some can predate motor disfunction (Poewe et al. 2017). NMSs are heterogeneous – e.g. disorders of sleep-wake cycle regulation, cognitive impairment, mood disorders, autonomic dysfunction, sensory symptoms and pain – and become increasingly prevalent throughout the illness (Chaudhuri et al. 2006). Thus, PD can manifest with different and complex clinical phenotypes, where the most severe one is characterized by dementia development (Poewe et al. 2017). Identifying different clinical trajectories in iPD is crucial to define the risk of developing a malignant type of pathology. Below, the main shapes of PD will be described: epidemiology, clinical features, and disease trajectories.

1.3.1. Epidemiology

PD is the most frequent movement disorder (De Lau and Breteler 2006). It is the fastest-growing neurological disorder, surpassing AD (Dorsey and Bloem 2018). It is expected that the number of PD patients will be double from 2015 to 2040, reaching 12.9 million people and leading to the definition of "Parkinson Pandemic" (Dorsey and Bloem 2018). The worldwide incidence of PD ranges from 8 to 18 new cases per 100000 persons yearly. PD rarely starts before 50 years of age; meanwhile, it affects about 1% of the world population over 60 years (De Lau and Breteler 2006).

The global prevalence of PD is estimated at 0.3% (De Lau and Breteler 2006). Similarly to incidence, the prevalence increases with age from 1% for people over 60 to 4% for people over 80, and it is rare before the age of 50 (De Lau and Breteler 2006). Gender influences the disease susceptibility in PD; indeed, males show higher prevalence and incidence than women, with a ratio of 2:1. Male sex is therefore reported as a risk factor for PD (Meoni et al. 2020). Different factors are hypothesized to participate in this male preponderance (see *1.10. Biological factors: sex and gender*).

Epidemiological studies provide evidence for the role of environmental, behavioural, and genetic factors in the pathogenesis of PD. Environmental and behavioural risk factors associated with an increased risk for sporadic PD include pesticides, herbicides, heavy metals, dairy products (such as large amounts of milk), cancer (the association between PD and melanoma), and traumatic brain injury (Ascherio and Schwarzschild 2016). The protective factors negatively associated with sporadic PD are tobacco, coffee, alcohol, and physical activity (Ascherio and Schwarzschild 2016).

Regarding the genetic factor, complex gene-environment interactions contribute in increasing (or decreasing) the risk for PD (De Lau and Breteler 2006). Genome-wide association studies (GWAS) and candidate gene association studies reveal SNCA, LRRK2 as risk factors for the dominant autonomic form of PD. Rare and common mutations of the SNCA gene – which encodes α-synuclein – can influence the risk of developing PD (Billingsley et al. 2018). Specific mutations of this gene (deleterious point mutations and multiplications) induce a severe early-onset form of PD with an autosomal dominant inheritance pattern, clinically characterized by akinetic-rigid predominance, pyramidal signs, psychiatric symptoms, mental decay and an inadequate response to dopaminergic treatment. Moreover, the variability in the non-coding section within this

locus predisposes to genetically complex forms of PD (Billingsley et al. 2018). The leucine-rich repeat kinase 2 (LRRK2) gene point mutations have been found in 4% of autosomal dominant PD and 1% sporadic PD. The risk of PD for LRRK2 mutation carriers ranges from 28% at 59 years to 51% at 69 years, reaching up to 74% at 79 years of age (Healy et al. 2008). The clinical phenotypes of this form of PD are similar to typical clinical manifestations of idiopathic (i)PD. In these circumstances, cognitive deficiency is quite unusual (Thenganatt and Jankovic 2014). In addition to autosomal dominant forms of PD mediated by the SNCA and LRRK2 genes, there are also autosomal recessive forms of PD, which involve *parkin,* PINK1 and DJ-1 gene. *Parkin* and PINK1 work together to remove damaged mitochondria, and DJ-1 preserve mitochondria from oxidative stress (Kalia and Lang 2015). In patients with PD onset before 45 years, *parkin* mutations have been found in 50% of familial cases and about 15% of sporadic cases (Lücking et al. 2000; Periquet et al. 2003). In contrast, mutations in PINK1 and DJ-1 are less common, affecting 1 to 8% and 1 to 2% of the sporadic PD cases with early-onset, respectively (Singleton et al. 2013). Last, heterozygous mutations in the GBA gene – which encodes for the enzyme glucocerebrosidase –are the most prominent genetic risk factor for developing PD (Sidransky et al. 2009). Given that GBA variants occur with frequencies $< 5\%$, this gene was initially omitted from GWAS analyses. Glycosylceramide[5] might cause the accumulation of α-synuclein, and conversely, the accumulation of α-synuclein may lead to a decrease in glucocerebrosidase activity (Mazzulli et al. 2011). Overexpression of α-synuclein led to decreased glucocerebrosidase levels in brain tissue (Chiasserini et al. 2015; Murphy et al. 2014), cerebrospinal fluid,(Parnetti et al. 2017) and peripheral blood of PD patients (Alcalay et al. 2015; Avenali et al. 2021). All in all, these studies indicate a malignant neurotoxic cycle that GBA mutations may trigger. Compared to idiopathic PD, GBA-PD shows an earlier onset and a higher risk for cognitive impairment. They are characterized by an earlier cognitive decline involving memory and visuospatial abilities, abstraction and orientation domains, working and visual-short memory, and executive functions (Balestrino and Schapira 2018). GBA-PD patients seem to be particularly vulnerable to psychiatric clinical manifestations. Finally, they report depression, anxiety, and apathy more frequently, although there are conflicting results (Balestrino and Schapira 2018).

[5] The substrate of glucocerebrosidase

1.3.2. Clinical features

PD clinical picture is characterized by a range of motor and NMSs, whose expression might vary among patients (Figure 11); however, all patients must exhibit the core clinical motor features and respond to dopaminergic therapy to meet the criteria for PD diagnosis (Postuma et al. 2015).

In most patients, motor symptoms began on one side of the body, with the contralateral side became affected within a few years. The body posture becomes bent (camptocormia), with axial and limb rigidity, a tendency for a shuffling gait and insufficient arm swing when walking. Although limb bradykinesia [6] is mandatory for PD diagnosis, it can also involve voice, face, and axial/gait domains (Postuma et al. 2015). Specifically, bradykinesia may lead to a lack of facial expression (hypomimia) and reduced handwriting amplitudes (micrographia).

The rigidity can be described as a resistance to passive movement and is usually accompanied by the "cogwheeling" phenomenon [7]. It can present an axial or limb involvement (Caproni and Colosimo 2020). The tremor in PD occurs at rest with a frequency ranging from 4 to 6 Hz and tends to manifest asymmetrically, usually affecting the body's extremities, together with the chin, lips, and tongue (Caproni and Colosimo 2020). Around 80% have limb tremors usually characterized by resting "pill-rolling type" of tremor. Pill rolling can be described as the tendency of the thumb and the index finger to get into contact performing circular movements (Jankovic 2008).

Freezing is another motor sign observed in the middle or advanced PD and is defined as a temporary inability to move (Caproni and Colosimo 2020). It commonly affects the legs (freezing of gait) and eyelids opening, closing, writing, or speaking (Caproni and Colosimo 2020). Postural instability is a balance disorder that affects maintaining or changing postures, such as standing and walking (Kim et al. 2013). It is a typical symptom of the late stage of the disease and is related to increased falls and loss of independence. Sources of postural instability include camptocormia or Pisa syndrome, abnormal forward and lateral flexion of the trunk (Kim et al. 2013).

[6] Bradykinesia is defined by the slowness of movement and reduced amplitude or speed (Postuma et al. 2015).
[7] It is a jerky that the patients can feel when moving or rotating the affected limb or joint. It is an early effect of PD.

Beyond the motor impairments, several NMSs can occur in PD, such as sleep disorders, sensory, neuropsychiatric, autonomic, and gastrointestinal impairments (Chaudhuri et al. 2006). Sensory abnormalities include olfactory dysfunctions and pain (Chaudhuri et al. 2006). Hyposmia affects 90% of PD patients, and over 70% are unaware of their impaired sense of smell (Doty, Deems, and Stellar 1988). Various classes of pain are frequent in PD (almost 50% of patients): musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, primary or central parkinsonian pain and akathitic discomfort (Pfeiffer 2016). Neuropsychiatric symptoms include depression, anxiety, and apathy (Chaudhuri et al. 2006). Major depressive disorder, minor depression, and dysthymia are reported by 17%, 22% and 13% of PD patients, respectively (Reijnders et al. 2008).

Dysautonomia in PD principally consists of gastrointestinal dysfunction, urinary abnormalities, sexual dysfunction, and cardiovascular problems with orthostatic hypotension (Lee and Gilbert 2016). Moreover, sleep disorders have a prevalence of 90% in PD patients, and they include RBD, periodic limb movements of sleep, restless legs syndrome, excessive daytime sleepiness and insomnia (Lee and Gilbert 2016).

1.3.3. Differential clinical diagnosis

The main clinical entities relevant in the differential diagnosis of PD are essential tremor (ET), secondary parkinsonism, and atypical parkinsonism (Balestrino and Schapira 2020). In contrast with the resting tremor typical of PD, ET expresses asymmetric postural and action tremor with a 5-12 Hz frequency. ET mainly involves hands, head and/or voice. As opposed to PD, in ET, the resting tremor increases during movement. ET exhibit tremulous handwriting and not micrography as in PD; moreover, these patients might show mild cerebellar signs, cognitive impairment, psychiatric symptoms, and sensory abnormalities. Disease progression is slow and can be alleviated through alcohol, propranolol, and primidone, which are ineffective in PD (Balestrino and Schapira 2020). Drug-induced parkinsonism represents the most common secondary parkinsonism and the second most frequent cause of parkinsonian symptoms after iPD (Brigo et al. 2014). Hyposmia seems to be the most accurate clinical manifestation to differentiate drug-induced parkinsonism from PD (Balestrino and Schapira 2020).

Moreover, some motor features can differ between two conditions: symmetric symptoms, absence of resting tremor, oromandibular dyskinesias, and absence or minimal response to dopaminergic medication (Balestrino and Schapira 2020).

The differential diagnosis between PD and atypical parkinsonism is challenging. MSA, especially MSA-P, includes hypokinetic and rigid parkinsonism differing from PD by the presence of more symmetrical presentation, less responsiveness to levodopa, and rare pill-rolling resting tremor (Levin et al. 2016). Extrapyramidal signs are observed in 30 to 50% of cases with MSA but not in PD (Levin et al. 2016). Parkinsonian symptoms may also be found in DLB, although their manifestation is milder than PD, and tremor is uncommon compared to PD. Moreover, DLB is characterized by alertness and attention fluctuations, absent in PD (Balestrino and Schapira 2020).

PD shared some clinical features also with tauopathies, including Progressive Supranuclear Palsy (PSP) and Corticobasal degeneration (CBD) (Stamelou and Bhatia 2015). PSP and PD show different postural abnormalities: head and trunk hyperextension/retrocollis and camptocormia, respectively (Balestrino and Schapira 2020). In PSP, postural abnormalities and falls appear in the first phases of the disorder, while in PD, they are observed with the disease progression (Balestrino and Schapira 2020). The clinical picture of PSP includes supranuclear palsy of vertical gaze, pseudobulbar palsy, subcortical-type dementia, frontal release signs and motor perseveration, a clinical picture absent in PD (Balestrino and Schapira 2020). Clinical differences are present also between PD and CBD. Compared to PD, CBD patients show asymmetric rigidity and bradykinesia together with dystonia and myoclonus. In CBD, tremor is rare, and, when present, it occurs in combination with action or postural tremor rather than at rest.

1.3.4. Parkinson's disease subtypes

A complex and heterogeneous clinical picture characterizes PD. As mentioned above, in addition to cardinal motor symptoms, many NMSs can occur in PD in the preclinical phase and during disease progression (Postuma et al. 2015). Indeed, a prodromal phase of years or even decades – characterized by specific and heterogeneous NMSs (prodromal PD) – precedes the diagnosis of PD (Poewe et al. 2017). Similarly,

during the disease course, patients with PD may develop variable severity of NMSs; among them, dementia development represents the worst condition. Figure 11 depicts this complex clinical expression.

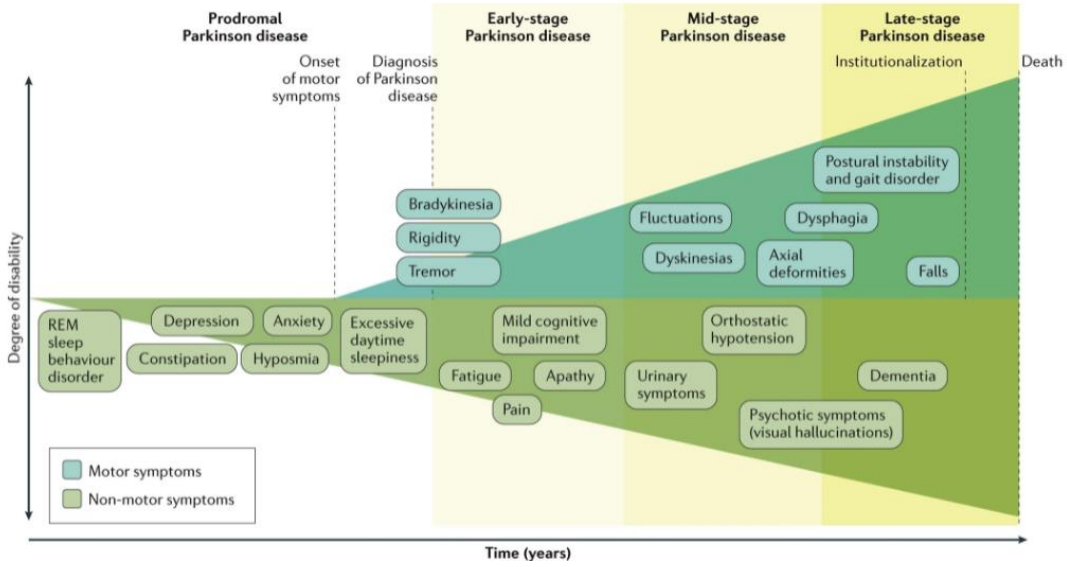

Figure 11. The clinical picture of PD (Open Access Source).

The figure shows the degree of disability occurring in PD from the early preclinical stage to the last stage of the disease. Even if NMSs become increasingly prevalent and evident throughout the illness, they can be present to a variable degree throughout all stages of PD. Indeed, the progression of PD is very heterogeneous. Patients can show cognitive deterioration ranging from subtle cognitive deficits to severe dementia, or others can remain cognitively stable. This figure is derived from (Poewe et al. 2017).

PD patients express significant variability in the range of clinical features and disease course; some are benign diseases and have a continuous response to levodopa with minimal non-dopaminergic symptoms, while others show a more malignant course, with an early predominance of NMSs (Obeso et al. 2017). The heterogeneity of PD performance and prognosis suggests dividing it into different subtypes (Berg et al. 2014). The National Institutes of Health regard the identification of PD subtypes as one of the three major clinical research priorities for PD (Sieber et al. 2014).

Subtyping considers presenting clinical features, rates of disease advancement, and/or the presence of distinct phenotypical manifestation during the disease (e.g., the occurrence of dementia) (Obeso et al. 2017). Specifically, two main approaches have been applied to identify different PD subtypes: empirical and data-driven analytic classifications approaches (Figure 12).

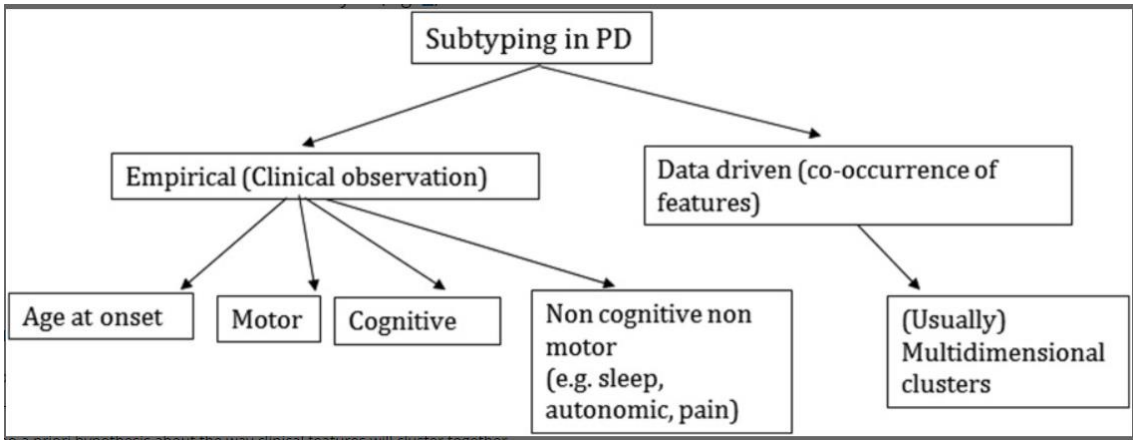

Figure 12. Approaches to PD subtyping (Open Access Source).

Several PD clinical subtypes have been proposed by literature following two main approaches: empirical and data-driven analytic classifications. Figure from (Marras and Chaudhuri 2016).

PD patients are grouped on observed clinical features in the empirical clinical approach, such as age-at-onset categories, major motor phenotypes, patterns of cognitive impairment, and NMSs (Marras and Chaudhuri 2016). PD subtyping according to cardinal motor features is the most commonly used. Indeed, clinical forms of PD have been described concerning the prevalence of some of the cardinal motor features on the others: these encompass the tremor-dominant, the akinetic-rigid dominant and the Postural Instability Gait Difficulty (PIGD). In this way, patients with a tremor-dominant form have been distinguished from a postural instability gait disorder or akinetic/rigid dominant form, and some patients matched an indeterminate category (Thenganatt and Jankovic 2014). The tremor-dominant patients frequently show a slow and benign motor progression. Some studies also evaluate the occurrence and severity of NMSs in these PD subtypes, revealing that the non-motor dominant groups had early autonomic dysfunctions and later cognitive decline (Marras and Chaudhuri 2016), suggesting more advanced and diffuse neurodegeneration. However, the solidity of these motor PD subtypes is still debated. For example, it has been hypothesised that the different severity of each motor subtype might represent simply different phases of the disease rather than distinct biological subtypes (Nutt 2016).

On the other hand, PD clinical subtyping can also derive from a data-driven analytic approach that does not have a priori hypotheses (Van Rooden et al. 2010). Also, data-driven studies propose a large number of PD subtypes. These studies usually

incorporate several clinical features, such as motor information (encompassing the progression rate), age-onset, levodopa-related complication, and NMSs such as cognitive dysfunctions, depression, and anxiety (Obeso et al. 2017). Following this approach, Fereshtehnejad and colleagues (2017) developed new clinical criteria for the classification of PD using a comprehensive clinical and biomarker (i.e. neuroimaging, genetic, blood, and cerebrospinal fluid (CSF) biomarkers) assessment. Three clinical subtypes of PD emerged: mild motor-predominant subtype, intermediate subtype, and diffuse malignant subtype. Individuals with diffuse malignant PD have an earlier and more severe motor symptoms and NMSs, inadequate medication response, and rapid disease worsening (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). Patients with mild motor predominant subtype showed mild impairment of motor symptoms and NMSs, slower progression, younger age at onset, and good medication response (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). The intermediate subtype represents a middle clinical condition characterized by onset, clinical severity, and progression rate located halfway between the mild and the malignant phenotypes (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). Notably, patients with the diffuse malignant subtype have a more prominent striatal dopaminergic deficit, showing the highest level of caudate denervation compared to other subtypes (Fereshtehnejad et al. 2017). Of note, the prognostic value of this subtype classification was further confirmed by longitudinal clinical disease course and survival data and neuropathologic correlation in an independent PD cohort (De Pablo-Fernández et al. 2019).

The onset and progression of motor and NMSs can differ enormously between individuals, leading to a broad characterization of PD. So, it is crucial to identify risk factors for the progression toward malignant phenotypes. Several preclinical, clinical, biological and genetic factors have been proposed to stratify PD patients according to the progression of their disease (Figure 13).

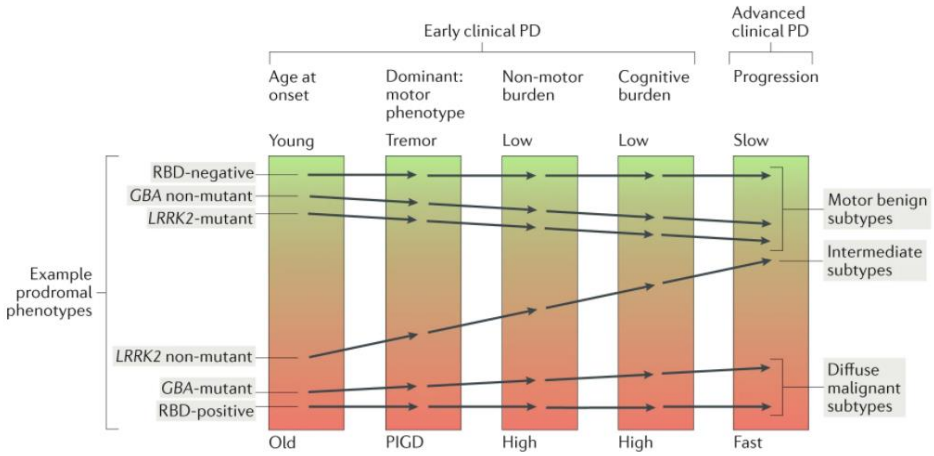

Figure 13. PD subtypes clinical trajectories (Open Access Source).

PD manifest clinical heterogeneity since the earliest prodromal stages, showing a broad range of motor and non-motor symptoms. The major challenge is identifying PD subtypes since the prodromal stages to distinguish patients with high risk to develop a malignant phenotype from those with a more benign course. Figure from (Berg et al. 2021).

The most significant challenge is identifying reliable prognostic markers since the prodromal PD phases representing the key to understand PD clinical variability (Berg et al. 2021). Identifying the precursor PD subtypes and fully understanding the variability at this stage of the disease is essential for an accurate early diagnosis and prognosis, ensuring the future efficacy of neuroprotective interventions.

1.3.5. Risk factor for malignant subtype: progression to dementia

Among NMSs occurring during the PD disease course, dementia represents the most severe condition, with a mean prevalence of 31.5% in PD patients (Janvin et al. 2006). The main risk factors for dementia development are advanced age, advanced disease stage, akinetic-rigid PD motor subtype, cognitive impairment, RBD and dysautonomia (Y. Xu, Yang, and Shang 2016). The following paragraphs provide an overview of the most critical risk factors for dementia in PD, namely cognitive impairment, RBD, and dysautonomia.

1.3.5.1. Neuropsychological profile

Dementia in PD represents a complex clinical manifestation involving cognitive and behavioural symptoms (Emre et al. 2007; Goldman et al. 2014; Gratwicke et al. 2015). Cognitive deficits affect different domains, i.e. executive functions, attention, memory, visuospatial abilities and language (Emre et al. 2007; Goldman et al. 2014; Gratwicke et al. 2015). On the other hand, behavioural symptoms consist of apathy, mood and personality changes, hallucinations, delusions and excessive daytime sleepiness (Emre et al. 2007).

Even non-demented PD patients may show cognitive deficits; thus, it is crucial to identify those cognitive domains which distinguish PD typical patients from those who develop dementia. Williams-Gray and colleagues (2007) showed that age, non-tremor-dominant motor phenotype, semantic language deficiency and visuospatial impairments (measured with pentagon copying neuropsychological tests) are valuable indicators of a global cognitive decline in PD (Williams-Gray et al. 2007). All these deficits are related to a posterior-cortical involvement (Williams-Gray et al. 2007) (see *1.1.1. The dual syndrome hypothesis*). Later the same authors confirmed the previous findings with a ten years follow-up study (Williams-Gray et al. 2013), indicating as predictors of dementia: age, semantic fluency and impaired pentagon copying (i.e. visuospatial abilities) (Williams-Gray et al. 2013). On the contrary, the authors found no association between executive dysfunction and the onset of dementia. These findings suggest that while deficits in semantic fluency and visuospatial domains could represent a significant risk factor for dementia development, the dysexecutive syndrome common in PD patients does not predict progression to dementia (Goldman et al. 2014; Williams-Gray et al. 2013). These findings were replicated by other groups (Burn et al. 2006; Muslimović et al. 2007; Pagonabarraga et al. 2008). Together, these studies introduced the identification of two different phenotypes in the course of PD progression, based on the rate of cognitive decline: 1) executive deficits due to frontostriatal dopaminergic dysfunction, not associated with dementia; and 2) posterior-cortical involvement with language and visuospatial deficits, representing the early stages of a dementing process (Goldman et al. 2014). These two phenotypes form the basis of the so-called "dual syndrome hypothesis" (Kehagia et al. 2013), which will be deeply described later in this chapter.

1.3.5.2. REM sleep behaviour disorder

Increasing evidence shows that the presence of iRBD has an impact on PD clinical phenotype: iRBD may represent a red flag for severe clinical presentation in PD (Lin and Chen 2018). PD patients with RBD (PD+RBD) usually express a non-tremor-dominant motor or kinetic-rigid motor phenotypes (Postuma et al. 2008; Lee et al. 2010; Kumru et al. 2007). Autonomic deficits, visual hallucinations and cognitive dysfunction are more common in PD+RBD than in those without RBD (PD-RBD) (Kim and Jeon 2014). Moreover, mild cognitive impairment (MCI) diagnosis is significantly more frequent in iRBD patients and PD+RBD than in PD-iRBD, suggesting RBD as a significant risk factor for developing MCI (Gagnon et al. 2009).

Growing evidence supports the association between RBD and PD with dementia (PDD). Marion and colleagues (2008) demonstrated that iRBD is significantly linked to the dementing process in PD patients. Specifically, the authors observed that PD+RBD had a significantly higher occurrence of dementia, as well as a more rapid cognitive decline, compared to PD-RBD (Marion et al. 2008). Postuma and colleagues (2012) found a strong link between the presence of iRBD and the future development of dementia. In a longitudinal four-year follow-up study, the authors enrolled 45 initially free-dementia PD patients and found that 48% of PD+RBD patients developed dementia during the follow-up period, compared to none of those PD-RBD (Postuma et al. 2012). Moreover, Fereshtehnejad et al. (2015) followed 76 PD patients for an average of four years, showing that RBD combined with MCI and orthostatic hypotension (OH) identified the diffuse/malignant phenotype of PD patients, characterized by the most rapid deterioration (Fereshtehnejad et al. 2015). Another follow-up study in 421 PD patients supported this finding after a mean of 2.5 years, demonstrating that iRBD is one of PD's most pivotal prognosis determinants (Fereshtehnejad et al. 2017).

Previous studies demonstrated that the advancement of cognitive deterioration in iRBD patients predicts the risk of dementia (Gagnon et al. 2019; Génier Marchand et al. 2018). A recent longitudinal study investigated a cohort of iRBD patients classified as PD, DLB or still-idiopathic after six years of follow-up (Génier Marchand et al. 2018). Attention and executive impairments predated the dementia diagnosis by six years and characterized patients who developed DLB. Verbal episodic learning and memory

impairments occurred later, becoming clinically significant at one to two years before the diagnosis (Génier Marchand et al. 2018).

All the above demonstrates that iRBD is associated with an increased risk of PDD/DLB, thus suggesting iRBD as a risk factor for a more diffuse and malignant PD subtype.

1.3.5.3. Autonomic dysfunction

Cardiovascular dysautonomia is a common feature of autonomic dysfunction in PD together with OH, urinary/sexual dysfunction, and constipation (Poewe 2007). Existing evidence suggests that autonomic dysfunction are associated with cognitive decline and dementia in PD and DLB (Anang et al. 2014; Kim et al. 2009; Oh et al. 2011; Peralta et al. 2007; Poewe 2007).

The primary autonomic manifestation that strongly predicts dementia is OH. OH is usually a late feature of PD, although it can also be present in the early phase (Coon, Cutsforth-Gregory, and Benarroch 2018). From a neuropathological point of view, OH is probably associated with cardiac sympathetic efferences and lesions in central cardiovascular regulatory pathways (Poewe 2007). Although OH is an essential symptom of PD, it can also be because of dopaminergic medications. The OH occurs more frequently in PD with dementia than in PD with a stable clinical picture. Thus, it has been associated with impaired cognitive performance, specifically with attention deficit and fluctuating cognition (Anang et al. 2014; Peralta et al. 2007).

Of note, the most consistent findings of the presence of dysautonomia in PD derive from 123I-MIBG-SPECT studies. [123I]MIBG is a physiologic analogue of norepinephrine (NE), and, specifically, [123I]MIBG-SPECT is used to assess cardiac sympathetic innervations. [123I]MIBG-SPECT represents a valid biomarker of dysautonomia in PD (see *1.7. Neuroimaging biomarkers for diagnosis and progression*). As measured by [123I]MIBG-SPECT, worse myocardial sympathetic denervation is associated with more significant cognitive impairment and risk of progression to dementia in PD (Kim et al. 2009).

1.3.6. The dual syndrome hypothesis

Long-term longitudinal data reported that most PD patients develop dementia after ten years from the first diagnosis (Aarsland et al. 2017). Indeed, about 80% of PD patients will ultimately develop dementia during the disease (Janvin et al. 2006). Cognitive decline widely varies among individuals with PD regarding the timing, profile and rate of progression.

In this context, the "Dual Syndrome Hypothesis" suggests the existence of two different profiles characterizing the progression of PD (Kehagia et al. 2013). The rate of cognitive decline allows identifying two phenotypes of PDD:

1. A dysexecutive syndrome characterizes the first phenotype due to dysfunctions in the frontostriatal dopaminergic system. These patients have a slower cognitive decline and show a tremor-dominant motor profile (Kehagia et al. 2013).
2. The second phenotype is characterized by visuoperceptual, memory and psychiatric deficits related to a posterior-cortical impairment. These patients have a faster cognitive decline that leads to dementia in a short time, associated with an additional dysfunction in cholinergic networks. This second phenotype usually shows an akinetic-rigid motor profile (Kehagia et al. 2013).

The heterogeneity of cognitive symptoms suggests that PD should be considered a multisystem disorder affecting catecholaminergic and cholinergic systems (Kehagia et al. 2013; Gratwicke et al. 2015). First of all, PD is characterized by early and progressive degeneration of the dopaminergic neurons in the SN, which is considered the leading cause of motor symptoms (Kehagia et al. 2013). This degenerative process advances through a dorso-ventral gradient within the basal ganglia, and it impacts different dopaminergic pathways, i.e. the frontostriatal and the mesocorticolimbic ones (Kehagia et al. 2013). Precisely, the dysfunction of the frontostriatal circuit underlies deficits in planning, working memory and executive functions, leading to the dysexecutive syndrome, which characterizes the tremor-dominant PD phenotype with slower cognitive decline (Kehagia et al. 2013). This phenotype features non-demented PD patients with MCI and gains benefit from dopaminergic medication (Kehagia et al. 2013). In PD cholinergic system can also be affected. The cholinergic system dysfunction suggests posterior regions involvement with visuospatial abilities and semantic fluency deficits

(Kehagia et al. 2013). These features are characteristic of the akinetic-rigid PD subtype associated with a rapid progression to dementia and may benefit from cholinergic treatment (Kehagia et al. 2013).

During stage III of the Braak staging hypothesis, LB and LN appear not only in the SN but also in the magnocellular nuclei of the basal forebrain, i.e. medial septal nucleus, interstitial nucleus of the diagonal band, nucleus basalis of Meynert (NBM) (Braak et al. 2003). The degeneration of NBM cholinergic neurons has been associated with cognitive decline and dementia in PD patients (Müller and Bohnen 2013; Shimada et al. 2009). *In vivo* cholinergic Positron Emission Tomography (PET) studies have revealed cholinergic deficits in PD without dementia, PDD and DLB patients (Müller and Bohnen 2013; Shimada et al. 2009; Klein et al. 2010). In line with Braak´s staging scheme, it has been demonstrated that cholinergic denervation occurs early in PD, also in patients who do not progress to dementia (Shimada et al. 2009). However, the reduction of Acetylcholinesterase[8] (AChE) activity levels in the cerebral cortices (i.e. posterior cortical areas) of PDD and DLB patients are more severe and widespread than PD patients without dementia (Shimada et al. 2009), thus supporting the fundamental role played by brain cholinergic dysfunction in PD cognitive decline. This reduction does not differ between PDD and DLB groups, supporting the hypothesis that these two clinical entities may share the same cholinergic dysfunction (Shimada et al. 2009). In line with these results, Klein and colleagues (Klein et al. 2010) compared PD, PD with dementia and DLB patients in a multitracer PET study, evaluating dopaminergic, cholinergic and glucose metabolism. The authors observed dopaminergic deficits in all groups independently from their cognitive status (Klein et al. 2010), suggesting that the degeneration of the dopaminergic system alone is not sufficient for the progression to dementia (Klein et al. 2010). PDD and DLB showed similar and severe cholinergic deafferentation of the neocortex, specifically the occipital cortex (Klein et al. 2010). On the contrary, PD patients without dementia showed only a mild cholinergic deficit, thus highlighting the role of cholinergic dysfunction in the development of dementia (Klein et al. 2010). Additionally, hypometabolism – as measured throughout 18fluorodeoxyglucose ([18F]FDG)-PET – was topographically widely congruent to

[8] It is an enzyme that catalyses the breakdown of acetylcholine

cholinergic deficit affecting parieto-occipital brain regions in both PDD and DLB patients (Klein et al. 2010).

All in all, these findings support the "dual syndrome hypothesis" of cognitive impairment in PD proposed by Kehagia and colleagues (2013) (Kehagia et al. 2013). The dysfunction of the frontostriatal dopaminergic pathway is associated with the tremor-dominant motor phenotype and dysexecutive syndrome. On the contrary, the development of dementia seems to be related to a posterior cholinergic deficit causing visuospatial and semantic fluency impairments (Figure 14) (Kehagia et al. 2013).

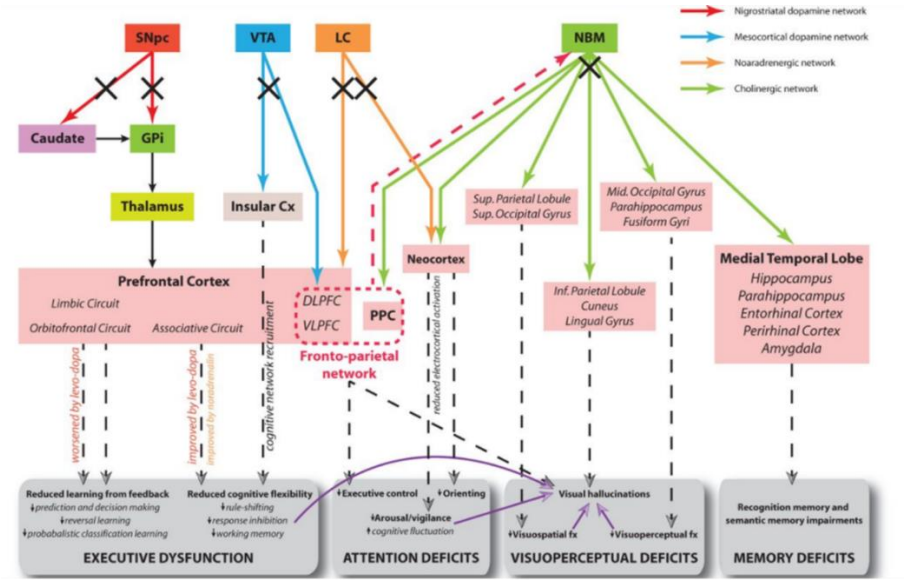

Figure 14. Dementia in PD as a multisystem condition (Open Access Source).

The cognitive symptoms of PDD are heterogeneous and related to the impairment of distributed neurotransmitters systems throughout the brain. Thus, PDD is considered a multisystem disorder. Specifically, cholinergic impairment seems to play a pivotal role in the fast progression toward dementia. Figure adapted from (Gratwicke et al. 2015).

1.3.7. Dementia with Lewy Bodies and Parkinson Disease Dementia: Is it the Same Disease?

PDD presents overlapping clinical features with DLB (Jellinger and Korczyn 2018). Today, indeed, some doubts exist on the separation of these nosographic entities.

It can be challenging to differentiate PDD from DLB due to overlapping clinical features. DLB is characterized by a progressive cognitive deterioration affecting normal life functions and expresses four core clinical features (*see Dementia with Lewy Bodies*) (McKeith et al. 2017). The "one-year rule" is nowadays the only existing criteria to make a diagnosis of PDD or DLB (McKeith et al. 2017). This rule claims that in PDD, dementia occurs after at least one year from the onset of motor symptoms; meanwhile, in DLB, dementia precedes the development of parkinsonian symptoms (McKeith et al. 2017). No clinical or pathological data support the existence of a specific time interval between the development of motor symptoms and dementia onset (Emre et al. 2007; Friedman 2018).

PDD and DLB share similar neuropsychological profiles. Deficits in planning, abstract thinking, multitasking, adaptability to environmental requests and visuospatial dysfunction are first manifesting symptoms (Friedman 2018). As dementia advances, other cognitive impairments emerge, i.e. memory, language and praxis (Friedman 2018).

PDD and DLB also show similar behavioural symptoms, such as depression, anxiety, apathy and psychotic symptoms (e.g. hallucinations and delusions) (Emre et al. 2007; Friedman 2018). Fluctuating cognition, a DLB' core feature, may also be present in PDD (Emre et al. 2007; Friedman 2018).

Moreover, iRBD represents a risk factor for developing PDD and DLB (Génier Marchand et al. 2018; Marion et al. 2008; Postuma et al. 2012) (Génier Marchand et al., 2018; Marion et al., 2008; Postuma et al., 2012). Thus, iRBD may be an important marker of the future development of a more severe form of PD with progression to dementia.

From a neuropathological point of view, current studies failed to differentiate PDD from DLB (Ballard et al. 2006; Friedman 2018; Irwin et al. 2017; Lippa et al. 2007). Both disorders present widespread LB, specifically in the later stages, thus making PDD and DLB indistinguishable (Friedman 2018; Lippa et al. 2007).

In conclusion, neuropsychological, neuropsychiatric, neuropathological, neurophysiological and clinical profiles are not capable to differentiate PDD and DLB. The temporal sequence represents the primary distinction: the onset of dementia compared to the onset of motor symptoms (Friedman 2018; Lippa et al. 2007). It is reasonable discussing whether these progression phenotypes are separate and independent or more likely comparable pathological entities.

1.4. Dementia with Lewy bodies (DLB)

DLB represents the second most common dementia (Chin et al. 2019). According to the current clinical criteria, DLB is characterized by four core clinical features: cognitive fluctuations, recurrent visual hallucinations, iRBD preceding cognitive decline, and parkinsonism (McKeith et al. 2017). The neuropathological hallmark of DLB is the progressive accumulation and aggregation of α-synuclein as LB and LN in the brainstem, limbic and neocortical regions (Chin et al. 2019). The clinical underdiagnosis of DLB (Vann Jones and O'Brien 2014) and the overdiagnosis of PD (Schrag et al. 2002) led most LBD studies focusing on PD and PDD, making DLB under-studied compared to the relative population incidence. The increasing recognition of DLB as widespread age-related dementia has motivated more research on its ae etiopathogenesis. In this chapter, genetics, clinical and preclinical features are summarized and discussed.

1.4.1. Epidemiology

In community-based studies, the average prevalence of DLB was 4.2%, and in clinical-based studies was 7.5% – considering dementia cases (Vann Jones and O'Brien 2014). However, autopsy results report DLB pathology in 20% to 25% of dementia patients. DLB is more common in 70 to 85 years old subjects, especially among men than women (Galasko 2017). Although the understanding of the genetic causes of DLB is limited, many studies have demonstrated the role of genetic factors in this disease (Outeiro et al. 2019). The strongest genetic risk factors for DLB are GBA and APOE ε4 mutations (Outeiro et al. 2019). The association between DLB and GBA is powerfully demonstrated (Nalls et al. 2013). Patients with DLB were reported to be eight times more likely to be carriers of GBA mutation than the healthy population (Nalls et al. 2013). Moreover, the risk of GBA mutation in DLB patients is significantly higher than in PD ones (Sidransky et al. 2009). The risk is associated with a DLB clinical manifestation characterized by earlier onset age and disease progression severity (Outeiro et al. 2019).

A higher risk of DLB seems to be associated with APOE ε4. Specifically, a higher LB pathology burden has been described in cases with APOE ε4 (Singleton et al. 2002; Dickson et al. 2018; Keogh et al. 2016). Despite families with SNCA mutations usually do not express DLB, multiple studies demonstrated the role of SNCA locus in sporadic

DLB (Bras et al. 2014; Guerreiro et al. 2018). Indeed, the 3' and 5' regions of the SNCA gene may influence gene expression and LB pathology distribution in the brain, showing an association with PD and DLB phenotypes, respectively (Outeiro et al. 2019).

1.4.2. Clinical features

The clinical definition of DLB began with the introduction of the first diagnostic criteria in 1996 (McKeith et al. 1996), and was finally updated in 2017 by the fourth consensus report of the DLB consortium (McKeith et al. 2017). Recent diagnostic criteria distinguish between possible and probable DLB based on clinical characteristics (core and supportive) and diagnostic biomarkers (indicative and supportive) (McKeith et al. 2017). An essential requirement for diagnosing both types of DLB is dementia manifestations, defined as progressive cognitive decline that is sufficient to hinder normal social or professional functions or daily activities (McKeith et al. 2017). Further cognitive features include attention, executive function, and visual processing deficits related to memory and naming (Outeiro et al. 2019). As mentioned earlier, the core clinical features include cognitive fluctuations, recurring hallucinations, spontaneous parkinsonism, and RBD (McKeith et al. 2017). Fluctuations include changes in attention and alertness, and they may appear as rapid and slow changes. Their periodicity and amplitude differ between subjects and within the same person (McKeith 1996). 80% of DLB patients report hallucinations with different degrees of insight and emotional response (McKeith et al. 2017). Usually, these hallucinations are well-formed, and their content involves people, children, or animals (McKeith et al. 2017). DLB is usually characterized by spontaneous parkinsonian features, with more than 85% of cases reported (McKeith et al. 2017). The diagnosis of DLB requires just one main feature among bradykinesia, resting tremor or rigidity (Outeiro et al. 2019). Notably, iRBD is now included as a core feature in DLB clinical criteria (McKeith et al. 2017), in contrast to previous diagnostic criteria (McKeith et al. 2005) given its incidence rate of 76% in autopsy-confirmed DLB cases compared to 4% of those without autopsy confirmation (Ferman et al. 2011).

1.4.3. Differential clinical diagnosis

The primary differential diagnoses of DLB include AD and PDD (Mckeith et al. 2004). DLB has similarities with AD in survival time, disease course (cognitive decline of 10% of points lost per year), and pathology. Indeed, some DLB cases may have AD pathology, including cortical amyloid plaques and neurofibrillary tangles (Ballard et al. 2001; Hanyu et al. 2009). Of note, more aggressive clinical and cognition deterioration are associated with high amyloid load in DLB (Chin et al. 2019). AD and DLB have a similar topographical distribution of amyloid deposition; however, DLB show increased binding in the frontal, posterior cingulate and precuneus, temporoparietal region, and the striatum (Donaghy et al. 2015). Even though DLB and AD share several clinical features, some differences also exist. Compared with AD, DLB patients are more prone to cognitive fluctuations, visual hallucinations, and extrapyramidal symptoms such as motor retardation, masking, and postural instability (Morra and Donovick 2014). In addition, they express more depressive symptoms (Yamane et al. 2011) and autonomic dysfunction, including incontinence, constipation, and orthostatic hypotension (Allan et al. 2007). From a neuropsychological standpoint, visuospatial abilities in DLB show a more significant impairment than AD patients, representing a crucial marker for clinical assessment. Accordingly, in 2013, Caffarra validated a qualitative scoring method for the pentagons copy test (QSPT) of Mini-Mental State Examination (MMSE), a measure of visuospatial abilities able to efficacy differentiate DLB from AD (Caffarra et al. 2013; Mitolo et al. 2014), since the earliest disease phase (Cagnin et al. 2015). Last, the presence of RBD represents a crucial discrimination marker between DLB and AD (Levin et al. 2016).

In the context of differential diagnosis, the relationship between DLB and PDD represents an important issue to address (Outeiro et al. 2019). DLB and PDD form a spectrum lacking clear clinical or neuropathological boundaries (see *1.3.7. Dementia with Lewy Bodies and Parkinson Disease Dementia: Is it the Same Disease?)*. DLB is typically characterized by cognitive impairment with often mild extrapyramidal motor features until the late stages. On the contrary, PDD is defined by notable extrapyramidal motor features since early stages (mandatory for the diagnosis), with later development of neuropsychiatric and cognitive symptomatology (Outeiro et al. 2019). The differentiation between the two diseases is founded on dementia and parkinsonism onset timing (1-year

rule). However, the 1-year rule may not be the best way to diagnose these diseases, as the cognitive deterioration can begin even six years before diagnosing PD (Jellinger and Korczyn 2018). In addition, the cognitive features of DLB and PDD overlap, including progressive executive dysfunction, visual-spatial abnormalities, and memory impairment (Lippa et al. 2007). It is worth noting that the course of dementia for these two diseases is the same (Friedman 2018). PDD and DLB have in common behavioural problems, especially depression, anxiety, fatigue, apathy, and RBD (Friedman, 2018). Both diseases also exhibit cognitive fluctuations, typical diagnostic features of DLB and psychotic symptoms, including hallucinations and delusions (Friedman, 2018). In addition, autonomic dysfunction is the same in these two neurodegenerative diseases(Friedman 2018).

1.4.4. Early clinical markers

The first clinical manifestations of DLB can appear 15 years or more before the onset of dementia, emphasizing the importance of prodromal DLB. The prodromal DLB include cognitive deficits, movement disorders, autonomic dysfunction, sleep and neuropsychiatric disorders (McKeith et al. 2020). Three different prodromes DLB subtypes have been described: DLB-MCI onset, DLB-delirium onset, and DLB-psychiatric onset (Mckeith et al. 2016). Regarding MCI variants, Ferman and colleagues followed 337 MCI patients for 2-12 years and proved that patients with non-amnestic MCI showed a higher possible DLB progression rate than AD. In addition, 88% of patients who may have DLB show a baseline MCI diagnosis, including attention and/or visuospatial deficits (Ferman et al. 2013). Since delirium is an early presenting characteristic of DLB, a delirium-onset DLB is also observed (McKeith et al. 2020). 25% of DLB reported previous episodes of delirium, instead of 7% of AD patients (Vardy et al. 2014), and the incidence of delirium in DLB was higher than AD in the year before diagnosis, 17.6 and 3.2 per 100 cases yearly, respectively (FitzGerald et al. 2019). Long-term delirium seems to increase the risk of DLB, but the link between delirium and DLB needs further clarification (McKeith et al. 2020). Although less recognized, DLB psychotic episodes represent another prodrome DLB subtype, and its most common manifestations are late-onset psychosis and late-onset major depression (Mckeith et al.

2016; McKeith et al. 2020). The presence of prodromal DLB in patients with depressive disorder is suggested by the occurrence of parkinsonian signs, such as resting tremor and rigidity; however, psychotropic-induced parkinsonism may complicate the diagnosis (Takahashi et al. 2016; McKeith et al. 2020). iRBD represents another important biomarker of prodromal DLB. Notably, considered by several lines of literature the same disorder (Friedman 2018), DLB and PDD can be predated by iRBD (Gagnon et al. 2009) in up to 90% of patients more than ten years (Iranzo et al., 2016).

Since several findings show that iRBD conversion to DLB occurs with equal, and perhaps more significant, frequency than PD, a study recently described the iRBD-MCI-DLB continuum (Boeve 2019). Specifically, it has been postulated that the iRBD condition is followed by iRBD plus MCI – representing the prodromal DLB – reaching the diagnosis of over DLB as the last step.

1.5. Multiple system atrophy (MSA)

MSA is a rare neurodegenerative disorder presenting adult-onset, gradual autonomic failure, parkinsonian, and cerebellar symptoms in different combinations (Fanciulli et al. 2019). Historically, the clinical term was born in 1969 in the attempt to group the following conditions: striatonigral degeneration, olivopontocerebellar ataxia, and Shy-Drager syndrome (Graham and Oppenheimer 1969). According to the predominance of parkinsonism or cerebellar ataxia, two types of MSA are defined, namely MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) (Gilman et al. 2008). The mechanisms underlying MSA pathogenesis are yet largely unknown. However, preclinical and *postmortem* evidence suggests that neuronal and glial dysfunctions play a role in developing this disorder, which indeed takes the name of oligodendroglio-neural α-synucleinopathy (Ahmed et al. 2012; Jellinger 2018).

1.5.1. Epidemiology and genetic risk factors

The incidence of MSA is around 0.6 to 0.7 cases per 100000 people per year; the prevalence amounts to about 3.4 to 4.9 cases per 100000 population, reaching 7.8 per 100000 people after the forties (Fanciulli and Wenning 2015). MSA has always been considered a sporadic disease; however, the research of genetic mutations increased in recent years (Meissner et al. 2019).

Families with MSA cases feature a mutation (loss of function) in the COQ2 gene, encoding the coenzyme Q10–synthesizing enzyme[9] (Multiple-System Atrophy Research Collaboration 2013). However, subsequent GWAS findings could not confirm COQ2 mutation in European and North American natives patients with MSA (Sailer et al. 2016). The same study identified single-nucleotide polymorphisms in the genes FBXO47, ELOVL7, EDN1, and MAPT but did not find any association between two single-nucleotide polymorphisms of the SNCA locus and MSA, detected in a previous study (Scholz et al. 2009). All the above well describe the genetic challenges still open in MSA studies. Additional genes have been investigated. Variants of the GBA gene seem to be associated with MSA, like in PD (Mitsui et al. 2015; Sklerov et al. 2017). In addition, G2019S LRRK2 gene mutation – a typical familiar PD genetic mutation – was reported in an early-onset, slowly progressing MSA case with *postmortem* confirmation (Riboldi et al. 2019), although the same association did not emerge in a previous study (Ozelius et al. 2007). These findings suggest a possible connection between PD and MSA, with both disorders being extremes of the same spectrum. However, the genetic findings regarding MSA patients are still controversial, making this assumption only mere speculation.

1.5.2. Clinical features

MSA generally starts around 60 years of age and progresses with a 6-10 years survival time since symptoms onset (Fanciulli and Wenning 2015). MSA is characterized by a combination of clinical features, including autonomic failure, urogenital dysfunction, cerebellar ataxia, pyramidal signs, and poorly responsive to levodopa parkinsonism (Stefanova et al. 2009). Types of motor symptoms determine two MSA phenotypes:

[9] Coenzyme Q is a crucial part of the mitochondrial respiratory process (Acosta et al. 2016).

MSA-P with predominant parkinsonian motor features and MSA-C with prominent cerebellar motor features (e.g. gait and limb ataxia, scanning dysarthria, and cerebellar oculomotor disturbances, such as gaze-evoked nystagmus and hypometric saccades). However, parkinsonian and cerebellar clinical synonyms overlap in many patients, leading to a definition of mixed phenotype (Wenning et al. 2013). Parkinsonian symptoms usually manifest in MSA patients are rigidity and akinesia, with a bilateral presentation in most cases, even though asymmetric forms can occur (Batla et al. 2013; Tison et al. 2002). Pyramidal signs are also observed in 40–50% of MSA patients, especially MSA-C ones (Köllensperger et al. 2010; Roncevic et al. 2014).

Autonomic failure and urogenital symptoms are the most common symptoms in MSA-C and MSA-P (96% and 88% of cases, respectively) (Wenning et al. 2013). Of note, early and severe dysautonomia is a marker of a more aggressive disease progression (Glasmacher et al. 2017). In the early stage of the disease, urogenital problems are sometimes the most debilitating symptoms; indeed, about 43% of patients undergo prostatic and bladder neck surgery with any advantages (Iodice et al. 2012; Jecmenica-Lukic et al. 2012). Moreover, erectile dysfunction characterizes up to 97% of men with definite MSA and is reported as the first symptom in 48% of male patients (Iodice et al. 2012; Jecmenica-Lukic et al. 2012). Unfortunately, data about sexual dysfunction are not available for females due to likely assessment difficulties (Oertel et al. 2003). Among the cardiovascular autonomic symptoms, OH is the most frequent. Specifically, OH is due to inadequate noradrenergic neurotransmission with decreased noradrenaline release from sympathetic vasomotor neurons (Freeman et al. 2011). The impairment site differs between MSA and PD, where MSA shows central noradrenergic failure and relatively spared peripheral innervation (Benarroch et al. 2005; Benarroch et al. 2006). Neuropsychiatric syndromes are also common in MSA, like depression and apathy (Bhatia and Stamelou 2017).

A recent study demonstrated that MSA-P and MSA-C patients show similar levels of depression, but MSA-P patients express a higher apathy prevalence than MSA-C patients (Santangelo et al. 2020). Interestingly, after one year of follow-up, apathy increased in MSA-C and MSA-P, and depression decreased only in MSA-C (Santangelo et al. 2020). This study also evaluated the neuropsychological profile in MSA groups. At the baseline, MSA-C and MSA-P patients had low scores on tests assessing repetition

abilities, executive functions, and attention than controls (Santangelo et al. 2020). However, MSA-C patients significantly worsen in spatial planning and psychomotor speed after one year, whereas MSA-P patients in spatial planning, functional autonomy, prose memory, and repetition abilities (Santangelo et al. 2020).

According to the current clinical criteria, three different levels (possible, probable, and definite) exist for MSA diagnosis (Gilman et al. 2008) (Figure 15). Autonomic symptoms with parkinsonism or cerebellar ataxia or both appear to be the clinical core features for the diagnosis of "possible" or "probable" MSA and the requirement of *postmortem* confirmation for a diagnosis of "definite" MSA. The presence of additional features is mandatory for the diagnosis of "possible" MSA. These include brain-imaging findings (e.g., atrophy on MRI of the putamen, middle cerebellar peduncle, pons, or cerebellum for "possible" MSA-P) and some clinical red flag signs (i.e., stridor, early postural instability, and early dysphagia).

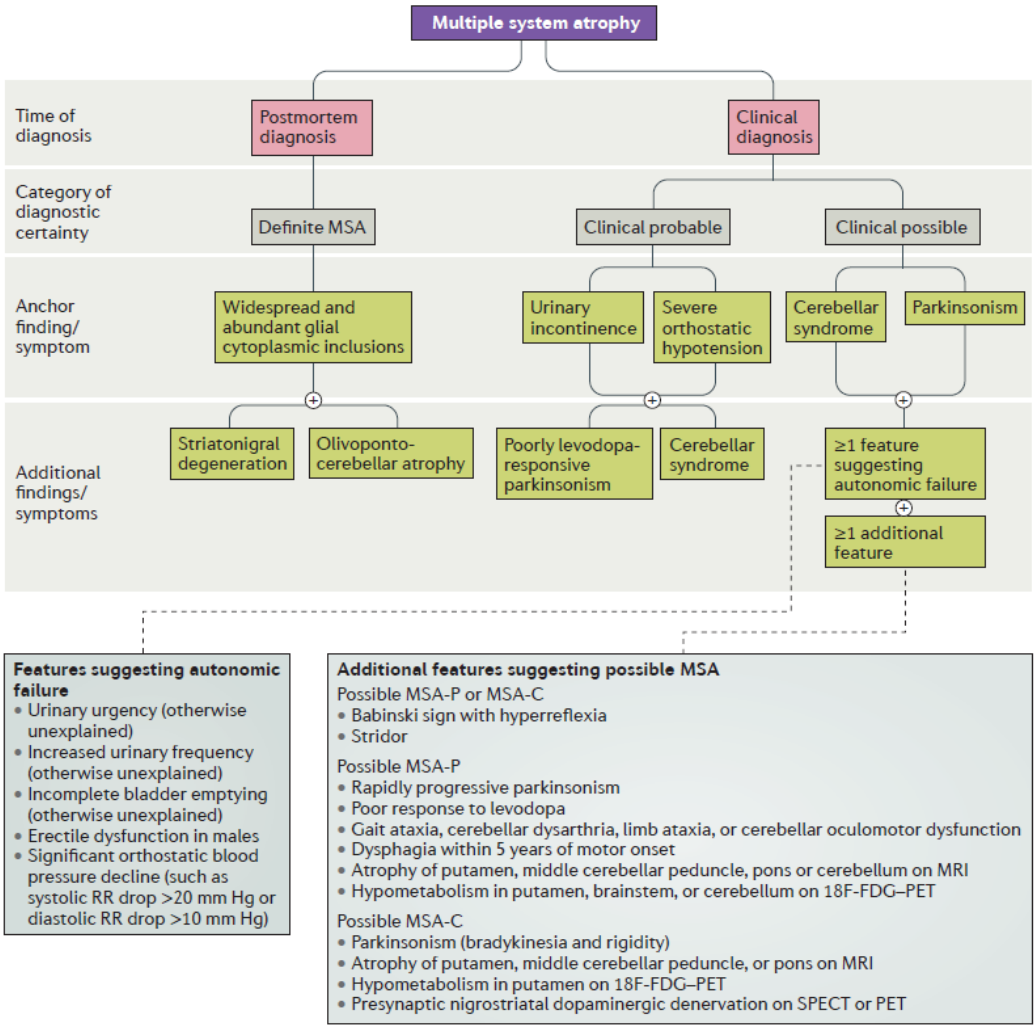

Figure 15. MSA clinical criteria (Open Access Source).

This figure depicts a flowchart of the current consensus diagnostic criteria for MSA. Figure from (Krismer and Wenning 2017).

Finally, specific neuropathological findings define MSA, namely a widespread and abundant α-synuclein–positive GCIs in the central nervous system, with degeneration in striatonigral or olivopontocerebellar structures (Trojanowski and Revesz 2007).

1.5.3. Differential clinical diagnosis

PD, DLB and PSP are the most frequent disorders misdiagnosed as MSA (Palma et al. 2018). PD is the most confusing disease with MSA-P in the early stages due to resting tremor or asymmetries in akinesia and rigidity present in both disorders (Wenning et al. 2004). However, since MSA does not respond to levodopa therapy, distinguishing between PD and MSA is possible (Palma et al. 2018). Indeed, in MSA, the beneficial effect of dopaminergic treatment is usually short-lived and, within three years of diagnosis, only a small part of patients still reports advantages from levodopa. Notably, when patients show a good levodopa response, they express serious complications, such as craniocervical region dyskinesia even after short-term use, with limb dyskinesias in a minority of patients (Palma et al. 2018).

In addition to PD, DLB and PSP show some similarities with MSA (Koga et al. 2015). Specifically, DLB is frequently misdiagnosed as MSA for the presence of autonomic failure, whereas PSP for cerebellar ataxia (Koga et al. 2015). However, some clinical differences exist among these pathologies. MSA presents more frequent urinary incontinence, limb ataxia, nystagmus, and pyramidal signs than DLB. On the other hand, DLB is characterized by more common cognitive impairment and visual hallucinations (Koga et al. 2015). MSA patients show more frequent urinary incontinence, constipation, orthostatic hypotension, and RBD than PSP (Koga et al., 2015). In addition, MSA and PSP manifest early falls and postural instability, but an accurate examination of typical PSP eye movement abnormalities and early frontal-subcortical dysfunction can exclude MSA diagnosis (Stamelou and Bhatia 2015). In conclusion, MSA diagnosis is excluded by several factors, like the presence of pill-rolling rest tremor, significant neuropathy, not-drug induced hallucinations, onset after 75 years, dementia, early slowness of saccades, family history of ataxia or parkinsonism, and white matter lesions suggesting multiple sclerosis (Gilman et al. 2008).

1.5.4. Early clinical markers

The existence of a prodromal or premotor entity of MSA is lacking, even though the necessity for such a diagnosis is increasingly near (Palma et al. 2018). Although iRBD is a valid predictor for PD and DLB, it is fully established that a tiny percentage of these

patients convert to MSA (around 5%) (Iranzo et al. 2014; Postuma et al. 2015). iRBD seems to be present in 100% of patients with MSA (Högl et al. 2018). A recent prospective study demonstrated that all patients with pure autonomic failure (PAF) who converted to MSA within four years of follow-up had probable iRBD at the baseline (Kaufmann et al. 2017). Patients who showed younger age onset of autonomic failure, severe bladder/bowel dysfunction, unimpaired olfaction, and a cardiac chronotropic response upon tilt more significant than ten beats, appear to convert to MSA (Kaufmann et al. 2017).

1.6. Neuroimaging biomarkers for diagnosis and progression

Since patients with different neurodegenerative diseases show some overlap in clinical patterns, the whole diagnostic process may become challenging for the clinician. In the past few decades, the clinical research framework has gradually gone from purely clinical diagnosis to biomarker-supported diagnosis (Perani et al. 2020). Neuroimaging advance has played a leading role in the research and diagnosis of dementia (McKhann et al. 2011; Gorno-Tempini et al. 2011; Armstrong et al. 2013; Sperling et al. 2011; Albert et al. 2011; McKeith et al. 2017; Rascovsky et al. 2011). Specifically, neuroimaging approaches can be divided into three macro-areas: structural imaging (revealing brain anatomy and measuring volume and/or other tissue characteristics), molecular imaging (detecting biological events such as protein aggregation, neuroinflammation, and related processes), and functional neuroimaging (showing brain activity, blood flow, and glucose metabolism) (Risacher and Saykin 2019).

The main applications of biomarkers are prediction, screening, diagnosis and differential diagnosis, staging, prognostic evaluation and therapy. Multimodal neuroimaging plays an essential role in studying the structural and functional brain changes of pathological conditions and can identify disease-specific features (Saeed et al. 2017). These “disease-specific features” can work as effective biomarkers to improve the sensitivity and specificity of clinical diagnosis (Saeed et al. 2017).

Taking into account the increasing number of PD patients, the overlap of their clinical manifestations with other α-synucleinopathies, and the overall heterogeneity of

PD manifestations and prognosis, the validation of PD prognostic and diagnostic biomarkers have become more and more critical since its earliest preclinical phases (i.e. iRBD) (Perani et al. 2020). Identifying specific PD biomarkers can clarify the neuroanatomical and pathophysiological basis of this disease and predict the disease's trajectory, thereby achieving a more accurate diagnosis and effective therapeutic intervention (Saeed et al. 2017).

1.6.1. Magnetic Resonance Imaging (MRI)

Structural MRI might help differentiate neurodegenerative and symptomatic parkinsonism due to other pathologies like multiple sclerosis, brain tumours, normal pressure hydrocephalus, vascular aetiology, or other causes (Heiss and Hilker 2004).

Several volumetric data contributed to describing the regional brain volume differences in α-synucleinopathies (Paviour et al. 2006b; 2006a; Messina et al. 2011; Massey et al. 2012; Burton et al. 2004; Tinaz et al. 2010). However, structural MRI seems to be suboptimal, especially in the early disease stages, making difficult the distinction between parkinsonian disorders and healthy controls (HC) (Gonzalez-Redondo et al. 2014; Seppi and Schocke 2005).

iRBD - Several studies investigated the alteration of grey matter in iRBD, also considering the absence/presence of cognitive impairment. Heterogeneous results emerged from the literature. Some studies reported a lack of volume differences between iRBD and HC (Lee et al. 2014; Rolinski et al. 2016). Other findings revealed reduced grey matter volume in iRBD than HC in frontal lobes, anterior cingulate gyri, cerebellum, pontine tegmentum, parahippocampal gyrus, and caudate nucleus (Hanyu et al. 2012). One study reported minor differences instead, namely increased grey matter volume in the bilateral hippocampus in iRBD (Scherfler et al. 2011).

Two studies performed by the same research group investigated cortical grey matter thickness in two iRBD cohorts, revealing different alteration patterns. In one study, iRBD showed cortical thinning in the frontal cortex, lingual gyrus and fusiform gyrus (Rahayel et al. 2015); in the other study, iRBD were characterized by grey matter abnormalities in the right dorsolateral primary motor cortex (Rahayel et al. 2018) (Figure

16). Of note, the second study used an enlarged sample of iRBD patients, including those studied in the first one.

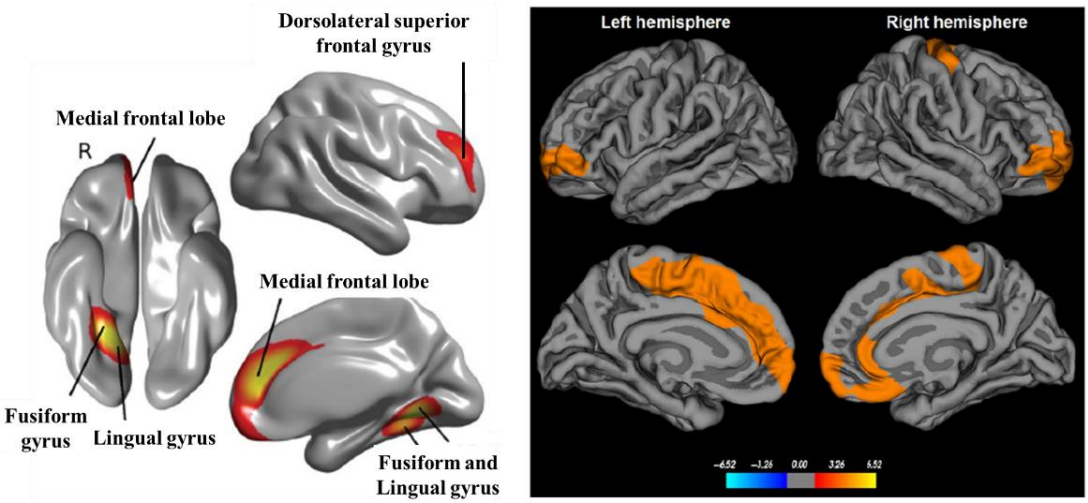

Figure 16. iRBD patterns of cortical thinning (Open Access Source).

The figure represents the two different patterns of cortical thickness that emerged in two iRBD cohorts. The second study (left side) used an enlarged sample of iRBD patients, including those studied in the first (right side). Figure adapted from (Rahayel et al. 2015; Rahayel et al. 2018).

The reduction of frontal lobes volume has been associated with the disease duration of iRBD and age at onset: higher grey matter reduction was associated with longer disease duration and early age at onset (Rahayel et al. 2018). Surface-based approaches discovered that cortical reduction volume in precentral and postcentral gyri are associated with MCI, whereas reduced occipital cortical thickness correlates with visuospatial deficits (Rahayel et al. 2018). Rahayel and colleagues (2018) also evaluated the difference in the grey matter between iRBD patients with MCI (iRBD+MCI) and iRBD patients without MCI (iRBD-MCI) (Rahayel et al. 2018). iRBD+MCI showed higher grey matter alteration in the frontal, cingulate, temporal, and occipital cortices than iRBD-MCI, which had cortical thinning limited to the frontal cortex. Specifically, anterior temporal cortex alteration was the most discriminative feature between groups, with an accuracy of 91% (Rahayel et al. 2018).

Some data are available also for subcortical grey matter alterations (Ellmore et al. 2010; Lee et al. 2014; Rahayel et al. 2018; Rahayel et al. 2018). Findings showed a

reduced volume of the bilateral putamen (Ellmore et al. 2010; Rahayel et al. 2018); others did not found differences between iRBD and HC (Lee et al. 2014). The most recent studies also evaluated the shape contraction of subcortical structures using vertex-based shape analysis (Rahayel et al. 2018; Rahayel et al. 2018). Shape contraction in the bilateral pallidum and right putamen was associated with reduced motor speed – measured throughout finger tapping (Rahayel et al. 2018). Moreover, iRBD+MCI had a greater contraction of the left putamen and thalamus than iRBD-MCI (Rahayel et al. 2018). Higher impairments within the visuospatial and memory domains were associated with hippocampus abnormal surface expansion (Rahayel et al. 2018). All the above evidence suggests heterogeneous cortical and subcortical grey matter abnormalities in iRBD patients, particularly in patients with cognitive impairment, suggesting that this approach might yield limited utility for identifying a specific neurodegeneration biomarker in such intrinsically heterogeneous condition.

Other studies have used innovative MRI sequences such as neuromelanin-sensitive to detect brain alterations in iRBD patients. Neuromelanin-sensitive imaging revealed a reduced volume of SN (Pyatigorskaya et al. 2017) and LC/ locus subcoeruleus in iRBD (Ehrminger et al. 2016; Knudsen et al. 2018). The neuromelanin signal intensity of LC correlated with the severity of iRBD manifestation and RSWA (Ehrminger et al. 2016). LC pathology in iRBD patients is already comparable to diagnosed iPD (Knudsen et al. 2018).

PD - Structural brain alterations are subtle in early PD and not consistently detectable by conventional MRI (Saeed et al. 2017). Indeed, MRI studies usually report a brainstem and subcortical involvement in early-stage PD and the cortical structures in the late stage of PD or PD with MCI (PD+MCI), PDD and DLB patients (Saeed, Lang, and Masellis 2020).

Voxel-based morphometry (VBM) studies on PD showed atrophy in basal ganglia (X. Xu et al. 2020; Tinaz, Courtney, and Stern 2011; Pitcher et al. 2012; Tanner, McFarland, and Price 2017), frontal lobe (Burton et al. 2004), and with a variable extent in the hippocampus (Tanner, McFarland, and Price 2017), left anterior cingulate and superior temporal gyri (Summerfield et al. 2005). Moreover, some studies found cortical thickness affecting orbitofrontal, ventrolateral prefrontal, and occipitoparietal cortical regions (Tinaz, Courtney, and Stern 2011; Pitcher et al. 2012). Specifically, the volume

of posterior cortical regions seems to be associated with freezing gait symptomatology in PD (Tessitore et al. 2012). PD patients with olfactory dysfunctions show reduced volume in the olfactory bulb and tract compared to HC and MSA patients (Chen et al. 2014), suggesting that atrophy of the olfactory bulb may potentially be helpful for differential diagnosis of PD from MSA. Other studies reported no relevant volumetric differences between PD and HC (Tessitore et al. 2012; Schulz et al. 1999).

Compared with PD without MCI (PD-MCI), patients with PD+MCI have a lower volume of the thalamus, amygdala, and nucleus accumbens (Mak et al. 2014; Hanganu et al. 2014). Longitudinal data show that, in comparison with cognitively stable PD, patients with PD+MCI have a higher rate of cortical thinning in the temporal lobe, occipital lobe, parietal lobe, and supplementary motor area (SMA) (Hanganu et al. 2014). SMA atrophy has been proposed as a specific biomarker of cognitive deterioration in PD (Hanganu et al. 2014; Monchi et al. 2016); however, significant occipital involvement may be the basis for the development of hallucinations in PD+MCI patients (Monchi et al. 2016). A recent study found loss of grey matter and increased diffusion tensor imaging (DTI) mean diffusivity in the nucleus NBM and thalamus of patients with PD+MCI (Figure 17). They also reported that the degeneration of the NBM precedes and predicts the start of cognitive dysfunction without the influence of other clinical and non-clinical features of PD (Schulz et al. 2018). This vulnerability is consistent with the view that cholinergic dysfunction leads PD to develop dementia.

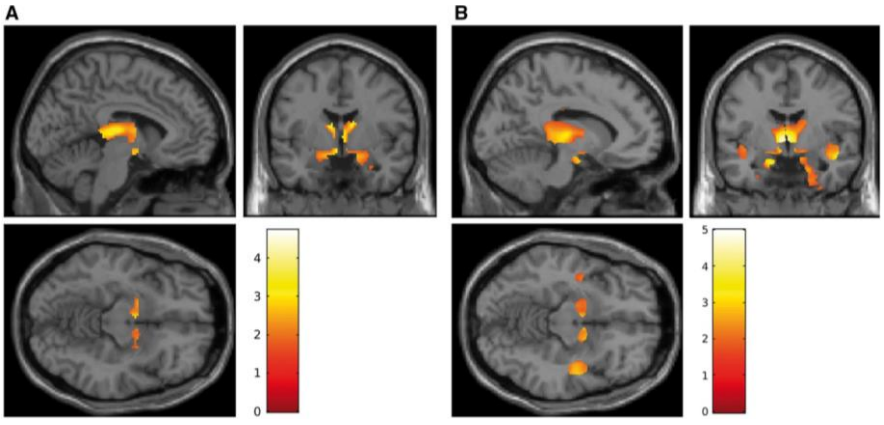

Figure 17. Grey and withe matter abnormalities underlying cognitive deterioration in PD (Open Access Source).

The figure shows (a) reductions in grey matter and (b) increases in mean diffusivity in cognitively impaired compared to cognitively normal patients with PD. Yellow–red areas represent voxel clusters with decreased(a)/increase(b) values. Figure from (Schulz et al. 2018).

DLB - In DLB, MRI often provided non-specific and variable evidence. Most MRI studies employed VBM and regions of interest (ROIs) analysis to compare DLB with PDD, AD and controls. Few MRI studies investigated the pattern of grey cortical atrophy in DLB, leading to inconsistent results. Some studies reported a limited reduction of cortical and subcortical volumes in DLB compared to HC involving the insula, thalamus, dorsal midbrain, hippocampus (Beyer, Larsen, and Aarsland 2007; Whitwell et al. 2007). Other studies, instead, showed widespread cortical atrophy affecting the medial temporal, frontal, parietal lobes and insular cortex (Yousaf et al. 2019; Oppedal et al. 2019).

DLB and PDD comparison show that DLB expresses more severe atrophy than PDD (Elijah Mak et al. 2014); however, the topography of grey matter reduction in DLB relative to PDD varies among studies. One study reported reductions in the temporal, parietal and occipital lobes in DLB compared to PDD (Beyer, Larsen, and Aarsland 2007); another research alongside these grey matter reductions – temporal, parietal and occipital – reported striatal atrophy DLB (Lee et al. 2010). Conversely, a study by Burton and her team reveals similar atrophy patterns in the two α-synucleinopathies (Burton et al. 2004); however, atrophy was generally less widespread in DLB with a partial sparing of the medial temporal brain structures (Burton et al. 2002; Karas et al. 2003; Burton et al. 2009). Indeed, the absence of medial temporal atrophy is considered a specific biomarker for distinguishing DLB from AD (Watson and Colloby 2016). Cortical thickness assessment showed that AD patterns of cortical thinning included the temporal pole, subgenual cingulate regions and the parahippocampus; DLB pattern was composed by superior temporo-occipital and lateral orbito-frontal regions, as well as the middle and posterior cingulate (Lebedev et al. 2013). Regarding subcortical structures, DLB shows more severe mesopontine grey matter atrophy than AD, suggesting a more significant cholinergic impairment in DLB (Whitwell et al. 2007). Recently, the swallowtail sign [10] has been proposed as a promising biomarker in the differential diagnosis between DLB and AD (Shams et al. 2017; Kamagata et al. 2017).

[10] The swallow tail sign describes the normal detection of nigrosome-1 within the SN using high-resolution T2*/ iron-sensitive susceptibility-weighted imaging MRI. Nigrasome-1 contains the largest number of neurons impaired in PD, causing the absence of normal high SWI signal within nigrosome-1.

MSA - MSA atrophy has been extensively studied with MRI. In MSA-P, MRI showed atrophy of the putamen, middle cerebellar peduncles (MCP), cerebellum, or pons; in MSA-C, atrophy of the putamen, MCP, or pons (Fanciulli and Wenning 2015). The comparison of MSA-C and MSA-P reveals small regions of grey matter reduction in the basal parts of the cerebellum in MSA-C patients (Minnerop et al. 2007) (Figure 18).

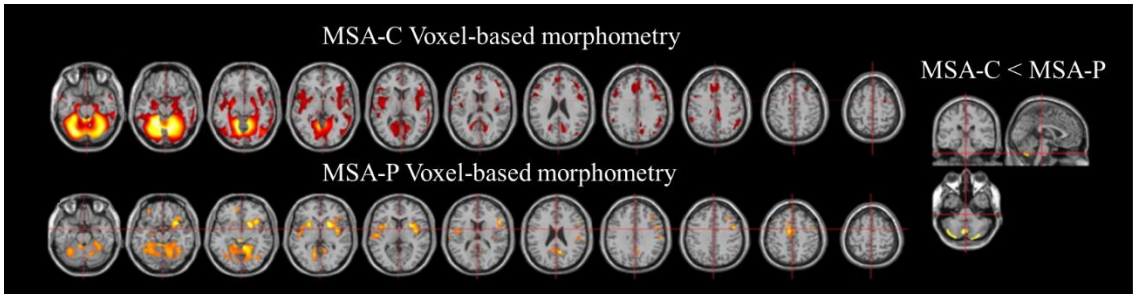

Figure 18. Brain atrophy patterns of MSA clinical phenotype (Open Access Source).

The figure shows the reduction of grey matter in MSA-C (up) and MSA-P (bottom). The right side of the figure reports the direct comparison between MSA-C and MSA-P. Figure adapted from (Minnerop et al. 2007).

MRI expert evaluation is a milestone of the biomarker supportive of the clinical diagnosis of MSA; indeed, several signs have been described on both T1- and T2-weighted MRI images (Chelban et al. 2019) (Figure 19).

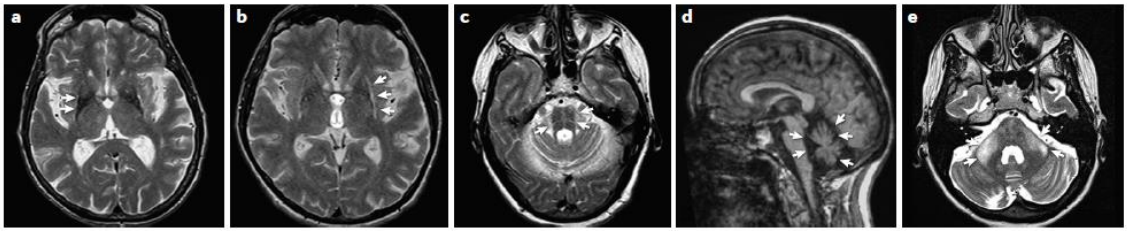

Figure 19. MRI biomarkers in MSA (Open Access Source).

A) T2-weighted image showing putamen hypointensity in MSA patients. B)Tthe dorsolateral margin of the putamen with a hyperintense rim (arrows). C) The 'hot cross bun' sign represents the degeneracy of the pons and pontocerebellar fibres with the preservation of corticospinal ones. D) Cerebellar atrophy (arrows) in T1 images. E) T2-weighted images showing a bilateral hyperintensity of the middle cerebellar peduncle (arrows). Figure from (Krismer and Wenning 2017)

Most MRI imaging studies aim to provide atrophy signatures to correctly identify the two clinical forms of MSA (MSA-P and MSA-CA) (Chelban et al. 2019). In this regard, the 'hot cross-bun' (Figure 19C) is considered a good hallmark for MSA-C with high specificity (97%) but low sensitivity (50%) (A Schrag et al. 2000). Instead, the 'putaminal rim' (Figure 19B) sing is an imaging feature usually found in MSA-P showing 90% specificity for this subgroup but only 72% sensitivity (E. Lee et al. 2004). Moreover, even though putamen atrophy shows high specificity (92.3%), it has low sensitivity (44.4%) to differentiate MSA-P and PD (Feng et al. 2015).

1.6.2. Neuroimaging of the presynaptic dopaminergic system

The integrity and density of presynaptic dopaminergic terminals and postsynaptic DA receptors can be assessed using PET, and Single Photon Emission Computed Tomography (SPECT) approaches in parkinsonian disorders. Different radiotracers allow measuring distinct molecular aspects related to presynaptic DA activity – DAT [11] availability, vesicle transporter[12] and DA storage – and postsynaptic DA system – D2/D3 receptors (Politis 2014) (Figure 20).

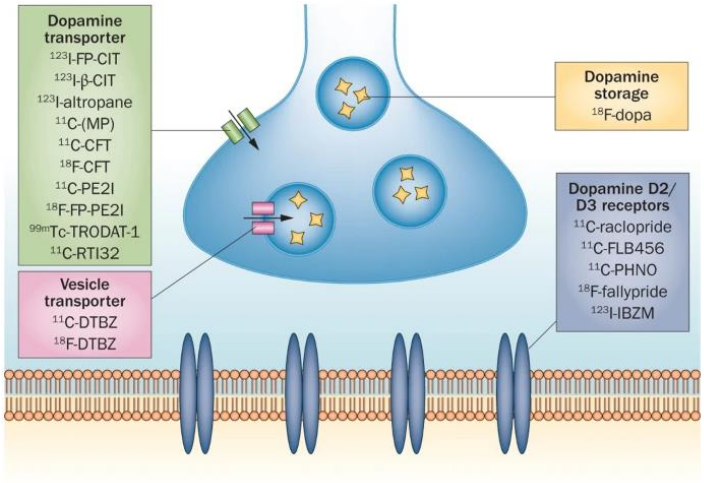

Figure 20. Radiotracers for dopaminergic system assessment (Open Access Source).

Figure from (Politis 2014).

[11] DAT regulates the reuptake of DA from the synaptic cleft (Saeed et al. 2017).
[12] Implicated in the transport of DA from the cytoplasm into secretory vesicles (Hughes et al. 1992).

DAT imaging mainly uses SPECT, specifically the 123I-FP-CIT ligand (also known as 123I-iodoflurane or DaTSCAN) (Politis 2014; Palermo and Ceravolo 2019). In PD, a lower membrane DAT expression on presynaptic terminals may be associated with striatal DA terminal loss and the progressive reduction of nigral cells (Palermo and Ceravolo 2019). Consequently, the Movement Disorder Society (MDS considers the presence of a normal DaTSCAN one of the exclusion criteria for PD diagnosis (Postuma et al. 2015). Reduced DAT levels are also observed in MSA, PDD/DLB and PSP, contrary to healthy people and patients with essential tremor ET, drug-induced or psychogenic parkinsonism (Politis 2014). Indeed, DatSCAN shows high sensitivity (87–98%) and specificity (80–100%) in differentiating α-synucleinopathies and PSP from ET and HC (Acton, Mozley, and Kung 1999; Asenbaum et al. 1998; Benamer et al. 2000; 2003; Group 2000). Within the α-synucleinopathies spectrum, also DLB is characterized by nigrostriatal dopaminergic neuronal loss (Outeiro et al. 2019). Abnormal DaTSCAN has 78% sensitivity and 90% specificity in distinguishing probable DLB from other forms of dementia compared with clinical diagnosis (McKeith et al. 2007). Moreover, presynaptic dopaminergic assessment in the preclinical stage of α-synucleinopathies, like iRBD, can help predict the early conversion to overt α-synucleinopathy (Bauckneht et al. 2018). However, DAT imaging is not efficient to differentiate PD from other parkinsonian syndromes, such as PDD/DLB, PSP, corticobasal syndrome (CBS), or MSA (Outeiro et al. 2019).

iRBD - The presynaptic dopaminergic integrity has been extensively assessed in iRBD using several radiotracers for PET and SPECT imaging (Bourgouin et al. 2019). Few studies evaluated postsynaptic dopaminergic functioning without revealing significant differences between iRBD and HC (Eisensehr et al. 2000; Eisensehr et al. 2003). The percentage of iRBD patients with presynaptic dopaminergic impairment in the striatum varies among studies ranging from 12.5% to 100% (Iranzo et al. 2010; 2011; Kim et al. 2010; Knudsen et al. 2018; Rolinski et al. 2016; Rupprecht et al. 2013; Stiasny-Kolster et al. 2005; Eisensehr et al. 2000; Frosini et al. 2017; Iranzo et al. 2017; Stokholm et al. 2017). Specifically, in most studies, the putamen deafferentation is more severe than caudate (Albin et al. 2000; Arnaldi et al. 2015; Eisensehr et al. 2000; Eisensehr et al. 2003; Iranzo et al. 2010; Knudsen et al. 2018; Stokholm et al. 2017). A continuum of putaminal dopaminergic dysfunction from iRBD toward PD pathology has been

proposed. Specifically, a recent meta-analysis demonstrated that dopaminergic dysfunction in the putamen progressively worsens from controls to iRBD patients to PD-RBD, reaching the lowest level of tracer uptake in PD+RBD (Figure 21) (Bauckneht et al. 2018).

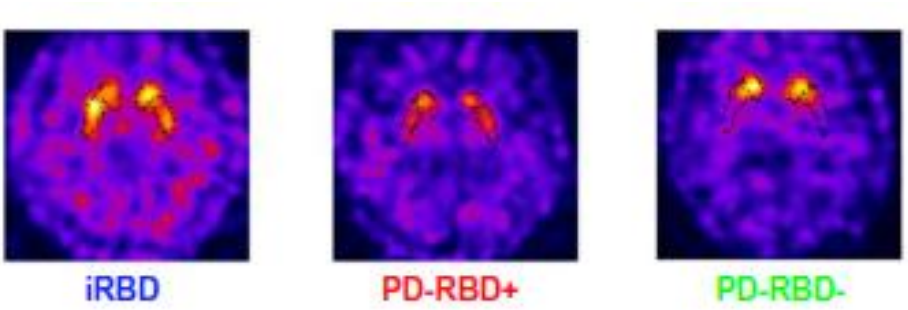

Figure 21. Dopaminergic dysfunction continuum from iRBD to PD-RBD and PD+RBD (Open Access Source).

The figure shows the gradual deterioration of DAT binding – measured with [123I]FP-CIT-SPECT – from iRBD to PD-RBD and PD+RBD. Figure from (Bourgouin et al. 2019).

Regarding the caudate nucleus, one study showed that iRBD and PD+RBD patients have a more severe dopaminergic dysfunction in the caudate nucleus than PD-RBD (Arnaldi et al. 2015). The same findings are not confirmed by a meta-analysis (Bauckneht et al. 2018), which shows that dopaminergic deficit progression in nucleus caudate is similar to that described above for the putamen (Figure 21).

The degree of striatal dopaminergic deafferentation is associated with the severity of iRBD clinical manifestation; dopaminergic deficit worsens with the disease progression (Eisensehr et al. 2003; Iranzo et al. 2017). Consistently iRBD subjects with abnormal striatal DAT binging shows higher scores at Unified Parkinson's Disease Rating Scale part III (UPDRS-III) than subjects with normal scans (Rupprecht et al. 2013). Longitudinal studies demonstrated that greater striatal DA impairment is associated with a higher risk of phenoconversion in a full-blown α-synucleinopathy (Iranzo et al. 2010; 2011; Iranzo et al. 2017; Li et al. 2017). Specifically, Iranzo and colleagues (2017) demonstrated that a reduction of DAT putaminal binding of more than 25% predicts a conversion within three years. The above mentioned evidence suggests that presynaptic striatal DA impairment is a potential biomarker of neurodegeneration in iRBD patients (Bauckneht et al. 2018). However, a recent multicentric study

demonstrated that presynaptic DA impairment is not a predictive biomarker to differentiate between patients converting to primary dementia (PDD/DLB) versus parkinsonism (PD) (Postuma et al. 2019). Thus, the striatal dopaminergic deficit should be considered a biomarker that predicts early conversion to unspecific α-synucleinopathy.

PD - A degeneration of the presynaptic dopaminergic nigrostriatal nerve fibres is a neuropathological hallmark of PD. In PD, the postsynaptic side bearing the striatal receptors remains unaffected (Politis 2014). PET and SPECT imaging studies consistently show an asymmetric presynaptic striatal impairment in PD patients where the tracer uptake in the posterior part of putamen contralateral to the most affected body side is more severe than the ipsilateral one (de Natale et al. 2018) (Figure 22).

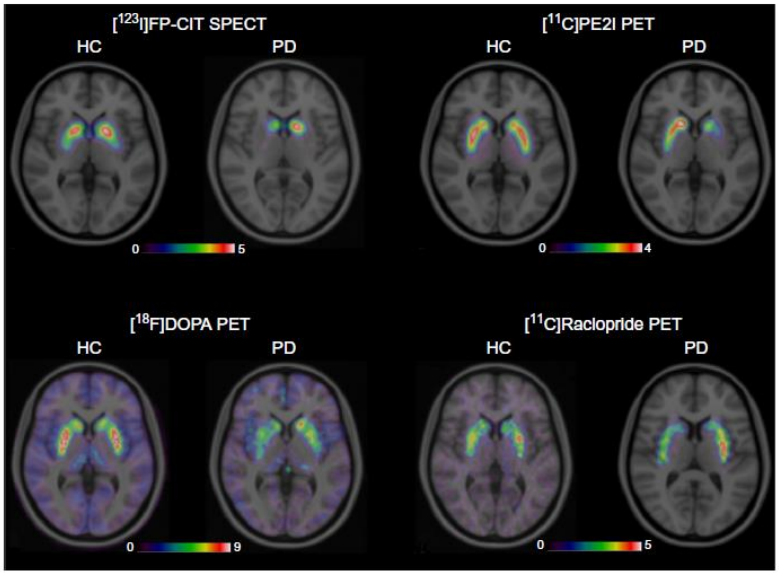

Figure 22. Dopaminergic striatal molecular assessment in PD (Open Access Source).

The figure depicts the presynaptic and postsynaptic dopaminergic molecular imaging of PD patients and controls. Presynaptic dopaminergic assessment (top) reveals a degeneration process with an asymmetric presentation. Postsynaptic dopaminergic functioning (bottom) is not affected in PD. Figure from (de Natale et al. 2018).

Moreover, in PD patients, the posterior putamen shows the highest degree of impairment and the caudate nucleus the least; this phenomenon is the so-called rostral-caudal gradient (Figure 22) (Guttman et al. 1997; Broussolle et al. 1999). The severity of DAT decline is inversely correlated with bradykinesia and rigidity scores obtained from the UPDRS-III assessment (Rinne et al. 1999; Moccia et al. 2014; Huang et al. 2001).

Notably, tremor severity is not associated with dopaminergic impairment (Rinne et al. 1999; Moccia et al. 2014; Huang et al. 2001), suggesting that it may have different pathophysiology, not primarily related to the dopaminergic system. Accordingly, PD motor subtypes show a different level of dopaminergic impairment, where akinetic-rigid and PIGD subtypes exhibit a more severe dopaminergic depletion than tremor-dominant ones (Kaasinen et al. 2014; Santangelo et al. 2015).

In PD patients, the striatal dopaminergic deficit progress over time, showing 11% of the annual decline of DAT density compared to 0.8% of the healthy population (Pirker et al. 2003). Specifically, putamen seems to lose 13.1% of DAT density and caudate nucleus 12.5% annually (Nurmi et al. 2000). One longitudinal study demonstrates that the dopaminergic damage progression does not follow a linear pattern, slowing over time. Indeed PD patients lost 7.5% in the first two years and 5.6% in the following three years (Marek et al. 2001). Of note, in PD patients with long-standing disease duration, the dopaminergic deficit's progression is slow and reaches a plateau (Hely et al. 2005; 2008), whereas a significant progression of DA depletion characterizes patients who develop dementia (Colloby et al. 2005). The dopaminergic deficit seems to have some prognostic implication, where decreased DAT binding in putamen is related to the progression of motor symptoms, whereas in the caudate nucleus to the development of dementia (Johansen et al. 2010).

DLB - DLB patients consistently show a disruption of the dopaminergic pathway (Colloby et al. 2005; Klein et al. 2010; O'Brien et al. 2004; Walker et al. 2007). Regarding the postsynaptic dopaminergic assessment, contrary to PD, D2 receptors are significantly reduced in DLB relative to controls or AD (Walker et al. 1997; Hu et al. 2000).

Using several tracers, which reflect the presynaptic dopaminergic function, studies reported lower levels in the striatum, with comparable impairment of both the caudate and putamen (Figure 23) (Colloby and O'Brien 2004; Klein et al. 2010; Walker et al. 2007).

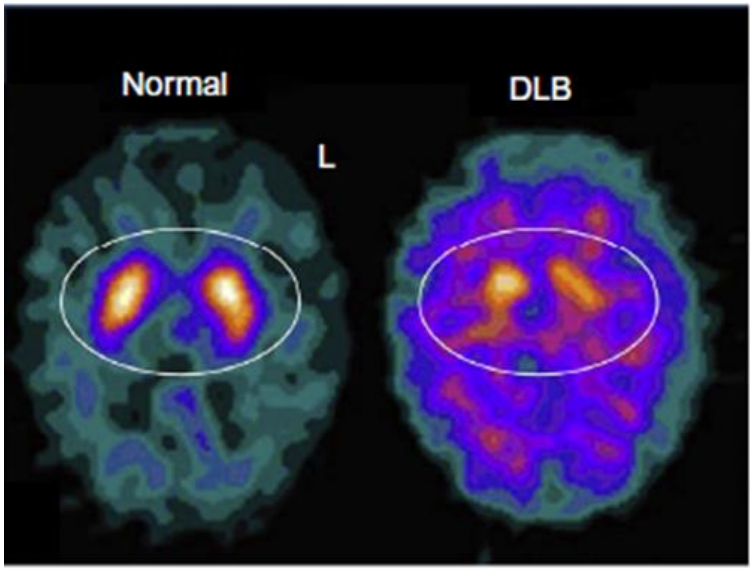

Figure 23. Presynaptic dopaminergic damage in DLB (Open Access Source).

The figure shows reduced DAT availability – measured by [123I]FP-CIT-SPECT – in a DLB patient compared to the integrity of presynaptic striatal dopaminergic innervation in an HC. Figure adapted from (Risacher and Saykin 2019).

DLB patients show striatal lateralized impairment associated with the clinically most affected side (Klein et al. 2010), although less pronounced than PD (Walker et al. 2004), suggesting a uniform decrease in the DA. Dopaminergic assessment in DLB assumes significant clinical importance in distinguishing DLB from AD, with DaTSCAN achieving very high diagnostic specificity and sensitivity (Lim, Fox, and Lang 2009; Mckeith et al. 2004; Walker et al. 2007). Indeed the dopaminergic assessment is used in clinical practice and is part of the diagnostic criteria of DLB (McKeith et al. 2017).

Given the pathological and clinical overlap between DLB, PDD and PD, similarities have been reported in these conditions (Tatsch and Poepperl 2013). Comparable levels of 123I-FP-CIT striatal binding have been observed in DLB and PD patients (Colloby and O'Brien 2004; O'Brien et al. 2004; Walker et al. 2004). Some differences emerged in few studies. Walker et al. (2004) detected lower caudate binding in DLB compared to PD, whereas no significant difference was found in putamen between the two groups (Walker et al. 2004). O'Brien and colleagues (2004) reported a similar loss in the putamen and caudate in DLB and PD, whereas putamen, compared to caudate, was markedly more affected in PD (O'Brien et al. 2004).

MSA - MSA is characterized by decreased dopaminergic functioning in the caudate, putamen, ventral striatum, and globus pallidus (Ghaemi et al. 2002; Brooks et al. 1990; Rinne et al. 1995; Otsuka et al. 1997; Lewis et al. 2012). MSA-P patients feature striatal presynaptic dopaminergic denervation (Nocker et al. 2017); however, a substantial percentage of MSA-C (43%) patients express a nigrostriatal presynaptic dopaminergic denervation too (Nocker et al. 2017; Vergnet et al. 2019). MSA-C patients show a distinct topography of reduced DAT availability, mainly affecting the midbrain, and pontine monoaminergic transporter binding, whereas striatal dopaminergic functioning is less affected in MSA-C than MSA-P (Nocker et al. 2017) (Figure 24).

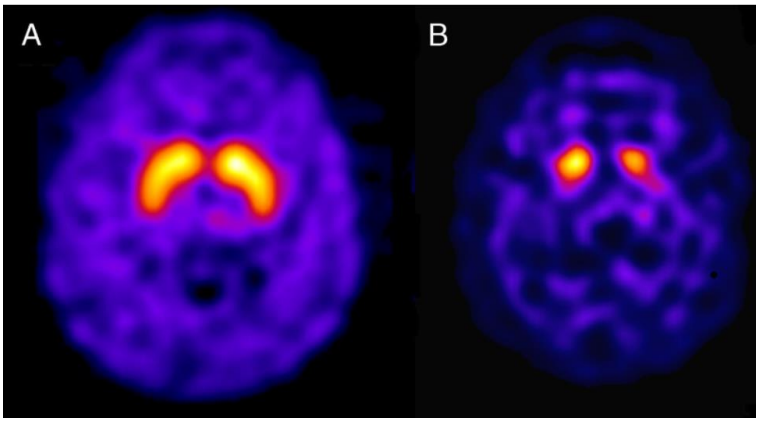

Figure 24. Striatal DAT binding in MSA-C and MSA-P (Open Access Source).

The figure shows a normal scan in (A) MSA-C and a reduced DAT availability in (B) MSA-P patients, as measured [123I]-FP-CIT SPECT. Figure from (Nicastro et al. 2018).

Although it is generally believed that dopaminergic SPECT imaging cannot distinguish various parkinsonisms (Brucke et al. 2000; Knudsen et al. 2004; Cilia et al. 2005), recent evidence has shown subtle differences between MSA and other parkinsonisms. MSA-P shows a faster disease progression than PD with more severe impairment of caudate nucleus and anterior putamen uptake, as measured by [123I]-FP-CIT SPECT (Nocker et al. 2012; Badoud et al. 2016). Moreover, a lower ventral putamen uptake has been described in MSA-P than PD (Oh et al. 2012). In addition, MSA-C subjects with mild or no parkinsonian symptoms may show limited presynaptic dopaminergic uptake or even normal scans (McKinley et al. 2014). Of note, when MSA-P from MSA-C are compared, some differences emerge (Kim et al. 2016). Patients with

MSA-P express more significant DAT loss in the striatum than MSA-C, while patients with MSA-C show more diffuse DAT loss than MSA-P (Kim et al. 2016).

Overall, DAT imaging represents a useful tool in investigating the presynaptic dopaminergic nigrostriatal pathway (Palermo and Ceravolo 2019) and distinguishing between PD and non-degenerative parkinsonian's syndromes (Ba and Martin 2015). However, given that DaTSCAN patterns overlap in these neurodegenerative conditions, it may fail for providing proper differential diagnosis (Palermo and Ceravolo 2019) and may, hence, show limited prognostic relevance for clinical practice (Ba and Martin 2015). Despite the crucial role of dopaminergic molecular imaging in α-synucleinopathies, no imaging measures of dopaminergic neurotransmission can accurately differentiate between different α-synucleinopathies (e.g., PD, PDD/DLB, MSA) (Politis 2014; de Natale et al. 2018; Risacher and Saykin 2019).

1.6.3. [123I]MIBGmyocardial scintigraphy

The MIBG is a physiological analogue of the neurotransmitter NE, without a pharmacological activity (Braune 2001). MIBG and NE shared the uptake, storage, and release mechanisms. MIBG can be radiolabeled with iodine-123 [123I], [123I]MIBG used for the myocardial scintigraphy that allows non-invasively assessing the postganglionic presynaptic cardiac sympathetic nerve endings (Orimo et al. 2016). Upon depolarization, [123I]MIBG is released, similarly to NE, but remains unmetabolized (Saeed et al. 2017). Thus, [123I]MIBG remains in sympathetic nerve endings. Therefore, the uptake of [123I]MIBG reflects the positioning and functional integrity of the sympathetic nerves and represents an index of the patient's cardiovascular function (Braune 2001).

The cardiac uptake is obtained by calculating the heart-to-mediastinum (H/M) ratio by setting ROIs over the heart and the upper mediastinum on the anterior planar view of the chest (Orimo et al. 2016). Although [123I]MIBG myocardial scintigraphy was developed to assess sympathetic nerve damage in heart diseases, it has been recently used for neurodegenerative disorders, especially α-synucleinopathies, where cardiovascular dysautonomia can occur (Saeed et al. 2017). Cardiac [123I]MIBG uptake is reduced in LB diseases, including PD (Orimo et al. 1999; Yoshita 1998) and DLB

(Watanabe et al. 2001), and it can help to differentiate PD from other forms of parkinsonism, as well as DLB from AD (Orimo et al. 2016). A meta-analysis demonstrated that [123I]MIBG-SPECT could distinguish LB-related disorders (PD, DLB, RBD) from non-LB related disorders (AD, MSA, PSP) with 94% of sensitivity and 91% of specificity (King, Mintz, and Royall 2011a). Patients with PSP, MSA, and CBS show normal or slightly reduced [123I]MIBG uptakes, aiding the distinction between PD and atypical parkinsonism (Saeed et al. 2017).

iRBD - Most of the iRBD subjects present already abnormal H/M rations, with the percentage ranging from 82% to 100% (Knudsen et al. 2018; Miyamoto et al. 2006; Miyamoto et al. 2008). The severity of peripheral sympathetic denervation is comparable to PD and DLB (Kashihara et al. 2010; Knudsen et al. 2018; Miyamoto et al. 2006; Miyamoto et al. 2008). A longitudinal study demonstrated that measures of [123I]MIBG-SPECT were similar at baseline and after a 2.5 years follow-up (Miyamoto et al. 2011). All the above suggests that the peripheral system is early affected in the disease, supporting the caudal-rostral model of α-propagation proposed by Braak and colleagues (Braak et al. 2004). However, [123I]MIBG-SPECT measures seems not reliable progression biomarkers in iRBD.

PD - PD patients are characterized by a severe loss of cardiac sympathetic denervation as measured by [123I]MIBG-SPECT (Knudsen and Borghammer 2018). Of note, this neurotransmission system – the peripheral postganglionic noradrenergic innervation – seems to be the most affected in PD. In general, 90% of PD patients reach pathological measures at [123I]MIBG-SPECT (Chung and Kim 2015). However, about 40%-50% of PD patients may have normal [123I]MIBG-SPECT scans in the early stage of pathology – at Hoehn and Yahr stage I – (Chung and Kim 2015; Orimo et al. 1999; Yoshita 1998; Tateno et al. 2011; Slaets et al. 2015), whereas almost all PD patients became pathological during the disease course – at Hoehn and Yahr stage III (Nagayama et al. 2005; Kashihara et al. 2010). These data support the existence of two theoretical starting points of LB disorder: gut-first and brain-first (Figure 7) (Borghammer & Van Den Berge 2019).

Distinct PD subtype shows different degrees of severity in [123I]MIBG alteration. PD patients with tremor-dominant phenotype have less severe cardiac sympathetic

denervation than the akinetic-rigid phenotype (Saiki et al. 2004). Moreover, PD-RBD shows higher [123I]MIBG measures than PD+RBD (Nomura et al. 2010; Kim et al. 2017). Of note, near all iRBD subjects show a loss of cardiac signal (Iranzo et al. 2013) comparable to those found in PD in the Hoehn andYahr stage III–V (Kashihara et al. 2010; Miyamoto et al. 2006; Knudsen et al. 2018). These findings suggest that in PD+RBD patients, the alteration of this neurotransmission system occurs very early. Since there is a lack of strict correlation between [123I]MIBG measures and the disease stage (Orimo et al. 2016), it is plausible to postulate that degeneration of the peripheral autonomic nervous system is more associated with specific clinical phenotypes than with disease stage, mainly defined by motor symptom progression. Recently the prognostic value of cardiovascular dysautonomia has also been proposed. Indeed, [123I]MIBG alteration show an association with the risk of progression to PDD/DLB (Peralta et al. 2007; Oh et al. 2011; Anang et al. 2014; Kim et al. 2009). Consistently, PD patients with severer myocardial sympathetic denervation deficits show greater cognitive impairment and risk of progression to PDD/DLB (Kim et al. 2009)

[123I]MIBG exam is often non-pathologic in atypical form of parkinsonism (i.e. PSP and CBD), suggesting [123I]MIBG-SPECT as an accurate biomarker in the differential diagnosis of PD. Indeed, the sensitivity and specificity in differentiating PD from MSA, PSP, and CBD by using the early H/M ratio are 82.6% and 89.2%, respectively, and using the delayed H/M ratio are 89.7% 82.6%, respectively (Orimo et al. 2016). Regarding MSA patients, they usually show a normal [123I]MIBGscan; however, in 10-20% of cases [123I]MIBG uptake is abnormal (*see MSA subparagraph*).

DLB - Most DLB patients have pathological [123I]MIBG scintigraphies scans (Chung and Kim 2015). Indeed, abnormal [123I]MIBG-SPECT myocardial scintigraphy is recently included as an indicative biomarker in the fourth DLB consensus criteria (McKeith et al. 2017). DLB and PDD patients show a more severe cardiac [123I]MIBG alteration than PD (Oka et al. 2007), supporting the association with more severe myocardial sympathetic denervation deficit and dementia. Oda and colleagues demonstrated the high accuracy of [123I]MIBGscintigraphy in predicting the conversion to probable DLB in patients with possible DLB after one year of follow-up (Oda et al. 2013). Washout rate, early and delayed H/M ratio showed 0.884, 0.935, 0.936 of accuracy, respectively (Oda et al. 2013). Several studies demonstrate high sensibility and

sensitivity of [123I]MIBG-SPECT in DLB diagnosis. Of note, a recent multicentric study investigated with a longitudinal approach the accuracy of [123I]MIBG myocardial scintigraphy in discriminating DLB from AD since the early disease stage (Komatsu et al. 2018). Komatsu and colleagues analyzed 133 patients with probable or possible DLB or probable AD for three years. Interestingly, based on initial clinical diagnosis at baseline, [123I]MIBG myocardial scintigraphy showed 69% sensitivity and 89% specificity in differentiating probable DLB from AD. However, based on the final diagnosis at the 3-year follow-up, [123I]MIBG assessment at baseline showed better diagnostic accuracy (77% sensitivity and 97% specificity) than the initial evaluation (Komatsu et al. 2018). This study strongly supports that [123I]MIBG myocardial scintigraphy is a valuable diagnostic tool in the early stage of DLB (Komatsu et al. 2018).

MSA - Although most [123I]MIBG scintigraphy findings have shown that the sympathetic innervation of the myocardium is normal in patients with MSA, mild reductions have been reported in some cases (10-20% of cases) (King, Mintz, and Royall 2011b; Orimo et al. 2012; Treglia et al. 2011). Of note, [123I]MIBG imaging can help distinguish between PD and MSA in advanced phases of diseases, but it is unreliable in the initial stages because patients with early PD may express non-pathologic cardiac sympathetic innervation (King, Mintz, and Royall 2011b; Orimo et al. 2012; Treglia et al. 2011). These imaging findings fit with the neuropathological ones. In most MSA patients, the postganglionic system is spared (Gray, Vincent, and Hauw 1988; Wenning et al. 1997). However, some studies show the involvement of postganglionic neurons in MSA patients (Nishie et al. 2004; Sone et al. 2005), and in some cases, a moderate reduction of tyrosine hydroxylase-immunoreactive cardiac nerve fibres (Orimo et al. 2007).

1.6.4. [18F]FDG-PET imaging

The radiotracer [18F]FDG is an analogue of glucose, which is the principal metabolic substrate of the brain; Brain activity requires energy in terms of adenosine triphosphate (ATP) (Meles et al. 2021). The glucose metabolism creates such energy (glycolysis) (Meles et al. 2021). Since glycogen storage present in the brain is not enough, blood furnishes further glucose to the brain; thus, glucose is transported through the blood-brain barrier and undergoes several transformations to produce brain energy (ATP)

(Meles et al. 2021). The enzyme hexokinase promotes the first step of metabolic pathways that transforms glucose into ATP: the phosphorylation of glucose in glucose-6-phosphate (Meles et al. 2021). Measuring the functioning of this enzyme is equivalent to assess the glucose utilization rate of the brain. As the glucose, the tracer [18F]FDG passes through the blood-brain barrier and enters in the glycolysis – [18F]FDG is a metabolite of enzyme hexokinase – but its phosphorylated form ([18F]FDG-6-PO) is trapped in the brain tissue because it cannot be metabolized further (Figure 25). Thus, [18F]FDG is considered an accurate and reliable measure of brain glucose utilization.

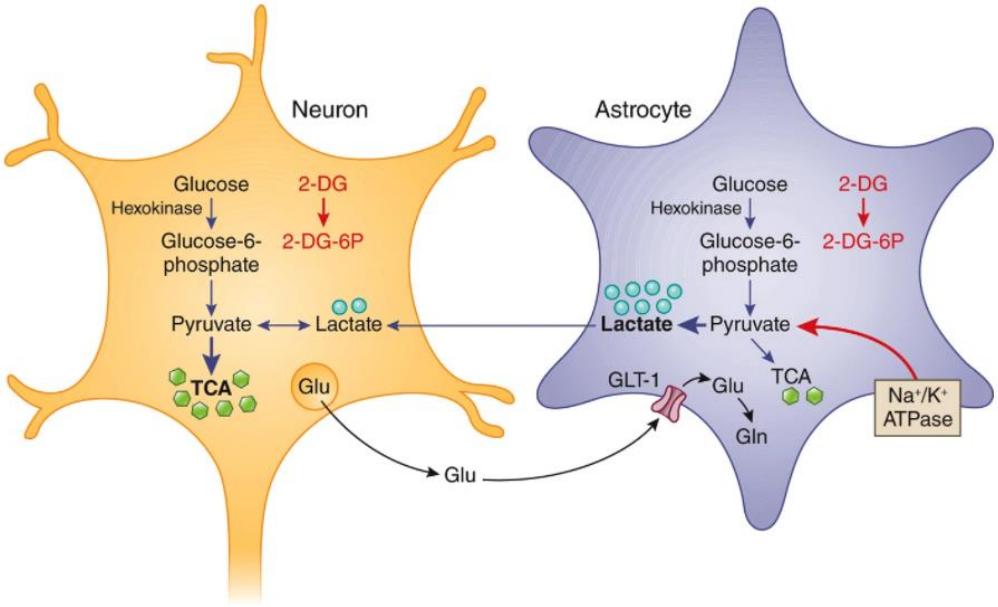

Figure 25. Glucose utilization in neurons and astrocytes (Open Access Source).

Figure adapted from (Stoessl 2017).

Tracer concentration in the brain tissues (obtained by PET) and in arterial plasma should be collected to measure the absolute accumulation of [18F]FDG-6-PO (Reivich et al. 1979). In this context, several PET images can be acquired in a dynamic protocol, ensuring an absolute measuring (in physiological units) of glucose's regional cerebral metabolic rate. This method implies an arterial blood sampling for each acquisition – an invasive and time-consuming procedure. Fortunately, relative regional a semi-quantitative distribution of [18F]FDG can be obtained by applying validated statistical approaches to raw [18F]FDG images, representing a reliable measure of glucose metabolism as well (Perani et al. 2020). Today, in clinical and most research contexts, the

regional distribution of glucose metabolism is assessed using semi-quantitative [18F]FDG measurement and not the absolute one avoiding invasive procedures and the resulting patient discomfort (Varrone et al. 2009).

Fundamentals of [18F]FDG-PET have been extensively studied and described (Perani et al. 2020). [18F]FDG-PET signal reflects resting potentials (15%), action potentials (16%) and synaptic processes (44%) (Howarth, Gleeson, and Attwell 2012). Moreover, the hypothesis that [18F]FDG-PET signal reflects astrocyte/neuron coupled energy consumption is increasingly accepted (Sokoloff 1981; Kadekaro et al. 1987; Pellerin and Magistretti 1994; Lundgaard et al. 2015; Stoessl 2017). Astrocytes produce lactate by gycolisis, which is transported to neurons to be used as an energy source (Pellerin and Magistretti 1994). Indeed, Zimmer et al. demonstrated that astrocytes are responsible for a large percentage of glucose consumption, further describing this coupling (Zimmer et al. 2017) (Figure 27). According to this model, excitatory neural activity leads to the release of glutamate from neurons, which is taken up in astrocytes. Glutamate in astrocytes stimulates aerobic glycolysis, producing pyruvate transported in neurons for efficient ATP production. Thus, higher regional glucose metabolism reflects excitatory synapses activity, but the pure glucose consumption seems to take place in astrocytes, not neurons (Zimmer et al. 2017).

Synaptic dysfunction and subsequent degradation may be related to an impaired intracellular signal pathway and mitochondrial bioenergetics, altered neurotransmitter mechanisms, and gathering of pathologic protein species; these events lead to decreased brain metabolism (Kato et al. 2016; Perani 2014). [18F]FDG-PET shows high sensitivity in capturing neurodegeneration, which can be due to local biochemical alterations and long-distance functional deafferentations (Kato et al. 2016). Thus, [18F]FDG-PET detects significant brain metabolism alteration before the neuronal loss, measuring the ongoing molecular changes affecting physiological synaptic functioning (Perani et al. 2020).

A growing body of studies has provided consistent evidence that different dementia conditions are characterized by specific [18F]FDG-PET hypometabolism topography (Perani et al. 2020). Unlike DAT imaging, which cannot differentiate particular forms of neurodegenerative parkinsonism, [18F]FDG-PET can detect distinct metabolic patterns of regional glucose metabolism in such disorders (Brajkovic, Kostic,

Sobic-saranovic, et al. 2017). In particular, several studies revealed distinct brain hypometabolism patterns in parkinsonian syndromes (Teune et al. 2013; Perani et al. 2020), leading to the inclusion of [18F]FDG-PET hypometabolism in support of most of the clinical/research diagnostic criteria (McKeith et al. 2017; Gilman et al. 2008; Armstrong et al. 2013).

Notably, the diagnostic accuracy of [18F]FDG-PET is critically influenced by the modality implemented to measure [18F]FDG-PET patterns (Perani et al. 2020; Meles et al. 2021), and selecting proper and validated procedures represents a crucial issue in data analysis (Perani et al. 2020). In literature, two well-validated approaches have been used to evaluate disease-specific hypometabolism patterns in α-synucleinopathies: univariate Statistical Parametric Mapping (SPM)-single subject procedure (Perani et al. 2014; Della Rosa et al. 2014) and multivariate Scaled Subprofile Model/Principal Component Analysis (SSM/PCA) (Eidelberg 2009; Spetsieris et al. 2013). This paragraph addresses these two methods, focusing on the result regarding the α-synuclein clinical spectrum.

1.6.4.1. The univariate approach of analyses

Since the diagnostic accuracy of [18F]FDG-PET is dependent on methods by which objective measurements are obtained, several voxel-wise tools for the semi-quantification have been developed, such as Neurostat, 3D-SSP, and SPM (Perani et al. 2020). Each tool provides statistical maps of brain hypometabolism derived from comparing a patient's brain metabolism with normative data. Our group has developed an optimized SPM-based voxel-wise [18F]FDG-PET procedure (Della Rosa et al. 2014; Perani et al. 2014), validated for utilization with different scanners (Presotto et al. 2017). This SPM procedure can identify disease-specific hypometabolism patterns in single patients (Perani et al. 2014). Each [18F]FDG-PET patient image is evaluated for relative hypometabolism through a comparison with a reference group of cognitively normal subjects on a voxel-by-voxel analysis using a two-sample t-test analysis (Perani et al. 2014). In the original model validation, a database of 112 HC aged from 50 to 80 years was employed (Perani et al. 2014), with the consequent recommendation of including at least 50 PET scans as a reference group (Gallivanone et al. 2017). Of note, our research group has recently validated two well-selected HC samples – ready-to-use in research and

clinical contexts – highlighting the importance of the reference group' selection for reliable estimation of hypometabolism patterns (Caminiti et al. 2021). These two large HC datasets derived from a European and American database are available for single-subject brain metabolism assessment, consequently promoting the quality and reliability of brain metabolism estimation in the clinical and research community (Caminiti et al. 2021).

Additionally, the SPM single-subject procedure utilises an optimized spatial normalization based on an [18F]FDG-PET dementia-specific template (https://github.com/PasqualeDellaRosa/Dementia-Specific-18F-FDG-PET-template). It is realized with 120 [18F]FDG-PET images, namely 60 from HC and 60 from patients with various forms of dementia, matched pair-wise for age and sex (Della Rosa et al. 2014; Perani et al. 2014). The spatial normalization of pathological scans using a template derived from HC scans potentially confounds anatomical and metabolic differences, making pathological brains similar to normal ones (Della Rosa et al. 2014). Thus, nowadays, the use of the dementia-specific template is mandatory.

Since the prodromal phases, the optimized SPM single-subject procedure has high accuracy in discriminating specific dementia and atypical parkinsonian conditions, thus predicting the risk of progression (Iaccarino, Sala, et al. 2017; Perani et al. 2020). This method can identify specific brain hypometabolism patterns preceding different phenotypical trajectories in PD (Pilotto et al. 2018). Moreover, in DLB patients, the SPM single-subjects approach shows an increase of ~50% accuracy compared to the initial clinical evaluation alone and accuracy of > 90% in differentiating DLB from AD and PD (Caminiti et al. 2019).

iRBD - Some studies have explored [18F]FDG-PET metabolism features in PSG-confirmed iRBD, only two throughout SPM approaches (Liguori et al. 2019; Ge et al. 2018). Indeed, previous literature mainly applied the SSM/PCA approach to evaluate iRBD metabolic features (see *1.6.4. The multivariate approach of analyses*). Both two SPM studies applied statistical analyses at the group level (Liguori et al. 2019; Ge et al. 2018) using a limited number of normal controls as the reference group. Heterogeneity in hypometabolism and hypermetabolism patterns emerged, possibly due to the intrinsic variableness within the iRBD cohorts (Figure 26). One study described a regional hypometabolism predominantly located in the occipital lobes and increased metabolism

in the supplementary motor area, cingulate and hippocampus/parahippocampal gyri (Ge et al. 2018) (Figure 26A). The second study described hypometabolism in the temporal-parietal cortex and hypermetabolism in the brainstem, limbic and frontal lobes (Liguori et al. 2019) (Figure 26B). These results are obtained by group-level analyses that might have limited utility for identifying a useful biomarker in an intrinsically heterogeneous condition.

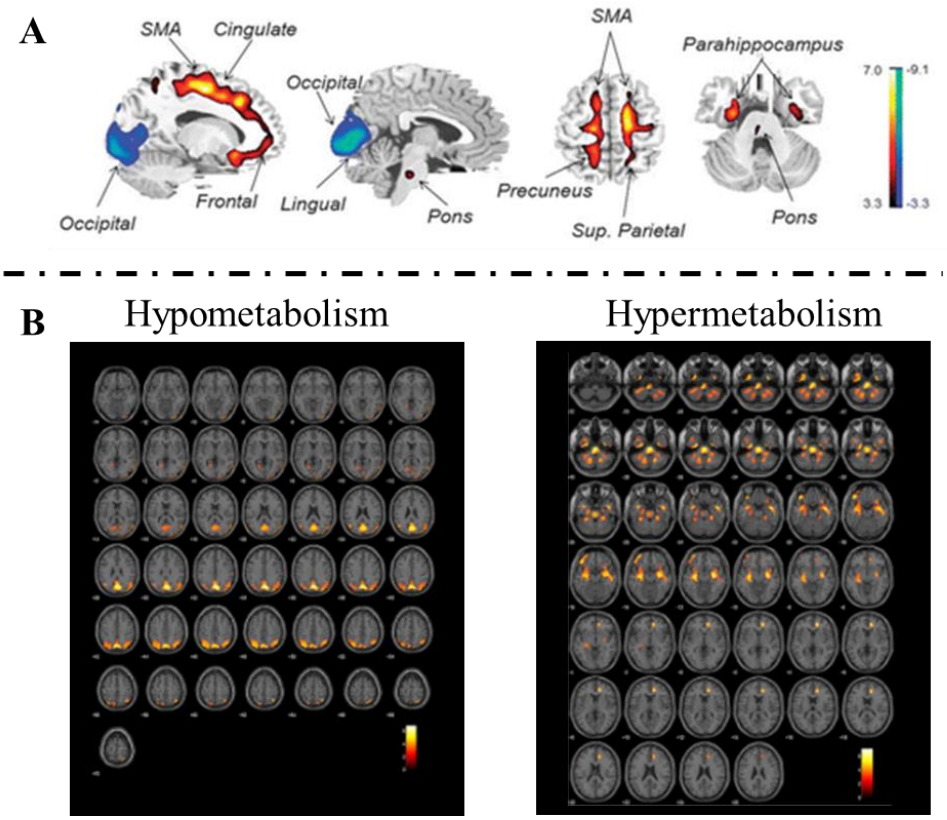

Figure 26. SPM comparison between iRBD and HC (Open Access Source).

Panel A depicts results of group comparison between 21 iRBD and 21 HC. iRBD patients were characterized by decreased metabolism in the occipital regions and increased metabolism in the supplementary motor area, cingulate, hippocampus/parahippocampus (Ge et al. 2018). *Panel B represents SPM results comparison between 44 iRBD and 35 HC. iRBD patients showed hypermetabolism in temporo-parietal cortices and increased metabolism in the brainstem, limbic and frontal regions* (Liguori et al. 2019).

<u>*PD*</u> - Several studies investigated metabolic features in PD patients using the univariate approach at the group and single-subject levels. PD patients show hypometabolism in the bilateral parietal, premotor and supplementary motor regions relative to controls (Poston and Eidelberg 2010; Zhao, Zhang, and Gao 2012). Moreover,

a recent meta-analysis demonstrated that PD patients are characterized by hypometabolism in the inferior parietal cortex and the caudate nucleus (Albrecht et al. 2019). However, some interesting results emerged when PD patients were grouped according to the clinical symptomatology (Albrecht et al. 2019). Hypometabolism in the caudate nucleus and cortical motor regions characterizes PD patients with just motor symptoms, while patients with cognitive deterioration showed prevalent parietal involvement (Albrecht et al. 2019). Consistently, several studies demonstrated a prevalent occipital and posterior parietal-temporal hypometabolism at a group level in patients with PD who converted to dementia (Pappatá et al. 2011; Gasca-Salas et al. 2016; Lyoo et al. 2010; Tard et al. 2015; Baba et al. 2017). These group-level results highlighted the urgency to study PD cohorts of patients at a single-subject level to identify those with different clinical trajectories. Pilotto and colleagues have responded to this need, applying the SPM single-subject procedure in a longitudinal study involving patients with PD (Figure 27) (Pilotto et al. 2018). Precisely, they followed a cohort of 54 PD patients for four years. They explored the hypometabolic features at each patient's baseline and evaluated the prognostic role of the hypometabolism pattern at single-subject levels. At the baseline, different single-subject FDG-PET patterns have been identified (Figure 27). 29 PD patients were characterized by no brain hypometabolism at all or by heterogeneous hypometabolism, including motor and premotor regions, somatosensory cortex, anterior cingulate, frontal cortex, and subcortical level globus pallidus and putamen (Pilotto et al. 2018). This hypometabolic pattern was called the “PD-typical pattern”. In addition, four atypical PD-patterns have been reported in the remaining patients: DLB-like pattern (n=12), defined by temporal-parietal and occipital hypometabolism, with variable frontal involvement; AD-like pattern (n=6), with bilateral temporal-parietal hypometabolism; CBS-like pattern (n=5), with asymmetric frontal-parietal hypometabolism; and finally frontotemporal dementia (FTD)-like pattern (n=2), with frontal-temporal hypometabolism (Pilotto et al. 2018).

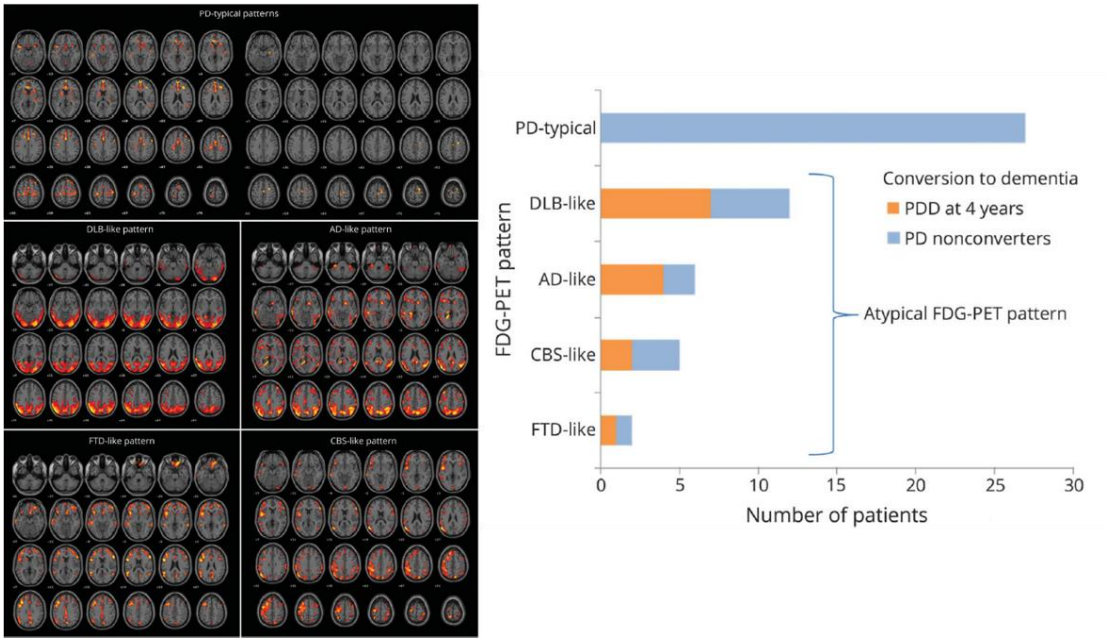

Figure 27. PD SPM single-subject hypometabolism patterns (Open Access Source).

The figure shows the five hypometabolism patterns described at the single-subject level by Pilotto and colleagues (on the left). On the right is reported the proportion of patients converted to dementia for each different FDG-PET pattern. Figures adapted from (Pilotto et al. 2018).

After four years of follow-up, PD patients with the "typical-PD" pattern remained stable in cognitive performance. Instead, 13 patients, each showing atypical [18F]FDG patterns, progressed to dementia. Specifically, DLB- and AD-like patterns were the best predicting biomarkers for progression to dementia, suggesting that posterior brain dysfunction was an early biomarker for dementia progression (i.e. PDD/DLB) (Pilotto et al. 2018).

DLB - DLB patients are characterized by hypometabolism affecting the temporo-parietal and occipital cortex (Caminiti et al. 2019) (Figure 28A). Of note, this typographical distribution is highly consistent also at the single-subject level (Figure 28B) (Caminiti et al. 2019).

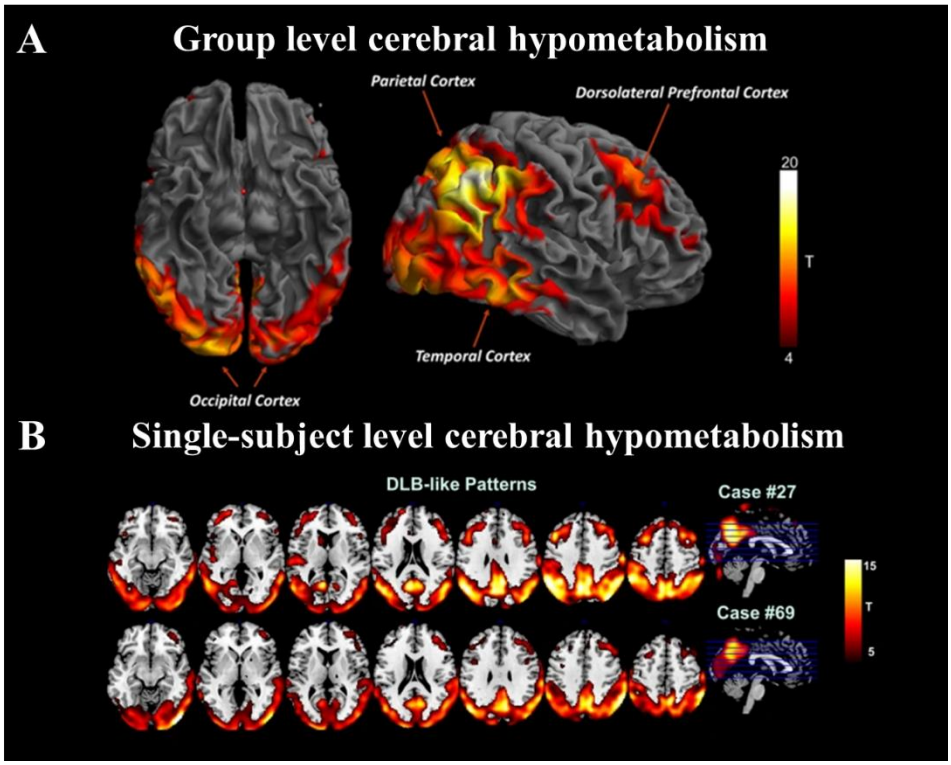

Figure 28. DLB hypometabolism pattern (Open Access Source).

The figure depicts the topographical distribution of hypometabolism in a cohort of DLB (A) and some single cases (B). The yellow/red colour bars represent the severity of hypometabolism. Figure adapted from (Caminiti et al. 2019).

The temporo-parietal hypometabolism has also been described in AD patients (Teune et al. 2010; Kantarci et al. 2012). However, the presence of occipital hypometabolism – occipital cortex and primary visual areas – is considered the metabolic hallmark of DLB (McKeith et al. 2017). Indeed, occipital hypometabolism had high accuracy (0.90) in distinguishing DLB from AD and PD (Figure 29). DLB differed from AD in the degree of metabolic decline in the hippocampus, where DLB shows less severe hypometabolism than AD.

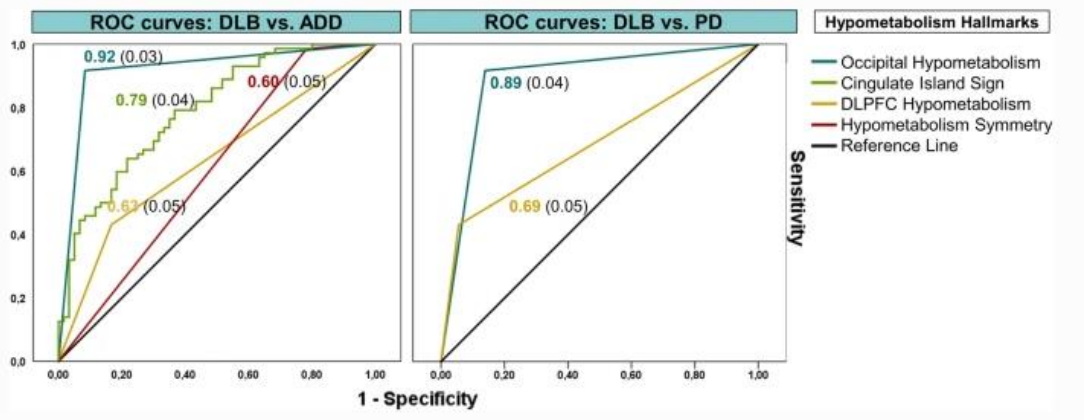

Figure 29. Hypometabolic hallmarks of DLB (Open Access Source).

The figure shows the accuracy of crucial hypometabolism hallmarks in DLB. Occipital hypometabolism (blue), cingulate sing island (green), dorsolateral prefrontal cortex (DLPFC) hypometabolism (yellow) and hypometabolism symmetry (dark red) were evaluated. Figure from (Caminiti et al. 2019)

PDD and DLB may show a comparable pattern of glucose hypometabolism. However, in a direct comparison between PDD and DLB, DLB patients show a more prominent hypometabolism in the anterior cingulate cortex (Yong et al. 2007). Klein and colleagues did not replicate these findings (Klein et al. 2010).

The pathological mechanisms underpinning the occipital metabolic impairment are still controversial (Teune et al. 2010). Neuropathological investigation revealed that LB and α-synuclein immunoreactivity are less frequent in the occipital areas than in other brain regions (Kasanuki et al. 2012). Thus, it has been hypothesized that the occipital hypometabolism associated with the DLB condition may represent a secondary metabolic defect, probably caused by degeneration of long projections innervating the occipital area (Kasanuki et al. 2012). Of note, following this hypothesis, the hypometabolism in the occipital cortex in DLB patients seems to be associated with the degeneration of the cholinergic neurotransmitter system (Marcone et al. 2012; Shimada et al. 2009; Klein et al. 2010).

MSA - Hypometabolism affecting the basal ganglia, putamen, pons and cerebellum characterizes MSA patients (Brajkovic, Kostic, Sobic-Saranovic, et al. 2017). Thus, the topographical distribution of hypometabolism involving putamen, brainstem or cerebellum is part of the diagnostic criteria for possible MSA (Gilman et al. 2008).

[18F]FDG-PET reveals specific hypometabolic features of MSA-P and MSA-C. Bilateral hypometabolism in the putamen occurs in MSA-P, and the hypometabolism in pons and cerebellum in the MSA-C (Caminiti et al. 2017; Zhao, Zhang, and Gao 2012) in line with the neuropathology feature of these MSA subtypes (Figure 30) (Ozawa et al. 2004).

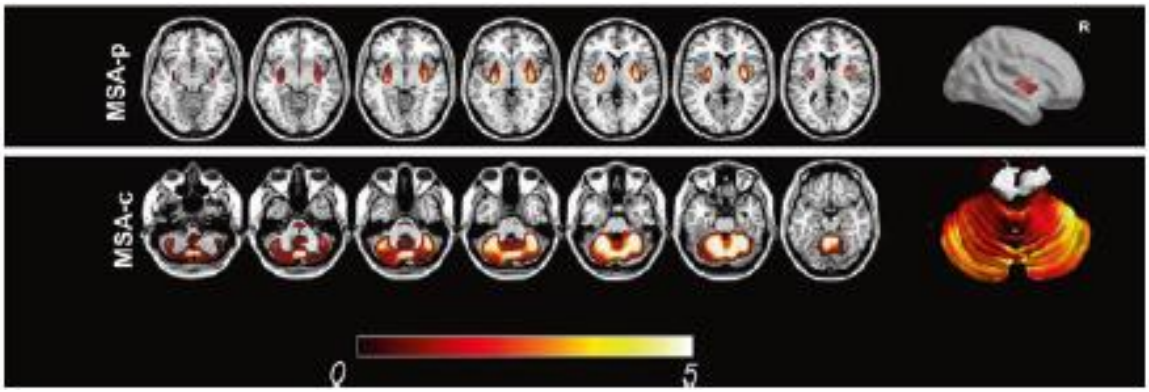

Figure 30. Brain hypometabolic patterns of clinical subtypes of MSA (Open Access Source).

The figure shows representative hypometabolism patterns at the single-subjects level in the case of MSA-P (top) and a casa of MSA-C (bottom). The red/yellow colour bar indicates values of T-scores, corrected for age and derived from the comparison between one patient and 112 HC, rendered on a high-resolution anatomical template Figure adapted from (Perani et al. 2020).

1.6.4.2. The multivariate approach of analyses

The SSM is a multivariate spatial covariance method based on the PCA approach (Eidelberg 2009). The SSM/PCA approach was developed for the first time by Moeller and colleagues for ROI data (Eidelberg et al. 1994; Moeller et al. 1987; Moeller and Strother 1991) and later extended to whole-brain voxel-wise analyses (Habeck et al. 2008; Ma et al. 2007a; Spetsieris and Eidelberg 2011; Eidelberg 2009). This method allows finding patterns that can distinguish different neurodegenerative conditions (Meles et al. 2021), providing biomarkers that differentiate between HC and disease groups (Spetsieris et al. 2013). Moreover, SSM/PCA procedure generates network-based scores correlating with clinical aspects of neurodegenerative conditions (Spetsieris et al. 2013).

In detail, SSM/PCA detects significant spatial covariance patterns from a dataset of images including patients and control scans (Spetsieris et al. 2009; Ma et al. 2007b; Habeck et al. 2008). This method produces a set of linearly independent principal

components (PCs) to detect spatial covariance patterns related to neurodegenerative disorders (Eidelberg 2009). There are several ways to establish which PCs constitute the final disease-related pattern (Spetsieris and Eidelberg 2011). PCs can be selected following the role of 50% of the total variance. In that case, the researcher should select all PCs that account for 50% of the total data variance, assuming that under 50% includes only noisy components (Meles et al. 2021). Another method is the Akaike Information Criterion (AIC). According to this approach, the optimal PCs' combination is one with the lowest AIC value of the model (Akaike 1974) (for a detailed explanation of SSM/PCA procedure see (Spetsieris et al. 2013)). If the pattern successfully differentiates between patients and controls, this pattern can be likely interpreted as disease-related (Meles et al. 2021).

Once the disease-specific pattern has been correctly identified, the pattern expression can be quantified in individual subjects (i.e. PC scalars or subjects scores). These subjects score for the pattern are z-transformed basing on the original set of images (patients and controls) (Eidelberg 2009).

SSM/PCA model has been extensively applied in parkinsonian's syndromes (Eckert et al., 2008; Ge et al., 2018; Ma et al., 2007; Meles et al., 2017; Niethammer et al., 2014) and also prodromal conditions (Wu et al. 2014; Meles et al. 2018). Notably, *postmortem* confirmations further corroborated the validity of this method in idiopathic PD, MSA and PSP patients (Tang et al. 2010). It has been demonstrated that PD patients accurately differed from those with other atypical parkinsonisms; the AUC for idiopathic PD was 0.97. MSA patients were accurately classified compared to those with non-MSA; the AUC for MSA was 0.95. PSP patients were also accurately classified compared to those with non-PSP; the AUC for PSP was 0.93 (Tang et al. 2010).

iRBD - A specific disease-related pattern has been described for iRBD patients: relative hypermetabolism in the cerebellum, brain stem, thalamus, sensorimotor cortex, hippocampus, and relative hypometabolism in the middle cingulate, temporal, occipital, and parietal cortices (Peralta et al. 2019). Specifically, the iRBD related pattern (RBDRP) has been identified in two different iRBD cohorts (Meles et al. 2018; Wu et al. 2014). However, Wu's and Meles' studies described quite different topographies (Meles et al. 2018; Wu et al. 2014) (Figure 31). In the first study, a more prominent hypometabolism

in the occipital cortex characterized iRBD (Wu et al. 2014) (Figure 31A). In contrast, the second one featured a more salient hypometabolism of the parietal cortex (Meles et al. 2018) (Figure 31C). The differences between these disease-related patterns may be due to the intrinsical heterogeneity of the iRBD condition, in which a variable proportion of patients will develop DLB, PD, or MSA at an unknown interval time (Ferini-Strambi et al. 2019).

In both studies, the authors also compared the spatial topography of RBDRP and PD related pattern (PDRP). RBDRP and PDRP showed a good overlap (Figure 31B and 31D), even if PDRP presented more widespread metabolic alterations than RBDRP (Meles et al. 2018; Wu et al. 2014). These findings suggest that RBDRP could be the early manifestation of PDRP. In addition, Meles and colleagues evaluated the RBDRP in PD patients with and without cognitive impairment (Meles et al. 2018). They found that PD patients with MCI showed a higher expression of RBDRP than those with normal cognition.

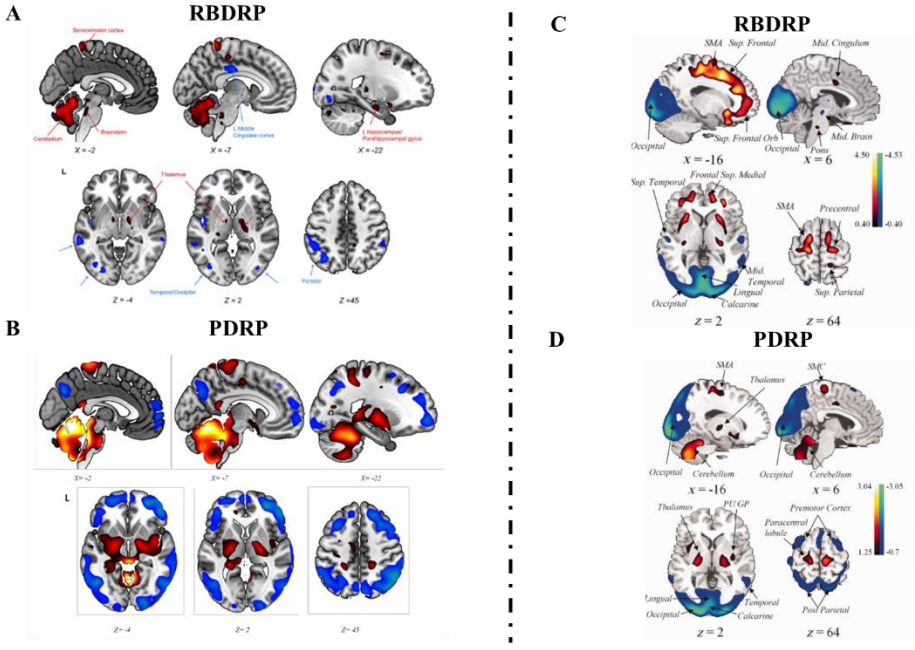

Figure 31. RBDRP in two different cohorts of patients (Open Access Source).

The figure represents the RBDRP identified in two different cohorts of iRBD patients (A and C). In both cases, RBDRP show similarities with relative PDRP (B and D), suggesting that RBDRP is the early manifestation of PDRP. Figure adapted from (Wu et al. 2014; Meles et al. 2018).

The PDRP expression was also evaluated in iRBD patients. iRBD manifests abnormal PDRP expression changes (Holtbernd et al. 2014; Arnaldi et al. 2019); specifically, higher baseline expression was associated with a greater likelihood of developing PD or DLB. A recent longitudinal study evaluates the PDRP expression in 20 iRBD subjects (Kogan et al. 2020). The patients underwent two [18F]FDG-PET scans, one at baseline and another after 3.7 years. At baseline, 20% of iRBD expressed PDRP, four of whom photoconverted clinically toward PD. Moreover, PDRP pattern expression increased in all subjects from the first to the second scan. This study suggests that significant PDRP expression and a high score rate of change may be associated with a short-term risk for phenoconversion.

PD - A disease-specific pattern for PD, also known as PDRP, was first identified by Eidelberg and colleagues (Eidelberg et al., 1994; Ma et al., 2007). It is characterized by relative hypermetabolism in the globus pallidus and putamen, thalamus, cerebellum, pons, and sensorimotor cortex, associated with relative hypometabolism in the lateral frontal and parieto-occipital areas (Meles, Teune, et al. 2017). It has also been validated in multiple independent populations (Meles et al. 2020; Teune et al. 2013; Wu et al. 2013; Niethammer and Eidelberg 2012). However, a crucial study with *postmortem* confirmation described a PDRP consisting of restricted hypermetabolism in globus pallidus, thalamus, cerebellum, and pons, completed by relatively decreased metabolism in the premotor cortex, supplementary motor area, and parietal association regions (Figure 32) (Tang et al. 2010).

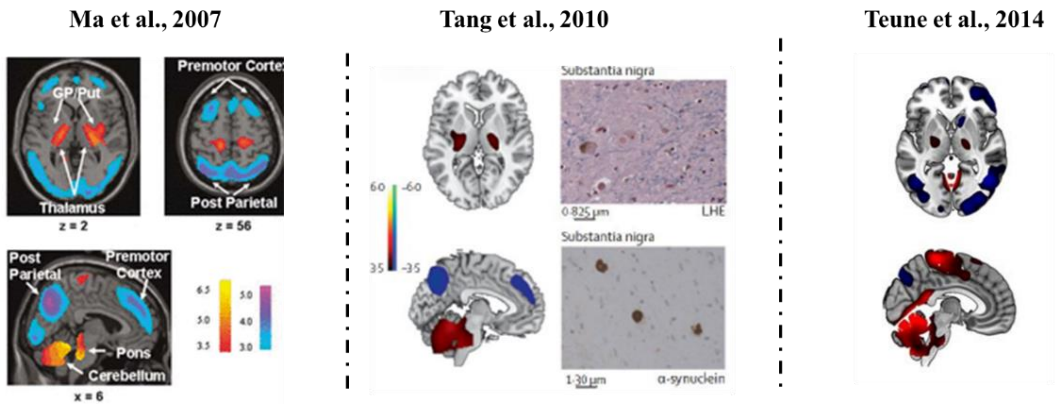

Figure 32. Example of PDRP in different cohorts of patients (Open Access Source).

The figure represents examples of PDRP described by previous literature. Of note, the study with postmortem confirmation (middle panel) described a more limited PDRP consisting of restricted hypermetabolism in globus pallidus, thalamus, cerebellum, and pons, completed by relatively decreased metabolism in the premotor cortex, supplementary motor area, and parietal association regions. Figure adapted from (Huang et al. 2007; Tang et al. 2010; Teune et al. 2014).

Generally, PDRP expression can precede the onset of motor symptoms by several years in prodromal patients (Holtbernd et al. 2014; Tang, Poston, Dhawan, et al. 2010; Meles, Teune, et al. 2017). Furthermore, it can increase with disease progression (Huang et al. 2007; Kogan et al. 2020) and decrease with an efficient treatment for PD symptomatology (Rodriguez-Rojas et al. 2020).

MSA - MSA-related pattern (MSARP) is characterized by hypometabolism in putamen and cerebellum (Poston et al. 2012; Eckert et al. 2008), defined in an MSA cohort with relative *postmortem* confirmation (Figure 33) (Tang et al. 2010).

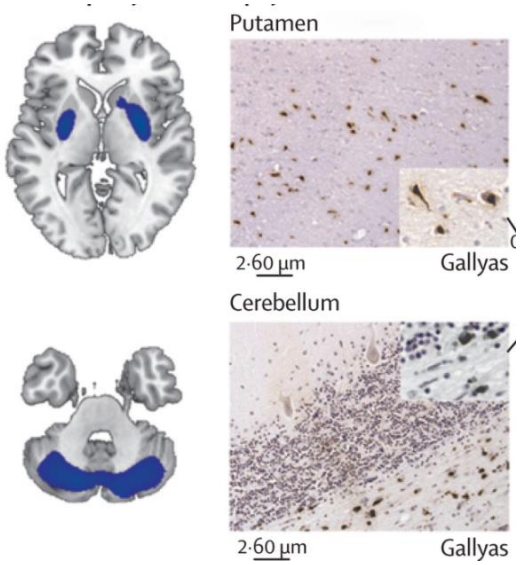

Figure 33. MSARP and postmortem data (Open Access Source).

The figure shows MSARP, which is composed of hypometabolism in the putamen and cerebellum bilaterally. The neuropathological confirmation is on the right side. Figures adapted from (Tang et al. 2010).

A study with 33 MSA patients and 20 idiopathic PD patients demonstrated that MSARP – not PDRP expression – correlates with disease severity and duration in MSA (Poston et al. 2012). In the same study, two MSA patients with longitudinal imaging

acquisition after seven years showed progressive increases in MSARP expression, whereas their PDRP expression ranged within the normal range (Poston et al. 2012). Moreover, patients with MSA-C and MSA-P reported some differences in regional metabolism, but MSARP expression was substantially similar (Poston et al. 2012).

For the sake of completeness regarding parkinsonian syndromes, it should be underlined that PSP-related patterns (PSPRP) and CBD-related patterns (CBDRP) have been detected (Eckert et al. 2008; Ge et al. 2018; Niethammer et al. 2014). Even for PSPRP, the disease-related pattern has been validated in a cohort of patients with *postmortem* confirmation (Tang et al., 2010). Unfortunately, there is a lack of study regarding DLB condition.

1.7. Biological and environmental factors influencing neurodegenerative clinical trajectories

Considerable phenotypic variability characterizes α-synucleinopathy syndromes (Halliday et al. 2011). In general, the clinical phenotypes of the neurodegenerative condition depend on fixed (e.g., genotype and gender) and flexible (e.g., education, occupation and leisure activity) factors. These notions complement the brain (BR) and cognitive reserve (CR) concept, whereby education, occupation, and lifestyle – as well as inherited factors – may contribute to differences in brain structure and function (Barulli and Stern 2013). These differences modulate the resistance and resilience (coping) against neurodegenerative damages (Montine et al. 2019). In addition, mounting evidence supports sex and gender-associated differences in the risk of different proteinopathies and their clinical manifestations (Mazure and Swendsen 2016; Cerri et al. 2019; Meoni et al. 2020). Gender represents, therefore, an essential epidemiological variable that could influence the clinical expression of neurodegenerative diseases.

Studies regarding the modulation of BR, CR and gender of neurodegenerative processes related to α-synuclein pathology are growing. This section describes the most relevant findings, defining the importance of considering how biological and environmental factors influence neurodegenerative clinical trajectories.

1.7.1. Cognitive and brain reserve

The concept of "reserve" explains differences between subjects in susceptibility to age- and pathology-related brain changes (Stern 2012). Specifically, the reserve seems to protect against pathological cognitive decline, as in the case of neurodegenerative diseases (Barulli and Stern 2013). Individuals with a high reserve have greater neural resources, requiring more pathology burden to reach the critical threshold needed to clinical manifest ongoing pathological mechanisms (delay in the onset of clinical symptoms) (Hall et al. 2007; Stern et al. 1999). However, after reaching the threshold, the decline is fast (Hall et al. 2007; Stern et al. 1999). The rapid worsening of the clinical picture may be due to a high level of accumulated pathology (Figure 34).

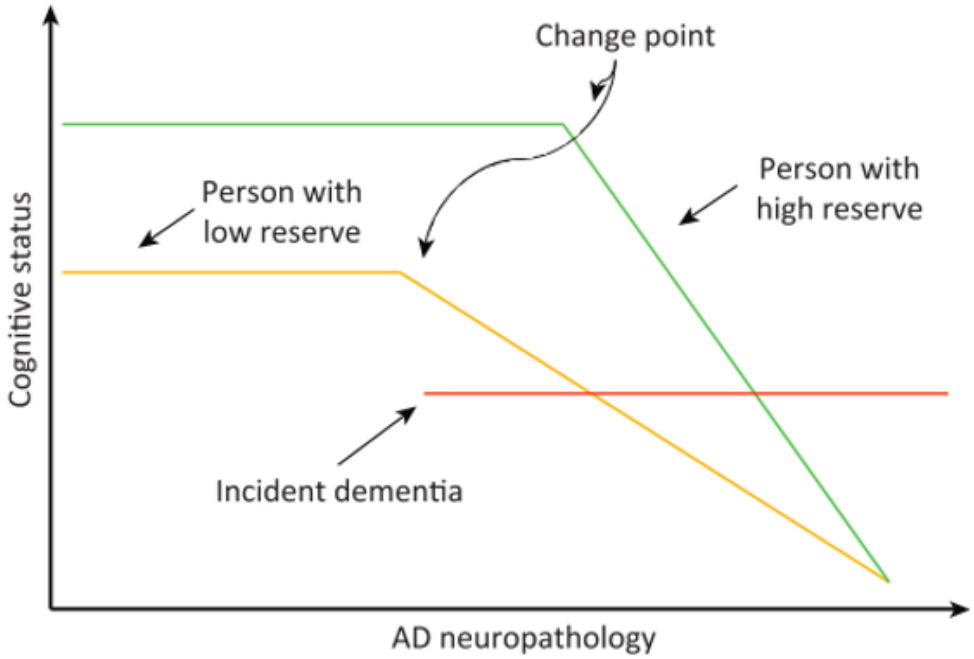

Figure 34. Reserve model in neurodegenerative diseases (Open Access Source).

The figure depicts the mediating action of the reserve on the relationship between AD pathology and its phenotypical manifestation. Figure from (Barulli and Stern 2013).

This reserve capacity might reflect the resilience and plasticity of cognitive brain networks that protect individuals from the adverse effects of ageing and pathology.

According to the classical theoretical framework, two types of reserves can contribute independently and interactively to preserve brain functioning: BR and CR (Stern 2009).

The original concept of BR was quantitative and with an innate definition, namely brain size, the number of neurons or synapses available among individuals. Expressly, the BR hypothesis assumes that people's differential susceptibility to brain damage or pathology is a function of a purely quantitative measure of BR capacity; when the disease reduces the BR capacity beyond a certain threshold, the functional decline happens (Satz et al. 2011). This mechanism may explain how a relatively similar amount of pathology underlies people with different cognitive performances (Stern 2002). Although BR is born as an innate feature, increasing evidence demonstrates that environmental factors can modulate the BR capacity by determining neurogenesis, upregulation of the brain-derived neurotrophic factor, and consequently, neural plasticity (Brown et al. 2003; Van Praag et al. 1999).

CR represents the resilience (i.e., efficiency, capacity, flexibility) of cognitive processes that help to clarify the differential vulnerability of different subjects to brain ageing, pathology, or insult (Stern et al. 2020). Epidemiological data showed that CR has a role in the incidence of dementia. The current model of CR in neurodegenerative condition states that subjects with a higher level of education, occupational attainment (Stern et al. 1994) and leisure activities (Crowe et al. 2003; Friedland et al. 2001; Scarmeas et al. 2001) show a decreased risk to develop a specific neurodegenerative disease.

The CR proxies include the intelligence quotient (IQ) (Alexander et al. 1997), education (Stern et al. 1992), literacy (Manly et al. 2005), professional realization (Staff et al. 2004), commitment to leisure time activities (Wilson et al. 2002) and the integrity of social relations (Bennett et al. 2006). Personality variables are also important; for instance, distress proneness and neuroticism were associated with increased risk of dementia (Wilson et al. 2006). It has been demonstrated that also bilingualism acts as a proxy of CR (Perani et al. 2017; Perani and Abutalebi 2015).

Many of these CR variables are inter-related and give independent but synergistic contributions, which accumulate throughout life. Thus, different life-long experiences seem to contribute differently to the modulation of brain functioning by promoting neural plasticity (Cotman et al. 2002; Gaser and Schlaug 2003) and developing new cognitive

strategies (Lövdén et al. 2013). Thus, different proxies of CR contribute independently to BR. In particular, BR represents the neural substrate of CR, including all neural mechanisms that allow brain plasticity and adaptability. Therefore, disentangle these two concepts (CR and BR) is challenging. In conclusion, CR and BR influence each other, and they are interconnected, providing concomitant contributions to explain individual differences in clinical resistance to pathological brain processes (Barulli and Stern 2013).

The concept of brain maintenance (BM) – i.e. the brain is modifiable based on experience – was born to overcome the discrepancy between life experience (CR) and its neurobiological correlates (BR). This means that both genetics and lifestyle can impact BM (Stern et al. 2020). Despite BR and BM being related concepts, it remains unclear whether they can be considered the same construct viewed at the marco- and microscale levels, respectively. Indeed, BM reflects the overall maintaining brain process against the ageing or pathology, whereas BR is the specific brain meachinism (e.g. neural reserve or compensation) acting in a time point.

iRBD - Although studies on reserve are particularly significant in the preclinical stage of neurodegenerative diseases, there is no evidence regarding CR and BR in iRBD. Recently, a cross-sectional study evaluated the possible moderating action of education in subjects diagnosed with probable RBD (questionary based diagnosis). The authors demonstrated that a high level of education delays the onset of cognitive and motor decline in these patients (Chen et al. 2020).

PD - The interest in studying CR, BR and PD is growing, and most studies focus on cognition. There is a general agreement regarding the protective action of education – a proxy of CR – on the cognitive functioning of PD. Specifically, cross-sectional studies consistently demonstrate that higher education is associated with better neuropsychological performance in global cognitive functioning, attention, executive, memory and visuospatial functions (Hindle, Martyr, and Clare 2014). The importance of education on executive functions is a crucial topic since an impairment of executive function strongly affects daily living activity and thus the quality of life in PD (Foster and Hershey 2011; Bronnick et al. 2006). Of note, PD patients with higher CR show more preserved executive function, resulting in a better quality of life (Cubo et al. 2002).

Regarding the association between education and the rate of cognitive decline or dementia diagnosis, the results are more controversial (Hindle, Martyr, and Clare 2014). Poletti and colleagues showed that higher levels of education protect against cognitive decline in PD (Poletti, Emre, and Bonuccelli 2011). From a neuropathological standpoint, education may protect PD patients against cognitive worsening since education moderate the relationship between β-amyloid deposition and cognition (Lucero et al. 2015). However, longitudinal studies showed that CR modulates performance on cognitive tests but has a limited effect on PD-related cognitive decline and dementia risk (Hindle et al. 2016; Lee et al. 2019). A recent longitudinal study demonstrates that higher education is associated with better baseline cognitive performance and delayed incidence of Hoehn and Yahr scale > 3 (Lee et al. 2019). Still, education did not show an association with the rate of cognitive decline.

Fewer studies focused on evaluating CR proxies on motor functions in PD, the majority of which with a cross-sectional experimental design. PD patients with high education showed better performance in balance assessment (de Oliveira Souza et al. 2013) and less severity of motor impairments as measured by UPDRS-III (Kotagal et al. 2015; Sunwoo et al. 2016); the same association emerged in those patients with advanced PD having the deep brain stimulation (Blume et al. 2017). The longitudinal approach supports these data, describing that the more educated patients had better baseline motor performances, but they worsened at the same rate as less educated patients. Moreover, the patients with higher educational levels needed more time to reach the most severe clinical stages as measured by Hoehn and Yahr scale (Lee et al. 2019).

DLB - There is a paucity of studies investigating the CR and BR in DLB, focused just on education as a proxy of CR (Perneczky et al. 2007; 2009; 2008; Lamotte et al. 2016). Perneckzy and collaborators published three studies to address the role of education as a proxy for CR in the LB spectrum, using [18F]FDG-PET to measure BR. In 2007 the authors started to investigate education in a cohort of DLB patients (Perneczky et al. 2007). They found an inverse association between years of education and glucose metabolism in the left temporo-parieto-occipital cortex. One year later, the same group explored the association between the regional hypometabolism and activities of daily living (ADL) scores in a sample composed of DLB, PDD and PD stratified

according to levels of education. They found an inverse association between hypometabolism and ADL in the prefrontal, temporoparietal, and occipital association cortices and the precuneus (Perneczky et al. 2008). The association in the right middle occipital gyrus was more robust in the low-educated group than the high-educated group. In 2009 the authors applied a similar approach to 21 DLB patients (Perneczky et al. 2009). They found a significant association between hypometabolism and impaired ADL performance in the right temporoparietal cortex. Highly educated DLB patients showed a more severe hypometabolism in the right middle occipital gyrus (BA 19) than DLB patients with low education. Of note, this last finding exposed a quite different topography distribution compared to the first study (Perneczky et al. 2007), suggesting the necessity of further investigation to explain the beneficial role of education in DLB. The most recent study demonstrated that high-educated DLB patients showed higher DAT binding in the striatum, suggesting that education modulates the degeneration of the nigrostriatal dopaminergic pathway (Lamotte et al. 2016).

All the above demonstrates a protective role of education in the α-synuclein spectrum, supporting that CR is a general phenomenon not depending on the underlying neuropathology. However, there is still a strong urgency to explore the role of CR and BR in preclinical stages – iRBD – and rare clinical entities – MSA. Of note, contrary to the AD spectrum (Garibotto et al. 2008; 2012), no study investigated the effect of specific CR proxies on the BR in α-synucleinopathies, measuring the occupational aspect of patients' lives. More importantly, besides the general occupation levels, specific skills involved in the different jobs can better define the influence on brain function (Dodich et al. 2018; Spreng et al. 2010).

1.7.2. Sex and gender-related differences

Sex and gender differences are considered essential factors for the population susceptibility to a specific neurodegenerative disorder (Podcasy and Epperson 2016) (Figure 35). Sex-determining genes and fetal hormonal programming are the primary mechanisms that generate sex divergence in brain structure and function, thus showing a significant involvement in brain-based disease risk (Picillo et al. 2017). Sex-specific genetic and hormonal factors contribute to biological differences in the expression of

neurodegenerative diseases, including α-synucleinopathies (Picillo et al. 2017). In addition, several cultural factors associated with gender differences (e.g. role expectations and social attitudes) may play a role in the risk, progression and prognosis of neurodegenerative diseases (Bellou et al. 2016).

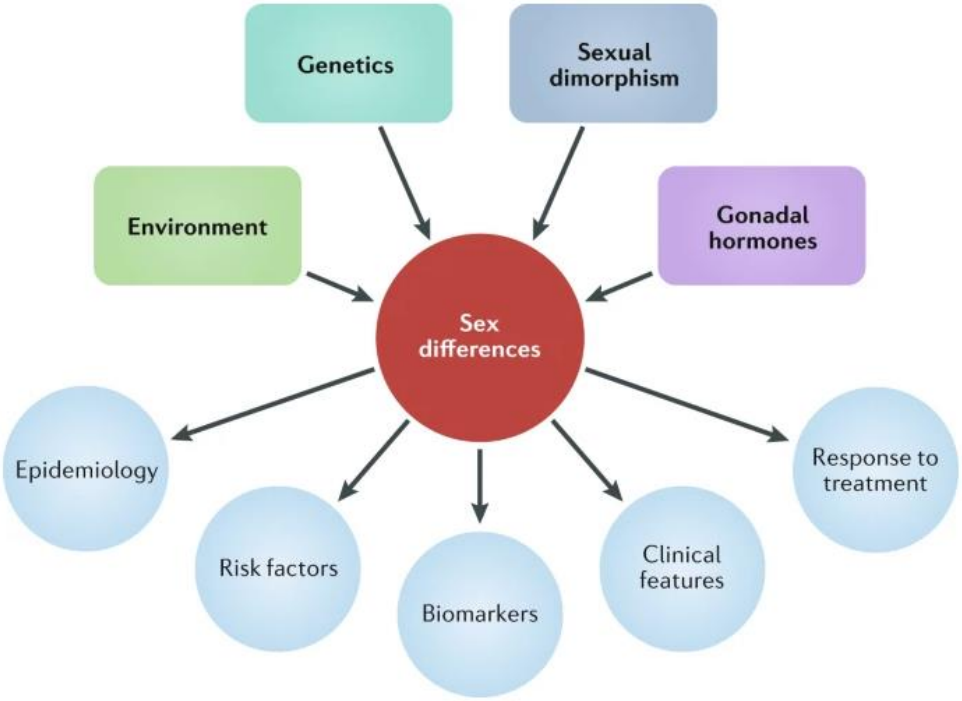

Figure 35. Interacting factors in gender and sex differences (Open Access Source).

Different biological and environmental factors contribute to sex and gender differences in neurodegenerative disease features. Figure from (Meoni et al. 2020).

Concerning the α-synuclein-related pathology, gender differences are described since the early preclinical stage, namely iRBD subjects that show a male predominance. Several studies in PD and DLB provided evidence of links between sex or gender and risk for diagnosis, clinical manifestation or mortality (Cerri et al. 2019; Meoni et al. 2020; Podcasy and Epperson 2016). Although the paucity of studies regarding MSA patients, gender difference also modulates cognitive and behavioural presentations in this condition (Cuoco et al. 2020). This section discusses gender in the α-synuclein clinical spectrum and its clinical and research implications.

iRBD - The high prevalence of males among iRBD patients has always been a typical epidemiological feature of this preclinical condition (90% of males) (Postuma et al. 2009; Iranzo et al. 2005). However, increasing evidence is challenging this assumption

(Haba-Rubio et al. 2018; Yo El Ju et al. 2009; Schenck et al. 1993; Sforza et al. 1997). It seems more probable that women with iRBD remain underdiagnosed for two main reasons: i) females manifest less aggressive and violent REM sleep behaviours and ii) decreased PSG sensitivity in detecting woman iRBD (Bodkin 2019). It has been hypothesised that estrogens may have a role in these phenotypical differences. Estradiol seems to modulate some neurotransmission systems: serotonin, NE and DA (McEwen and Alves 1999). Specifically, higher estrogen levels seem to be associated with low NE transmission, leading to reduced phasic REM activity (Schwarz et al. 2008). Of note, women in the healthy population showed fewer legs' phasic muscle activity and shorter duration of movements than men (Stefani et al. 2015; McCarter et al. 2014). The above mentioned evidence explain why video-PSG can be less sensitive in women, significantly when arms EMG electrodes are not considered.

The ratio of women in recent studies is growing, suggesting a greater awareness of women with RBD (Bodkin 2019). Recognize both males and females iRBD is crucial since there are no gender differences in the risk of developing a neurodegenerative disease (Postuma et al. 2009).

PD - The risk of developing PD is twice in males than females (Baldereschi et al. 2000; Solla et al. 2012). Male sex is also associated with an increased mortality rate in PD (De Lau et al. 2014; Pinter et al. 2015; J. Xu et al. 2014). Indeed, the factors usually predicting higher mortality in PD, like cognitive impairment, higher postural instability and gait disorders, are much more common in men than women (De Lau et al. 2014; Pinter et al. 2015; J. Xu et al. 2014). The motor symptoms of PD tend to emerge later in women than in males (Cerri et al. 2019). A higher baseline striatal dopaminergic activity explains this connection due to a possible protective effect of estrogens (Meoni et al. 2020; Cerri et al. 2019; Haaxma et al. 2007). Estradiol has suppressive effects on DAT, leading to a higher amount of striatal DA availability (Gillies and McArthur 2010). Thus, the development of symptomatic PD is delayed in women by higher physiological DA levels on the striatum due to the activity of estrogens. The estradiol-induced neuroprotection might be an adaptive response in surviving neurons, restoring striatal dopaminergic functionality until 60% of neurons die (Gillies and McArthur 2010).

A more benign PD phenotype generally characterizes PD females, with later disease onset and milder motor symptoms at onset than men (Haaxma et al. 2007; Cerri et al. 2019). Accordingly, women more frequently manifest the benign tremor dominant PD subtype (67% vs 48%), associated with less severe motor deterioration and a slower disease progression (Reekes et al. 2020; Haaxma et al. 2007). As for cognitive deterioration, PD males show more severe executive and processing speed impairments than females, suggesting a vulnerability to cognitive decline (Reekes et al. 2020). A study in autopsy-confirmed PD found that the diffuse malignant phenotype is more frequent in men than women (De Pablo-Fernández et al. 2019). On the other hand, mood symptoms, such as sadness, anxiety, lack of motivation and depression, are more frequent and severe in PD women than men (Meoni et al. 2020). The mechanism underlying these differences might resid in the possible diverse gender vulnerability of neurotransmitters circuits responsible for psychiatric manifestation, such as the dopaminergic mesolimbic system (Castrioto et al. 2016; Gustafsson, Nordström, and Nordström 2015). Still, there is a lack of studies on gender differences in DAT binding in the mesolimbic dopaminergic system.

DLB - Some data demonstrate a lower prevalence of DLB in women than in men (Kane et al. 2018; Podcasy and Epperson 2016) although a few report the opposite (Mouton et al. 2018; Price et al. 2017). Autoptic data reveal a close relationship between male gender and risk for dying with cortical DLB pathology (Nelson, Schmitt, et al. 2010). Males have a higher risk for neocortical LB, and this effect seems not to be related to confounding factors such as the age of death, education, smoking status, or ApoE alleles (Nelson, Schmitt, et al. 2010). Of note, other *postmortem* results showed that men more frequently died from "pure" DLB pathology than women, and women more often expressed mixed pathology (DLB + AD) (Nelson, Jicha, et al. 2010; Barnes, Lamar, and Schneider 2019; Van De Beek et al. 2020). Women show a more severe disease course in DLB than men (Van De Beek et al. 2020), with more frequent visual hallucinations and severe cognitive impairments. Depression or anxiety conditions are more common among women than men (Boot et al. 2013).

A recent study on patients with DLB diagnosis and *postmortem* confirmation has failed to confirm the higher occurrence of visual hallucination in women than males (Bayram et al. 2021). In this study, DLB females died later, had a higher Tau burden, and

less frequent manifested the core clinical features of DLB. Thus, the authors suggest that although women and men show similar underlying LB pathology, the first manifest less frequently core DLB features, thus remaining clinically underdiagnosed.

MSA - Very few data are available regarding gender differences in MSA patients. Only a recent longitudinal study evaluated the gender effects on 55 patients with MSA (Cuoco et al. 2020). At baseline, women patients with MSA showed lower global cognitive status, poorer visuospatial abilities and higher depression and anxiety than males. Females worsen more over time in motor function and attention deficits than males.

2. Aim of the work

This thesis investigates the neurobiological mechanisms and cognitive features of PD patients with a severe clinical phenotype – developing cognitive deterioration, reaching dementia condition – since the preclinical phases. Specifically, the studies address neurobiological mechanisms with multiple methodological approaches to neuroimaging data and the cognitive picture throughout cross-sectional and longitudinal experimental designs. Works investigate three fields: 1) Biomarkers and neurobiological substrates of LB related neurodegeneration (Part 1); 2) Clinical and cognitive features in different LB disease stages (Part 2); 3) Biological, gender and environmental sources of phenotypic variability of LB disorders (Part 3).

Part 1. This section includes studies focusing on the PET imaging of brain metabolism and presynaptic dopaminergic activity and their relationships with clinical manifestations and prognosis. Studies Ia and II evaluate the neurobiological changes (through [18F]FDG-PET) in iRBD to identify similarities and differences with PD and DLB. Study IIIa investigates neurodegenerative processes in iRBD, combining PSG measures and multivariate [18F]FDG-PET analytical approach. Study IVa assesses the integrity of brain striatal and extra-striatal pathways in PD patients bearing heterozygous GBA mutations (i.e. GBA-PD), compared with a group of iPD stratified by age at disease onset (i.e. early and late-onset iPD).

Part 2. This section focuses on clinical and cognitive features characterizing LB disorders. Studies Ib and IIIb allow identifying cognitive impairments occurring since the prodromal stage of LB disorders. Study IVb describes the clinical and cognitive progression of GBA-PD patients compared to early and late-onset iPD. Study V addresses the neural substrate of visuoconstructive deficits in DLB as a crucial cognitive signature characterizing the neuropsychological profile of dementia in LB disorders.

Part 3. This part assesses the biological, environmental and gender sources of phenotypical variability in PD and DLB patients. Studies VI and VII discuss gender differences in endophenotypes (as measured by [18F]FDG-PET and [123I]FP-CIT-SPECT) and clinical manifestations in PD patients with stable disease progression (Study

VI) and PD with different clinical subtypes (Study VII). Study VIII evaluates the effects of CR and BR on the LB neurodegeneration process in DLB patients.

3. Results

3.1. Part 1. Biomarkers and neurobiological substrates of LB related neurodegeneration

3.1.1. Study Ia: In-vivo signatures of neurodegeneration in isolated rapid eye movement sleep behaviour disorder. (Carli et al. 2020) - ***Published article*** -

iRBD is considered the preclinical stage of α-synucleinopathies (PD, PDD/DLB and MSA) (Högl et al. 2018). More than 90% of iRBD subjects convert to overt α-synucleinopathy after 15 years of disease duration (Galbiati et al. 2019). 30-50% of PD patients, 75% of DLB and 100% of MSA present RBD in their clinical history (Högl et al. 2018). It is increasingly accepted that iRBD marks a specific malignant PD subtype, rapidly progressing toward dementia (Fereshtehnejad et al. 2015). Identifying biomarkers to detect the ongoing pathology and predict the risk of progression to specific α-synucleinopathy is an urgent issue in the iRBD research framework.

[18F]FDG-PET is an excellent candidate for detecting synaptic dysfunction, as it detects significant brain hypometabolism patterns from the earliest disease phase when neuronal death has not yet occurred (Iaccarino, Sala, et al. 2017; Perani et al. 2020). Only a few studies have explored hypometabolism brain features in iRBD (Meles et al. 2018; Ge et al. 2018; Liguori et al. 2019; Wu et al. 2014). These studies used group-level statistical approaches to determine the topographical distribution of hypometabolism, providing heterogeneous results (See *1.6.4. [18F]FDG-PET imaging*). Group-level approaches might yield limited utility in iRBD that is an intrinsically heterogeneous condition. The SPM single-subject procedure can overcome this issue by identifying specific hypometabolism patterns at the individual level (Perani et al. 2014). The SPM single-subject procedure showed high accuracy in discriminating different forms of dementia and atypical parkinsonian conditions and in the prodromal phases, thus predicting the risk of progression (Caminiti et al. 2019; Pilotto et al. 2018; Cerami et al. 2017; Caminiti et al. 2017; Caminiti et al. 2018; Iaccarino, Chiotis, et al. 2017) (see *1.6.4.1. The univariate approach of analyses*).

In this study, we applied [18F]FDG-PET SPM single-subject approach to assess the ongoing neurodegenerative processes in 37 PSG confirmed iRBD patients in terms of the presence and topography of the brain hypometabolism. Moreover, we aimed to verify whether iRBD neurodegeneration processes resemble PD patients with stable disease progression, DLB patients or both. Thus, we also compared hypometabolism of iRBD patients with brain hypometabolism of well-defined PD and DLB cohorts to evaluate similarities and differences. *In-vivo* biomarker evidence of neurodegeneration from the iRBD phase would provide crucial information on the temporal sequence of ongoing pathology, which would be helpful in monitoring and predicting disease progression in synucleinopathies. This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital (Milan), collaborating with the Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Italy. The present study and relative datasets were already published in the European Journal of Neurology on 14th March 2020 (https://doi.org/10.1111/ene.14215).

We included 37 iRBD subjects, 29 PD patients without cognitive impairment (age [mean ± standard deviation (SD)], 62.68 ± 10.83 years; disease duration [mean ± SD], 4.25 ± 2.59 years) and 30 DLB (age [mean ± SD], 74.00 ± 6.62 years; disease duration [mean ± SD], 2.47 ± 2.63 years) (See *5.1. Participant underwent [18F]FDG-PET exam*). All iRBD patients showed an absence of parkinsonian symptoms (normal scores at UPDRS-III). In Table 1 are reported demographic, clinical, and PSG features of iRBD subjects; for neuropsychological results, see Part 2 Study Ib.

As regard hypometabolic features, the commonality analysis revealed a common hypometabolic pattern in iRBD patients encompassing the occipital cortex (calcarine cortex bilaterally) (Figure 36-IA). The single-subject level SPM procedure identified heterogeneous hypometabolism patterns (Figure 36-IB). Five iRBD cases had selective occipital hypometabolism, 13 occipitoparietal hypometabolism, 13 occipital and cerebellar hypometabolism and 1 case selective cerebellar hypometabolism. Notably, the patient with selective cerebellar hypometabolism was the only one with pathological scores in the Scale for Outcomes for Parkinson's Disease—autonomic function (SCOPA-AUT) questionnaire (score 26). Five iRBD cases did not show brain hypometabolism (normal [18F]FDG-PET scans). We also found 19 hypometabolic hallmarks that were present in most iRBD subjects (Figure 36-II). The left (Hypometabolism, 94.6%; k>100,

72.9%) and right (Hypometabolism, 83.78%; k>100, 70.3%) calcarine cortex and right lingual gyrus (Hypometabolism, 89.19%; k>100, 70.3%) were the most frequently affected regions.

Table 1. Demographic, clinical and PSG data in iRBD.

	Cut-off	**All iRBD (Mean±SD)**
Number of subjects		37
Gender	-	32(M)/5(F)
Age in years	-	69.31±6.49
Education in years	-	11.14±4.65
Disease duration years	-	5.35±3.19
MMSE corrected score	23.8	27.84±2.13
SCOPA-AUT	8.8±5.4	7.75±6.21
UPDRS III	-	0.57±1.21
TST (min)	-	371.17±60.41
SL (min)	-	29.36±25.30
WASO (min)	-	61.58±34.87
SE (%)	-	79.70±11.02
NAWK (N°)	-	14.02±7.63
N1 (%)	-	11.65±3.98
N2 (%)	-	50.84±7.13
SWS (%)	-	18.41±8.71
REM (%)	-	21.01±7.41
LREM (min)	-	89.30±50.56

iRBD: isolated REM behaviour disorder; SD: standard deviation; MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; TST: Total sleep time; SL: Sleep latency; WASO: wake after sleep onset; SE: Sleep efficiency; NAWK: numbers of awakenings; N1: sleep stage 1; N2: sleep stage 2; N3: Slow Wave Sleep; REM: rapid eye movement; LREM: REM sleep latency.

Then, we evaluated hypometabolism differences and similarities among iRBD, PD and DLB. We found that subjects with iRBD and DLB shared the same occipital hypometabolism signature, encompassing the calcarine cortex, middle and inferior occipital gyrus bilaterally (Figure 36-III). Patients with DLB showed a widespread brain hypometabolism pattern at the group level, reaching parietal regions compared with

subjects with iRBD (Figure 36-IIIc). iRBD and PD patients did not show any overlapping regional hypometabolism (Figure 36-IIIa). Consistently, iRBD showed significantly reduced metabolism in the occipital regions compared to PD (Figure 36-IIIc). DLB and PD groups did not show any overlapping regional hypometabolism, and the DLB group showed statistically significantly reduced metabolism in the occipito-parietal regions compared to the PD group (Figure 36-IIIa and c).

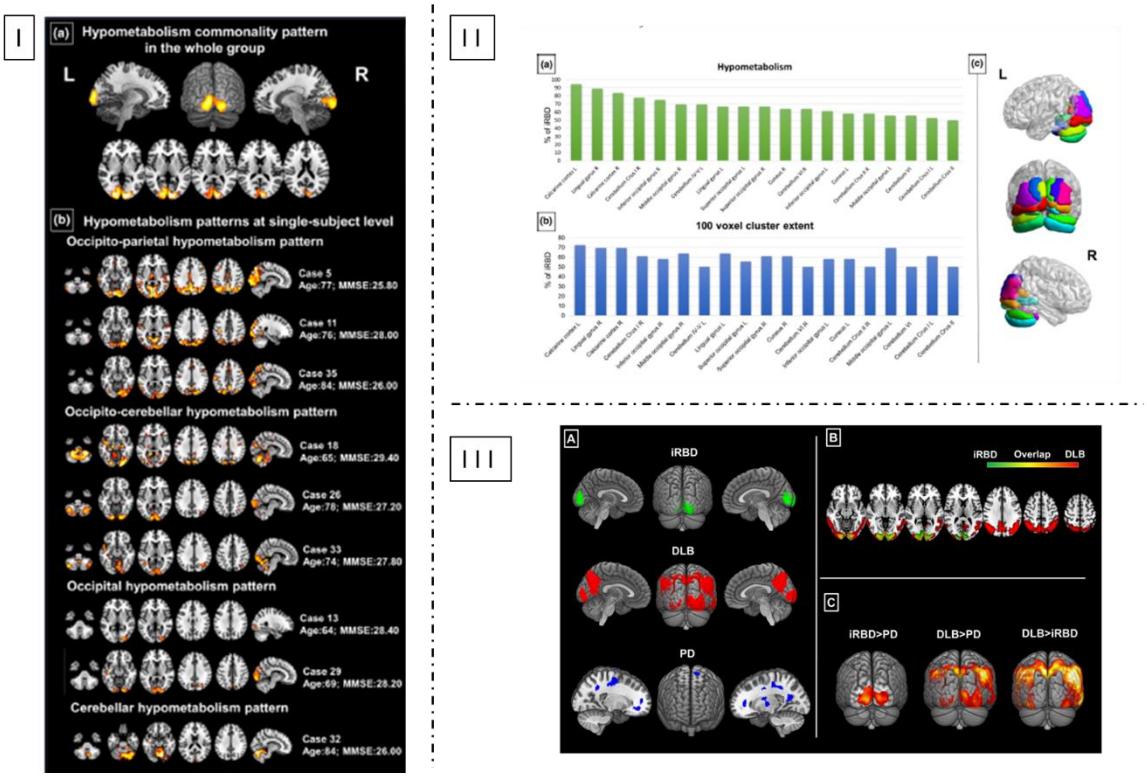

Figure 36. Hypometabolic features of iRBD, PD and DLB (Fair use).

On the left (I) is depicted the hypometabolic commonality pattern at group-level (a) and examples of single-subjects hypometabolism patterns. On the right are reported the hypometabolic hallmarks of iRBD (top-II) and comparison among iRBD, PD and DLB (Bottom-III). Specifically, hypometabolic hallmarks (II) were obtained considering percentages of iRBD with (a) hypometabolism values and (b) >100 voxels of cluster extent. (c) Graphical brain representation of hypometabolic hallmarks. Section III on the right shows brain hypometabolism patterns at group level in iRBD, DLB and PD cohorts (a). The similarities (b) and differences (c) were also represented. Abbreviations: L, left; MMSE, Mini-Mental State Examination; R, right. The figure is adapted from (Carli et al. 2020) *in accordance to the fair use principle.*

In conclusion, we have identified common and consistent but also distinct patterns of brain hypometabolism in single individuals, indicating a specific underlying neurodegenerative process in iRBD. In most cases (31/37 patients), there was occipital

hypometabolism; 26 cases showed a more extended pattern of hypometabolism, reaching the parietal lobe, temporal area and/or cerebellum (Figure 41-Ia). Such patterns indicate the presence of neurodegeneration, and its topography is related to specific α-synuclein brain vulnerability. As indicated by the specific hypometabolic patterns, we hypothesized that there might be different phenoconversion trajectories in iRBD, which can only be captured at the individual level. The reported pattern of low occipital metabolism may represent an early feature of neurodegeneration, which will spread to other posterior cortical areas, like in LB disease. The low metabolism of the occipital lobe is a hallmark feature of DLB (Caminiti et al. 2019). Consistently, iRBD and DLB patients shared similar occipital hypometabolism – calcarine cortex, middle and inferior occipital gyrus bilaterally –, whereas iRBD and PD did not have overlap in brain hypometabolism. Compared with the iRBD group, the DLB group showed a more extended cortical hypometabolism, including the parietal area, indicating a possible temporal sequence of ongoing pathology. The [18F]FDG-PET pattern of 5 iRBD subjects was negative, and none of them had cognitive deficits. These iRBD subjects may represent cases in stable disease or in the process of developing idiopathic PD without dementia. Consistently, it has been shown that patients with stable PD (without cognitive worsening during time) exhibit a pattern of hypometabolism, characterized by the absence of cerebral hypometabolism or very limited cortical hypometabolism (Pilotto et al. 2018). As Boeve recently proposed, patients with iRBD have gradual but subtle changes in clinical (mainly motor) measurement and substantia nigra striatum uptake, but negative [18F]FDG -PET may turn to idiopathic PD without dementia. In contrast, patients with iRBD who have progressive but subtle cognitive changes on [18F]FDG-PET with neocortical brain hypometabolism may convert to DLB (Boeve 2019).

3.1.2. Study II: Impaired metabolic brain networks associated with neurotransmission systems in the α-synuclein spectrum. (Carli et al. 2020) – *Published article -*

A-synuclein aggregations play a crucial role in the neurotransmitter impairment observed in LB disorders since the preclinical stages (Knudsen et al. 2018), affecting different systems, namely the dopaminergic, noradrenergic and cholinergic ones (Uchihara & Giasson 2016). The impairment of multiple neurotransmitter systems in α-

synucleinopathies is documented by previous literature (Knudsen et al. 2018; Hall et al. 2014; Goedert et al. 2017; Braak et al. 2004; Borghammer & Van Den Berge 2019); however, evidence on their metabolic connectivity reconfiguration in the whole disease spectrum is lacking.

A promising approach for the investigation of neurodegenerative disorders – such as α-synucleinopathies – is the network analysis of glucose metabolism with [18F]FDG-PET (Caminiti et al. 2017; Sala et al. 2017; Caminiti et al. 2017; Meles, Vadasz, et al. 2017; Kogan et al. 2020; Teune et al. 2010). Studies exploring *in vivo* neurotransmitter circuits' alterations in the α-synuclein clinical spectrum, starting from the early phases, can identify the most vulnerable systems to the pathology, representing possible therapeutic targets for treatment and interventions. The application of multivariate analysis to [18F]FDG-PET data can reliably assess brain metabolic connectivity patterns within and between neurotransmitter systems, providing an *in vivo* access to the biochemical architecture of the brain (for detailed reviews see (Yakushev, Drzezga, and Habeck 2017; Sala and Perani 2019; Carli et al. 2021)). Metabolic connectivity research based on [18F]FDG-PET relies on i) the specific characteristics of [18F]FDG-PET signal and the availability of neurochemical evidence regarding the molecular architecture of the neurotransmission pathways of interest (Carli et al. 2021; Sala and Perani 2019).

In this study, we applied brain metabolic connectivity analyses to investigate *in-vivo* multiple neurotransmitter systems, namely the nigro-striato-cortical dopaminergic, noradrenergic and cholinergic neural networks, in iRBD, PD and DLB patients. We expected molecular alterations (shared and disease-specific) to occur in both the prodromal and the overt disease phases within the α-synuclein-spectrum, with different severity, justifying different clinical pictures. This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital (Milan) in collaboration with the Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia (Brescia), Italy. The present study and relative datasets were already published in the Parkinsonism & Related Disorders on 21st October 2020 (https://doi.org/10.1016/j.parkreldis.2020.10.036).

We retrospectively selected 34 iRBD, 29 iPD and 30 DLB. We also considered a group of 50 HC from the internal database of the In Vivo Human Molecular and Structural Neuroimaging Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy (See *5.1.*

Participant underwent [18F]FDG-PET exam for diagnostic details of each clinical group). Demographic and clinical characteristics of clinical groups are reported in Table 2.

Table 2. Demographic and Clinical features of iRBD, PD, DLB and HC.

	iRBD	PD	DLB	HC	Test value
Number of subjects, N	34	29	30	50	-
Gender, N (F/M)	4/30	13/16	8/22	22/28	p=0.020[1 a, b *]
Age, years (Mean±SD)	69.24±6.58	62.68±10.83	74±6.62	68.38±9.03	p=0.000[2 a, b #]
Education, years (Mean±SD)	10.85±4.72	8.25±4.26	8.13±4.20	-	p=0.030[2 c]
Disease duration, years (Mean±SD)	5.11±3.20	4.25±2.59	2.47±1.63	-	p=0.000[2 b, d]
MMSE score (Mean±SD)	27.55±2.09	28.71±1.49	19.47±5.83	-	p=0.000[2 b, d]

[1]Chi-squared test
[2]Oneway ANOVA
Significant differences at post-hoc comparisons, significant at p<0.05, using Bonferroni-correction for multiple comparisons:
[*]= HC differed from iRBD;
[#]= HC group differed from DLB and PD;
a= PD and iRBD groups differ;
b= DLB and PD groups differ;
c= Groups do not differ;
d= DLB and iRBD groups differ;
MMSE scores are reported corrected for age and education, following the Italian normative data (Measso et al. 1993)
Abbreviations: iRBD= isolated REM behaviour disorder; PD= Parkinson's disease; DLB= dementia with Lewy Bodies, MMSE= Mini Mental State Examination; SD= standard deviation.

Nigro-striato-cortical dopaminergic network - The dopaminergic system was minimally affected in iRBD and moderate to severe in patients with DLB and PD. Specifically, iRBD subjects showed limited connectivity changes in the dopaminergic network (5.5% of altered metabolic connections), affecting only a portion of ROIs (GI = 0.54). On the other hand, PD patients showed severe (15.43% of altered metabolic connection) and extended (GI = 0.38) metabolic connectivity reconfiguration. In DLB, the nigro-striato-cortical dopaminergic network showed significant metabolic

connectivity alterations (8.02% of altered metabolic connection), although not involving all ROIs (GI = 0.54). In the DLB cohort, the caudate nucleus emerged as a pathological hub – differently from PD patients – presenting a disproportion of altered connection compared to other ROIs (the 28% of altered metabolic connections). For all considered ROIs see Appendix Table A1. Figures 37 and 40 represent dopaminergic network analyses and metrics. For GI values, see Appendix Table A6.

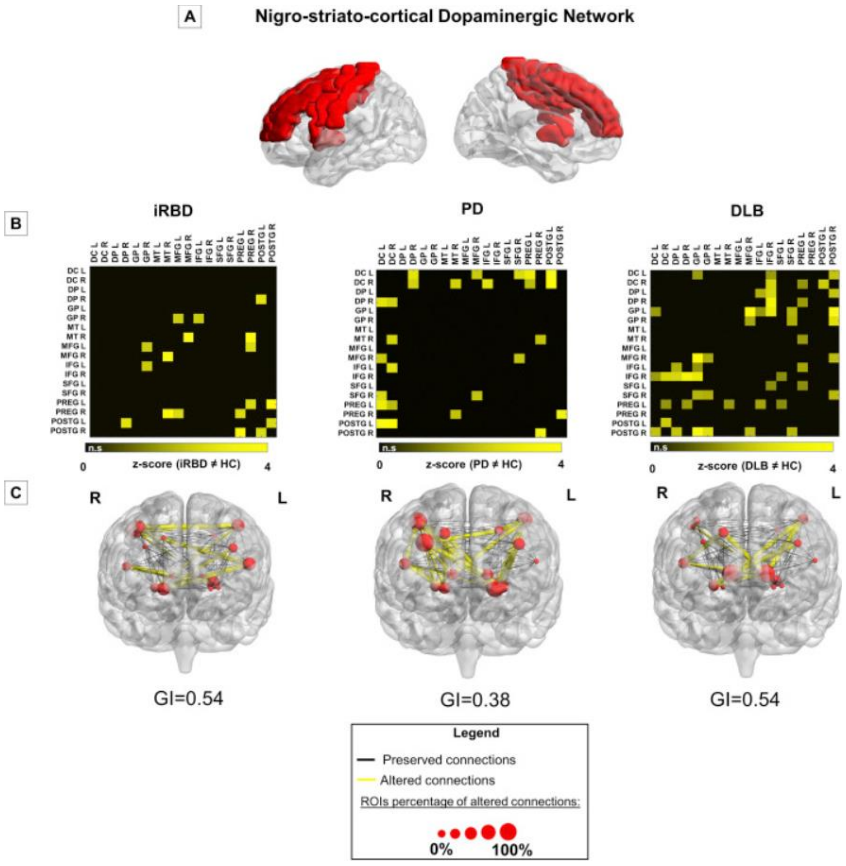

Figure 37. Network analyses: the nigro-striato-cortical dopaminergic system (Fair use).

Panel A depicts the whole ROIs selected for nigro-striato-cortical network analysis on a 3D brain template. Panel B shows the matrices with the significant differences obtained comparing partial correlation coefficients: iRBD≠HC, PD≠HC and DLB≠HC. The altered connections are shown in yellow; the unchanged connections are in black. Panel C represents iRBD, PD and DLB brain connectivity graphs displayed on a 3D brain template. Both the altered connections (in yellow) and unchanged (in black) are reported. The total node number of altered connections defines the radius of each ROI. The GI highlights a possible evolution of the dopaminergic dysfunction along the spectrum. Abbreviation: ROIs = Regions of interest; n.s. = non-significant; iRBD = isolated REM sleep behavioural disorder; PD= Parkinson's disease; DLB = Dementia with Lewy bodies; GI: Gini Index; L = left; R = right; DC = dorsal caudate; DP = dorsal putamen; GP = Globus Pallidus; MT = Motor section of thalamus; FIG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; POSTG = postcentral gyrus; PRECG = precentral gyrus. The figure is adapted from (Carli et al. 2020) *in accordance to the fair use principle.*

Noradrenergic network - The noradrenergic network was severely affected in all clinical groups. Specifically, iRBD patients expressed an extensive reconfiguration of the noradrenergic network (GI = 0.29). The right cerebellar crus represented a pathological hub because it was disproportionally affected than other ROIs (39% of altered metabolic connections arising from this region). The PD and DLB groups also showed an extensive alteration of metabolic connectivity in the noradrenergic network (GI PD = 0.22, GI DLB = 0.12), where all ROIs were equally affected. For all considered ROIs see Appendix Table A3. Figures 38 and 40 show noradrenergic network analyses and metrics. For GI values, see Appendix Table A6.

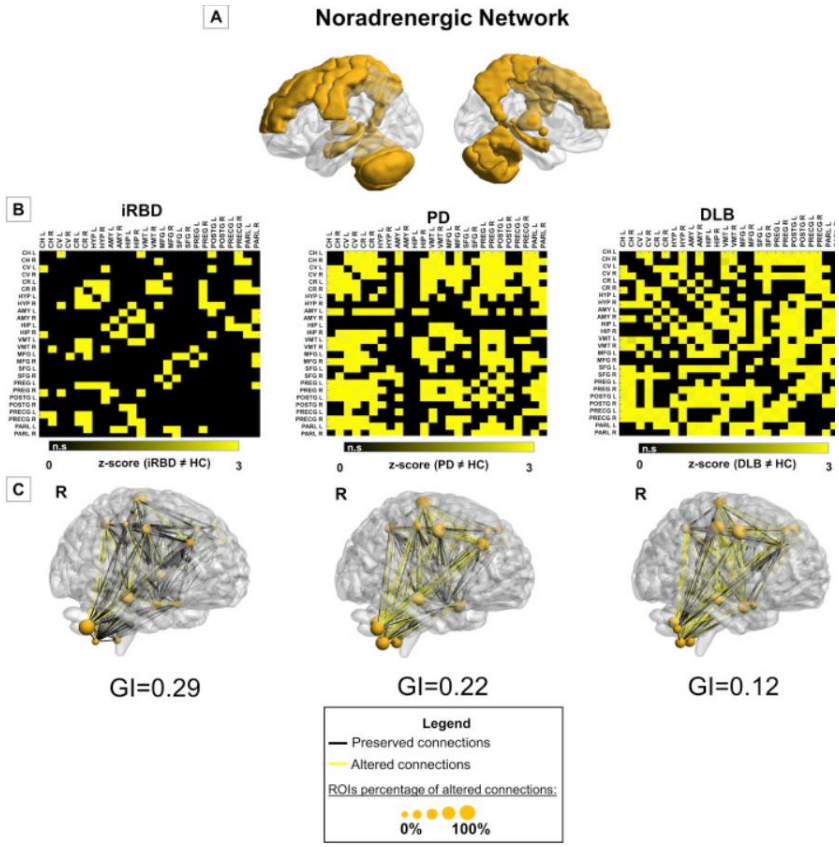

Figure 38. Network analyses: the noradrenergic system (Fair use).

Panel A depicted the whole ROIs selected for noradrenergic network analysis on a 3D brain template. Panel B shows the matrices with the significant differences obtained comparing partial correlation coefficients: iRBD≠HC, PD≠HC and DLB≠HC. The altered connections are shown in yellow; the unchanged connections are in black. Panel C represents iRBD, PD and DLB brain connectivity graphs displayed on a 3D brain template. Both the altered connections (in yellow) and unchanged (in black) are reported. The total node number of altered connections defines the radius of each ROI. GI close to zero in all clinical groups suggest a global connectivity

derangement and reconfiguration of the noradrenergic network across the spectrum. Abbreviations: ROIs: Regions of interest; n.s. = non-significant; iRBD = isolated REM sleep behavioural disorder; PD= Parkinson's disease; DLB = Dementia with Lewy bodies; L = left; R = right; GI: Gini Index; CH = cerebellum hemisphere; CV = cerebellum vermis; CR = cerebellum Cruss; HYP = hypothalamus; AMY = amygdala; HIP = hippocampus; VMT = ventromedial thalamus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; PREG = precentral gyrus; POSTG = postcentral gyrus; PREC = praecuneus; PRAL = paracentral lobule. The figure is adapted from (Carli et al. 2020) *in accordance to the fair use principle.*

Cholinergic network divisions - As for the cholinergic networks, we found altered metabolic connectivity along the whole α-synuclein spectrum, particularly affecting the perisylvian and medial Ch4 divisions. DLB group presented the most severe and diffuse cholinergic impairment. The iRBD group showed limited altered metabolic connectivity in three cholinergic divisions: perisylvian Ch-4 (GI = 0.83), medial Ch4 (GI = 0.84) and Ch5-Ch6 (GI = 0.67). PD patients expressed metabolic connectivity reconfiguration limited to few ROIs in the perisylvian (GI = 0.75) and medial Ch4 (GI = 0.63) divisions networks. The DLB group showed an extensive reconfiguration in Ch3 (GI = 0.17), medial Ch4 (GI = 0.37) and Ch5-Ch6 (GI = 0.42) divisions networks. The lateral perisylvian Ch4 division network was the less affected network, with a GI = 0.57 and a reconfiguration limited to 5 out of 10 ROIs. For all considered ROIs see Appendix Table A4 and A5. Figures 39 and 40 depict cholinergic network divisions analyses and metrics. See Appendix Table A6 for GI values.

According to the wDC coefficient analyses, DLB and PD shared connectivity changes mainly in noradrenergic and Ch4-Perysilvian cholinergic networks (wDCnoradrenergic = 3.09 and wDCperysilvianCh4 = 2.91). The iRBD and DLB groups showed high similarity in noradrenergic and Ch5-Ch6 cholinergic networks (wDCnoradrenergic = 2.14 and wDCCh5-Ch6 = 1.85). Finally, iRBD and PD showed a high degree of similarity in the noradrenergic network (wDCnoradrenergic = 1.18). See Figure 40 for network analyses metrics. For wDC values, see Appendix Table A7.

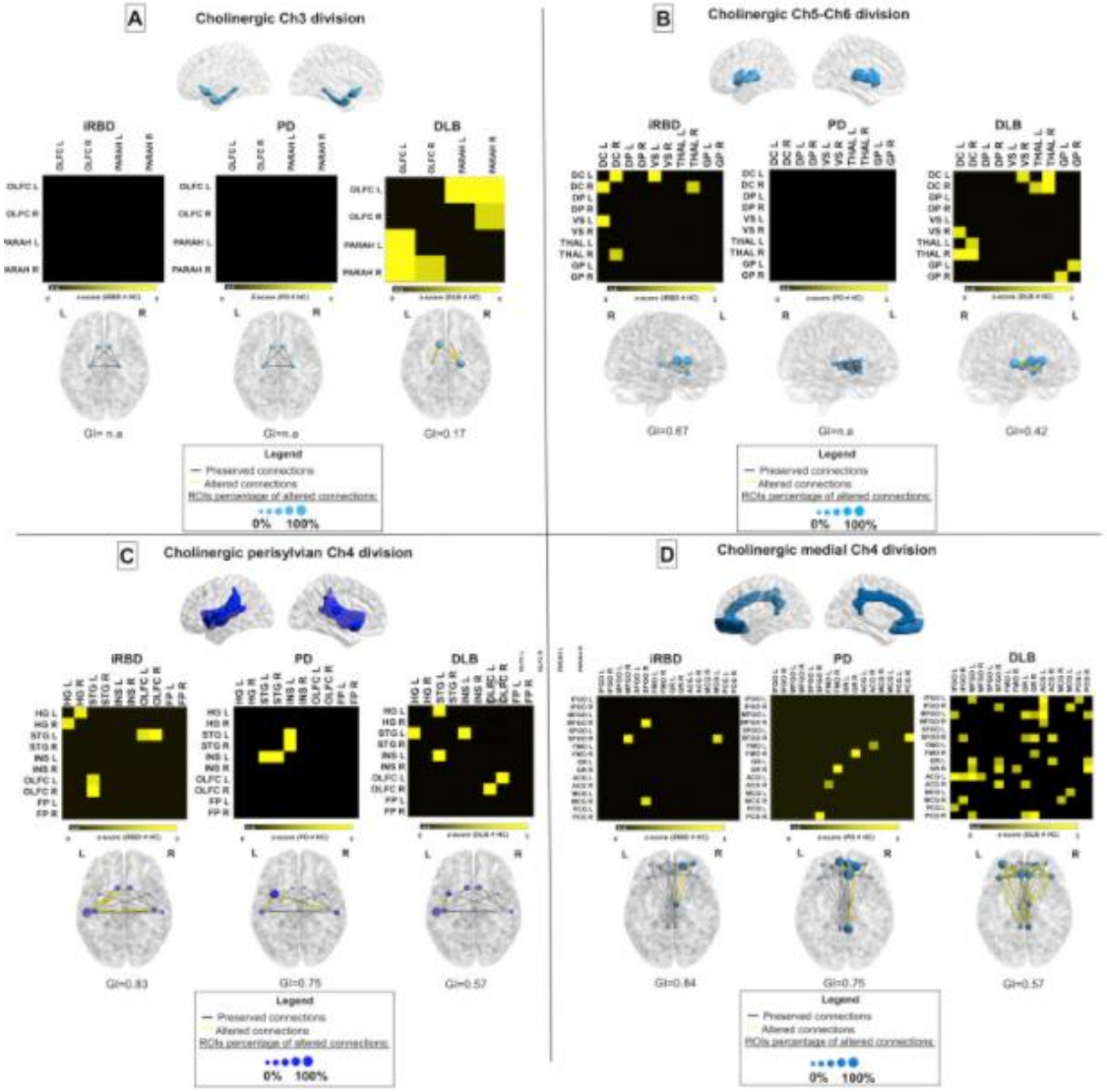

Figure 39. Network analyses: cholinergic system divisions (Fair use).

A,B,C,D) 3D brain template displays the ROIs selected for cholinergic network analysis. A) Cholinergic Ch3 division network B) Cholinergic Ch5-Ch6 divisions networks; C) Cholinergic perisylvian Ch4 division network; D) Cholinergic medial Ch4 division network. The matrices represent the significant differences obtained comparing partial correlation coefficients in each panel: iRBD≠HC, PD≠HC and DLB≠HC. The altered connections of patients in comparison to HC are shown in yellow, with the unchanged connections in black. 3D brain template displays iRBD, PD and DLB brain connectivity graphs. Both the altered connections (in yellow) and preserved connections (in black) are shown. The total node number of altered connections defines the radius of each ROI. Abbreviations: ROIs = Regions of interest; n.s. = non-significant; iRBD = isolated REM sleep behavioural disorder; PD= Parkinson's disease; DLB = Dementia with Lewy bodies n.a. = not applicable; GI: Gini Index;L = left;R = right;OLFC = olfactorycortex; PARAH = parahippocampus; DC = dorsal caudate; DP = dorsal putamen; VS = ventral striatum; THAL = thalamus; GP = globus pallidus; HG = heschel gyrus; STG = superior temporal gyrus; INS = insula; FP = frontoparietal operculum; IFGO = inferior frontal gyrus; pars. Orbitalis; MFGO = middle frontal gyrus pars. Orbitalis; SFGO = superior frontal gyrus

pars. Orbitalis; FMO = medial frontal cortex pars. Orbitalis; GR = gyrus rectus; ACG = anterior cingulate gyrus; MCG = middle cingulate gyrus; PCG = posterior cingulate gyrus. The figure is adapted from (Carli et al. 2020) *in accordance to the fair use principle.*

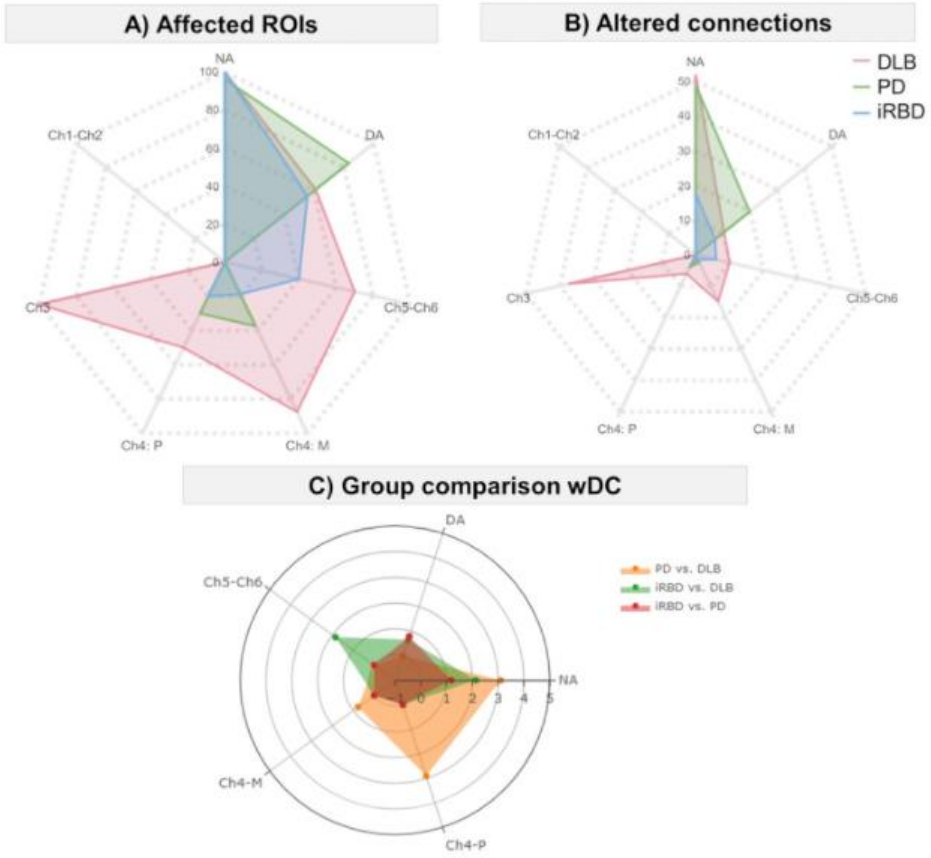

Figure 40. Metabolic connectivity profiles (Fair use).

A) Percentage of affected ROIs in each neurotransmission network, depicting altered metabolic connections in DLB (red), PD (green), iRBD (blueThe dopaminergic system is least affected in iRBD and moderate to severe in patients with DLB and PD. The noradrenergic system of all groups was severely affected, and the DLB group showed the most severe and diffuse cholinergic disorder; B) Percentage of mean altered connection for each ROI in DLB (red), PD (green), iRBD (blue). This connectivity index confirms the local damage of the dopaminergic network in iRBD, as well as the moderate to severe damage of DLB and PD, the severe changes in the noradrenergic network in all the three groups, and the most severe cholinergic impairment in DLB patients; C) Similarity analysis results as expressed by wDC coefficient in PD vs. DLB (orange); iRBD vs. DLB (green); iRBD vs. PD (red). Abbreviations: ROIs: Regions of interest; iRBD = isolated REM sleep behaviour disorder, PD= Parkinson's disease; DLB = Dementia with Lewy Bodies; wDC = weighted DICE coefficient; NA= Noradrenergic network; DA = Dopaminergic network; Ch5-Ch6 = Cholinergic Ch5-Ch6 divisions networks; Ch4-M = Cholinergic medial Ch4 division network; Ch4-P= Cholinergic lateral Perysilvian Ch4 division networks; Ch3 = Cholinergic Ch3 division network; Ch1-Ch2 = Cholinergic Ch1- Ch2 division network. The figure is adapted from (Carli et al. 2020) *in accordance to the fair use principle.*

This study applied a comprehensive neural network perspective comparing the different clinical entities of the α-synuclein disease spectrum. Specifically, we proved the changes of several neural transmission networks in iRBD, PD and DLB through different brain metabolic connectivity parameters. From a methodological standpoint, our findings based their foundation on a novel molecular connectivity approach. Recent evidence demonstrated the applicability and reproducibility of brain molecular connectivity approaches analysing hundreds of PET scans, using three different tracers – [18F]FDG, FDOPA, for dopamine synthesis and SB217045 for serotonin 5HT4 receptor density – (Veronese et al. 2019).

These metabolic connectivity findings suggest that α-synucleinopathies have to be considered multisystem disorders, dynamically involving several neurotransmitters systems alteration, already in the preclinical/prodromal phases. The nigro-striato-cortical dopaminergic system showed a progressive impairment: localized in iRBD and sparse in PD. Instead, the noradrenergic system represented an early vulnerable site, extensively affected in the whole spectrum, supporting the caudorostral model of α-synuclein propagation (Braak et al. 2004). In the end, the limited cholinergic alterations in PD support a less severe vulnerability of this system in overt α-synucleinopathies without cognitive deterioration (Klein et al. 2010); meanwhile, the shared cholinergic alterations in iRBD and DLB may indicate an early occurrence impairment of this system and its role in specific phenotypic expressions.

3.1.3. Study IIIa: Exploring the functional role and neural correlates of K-complexes in isolated rapid eye movement sleep behaviour disorder. (Galbiati et al. 2021) *- Published Article -*

Although RSWA represents the core pathophysiological feature of iRBD, electroencephalogram (EEG) studies reveal a slowing during both sleep and wakefulness in patients with iRBD (Massicotte-Marquez et al. 2005; Fantini et al. 2003; Sasai, Matsuura, and Inoue 2013; Bang et al. 2017). Specifically, these alterations seem to predict neurodegeneration and are associated with cognitive decline (Brazète et al. 2016; Sasai, Matsuura, and Inoue 2013). Some studies emphasised the importance of non-REM sleep features – specifically Slow Wave Sleep (SWS) – in protecting the brain from degeneration and cognitive decline (Mander et al. 2015; Ju et al. 2017; Cordone et al.

2019). SWS seems to balance the β-amyloid and α-synuclein accumulation through glymphatic clearance (Xie et al. 2013; Schreiner et al. 2019).

The K-complex (KC) is a crucial non-REM sleep element, representing a forerunner of SWS (De Gennaro, Ferrara, and Bertini 2000). It is characterized by a short and transient positivity in the EEG followed by a slower, larger surface negative complex, and then a final positivity peaking (Cash et al. 2009). Recently, it has been demonstrated that in AD patients, a decrease density of KCs during non-REM sleep stage 2 is connected with the global cognitive decline (De Gennaro et al. 2017). KC density resulted in a sensitive marker differentiating AD patients from controls (De Gennaro et al. 2017). Despite the promising diagnostic role of KC in the neurodegenerative research field, there is a lack of evidence regarding the meaning of this EEG element of non-REM sleep in α-synuclein related neurodegeneration. The role of non-REM slow waves in iRBD is still unexplored. Studies exploring the correlates of these sleep alterations in iRBD are necessary to understand the progression of underlying pathological mechanisms and identify early vulnerable systems that may represent a valuable therapeutic target for the treatment.

Synaptic dysfunction is a key feature of α-synucleinopathies (Uchihara & Giasson 2016) and might alter neurotransmitter release and regulation of synaptic plasticity mechanisms, resulting in alterations in neural networks (Palop, Chin, and Mucke 2006). The application of multivariate methods to [18F]FDG-PET data reliably assesses brain connectivity patterns within and between large-scale brain networks, providing an *in vivo* access to the biochemical architecture of the brain (Sala and Perani 2019). The functional global brain network connectome disorganisation is documented in iRBD (Byun et al. 2020; Park et al. 2019; Campabadal et al. 2020; Y Ju et al. 2013). However, the changes in brain networks involved in sleep alterations are understudied. The generation of SWS is associated with large currents in the brain region that maximally overlap with many parts of the anterior default mode network (ADMN) (Murphy et al. 2009).

This study aimed to investigate: i) the functional role of KCs exploring their relationship with neuropsychological functioning and ii) the neural bases of KCs, studying brain metabolic correlates underlying KC in iRBD patients. We applied a univariate approach (a voxel-wise whole-brain linear regression analysis) without a priori hypothesis to identify possible local neural substrate of KC, and a multivariate metabolic

connectivity approach (seed-based interregional correlation analysis (IRCA)), to assess metabolic connectivity changes of ADMN. Following the hypothesis that SWS might play a protective role in neurodegeneration processes, we hypothesize that increased KC density (a forerunner of SWS) would have been associated with more preserved cognitive functioning and molecular pathways, synapses, neuronal activity subpopulations, local circuits as well as higher-order neural networks, measured through [18F]FDG-PET. This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital (Milan) in collaboration with the Sleep Disorders Center of San Raffaele Hospital (Milan) and the department of Psychology of Sapienza University (Rome). The present study and relative datasets were already published in the journal Cortex on 5th October 2021 (https://doi.org/10.1016/j.cortex.2021.08.012).

We included 33 iRBD patients (28 male patients, age [mean ± SD], 68.82 ± 6.81 years; education [mean ± SD], 10.64 ± 4.14 years) (see *5.1. Participant underwent [18F]FDG-PET exams*). iRBD subjects showed a reduction of sleep efficiency (SE) and increased wake after sleep onset (WASO) (Baglioni et al. 2014).

Table 3. Sleep macrostructure of iRBD.

PSG results	Mean ± SD (N=33)
TST (min)	371.21 ± 52.27
SL (min)	30.78 ± 26.13
WASO (min)	57.60 ± 31.29
SE (%)	80.28 ± 9.64
NAWK	16.87 ± 15.78
N1	11.36 ± 4.03
N2	50.62 ± 6.79
SWS	18.20 ± 7.00
REM	21.00 ± 7.45
LREM	98.06 ± 56.70

SD: standard deviation; min: minutes; PSG: Polysomnography; TST: Total sleep time; SL: Sleep latency; WASO: wake after sleep onset; SE: Sleep efficiency; NAWK: numbers of awakenings; N1: sleep stage 1; N2: sleep stage 2; N3: Slow Wave Sleep; REM: rapid eye movement; LREM: REM sleep latency.

A significant decrease of KC density emerged throughout sleep cycles was observed (linear trend: $F_{1,32}=33.25$; $p < 0.001$), where the mean of KC density was 1.28 ± 0.74 for the first sleep cycles, 1.02 ± 0.52 for the second and 0.74 ± 0.40 for the third (Figure 41). See *Part 2 Study IIIb* for the relationship between KC and neuropsychological variables.

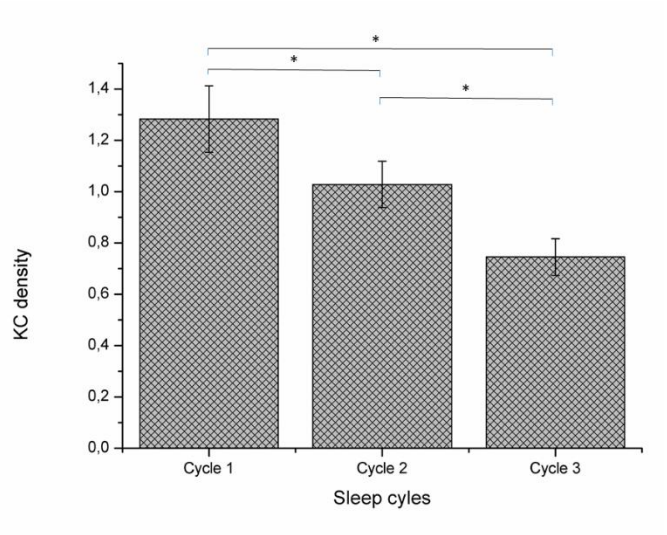

Figure 41. KC density throughout sleep cycles (Fair use).

Abbreviations: KC: K complex. *The figure is adapted from* (Galbiati et al. 2021) *in accordance to the fair use principle.*

The regression analysis showed an association between lower KC density and lower brain metabolism in the right superior medial frontal cortex (Figure 42).

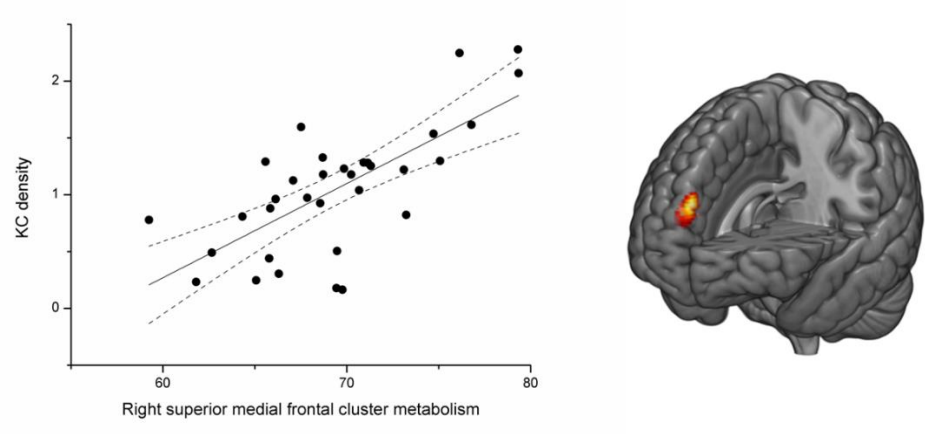

Figure 42. Relationship between KC density and brain metabolism (Fair use).

The significant positive correlation between metabolism in the left superior medial frontal cluster emerged and KC density ($p<0.001$; $r=0.666$). 3D rendering represents the significant left superior medial cluster ($p<0.005$ uncorrected; $k\geq100$). Abbreviations: KC: K complex. The figure is adapted from (Galbiati et al. 2021) *in accordance to the fair use principle.*

According to the mean values KC density (mean: 1.05), iRBD patients were divided into two sub-groups: iRBD with low KC density (N=16) or high KC density (N=17). These sub-groups showed a significant difference in metabolic connectivity of ADMN (Dice coefficient=0.38). Specifically, iRBD with high KC density expressed a more preserved connectivity in ADMN (N° voxel = 4133) than the sub-group with low KC density (N° voxel =1312). The SPM interaction analysis showed that the slope of the correlation between the seeds of the ADMN (the anterior cingulate cortex/ventromedial prefrontal cortex) and left middle and bilateral superior frontal gyri was steeper in the sub-group with high KC density (r = 0.92) as compared to the sub-group with low KC density (r = 0.67) (Figure 43).

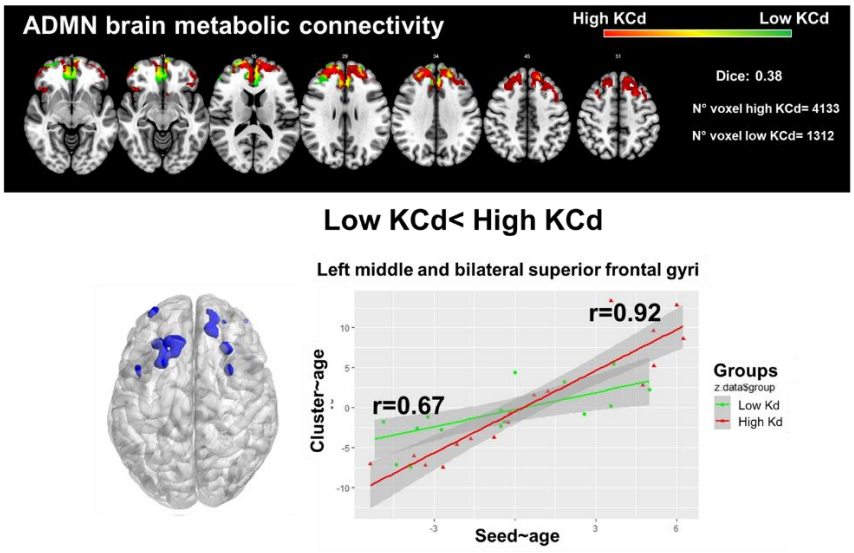

Figure 43. Brain metabolic connectivity analyses ADMN in iRBD stratified according to KC density (Fair use).

The figure shows ADMN topography in iRBD high KC density (KCd) (Red) and low KCd (Green) (Top panel). The overlap areas are yellow. The Dice coefficient and the number of correlated voxels for each group are reported on the right side. The bottom panel depicts the graphical plot representing the slope and magnitude of coefficients of the correlations between mean [18F]FDG in the seed region and brain structures where the two sub-groups differed in strength of metabolic connectivity. Abbreviations: KCd: K complex density; ADMN: anterior default mode network. The figure is adapted from (Galbiati et al. 2021) *in accordance to the fair use principle.*

This study investigated the functional role of the KCs in iRBD and its neural bases for the first time. We evaluated the KC density related neural correlate through two different approaches to [18F]FDG-PET data. We found that patients characterized by increased levels of KCd were associated with preserved neural activity in medial frontal regions and higher integrity of metabolic connectivity in the ADMN. All the above suggests a protective role of this EEG element of non-REM sleep in the α-synuclein related pathological process since this early stage.

3.1.4. Study IVa: Clinical and Dopamine Transporter Imaging Trajectories in a Cohort of Parkinson's Disease Patients with GBA Mutations. (Caminiti, Carli, et al. 2021)*. - Published Article -*

The most frequent genetic risk factor for α-synucleinopathies is heterozygous mutations in the *GBA* gene, encoding for lysosomal enzyme glucocerebrosidase (GCase) (Neumann et al. 2009). GBA-PD patients have an earlier disease onset, faster cognitive deterioration, and lesser benefit from traditional drug interventions than iPD patients (Tayebi et al. 2003; Ryan et al. 2019; Petrucci et al. 2020).

Age plays a critical role in the gradual decline of dopaminergic function and the occurrence of PD (Critchley 1931). Late-onset iPD is associated with greater impairment of dopaminergic function, fast clinical progression (Van Rooden et al. 2010). Conversely, early-onset iPD manifests by slow disease progression and more preserved cognitive functioning (Anette Schrag and Schott 2006). The clinical picture described in GBA-PD patients is similar to the "diffuse malignant PD subtype" (Fereshtehnejad et al. 2015), but the average age of onset is earlier.

Of note, in the early phases of the disease, GBA-PD is phenotypically indistinguishable from the iPD; although GBA-PD is characterized by a worse clinical prognosis than iPD (Adler et al. 2017; Cilia et al. 2016; Simuni et al. 2020).

Here, we analysed a large PD cohort obtained from the Parkinson's Progression Markers Initiative (PPMI) (www.ppmi-info.org/database) with and without GBA mutations to evaluate: i) the early clinical presentation (baseline) and progression (considering two-time point follow-ups) and ii) the role of progressive striatal and extra-striatal pathways dysfunction in accelerating phenotypic course. Specifically, we compared the GBA-PD cohort with iPD patients stratified according to age at onset (early and late-onset iPD).

We collected clinical and imaging data of 46 GBA-PD and 338 iPD patients from PPMI database, the latest grouped by disease onset: 58 early-onset iPD (early-iPD) (<50 years) and 281 late-onset (late-iPD) (iPD > 50 years) (Chen et al. 2020; Schirinzi et al. 2020; Willis et al. 2013). We also included 59 HC subjects (36 Males, age [mean ± SD] 59.19 ± 10.75) for imaging analysis (see *Participant underwent [123IF]FP-CIT-SPECT exams*). All subjects had available MRI and [123I]FP-CIT-SPECT acquisitions at baseline. This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital

(Milan), collaborating with IRCCS Mondino Foundation, Pavia, Italia. For the details of clinical and cognitive progression results, see Part 2 Study IVb. The present study and relative datasets were already published in the journal Movement Disorder on 1st October 2021 (https://doi.org/10.1002/mds.28818).

Table 4 summarizes the [123I]FP-CIT imaging data at baseline**.** The GBA-PD, early-iPD, and late-iPD patients shared pathological [123I]FP-CIT-SPECT Specific Uptake Value ratio (SUVr) (lower than HC) in all the considered ROIs, except for ventral striatum, hippocampus and amygdala bilaterally. Differently from iPD groups, the GBA-PD cohort had lower DAT SUVr in bilateral ventral striatum than HC. The GBA-PD group showed a significantly decreased [123I]FP-CIT-SPECT SUVr in the whole contralateral putamen, anterior and motor putamen, globus pallidus, hippocampus, and amygdala than the early-iPD group. In bilateral ventral striatum, GBA-PD patients presented significantly lower DAT SUVr than early-iPD and late-iPD. Figure 44 shows the significant differences in [123I]FP-CIT-SPECT SUVr among clinical groups.

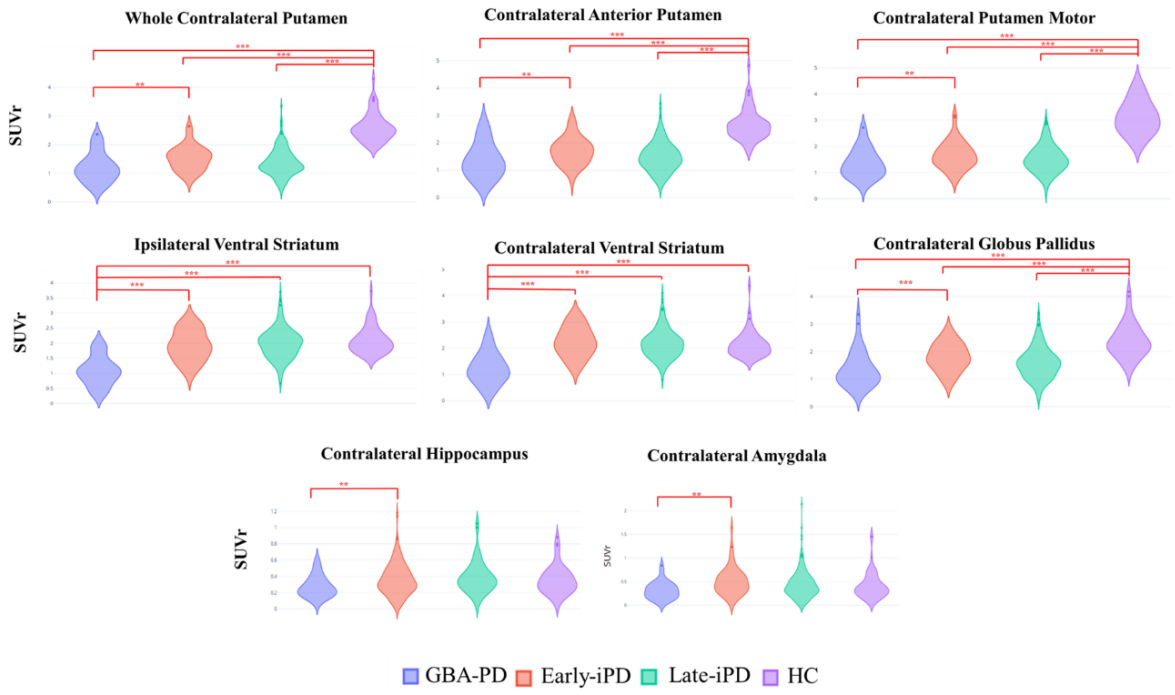

Figure 44. [123I]FP-CIT imaging significant differences between GBA-PD and iPD groups (Fair use).

Panel with violin plots depicting significant differences in 123I-FP-CIT binding data of ROIs in the four considered clinical groups: GBA-PD (Purple), early-iPD (Orange), late-iPD (Green) and HC (Violet). Abbreviations: SUVr: Specific Uptake Value ratio; i: Idiopathic; PD:

Parkinson's disease. The figure is adapted from (Caminiti, Carli, et al. 2021) *in accordance to the fair use principle.*

Of note, the three groups also differed in their DAT binding and motor asymmetry characteristics (X^2=9.747; p=0.008), where GBA-PD (45.65%) and late-iPD (55.16%) patients showed less DAT binding and motor asymmetry than the early-iPD group (74.14%).

Table 4. [123I]FP-CIT-SPECT imaging features at baseline in GBA-PD and iPD groups.

	GBA-PD (N=46) Mean(SD)	**Early-iPD (N=58) Mean(SD)**	**Late-iPD (N=281) Mean(SD)**	**HC (N=59)**	**P-value (F-statistic) HC comparison[a]**	**GBA vs PD-early***	**GBA vs PD-late***	**PD-early vs PD-late***
Whole Ipsilateral Caudate N	1.17±0.45 †	1.18±0.43 †	1.18±0.42 †	1.97±0.49	**0.000**	1.000	1.000	1.000
Whole Contralateral Caudate N	1.29±0.56 †	1.37±0.5 †	1.28±0.43 †	1.95±0.45	**0.000**	1.000	1.000	1.000
Whole Ipsilateral Putamen	0.95±0.42 †	1.1±0.33 †	1.09±0.40 †	2.48±0.49	**0.000**	0.287	0.122	1.000
Whole Contralateral Putamen	1.2±0.51 †	1.53±0.43 †	1.37±0.46 †	2.60±0.49	**0.000**	**0.010**	0.096	0.408
Ipsilateral Anterior Putamen	1.07±0.54 †	1.25±0.4 †	1.19±0.46 †	2.66±0.50	**0.000**	0.378	0.235	1.000
Contralateral Anterior Putamen	1.36±0.64 †	1.7±0.50 †	1.48±0.52 †	2.66±0.57	**0.000**	**0.038**	0.384	0.349
Ipsilateral Posterior Putamen	0.72±0.29 †	0.75±0.21	0.8±0.32	2.35±0.51	**0.000**	1.000	1.000	1.000
Contralateral Posterior Putamen	0.93±0.39 †	1.13±0.37 †	1.04±0.40 †	2.41±0.53	**0.000**	0.068	0.653	0.330
Ipsilateral Caudate N **Motor**	1.31±0.57 †	1.22±0.59 †	1.2±0.55 †	2.32±0.77	**0.000**	0.467	0.518	1.000
Contralateral Caudate N**Motor**	1.47±0.71 †	1.41±0.66 †	1.36±0.58 †	2.29±0.73	**0.000**	0.865	0.935	1.000
Ipsilateral Putamen Motor	1.03±0.49 †	1.09±0.38 †	1.17±0.46 †	2.99±0.68	**0.000**	1.000	0.422	1.000
Contralateral Putamen Motor	1.35±0.55 †	1.66±0.52 †	1.51±0.52 †	3.11±0.64	**0.000**	**0.038**	0.211	0.598
Ipsilateral Ventral Striatum	1.07±0.48 †	1.92±0.51	1.99±0.49	2.09±0.44	**0.000**	**0.000**	**0.000**	0.571
Contralateral Ventral Striatum	1.23±0.58 †	2.24±0.57	2.15±0.53	2.14±0.49	**0.000**	**0.000**	**0.000**	1.000
Ipsilateral Globus Pallidus	1.17±0.53 †	1.34±0.42 †	1.36±0.50 †	2.46±0.63	**0.000**	0.318	0.160	1.000
Contralateral Globus Pallidus	1.35±0.63 †	1.8±0.5 †	1.57±0.56 †	2.38±0.62	**0.000**	**0.003**	0.161	0.083
Ipsilateral Thalamus	0.52±0.24 †	0.48±0.18 †	0.49±0.22 †	0.65±0.21	**0.000**	0.750	0.105	1.000
Contralateral Thalamus	0.55±0.19	0.52±0.18 †	0.50±0.21 †	0.65±0.21	**0.000**	1.000	0.083	0.119
Ipsilateral Hippocampus	0.29±0.12	0.36±0.2	0.34±0.18	0.33±0.18	0.180	0.150	1.000	0.321
Contralateral Hippocampus	0.27±0.13	0.38±0.19	0.36±0.19	0.35±0.18	**0.020**	**0.007**	0.259	0.122
Ipsilateral Amygdala	0.34±0.18	0.46±0.34	0.41±0.24	0.45±0.29	0.265	0.121	1.000	0.244
Contralateral Amygdala	0.31±0.18	0.34±0.51	0.43±0.28	0.42±0.27	**0.027**	**0.003**	0.176	0.094

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus. † Significantly differed from HC p<0.05; a F-statistic of comparison between patients and HC controlling for age, gender and ROIs volumes(cm3); +Partial eta square(η2) was used as the effect size for the MANOVA model comparing PD patients' cohorts and HC; * Corrected for Bonferroni, controlling gender, disease duration, ROIs volumes(cm3) and UPDRS part III.

We collected [123I]FP-CIT-SPECT scans also at a follow-up time point ("≈2-yrs" visit) to explore the dopaminergic damage progression in each clinical group. At the "≈2-yrs" visit, no statistically significant differences emerged among groups (Appendix Table A11). From baseline to "≈2-yrs" follow-up, we found that the early-iPD and late-iPD groups significantly increased their SUVr rate of change in the ventral striatum in comparison with the GBA-PD group, namely higher binding reductions over time (early-iPD *vs.* GBA-PD p=0.024; late-iPD *vs.* GBA-PD p<0.001) (Figure 45).

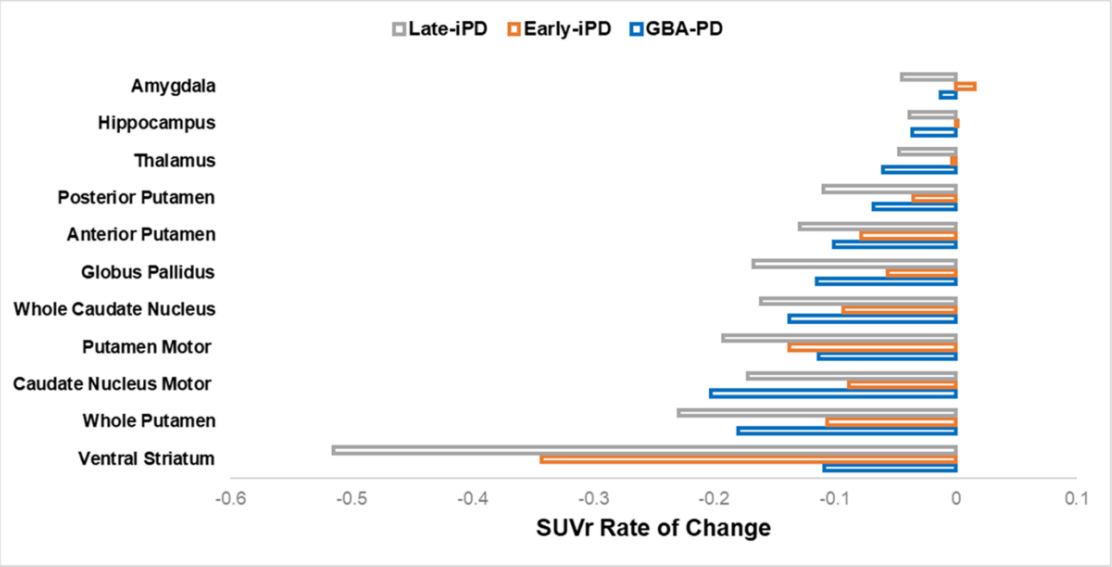

Figure 45. [123I]FP-CIT SUVr rate of changes (Fair use).

Horizontal bar plot depicting the rate changes per year of [123I]FP-CIT binding data extracted from subject-specific regions of interest for each PD group (GBA-PD in blue, early-iPD in orange and late-iPD in grey). Abbreviations: SUVr: Specific Uptake Value ratio; i: idiopathic; PD: Parkinson's disease. The figure is adapted from (Caminiti, Carli, et al. 2021) *in accordance to the fair use principle.*

The baseline imaging results suggest that GBA mutation accelerates neurodegenerative processes causing widespread and severe striatal and extra-striatal involvement, already in the early stage of the disease. The longitudinal analysis emphasizes an early involvement of ventral striatum in the GBA-PD group, further

supporting the hypothesis about the role of GBA mutations in causing severe and more extended dopaminergic damage than the idiopathic forms. Indeed, early and late-iPD reach the same dopaminergic damage severity of GBA-PD patients two years later.

3.2. Part 2. Clinical and cognitive features in different LB disease stages

3.2.1. Study Ib: In-vivo signatures of neurodegeneration in isolated rapid eye movement sleep behaviour disorder. (Carli et al. 2020) - *Published article* -

The neuropsychological assessment results revealed that 22 out of 37 iRBD subjects did not present any cognitive deficits. Fifteen subjects with iRBD showed neuropsychological impairments affecting several cognitive domains (iRBD with cognitive impairments (-CI)). Specifically, iRBD-CI patients showed defective performance in executive, language, short-term memory, long-term memory and visuo-constructional tasks. The highest percentage of subjects with iRBD-CI (46%) showed visuospatial/visuoperceptive impairments as measured by Rey–Osterrieth complex figure (ROCF) copy. Table 5 contains neuropsychological features of the iRBD cohort.

Table 5 Neuropsychological features of 37 iRBD.

	Cut-off values (corrected scores)	**All iRBD (Mean±SD) (n 37)**	**iRBD-NC (Mean±SD) (n 22)**	**iRBD-CI (Meand±SD) (n 15)**	**%iRBD-CI with pathological performance (n 15)**
Attentional Matrices	31.00	48.11±6.79	49.67±5.30	45.93±8.16	6.70%
Raven Colored Progressive Matrices	18.00	30.38±6.23	32.80±5.64	27.00±5.54	0.00%
Verbal fluency with phonemic cue	17.00	31.56±9.79	34.71±9.15	27.13±9.17	6.70%
Verbal fluency with semantic cue	25.00	43.58±8.62	46.91±6.80	38.93±8.95	6.70%
Token Test	26.50	31.76±2.19	32.31±1.53	30.88±2.82	15.40%
Digit Span Forward	4.26	5.73±0.90	5.97±0.81	5.39±0.94	13.33%
Digit Span Backward	2.65	4.13±1.28	4.61±1.35	3.45±0.83	6.70%
Corsi block-tapping test	3.46	5.01±0.95	5.14±0.84	4.83±1.09	6.70%

ROCF recall.	9.47	18.78±6.99	21.26±6.55	15.30±6.21	13.30%
RAVLT immediate recall	28.53	41.58±9.75	45.51±8.82	36.08±8.42	20.00%
RAVLT delayed recall	4.69	9.11±2.95	9.82±3.00	8.12±2.67	6.70%
ROCF copy	28.88	32.50±4.22	34.83±1.50	29.23±4.66	46.70%
iRBD-NC: isolated REM behaviour disorder-normal cognition; CI: cognitive impairment; SD: standard deviation; RAVLT: Rey Auditory Verbal Learning test; ROCF: the Rey-Osterrieth complex figure.					

The QSPT is a sensitive tool that detects subtle visuoperceptual changes in iRBD (Galbiati, Carli, et al. 2019). Thus, in addition to the standard neuropsychological battery, we evaluated QSPT measures in our cohort of iRBD patients. Of note, 19% (7 out of 37) of iRBD subjects presented pathological total QSPT scores, further highlighting the prevalence of visuospatial/visuoperceptive deficits in iRBD (Table 6).

Table 6. QSPT measures in 37 iRBD.

	Cut-off values (Lowest quartile)	**iRBD (Mean±SD) (n 37)**	**iRBD under cut-off (%) (n 37)**
Number of angles QSPT	4.00	3.88±0.34	13.50%
Distance/Intersection QSPT	4.00	3.61±0.97	21.60%
Closure/opening QSPT	0.5	0.95±0.69	18.90%
Rotation QSPT	1.5	1.66±0.53	18.90%
Closing-in QSPT	1.00	0.96±0.14	8.10%
Total score QSPT	10.5	11.05±1.52	18.9%
QSPT: qualitative scoring of Pentagon Test; iRBD: isolated REM behaviour sleep disorder; SD: standard deviation.			

Considering hypometabolic features, most subjects with iRBD-CI expressing the occipitoparietal hypometabolism pattern showed visuo-constructional deficits (5 out of 7). One patient showed both visuo-constructional and language comprehension deficits and one executive, language, short- and long-term memory impairments. Among iRBD-CI patients with occipito-cerebellar hypometabolism pattern, four had short-term memory deficits, language deficits, two visuo-constructional deficits and one executive impairment. For the iRBD-CI subject with occipital hypometabolism pattern, only short-

term memory impairment was detected. Last, the iRBD-CI subject with a cerebellar hypometabolism pattern showed only working memory deficits (Table 7).

Table 7. Cognitive impairments in iRBD-CI grouped by hypometabolism features.

	iRBD-CI with OP (n 7)	**iRBD-CI with OCBL (n 6)**	**iRBD-CI with O (n 1)**	**iRBD-CI with CBL (n 1)**
Executive deficits (Attentional matrices, Raven Colored Progressive Matrices, Phonemic and semantic verbal fluency)	14.29% (1/7)	16.67% (1/6)	0.00% (0)	0.00% (0)
Language deficits (Phonemic and semantic verbal fluency, Token test)	14.29% (1/7)	33.33% (2/6)	0.00% (0)	0.00% (0)
Short-term memory deficits (Digit span forward and backward, RAVLT immediate recall, Corsi block-tapping test)	14.29% (1/7)	66.67% (4/6)	100.00% (1)	100.00% (1)
Long-term memory deficits (RAVLT delayed recall and ROCF recall)	14.29% (1/7)	0.00% (0)	0.00% (0)	0.00% (0)
Visuo-constructional deficits (ROCF copy)	71.43% (5/7)	33.33% (2/6)	0.00% (0)	0.00% (0)

IRBD-CI: isolated REM sleep behaviour disorder with cognitive impairment; RAVLT: Rey Auditory Verbal Learning Test; ROCF: the Rey-Osterrieth complex figure; OP: occipito-parietal hypometabolism pattern; OCBL: occipito-cerebellar hypometabolism pattern; O: occipital hypometabolism pattern; CBL: cerebellar hypometabolism pattern.
% of subjects presenting cognitive deficits

These results emphasise that the visuo-constructive domain is susceptible to deterioration in iRBD (Table 5 and 6), representing an early cognitive marker of the underlying neurodegeneration process. Cognitive deficits were also related to the topography and cluster extent of brain hypometabolism. Visuo-constructive impairments characterized iRBD-CI patients with extended occipital hypometabolism (occipito-parietal and occipito-cerebellar), namely the majority of iRBD-CI (87%) (Table 7). However, occipito-parietal iRBD patients presented homogeneous neuropsychological profiles, consisting of visuoconstructional deficits (Table 7); the occipito-cerebellar subgroup presented heterogeneous neuropsychological profiles instead, characterized by executive, language, short-term and working memory deficits in addition to the visuo-

constructive ones (Table 7). Of note, iRBD patients with [18F]FDG-PET negative scans did not present cognitive impairments.

3.2.2. Study IIIb: Exploring the functional role and neural correlates of K-complexes in isolated rapid eye movement sleep behaviour disorder. (Galbiati et al. 2021) *- Published Article -*

The neuropsychological evaluation showed that a relevant percentage of patients had cognitive impairments, especially in visuospatial abilities (ROCF copy) and short-term memory (Rey Auditory Verbal Learning Test (RAVLT) immediate recall). 51.5% of the subjects satisfied the criteria for the presence of MCI (Albert et al. 2011). Table 8 describes neuropsychological evaluation.

Table 8 Neuropsychological evaluation of iRBD cohort.

Neuropsychological tests	**Cut-off values (corrected scores)**	**Mean corrected* scores ± SD**	**% of patients with impaired performance**
MMSE	23.80	28.07 ± 1.99	0%
Attentional Matrices	31.00	48.22±6.30	3.2%
Raven Colored Progressive Matrices	18.00	29.88±4.06	0%
Verbal fluency with phonemic cue	17.00	32.16±11.54	0%
Verbal fluency with semantic cue	25.00	44.12±8.59	3.2%
Token Test	26.50	33.51±1.76	3.4%
Digit Span forward	4.26	5.87±1.02	6.5%
Digit Span backward	2.65	4.33±1.22	3.2%
Corsi block-tapping test	3.46	5.13±0.90	6.5%
RAVLT immediate recall	28.53	43.13±9.45	12.9%
RAVLT delayed recall	4.69	9.26±2.72	3.2%
ROCF copy	28.88	32.78±2.96	16.1%
ROCF recall	9.47	19.43±5.56	0%

SD: standard deviation; RAVLT: Rey Auditory Verbal Learning test; ROCF: the Rey-Osterrieth complex figure.

The KC density positively correlated with MMSE scores ($r = 0.33$ $p < 0.05$). Of note, higher KC density was significantly associated with better performances in visuo-constructive abilities (ROCF Copy) ($r= 0.49$ $p < 0.005$) and executive functions (Raven Colored Progressive Matrices) ($r = 0.54$ $p < 0.001$) (Figure 46). By dividing the sample in patients with and without MCI we found that the first were characterized by a significant decrease in KC density (iRBD+MCI 0.81 ± 0.61 vs. iRBD-MCI 1.28 ± 0.38, $p < 0.05$) (Figure 46).

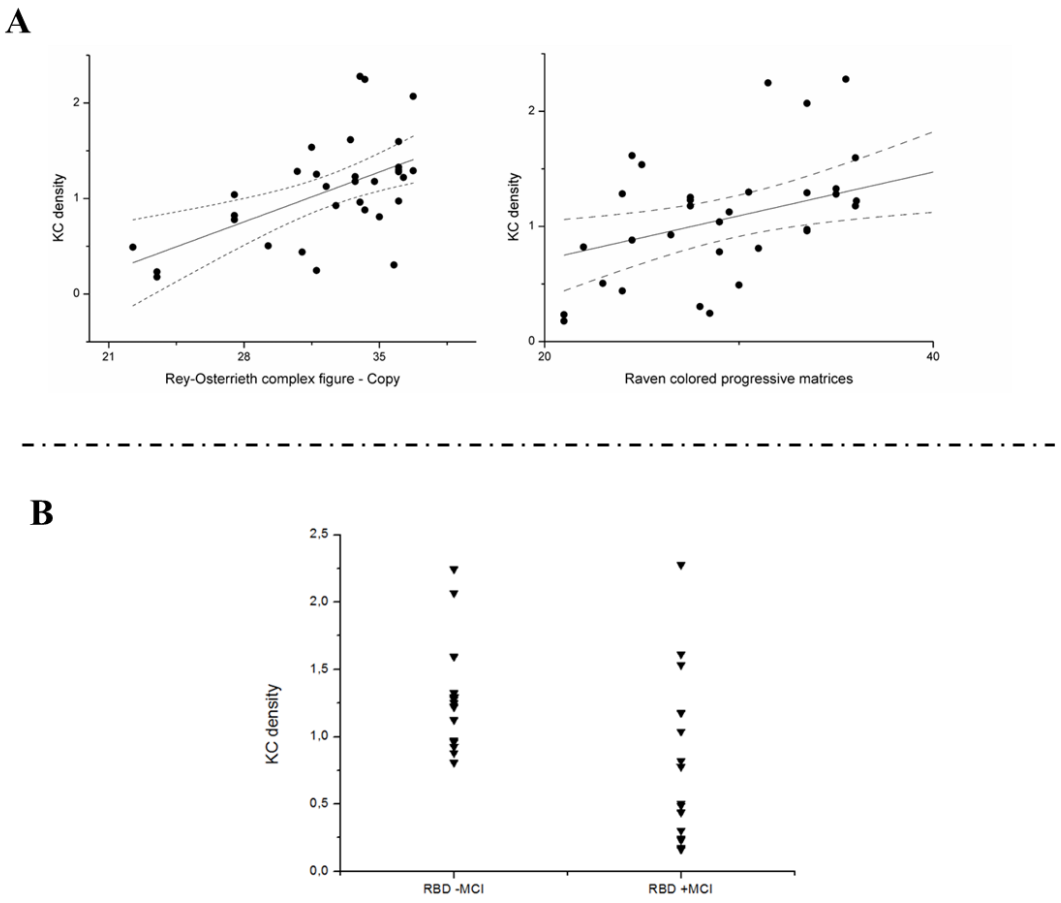

Figure 46. Relationship between KC density and cognitive functioning in iRBD (Fair use).

Panel A depicts significant correlations between KC density and performances in ROCF copy and Raven matrices. Panel B KC density in RBD+MCI and RBD-MCI patients. Abbreviations: KC: K complex; RBD: REM sleep behaviour disorder; MCI: Mild cognitive impairment. The figure is adapted from (Galbiati et al. 2021) *in accordance to the fair use principle.*

Thus, we found that patients characterized by increased levels of KC density showed a more preserved cognitive functioning, specifically regarding visuo-spatial and executive

abilities. All the above suggests a protective role of this EEG element of NREM sleep in the α-synuclein related pathological process since this early stage.

3.2.3. Study IVb: Clinical and Dopamine Transporter Imaging Trajectories in a Cohort of Parkinson's Disease Patients with GBA Mutations. (Caminiti, Carli, et al. 2021)*. - Published Article -*

Regarding clinical variables, the GBA-PD group showed significantly higher scores in Hoehn and Yahr, UPDRS-III, UPDRS total, and SCOPA-AUT than early-iPD. However, they did not differ from late-iPD. In RBD Questionnaire (RBDSQ), the GBA-PD group had higher values than both the early-iPD and late-iPD groups. Regarding cognitive functioning, GBA-PD' MoCA scores were lower than the early-iPD but comparable to the late-iPD (Table 9).

Table 9 Demographic and clinical features at baseline in GBA-PD and iPD groups.

Baseline	**GBA-PD (N=46) Mean±SD**	**Early-iPD (N=58) Mean±SD**	**Late-iPD (N=281) Mean±SD**	**Statistic**	**GBA-PD vs. Early-iPD**	**GBA-PD vs. Late-iPD**	**Early-iPD vs. Late-iPD**
Gender(M/F)	26/20	33/25	193/88	p=0.091	--		
Age onset(years)	57.4±10	44.5±5.5	63.6±7.0	**p=0.000**	**p=0.000**	**p=0.001**	**p=0.000**
Age baseline(years)	58.9±9.6	47±4.8	64.8±7.1	**p=0.000**	**p=0.001**	**p=0.000**	**p=0.000**
Age(years; MIN-MAX)	29-81	33-54	51-84	--	--	--	--
Education(years)	15.9±2.9	15.7±2.8	15.4±3.1	p=0.333	--	--	--
Disease Duration(years)	1.5±1.4	2.5±3.2	1.3±1.6	**p=0.003**	p=0.441	p=0.693	**p=0.003**
Hoehn and Yahr scale b	1.9±0.3	1.6±0.5	1.8±0.6	**p=0.001**	**p=0.002**	p=0.673	**p=0.003**
UPDRS part III b	28.9±10.2	21.7±10.8	26.7±12.2	**p=0.002**	**p=0.003**	p=0.654	**p=0.006**
UPDRS Total score b	41.5±12.6	33.7±16	38.0±15.6	**p=0.012**	**p=0.013**	p=0.516	p=0.057
MoCA Total score b	26.9±2.5	28.1±2.3	27.0±2.3	**p=0.003**	**p=0.016**	p=1.000	**p=0.004**
SCOPA-AUT Total score b	15.7±12.4	11.4±7.8	14.1±9.4	**p=0.004**	**p=0.017**	p=1.000	**p=0.006**
RBDSQ score b	4.4±3.0	3±2.3	3.1±2.6	**p=0.004**	**p=0.027**	**p=0.003**	p=1.000

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus; n: Number; SD: Standard Deviation; UPDRS: Unified Parkinson's Disease Rating Scale; RBDSQ: Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT: Scale for Outcomes for Parkinson's Disease—autonomic function. * Corrected for Bonferroni; b Controlled for disease duration and gender.

After a mean of 1.75 years ("≈2-yrs" Follow-up), the GBA-PD and late-iPD groups showed significantly higher SCOPA-AUT scores than early-iPD (Table 10).

Table 10. Demographic and clinical features at Follow-up 1 in GBA-PD and iPD groups.

Follow-up-1 (Mean of 1.75 years)	**GBA-PD (N=22) Mean±SD**	**Early-iPD (N=19) Mean±SD**	**Late-iPD (N=135) Mean±SD**	**Statistic**	**GBA-PD vs. Early-iPD**	**GBA-PD vs. Late-iPD**	**Early-iPD vs. Late-iPD**
Age at Follow-up (years)	58.1 ±7.5	47.2 ±5.1	65.8 ±7.5	**p=0.000**	**p=0.000**	**p=0.000**	**p=0.000**
Age (years, MIN-MAX)	39-78	34-55	52-85	--	--	--	--
FU duration (years)	2.0±1.3	2.1±1.9	1.7 ±1.1	p=0.226	--	--	--
Disease duration (years)	3.5±2.7	3.6±3.6	2.8±2.2	p=0.222	--	--	--
LEDD	461±301.1	403.2±275.9	400.8±364.1	p=0.753	--	--	--
Hoehn and Yahr scale b	1.8±0.4	1.8±0.4	1.9±0.5	p=0.632	p=1.000	p=1.000	p=1.000
UPDRS part III b	27.2±8.9	25.0±9.3	28.0±11.2	p=0.595	p=1.000	p=1.000	p=0.947
UPDRS Total score b	43±16.2	40.4±16.7	43.7±16.2	p=0.774	p=1.000	p=1.000	p=1.000
MoCA Total score b	26.3±3.7	27.3±3.4	25.7±3.3	p=0.203	p=0.990	p=1.000	p=0.236
SCOPA-AUT Total score b	14.9±8.9	8.2±5.1	12.2±6.4	**p=0.006**	**p=0.004**	p=0.243	**p=0.044**

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus; n: Number; SD: Standard Deviation; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; RBDSQ: Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT: Scale for Outcomes for Parkinson's Disease—autonomic function; * Corrected for Bonferroni; b Controlled for LEDD.

After the 6-year follow-up ("≈6-yrs" Follow-up), the GBA-PD patients presented significantly more severe UPDRS-III and MoCA scores than early-iPD (Table 11).

Table 11. Demographic and clinical features at Follow-up 1 in GBA-PD and iPD groups.

Follow-up-2 (Mean of 6 years)	**GBA-PD (N=45) Mean±SD**	**Early-iPD (N=56) Mean±SD**	**Late-iPD (N=269) Mean±SD**	**Statistic**	**GBA-PD vs. Early-iPD**	**GBA-PD vs. Late-iPD**	**Early-iPD vs. Late-iPD**
Age at Follow-up (years)	58.9±9.6	47.0±4.8	64.8±7.1	p=0.000	**p=0.001**	**p=0.000**	**p=0.000**
Age at Follow-up(years)	38-88	39-62	55-91	--	--	--	--
Age(years, MIN-MAX)	6.0±2.0	6.3±1.7	6.1±2.0	p=0.897	--	--	--
FU duration(years)	7.6±2.7	8.7±3.2	7.4±2.5	**p=0.015**	p=0.180	p=1.000	**p=0.012**

Disease duration(years)	214.6±311.2	323.5±413.8	408.7±1248	p=0.325	--	--	--
LEDD	2.0±0.7	1.9±0.5	1.9±0.6	p=0.516	p=1.000	p=0.797	p=1.000
Hoehn and Yahr scale b	30.4±14.5	21.9±9.4	26.3±12.0	**p=0.044**	**p=0.043**	p=0.180	p=0.540
UPDRS part III b	46.6±17.7	36.0±13.5	41.3±17.2	p=0.078	p=0.083	p=0.258	p=0.705
UPDRS Total score b	24.6±6	28.3±2.5	25.1±4.5	**p=0.011**	**p=0.018**	p=1.000	**p=0.017**
MoCA Total score b	20.9±11.2	16.0±10.6	21.1±11.7	**p=0.033**	p=0.193	p=1.000	**p=0.027**

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus; n: Number; SD: Standard Deviation; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; RBDSQ: Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT: Scale for Outcomes for Parkinson's Disease—autonomic function. * Corrected for Bonferroni; b Controlled for LEDD, disease duration and gender.

The longitudinal progression analysis from "≈2-yrs" to "≈6-yrs" visits showed a significantly faster global cognitive deterioration in the GBA-PD group than in the early-iPD group (p=0.043) (Figure 47). Over this follow-up period, GBA-PD patients lost 0.29 MoCA points per year, and early-iPD patients remained stable. The three groups had no significant differences in the other considered clinical variables. Of note, at "≈6-yrs" follow-up, the 10% of GBA-PD and the 17% of late-iPD patients were below the MoCA cut-off score of 26, with 1.63 MoCA points lost per year in GBA-PD and 1.34 points lost per year in late-iPD. The 75% (3 out of 4) of sGBA genotype moved from normal to pathological MoCA values from baseline to "≈6-yrs" visit. The early-iPD group was instead stable over time. Figure 47 shows the clinical progression of each clinical group in all clinical variables, considering three time points – baseline, "≈2-yrs","≈6-yrs" visits.

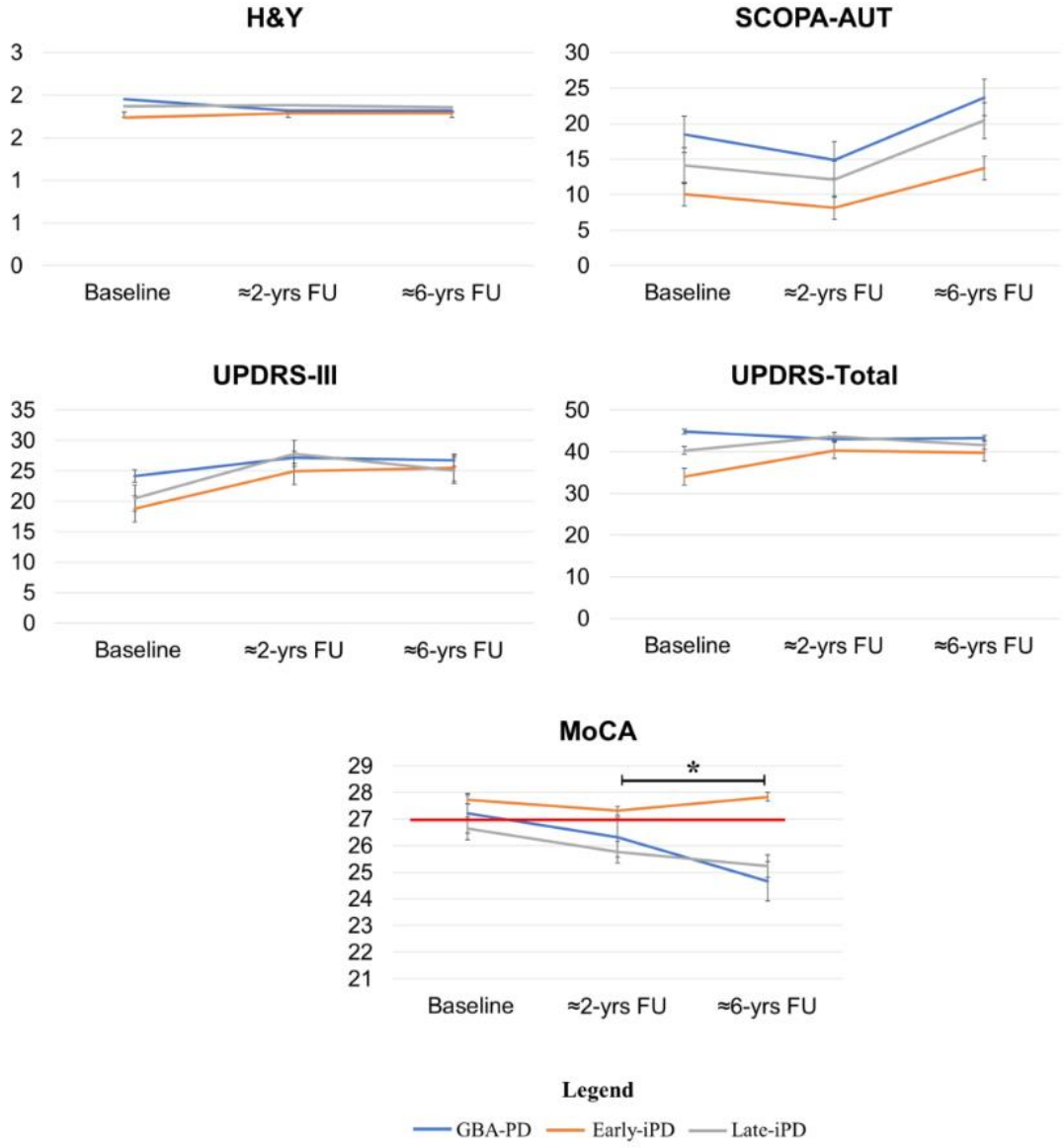

Figure 47. Clinical progression at three time-point of GBA and iPD groups (Fair use).

*Longitudinal changes in outcomes of interest in GBA-PD and iPD groups (GBA-PD in blue, early-iPD in orange, and late-iPD in grey) at three time-points (GBA=22; Early-iPD=19 and Late-iPD=127). Mean follow-up duration in the entire population at early follow-up = 1.74 years and last available follow-up = 6.40 years. The Redline in the MoCA panel represents the clinical cut-off. * Significant differences in the rate of changes. The dark line represents the longitudinal time frame from 2 to 6 years follow-up. Abbreviations: H&Y= Hoen & Yahr; SCOPA-AUT= Scales for Outcomes in Parkinson's disease – Autonomic dysfunction; UPDRS= Unified Parkinson's Disease Rating Scale; MoCA= Montreal Cognitive Assessment; iPD= idiopathic Parkinson 'disease; y= years; FU = follow-up. The figure is adapted from* (Caminiti, Carli, et al. 2021) *in accordance to the fair use principle.*

Clinical and cognitive results demonstrated that GBA-PD and late-iPD manifest a comparable clinical and cognitive deterioration, compatible with the definition of "diffuse malignant" PD clinical phenotype. On the other hand, early-iPD represents a PD clinical condition characterized by a slow disease course, stable cognitive progression, and limited dopaminergic deficits (see *Part 1 Study IVa*).

3.2.4. Study V: Distinct brain dysfunctions underlying visuo-constructive deficit in DLB and AD. (Beretta et al. 2021)*. - Published Article -*

Drawing and copying performance is widely used to identify visual perception and visual construction capabilities because it is easy to manage and sensitive to neurodegeneration (Ericsson et al. 1996). In drawing tasks, ROCF-c is the most commonly used (Caffarra et al. 2002; Di Pucchio et al. 2018). Specifically, ROCF-c performance seems to be regulated by specific skills mediated by different brain regions, namely, visual perception (mediated by the occipital regions), visual-spatial processing and integration (mediated by the parietal lobe), or executive skills (mediated by the frontal regions) (Kravitz et al. 2011; Trojano and Gainotti 2016). Thus, considering its complexity, ROCF-c deficits might be due to several different pathological mechanisms.

The presence of visuo-constructive impairments is a cognitive marker in DLB patients (Trojano and Gainotti 2016). Occasionally also AD might exhibit visuo-constructive deficits, even if with a lower degree of severity compared to DLB (Gurnani and Gavett 2017). It is unclear whether the neuropsychological and neuroanatomical basis of visuo-constructive impairments in DLB differs from AD. In DLB patients, for example, pure visuoperceptive errors (occipitally-mediated) are more likely, whereas, in AD patients, visuospatial errors (parietally-mediated) may be more likely to occur with preserved visuoperceptive processing (Beretta et al. 2019). It is well-known that a significant relationship between cognition and brain hypometabolism in dementia exists (Perani 2013). This study aimed to examine whether ROCF-c performances in DLB and AD were associated with different anatomical dysfunctional substrates, as measured by [18F]FDG-PET. We hypothesized distinct correlations in the DLB group and the typical-AD group. This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital (Milan) in collaboration with the Section of Neuroscience of the University of Parma (Parma).

The present study and relative datasets were already published in the Journal of Brain Imaging and behaviour on 7th September 2021 (https://doi.org/10.1007/s11682-021-00515-7).

We included 45 patients with probable DLB and 34 with probable typical-AD (see *5.1. Participants underwent [18F]FDG-PET exam*). Table 12 contains all demographic and clinical features of DLB and AD cohorts of patients. DLB and AD patients had altered performances in almost all cognitive tests. When we compared DLB and AD groups, we found that DLB patients had lower scores in the ROCF-c test than typical-AD patients; whereases typical-AD patients performed worse than DLB patients at the Short Story test. No significant differences between the two groups were found in the other cognitive tests.

Table 12. Demographic and clinical features of DLB and AD patients.

DEMOGRAPHIC FEATURES				
VARIABLES		**DLB (N = 45)**	**Typical-AD (N = 34)**	**p-value**
Gender		17 F – 28 M	17 F – 17 M	p = 0.196
Age		72.16 ± 7.33	66.41 ± 7.26	**p = 0.001 ***
Education		9.24 ± 4.13	12.13 ± 4.22	**p = 0.006 ***
Disease Duration		2.61 ± 2.05	2.57 ± 1.56	p = 0.902
DLB CORE CLINICAL FEATURES				
Hallucination (N, %)		23 (51%)	-	-
Cognitive fluctuations (N, %)		11 (24%)	-	-
Parkinsonism (N, %)		78 (35%)	-	-
RBD (N, %)		17(38%)	-	-
NEUROCOGNITIVE ASSESSMENT				
TESTS	**Cut-off (and range)**	**DLB (N = 45)**	**Typical-AD (N = 34)**	**p-value**
M.M.S.E.	< 24 (0 - 30)	21.03 ± 4.59	19.50 ± 4.33	p = 0.143 [a]
Semantic fluency	< 25 (0 - ∞)	25.16 ± 7.71	22.06 ± 11.23	p = 0.153 [a]
Phonemic fluency	< 17 (0 - ∞)	18.43 ± 11.24	16.09 ± 11.47	p = 0.373 [a]
Digit span – forward	< 4.26 (0 – 9)	4.86 ± 0.98	4.85 ± 0.92	p = 0.956 [a]
Corsi span – forward	< 3.46 (0 – 9)	2.75 ± 1.83	3.14 ± 0.86	p = 0.914 [b]
Short story	< 8 (0 – 28)	5.95 ± 4.58	2.02 ± 2.35	**p = 0.000** [b] *
ROCF– delayed recall	< 9.47 (0 – 36)	4.82 ± 4.90	5.32 ± 4.07	p = 0.598 [b]
ROCF – copy	< 28.88 (0 – 36)	12.11 ± 8.83	17.60 ± 10.14	**p = 0.012** [a] *
Attentive matrices	< 31 (0 – 60)	26.92 ± 12.93	27.59 ± 13.09	p = 0.825 [a]

Raven's coloured progressive matrices	< 18 (0 – 36)	19.14 ± 8.48	19.80 ± 6.13	p = 0.732 [a]
DLB: Dementia with Lewy bodies, AD: Alzheimer's dementia, N: sample size, F: female, M: male, ROCF: Rey-Osterrieth Complex Figure a: ANOVA, b: Mann-Whitney, *: significant effect ($p \leq 0.05$), in bold. Core symptoms are defined according to (McKeith et al. 2017).				

Regarding the hypometabolic features of the two groups, the DLB and AD showed distinct topography of hypometabolism distribution. DLB patients expressed a pattern of brain hypometabolism, involving bilaterally the lateral and medial occipital cortex, accompanied by hypometabolism in the temporo-parietal and frontal cortex. The typical-AD group was characterized by bilateral temporo-parietal hypometabolism, involving the precuneus and posterior cingulate cortex (Figure 48A).

In the whole group emerged a significant negative correlation between ROCF-c test scores and regional hypometabolism involving three clusters: right occipital area (calcarine cortex and middle occipital gyrus), calcarine cortex and temporo-parietal cortex. Thus, a more severe ROCF-c impairment corresponded to a greater regional hypometabolism in these regions. When we tested this relationship in clinical groups separately, different effects emerged. The DLB group showed a significant correlation between the lower performances at the ROCF-c test and the hypometabolism in the right occipital areas, calcarine cortex, bilaterally, and temporo-parietal cortex. The typical-AD group showed only a trend towards a negative correlation in the temporo-parietal cortex. Figure 48B gathers all these results. Presence/absence of DLB core clinical features (parkinsonism, hallucination, cognitive fluctuation, or RBD) did not modulated the correlation between the ROCF-c scores and brain hypometabolism (right occipital areas (cluster1): R Square Change=0.113, p=0.207; calcarine cortex (cluster2): R Square Change=0.021, p=0.882; temporo-parietal cortex (cluster3): R Square Change=0.071, p= 0.486).

These results demonstrated that ROCF-c impairments in DLB and AD patients result from the different anatomical dysfunctions. Specifically, in DLB, visuo-constructive deficits might be related to alterations in visuoperceptual processes (resulting from severe occipital hypometabolism), while, in AD, the same deficit might be due to visuospatial processes (arise from temporo-parietal hypometabolism).

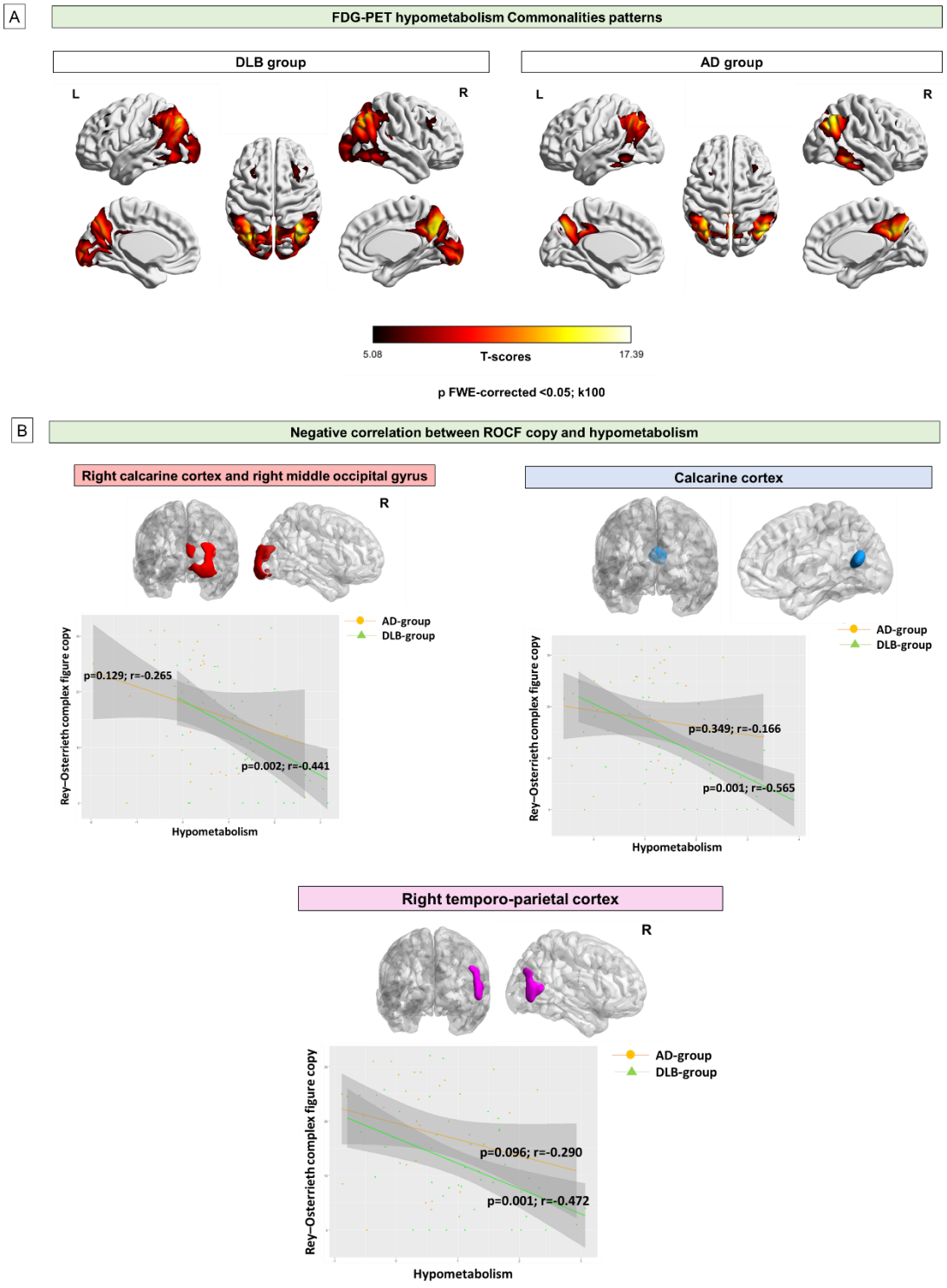

Figure 48. Hypometabolic correlates of ROCF-c (Fair use).

Panel A reports [18F]FDG-PET brain hypometabolism patterns in DLB and AD groups. The yellow/red intensity scale represents the distribution of t values. Panel B depicts the correlation between [18F]FDG-PET and ROCF-c scores in DLB and AD groups. Abbreviations: AD: Alzhaimers'disease, DLB: Dementia with Lewy Bodies; ROCF: Rey–Osterrieth Complex Figure;

FWE: Family Wise Error; R: right and L: left. The figure is adapted from (Beretta et al. 2021) *in accordance to the fair use principle.*

3.3. Part 3. Biological, gender and environmental sources of phenotypic variability of LB disorders

3.3.1. Study VI: Gender-related vulnerability of dopaminergic neural networks in Parkinson's disease. (Boccalini et al. 2020)*. - Published Article -*

LB are the pathologic hallmark of PD (McCann et al. 2014). The LB inclusions lead to neurodegeneration of SN neurons and their projections to basal ganglia leading to alteration of movements (Obeso et al. 2017). Moreover, variable levels of dopaminergic neural loss in the VTA have been documented by *postmortem* data (Surmeier and Sulzer 2013). The projections of VTA dopaminergic neurons give rise to the mesolimbic dopamine system – reaching the nucleus accumbens, amygdala, hippocampus, and prefrontal cortex (Barth, Villringer, and Sacher 2015). Nonmotor features that characterize PD (e.g. depression and anxiety) can be associated with damage in the dopaminergic mesolimbic system (Castrioto et al. 2016; Gustafsson, Nordström, and Nordström 2015).

PD has a different clinical and endophenotypic manifestation in males and females (see *1.7.2. Sex and gender-related differences*). Dopaminergic preservation in striatal structures of women compared to men has been demonstrated by different molecular imaging studies (Kaasinen et al. 2015; Koch et al. 2014; Eusebio et al. 2012). However, there is a lack of data on gender differences in the mesolimbic dopaminergic system, which may be related to neuropsychiatric symptoms. Thus, studies exploring *in vivo* the gender influence on neurotransmitter circuits in PD can optimise individual treatments and interventions.

Applying multivariate methods to [18F]FDG-PET data can reliably assess key brain characteristics, such as metabolic network connections (see *Part 1 Study II*). In particular, brain metabolic connections are affected by multiple pathological events, including altered neurotransmission (Sala and Perani 2019). Previous evidence reveals a significant coupling between neurotransmission disorders and metabolic network integrity (Niethammer et al. 2013; Ko, Lee, and Eidelberg 2017; Massa et al. 2019; Huber

et al. 2020). In PD and DLB, [18F]FDG-PET based metabolic network expression and dopamine availability provided consistent information for the disease process (Caminiti et al. 2017; Caminiti et al. 2017; Sala et al. 2017).

This study used the brain metabolic connectivity approach to investigate gender differences in the nigro-striato-cortical and mesolimbic dopaminergic networks in a cohort of idiopathic PD patients. Following previous evidence in the literature and the estrogen-induced neuroprotection hypothesis, we can expect two scenarios: (i) a more severe metabolic connectivity alteration in the nigro-striato-cortical system in PD males; and (ii) more significant connectivity alterations in the female mesolimbic system due to the high frequency and severity of neuropsychiatric symptoms in PD females (Martinez-Martin et al. 2012). This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital (Milan) in collaboration with the Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia. The present study and relative datasets were already published in the Journal of Brain Connectivity on 12th February 2021 (https://doi.org/10.1089/brain.2020.0781).

We included 34 PD patients (age [mean ± SD] 62.97±10.48 years; gender [F/M]: 16/18) without cognitive impairment at baseline and after eight years of follow-up (see 5.1. *Participant underwent [18F]FDG-PET exams*). Table 13 contains the demographic and clinical features of iPD females and males. Forty-four healthy age-matched volunteers (age [mean ± SD] 62.52±4.52 years; gender [F/M] 16/18) were also included for brain metabolic connectivity analysis as the control group. Males and females not differed in demographical and clinical data, including medication state.

The metabolic connectivity analyses on the nigro-striato-cortical dopaminergic network revealed a widespread alteration of metabolic connectivity in PD males (34.69% of altered connections in comparison to HC) (Figure 48). The same network resulted relatively spared in PD females (17.35% changes compared to HC) (Figure 48). When we compared PD males and females, we found that the metabolic connectivity alteration of nigro-striato-cortical network was significantly more severe in PD males compared to PD females ($X2= 7.65$, p-value < 0.005) (Figure 49).

Regarding the mesolimbic dopaminergic system, we found widespread connections alterations in PD females (55.10% of altered connections compared to HC). PD males showed limited alteration in the same network (1.02% of altered connections

compared to HC) (Figure 49). All the presented connectivity results had a p-value <0.01, corrected for Bonferroni multiple comparisons. The comparison between PD males and females confirmed a significantly more severe alteration in PD females compared to PD males (X2= 70.99, p-value < 0.00001) (Figure 49).

Table 13. Demographic and clinical features of iPD females and males.

	PD whole Group	**PD Females**	**PD Males**	***Statistic***
Number of patients	34	16	18	
Gender (F/M)	16/18	-	-	-
Age in year, y (means ± S.D)	62.97±10.48	63.35±11.36	63.31±10.54	p=0.935
Disease durations, y (means ± S.D)	4.16±2.52	4.00±2.41	4.31±2.67	p=0.741
MMSE, corrected scores (means ± S.D)	28.56±1.54	28.50±1.60	28.62±1.54	p=0.830
Years of education, y (means ± S.D)	8.03±4.19	6.92±4.00	9.00±4.22	p=0.181
UPDRS III, corrected scores (means ± S.D)	14.63±6.94	15.14±7.79	14.18±6.33	p=0.714
Daily LEDD, mg (means ± S.D)	125.08±128.35	126.45±156.81	124.06±107.79	p=0.962

M: male, F: female; Y: years; S.D: standard deviation; MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; LED: levodopa equivalent dose; p: p-value.
The differences were tested using ANOVA

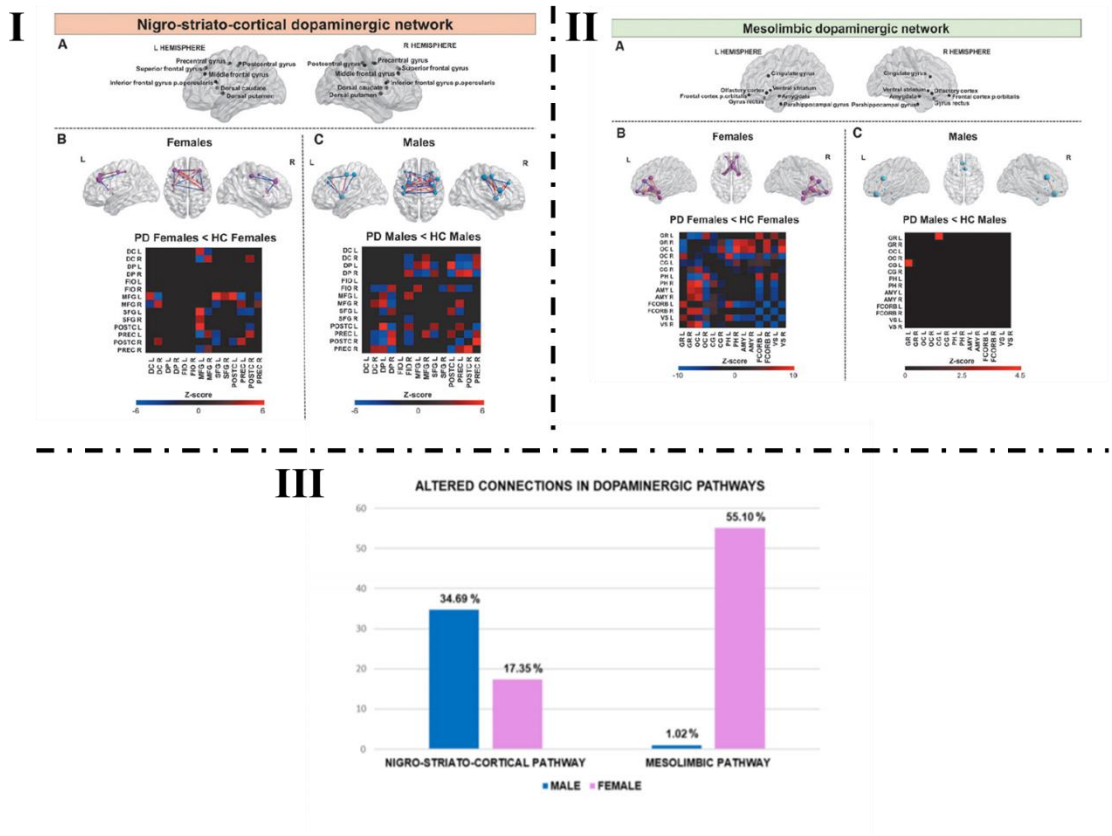

Figure 49. Gender differences in metabolic connectivity of dopaminergic networks (Fair use).

3D brain templates display (I and II A) the nodes of the network in the left and right hemispheres; (I and II B) the PD network connectivity graphs for females; and (I and II C) the PD network connectivity graphs for males. The altered connections are presented in (I and II B, C): the increased and the decreased connections compared with HC. The dimension of each node (dot size) depends on the total node number of connections. Below, dopaminergic nigro-striato-cortical and mesolimbic network's connectivity matrices of PD females (I and II B) and males (I and II C) are displayed. The matrices represent the significant differences obtained when comparing partial correlation coefficients between PD females < HC (I and II B) and PD males < HC (I and II C) in the dopaminergic nigro-striato-cortical network. The colour bar displays the Z scores' values for the comparison of partial correlation coefficients' strengths. The III panel depicted the histograms representing the percentage of altered connections in the dopaminergic pathways compared with the control group: nigro-striato-cortical and mesolimbic networks in PD females (pink) and males (blue). For abbreviations, see Supplementary Table A 1 and A2. 3D: three-dimensional; PD: Parkinson's disease; HC: healthy controls. The figure is adapted from (Boccalini et al. 2020) *in accordance to the fair use principle.*

Our results suggest a specific gender vulnerability of the dopaminergic networks in PD, proposing that different pathological substrates might underly motor and psychiatric symptoms characterize male and female PD (Cerri et al. 2019).

3.3.2. Study VII: Gender differences in dopaminergic dysfunction and molecular connectivity in Parkinson's disease clinical subtypes (Boccalini, Carli*, Pilotto et al., 2021, Submitted Neurobiology of Disease).*

Different PD clinical subtypes have recently been described: mild motor predominant, intermediate, and diffuse malignant (Fereshtehnejad et al. 2017). Patients with diffuse malignant PD have an earlier and more severe motor and non-motor symptoms, insufficient response to drugs and rapid disease deterioration (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). Patients with mild motor predominant subtype are characterized by moderately impaired motor and non-motor functions, slower progression, younger age of onset, and good drug response (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). The intermediate subtype represents an intermediate clinical condition characterized by onset, clinical severity, and progression rate between mild and malignant phenotypes (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). Patients with diffuse malignant subtypes have more prominent striatal dopaminergic defects. Indeed, compared with other subtypes, the level of caudate nucleus denervation is the highest (Fereshtehnejad et al. 2017). This PD classification is in line with the spectrum between relatively SN-based diseases and multi-pathway diffuse neurodegenerative diseases (Armstrong and Okun 2020; Fereshtehnejad et al. 2017). The prognostic value of this subtype classification is further confirmed by the longitudinal clinical course and survival data and neuropathological correlation in the independent PD cohort (De Pablo-Fernández et al. 2019).

Despite increasing interest in PD gender-related vulnerabilities, the effect of gender on different PD subtypes (with different clinical trajectories) is unclear. Gender and phenotype can interact, leading to distinct vulnerabilities. For example, it can be assumed that gender differences may decrease as the severity of the disease increases; a large amount of pathological load may flatten differences based on hormonal compensation or environmental risk factors. This study aims to investigate gender differences in PD clinical subtypes because of their relevance in the clinical trajectories and underlying neurodegeneration (De Pablo-Fernández et al. 2019; Fereshtehnejad et al. 2017). In a large PPMI cohort of newly diagnosed and drug-naïve idiopathic PD, we investigated whether gender modulates the endophenotype and clinical phenotype of iPD patients stratified according to clinical criteria of PD subtypes (Fereshtehnejad et al.

2017). Specifically, we take into consideration i) the presenting symptom, ii) the amount of dopaminergic presynaptic dysfunction in striatal and extra-striatal regions assessed using [123I]FP-CIT-SPECT, and iii) the gender-related vulnerability in the molecular architecture of dopaminergic systems (nigrostriatal and mesolimbic pathways).

We included 286 drugs naïve iPD who underwent baseline [123I]FP-CIT-SPECT imaging and T1-weighted MRI within one year (see *5.2. Participants underwent [123I]FP-CIT-SPECT exam*). For all iPD subjects, we collected clinical baseline data from the PPMI database (Marek et al. 2018; Marek et al. 2011).

Following the practical clinical classification method (Fereshtehnejad et al. 2017), we assigned each iPD patient to a specific subtype: the mild motor predominant (N=155), the intermediate (N=119), and the diffuse malignant (N=12). We also included 73 HC subjects (age [mean ± SD] 65.54 ± 9.67 years; gender [F/M] 34/39) as a control group for DA connectivity analysis.

Clinical gender differences

Whole iPD - In the whole iPD group, male patients presented a significantly higher visuospatial performance, assessed by Benton Judgment of Line Orientation (JOLO), compared to females. Females showed significantly higher State-Trait Anxiety Inventory (STAI), SCOPA-AUT, Hopkins Verbal Learning Test (HVLT), Semantic fluency, and Symbol-Digit Modalities Test (SDMT) scores than males. The thermoregulatory component produced the significant gender difference in SCOPA-AUT, where females showed higher scores than males (females = 1.54±1.51; males = 0.91±1.21; p=0.000). Female patients showed higher motor symptoms asymmetry than males (females = 8.15±4.65; males = 7.02±4.06; p=0.066). Table 14 shows the demographic and clinical comparison between females and males in the whole iPD cohort.

Table 14. Demographic and clinical differences between females and males in the whole iPD cohort.

	iPD Males	**iPD Females**	***statistic***
Demographic Features			
N	189	97	
Age (mean±sd)	62.32±9.69	61.35±9.65	*p=0.24*
Education (mean±sd)	15.71±2.80	15.02±3.06	***p=0.03***
Disease Duration, y (mean±sd)	2.05±2.15	2.14±2.34	*p=0.561*
Clinical non-motor assessment (mean±sd)			
MoCA	27.02±2.30	27.41±2.24	*p=0.233*
REM Sleep Disorder Questionnaire	4.40±2.90	4.26±2.61	*p=0.748*
Epworth Sleepiness Scale	5.94±3.33	5.51±3.42	*p=0.33*
SCOPA-AUT	10.99±8.68	15.89±9.65	***p=0.000***
UPSIT	22.08±8.18	24.05±8.63	*p=0.096*
Motor assessment (mean±sd)			
Schwab and England ADL scale	93.54±5.77	93.65±6.09	*p=0.775*
Hoehn and Yahr Staging	0.45±0.85	0.42±0.66	*p=0.472*
UPDRS total score	31.67±13.69	31.21±13.51	*p=0.893*
UPDRS I	5.48±3.96	6.27±4.68	*p=0.129*
UPDRS II	5.7±4.04	5.59±4.53	*p=0.921*
UPDRS III	20.5±9.17	19.34±8.02	*p=0.369*
Neurobehavioral assessment (mean±sd)			
GDS	5.3±1.46	5.27±1.23	*p=0.792*
QUIP	0.31±0.781	0.42±1.11	*p=0.368*
STAI- state score	46.81±5.40	48.48±5.29	***p=0.012***
STAI- trait score	45.66±4.57	47.01±3.60	***p=0.01***
STAI- total score	92.47±8.44	95.49±7.03	***p=0.002***
Cognitive assessment (mean±sd)			
Benton Judgment of Line Orientation	12.53±2.75	11.19±3.05	***p=0.000***
Letter Number Sequencing	11.33±2.63	11.42±2.78	*p=0.862*
HVLT total immediate recall t-score	43.81±10.98	48.91±9.93	***p=0.000***
HVLT delayed recall t-score	43.38±10.83	47.27±11.10	***p=0.005***
HVLT recognition t-score	43.84±10.862	46.55±11.83	*p=0.064*
Semantic Fluency t-score	46.05±10.62	52.65±11.05	***p=0.000***
Symbol Digit t-score	44.68±8.85	47.89±8.50	***p=0.004***

Abbreviations: iPD, idiopathic Parkinson's disease; N, Number; sd, standard deviation; y, years; MoCA, Montreal Cognitive Assessment; UPSIT, Smell identification test; UPDRS, Unified Parkinson's Disease Rating Scale; GDS, Geriatric Depression Scale; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; STAI, State-Trait Anxiety Inventory; HVLT, Hopkins Verbal Learning Test

Mild motor subtype - Females showed significantly higher performance in memory (HVLT), executive function (Semantic fluency), and processing speed (SDMT) than males. Female and male patients did not differ in motor symptoms asymmetry (p=0.183).

Intermediate subtype - Males presented significantly higher visuospatial performance (JOLO) than females, and more severe sleep disorders, as measured by Epworth Sleepiness Scale and RBDSQ than females. Females showed significantly higher anxiety (STAI) and autonomic deficits (SCOPA-AUT) and better cognitive performances – memory (HVLT), executive function (semantic fluency), and processing speed (SDMT) – than males. Female and male patients did not differ in motor symptoms asymmetry (p=0.225).

Diffuse malignant subtype - Males presented significantly higher UPDRS total and UPDRS-III scores than females. Female and male patients did not differ in motor symptoms asymmetry.

Table 15 shows all demographic and clinical differences between females and males in iPD clinical subtypes.

Table 15. Gender demographic and clinical differences of iPD clinical subtypes.

	Mild Motor-Predominant			**Intermediate**			**Diffuse Malignant**		
	M	**F**	**t**	**M**	**F**	**t**	**M**	**F**	t
Demographic Features									
N	116	39		68	51		5	7	
Age	60.58± 9.60	59.36± 9.09	p=0.24	64.53± 9.12	63.55± 9.62	p=0.505	72.6± 8.50	56.43± 9.98	**p=0.018**
Education, y	15.89± 2.90	15.38± 3.21	p=0.322	15.26± 2.612	14.65± 2.81	p=0.157	17.8± 1.30	15.71± 4.07	p=0.343
Disease Duration, y	1.78± 1.46	1.91± 1.54	p=0.389	2.47± 2.98	2.30± 2.89	p=0.859	2.67± 1.36	2.16± 1.66	p=0.432
Clinical non-motor Assessment (mean ± SD)									
MoCA	27.4± 2.08	27.7± 1.89	p=0.572	26.31± 2.50	26.96± 2.50	p=0.177	26.00± 1.58	28.71± 1.11	p=0.073
RBDQ	3.54± 2.31	3.67± 2.02	p=0.733	5.66± 3.14	4.36± 2.61	**p=0.019**	7.20± 4.21	6.86± 4.02	p=0.805
Epworth Sleepiness Scale	5.59± 3.24	5.90± 3.63	p=0.599	6.56± 3.45	5.08± 3.14	**p=0.019**	5.60± 3.36	6.43± 4.16	p=0.485
Scopa-AUT	6.84± 3.57	6.95± 3.19	p=0.768	17.5± 10.59	21.7± 7.71	**p=0.008**	18.00± 2.0	23.71± 6.75	**p=0.046**
UPSIT	23.2± 7.89	25.2± 7.71	p=0.207	20.5± 8.46	23.0± 9.20	p=0.169	16.60± 6.35	24.14± 9.60	p=0.362
Motor Assessment (mean ± SD)									

Schwab and England ADL scale	93.9± 5.08	94.7± 5.49	p=0.292	93.3± 6.55	93.8± 5.85	p=0.65	87± 6.70	86.43±6.90	p=0.66
Hoehn and Yahr Staging	0.26± 0.53	0.28± 0.56	p=0.133	0.78± 1.17	0.46± 0.68	p=0.962	0.40± 0.55	0.86± 0.90	p=0.36
UPDRS total score	28.3± 11.89	25.56 ±9.59	p=0.241	35.06± 12.43	32.18± 11.94	p=0.223	63.8± 18.56	55.71± 15.16	**p=0.008**
UPDRS I	4.31± 3.19	4.33± 2.91	p=0.926	6.94± 4.13	6.7± 4.32	p=0.652	12.6± 4.393	14± 6.758	p=0.691
UPDRS II	4.97± 3.73	3.79± 2.20	p=0.072	6.43± 3.97	5.48± 3.48	p=0.224	12.6± 4.61	16.43± 6.16	p=0.749
UPDRS III	19.0± 8.28	17.4± 7.43	p=0.36	21.6± 8.48	20.0± 8.13	p=0.306	38.6± 16.72	25.29± 7.74	**p=0.000**
Neurobehavioral assessment (mean ± SD)									
GDS	5.25± 1.33	5.15± 1.04	p=0.613	5.44± 1.67	5.36± 1.36	p=0.700	4.4± 1.14	5.29± 1.38	p=0.31
QUIP	0.22± 0.57	0.31± 1.30	p=0.549	0.49± 1.04	0.46± 0.99	p=0.842	0.2± 0.44	0.71± 0.75	p=0.089
STAI- state score	46.86± 5.53	47.82± 4.82	p=0.326	46.97± 5.18	49.06± 5.34	**p=0.034**	43.4± 5.32	48± 7.59	p=0.099
STAI- trait score	45.63± 4.63	46.85± 3.65	p=0.124	45.96± 4.5	47.58± 3.13	**p=0.03**	42.4± 3.36	43.86± 5.17	p=0.346
STAI- total score	92.49± 8.48	94.67± 6.81	p=0.137	92.93± 8.38	96.64± 6.48	**p=0.01**	85.8± 6.79	91.86± 10.68	p=0.094
GDS	5.25± 1.33	5.15± 1.04	p=0.613	5.44± 1.67	5.36± 1.36	p=0.700	4.4± 1.14	5.29± 1.38	p=0.31
Cognitive Assessment (mean ± SD)									
Benton Judgment of Line Orientation	13.1± 2.27	12.4± 2.81	p=0.081	11.4± 3.24	10.27± 3.00	**p=0.038**	12.19± 0.99	10.81± 2.43	p=0.089
Letter Number Sequencing	11.6± 2.49	11.3± 2.49	p=0.382	10.8± 2.86	11.30± 3.05	p=0.381	10.40± 0.55	12.86± 2.04	p=0.12
HVLT total immediate recall t-score	44.8± 10.52	49.2± 8.63	**p=0.021**	42.1± 11.93	48.76± 11.21	**p=0.002**	42.2± 3.70	47.86± 7.86	p=0.218

HVLT delayed recall t-score	44.8± 10.67	48.1± 97.73	p=0.095	40.9± 11.02	46.8± 11.56	**p=0.005**	42.2± 6.09	45.71± 15.73	p=0.41
HVLT recognition t-score	44.8± 11.00	47.5± 11.38	p=0.214	42.8± 10.15	46.2± 12.27	p=0.103	34± 12.981	43.43± 12.15	p=0.53
Semantic Fluency t-score	47.4± 10.10	56.1± 13.06	**p=0.000**	43.9± 11.09	50.28± 8.44	**p=0.002**	41.60± 12.3	50.29± 11.81	p=0.727
Symbol Digit t-score	46.2± 7.44	49.8± 8.66	**p=0.012**	42.6± 10.36	47.02± 8.40	**p=0.014**	35.50± 6.66	43.00± 5.73	p=0.079

Abbreviations: M: Males; F: Females; N, Number; sd, standard deviation; y, years; MoCA, Montreal Cognitive Assessment; UPSIT, Smell identification test; UPDRS, Unified Parkinson's Disease Rating Scale; GDS, Geriatric Depression Scale; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; STAI, State-Trait Anxiety Inventory; HVLT, Hopkins Verbal Learning Test

[123I]FP-CIT-SPECT SUVr differences

Whole iPD cohort – Males showed significantly less decreased [123I]FP-CIT-SPECT SUVr than female patients in ROIs innervated by the mesolimbic dopaminergic system, namely the amygdala, the parahippocampus and hippocampus, the insula, the anterior and middle cingulate cortex, the thalamus, bilaterally. In addition, the pallidum and the precentral cortex of females were more depleted than males. Males showed significantly less DAT asymmetry in the putamen than females (Females = 0.36±0.23; Males = 0.32±0.27; p=0.043). Table 16 shows the described gender differences. We observed a significant negative correlation between MDS-UPDRS III and SUVr in the putamen and globus pallidus in males ($p = 0.001$, $r = -0.233$; $p = 0.037$, $r = -0.139$, respectively) and in the precentral gyrus and the opIFG in females ($p = 0.048$, $r = -0.190$; $p = 0.029$, $r = -0.216$, respectively).

Table 16. [123I]FP-CIT-SPECT SUVr gender differences in the whole iPD.

	iPD Males N=189	HC Males N=39	Statistic M HC vs M iPD	iPD Females N=97	HC Females N=34	statistic F HC vs F iPD	statistic M iPD vs F iPD
Ipsilateral Caudate	1.26±0.42	1.55±0.30	p=0.000	1.25±0.45	1.55±0.25	p=0.000	p=0.649
Contralateral Caudate	1.37±0.43	1.53±0.30	p=0.021	1.44±0.49	1.54±0.24	p=0.140	p=0.394
Ipsilateral Putamen	1.09±0.37	2.29±0.29	p=0.000	1.06±0.45	2.23±0.24	p=0.000	p=0.286
Contralateral Putamen	1.40±0.46	2.14±0.26	p=0.000	1.43±0.55	2.06±0.24	p=0.000	p=0.911
Ipsilateral Dorsal Caudate	1.32±0.54	1.61±0.34	p=0.002	1.26±0.61	1.63±0.27	p=0.001	p=0.183
Contralateral Dorsal Caudate	1.45±0.58	1.55±0.32	p=0.198	1.53±0.63	1.60±0.26	p=0.465	p=0.594
Ipsilateral Dorsal Putamen	1.19±0.44	2.56±0.32	p=0.000	1.07±0.48	2.50±0.24	p=0.000	**p=0.018**
Contralateral Dorsal Putamen	1.56±0.53	2.56±0.30	p=0.000	1.52±0.60	2.47±0.26	p=0.000	p=0.302
Ipsilateral Ventral Striatum	2.11±0.45	2.87±0.40	p=0.000	2.09±0.47	2.80±0.30	p=0.000	p=0.783
Contralateral Ventral Striatum	2.27±0.51	3.27±0.44	p=0.000	2.32±0.54	3.27±0.37	p=0.000	p=0.484
Ipsilateral Thalamus	0.57±0.22	1.12±0.16	p=0.000	0.38±0.16	1.05±0.16	p=0.000	**p=0.000**
Contralateral Thalamus	0.57±0.21	1.18±0.16	p=0.000	0.40±0.16	1.11±0.18	p=0.000	**p=0.000**
Ipsilateral Globus Pallidus	1.42±0.51	0.20±0.10	p=0.000	1.15±0.46	0.11±0.06	p=0.000	**p=0.000**
Contralateral Globus Pallidus	1.66±0.58	0.18±0.08	p=0.000	1.43±0.56	0.12±0.07	p=0.000	**p=0.001**
Ipsilateral Amygdala	0.42±0.25	0.71±0.22	p=0.000	0.31±0.24	0.64±0.17	p=0.000	**p=0.000**

Contralateral Amygdala	0.46±0.30	0.73±0.18	p=0.000	0.32±0.25	0.57±0.18	p=0.000	**p=0.000**
Ipsilateral Hippocampus	0.37±0.19	0.57±0.17	p=0.000	0.24±0.14	0.48±0.14	p=0.000	**p=0.000**
Contralateral Hippocampus	0.40±0.20	0.59±0.16	p=0.000	0.25±0.15	0.49±0.15	p=0.000	**p=0.000**
Ipsilateral Parahippocampus	0.26±0.18	0.30±0.14	p=0.163	0.14±0.15	0.21±0.13	p=0.024	**p=0.000**
Contralateral Parahippocampus	0.27±0.18	0.29±0.16	p=0.624	0.14±0.13	0.22±0.12	p=0.006	**p=0.000**
Ipsilateral Insula	0.38±0.15	0.67±0.13	p=0.000	0.29±0.12	0.63±0.15	p=0.000	**p=0.000**
Contralateral Insula	0.40±0.16	0.61±0.13	p=0.000	0.36±0.16	0.59±0.13	p=0.000	**p=0.033**
Ipsilateral Olfactory	0.57±0.37	1.03±0.25	p=0.000	0.54±0.37	0.96±0.25	p=0.000	p=0.531
Contralateral Olfactory	0.59±0.37	1.05±0.26	p=0.000	0.59±0.39	1.03±0.23	p=0.000	p=0.959
Ipsilateral Anterior Cingulate	0.25±0.14	0.42±0.11	p=0.000	0.14±0.09	0.34±0.12	p=0.000	**p=0.000**
Contralateral Anterior Cingulate	0.26±0.14	0.41±0.13	p=0.000	0.15±0.09	0.35±0.12	p=0.000	**p=0.000**
Ipsilateral Middle Cingulate	0.27±0.14	0.47±0.13	p=0.000	0.15±0.09	0.37±0.12	p=0.000	**p=0.000**
Contralateral Middle Cingulate	0.28±0.14	0.46±0.13	p=0.000	0.15±0.09	0.38±0.12	p=0.000	**p=0.000**
Ipsilateral opIFG	0.16±0.15	0.18±0.09	p=0.890	0.11±0.10	0.19±0.12	p=0.003	**p=0.016**
Contralateral opIFG	0.13±0.13	0.15±0.09	p=0.534	0.10±0.11	0.14±0.08	p=0.060	p=0.075
Ipsilateral precentral	0.13±0.13	0.28±0.10	p=0.000	0.06±0.06	0.22±0.12	p=0.000	**p=0.000**
Contralateral precentral	0.09±0.09	0.30±0.11	p=0.000	0.05±0.06	0.23±0.10	p=0.000	**p=0.007**

Abbreviations: iPD, idiopathic Parkinson's disease; HC, healthy controls; N, number; opIFG, inferior frontal gyrus pars opercularis.

Mild motor subtype - Similarly to the whole group, females showed lower SUVr than males in dopaminergic mesolimbic targets, namely the amygdala, the parahippocampus and hippocampus, the insula, the anterior and middle cingulate cortex, thalamus, bilaterally. However, female and male patients did not differ in putamen DAT asymmetry (p=0.574). A significant correlation between MDS-UPDRS III and SUVr in the putamen and globus pallidus was found only in males ($p = 0.007$, $r = -0.247$; $p = 0.020$, $r = -0.209$, respectively). In females, lower SUVr in the amygdala was associated with higher STAI (trait score) ($p = 0.035$, $r = -0.393$).

Intermediate subtype - Once again, female patients showed significantly decreased SUVr than males in ROIs belonging to the mesolimbic pathway, namely the amygdala, the hippocampus and parahippocampus, the anterior and middle cingulate cortex, bilaterally, and the ipsilateral insula. Female patients showed significant higher DAT asymmetry in the putamen than males (Females = 0.34±0.21; Males = 0.28±0.27; p=0.024). We observed a significant correlation between SUVr in the opIFG and STAI (trait score) in females ($p = 0.029$, $r = -0.329$).

Diffuse malignant subtype - Females showed significantly more preserved DAT binding in the ipsilateral putamen compared to males. Female patients presented less significantly decreased SUVr than males in some dopaminergic mesolimbic targets, namely in the ipsilateral ventral striatum, ipsilateral anterior cingulate, contralateral insula, and ipsilateral opIFG. Female and male patients did not differ in DAT asymmetry in the putamen (p=0.082).

Table 17. [123I]FP-CIT-SPECT gender differences in iPD clinical subtypes.

	Mild Motor-Predominant			**Intermediate**			**Diffuse Malignant**		
	Males	**Females**	***t-statistic***	**Males**	**Females**	**t-statistic**	**Males**	**Females**	**t-statistic**
	N=116	N=39		N=68	N=51		N=5	N=7	
Ipsilateral Caudate	1.27± 0.42	1.29± 0.45	*p=0.915*	1.24± 0.43	1.21± 0.45	*p=0.879*	1.31± 0.49	1.24± 0.54	*p=0.326*
Contralateral Caudate	1.37± 0.41	1.43± 0.45	*p=0.689*	1.37± 0.45	1.44± 0.52	*p=0.464*	1.35± 0.40	1.47± 0.51	*p=0.142*
Ipsilateral Putamen	1.08± 0.36	1.03± 0.35	*p=0.249*	1.12± 0.39	1.07± 0.49	*p=0.531*	1.09± 0.25	1.18± 0.57	***p=0.045***
Contralateral Putamen	1.42± 0.45	1.40± 0.54	*p=0.634*	1.39± 0.49	1.41± 0.55	*p=0.887*	1.32± 0.34	1.66± 0.71	*p=0.079*
Ipsilateral Dorsal Caudate	1.34± 0.52	1.42± 0.66	*p=0.673*	1.29± 0.57	1.19± 0.56	*p=0.324*	1.44± 0.51	0.90± 0.29	*p=0.756*
Contralateral Dorsal Caudate	1.47± 0.59	1.63± 0.60	*p=0.505*	1.41± 0.56	1.48± 0.68	*p=0.602*	1.39± 0.59	1.36± 0.38	*p=0.704*

Ipsilateral Dorsal Putamen	1.18± 0.44	1.07± 0.43	*p=0.127*	1.22± 0.45	1.09± 0.52	*p=0.141*	1.16± 0.38	0.99± 0.48	*p=0.150*
Contralateral Dorsal Putamen	1.57± 0.51	1.51± 0.60	*p=0.218*	1.55± 0.56	1.53± 0.60	*p=0.736*	1.39± 0.57	1.48± 0.71	*p=0.375*
Ipsilateral ventral Striatum	2.08± 0.45	2.08± 0.41	*p=0.963*	2.14± 0.46	2.08± 0.45	*p=0.478*	2.24± 0.26	2.23± 0.90	***p=0.042***
Contralateral ventral Striatum	2.27± 0.49	2.29± 0.50	*p=0.854*	2.28± 0.55	2.32± 0.50	*p=0.597*	2.34± 0.37	2.54± 0.99	*p=0.096*
Ipsilateral Thalamus	0.58± 0.22	0.38± 0.16	***p=0.000***	0.55± 0.22	0.38± 0.16	***p=0.000***	0.48± 0.17	0.35± 0.09	*p=0.301*
Contralateral Thalamus	0.58± 0.22	0.41± 0.17	***p=0.000***	0.56± 0.20	0.40± 0.16	***p=0.000***	0.47± 0.12	0.37± 0.11	*p=0.734*
Ipsilateral Globus Pallidus	1.45± 0.49	1.11± 0.42	***p=0.000***	1.38± 0.54	1.18± 0.50	*p=0.067*	1.43± 0.36	1.16± 0.38	*p=0.284*
Contralateral Globus Pallidus	1.69± 0.61	1.42± 0.57	***p=0.012***	1.62± 0.52	1.42± 0.55	*p=0.076*	1.61± 0.52	1.63± 0.58	*p=0.478*
Ipsilateral Amygdala	0.42± 0.26	0.27± 0.17	***p=0.001***	0.42± 0.25	0.31± 0.28	***p=0.028***	0.49± 0.16	0.47± 0.23	*p=0.262*
Contralateral Amygdala	0.45± 0.30	0.33± 0.22	***p=0.014***	0.48± 0.29	0.28± 0.27	***p=0.000***	0.48± 0.27	0.48± 0.25	*p=0.171*
Ipsilateral Hippocampus	0.37± 0.18	0.22± 0.11	***p=0.000***	0.37± 0.20	0.24± 0.15	***p=0.000***	0.31± 0.19	0.35± 0.21	*p=0.148*
Contralateral Hippocampus	0.39± 0.20	0.25± 0.14	***p=0.000***	0.40± 0.20	0.24± 0.15	***p=0.000***	0.42± 0.13	0.33± 0.20	*p=0.269*
Ipsilateral Parahippocampus	0.27± 0.17	0.14± 0.12	***p=0.000***	0.25± 0.19	0.14± 0.17	***p=0.003***	0.27± 0.19	0.19± 0.21	*p=0.416*
Contralateral Parahippocampus	0.28± 0.19	0.15± 0.14	***p=0.000***	0.28± 0.19	0.13± 0.13	***p=0.000***	0.27± 0.16	0.22± 0.17	*p=0.625*
Ipsilateral Insula	0.37± 0.16	0.28± 0.13	***p=0.000***	0.40± 0.16	0.29± 0.11	***p=0.000***	0.38± 0.07	0.37± 0.18	*p=0.110*
Contralateral Insula	0.41± 0.17	0.35± 0.15	***p=0.030***	0.40± 0.17	0.38± 0.15	*p=0.488*	0.41± 0.07	0.35± 0.29	***p=0.018***
Ipsilateral Olfactory	0.56± 0.38	0.49± 0.33	*p=0.227*	0.60± 0.38	0.53± 0.31	*p=0.378*	0.64± 0.25	0.94± 0.78	*p=0.148*
Contralateral Olfactory	0.58± 0.36	0.53± 0.35	*p=0.485*	0.60± 0.39	0.58± 0.35	*p=0.796*	0.76± 0.32	0.98± 0.69	*p=0.065*
Ipsilateral Anterior Cingulate	0.25± 0.14	0.14± 0.11	***p=0.000***	0.27± 0.15	0.14± 0.08	***p=0.000***	0.34± 0.12	0.13± 0.11	***p=0.034***
Contralateral Anterior Cingulate	0.26± 0.14	0.15± 0.10	***p=0.000***	0.28± 0.16	0.15± 0.09	***p=0.000***	0.30± 0.06	0.16± 0.16	*p=0.213*
Ipsilateral Middle Cingulate	0.27± 0.14	0.15± 0.10	***p=0.000***	0.29± 0.15	0.16± 0.09	***p=0.000***	0.27± 0.08	0.13± 0.09	*p=0.930*
Contralateral Middle Cingulate	0.28± 0.15	0.15± 0.10	***p=0.000***	0.29± 0.14	0.16± 0.09	***p=0.000***	0.28± 0.10	0.13± 0.10	*p=0.494*
Ipsilateral opIFG	0.15± 0.16	0.11± 0.09	*p=0.151*	0.18± 0.16	0.13± 0.11	*p=0.072*	0.22± 0.08	0.07± 0.19	***p=0.031***
Contralateral opIFG	0.13± 0.13	0.11± 0.12	*p=0.294*	0.14± 0.14	0.10± 0.09	*p=0.063*	0.20± 0.13	0.17± 0.20	*p=0.531*
Ipsilateral precentral	0.12± 0.11	0.07± 0.07	***p=0.009***	0.13± 0.11	0.07± 0.06	***p=0.002***	0.13± 0.10	0.01± 0.04	*p=0.188*
Contralateral precentral	0.09± 0.09	0.07± 0.08	*p=0.284*	0.09± 0.10	0.05± 0.06	***p=0.047***	0.13± 0.11	0.04± 0.05	*p=0.514*
Abbreviations: N, number; opIFG, inferior frontal gyrus pars opercularis									

Dopaminergic systems molecular connectivity analyses

Whole iPD cohort - Males patients showed a significantly more severe alteration of molecular connectivity within the nigrostriatal dopaminergic system (15% altered

connections compared to HC) than females (6% changes in comparison with HC) (X^2 = 4.30, p=0.037). In the mesolimbic system, females (11% changes in comparison with HC) showed more connectivity alteration than males (7% changes in comparison with HC) without, however reaching the significant threshold (X^2 = 0.976; p=0.322). Figure 50 represents the brain molecular connectivity results in the whole iPD cohort.

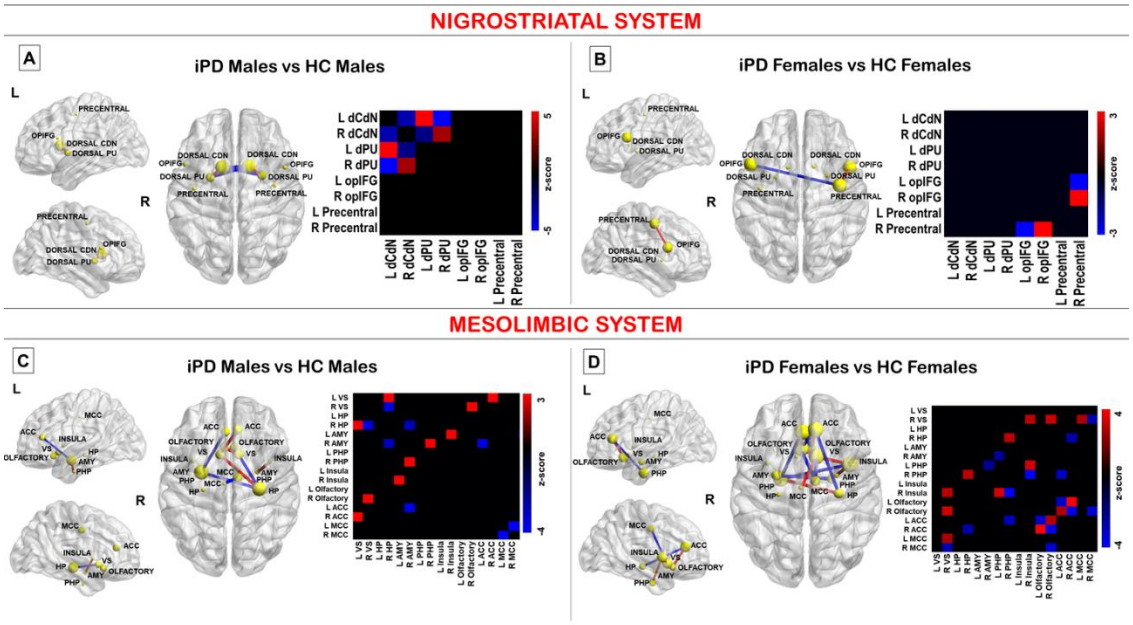

Figure 50. Molecular connectivity gender difference in whale iPD.

3D brain templates represent the nigrostriatal system connectivity for male (A) and females (B) iPD patients and the mesolimbic system connectivity for males (C) and females (D) iPD patients. In red are reported the increased and in blue the decreased connections compared with HC. The dimension of each node (dot size) depends on the total node number of connections. The matrices (close to 3D brain templates) depict the significant differences obtained with the following comparison: iPD males < HC (A, C) and iPD females < HC (B, D) in the dopaminergic networks. The colour bar displays the Z scores' values to compare partial correlation coefficients' strengths. Abbreviations: 3D, three-dimensional; iPD, idiopathic Parkinson's disease; HC, healthy controls, L, left; R, right; dCdN, dorsal caudate nucleus; dPU, dorsal putamen, opIFG, inferior frontal gyrus (pars opercularis); VS, ventral striatum, HP, hippocampus; AMY, amygdala; PHP, parahippocampus; ACC, anterior cingulate cortex, MCC, middle cingulate cortex.

Mild motor subtype - Males patients showed a significantly more severe alteration of molecular connectivity within the nigrostriatal dopaminergic system (18% altered connections compared to HC) than females (3% changes in comparison with HC) (X^2 = 11.97, p=0.000). In the mesolimbic system, females (17% changes in comparison with

HC) showed more connectivity alteration than males (15% changes in comparison with HC) without reaching the significant threshold (X^2 = 0.148; p=0.699).

Intermediate subtype - Males patients showed a significantly more severe alteration of molecular connectivity within the nigrostriatal dopaminergic system (15% altered connections compared to HC) than females (12% changes in comparison with HC) (X^2 = 11.97, p=0.000). In males, the connectivity alterations involved the dorsal caudate and dorsal putamen bilaterally, whereas females' reconfiguration was characterised by altered connections between the dorsal caudate, the contralateral precentral gyrus, and the ipsilateral opIFG. In the mesolimbic system, females (17% changes in comparison with HC) showed significantly more connectivity alteration than males (7% changes in comparison with HC) (X^2 = 4.73, p=0.029).

Figure 51 represents the brain molecular connectivity results in the iPD clinical subtypes.

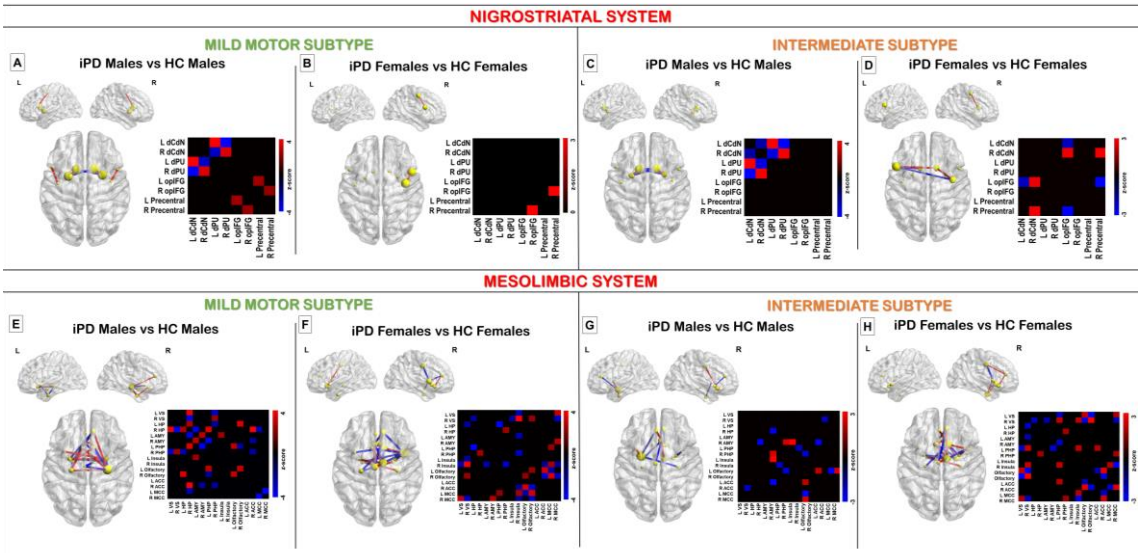

Figure 51. Brain molecular connectivity gender differences in iPD clinical subtypes.

3D brain templates represent the nigrostriatal system connectivity for male (A, B) and females (B, F) iPD patients with different clinical subtypes, and the mesolimbic system connectivity for males (C, G) and females (D, H) iPD patients with different clinical subtypes. In red are reported the increased and in blue the decreased connections compared with HC. The dimension of each node (dot size) depends on the total node number of connections. The matrices (close to 3D brain templates) depict the significant differences obtained with the following comparison: iPD males < HC (A, E, C, G) and iPD females < HC (B, F, D, H) in the dopaminergic networks. The colour bar displays the Z scores' values to compare partial correlation coefficients' strengths. Abbreviations: 3D, three-dimensional; iPD, idiopathic Parkinson's disease; HC, healthy controls; L, left; R, right; dCdN, dorsal caudate nucleus; dPU, dorsal putamen, opIFG, inferior

frontal gyrus (pars opercularis); VS, ventral striatum, HP, hippocampus; AMY, amygdala; PHP, parahippocampus; ACC, anterior cingulate cortex, MCC, middle cingulate cortex.

Our results provide the first evidence of remarkable gender differences in clinical subtypes of iPD. Since the early stage, the male vulnerability of the dopaminergic nigrostriatal system emerged and was consistent across different subtypes, suggesting possible neuroprotection by estrogens in females. In females, instead, the extended alterations of the mesolimbic system suggest an early vulnerability probably associated with a significant psychopathological state. Our findings indicate that males and females differently express the disease at endophenotypic and clinical levels since the early phase and independently from the clinical subtypes.

3.3.3. Study VIII: Specific occupational profiles as proxies of cognitive reserve induce neuroprotection in dementia with Lewy bodies. (Carli et al. 2020)*. - Published Article -*

Most studies tested the CR and BR hypothesis in AD patients. Instead, very little evidence is available on DLB, providing heterogeneous findings (Perneczky et al. 2007; 2009) (see *1.7.1. Cognitive and brain reserve*). The current findings demonstrate that highly educated patients cope better with DLB-associated neurodegeneration in brain regions primarily affected by the disease.

The imaging results are mainly based on univariate methods. However, the emerging multivariate approaches are paving the way for evaluating new brain features, such as the large scale brain network (Sala and Perani 2019). The advantage of using multivariate methods is that they allow assessing changes in the relationship between brain regions (connectivity) beyond traditional local changes, which univariate methods can measure. Changes in large-scale brain network organization reflect possible different neural responses to a brain injury: maladaptive processes (e.g. transneuronal degeneration and dedifferentiation) and adaptation mechanisms (e.g. compensation) (Palop, Chin, and Mucke 2006). Therefore, the study of functional metabolic connections can reveal how CR and BR interact with brain dysfunction.

Previous findings on metabolic networks connectivity (measured by [18F]FDG-PET) demonstrated significant effects of education, occupation and bilingualism on

cognitive resilience in AD patients (Malpetti et al. 2017; Perani, Farsad, Ballarini, Lubian, Malpetti, Fracchetti, et al. 2017). Unfortunately, evidence regarding the effect of CR proxies on the brain metabolic functional reserve in DLB (metabolic functional connectivity) is still lacking. In addition to general education and professional level, specific skills involved in different jobs can better define the impact on brain function (Dodich et al., 2018; Spreng et al., 2010). Thus, this study aims to investigate the impact of education, occupational level, and critically specific occupational profile (proxies of CR) on functional BR (measured with [18F]FDG-PET) in a group of well-characterized DLB patients. Together with the traditional univariate approach, we also applied the seed-based IRCA to assess the CR impact on large-scale networks mainly involved in DLB (Caminiti et al. 2017; Sala et al. 2019; Franciotti et al. 2013): the primary (PVN) and high visual networks (HVN), the frontal executive control network (ECN), the attentional network (ATTN), anterior and posterior default mode network (ADMN and PDMN). This study was performed at the Nuclear Medicine Unit of San Raffaele Hospital (Milan). The present study and relative datasets were already published in the Journal of Brain Imaging and Behaviour on 1st August 2020 (https://doi.org/10.1007/s11682-020-00342-2).

We included 33 DLB patients with detailed information about the occupation. Table 18 contains the demographic and clinical data of the cohort.

Table 18. Demographic and clinical data of DLB patients.

Demographic	**Values**
Number of patients	33
Gender (M/F)	15/18
Age, y (means ± S.D)	74.52±8.58
MMSE, corrected scores (means ± S.D)	20.49±5.10
Years of education, y (means ± S.D) Occupation, Vemuri Index (mode)	10.64±4.64 2
Core clinical features	**Values**
Visual hallucinations (n°+/total sample)	20/33
Cognitive Fluctuations (n°+/total sample)	14/33
Parkinsonisms (n°+/total sample)	24/33
RBD (n°+/total sample)	12/33
M: male, F: female; Y: years; MMSE: Mini-Mental State Examination; n°+: Number of patients with clinical symptom; RBD: REM sleep Behaviour disorder	

We considered four proxies of CR: education, occupation, reserve index (RI, combination of education and occupation) and specific occupational profile derived from O*Net database (problem-solving, visual abilities, social skills, and visual-constructive abilities) (see *5.12.2. Proxies of cognitive reserve*). The traditional univariate approach revealed that education and 6-levels occupation did not show significant correlations with brain hypometabolism. However, RI showed a significant positive correlation with hypometabolism in the left parietal, temporal and dorsolateral-prefrontal regions ($p = 0.000$, $r = 0.606$). Regarding the O*Net occupational profiles, we found that higher problem-solving and visual skills were associated with more severe hypometabolism in the right supramarginal gyrus ($p = 0.000$; $r = 0.651$) occipital cortex ($p = 0.000$; $r = 0.729$), respectively. Social and visual-constructive skills were associated to greater hypometabolism in the anterior temporal regions ($p = 0.000$; $r = 0.651$) and left fronto-parietal regions ($p = 0.000$; $r = 0.651$), respectively. Figure 52 shows the univariate results.

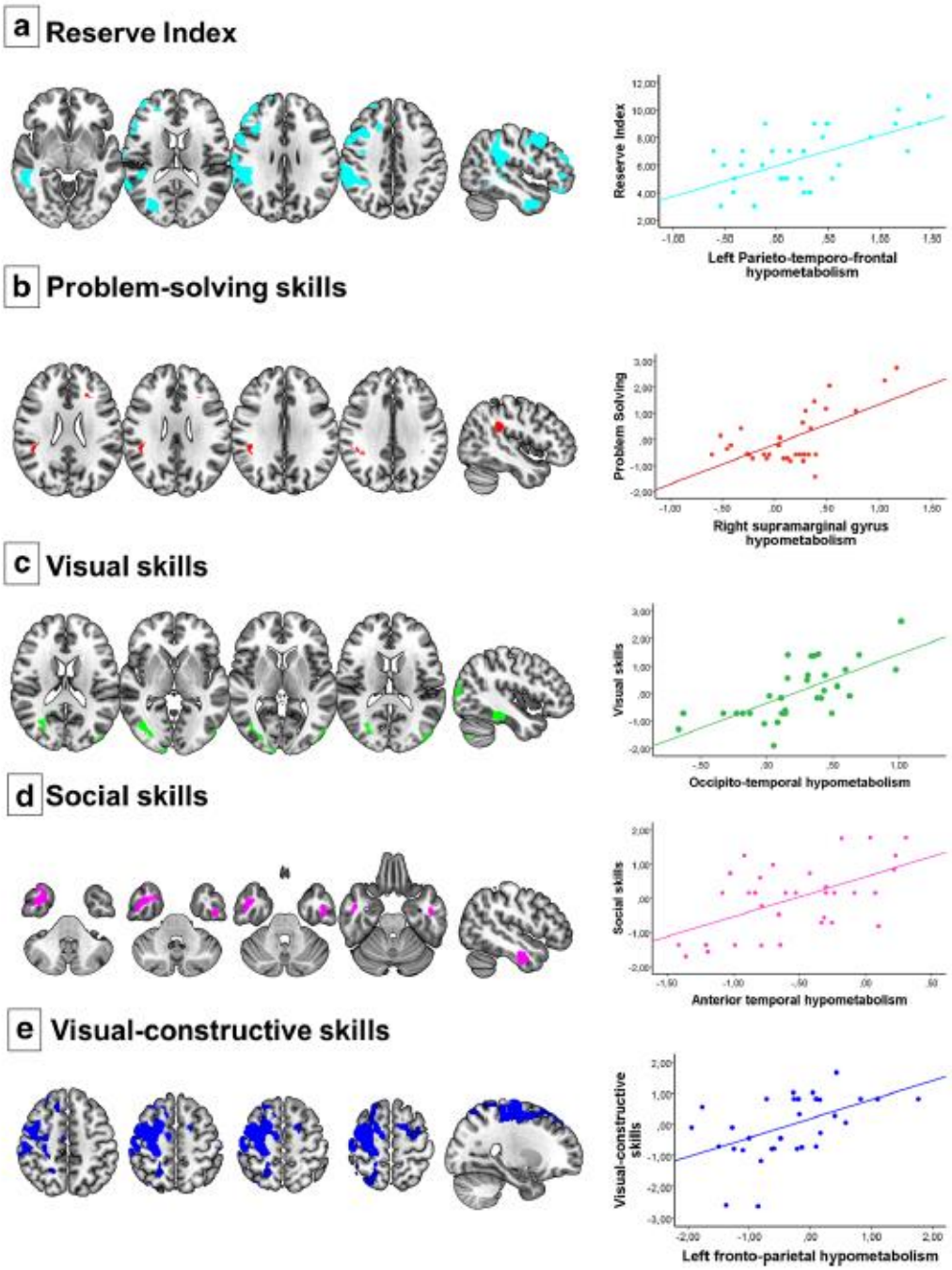

Figure 52. Linear regression analyses results (Fair use).

*Significant cluster resulting from linear regression analyses considering A) Reserve Index and O*Net occupational profiles, namely B) problem-solving skills, C) visual skills, D) social skills, and E) visuo-constructive skills as independent variables and brain hypometabolism as dependent one (TFCE $p < 0.05$). The right scatterplots show the relationship between CR proxies and hypometabolism in the significant hypometabolic clusters. The figure is adapted from* (Carli et al. 2020) *in accordance with the fair use principle.*

To study the CR on brain metabolic connectivity, we divided the DLB cohort into sub-groups according to mean values of CR proxies (Table 19).

Table 19. Demographic and clinical features of the DLB sub-groups.

	EDUCATION			**OCCUPATION**		
	HIGH (Means ± S.D)	**LOW** (Means ± S.D)	*Statistic*	**HIGH** (Means ± S.D)	**LOW** (Means ± S.D)	*Statistic*
Number of patients	19	14	-	13	20	-
Age, y	73.63±10.07	75.43±6.44	0.563[a]	75.77±7.78	73.5±9.24	0.469[a]
MMSE, corrected score	19.93±5.9	21.25±3.84	0.653[b]	19.11±5.78	21.39±4.54	0.235[b]
Disease duration, y	3.01±1.47	2.65±2.87	0.678[a]	2.46±1.47	3.19±2.57	0.391[a]
O*NET OCCUPATIONAL PROFILES						
	PROBLEM SOLVING			**VISUAL ABILITIES**		
	HIGH (Means ± S.D)	**LOW** (Means ± S.D)	*Statistic*	**HIGH** (Means ± S.D)	**LOW** (Means ± S.D)	*Statistic*
Number of patients	12	21	-	14	19	-
Age, y	74.67±7.87	74.24±9.24	.894[a]	75.79±6.97	73.37±9.75	.436[a]
MMSE, corrected score	19.45±5.98	21.09±4.58	.427[b]	19.54±5.41	21.19±4.89	.377[b]
Disease duration, y	2.69±1.99	2.97±2.28	.746[a]	2.31±1.8	3.32±2.34	.234[a]
	SOCIAL SKILLS			**VISUAL-CONSTRUCTIVE ABILITIES**		
	HIGH (Means ± S.D)	**LOW** (Means ± S.D)	*Statistic*	**HIGH** (Means ± S.D)	**LOW** (Means ± S.D)	*Statistic*
Number of patients	20	13	-	17	16	-
Age, y	72.35±9.13	77.54±7.03	.092[a]	73.53±9.15	75.31±8.26	.562[a]
MMSE, corrected score	20.31±5.64	20.77±4.35	.986[b]	19.08±4.89	22±5.03	.118[b]
Disease duration, y	3.47±2.51	2.24±1.53	.144[a]	2.98±2.44	2.72±1.85	.761[a]

Y: years; MMSE: Mini Mental State Examination; S.D: standard deviation.
[a] One-way ANOVA
[b] Kruskal-Wallis

The IRCA analyses showed the presence of two primary BR mechanisms: neural reserve and compensation.

Education- Major differences in metabolic connectivity were found in ECN (0% of overlap), ATTN (12% of overlap) and PDMN (6% of overlap). Highly educated DLB

showed increased metabolic connectivity within networks than low educated patients (Figure 53A). Moreover, DLB patients with high education had a greater percentage of overlap with HC in ATTN (22%), ECN (20%) and PDMN (22%) in comparison to DLB patients with lower education (ATTN 11%; ECN 0%; PDMN 13%) (Figure 55A). These results suggest a compensatory mechanism due to education.

6-levels occupation- Main differences in metabolic connectivity were found in ADMN (4% of overlap) and HVN (12% of overlap). DLB patients with high occupation levels showed decreased metabolic connectivity than those with low levels (Figure 53B). Moreover, DLB patients with high occupational levels showed a lower percentage of overlap with HC in ADMN (18%) and HVN (57%) in comparison to DLB patients with low occupational levels (ADMN 8%; HVN 31%) (Figure 55B). These results provide evidence for neural reserve mechanisms associated with occupational attainment.

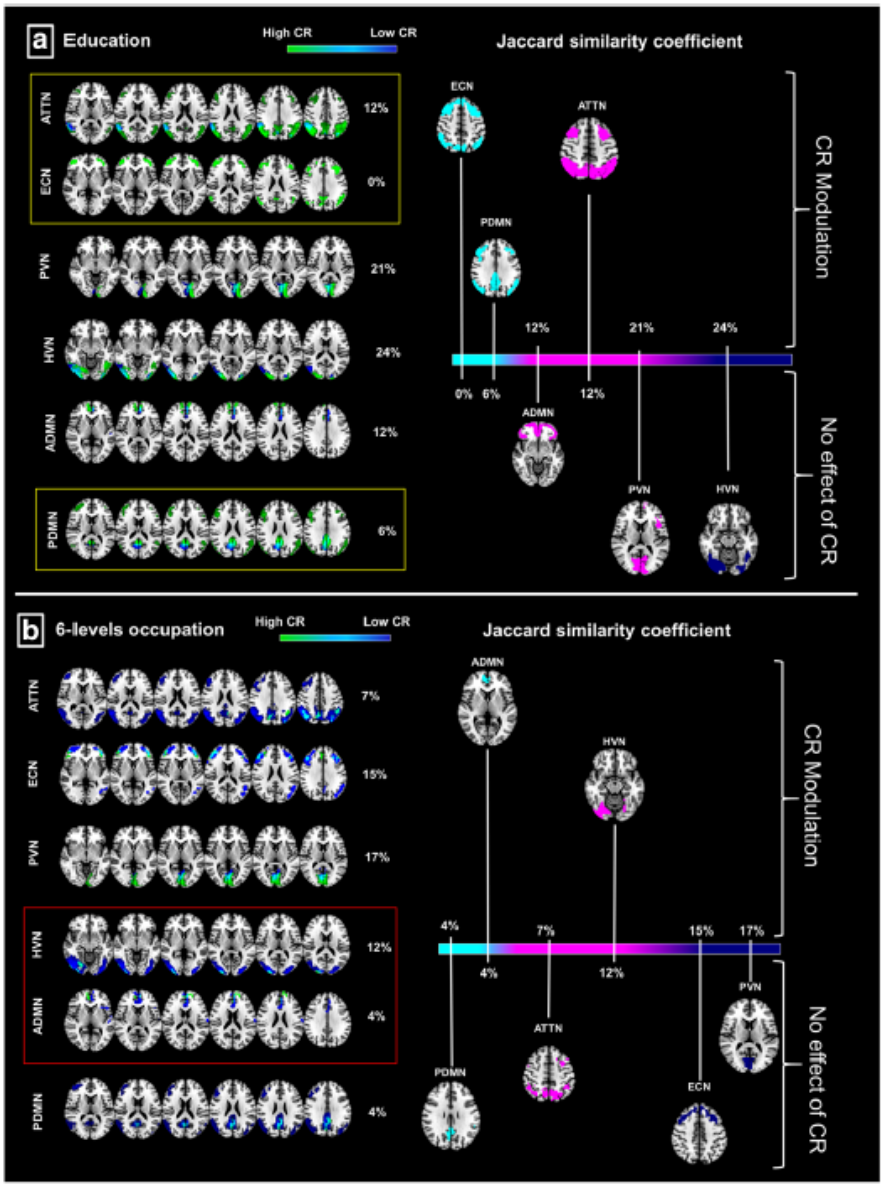

Figure 53. Education and occupation as CR proxies: IRCA results (Fair use).

On the left, A and B depict the topography of large-scale brain networks (ECN, ATTN, PVN, HVN, ADMN, PDMN) in high education/occupation (green) and low education/occupation (blue) DLB sub-groups (overlap areas are light blue). Red and yellow boxes highlight the networks that show more significant decreases and increases in connectivity, respectively, in DLB patients with high CR than those with low reserve. Large-scale networks are ordered according to the degree of similarity between sub-groups, as measured by JSC (right side of A and B panels). Abbreviations: ADMN: Anterior Default Mode Network; PDMN: Posterior Default Mode Network; HVN: High Visual Network; PVN: Primary Visual Network; ECN: Executive control network; ATTN: Attentive network; CR: Cognitive reserve. The figure is adapted from (Carli et al. 2020) *in accordance with the fair use principle.*

O*Net occupational profiles

Problem-solving skills - Problem-solving mainly modulated the PVN (15% of overlap), HVN (2% of overlap), ADMN (7% of overlap). DLB patients with high problem-solving skills showed a decreased connectivity in these networks compared to those with low skills (Figure 54A). DLB patients with high problem-solving skills showed a lower percentage of overlap with HC in PVN (6%), HVN (0.08%) and ADMN (1.3%) in comparison to DLB patients with lower problem-solving skills (PVN 27%; HVN 36%; ADMN 10%) (Figure 55C). These results support neural reserve mechanisms associated with problem-solving.

Visual skills - Similarly to problem-solving, the main differences in connectivity were found in PVN (54%), HVN (20%) and ADMN (8%) (Figure 59B). DLB patients with higher visual skills showed more impaired metabolic connectivity than DLB patients with low skills (Figure 59B). Moreover, patients with high visual skills showed a lower percentage of overlap with HC in HVN (9.7%) in comparison to DLB patients with lower skills (24%) (Figure 55D). This result highlights the role of visual abilities in modulating HVN. All the above suggest the presence of neural reserve mechanisms due to visual skills.

Visual-constructive skills - ADMN showed a lower overlap between patients with high and low visuo-constructive skills (15%). Specifically, patients with high visual-constructive skills showed decreased connectivity in ADMN compared to those with low skills (Figure 54C). DLB patients with high and low visuo-constructive skills showed similar low percentage overlap with HC in most large-scale brain networks (Figure 55E). These results suggest the presence of neural reserve mechanisms due to visuo-constructive skills on ADMN.

Social skills - Main differences in metabolic connectivity were found in ATTN (12% of overlap), ECN (1 % of overlap), ADMN (3% of overlap) and PDMN (7% of overlap). Highly demanding social jobs were associated with increased metabolic connectivity in ATTN, ECN and PDMN and decreased metabolic connectivity in ADMN (Figure 54D). Moreover, DLB patients with high social skills showed a higher percentage of overlap with HC, especially in ECN (35%) in comparison to DLB patients with lowers

social skills (0.07%). These results suggest both neural reserve and compensation mechanisms due to social skills on different large-scale networks.

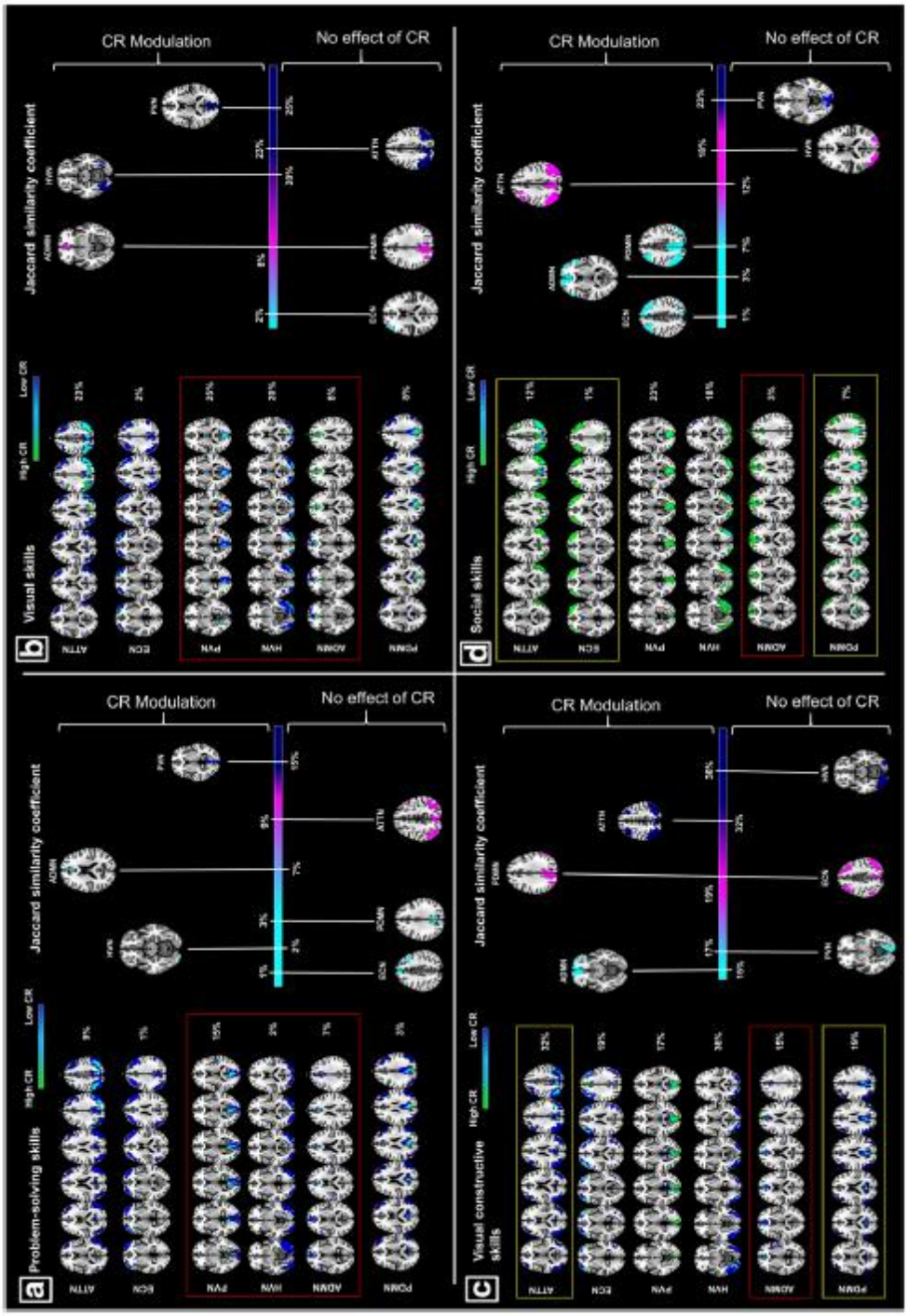

Figure 54. O*Net variables as CR proxies: IRCA results (Fair use).

On the left, A, B, C and D depict the topography of resting-state networks (ECN, ATTN, PVN, HVN, ADMN, PDMN) in high reserve (green) and low reserve (blue) DLB sub-groups (overlap

areas are light blue). Red and yellow boxes highlight the networks that show greater decreases and increases in connectivity, respectively, in DLB patients with high reserve compared to those with low reserve. Large-scale networks are ordered according to the degree of similarity between sub-groups, as measured by JSC on the right A, B, C and D. Abbreviations: ADMN: Anterior Default Mode Network; PDMN: Posterior Default Mode Network; HVN: High Visual Network; PVN: Primary Visual Network; ECN: Executive control network; ATTN: Attentive network; CR: Cognitive reserve. The figure is adapted from (Carli et al. 2020) *in accordance with the fair use principle.*

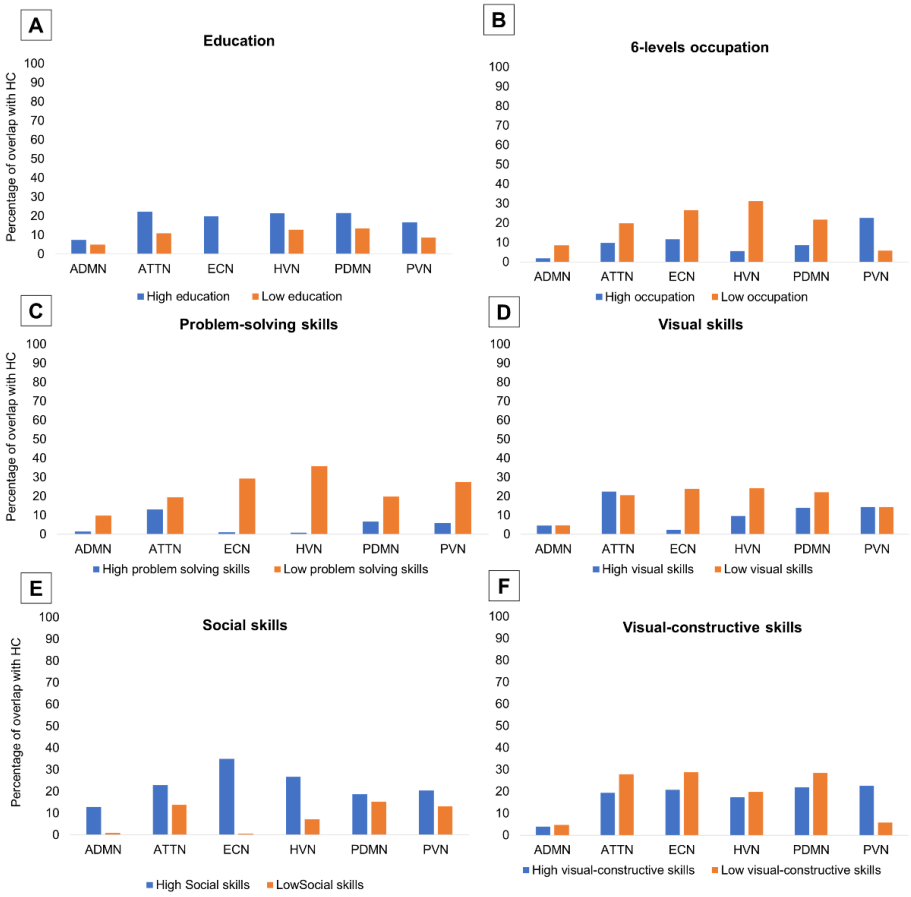

Figure 55. Percentage of overlap between DLB and HC (Fair use).

A) education, B) 6-levels occupation; C) problem-solving skills, D) visual skills, E) social skills, F) visual-constructive skills. Abbreviations: ADMN: Anterior Default Mode Network; PDMN: Posterior Default Mode Network; HVN: High Visual Network; PVN: Primary Visual Network; ECN: Executive control network; ATTN: Attentive network. The figure is adapted from (Carli et al. 2020) *in accordance with the fair use principle.*

Our findings suggest CR proxies might act as protective factors against DLB-related neurodegeneration, encompassing two main mechanisms: neural reserve and neural compensation. Life-long use of cognitive abilities would result in structural and

functional changes in the brain, such as increased grey and white matter densities and connectivity changes in specific large-scale networks (also in terms of networks efficiency and capacity) (Perani and Abutalebi 2015). The reduction of functional connections (neural reserve) was found mainly in those networks located in areas affected by the disease (visual and attentive networks), following the posterior vulnerability of DLB (Caminiti et al. 2019). The increase in connectivity involved mainly frontal areas, which are the most preserved brain regions by the disease (Caminiti et al. 2017; Pievani et al. 2014), and can be therefore recruited to cope with the posterior neurodegeneration, suggesting compensatory mechanisms.

4. Discussion

For some years, the World Health Organization has recognized counteracting the insurgence of dementia as a priority (Word Health Organization 2015). The Lancet Commission on dementia prevention, Intervention and Care published several reports stressing the possibility of specific interventions for preventing and managing dementia (Livingston et al. 2017; Orgeta et al. 2019; Livingston et al. 2020). These reports show that although no disease-modifying treatment is currently available, early modulation of risk factors might impact dementia rates (e.g. education, hypertension, obesity, smoking, depression, and physical inactivity). Recent evidence demonstrates that changes have occurred, with decreases in the age-specific incidence or prevalence in the United States, United Kingdom, Sweden, Netherlands, France, and Canada, probably reflecting reduced exposure to risk factors or increased resilience to cognitive decline (Chan et al. 2013; Okamura et al. 2013). Prevention is always preferable to treatment, and it is imperative given the lack of disease-relief treatment for the proteinopathies. Identifying and modifying risks could greatly benefit individuals, society and the healthcare system; any delay in the onset of dementia will be associated with significant personal and social health benefits (Livingston et al. 2017; Orgeta et al. 2019; Livingston et al. 2020). Accurate early diagnoses are the first step for effective prevention strategies. In this direction, many efforts have been spent to validate biomarker-supported clinical diagnosis pipelines maximizing the chance of early accurate dementia detection. All the

above emphasises the urgent need for accurate and standardized biomarkers to diagnose dementia – in both research and clinical frameworks – especially in the preclinical/prodromal phase. Providing precise indications regarding the risk factors for specific dementia and guidelines for the routine use of biomarkers in the diagnostic process will increase the chances of effective prevention, monitoring of disease progression and future treatments. Risk factors, biological and cognitive markers might be crucial to understanding the intersubjective clinical variability and getting closer to proper precision medicine.

Cognitive impairments occur in PD patients with a prevalence of 20% after five years of disease duration (Aarsland and Kurz 2010), reaching 83% at ten years (Hely et al. 2008). After about 20 years of disease duration, cognitive deterioration is almost inevitable (Hely et al. 2008). Executive deficits are present in up to 50% of cases (Williams-Gray et al. 2007). However, the insurgence of frank dementia (PDD) has a distinctive pattern of rapid cognitive decline, characterized by visuo-perceptual, memory and psychiatric deficits related to a posterior-cortical impairment (Kehagia et al. 2013) (see *1.3.6. The dual syndrome hypothesis*). This clinical condition seems to be neuropathologically and clinically indistinguishable from DLB (Friedman 2018), making experts wonder whether they are the same disease. PDD represents an essential aspect of clinical heterogeneity because it affects PD patient mortality and quality of life (Levy et al. 2002).

The studies included in this dissertation contributed to identifying risk factors, biological and cognitive markers, and sources of clinical variability of PDD/DLB, starting from the preclinical phases, namely iRBD.

4.1. Part 1: Biomarkers and neurobiological substrates of LB related neurodegeneration

Increasing evidence proves that iRBD should be considered a red flag for a severe phenotype of α-synucleinopathies (PDD/DLB) (Lin and Chen 2018); starting to refer to this preclinical condition as a possible risk factor for a diffuse malignant clinical subtype of PD (PDD) (Fereshtehnejad et al. 2017). In *Part 1* of this elaborate, we demonstrated that iRBD shared more biological mechanisms with DLB than PD with a stable clinical progression (eight-year follow-up), supporting the role of iRBD as a risk factor for

dementia development. Our evidence shows that most iRBD patients express an occipital vulnerability, emerging as the most common hypometabolic feature among these subjects (hypometabolic hallmark) (*Study Ia*). Hypometabolism in occipital brain regions is the hallmark feature of DLB (Caminiti et al. 2019). Consistently, in our study, iRBD and DLB groups shared the same occipital hypometabolism. DLB group showed more extended cortical hypometabolism than the iRBD, also reaching parietal regions, suggesting a possible temporal sequence of ongoing pathology. There were no overlapping brain hypometabolism features between iRBD and PD groups. Indeed, only a few iRBD subjects had negative [18F]FDG-PET scan, resulting in similar hypometabolism to stable PD patients (absence of brain hypometabolism/very limited cortical hypometabolism) (Pilotto et al. 2018). None of them presented cognitive deficits. These iRBD subjects could represent a stable condition or cases that develop iPD without dementia. As recently proposed by Boeve, the iRBD patients with progressive but subtle changes on clinical (mainly motor) measures and progressive changes in nigrostriatal uptake, but negative [18F]FDG-PET, are likely to convert to iPD without dementia. In contrast, those iRBD patients with progressive but subtle cognitive changes accompanied by neocortical brain hypometabolism on [18F]FDG-PET are likely to convert to DLB (Boeve 2019).

Posterior cerebral hypometabolism is associated with cholinergic dysfunction, an essential neurobiological aspect of DLB (Roy et al. 2016). Recent multimodal imaging data documented peripheral cholinergic dysfunction also in iRBD (Knudsen et al. 2018). Cholinergic deficits may represent one of the pathological processes in common between iRBD and DLB. Occipital hypometabolism was frequently accompanied by hypometabolism in the cerebellum in our iRBD cohort. Altered cerebellar metabolic connectivity was reported in PD and DLB patients, suggesting a cerebellar vulnerability as a communal pathological substrate (Sala and Perani 2019). The cerebellar hypometabolism pattern may reflect a noradrenergic dysfunction. LB pathology affects LC in the earliest phases (Stage II) (Braak, Del, et al. 2003), consistently, iRBD subjects already present a fully developed pathology in LC (Knudsen et al. 2018).

We confirmed these hypotheses (regarding neurotransmission systems) by a subsequent study investigating shared and disease-specific neural vulnerabilities of the nigro-striato-cortical dopaminergic, noradrenergic, and cholinergic systems within the α-

synuclein spectrum, using metabolic connectivity approach (*Study II*). Our results again emphasised shared mechanisms between iRBD and DLB, specifically regarding cholinergic dysfunction. We found a significant alteration in the Ch5-Ch6 division's networks in DLB and iRBD, but PD spares. These networks project to the thalamus, striatum and globus pallidus (Mesulam 2004). Thalamic cholinergic denervation in PD patients without dementia is relatively uncommon (Bohnen et al. 2012) but characterize DLB patients (Delli Pizzi et al. 2015; Mazère et al. 2017). Thalamic cholinergic imbalance is associated with fluctuating cognition in these patients (Delli Pizzi et al. 2015). Our data indicate that Ch5-Ch6 divisions' network impairment may represent one of the pathological substrates shared by iRBD and DLB. In this way, we further support the branch of research that considers iRBD as an antecedent marker of the severe α-synucleinopathy subtype (Lin and Chen 2018), with great density of α-synuclein deposition in most brain regions, fast motor and non-motor symptoms progression and neural vulnerabilities similar to those that characterize DLB phenotype (Boeve 2019). In this view, the connectivity alterations in the Ch5-Ch6 division's network may represent a malignant endophenotype, detectable since the iRBD preclinical phase.

We also found shared neurotransmission network reconfigurations across the spectrum (iRBD, PD and DLB) (Study III). The nigro-striato-cortical dopaminergic network showed limited connectivity changes in iRBD and moderate to severe alterations in DLB and PD, supporting and expanding previous molecular (Ferini-Strambi et al. 2019; Goedert et al. 2013) and connectivity findings (Carli et al. 2021). DLB patients had a more pronounced metabolic connectivity alteration in the caudate nuclei, whereas PD had a more severe alteration of metabolic connectivity in the putamen. These different patterns of striatal derangement are consistent with previous molecular data demonstrating a sparing of the caudate nucleus in PD and widespread involvement of basal ganglia in DLB (Walker et al. 2004). Our study thus suggests that the differences in striatal metabolic connectivity reconfiguration between DLB and PD could be related to the severity and extent of neurodegenerative processes. All the above indicates a possible evolution of the dopaminergic dysfunction along the spectrum, in which nigro-striato-cortical dopaminergic network connectivity is minimally affected in the iRBD prodromal stage but worsens along with the disease progression. Consistent changes in the whole α-synuclein-spectrum characterized the noradrenergic network. Of note, iRBD

already presented a severe noradrenergic impairment. Together with the nearly intact metabolic connectivity in the dopaminergic network, this result supports the caudo-rostral propagation of α-synuclein pathology (Braak et al. 2003). The noradrenergic dysfunction is considered an early pathological event in the α-synuclein-spectrum, especially in the subset of patients presenting with iRBD. It has been proposed that noradrenergic excitatory inputs contribute to the inactivation of motoneurons during REM sleep (Luppi et al. 2013). These findings also agree with previous molecular and *postmortem* observations of extensively impaired noradrenergic neurotransmission in both PD (Nahimi et al. 2018) and DLB (Vermeiren and De Deyn 2017) patients. There is increasing evidence that noradrenergic deficiency is the most affected neurotransmitter system because its involvement occurs early, reaching a high level of pathology burden during the disease progression (Vermeiren and De Deyn 2017). Cholinergic metabolic connectivity alterations emerged along the whole α-synuclein-spectrum, particularly in the perysilvian and medial *Ch4 divisions.* Although the degeneration of the basal forebrain cholinergic system is frequently associated with cognitive decline (Gratwicke et al. 2015), moderate cortical cholinergic deficits are documented in iPD without dementia (Hall et al. 2014; Shimada et al. 2009). Thus, together with the nigro-striato-cortical dopaminergic impairment and noradrenergic dysfunction, the moderate cortical cholinergic deficit may explain shared clinical features within the α-synuclein spectrum, such as deficits in planning, spatial working memory and attentional set-shifting (Gratwicke et al. 2015), also observed in preclinical disease phases (Ferini-Strambi et al. 2019).

In addition to neuroimaging biomarkers, EEG alteration during non-REM sleep could have an essential prognostic value in neurodegenerative diseases since it is associated with cognitive decline (Brazète et al. 2016; Sasai, Matsuura, and Inoue 2013; De Gennaro et al. 2017). However, limited evidence is available for non-REM EEG sleep alterations in α-synucleinopathies and their preclinical stage. Using a multimodal approach (PSG and [18F]FDG-PET), our results documented that iRBD-MCI had decreased KC density (EEG cortical graphoelement forerunner of SWS) (*Study IIIa*). In frank dementia, the same alterations are reported in association with cognitive decline (De Gennaro et al. 2017); thus, these findings support the role of iRBD as a risk factor for future dementia development. To investigate possible KC local neuronal substrates,

we explored the association between brain metabolism and KC density. Higher KC density correlated with increased brain metabolism in the right superior medial frontal cortex, confirming previous intracranial recording study in humans (Wennberg 2010). The medial frontal cortex is crucially involved in the ADMN, which is at the basis of top-down cognitive control (Seeley et al. 2007). Consistently, high KC density was also associated with the integrity of ADMN metabolic connectivity. The iRBD subjects with low KC density showed less strength metabolic connections between the anterior cingulate cortex (seed region) and left middle and bilateral superior frontal gyri than iRBD with high KC density. This finding suggests a possible protective role of KC in α-synuclein related neurodegeneration since the earliest phases. Of note, ADMN' brain regions are involved with cognitive control (Seeley et al. 2007), memory, attention and sensory integration (Gogolla 2017; Rodgers et al. 2008). A more preserved ADMN connectivity may underly the more preserved performance in executive and visuo-spatial functions observed in our series of iRBD with higher KC density. Cognitive dysfunction in PDD/DLB may be ascribable to the aggregate of α-synuclein in the cerebral cortex, including the medial prefrontal cortex (Espa et al. 2019). It has been recently reported that the integrity of SWS can slow down motor progression in PD (Schreiner et al. 2019), perhaps driving the metabolic clearance of adults' brains. Our study extends the importance of slow waves in α-synucleinopathies – since the prodromal stage – as a possible modifiable risk factor and its potential effect in reducing patients' risk of dementia.

Genetics has a pivotal role in determining the phenotypical trajectories in PD (Collins and Williams-Gray 2016). GBA mutation is considered one of the most important genetic risk factors for developing dementia (Collins and Williams-Gray 2016). However, a few studies – with heterogeneous results – investigate how the dopaminergic impairment might be affected by such genetic mutation (Simuni et al. 2020; Cilia at al. 2016). Specifically, these studies investigated [123I]FP-CIT imaging in GBA-PD compared to iPD, considering only putamen and caudate nucleus and without stratifying the cohorts according to age at symptoms onset (Cilia et al. 2016; Simuni et al. 2020). We combined cross-section and longitudinal designs to compare GBA-PD and iPD stratified by the age at onset. The measures of interest were clinical data and [123I]FP-CIT binding in striatum and extra-striatum targets (Nobin 1973; Cossette, Lévesque, and

Parent 1999; Hedreen 1999; Tziortzi et al. 2013) (*Study IVa and IVb*). The cross-sectional analysis emphasized widespread dopaminergic impairment in GBA-PD patients since early-stage (baseline) compared with idiopathic forms, supporting the role of GBA mutations in leading to faster neurodegeneration. Longitudinal data demonstrated that early and late-iPD reach the same dopaminergic injury severity in ventral striatum as GBA-PD patients after two years. Dopaminergic damage is more severe in patients with diffuse brain LB disease (PDD/DLB) compared to PD with stable clinical progression (Walker et al. 2004; Cilia et al. 2016). Thus, patients with GBA mutations are much closer to the diffuse malignant phenotype (PDD/DLB) within PD's clinical spectrum. The PD malignant phenotype manifests more severe motor and non-motor symptoms, more significant atrophy of the SN, and more dopaminergic deficits in SPECT (Fereshtehnejad et al. 2017). The key clinical markers of this subtype are iRBD, autonomic dysfunctions, and a more rapid decline in global cognition (a progressive worsening of MoCA scores)(Fereshtehnejad et al. 2017; Fereshtehnejad et al. 2015). In the present series, the GBA-PD group also showed higher RBDSQ scores than the two idiopathic groups. RBD in PD subjects is considered a marker of a more malignant phenotype (Fereshtehnejad et al. 2017) and is associated with diffusion and severe synuclein deposition (Postuma, Adler, et al. 2015). GBA-PD and the late-iPD patients lost more than 1 MoCA point per year, while the early-iPD cases showed global cognitive stability during the years (Figure 52). Thus, GBA-PD and late-iPD showed a comparable cognitive deterioration, compatible with the definition of "diffuse malignant" PD clinical phenotype. On the other hand, our findings support that early-iPD represents a PD clinical condition characterised by a slow disease course, stable cognitive progression, and more limited dopaminergic deficits. How GBA mutations affect DA integrity is still unclear. The glycosylceramide – the substrate of GCase – and α-synuclein seem to generate a vicious circle (Mazzulli et al. 2011). The first may cause the accumulation of α-synuclein, and, conversely, the accumulation of α-synuclein may lead to a decrease in GCase activity (Mazzulli et al. 2011). Overexpression of α-synuclein led to reduced GCase levels in brain tissue (Chiasserini et al. 2015; Murphy et al. 2014), cerebrospinal fluid (Parnetti et al. 2017), and peripheral blood of PD patients (Alcalay et al. 2015; Avenali et al. 2021). Furthermore, GCase defects impact cellular energy production and proteostasis; GCase deficiency is also associated with remarkable microglia activation, which indicates that

neuroinflammation is another major consequence of GBA mutation (Avenali et al. 2019). These studies indicate that GBA mutations may trigger a cycle of malignant neurotoxicity. However, the reasons for the fragility of specific neuron types have not yet been elucidated. Specific neurons are vulnerable to α-synuclein pathology (Braak, Rüb, et al. 2003), and these neurons share morphological traits: the presence of long and highly branched axons with a considerable number of transmitter release sites. The dopaminergic neurons arising from SN and projecting to the striatum present these morphologic characteristics (Sulzer and Surmeier 2013). Moreover, *postmortem* evidence demonstrated a widespread deficiency of GCase activity in GBA-PD brains, with the most severe defect located in the substantia nigra (58%) and putamen (48%) (Gegg et al. 2012). In conclusion, our findings confirm that the GBA mutations accelerate the neurodegenerative process, contributing to a severe phenotype with underlying widespread and severe striatal and extra-striatal binding deficiency since early disease stage.

4.2. Part 2: Clinical and cognitive features in different LB disease stages

In combination with reliable biomarkers, cognitive assessment can substantially improve dementia risk profiling in PD (Dubbelink et al. 2014). Some data (Williams-Gray et al. 2007) suggest that cortical posterior cognitive deficits (visuo-constructive and memory) lead to a high risk of dementia (Kehagia et al. 2013; Aarsland et al. 2021). A recent longitudinal study detected the cognitive prodrome of dementia in PD, showing high accuracy of Trail Making Test Part B (TMT-B, Executive functions), Verbal Fluency (semantic, Executive functions) and Block Design test (Visuospatial abilities) in predicting dementia development in PD (after four years of follow-up) (De Roy et al. 2020). Although TMT-B is considered an executive test, multiple cognitive domains influence its outcomes (MacPherson et al. 2019). Of note, higher visuospatial abilities are associated with better TMT-B performances (MacPherson et al. 2019). Following these results, our findings (*Part 2*) emphasize a possible association between dementia and visuospatial/visuo-constructive deficits in α-synucleinopathies since the preclinical stage. In our cohort of iRBD, most of the patients presented visuo-

constructional/visuoperceptive deficits (*Study Ib and Study IIIb*). These deficits showed a relationship with both metabolic and PSG measures.

Cognitive deficits in iRBD were related to the topography and cluster extent of brain hypometabolism (*Study Ib*). In RBD-CI, the occipital-parietal hypometabolism pattern was associated with the highest percentage of visuo-constructional/visuoperceptive deficits, as measured by ROCF and QSPT copy. Of note, the qualitative analysis of the QSPT pentagons drawing emerged as a sensitive measure of visuo-constructive abilities in DLB patients (Caffarra et al. 2013). In addition to visuo-constructional impairment, most of these subjects also had defective verbal short-term and long-term memory performance. Consistently, iRBD subjects who converted to DLB exhibit declining performance over time in verbal episodic memory and ROCF copy tests, already two or three years before overt dementia (Génier Marchand et al. 2018). According to the hypometabolic pattern, the cognitive scores of iRBD-CI subjects suggest that the occipito-parietal group presented homogeneous neuropsychological profiles mainly characterized by visuo-constructional deficits, further underling the crucial involvement of occipito-parietal regions in their occurrence. The occipito-cerebellar sub-group presented heterogeneous neuropsychological profiles instead, characterized by executive, language, visuo-constructive, short-term and working memory deficits. Consistently, the cerebellum is involved in a wide range of cognitive functions (Schmahmann et al. 2019), suggesting that the occipito-cerebellar pattern could imply a broader range of cognitive symptoms.

Regarding the EEG measures during non-REM sleep, we found a significant positive correlation between KC density and MMSE performance, visuo-constructive abilities and executive function (*Study IIIb*). This result is particularly relevant since these two domains are frequently impaired in iRBD patients when compared to HC (Manni et al. 2013; Galbiati, Carli, et al. 2019), and also because the impairment of these neuropsychological features is fundamental to predict the conversion of patients into overt α-synucleinopathies, in particular DLB/PDD or PD (Fantini et al. 2011; Youn et al. 2016; Génier Marchand et al. 2018).

Study V further supports the crucial involvement of occipital regions in the occurrence of visuo-constructive deficits (as measured with ROCF-c) characterizing DLB. Specifically, we demonstrated that patients with DLB and AD failed ROCF-c due

to different anatomical dysfunctions. DLB performed significantly worse than AD patients in the visuo-constructive domain (i.e. ROCF-c). ROCF-c performance in DLB is related to low metabolism, mainly in the occipital and parietal cortex, while typical-AD only shows the correlation in the temporo-parietal regions. These data are consistent with specific DLB brain vulnerabilities (McKeith et al. 2017).

Moreover, we indicated that ROCF-c defects are more related to the damage of visual perception processing in DLB and the visuospatial mechanism in AD. The lack of association between ROCF-c deficit and occipital hypometabolism in typical-AD patients describes a preserved perceptive processing. Consistently, we suggest a prevalent involvement of the ventral pathway ('what') (lateral occipital and temporal regions) and thus visuoperceptive alterations in DLB; the dorsal pathway ('where') (involving parietal regions) and thus visuospatial impairments in AD (Kravitz et al. 2011).

4.3. Part 3: Biological, gender and environmental sources of phenotypic variability of LB disorders

Male gender and low education are considered risk factors for the development of dementia in PD. Of note, also in DLB patients, education level modulates the underlying neurodegenerative process leading to a delay of dementia onset (see *1.7.1. Cognitive and brain reserve*). Accordingly, education is considered a modifiable risk factor for dementia development, which may help to delay the clinical manifestation being a crucial element for healthcare and therapeutic strategy planning (Livingston et al. 2017; Orgeta et al. 2019; Livingston et al. 2020). Both gender and CR are important sources of variance in PD clinical manifestation, characterized by marked heterogeneity and variable progression. Investigating in-depth these factors is essential to increase the prevention strategies and the chance of accurate clinical work-up. Our findings indicate gender-related vulnerability in the dopaminergic systems involved in PD (nigro-striato-cortical and mesolimbic), using an [18F]FDG-PET metabolic connectivity approach (*Study VI*). PD males have extended alterations of metabolic connectivity within the nigro-striato-cortical network compared to females, whereas PD females show widespread reconfiguration of the mesolimbic dopaminergic system compared to males. We also evaluated gender differences in PD subtype: mild-motor, intermediate and diffuse malignant (*Study VII*). We confirmed the male vulnerability of the dopaminergic

nigrostriatal system with [123I]FP-CIT-SPECT measures, showing high consistency across subtypes. We have also corroborated the extended alterations of the mesolimbic system in PD females, suggesting an early vulnerability, probably associated with a major psychopathological state.

Regarding cognitive outcomes, we found that males show lower cognitive performance than females in executive function, memory, and processing speed (*Study VII*). In the intermediate subtype, we found poorer visuospatial abilities in females than males, keeping with some previous studies (Riedel et al. 2008; Locascio, Corkin, and Growdon 2003). HC usually show similar gender differences in visuospatial abilities suggesting that our result is likely to mirror the healthy population where males usually outperform females in visuospatial functioning (Weiss et al. 2003; Curtis et al. 2019). This cognitive picture is consistent with recent work on cognitive function in iPD, suggesting that males are more vulnerable to cognitive impairment (Reekes et al. 2020). Moreover, males with the intermediate subtype showed higher scores in the RBD questionnaire. RBD is considered a clinical entity with pathophysiological and prognostic relevance, characterising patients with a severe phenotype of iPD (Fereshtehnejad et al. 2015; Anang et al. 2014; Postuma, Gagnon, and Montplaisir 2013). All in all, our results fit well with the evidence of the male sex associated with an increased risk of PD-related cognitive impairment and dementia (Anang et al. 2014; Pigott et al. 2015).

A supportive effect of oestradiol on DAT has been proposed, leading to a greater amount of striatal DA availability in women (Gillies and McArthur 2010). Thus, the development of symptomatic PD is delayed in women by higher physiological dopamine levels on the striatum due to the activity of oestrogens. The oestradiol-induced neuroprotection might be an adaptive response in the surviving neurons, restoring striatal dopaminergic functionality (Gillies and McArthur 2010). The mesolimbic system impairment usually shows high inter-subject variability, as demonstrated by *postmortem* (Surmeier and Sulzer 2013) and *in vivo* molecular data (Caminiti et al. 2017). Our findings suggest that gender may represent a crucial source of this variability in PD patients in this scenario. This finding is consistent with previous studies demonstrating that several psychiatric symptoms – apathy, depression, anxiety and fatigue – are more common and severe in women (Martinez-Martin et al. 2012). In PD, impairment in the mesolimbic dopaminergic system has been linked to non-motor symptoms, particularly

mood disorders, which may affect patients since or even before the initial clinical phase of PD (Gustafsson, Nordström, and Nordström 2015; Castrioto et al. 2016). Sociodemographic factors might explain the gender-related vulnerabilities in the mesolimbic circuit. Educational, behavioural and lifestyle choices could affect the organization of brain networks. Notably, limbic structures are sensitive to sex hormones, leading to the high-stress vulnerability of this system in females (McLaughlin, Baran, and Conrad 2009). Coherently, the mesolimbic dopamine system seems to be more sensitive to social defeat in females than males (Greenberg and Trainor 2015). These results enhance the knowledge on the biological basis of PD clinical phenotypes. It is crucial the understanding of how gender can create risk and resilience for PD, due to potentially different gender-based treatments and the effectiveness in targeting modifiable risk factors.

Lastly, we evaluated the modulation of CR proxies on the functional BR in DLB, as measured by [18F]FDG-PET brain connectivity. In agreement with previous evidence (Lamotte et al., 2016; Perneczky et al., 2009; Perneczky et al., 2007), we found that education influences BR through compensatory mechanisms, further confirm the protective role of education in the field of dementia (Livingston et al. 2017; Orgeta et al. 2019; Livingston et al. 2020). We also demonstrated the protective role of occupation and specific occupational profiles in DLB, which shapes and re-organises brain networks, encompassing two main mechanisms: neural reserve and neural compensation. In [18F]FDG–PET studies, connectivity changes are usually interpreted in brain function: connectivity decreases indicate functional disconnection between regions, while connectivity increases indicate increased functional coupling between regions (Pievani et al. 2014; Sala and Perani 2019). When increased connectivity affects metabolically preserved brain regions, it might indicate a “beneficial” compensatory process, with the recruitment of brain regions that are still unaffected and functionally active (Malpetti et al., 2017; Perani et al., 2017; Pievani et al., 2014). In this study, the reduction of functional connections was found mainly in those networks located in areas affected by the disease, such as visual and attentive networks, following the posterior vulnerability of DLB (Caminiti et al., 2019; Iaccarino et al., 2018; Sala et al., 2019).

On the other hand, the increase in connectivity involved mainly frontal areas, suggesting compensatory mechanisms, since the anterior brain regions are more

preserved by the disease (Caminiti et al., 2017; Pievani et al., 2014), and can be therefore recruited in order to cope with the posterior neurodegeneration. Increases in connectivity were found mainly in high CR sub-groups, suggesting adaptive compensatory mechanisms. However, the increased connectivity found in low CR sub-groups might be interpreted as a potential adaptation, detrimentally, to the neurodegenerative damage. Indeed, increased connectivity could be responding to either a compensatory mechanism or a pathologic spreading effect (Iturria-Medina and Evans 2015; Sala and Perani 2019). For instance, it has been reported that some networks are activated when they should be off, causing detrimental and disadvantageous effects in MCI patients (Gardini et al. 2015). In this perspective, the increases of functional connectivity in low CR sub-groups may represent the damaged brain's attempt to cope with neurodegeneration in the transition from functional neuroplastic compensatory mechanisms (as observed in high CR sub-groups) to maladaptive processes, suggesting that neurodegeneration leads to a loss of the network functional specificity. The present findings suggest a further clinically relevant consideration for the standardized neuropsychological assessment, as premorbid occupation should be considered a demographic variable in the adjusted scores. Moreover, occupation might represent an early modifiable risk factor that might impact dementia rates.

4.4. Conclusion

This dissertation provides new evidence regarding modifiable and non-modifiable risk factors that influence the occurrence of the severe phenotype of α-synucleinopathies and the timing of dementia symptoms onset. Moreover, we identify valuable biomarker and cognitive marker candidates for α-synucleinopathies dementia risk profiling since early preclinical stages. Specifically, the discussed studies support that a) iRBD, male gender, and GBA genetic mutation represent non-modifiable risk factors for severe forms of PD (i.e. PDD); b) improving education level, as well as empowering specific job skills (problem-solving, visual task and sociality) act as modifiable risk factors, delaying the onset of dementia symptoms; c) SPM single-subjects [18F]FDG-PET hypometabolism maps might represent valuable prognostic measures already in iRBD preclinical stage; d)

visuo-constructive deficits in α-synucleinopathies are due to visual perceptual alterations (occipitally-mediate), characterizing DLB/PDD since preclinical stage (iRBD).

These results should be cautiously interpreted. We acknowledge the lack of follow-ups for iRBD patients as the main limitation, narrowing the prognostic consideration about cognitive features and biomarkers in these patients (*Study I and III*). Notably, the COVID–19 pandemic slowed down longitudinal follow-up assessments that are currently ongoing in collaboration with the Sleep Disorders Centre of San Raffaele Hospital (Milan). However, a multicentric longitudinal iRBD cohort study project is starting, representing my future post-doc research trajectory. This study involves five centers: Vita-Salute San Raffaele University, University Medical Center Groningen, University of Tübingen and Berlin, Seoul National University College of Medicine and IRCCS Policlinico San Martino Hospital.

5. Material and methods

The studies included in this dissertation were built on PET, and SPECT-based imaging techniques ([18F]FDG-PET and [123I]FP-CIT-SPECT) and several imaging data approaches (univariate and advanced multivariate connectivity methods). Since many steps were shared among the studies, this section will first list the common analytical steps, with study-specific methodological details following, including the specific design, statistical models and approaches. Almost all of the methods described below were published in peer-reviewed journals and are currently available online.

5.1. Participants underwent [18F]FDG-PET exam

The following data have been published (Carli et al. 2020; Carli et al. 2020; Galbiati et al. 2021; Beretta et al. 2021; Carli et al. 2020; Boccalini et al. 2021).

iRBD (IRCCS San Raffaele Scientific Institute) - Subjects diagnosed with iRBD according to the ICSD-3 (American Academy of Sleep Medicine 2014) were consecutively recruited at the Sleep Disorders Centre of Turro San Raffaele Hospital, Milan, Italy. None of the subjects with iRBD in the study presented clinical history for cerebrovascular diseases. After an adaptation night, each iRBD subject underwent

nocturnal PSG recording in a sound-attenuated sleep laboratory room. Lights-out time ranged between 21.30-23.30 h based on typical individual bedtime. PSG was recorded based on the following signals: EEG (eleven electroencephalographic derivations F3, F4, C3, CZ, C4, T3, T4, P3, P4, O1, O2), electrooculogram (EOG), electromyography (EMG) of the submentalis, flexorum digitorum superficialis, and tibialis muscles, electrocardiogram (ECG). Sleep was scored and evaluated by a physician expert in sleep medicine following the American Academy of Sleep Medicine (AASM) (Berry et al. 2012). According to ICSD-3, RBD diagnosis depends on repeated episodes of sleep-related vocalization and/or complex motor behaviour during REM sleep and RSWA. These signs should be confirmed employing video-PSG. The gold standard for RSWA scoring is based on the visual analysis of the EMG, following guidelines for scoring of iRBD reported in the AASM manual (Medicine 2014). Specifically, AASM recommends identifying RSWA when both tonic and phasic activities are present in the chin or when phasic activity on the limbs is present in more than 27% of 30s REM sleep epochs.

iPD (Neurology Unit-Brescia) - iPD without cognitive impairment at baseline and follow-up (≥8 years) were retrospectively recruited from the clinical and imaging database of the Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. The clinical diagnosis of iPD patients was made according to the UK Brain Bank Criteria (Postuma et al. 2015), considering the entire medical history, neurological examination (including UPDRS-III in ON condition) and a standard neuropsychological assessment. All included patients underwent structural imaging (MRI or computed tomography (CT)) in order to exclude prominent cortical or subcortical cerebrovascular disease or brain/iron accumulation). The presence of deep brain stimulation, genetic mutation, concomitant psychiatric or other neurological disorder, hallucination, psychosis or antipsychotic drug use, history of drug or alcohol abuse were exclusion criteria.

DLB (IRCCS San Raffaele Scientific Institute) - Patients with probable DLB (McKeith et al. 2017) were retrospectively collected from the clinical and imaging database of San Raffaele Hospital, Milan, Italy. Clinical information (i.e., medical history, neurological examination and neuropsychological assessment) was evaluated by experts in dementia to check the clinical diagnosis for probable DLB in all patients. Instrumental data (i.e., MRI and FDG-PET) supported the clinical diagnosis.

AD (IRCCS San Raffaele Scientific Institute) - Thirty-four patients with a clinical diagnosis of probable typical-AD were retrospectively recruited from the clinical and imaging database of San Raffaele Hospital, Milan, Italy. According to the clinical research criteria, all the patients presented with diagnosed dementia, insidious onset of the symptoms, history of worsening of cognition, and both amnestic/non-amnestic presentation of cognitive deficits, according to the clinical research criteria (McKhann et al. 2011). In addition, each patient had a typical-AD hypometabolism pattern, involving bilaterally the temporo-parietal cortex, accompanied by hypometabolism in the precuneus and posterior cingulate cortex. Patients with either neoplastic or significant vascular lesions, clinically relevant psychiatric disorders or other neurological disorders, history of drug or alcohol abuse/dependence were not included.

HC (IRCCS San Raffaele Scientific Institute) - A group of 112 HC were used for most of the studies in this thesis [age (mean ± SD, 64.67 ± 9.34 years; Males/Females, 53/59]. 112 HC were included from the internal database of the *In Vivo* Human Molecular and Structural Neuroimaging Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy. They presented a negative medical history for neurological or psychiatric diseases or other chronic illnesses and were not taking psychoactive medication.

5.2. Participants underwent [123I]FP-CIT-SPECT exam

Part of the following data have been published (Caminiti, Carli, et al. 2021).

GBA-PD (PPMI database) - We considered the PPMI participants for whom whole exome or genome sequencing was available. The Exons 1-11 within the *GBA* gene were Sanger sequenced and screened for variants. Dual mutation carriers (LRRK2 and GBA) were excluded from this study. GBA variants were also classified according to mutation's severity (Petrucci et al. 2020): "mild" (N370S (mGBA)), "severe" (L444P, R463C, IVS2+1G>A (sGBA)), "risk" (E326K, T369M (rGBA)) and "unknown" (A456P, K(-27)R, R39C, R44C, I489L (uGBA)). We included 46 PD with GBA mutations (GBA-PD) who were drug-naïve.

iPD (PPMI database) - Patients diagnosed with iPD for two years or less who are not taking PD medications and without verified genetic mutations known to cause PD (GBA, LRRK2).

HC (PPMI database) - Fifty-nine HC are collected from the PPMI database. Control subjects without PD who are 30 years or older and do not have a first-degree blood relative with PD. HC subjects were characterized by normal cognition and motor functionality, as assessed by MoCA score >26 and Hoehn and Yahr stage = 0, respectively. In all HC, [123I]FP-CIT-SPECT was rated as negative according to a predefined ranking scale (Darcourt et al. 2010).

HC (Neurology Unit-Brescia) - A pool of 73 HC subjects were retrospectively collected from the imaging database of the Neurology Unit, Department of Clinical and Experimental Sciences, at the University of Brescia, Brescia, Italy. They underwent [123I]FP-CIT-SPECT scans, presented a negative medical history for neurological disease or other chronic illness and were not taking psychoactive medication.

5.3. [18F]FDG-PET Image acquisition

The following data have been published (Carli et al. 2020; Carli et al. 2020; Galbiati et al. 2021; Beretta et al. 2021; Carli et al. 2020; Boccalini et al. 2021).

[18F]FDG-PET images at Nuclear Medicine Unit, IRCCS San Raffaele Hospital, Milan, Italy, were acquired using a Discovery STE (GE Medical Systems, Milwaukee, WI) multi-ring PET tomography (PET-CT), and [18F]FDG-PET images at Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy by a Discovery 690 (GE Healthcare). All [18F]FDG-PET acquisition procedures conformed to the European Association of Nuclear Medicine guidelines (Varrone et al. 2009). Static emission images started 45 min after 185–250 MBq injection of [18F]FDG via a venous cannula, with 15-min acquisition scan duration. The images were reconstructed by means of an ordered subset-expectation maximization algorithm. CT scans are used for attenuation correction. Significant artefacts were excluded throughout the visual inspection of each reconstructed image. Image pre-processing was performed using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/ spm12/), running in Matlab (MathWorks Inc., Sherborn, MA, USA).

5.4. [18F]FDG -PET Image pre-processing and single-subject analysis

The following data have been published (Carli et al. 2020; Carli et al. 2020; Galbiati et al. 2021; Beretta et al. 2021; Carli et al. 2020; Boccalini et al. 2021).

Independently from the acquisition parameters, [18F]FDG-PET pre-processing followed the same pipeline developed and validated in our centre (Della Rosa et al. 2014; Perani et al. 2014). Our optimized [18F]FDG-PET SPM based method is based on a highly accurate spatial normalization of the images and a highly robust statistical comparison at the single-subject level, compounded by many HC (N=112) (Della Rosa et al. 2014; Perani et al. 2014). This procedure allows identifying disease-specific brain hypometabolism patterns independently from the scanner adopted (Presotto et al. 2017). The [18F]FDG-PET scans first undergo spatial normalization, using a dementia-specific [18F]FDG-PET template (Della Rosa et al. 2014). Spatially normalized images are then smoothed (Full-Width at Half Maximum: 8mm) and enter a statistical comparison with a large dataset of scans from normal controls which underwent the same pre-processing (Caminiti et al. 2021; Perani et al. 2014). The analysis also includes age as a nuisance factor, given that ageing is associated with changes in brain glucose metabolism (Della Rosa et al. 2014; Perani et al. 2014). This protocol and the number of HC utilise highly conservative and statistically robust measurements, i.e. $p<0.05$ with Family-Wise Error correction for multiple comparisons as a primary threshold with a minimum cluster extent of k:100 voxels. This optimized SPM procedure finally delivers patterns of brain hypometabolism at the voxel-level, or SPM-t thresholded maps, which can be evaluated by expert raters (Della Rosa et al. 2014; Perani et al. 2014). This pipeline also provides the so-called contrast images, which index relative hypometabolism and can be used for 2nd level statistical analysis.

5.5. [123I]FP-CIT-SPECT pre-processing and imaging analysis

Part of the following data have been published (Caminiti, Carli, et al. 2021).

The [123I]FP-CIT-SPECT and MRI images were downloaded from the PPMI database. Images were acquired on Siemens or General Electric SPECT tomographs, 3-4 h after [123I]FP-CIT injection. The imaging protocol for the PPMI scans has been previously documented (Marek et al. 2011; Marek et al. 2018). The MRI scans' coordinates were manually set to the anterior commissure as a first step. The volumetric cropped T1-weighted images in *native* space were segmented into different tissue types to obtain grey and white matter probability maps, using SPM12 (SPM, http://www.fil.ion.ucl.ac.uk/_spm/software/spm12). We integrated the grey and white tissue probability maps to realize a brain template in native space without non-brain tissue-specific for each patient. [123I]FP-CIT-SPECT images were rigidly co-registered with the obtained brain template in *native* space for each patient. A visual inspection was always performed to detect possible errors in the co-registration step. The spatial smoothing was not applied to limit blurring or spill-over.

The parameter of interest was the [123I]FP-CIT SUVr, and it was calculated as [(target region/reference region)-1] for each ROI. The lateral superior occipital cortex uptake was used as the background reference region.

We analyse subcortical striatal regions main target of dopaminergic midbrain neuron projections (whole caudate nucleus and putamen) and extra-striatal structures that receives variable degrees of dopaminergic innervation (globus pallidus, thalamus, amygdala, and hippocampus, bilaterally) (Smith and Villalba 2008; Cossette, Lévesque, and Parent 1999; Hedreen 1999; Tziortzi et al. 2013) (*Study IV* and *Study VII*) (Figure 56A). Since the moderate affinity of [123I]FP-CIT-SPECT for the serotonin transporter in extrastriatal regions (Abi-Dargham et al. 1996; Scheffel et al. 1997), the signal extracted from basal ganglia was defined as "DAT binding"; instead, the signal extracted from extra-striatal regions was defined as" [123I]FP-CIT-SPECT binding.

We obtained subject-specific ROIs through the automatic subcortical structure segmentation of each participant's MRI scans using the volbrain platform (Coupé et al. 2011; Manjón and Coupé 2016). We further segmented the whole putamen ROI into the anterior and posterior components (*Study IV*). The anterior and posterior putamen

boundary was the posterior aspect of the fornix in the axial plane (Figure 56B) (Hacker et al. 2012). The whole putamen and caudate were subdivided into functional subregions (Tziortzi et al. 2013), i.e., dorsal-motor and ventral divisions (*Study IV* and *Study VII*) (Figure 56B). Structural volumes in cm^3 have been extracted for each subject-specific ROI.

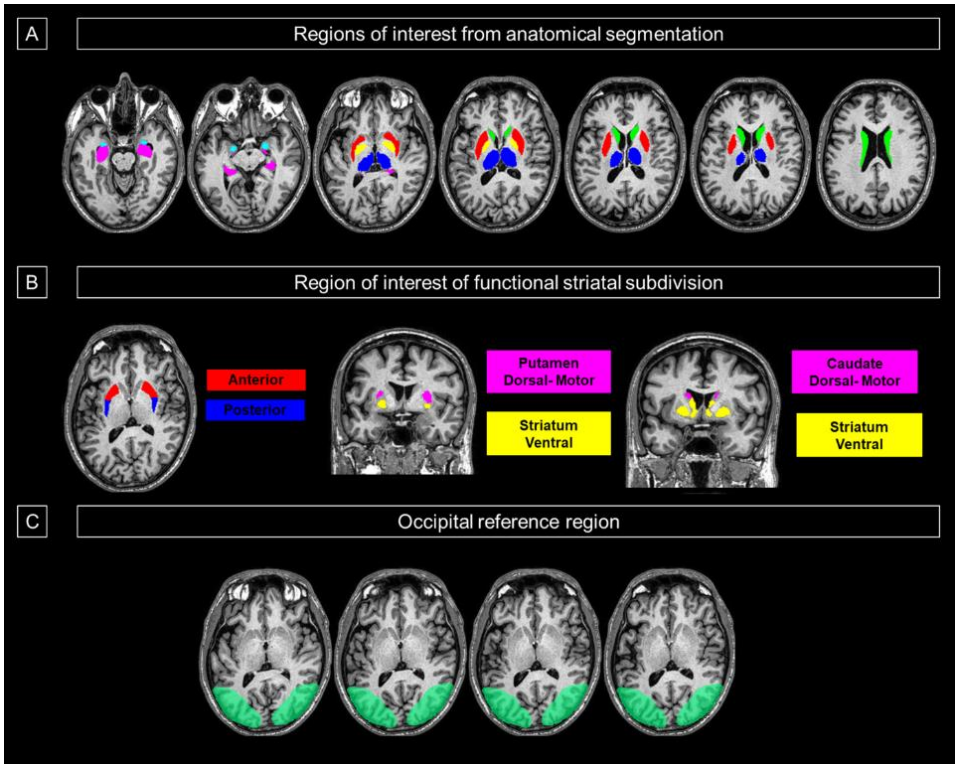

Figure 56. Subjects-specific ROIs for SUVr calculation (Fair use).

Example of anatomical subject-specific ROIs over-imposed on the relative MRI-T1 image in the native space of a GBA-PD patient. (A) ROIs obtained by the automatic anatomical segmentation of MRI scan, performed using volbrain. Fourteen ROIs were defined in each subject: whole caudate nucleus (green), whole putamen (red), globus pallidus (dark yellow), thalamus (blue), hippocampus (pink), amygdala (light blue). (B) The functional striatal subdivision following literature guidelines. The right panel shows the anterior (red) and posterior (blue) subdivisions of the whole putamen. The functional subdivision of the striatum includes dorsal-motor (pink) and ventral (yellow) divisions. (C) The last panel displays the lateral superior occipital cortex ROI used as the background reference region to calculate SUVr values. The figure is adapted from (Caminiti, Carli, et al. 2021) *in accordance to the fair use principle.*

The use of subject-specific ROIs avoids many inaccuracies in the calculation of SUVr because of morphological differences with the original structures. Indeed the obtained ROIs are less affected by the partial volume effects, ensuring high reliability of

the analysis (Niñerola-Baizán et al. 2018). Moreover, to further limits the partial volume effects across subjects, we co-variated ROIs structural volumes in the analysis of [123I]FP-CIT binding data.

We extracted mean SUVr values from left and right putamen to identify the predominant side of DAT binding defect in each PD patient, then we computed a DAT binding AI, adopting the following formula: - (right-left putamen SUVr)/(right + left putamen SUVr) (Kaasinen et al. 2015). The DAT AI values higher than 0.05 indicated left-lateralized asymmetry, and those lower than -0.05 indicated right-lateralized asymmetry. SUVr values for the selected ROIs were then flipped ROI-by-ROI according to the AI to set the predominant side of the DAT binding defect.

5.6. PET metabolic and molecular brain connectivity analyses

The following data have been published (Carli et al. 2020; Carli et al. 2020; Boccalini et al. 2021).

5.6.1. Neurotransmitters networks analyses

To investigate the molecular architecture of the major neurotransmission networks affected in α-synucleinopathies – i.e. the nigro-striato-cortical dopaminergic, mesolimbic dopaminergic, noradrenergic and cholinergic networks – we performed the following steps: i) selection of ROIs to reconstruct the neurotransmission network of interest, ii) average value of tracer uptake is then extracted from each ROI using specific imaging scans (scaled [18F]FDG-PET or parametric images [123I]FP-CIT-SPECT) and iii) application of partial correlation statistical analyses on matrices composed by extracted data. Thus, this approach relies on the combination of tracer data, multivariate analysis methods, and a priori selection of specific ROIs, providing reliable information on the molecular architecture of neurotransmission pathways in HC and neurodegenerative conditions (Sala and Perani 2019; Carli et al. 2021). The great advantage of using multivariate methods is that they allow assessing variations in the functional relationship between brain regions beyond regional changes (Sala and Perani 2019; Pievani et al. 2014; Yakushev, Drzezga, and Habeck 2017; Carli et al. 2021). This brain connectivity

approach assumes that regions with similar metabolic or molecular demands are functionally associated (Horwitz et al. 1987). Thus, assessing the relationship between brain regions is the main target of this approach (Sala and Perani 2019; Carli et al. 2021).

5.6.1.1. Neurotransmission networks reconstruction: ROIs selection

According to well-validated ROIs selection strategy (Caminiti et al. 2017; Sala et al. 2017; Caminiti et al. 2017), all the considered neurotransmitters networks was assembled by considering the topographical organization of projections originating by specific brain nuclei based on biochemical, histochemical and anatomopathological findings (Sala and Perani 2019; Carli et al. 2021).

Nigro-striato-cortical and mesolimbic dopaminergic networks - Previous biochemical, histochemical and anatomopathological findings allow us to identify ROIs highly innervated by ascending dopaminergic projections (Ciliax et al. 1999; Hall et al. 1999; Meador-woodruff et al. 1996; Ungerstedt and Herrera-marschitz 1970). According to the canonical description of these pathways, the nigro-striato-cortical system consisted of SNpc projections to dorsal caudate and dorsal putamen, globus pallidus, the motor section of the thalamus, frontal premotor, motor, executive dorsolateral frontal regions, and somatosensory cortex (Fallon 1988; Caminiti et al. 2017; Tziortzi et al. 2013; Sala et al. 2017). On the other hand, the mesolimbic dopaminergic pathways originated from VTA projections to the nucleus accumbens, the deep portion of the olfactory tubercle, and the ventral parts of the caudate nucleus and the putamen; it receives fibers from limbic and paralimbic cortices, as well as from the amygdala and the hippocampus (Caminiti et al. 2017; Fallon 1988; Parent and Hazrati 1995; Sala et al. 2017; Tziortzi et al. 2013; Caminiti et al. 2017).

All ROIs used for the connectivity analyses were derived from Automated Anatomical Labeling (AAL) atlas (http://www.gin.cnrs.fr/AAL), except for dorsal putamen, caudate nucleus, ventral striatum and globus pallidus for which we used ROIs derived from Harvard Oxford subcortical Atlas, the motor section of thalamus derived from Oxford thalamic connectivity atlas both available in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and the amygdala from ANATOMY atlas (Tziortzi et al. 2013; Behrens et al. 2003). Specifically, dorsal putamen, dorsal caudate nucleus and ventral striatum were obtained from a multimodal imaging study that

quantified the endogenous DA release after D-amphetamine administration with dopamine PET ligands (Tziortzi et al. 2013). In addition, the same study applied diffusion MRI and probabilistic tractography to better segment the striatal territories innervated by the nigrostriatal pathway. On the other hand, the motor section of the thalamus was obtained from a probabilistic atlas of 7 sub-thalamic regions, segmented according to their white-matter connectivity to cortical areas, calculated using probabilistic diffusion tractography multiple subjects (Behrens et al. 2003). See Appendix Table A1 and A2 for all ROIs composing these neurotransmitters networks.

Noradrenergic network - The noradrenergic system was reconstructed following the immunohistochemistry and biochemical anatomy studies in humans brains (Javoy-Agid et al. 1989; Samuels and Szabadi 2008). This system originates from NC that projects to several subcortical, profound and cortical brain regions, namely bilateral thalamus, amygdala, hippocampus, superior and middle frontal gyri, precentral gyrus, precentral gyrus, paracentral lobule, praecuneus and cerebellum (Javoy-Agid et al. 1989; Samuels and Szabadi 2008). Thus, we reconstructed the noradrenergic network following this immunohistochemistry and biochemical anatomy data. All ROIs used for the connectivity analyses were derived from AAL (http://www.gin.cnrs.fr/AAL) and ANATOMY toolbox atlases. In particular, frontal regions were derived from the AAL atlas and the amygdala, hippocampus and cerebellar regions from the ANATOMY toolbox atlas. According to Kroemer et al. guidelines (Kroemer et al. 2013), hypothalamus ROI was created using spherical ROIs with a 5-mm radius centred at [±8 -4 -4] MNI coordinates. See Appendix Table A3 for all ROIs composing this neurotransmitter network.

Cholinergic networks - The cortical and subcortical cholinergic projections originate from two main groups of nuclei localized in the midbrain (i.e. Ch5-Ch6) and basal forebrain (i.e. Ch1-Ch4). Specifically, the Ch1-Ch4 nomenclature was introduced to designate the cholinergic neurons within four cell groups in the basal forebrain (Mesulam et al. 1983; Mesulam et al. 1983; Mesulam and Geula 1988). Ch1 designates the cholinergic cells associated with the medial septal nucleus and Ch2 with the diagonal band's vertical nucleus according to this nomenclature. Together these nuclei Ch2 provide the primary cholinergic innervation for the hippocampal complex (Mesulam et al. 1983). The Ch3 nucleus corresponds to the horizontal limb of the diagonal band nucleus and

innervates the olfactory bulb (Mesulam et al. 1983; Mesulam et al. 1983; Mesulam and Geula 1988). Following the Ch1-Ch4 nomenclature, the Ch4 is associated with the NBM. Cholinergic fibres bundles originating from Ch4 formed a medial and a lateral pathway. The lateral pathway is further composed of a capsular component (travelling within the external capsule) and a perisylvian component (travelling within the clastrum) (Mesulam 2004). In detail, the Ch4 medial pathway reaches cingulate, retrosplenial, and orbitofrontal cortices; the Ch4 lateral perisylvian division joints olfactory and superior temporal cortices, plus the insula and the fronto-parietal operculum; the Ch4 lateral capsular division supplies the remaining frontal, parietal, temporal, and occipital cortices, as well as the amygdala (Mesulam 2004). Finally, the cholinergic nuclei of the brainstem (Ch5 and Ch6)[13] reach the thalamus, ventral and dorsal striatum, globus pallidus (Mesulam et al. 1983; Mesulam 2004). Thus, we reconstructed the cholinergic network consisting of these four divisions of the cholinergic network based on this neuroanatomy, cytochemistry, connectional topography and cortical distribution data.

Thus, the first division consisted of the brain regions innervated by the Ch1-Ch2 nuclei, namely the bilateral hippocampus and hypothalamus (Mesulam 2004; Hall et al. 2014). The second network represented the brain target of the Ch3 nucleus projections: the olfactory and parahippocampal cortices (Mesulam 2004). The third and fourth cholinergic divisions were represented by the pathways originating from Ch4 nuclei (Mesulam 2004; Hall et al. 2014). Namely, the Ch4 medial pathway projects to cingulate, retrosplenial, and orbitofrontal cortices (Mesulam 2004), and the Ch4 lateral pathway projects to perisylvian division reaching olfactory and superior temporal cortices, plus the insula and the fronto-parietal operculum (Mesulam 2004). The last cholinergic network originated from Ch5-Ch6 nuclei of the brainstem, reaching the thalamus, ventral and dorsal striatum, globus pallidus (Mesulam 2004). The multivariate method of analysis used to assess brain metabolic connectivity (see *Partial correlation analysis*) requires the sample size of the data to be substantially larger than the number of brain regions model (Sala and Perani 2019; Huang et al. 2010). For this methodological constraint, we did not consider the lateral capsular pathway originating from Ch4 nuclei because it comprises 56 ROIs (Caminiti et al., 2017) involving the frontal, parietal, temporal, and temporal occipital cortices (Mesulam 2004). All ROIs used for the connectivity analyses were

[13] Ch5 pedunculopontine tegmental nucleus and the Ch6 laterodorsal tegmental grey of periventricular area

derived from the AAL atlas, ANATOMY toolbox atlas and Harvard Oxford subcortical Atlas available in FSL. Hypothalamus ROI was created using spherical ROIs, as mentioned above. See Appendix Table A4 and A5 for all ROIs composing these neurotransmitter network' divisions.

In all the pathways mentioned above, we excluded the small output nuclei from which each molecular network originates (i.e. SNpc, VTA, LC, and Ch1, 2, 3, 4, 5, 6 nuclei) due to the limited spatial resolution of PET (see also (Caminiti et al. 2017; Sala et al. 2017)).

Each ROI was convolved with an 8mm FWHM Gaussian kernel, representing the effective reconstructed resolution of the images, in order to minimize the impact of the partial volume effect. Only voxels that, after convolution, had a value> 50% were used for the analyses, as they can be expected to be the least affected by contamination from neighbouring structures (Caminiti et al. 2017). Last, we acknowledge the absence of partial volume effect correction as a limit of this study. However, the combined use of anatomical and functional probabilistic atlases for ROIs segmentation and the strategy of picking only the centre of each volume represents a solution in case of lack of MRI measures (not available in all our subjects).

5.6.1.2. *Partial correlation analysis*

Partial correlation is a statistical approach that allows assessing metabolic connectivity between two ROIs while controlling for the contributions of other regions (Huang et al. 2010). Partial correlation analysis overcomes the limitations of simple correlation analysis, which captures pairwise information without considering the effects of multiple brain regions interaction (Huang et al. 2010). It is established that pairs of brain regions whose metabolism values are significantly correlated are also functionally associated, and the strength of the associations is proportional to the magnitude of the correlation coefficients (Huang et al. 2010). This method takes advantage of good reproducibility and general applicability within the range of experimental settings typical of PET neuroimaging studies (Veronese et al. 2019).

First, the PET/SPECT imaging scans underwent a specific pre-processing step to obtain scaled or parametric images accounting for between-subject tracer uptake

variability. Specifically, [18F]FDG-PET images were normalized using the global mean scaling, obtaining the so-called scaled images (Perani et al. 2014). Regarding [123I]FP-CIT-SPECT images, parametric images were generated for each subject using the Image Calculator (ImCalc) function in SPM12. Precisely, the DAT SUVr – the parameter of interest – was calculated as [(voxel(i)/reference region)-1] (Marek et al. 2011; Marek et al. 2018; Garrido et al. 2020). The lateral superior occipital cortex uptake was used as the background reference region (Huber et al. 2020).

Then, tracer uptake was extracted from each ROI composing different neurotransmitters networks using the REX toolbox for MATLAB (https://www.nitrc.org/projects/rex/). To estimate the molecular architecture of each neurotransmission network, we created a subject-by-ROI matrix for each clinical group (iRBD, PD, DLB and HC). Each matrix's entries comprised the mean tracer uptake values derived for a specific ROI and subject. Based on these subject-by-ROI matrices, we computed partial correlation coefficients. This analysis was run using MATLAB software (http://it.mathworks.com/products/matlab/)(Mathworks Inc., Sherborn, Mass., USA). The resulting partial correlation matrices were thresholded at $p < 0.01$, uncorrected for multiple comparisons, as a reasonable trade-off between statistical robustness and sensitivity (Bennett, Wolford, and Miller 2009). Age was included as a nuisance covariate in the analysis.

To assess the connectivity alterations of the neurotransmission networks in each clinical group, we tested whether the strength of the partial correlation coefficients (indexing the strength of the metabolic connection) differed between the clinical and the HC groups. We thus first applied Fisher's transformation to each coefficient resulting from partial correlation analysis (Myers and Sirois 2004). Then, we performed a z-test to test for significant changes in partial correlation coefficients (indexing a significant alteration in metabolic/molecular brain connectivity) (Bennett, Wolford, and Miller 2009).

5.6.2. Metabolic connectivity in large scale brain networks: interregional correlation analysis (IRCA)

To evaluate the metabolic connectivity in large scale brain networks, we applied IRCA, using a voxel-wise SPM procedure (Lee et al. 2008). We considered the large scale brain

networks primarily involved in DLB (Caminiti et al. 2017; Sala et al. 2019; Franciotti et al. 2013): the PVN and HVN, the ECN, ATTN, ADMN and PDMN (*Study VIII*). ADMN was also selected for its role in SWS generation (*Study III*) (Murphy et al. 2009). Seed ROIs were defined from the functional atlas of large scale brain networks (as defined by (Shirer et al., 2012)) (http://findlab.stanford.edu/functional_ROIs.html). The selected seeds are the following: the inferior parietal lobule for the ATTN, the anterior cingulate cortex/ventromedial prefrontal cortex for the ADMN, the posterior cingulate cortex for the PDMN, the dorsolateral prefrontal cortex for the ECN, the inferior and medial occipital cortex for HVN and the calcarine cortex for PVN. The mean [18F]FDG seed uptake, extracted separately for each sub-group (Study VIII: low and high CR; Study III: low and high KC density) was set as variable of interest in a multiple regression models, testing for voxel-level correlations with the whole brain metabolic activity in considered sub-groups. Statistical threshold was set at $p = 0.001$, FWE-corrected at cluster level, with $K \geq 100$ voxels. As regard the ADMN in Study VIII, the statistical maps of connectivity were thresholded with an explicit mask to constrain the analysis to defined regions known to be part of ADMN in HC (Malpetti et al. 2019).

5.7. Methods - Study I: In-vivo signatures of neurodegeneration in isolated rapid eye movement sleep behaviour disorder. (Carli et al. 2020) - Published article -

The following data have been published (Carli et al. 2020).

5.7.1. Neuropsychological assessment

Each iRBD patient received an evaluation of global mental status (i.e., MMSE) and comprehensive neuropsychological examination, including language (i.e., Token test), verbal and visuo-spatial memory (i.e., digit span forward, immediate and delayed recall of RAVLT, ROCF recall, Corsi block tapping test) attention and executive functions (i.e., Attentional Matrices, Raven Colored Progressive Matrices; digit span backward; verbal fluency with phonemic (P-F-L), and semantic cue (animals–fruits–car brands), and visuospatial abilities (i.e., ROCF copy).

In addition to the standard neuropsychological battery, a visuoperceptive evaluation with QSPT of MMSE was obtained. Specifically, an expert neuropsychologist evaluated the pentagons following the rules defined by Caffarra and colleagues (Caffarra et al. 2013). Five qualitative indexes were considered: numbers of angles (from 0 to 4 points), distance/intersection between the two figures (0–4), closing/opening of the contour (0–2), rotation of one or both pentagons (0–2), and closing-in (0–1). A score was assigned for each factor, where the highest score indicated the best performance (Caffarra et al. 2013). The lowest quartile of distribution for each item of QSPT was considered a cut-off score, as recommended.

5.7.2. Hypometabolism brain commonality

Brain hypometabolism commonalities were obtained in the whole iRBD group using a one-sample t-test entering the contrast images resulting from a first-order [18F]FDG-PET SPM based procedure. Contrast image represented SPM t-maps showing regions of hypometabolism with a strong level of significance corrected for age (statistical threshold set at $P = 0.05$, FWE-corrected, with $K \geq 100$ voxels).

5.7.3. Region of interest hallmark definition

The contrast images obtained with single-subject analysis were used to extract mean hypometabolism values from 116 ROIs obtained from the AAL atlas (http://www.gin.cnrs.fr/AAL) – covering all the brain – (Tzourio-Mazoyer et al. 2002). The extraction of mean hypometabolism values was performed using the REX toolbox for MATLAB (https://www.nitrc.org/projects/rex/). We computed the percentage of iRBD subjects presenting hypometabolism values (contrast values >0) and a minimum cluster extent of k:100 voxels for each ROI. Hypometabolic hallmarks were defined as those ROIs characterized by a regional hypometabolism with a minimum cluster extent of k:100 voxels in at least 50% of subjects with iRBD.

5.7.4. Comparison of [18F]FDG-PET patterns among iRBD, PD and DLB groups

We obtained [18F]FDG-PET hypometabolism patterns at the group level throughout comparing each clinical group and normal controls (statistical threshold set at P = 0.05, FWE-corrected, with K ≥ 100 voxels). We then statistically compared the regional brain hypometabolism among clinical groups using SPM two-sample t-test: iRBD vs. PD, iRBD vs. DLB and PD vs. DLB. We limited the comparison to the brain areas showing significant reductions in metabolism compared with HC (statistical threshold set at P uncorrected = 0.001 with K≥ 100 voxels). Age was entered as a variable of no interest in all SPM statistical models.

5.8. Methods - Study II: Impaired metabolic brain networks associated with neurotransmission systems in the α-synuclein spectrum. (Carli et al. 2020) – Published article –

The following data have been published (Carli et al. 2020).

5.8.1. Extent of connectivity alterations

To estimate the degree of metabolic connection changes in each network, we calculated the Gini Index (GI). GI is a metric commonly used in network research (Goswami, Murthy, and Das 2018), which provides a statistic about the sparsity/locality of changes in the connectivity of a particular network (Gini 1912). GI close to 0 indicates a homogeneous deviation from the normal distribution (that is, all ROIs are equally affected in the entire network), while a GI close to 1 indicates an unequal deviation from the normal distribution (that is, changes are restricted to a restricted number of ROIs). Distributions with GI between 0.5 and 0.7 are usually considered unequal. Therefore, a network with GI <0.5 is considered to indicate sparse connection reconfiguration, and a network with GI ≥ 0.5 is considered to indicate more local connection reconfiguration.

5.8.2. Identification of pathological hubs

As the first step, we estimated the total number of connections showing significant changes compared to HC for each ROI – based on statistically significant changes at z-test, $p < 0.01$. An ROI presenting a disproportionate number of altered connections compared to the remaining network's ROIs – i.e. two standard deviations above the total number of altered connections in the diagnostic group – was classified as a pathological hub.

5.8.3. Evaluation of similarity between clinical groups

We computed the weighted Dice Coefficient (wDC) to compare the networks' metabolic connectivity alterations amongst iRBD, PD and DLB (Mencarelli et al. 2020; Dice 1945). The wDC provides a similarity index that not only advantageously considers the spatial similarity – as the standard unweighted DICE coefficient – but also take into account the similarity of the connected signs (positive (higher connectivity than controls) and negative (lower connectivity than controls)). The wDC is a data-based similarity coefficient, which gives a similarity measure related to the specific data set under investigation. Therefore, this process allows quantifying the degree of similarity in connection changes between different clinical groups. Specifically, a wDC value below or close to 0 indicates that the similarity between the two groups is zero or very low.

5.9. Methods - Study III: Exploring the functional role and neural correlates of K-complexes in isolated rapid eye movement sleep behaviour disorder. (Galbiati et al. 2021) - Published Article -

The following data have been published (Galbiati et al. 2021).

5.9.1. Neuropsychological assessment

Each iRBD patient received an evaluation of global mental status (i.e., MMSE) and comprehensive neuropsychological examination, including language (i.e., Token test), verbal and visuo-spatial memory (i.e., digit span forward, immediate and delayed

recall of RAVLT, ROCF recall, Corsi block tapping test, attention and executive functions (i.e., Attentional Matrices, Raven Colored Progressive Matrices; digit span backward; verbal fluency with phonemic (P-F-L), and semantic cue (animals–fruits–car brands), and visuospatial abilities (i.e., ROCF copy).

5.9.2. Detection of K-complex density

An expert in sleep scoring (blind to the patient's clinical features) visually detected the presence of spontaneous KCs during N2 sleep on F3 and F4 referenced to the contralateral mastoids derivations. The identification of KCs followed four main criteria: a dynamic and multicomponent event with (i) a large and well-delineated negative sharp wave, immediately followed by a positive polarity component; (ii) maximum amplitude at frontocentral derivations; (iii) a minimum duration of 0.5 seconds and a maximum duration of 3 seconds (De Gennaro et al. 2017) and (iv) a minimum amplitude of 75 μV (De Gennaro, Ferrara, and Bertini 2000). When multiple KCs appeared in sequence, only the first one was counted (Bastien et al. 2009). To obtain the KCs density, we divided the number of KC by the minutes of N2 sleep. KC density was calculated for each sleep cycle: a non-REM sleep episode lasting at least 15 minutes followed by a REM sleep episode lasting at least 5 minutes. Then, the mean values of KC density (mean: 1.05) was used to identify iRBD patients with low (below the mean) and high (above the mean) KC density.

5.9.3. [18F]FDG–PET and KC density: regression analysis

The relationship between [18F]FDG-PET brain metabolism and KCd was evaluated using a voxel-wise linear regression model where KC density was entered as the independent variable and the whole brain metabolism as the dependent one. Age was used as a nuisance variable. The p-value was set at p uncorrected < .005 with cluster extent k≥100 voxels.

5.9.4. Evaluation of network topography and spatial extension

To compare large scale network connectivity between iRBD sub-groups (low and high KC density), we calculated Dice similarity coefficient. This index quantifies volume overlaps between two regions divided by their mean volume (Savio et al. 2017). The Dice coefficient can be calculated as follows

$$Dice\ coefficent = \frac{|A \cap B|}{(|A| \cup |B|)/2}$$

A and B represent the brain regions being compared (voxel counts measure the volumes). It is interpreted as follows <0.2 poor, 0.2-0.4 fair, 0.4-0.6 moderate, 0.6-0.8 good, and >0.8 excellent agreement (Savio et al. 2017). Then, to quantify differences in ADMN metabolic connectivity's spatial extension, the number of correlated voxels was obtained in each sub-group. It is possible to assume that the iRBD sub-group presenting a higher number of correlated voxels reflected a more preserved connectivity in ADMN (Ballarini et al. 2016).

5.9.5. Assessment of difference in connectivity strength

We used an SPM model to investigate voxel-wise the interaction between the group variables (i.e. low KC density vs. high KC density) and the mean ROI count from the seed (Ballarini et al. 2016; Sala et al. 2019), controlling for age. This analysis allows the identification of brain regions in which sub-groups show significantly different slopes (strength of the metabolic connection) in the relationship with the [18F]FDG uptake values extracted from the seed. The p-value images corrected by threshold-free cluster enhancement (TFCE) (Spisák et al. 2019) were thresholded at $p < 0.05$, with $K \geq 100$ voxels. Then, we assessed the correlation coefficients between these brain structures by mean of partial correlation analyses, controlling for age.

5.10. Methods - Study IV: Clinical and Dopamine Transporter Imaging Trajectories in a Cohort of Parkinson's Disease Patients with GBA Mutations. (Caminiti, Carli, et al. 2021). - Published Article -

The following data have been published (Caminiti, Carli, et al. 2021).

5.10.1. Clinical evaluation at baseline and follow-up

All patients underwent the PPMI standard test battery for motor and nonmotor features assessment (Malek et al. 2018; Lerche et al. 2017). In detail, the clinical assessment included the UPDRS, the MoCA, the RBDSQ, the Epworth Sleepiness Scale, and the SCOPA-AUT.

The motor symptom asymmetry index (AI) was obtained adopting the following formula: (right-left side UPDRS-III score)/(right + left UPDRS-III side score) (Kaasinen et al. 2015). Motor asymmetry was reported when 0.30 < AI < - 0.30 (Kaasinen et al. 2015).

The longitudinal clinical progression was also evaluated. We assessed the rate of change, considering two time-points in which all patients received L-dopa treatments – controlling for dopaminergic medications. As the first follow-up, we selected a visit after baseline (means±SD=1.74±1.23 years), defined "≈2-yrs" follow-up. As the second follow-up, we considered ìthe latest available clinical visit (means±SD=6.40±1.75 years), called "≈6-yrs" follow-up. Patients without all longitudinal data (at the two-time points) were excluded from longitudinal progression analysis, leaving 168 cases analyzed for progression (GBA=22; Early-iPD=19 and Late iPD=127).

We investigated the rate of change for clinical markers, calculating the number of points lost per year (score at follow-up – score at baseline/years of follow-up) (Caroli et al. 2015). Clinical data were acquired in OFF-medications.

5.10.2. Longitudinal dopaminergic progression

The ^{123}I-FP-CIT SPECT imaging' progression over time was assessed. We calculated the rates of change for regional DAT binding values across the groups from

baseline to "≈2-yrs" visit. We selected the "≈2-yrs" visit to include the largest number of subjects with ^{123}I-FP-CIT SPECT available, namely GBA-PD=16, Early-iPD=17, and Late-iPD=74. Similarly to clinical markers, the rate of change for imaging markers was obtained with the following formula: (score at follow-up – score at baseline/years of follow-up), representing the number of points lost per year. (Caroli et al. 2015) Imaging data were acquired in OFF-medications.

5.10.3. Statistical analyses

Chi-squared tests, MANCOVA, and ANOVA tests with Bonferroni correction for normally distributed variables and Kruskal Wallis with Bonferroni correction for non-parametric variables were applied to compare demographics, clinical, and imaging data among groups. In both individual and combined clinical groups, the relationship between ^{123}I-FP-CIT SPECT measures and clinical variables – measured as baseline and progression scores (i.e., rate of change of UPDRS total, UPDRS-III, MoCA, SCOPA-AUT scores from "≈2-yrs" to "≈6-yrs") – was investigated using partial correlation analysis, controlling for gender, disease duration, LEDD and ROIs structural volumes. We considered the following confounding variables for MANCOVA analysis comparing clinical measures among PD groups: i) gender and disease duration in baseline evaluation comparisons; ii) gender, disease duration, and LEDD in follow-up comparisons. Statistical analysis comparing the brain structural volumes among the different groups were adjusted for gender, UPDRS-III, and disease duration. Gender, disease duration, ROIs structural volumes, and UPDRS-III were used as nuisance variables in all the ^{123}I-FP-CIT imaging comparisons. The differences in the rate of change among groups were assessed using MANCOVA analysis. We also assessed the prediction of ^{123}I-FP-CIT binding at baseline for all the considered ROIs on the degree of clinical deterioration (i.e., rate of change of UPDRS total, UPDRS-III, MoCA, SCOPA-AUT scores from "≈2-yrs" to "≈6-yrs") through linear regression analyses. We considered ROIs structural volumes, disease duration, LEDD, and gender as nuisance variables. SPSS 26.0 software was employed for statistical analysis.

5.11. Methods - Study V: Distinct brain dysfunctions underlying visuo-constructive deficit in DLB and AD. (Beretta et al. 2021). - Published Article -

The following data have been published (Beretta et al. 2021).

5.11.1. Neuropsychological assessment

The DLB and AD patients underwent a full neuropsychological assessment. MMSE was employed for global cognition. Cognitive functions were assessed by a standard battery, namely: Semantic word Fluency (categories: animals, fruits and car brands) and Phonemic word Fluency (letters: F, P and L) for verbal fluency; Digit Span Forward for verbal short-term memory; Corsi Span Forward for visuospatial short-term memory; Short Story for verbal long-term memory; ROCF – delayed recall for long-term visuospatial memory; ROCF-c for visuoconstructive abilities; Attentive Matrices for selective attention and visual search; Raven's Coloured Progressive Matrices for logical reasoning. The presence/absence of DLB core clinical symptoms (McKeith et al. 2017) was obtained according to neurological and cognitive examinations and clinical interviews with patients and caregivers.

5.11.2. ROCF' brain [18F]FDG-PET correlates

To identify ROCF copy correlates, we performed a voxel-wise multiple regression analysis in the whole patient's cohort, including both DLB and typical-AD patients, using the ROCF-c scores as an independent variable. The statistical threshold was set at $p <$ 0.001 uncorrected, K≥ 100 voxels. Voxel-wise multiple regression analysis was not corrected for disease severity since the two groups not differed in disease duration and MMSE corrected scores. After identifying brain regions associated with the ROCF-c scores (in the whole group), we evaluated the correlations between regional hypometabolism and ROCF-c scores in each group separately. To do this, we used offline Pearson correlation analysis (threshold $p < 0.05$). A multiple regression equation with interaction terms was applied to evaluate whether the relationship between ROCF-c

scores and regional brain hypometabolism was modulated by the presence/absence of DLB core clinical features (moderator analysis with dichotomous moderators).

5.12. Methods - Study VI: Gender-related vulnerability of dopaminergic neural networks in Parkinson's disease. (Boccalini et al. 2020). - Published Article -

The following data have been published (Boccalini et al. 2020).

5.12.1. Connectivity measures and statistical analyses

This study applied partial correlation analysis to estimate the brain connectivity of two neurotransmitters networks: nigro-striato-cortico and mesolimbic dopaminergic networks (see *5.6.1. Neurotransmitters networks analyses*). The nigro-striato-cortical network consisted of the dorsal caudate and dorsal putamen, frontal premotor, motor, executive dorsolateral frontal regions, and somatosensory cortex. The mesolimbic network included the ventral striatum, ventral and medial frontal areas, anterior and middle cingulate cortices, as well as the amygdala and the parahippocampal cortex (see *5.6.1.1. Neurotransmission networks reconstruction: ROIs selection*).

We calculated the percentage of metabolic connections changed in both networks (i.e., connections linking two nodes in the same matrix derived from the comparison between patients and HC) to measure the degree of metabolic connectivity alterations in PD males and females. We computed the total number of connections and the number of altered connections within each network to calculate the percentage of altered metabolic connections. Then, we compared the percentage of altered metabolic connections between males and females for each network using the chi-squared test.

5.13. Methods - Study VII: Gender differences in dopaminergic dysfunction and molecular connectivity in Parkinson's disease clinical subtypes.

5.13.1. Clinical assessment

Clinical motor assessments of iPD sample included (MDS- UPDRS) and Hoehn and Yahr scales. Clinical non-motor assessments included Epworth Sleepiness Scale and the RBDSQ to assess sleep behaviour, SCOPA-AUT to assess autonomic function, and the 40- item University of Pennsylvania Smell Identification Test (UPSIT) to assess olfactory function.

Global cognition was assessed with the MoCA. Cognitive testing included the HLVT-Revised (-R) to assess memory; JOLO 15-item version to assess visuospatial function; SDMT to assess processing speed-attention; Letter-Number Sequencing (LNS) and semantic fluency to assess executive abilities-working memory. Neurobehavioral testing included the Geriatric Depression Scale (GDS), STAI, and Questionnaire for Impulsive-Compulsive Disorders (QUIP).

5.13.2. [123I]FP-CIT-SPECT analyses

For the pre-processing of [123I]FP-CIT-SPECT images, we follow the above-described pipeline based on the MRI segmentation approach (see *5.5. [123I]FP-CIT-SPECT pre-processing and imaging analysis*). In this study, we analysed both subject-specific ROIs for subcortical and profound brain structures (namely the whole caudate nucleus, whole putamen, dorsal caudate nucleus, dorsal putamen, ventral striatum, globus pallidus, thalamus, amygdala, and hippocampus) (see *5.5. [123I]FP-CIT-SPECT pre-processing and imaging analysis*) and standard cortical ROIs with high dopaminergic innervation. Specifically, according to a well-validated ROIs definition strategy (Sala et al. 2017; Caminiti et al. 2017; Tziortzi et al. 2013), we considered cortical ROIs with high dopaminergic innervations belonging to the nigrostriatal (frontal premotor, motor, executive dorsolateral frontal regions, and somatosensory cortex) and the mesolimbic (anterior and middle cingulate cortices, the olfactory cortex, the insula, the ventral and

medial frontal areas, as well as the amygdala, hippocampus, and parahippocampal cortex) dopaminergic pathways. Figure 57 contains all the considered ROIs.

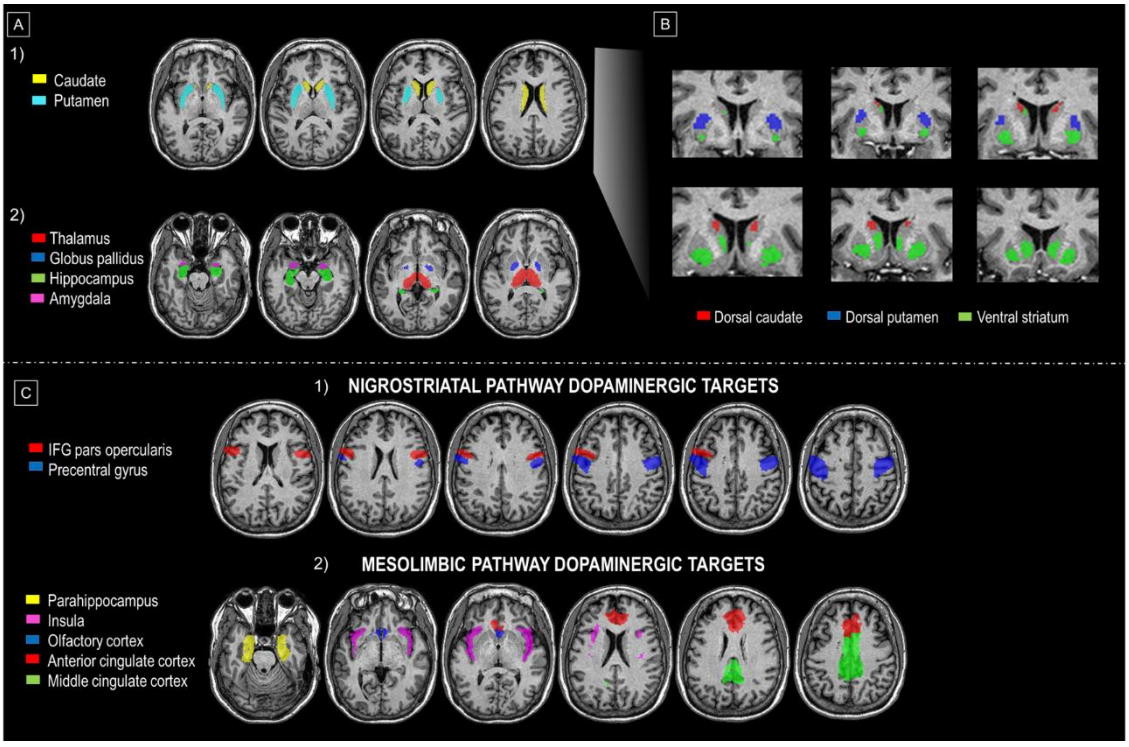

Figure 57. Subcortical, profound, and cortical ROIs.

The figure shows examples of anatomical ROIs over-imposed on the native MRI-T1 image of an iPD patient. ***A)*** *ROIs in axial view: whole caudate nucleus and putamen (yellow and light blue) in panel A.1, globus pallidus (blue), thalamus (red), hippocampus (green), and amygdala (violet) in panel A.2.* ***B)*** *The functional subdivision of the striatum in coronal view: ventral striatum (green), dorsal putamen (blue), dorsal caudate (red).* ***C)*** *ROIs in axial view belong to the nigrostriatal (1) and mesolimbic pathways (2). The nigrostriatal cortical targets are the inferior frontal gyri pars opercularis (red) and the precentral gyri (blue); the mesolimbic targets are the parahippocampus (yellow), the insula (violet), the olfactory cortices (blue), the anterior cingulate (red), and the middle cingulate (green).*

All cortical ROIs used for the connectivity analyses were derived from AAL (Tzourio-Mazoyer et al. 2002). Only the cortical dopaminergic targets that showed more tracer binding than the reference region (occipital cortex) in HC were selected for further analysis to ensure the binding specificity. Thus, we overcame the low specificity of DAT signal in the cortical regions by selecting the highly innervated ones based on biochemical, histochemical, and anatomopathological findings (Ciliax et al. 1999) and by considering only cortical targets that showed significant tracer binding in healthy

conditions. Moreover, we controlled the partial volume effects, including the individual mean grey-matter volumes for each ROI as a covariate in further analyses. We extracted the average grey-matter volumes throughout the volbrain (for volumes of the subcortical and profound subject-specific ROIs) (Manjón and Coupé 2016) and REX toolbox for MATLAB for cortical ROIs.

5.13.3. Statistical analysis

MANCOVA and ANOVA tests with Bonferroni correction were used to compare demographics, clinical, and SUVr imaging data between PD females and males. Age and education were entered as a covariate in the MANCOVA test for the comparison of clinical variables. Age, disease duration, UPDRS-III, and individual mean grey-matter volumes were used as nuisance variables in SUVr DAT imaging comparisons between sex. All analyses were run in the whole iPD group and three iPD subtypes. SPSS 26.0 software was used to perform statistical analysis. Mann–Whitney U test was used to test gender differences in the degree of DAT and motor asymmetry, as measured by the side-to-side differences (Kaasinen 2016).

Correlation analyses between DAT SUVr and clinical motor and behavioural scales showing significant gender differences were performed separately in females and males in the whole group, in the mild motor and intermediate subtypes. Age, disease duration, and ROIs' mean grey-matter volumes were used as covariates of no interest. We did not perform correlation analyses in the diffuse malignant subtype because of the small sample size. All analyses were run in the whole iPD group and three subtypes. We used SPSS 26.0 software to perform statistical analysis.

5.13.4. Molecular connectivity analyses

Assessment of molecular connectivity between targets of each dopaminergic pathway (nigrostriatal and mesolimbic) was performed via partial correlation analysis (see *5.6.1. Neurotransmitters networks analyses*). The ROIs considered for analyses included only cortical targets that showed significant tracer binding in healthy conditions (see *5.14.2. [123I]FP-CIT-SPECT analyses*). Thus, we considered a pool of N=16 ROIs belonging to

the mesolimbic dopaminergic pathway (L/R ventral striatum, L/R hippocampus, L/R amygdala, L/R parahippocampus L/R insula, L/R olfactory cortex, L/R anterior cingulate cortex (ACC), and L\R middle cingulate cortex (MCC)) and N=8 ROIs belonging the nigrostriatal dopaminergic pathway (L/R dorsal caudate nucleus, L/R dorsal putamen, L/R inferior frontal gyrus pars opercularis, and L/R precentral gyrus). Partial correlation analyses were performed in the whole group and subtypes of iPD (i.e., mild motor and intermediate). We did not perform connectivity analysis in diffuse malignant subtype because of the limited sample size. The samples sizes of the target population and the reference group of HC should be similar to ensure a robust statistical comparison of connectivity metrics. Thus, gender-matched subgroups of iPD were randomly selected for comparison, with the same number of the HC group (F/M=34/39). In male and female patients, we calculated the percentage of altered molecular connections in each network (i.e., connections linking two nodes in the same matrix derived from comparing patients and HC) to quantify the severity of molecular connectivity alterations. Then, we compared the percentage of altered metabolic connections between male and female patients for each network through the chi-squared test.

5.14. Methods - Study VIII: Specific occupational profiles as proxies of cognitive reserve induce neuroprotection in dementia with Lewy bodies. (Carli et al. 2020) – Published Article –

The following data have been published (Carli et al. 2020).

5.14.1. Participants

Among patients with a diagnosis of probable DLB (see *5.1. Participants underwent [18F]FDG-PET exam*), we selected those subjects with available detailed information about the occupation (N=33).

5.14.2. Proxies of cognitive reserve

Educational levels- According to previous literature, education was defined as the number of formal education' years (Vemuri et al. 2012) (range from 3 to 22 years of education).

Occupation levels- The occupation levels were classified using a categorical 6-point scale (Vemuri et al. 2012): 1) people without occupation, 2) private household occupations, service occupations, transportation, and material moving, 3) sales occupations, administrative support, protective services, farming, and machine operators, 4) technicians and precision production workers, 5) included executive, administrative, and managerial services, 6) included professional speciality occupations.

Reserve Index- We analysed the combined effect of education and 6-levels occupation by creating an indicator variable (RI) as the sum of the occupation score and the six-rank transformation of years of education, thus giving equal weight to educational and occupational contribution.

*Occupational Information Network (O*net)*- O*Net database (i.e., United States Department of Labor Standard Occupational Classification Network, United States Department of Labor, 1998) (https://www.onetonline.org/) contains hundreds of standardized and occupation-specific descriptors (almost 1.000 occupations). O*net is helpful to describe workers' characteristics by defining the main attributes related to jobs. We decided to consider the classification published in 1998 as the one better representing the job features of the included patients in their period of job-life-activity. According to O*net, occupational information can be applied across jobs (cross-job descriptors) and within occupations (job-specific descriptors). We focused on worker-oriented variables, including worker characteristics (e.g., cognitive and sensory abilities) and requirements (e.g., complex problem-solving skills), representing each occupation's cognitive and executive skills. Specifically, worker characteristics refer to features that may influence performance, acquiring knowledge' abilities and skills required for effective work performance. Worker requirements' descriptors refer to work-related attributes acquired and/or developed through experience.

We selected those O*net variables representing the early impaired cognitive skills in DLB (McKeith et al. 2017) (see *Appendix A 12* for all selected O*Net variables).

5.14.3. Principal component analysis (PCA)

The a priori selected O*net variables entered a PCA to collapse the O*Net descriptors into composite PCA scores. Four components captured 80% of the variance, and they were interpreted as the best dimensional representation of the entire dataset. Namely, the resulting components were 1) problem solving, 2) visual abilities, 3) social skills, and 4) visual-constructive abilities (see Appendix A 12 for O*Net descriptors included in each component). Component names were derived according to the nature of the grouped O*Net variables in the different factors.

5.14.4. Traditional univariate approach: linear regression analysis

We performed a set of multiple linear regression analyses with years of education, 6-levels occupation, RI or O*Net occupational profiles as independent variables, and hypometabolism as the dependent variable, controlling for gender and MMSE corrected scores. The p-value images corrected by TFCE (Spisák et al. 2019) were thresholded at $p < 0.05$.

5.14.5. Metabolic connectivity in large scale networks

To assess BR throughout metabolic connectivity, we considered the mean value of each CR proxy (education, occupation, RI and PCA factors) to split the DLB cohort into sub-groups characterized by high or low specific education and occupational skills. Software IBM SPSS statistics 21 was used to run the PCA analysis. We applied IRCA to explore metabolic connectivity in the DLB sub-groups (see *5.6.2. Metabolic connectivity in large scale brain networks: interregional correlation analysis (IRCA)*).

Jaccard similarity coefficient (JSC) is a well-established metric previously adopted for large-scale networks comparison ((Jovicich et al. 2016; Karahanoğlu and Van De Ville 2015; Sala et al. 2019). The JSC was calculated for each comparison. Jaccard's index measures similarity between large-scale networks by computing the normalized amount of their overlap. The JSC is considered as a measure of the percentage of spatial

overlap between sets. JSC ranges from 0, indicating no spatial overlap in the large-scale network across the two groups, to 1, indicating complete overlap.

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7. Appendix

The following data have been published (Carli et al. 2020; Boccalini et al. 2020; Carli et al. 2020; Caminiti, Carli, et al. 2021).

Table A 1. The ROIs composing the nigro-striato-cortical dopaminergic network.

Nigro-striato-cortical dopaminergic projections	**Origins**
Dorsal Putamen Left	FSL
Dorsal Putamen Right	FSL
Dorsal Caudate Left	FSL
Dorsal Caudate Right	FSL
Glopus pallidus Left	FSL
Globus pallidus Right	FSL
Motor section of thalamus Left	FSL
Motor section of thalamus Right	FSL
Inferior Frontal Gyrus p. Opercularis Left	AAL
Inferior Frontal Gyrus p. Opercularis Right	AAL
Middle Frontal Gyrus Left	AAL
Middle Frontal Gyrus Right	AAL
Superior Frontal Gyrus Left	AAL
Superior Frontal Gyrus Right	AAL
Precentral Gyrus Left	AAL
Precentral Gyrus Right	AAL
Postcentral Gyrus Left	AAL
Postcentral Gyrus Right	AAL

Table A 2. The ROIs composing the mesolimbic dopaminergic network.

Mesolimbic dopaminergic projections	**Origins**
Gyrus rectus right	AAL
Gyrus rectus left	AAL
Olfactory cortex left	AAL
Olfactory cortex right	AAL
Cingulate gyrus left	AAL
Cingulate gyrus right	AAL
Parahippocampal gyrus left	AAL
Parahippocampal gyrus right	AAL
Amygdala left	Anatomy
Amygdala right	Anatomy
Frontal cortex p. orbitalis left	AAL

Frontal cortex p. orbitalis right	AAL
Ventral Striatum left	FSL
Ventral Striatum right	FSL

Table A 3. The ROIs composing the noradrenergic network.

Noradrenergic cortical projections	**Origin**
Cerebellum Hemisphere Left	Anatomy
Cerebellum Hemisphere Right	Anatomy
Cerebellum Vermis Left	Anatomy
Cerebellum Vermis Right	Anatomy
Cerebellum Cruss Left	Anatomy
Cerebellum Cruss Right	Anatomy
Hypothalamus_Left	Sphere
Hypothalamus_Right	Sphere
Amygdala Left	Anatomy
Amygdala Right	Anatomy
Hippocampus Left	Anatomy
Hippocampus Right	Anatomy
Thalamus R	AAL
Thalamus L	AAL
Paracentral lobule Left	AAL
Paracentral lobule Right	AAL
Precuneus Left	AAL
Precuneus Right	AAL
Postcentral gyrus Left	AAL
Postcentral gyrus Right	AAL
Precentral gyrus Left	AAL
Precentral gyrus Right	AAL
Middle Frontal Gyrus Left	AAL
Middle Frontal Gyrus Right	AAL
Superior Frontal Gyrus Left	AAL
Superior Frontal Gyrus Right	AAL

Table A 4 The ROIs composing cholinergic networks: Ch1-Ch2, Ch3, Ch5-Ch6 network divisions.

Ch1-Ch2 divisions network	**Origins**	**Ch3 divisions network**	**Origins**
Hippocampus L	Anatomy	Olfactory Cortex L	AAL
Hippocampus R	Anatomy	Olfactory Cortex R	AAL
Hypothalamus L	Sphere	ParaHippocampal Gryus L	AAL
Hypothalamus R	Sphere	ParaHippocampal Gyrus R	AAL
Ch5-Ch6 divisions network	**Origins**	**Ch5-Ch6 division network**	**Origins**
Dorsal Putamen L	FSL	Globus Pallidus L	FSL
Dorsal Putamen R	FSL	Globus Pallidus R	FSL
Dorsal Caudate L	FSL	Thalamus L	AAL
Dorsal Caudate R	FSL	Thalamus R	AAL
Ventral Striatum L	FSL		
Ventral Striatum R	FSL		

Table A 5 The ROIs composing the cholinergic networks: Ch4 medial and lateral perisylvian divisions.

Ch4 medial division network	**Origins**	**Ch4 medial division network**	**Origins**
Inferior Frontal Gyrus p. Orbitalis L	AAL	Gyrus Rectus L	AAL
Inferior Frontal Gyrus p. Orbitalis R	AAL	Gyrus Rectus R	AAL
Middle Frontal Gyrus p. Orbitalis L	AAL	Anterior Cingulate Gyrus L	AAL
Middle Frontal Gyrus p. Orbitalis R	AAL	Anterior Cingulate Gyrus R	AAL
Superior Frontal Gyrus p. Orbitalis L	AAL	Median Cingulate Gyrus L	AAL
Superior Frontal Gyrus p. Orbitalis R	AAL	Median Cingulate Gyrus R	AAL

Superior Frontal Gyrus Medial p. Orbitalis L	AAL	Posterior Cingulate Gyrus L	AAL
Superior Frontal Gyrus Medial p. Orbitalis R	AAL	Posterior Cingulate Gyrus R	AAL
Ch4 Lateral perisylvian division network	Origins	Ch4 Lateral perisylvian division network	Origins
Heschl Gyrus L	AAL	Frontoparietal Operculum L	AAL
Heschl Gyrus R	AAL	Frontoparietal Operculum R	AAL
Superior Temporal Pole L	AAL	Olfactory Cortex L	AAL
Superior Temporal Pole R	AAL	Olfactory Cortex R	AAL
Insula R	AAL		
Insula L	AAL		

Table A 6. Distribution of altered connection in each neurotransmission network (measured with GI).

	NA	**DA**	**Ch5-Ch6**	**Ch4-M**	**Ch4-P**	**Ch3**	**Ch1-Ch2**
iRBD (GI)	0.29	0.54	0.67	0.84	0.83	n.a	n.a
PD (GI)	0.22	0.38	n.a	0.63	0.75	n.a	n.a
DLB (GI)	0.12	0.54	0.42	0.37	0.57	0.17	n.a

NA: Noradrenergic network; DA: Nigro-striato-cortical dopaminergic network; Ch5-Ch6: Cholinergic networks Ch5-Ch6 divisions; Ch4-M: Cholinergic networks Ch4 medial division; Ch4-P: Cholinergic networks Ch4 lateral perysilvian division; Ch3: Cholinergic networks Ch3 division; Ch1-Ch2: Cholinergic networks Ch1-Ch2 division; iRBD: isolated REM sleep behaviour disorder; PD: Parkinson's disease; DLB: Dementia with Lewy Bodies; GI: Gini Index; n.a.: not applicable

Table A 7. wDC values for each neurostrasmitters network.

wDC for each network	**iRBD vs. PD**	**iRBD vs. DLB**	**PD vs. DLB**
Noradrenergic Network	1.18	2.14	3.09
Nigro-striato-cortical dopaminergic Network	0	0.66	0.80
Cholinergic Ch5-Ch6 divisions network	0	1.85	0
Cholinergic Ch4-M division network	0	0	0.77
Cholinergic Ch4-P division network	0	0	2.91

iRBD: isolated REM sleep behaviour disorder; PD: Parkinson's disease; DLB: Dementia with Lewy Bodies; vs.: Versus, NA: Noradrenergic; DA: Dopaminergic; CH: Cholinergic; M: medial; P: lateral Perysilvian; wDC: weighted DICE index.

Table A 8. Demographic and clinical features at baseline in GBA-PD and iPD groups.

Baseline	GBA-PD (N=46) Mean±SD	Early-iPD (N=58) Mean±SD	Late-iPD (N=281) Mean±SD	Statistic	GBA-PD vs. Early-iPD	GBA-PD vs. Late-iPD	Early-iPD vs. Late-iPD
Gender(M/F)	26/20	33/25	193/88	p=0.091	--		
Age onset(years)	57.4±10	44.5±5.5	63.6±7.0	**p=0.000**	**p=0.000**	**p=0.001**	**p=0.000**
Age baseline(years)	58.9±9.6	47±4.8	64.8±7.1	**p=0.000**	**p=0.001**	**p=0.000**	**p=0.000**
Age(years; MIN-MAX)	29-81	33-54	51-84	--	--	--	--
Education(years)	15.9±2.9	15.7±2.8	15.4±3.1	p=0.333	--	--	--
Disease Duration(years)	1.5±1.4	2.5±3.2	1.3±1.6	**p=0.003**	p=0.441	p=0.693	**p=0.003**
Hoehn and Yahr scale b	1.9±0.3	1.6±0.5	1.8±0.6	**p=0.001**	**p=0.002**	p=0.673	**p=0.003**
UPDRS part III b	28.9±10.2	21.7±10.8	26.7±12.2	**p=0.002**	**p=0.003**	p=0.654	**p=0.006**
UPDRS Total score b	41.5±12.6	33.7±16	38.0±15.6	**p=0.012**	**p=0.013**	p=0.516	p=0.057
MoCA Total score b	26.9±2.5	28.1±2.3	27.0±2.3	**p=0.003**	**p=0.016**	p=1.000	**p=0.004**
SCOPA-AUT Total score b	15.7±12.4	11.4±7.8	14.1±9.4	**p=0.004**	**p=0.017**	p=1.000	**p=0.006**
RBDSQ score b	4.4±3.0	3±2.3	3.1±2.6	**p=0.004**	**p=0.027**	**p=0.003**	p=1.000

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus; n: Number; SD: Standard Deviation; UPDRS: Unified Parkinson's Disease Rating Scale; RBDSQ: Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT: Scale for Outcomes for Parkinson's Disease—autonomic function. * Corrected for Bonferroni; b Controlled for disease duration and gender.

Table A 9. Demographic and clinical features at Follow-up 1 in GBA-PD and iPD groups.

Follow-up-1 (Mean of 1.75 years)	GBA-PD (N=22) Mean±SD	Early-iPD (N=19) Mean±SD	Late-iPD (N=135) Mean±SD	Statistic	GBA-PD vs. Early-iPD	GBA-PD vs. Late-iPD	Early-iPD vs. Late-iPD
Age at Follow-up (years)	58.1 ±7.5	47.2 ±5.1	65.8 ±7.5	**p=0.000**	**p=0.000**	**p=0.000**	**p=0.000**
Age (years, MIN-MAX)	39-78	34-55	52-85	--	--	--	--
FU duration (years)	2.0±1.3	2.1±1.9	1.7 ±1.1	p=0.226	--	--	--
Disease duration (years)	3.5±2.7	3.6±3.6	2.8±2.2	p=0.222	--	--	--
LEDD	461±301.1	403.2±275.9	400.8±364.1	p=0.753	--	--	--
Hoehn and Yahr scale b	1.8±0.4	1.8±0.4	1.9±0.5	p=0.632	p=1.000	p=1.000	p=1.000
UPDRS part III b	27.2±8.9	25.0±9.3	28.0±11.2	p=0.595	p=1.000	p=1.000	p=0.947
UPDRS Total score b	43±16.2	40.4±16.7	43.7±16.2	p=0.774	p=1.000	p=1.000	p=1.000
MoCA Total score b	26.3±3.7	27.3±3.4	25.7±3.3	p=0.203	p=0.990	p=1.000	p=0.236
SCOPA-AUT Total score b	14.9±8.9	8.2±5.1	12.2±6.4	**p=0.006**	**p=0.004**	p=0.243	**p=0.044**

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus; n: Number; SD: Standard Deviation; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; RBDSQ: Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT: Scale for Outcomes for Parkinson's Disease—autonomic function; * Corrected for Bonferroni; b Controlled for LEDD.

Table A 10. Demographic and clinical features at Follow-up 1 in GBA-PD and iPD groups.

Follow-up-2 (Mean of 6 years)	**GBA-PD (N=45) Mean±SD**	**Early-iPD (N=56) Mean±SD**	**Late-iPD (N=269) Mean±SD**	**Statistic**	**GBA-PD vs. Early-iPD**	**GBA-PD vs. Late-iPD**	**Early-iPD vs. Late-iPD**
Age at Follow-up (years)	58.9±9.6	47.0±4.8	64.8±7.1	p=0.000	**p=0.001**	**p=0.000**	**p=0.000**
Age at Follow-up(years)	38-88	39-62	55-91	--	--	--	--
Age(years, MIN-MAX)	6.0±2.0	6.3±1.7	6.1±2.0	p=0.897	--	--	--
FU duration(years)	7.6±2.7	8.7±3.2	7.4±2.5	**p=0.015**	p=0.180	p=1.000	**p=0.012**
Disease duration(years)	214.6±311.2	323.5±413.8	408.7±1248	p=0.325	--	--	--
LEDD	2.0±0.7	1.9±0.5	1.9±0.6	p=0.516	p=1.000	p=0.797	p=1.000
Hoehn and Yahr scale b	30.4±14.5	21.9±9.4	26.3±12.0	**p=0.044**	**p=0.043**	p=0.180	p=0.540
UPDRS part III b	46.6±17.7	36.0±13.5	41.3±17.2	p=0.078	p=0.083	p=0.258	p=0.705
UPDRS Total score b	24.6±6	28.3±2.5	25.1±4.5	**p=0.011**	**p=0.018**	p=1.000	**p=0.017**
MoCA Total score b	20.9±11.2	16.0±10.6	21.1±11.7	**p=0.033**	p=0.193	p=1.000	**p=0.027**

GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus; n: Number; SD: Standard Deviation; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; RBDSQ: Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT: Scale for Outcomes for Parkinson's Disease—autonomic function. * Corrected for Bonferroni; b Controlled for LEDD, disease duration and gender.

Table A 11. [123I]FP-CIT-SPECT imaging at follow-up 1 in GBA-PD and iPD groups.

[123I]FP-CIT-SPECT at Follow-up (Mean of 1.75 years)	**GBA-PD (N=16) Mean±SD**	**Early-iPD (N=17) Mean±SD**	**Late-iPD (N=74) Mean±SD**	**GBA-PD vs Early-iPD**	**GBA-PD vs Late-iPD**	**Early-iPD vs Late-iPD**
Whole Ipsilateral Caudate Nucleus	0.93±0.39	0.97±0.45	0.86±0.33	0.934	0.363	1.000
Whole Contralateral Caudate Nucleus	0.85±0.29	0.92±0.44	0.77±0.32	1.000	0.653	1.000
Whole Ipsilateral Putamen	0.88±0.37	1.24±0.49	0.91±0.38	1.000	1.000	0.379
Whole Contralateral Putamen	0.68±0.33	0.91±0.40	0.67±0.30	1.000	1.000	1.000
Ipsilateral Anterior Putamen	0.96±0.48	1.40±0.60	1.00±0.49	1.000	1.000	0.520
Contralateral Anterior Putamen	0.76±0.41	1.05±0.51	0.74±0.38	1.000	1.000	0.489
Ipsilateral Posterior Putamen	0.72±0.23	0.96±0.34	0.75±0.28	1.000	1.000	0.415
Contralateral Posterior Putamen	0.55±0.23	0.65±0.24	0.54±1.99	1.000	1.000	0.489
Ipsilateral Caudate Nucleus Motor	0.78±0.57	1.11±0.64	0.96±0.54	1.000	1.000	0.489
Contralateral Caudate Nucleus Motor	0.92±0.44	0.93±0.48	0.80±0.43	1.000	1.000	1.000
Ipsilateral Putamen Motor	0.99±0.29	1.30±0.52	1.02±0.43	1.000	1.000	1.000
Contralateral Putamen Motor	0.73±0.31	0.83±0.36	0.72±0.28	1.000	1.000	1.000
Ipsilateral Ventral Striatum	0.86±0.48	1.17±0.54	0.88±0.42	1.000	1.000	0.689
Contralateral Ventral Striatum	0.73±0.38	1.05±0.52	0.76±0.40	1.000	1.000	1.000

Ipsilateral Globus Pallidus	1.05±0.52	1.55±0.57	1.12 ±0.52	0.216	1.000	0.085
Contralateral Globus Pallidus	0.80±0.39	1.19±0.42	0.91±0.45	0.611	1.000	1.000
Ipsilateral Thalamus	0.43±0.17	0.48±0.22	0.43±0.20	0.735	1.000	0.479
Contralateral Thalamus	0.41±0.15	0.42±0.25	0.41±0.19	1.000	1.000	0.764
Ipsilateral Hippocampus	0.24±0.15	0.32±0.21	0.24±0.15	1.000	1.000	1.000
Contralateral Hippocampus	0.22±0.15	0.28 ±0.21	0.21±0.13	0.916	1.000	1.000
Ipsilateral Amygdala	0.32±0.28	0.42±0.27	0.27±0.22	1.000	1.000	0.707
Contralateral Amygdala	0.30±0.26	0.38±0.33	0.24±0.21	1.000	1.000	1.000
GBA: glucosylceramidase beta; PD: Parkinson's disease; i: idiopathic; vs: Versus. * Corrected for Bonferroni, controlling gender, disease duration, and ROIs volumes (cm^3).						

Table A 12. PCA factors derived from O*Net variables

	PCA COMPONENTS			
	Problem-solving	**Visual abilities**	**Social skills**	**Visual-constructive abilities**
Fluency of ideas	,878	,238	,171	,162
Originality	,842	,188	,135	,142
Sensitivity	,731	,339	,249	,374
Deductive reasoning	,810	,243	,148	,452
Inductive reasoning	,826	,323	,141	,385
Flexibility of closure	,701	,515	,045	,257
Critical thinking	,959	,151	,015	,126
Active learning	,952	,173	,030	,050
learning strategies	,767	,165	,397	-,063
Monitoring	,906	,150	,201	,175
Coordination	,729	,172	,417	,329
Persuasion	,847	,102	,404	,176
Negotiation	,812	,140	,224	,225
Instructing	,759	,183	,512	,039
Problem identification	,931	,070	,038	,186
Information gathering	,866	-,080	,148	,345
Information organization	,722	-,210	,425	,451
Synthesis	,886	-,131	,152	,370
Idea generation	,946	,272	,088	,053
Idea evaluation	,965	,182	-,024	,058
Implementation planning	,907	,098	,238	,273
Solution appraisal	,940	,016	,048	,207
Far vision	,500	,717	,416	-,025
Visual colour discrimination	,143	,638	-,463	,011
Night vision	,259	,835	,324	-,111
Peripheral vision	,058	,858	,438	-,130

Depth perception	,125	,896	-,107	-,183
Glare sensitivity	,041	,779	,040	,136
Selective attention	,268	,217	,586	,394
Time sharing	,361	,445	,629	,410
Social perceptiveness	,480	,008	,822	,027
Service orientation	-,057	,030	,902	,121
Memorization	,365	,264	,688	,468
Information ordering	,477	-,039	-,034	,778
Category flexibility	,547	,246	,249	,591
Near vision	,156	-,137	,087	,777
Speed of closure	,605	,143	,335	,633
Perceptual speed	,075	-,156	,182	,864