Department of Neurology
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“A GREAT PERTURBATION IN NATURE”
- PARKINSON’S DISEASE AND SLEEP DISORDERS –

Ari Ylikoski

Academic Dissertation
To be publicly discussed with the permission of the Medical Faculty of the University of Helsinki
in the auditorium XIV, University of Helsinki Fabianinkatu 33,
on the 14nd of October, 2016, at 12:00 noon

Helsinki 2016
“Yet who would have thought the old man to have had so much blood in him?”

CONTENTS

LIST OF ORIGINAL PUBLICATIONS ........................................................................................................5

ABBREVIATIONS ................................................................................................................................6

ABSTRACT/LYHENNELMÄ .....................................................................................................................8

1. INTRODUCTION ..................................................................................................................................9

2. REVIEW OF THE LITERATURE ......................................................................................................10

3. HYPOTHESES AND AIMS OF THE STUDY ....................................................................................36

4. SUBJECTS AND METHODS ...........................................................................................................37

5. RESULTS ..........................................................................................................................................40

6. DISCUSSION ....................................................................................................................................44

7. CONCLUSIONS ...............................................................................................................................50

8. ACKNOWLEDGMENTS ....................................................................................................................51

9. REFERENCES ...................................................................................................................................52

ORIGINAL PUBLICATIONS ..................................................................................................................68
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals:


VI Ylikoski A, Martikainen K, Sieminski M, Partinen M. Sleep disordered breathing in Parkinson’s disease. (manuscript)
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
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<tr>
<td>AMPK</td>
<td>AMP-activated protein kinase</td>
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<td>ANS</td>
<td>autonomic nervous system</td>
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<td>αsyn</td>
<td>alpha-synuclein</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>BFB</td>
<td>basal forebrain</td>
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<td>BGA</td>
<td>brain-gut axis</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BQ</td>
<td>Berlin Questionnaire</td>
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<tr>
<td>CAM</td>
<td>complementary and alternative medicine</td>
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<tr>
<td>CH-RLSq</td>
<td>Cambridge-Hopkins diagnostic questionnaire</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>DPGi</td>
<td>dorsal GABAergic paragigantocellular reticular nucleus</td>
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<td>DR</td>
<td>dorsal raphe</td>
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<td>EDS</td>
<td>excessive daytime sleepiness</td>
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<td>EL</td>
<td>encephalitis lethargica</td>
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<td>ENS</td>
<td>enteric nervous system</td>
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<td>ESS</td>
<td>Epworth sleepiness scale</td>
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<tr>
<td>eVLPO</td>
<td>extended ventrolateral preoptic area</td>
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<tr>
<td>GCN</td>
<td>gene co-expression network</td>
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<td>GFAP</td>
<td>Glial fibrillary acidic protein</td>
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<td>GWAS</td>
<td>genome-wide association studies</td>
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<td>HDAC</td>
<td>histone deacetylase</td>
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<td>HRQL</td>
<td>health-related quality of life</td>
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<td>H&amp;Y</td>
<td>Hoehn and Yahr</td>
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<td>HTDI</td>
<td>Hening Telephone Diagnostic Interview</td>
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<tr>
<td>ICDS</td>
<td>International Classification of Sleep Disorders</td>
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<tr>
<td>iRLS</td>
<td>idiopathic RLS</td>
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<td>IRLSSG</td>
<td>International RLS Study Group</td>
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<td>ISCS</td>
<td>Inappropriate sleep composite score</td>
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<td>ISF</td>
<td>interstitial fluid</td>
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<td>LB</td>
<td>Lewy bodies</td>
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<td>LC</td>
<td>locus coeruleus</td>
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<td>LDT</td>
<td>laterodorsal tegmentum</td>
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<td>LMR</td>
<td>leg motor restlessness</td>
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<td>LPS</td>
<td>lipopolysaccharides</td>
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<td>MFI</td>
<td>Multidimensional Fatigue Inventory</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>MPP⁺</td>
<td>neurotoxin metabolite of MPTP</td>
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<tr>
<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
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<tr>
<td>MSLT</td>
<td>multiple sleep latency test</td>
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<tr>
<td>mTOR</td>
<td>serine/threonine protein kinase</td>
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<tr>
<td>MWT</td>
<td>Maintenance of Wakefulness Testing</td>
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<tr>
<td>NM</td>
<td>neuromelanin</td>
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<tr>
<td>NMS</td>
<td>non-motor symptom</td>
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<td>NMSS</td>
<td>Non-Motor Symptoms Scale</td>
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<tr>
<td>NMSQuest</td>
<td>Non-Motor Symptoms Questionnaire</td>
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<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
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<tr>
<td>NPAS2</td>
<td>neuronal Per-Arnt-Sim-type signal-sensor protein (PAS) domain protein 2</td>
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<tr>
<td>OSA</td>
<td>obstructive sleep apnea</td>
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<tr>
<td>PAG</td>
<td>ventral periaqueductal grey matter</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PDSS</td>
<td>Parkinson’s disease sleep scale</td>
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<td>PDQ-39</td>
<td>Parkinson’s disease questionnaire -39</td>
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<tr>
<td>PEP</td>
<td>postencephalitic Parkinsonism</td>
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<td>PFS</td>
<td>Parkinson Fatigue Scale</td>
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<tr>
<td>PINK1</td>
<td>PTEN-induced putative kinase 1</td>
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<td>PLM</td>
<td>periodic limb movements</td>
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<td>PPT</td>
<td>pedunculo-pontine tegmentum</td>
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<td>PSG</td>
<td>polysomnography</td>
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<tr>
<td>PSQI</td>
<td>Pittsburgh sleep quality index</td>
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<tr>
<td>RBD</td>
<td>rapid eye movement sleep behavior disorder</td>
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<td>RBD-I</td>
<td>Innsbruck RBD inventory</td>
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<tr>
<td>RLS</td>
<td>restless legs syndrome</td>
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<td>RLS-DI</td>
<td>RLS Diagnostic Index</td>
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<td>ROS</td>
<td>reactive oxygen species</td>
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<td>SDB</td>
<td>sleep breathing disordered</td>
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<td>SCN</td>
<td>suprachiasmatic nuclei</td>
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<td>SE</td>
<td>sleep efficiency</td>
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<tr>
<td>SN</td>
<td>substantia nigra</td>
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<tr>
<td>SSS</td>
<td>Stanford sleepiness scale</td>
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<tr>
<td>SubC</td>
<td>subcoeruleus nucleus</td>
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<tr>
<td>TCE</td>
<td>Trichloroethylene</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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<tr>
<td>UPS</td>
<td>ubiquitin protein system</td>
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<tr>
<td>vIPAG</td>
<td>ventrolateral periaqueductal gray</td>
</tr>
<tr>
<td>VMM</td>
<td>ventromedial medulla</td>
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<tr>
<td>WED</td>
<td>Willis-Ekbom disease</td>
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ABSTRACT

The diagnosis of Parkinson’s disease has remained essentially a clinical one. The diagnostic criteria consist of cardinal motor symptoms and signs, such as bradykinesia and at least one of the following: rest tremor, muscular rigidity or postural instability. However, non-motor symptoms (i.e. cognition, mood, sleep, pain, dysautonomy) constitute a major clinical challenge. The total burden of non-motor symptoms is likely to be more important than the motor symptoms in determining the quality of life across all stages of the disease.

The current study aims to evaluate, by means of a structured questionnaire approach, the occurrence of sleep disorders, sleeping difficulties, health-related quality of life and other comorbidities in a non-selected population of Finnish Parkinson patients. The response rate was 59% (N=854). The occurrence of rapid eye movement sleep behavior disorder was 39.0%, restless legs syndrome 20.3%, chronic insomnia disorder 36.9%, narcolepsy like symptoms 11.0%, sleep disordered breathing 22.1%, respectively. Low quality of life occurred in 45.0% of the participants, depression in 20.9%, excessive daytime sleepiness in 30.2%, fatigue in 43.9%.

LYHENNELMÄ

Parkinsonin tauti luetaan kuuluvaksi liikehäiriösairaudeksi. Tautidiagnostiikassa muita Parkinsonin tautiin liittyviä oireita ei oteta huomioon. Myös jatkossa ne voivat jäädä pienelle huomiolle. Muita oireita on koetettu luokitella jaotuksella kognition, mielialatekijöiden ja ahdistuksen, unen, kivun, fatiikin ja autonomisen hermoston oireisiin.

Käsillä olevassa tutkimuksessa keskitytään Parkinsonin tautiin liittyviin unihäiriöihin. Niiden käytännön merkitystä potilaalle selvitettiin kysymällä potilaiden unihäiröiden vaikutusta koettuun elämän laatuun. Vuonna 2011 Suomen Parkinson Liiton jäsenille postitettiin kohdistettu kysely univaikeuksista. Kyselyn kohortti oli 1447 henkilöä, joista osallistui 854 henkilöä. Vastattujen lomakkeiden määrä oli riittävän suuri tilastollisesti merkitsevien johtopäätösten esittämiseen. Suomalaisessa unihäiriöiden esiintyvyys kyselytutkimuksessa olivat behavorialinen unioireyhtymä esiintyi 39.0%:lla kyselyyn vastanneista. Vastaavasti kroonista unettomuutta oli 36.9%, päiväaikaista väsymystä 30.6%, levottomat jalat oireyhtymää 20.3%, mahdollista uniaapnea 22.1% ja narkolepsian kaltaisia oireita 11.0%. Masennusta esiintyi 20.9%:lla, koettua huonoa elämänlaatua 45.0%:lla, fatiikkia 43.9%:lla ja liiallista päiväaikaista väsymystä 30.2%:lla vastanneista.
1. INTRODUCTION

Among nonmotor manifestations of Parkinson’s disease (PD), sleep problems, sleep related phenomena, and excessive sleepiness occur frequently and they may affect negatively the quality of life and safety of the patients. A patient with PD can have different types of sleep disorders simultaneously such as restless legs syndrome (RLS), excessive daytime sleepiness (EDS), fatigue, insomnia, sudden onset of sleep episodes, rapid eye movement sleep behavior disorder (RBD) and obstructive sleep apnea (OSA).

PD is a chronic disease progressing slowly after onset over the life span, while it is unknown if RLS is a progressive condition or expressing different phenotypes during advancing age. The precise pathophysiology of RLS is not known. There are no shared neuronal degeneration nor Lewy Body deposition nor shared loci with RLS and PD. The central nervous system (CNS) iron differs between the two entities. While abnormal accumulation of iron in the brain has been implicated in PD, significant iron deficiency has been found in the neurons of substantia nigra in RLS patients. Even though both RLS and PD respond to dopaminergic drugs, the specific pulsatile treatment complications are augmentation of symptoms in RLS and dyskinesias in PD. The medical treatment of PD patients may induce augmentation of subclinical RLS.

Among different sleep disorders parasomnias have often been overlooked in PD studies. According to the latest International Classification of Sleep Disorders (ICDS-3) this class of disorders is divided to REM sleep parasomnias, NREM parasomnias, other parasomnias, and isolated symptoms. The diagnosis of typical parasomnias, other than RBD, can be based on history and clinical examination. The diagnosis of RBD can be based on history but the definitive diagnosis of RBD requires polysomnographic documentation as one of the essential diagnostic criterion is REM sleep without muscle atonia. Therefore the diagnosis is mainly based on questionnaires and interviews. For the majority of PD patients, sleep is disrupted. On the other hand, factors that fragment sleep, e.g. PD, can facilitate or precipitate parasomnias in predisposed individuals. Previous studies of the occurrence of parasomnias in patients with PD are scarce.

Although being different clinical entities, narcolepsy and PD share many symptoms. Patients with narcolepsy have symptoms of unstable sleep–wake regulation (daytime sleep attacks, nightly multiple awakenings), REM sleep dysregulation, cataplexy (loss of muscle tone during wakefulness), sleep paralysis and hypnagogic hallucinations. Among non-motor manifestations of PD, sudden onset of sleep attacks are frequent. Cataplexy-like symptoms have not been reported to occur in PD. It is not known whether narcolepsy like symptoms in PD patients are associated with RBD. In PD subjects, there is an increasing loss of hypocretin cells from 23% (stage I) to 62% (stage V) as measured by the Hoehn and Yahr rating scale. Therefore, the early loss of Hcrt cells may explain the frequent daytime sleep attacks in PD patients.

Aging is per se associated with a decrease in the quality of sleep, and sleep-disordered breathing (SDB), i.e. obstructive, central or mixed sleep apneas, may further disrupt the sleep architecture in older subjects. At the moment, the relation between PD and the prevalence of SDB is still debatable.

Among nonmotor symptoms of PD, disruptions of physiologic sleep affected up to two-thirds of PD patients in a community based sample. The sleep quality seems to deteriorate with the advancing of PD. As the disease progresses, PD has an increasing impact on health-related quality of life (HRQL). Sleep disturbances are associated to HRQL in PD. The underlying link between poor HRQL and sleep quality is not fully understood. One may speculate on potential mechanisms, e.g. an unrecognized confounder (such as sleep-disordered breathing) may lead both to an increased need for sleep and poor quality of life. Excessive sleeping difficulties can lead to diminished HRQL per se.
2. REVIEW OF LITERATURE

2.1 History

The first medical description of this disorder was presented by James Parkinson in 1817. In 1859 Brissaud formulated the hypothesis that the substantia nigra is the main brain nucleus pathologically affected in PD. In 1912 Friedrich Lewy described the protein aggregates that form in different areas of the brain of PD patients, including the dorsal vagal nucleus, locus coeruleus and globus pallidus. Trétiakoff validated Brissaud’s hypothesis in 1919 and, by examining post-mortem tissue, he described the protein aggregates in the substantia nigra and called them Lewy bodies. In 1940, Meyers reported first attempting to operate on the basal ganglia for the treatment of postencephalitic tremor. In 1960 Ehringer and Hornykiewicz identified reduced dopamine in striatum. In 1997 alpha-synuclein was implicated in PD because mutation of the alpha-synuclein gene on chromosome 4 (4q21-23) was identified in familial PD with autosomal dominant trait [1] After mutations of alpha-synuclein were found to cause PD, alpha-synuclein was identified as a major component of Lewy bodies by immunohistochemical staining. Over 50 proteins have been found in Lewy bodies of PD.

2.1.1 Von Economo’s studies and encephalitis lethargica

In May 1917, Romanian born Greek neurologist Constantin von Economo in Vienna, Austria observed a cluster of symptoms that were referred to as encephalitis lethargica (EL). The disease was recorded at the same moment in France, when in April 1917, Crucet, Montier and Calmette recorded a series of cases of “subacute encephalomyelitis”.[2] EL occurred in US and Western Europe between 1916 and 1926 with approximately 20-40% mortality (up to 0.5 million deaths worldwide). Of all surviving cases 34% remained chronic invalids. Twenty-eight subtypes of EL, such as somnolent-ophthalmoplegic, hyperkinetic (juvenile pseudopsychopathia), and amyostatic-akinetic (Parkinsonian) form, were characterized by symptomatology. Because the most typical and prominent sign was the compulsion to sleep, EL has been referred to as “sleeping sickness”, i.e. an atypical form of acute encephalitis with symptoms of lethargy, sleepiness, and stupor. According to the sleep theory of von Economo, infection occurred in the posterior wall of the third ventricle in the cases of hypersonmia, and in the lateral wall in the insomnia cases.[3]

Before the epidemic of encephalitis lethargica, Parkinsonism was very rare before the age of 40 years. Parkinsonism was observed during the course of EL, which was transitory, and in chronic sequelae, an amyostatic-akinetic form, which ensued usually six months to one year following resolution of initial symptoms. Postencephalitic Parkinsonism (PEP) was thus referred as a long-term complication of EL. Cases of PEP increased during the 1920s and 1930s. Future studies suggested that 50% of PEP patients had acute EL.[4] In 1963, Poskanzer and Schwab reviewed nearly 1000 cases of a Parkinsonian syndrome. The mean age of their cases diagnosed in 1950s was 27 years older than that of cases diagnosed in 1920s. Most importantly, only 11% of their cases could be linked to an overt encephalitic illness.[5] Nosological entities of EL (neurofibrillary tangles and lymphocytic infiltration into the basal ganglia), PEP (gliosis of substantia nigra), and idiopathic PD (Lewy bodies) can be considered distinct based on their respective neuropathology. Historically, EL occurred in close proximity of the 1918-1919 influenza A virus H1N1 pandemic which affected 25-30% of the world population and is thought to have killed at least 40 million people.[6] Previous major influenza epidemic swept Europe in 1889-1890, and it was reported to have numerous neurologic and psychiatric signs and symptoms, not unlike EL. The mysterious illness “La nona” started in the province of Mantua, Italy, spreading to adjacent areas of central Europe. The origin of the term nona has remained obscure: 1) “nine” in Italian referring to the number of days before death, 2) “grandmother” in Italian, 3) the year 1890 (nonagesimo=90th), 4) time of afternoon rest in the ninth hour of the day (3 P.M.). Historical reviewers have argued that not only EL/Nona and influenza, but also encephalitis acuta hemorrhagica, polioencephalitis, poliomyelitis and a collection of distinct historical disorders were all manifestations of a single disorder, “epidemic encephalomyelitis”. [7]

The cause of EL is still not known. In classical EL cases, virus-like particles in the cytoplasm and nuclei of midbrain neurons turned out to be enterovirus (poliovirus and anti-coxsackievirus B) by transmission electron microscopy and immunohistochemistry.[8] EL was not solely responsible for the etiology of PEP.[9] However, PEP occurs even today with clinical features similar to those recorded during the pandemic of EL.[10] While idiopathic PD has α-synuclein pathology, the yet undetermined infectious or toxic agent responsible for EL and the development of late-life parkinsonism and substantia nigra depigmentation, seem to exert its effects through α-synuclein-independent mechanisms for selective nigral degeneration.[11]
2.2 Pathophysiology

The motor symptoms appear when dopaminergic neurons in the striatum are lost. The substantia nigra in 80 year old humans contains approximately 550 000 pigmented and 250 000 non-pigmented neurons with a variation of about 20%. The total numbers of pigmented and non-pigmented neurons in substantia nigra from seven patients with Parkinson's disease were reduced by 66% and 24%, respectively, at the time of death.[12] Additionally the second main neuropathological hallmark of PD is the presence of Lewy bodies (LB) in the surviving neurons. The other pathological changes observed are widespread. LB inclusions appear in different areas of the brain (mesostriatal system, cortex, thalamus, hypothalamus, olfactory bulb or brainstem). The autonomic system (the spinal cord, sympathetic ganglia and myenteric plexus in the gastrointestinal tract) is altered. The widespread nature of this pathology is indicative that the disorder is not just a motor alteration but rather, a sensory, cognitive, psychiatric and autonomic disorder. Non-dopaminergic neuronal loss is also detected in some areas of the brain: 1) monoaminergic cells in the locus coeruleus [13] and raphe nuclei; 2) cholinergic cells in the nucleus basalis of Meynert [14] and in the pedunculopontine tegmental nucleus [15]; 3) hypocretin cells in the hypothalamus [16].

2.2.1 Alpha-synuclein

In 1988, a new protein was found localizing in the presynaptic nerve terminals and nucleus, and hence was referred to as synuclein.[17] The human homologue of torpedo synuclein is alpha-synuclein (αsyn), which is a 140 amino acid, natively unfolded protein (i.e., it lacks a well-defined stable tertiary structure when isolated). First of up to now known six missense mutations in αsyn gene was found to be associated with the familial PD in 1997.[1] A substantial portion of total protein in Lewy bodies and Lewy neuritis is composed of αsyn. Findings suggested that neurotoxic αsyn filaments were the cause of nerve cell death in PD.[18] Another explanation is loss of αsyn monomers, i.e. loss of function, as a cause of neurodegeneration.[19]

Last two decades αsyn has been in the center of research of overlapping degenerative disorders called synucleinopathies, such as PD, dementia with Lewy bodies (presence of Lewy bodies in both entities), multiple system atrophy (presence of glial cytoplasmic inclusions), and a number of less-characterized neuroaxonal dystrophies (presence of axonal spheroids).[20] Lewy bodies, which are mostly restricted to amygdala, are detected also in 61% of sporadic Alzheimer’s disease (AD) patients.[21] Neuropathologically verified Lewy body variant of AD has a distinct clinical phenotype.[22]

Despite all the research done, the exact function of αsyn has remained elusive.[20] αSyn in the human brain makes up 1% of protein content in the cytosol, expressed predominantly in neurons and to lesser extent in glial cells. In animal models, αsyn regulate the release of dopamine and influence memory and cognitive function. Reduced αsyn may reflect global impaired neuronal/synaptic function, or non-specific overall cognitive deterioration.[23] This function of αsyn becomes more important during increased synaptic activity and aging. Posttranslational modification of αsyn by phosphorylation, truncation, ubiquitination, or nitration, alters the protein to αsyn aggregation, Lewy body formation, and neurotoxicity. In addition to the accumulation of intracellular or extracellular protein aggregates, propagation of neurodegeneration is caused by the intercellular transfer of pathogenic proteins in a ‘prionlike’ manner.[24]

2.2.1.1 Braak hypothesis

LB pathology appears in a stereotypic pattern depending on how advanced the disease is. In stage 1, Lewy pathology (primarily Lewy neurites) is found in the olfactory bulb (and anterior olfactory nucleus) and the dorsal motor nucleus of the glossopharyngeal and vagal nerve. In stage 2, the Lewy pathology continues to ascend toward the brainstem, reaching the medulla oblongata and pontine tegmentum. In stage 3, the pathology appears in the amygdala and substantia nigra. The LBs, and to a larger extent Lewy neurites, are also found in the forebrain and cerebral cortex in stage 4. In stages 5 and 6, the pathology also appears initially in the anterior association and prefrontal areas of the prefrontal cortex and continues to spread toward the posterior association areas. Braak et al in 2003 proposed that neuroinvasion by a hypothetical neurotropic pathogen, such as misfolded αsyn molecular fragment, starts from enteric nervous system (VIP neurons within Auerbach plexus) entering the brain and invading subcortical nuclei and cortical areas in PD.[25] Autopsy study of two PD patients who had had transplants of embryonic dopamine neurons to treat their disease confirmed this propagating mechanism.[26] Posttranslational modifications and propagation of αsyn take
considerable time, since longitudinally it takes 13 years for αsyn aggregates to reach limbic areas and 18 years to reach association cortices.[27] However, the precise relationship between protein aggregation, cellular dysfunction, and the cell death underlying PD is still unknown. In familial PD with LRRK2 mutation, a spectrum of synuclein pathology among family members with manifesting PD is known to range from none to significant accumulation of αsyn aggregation. Hence, Lewy pathology is not necessary for nigral degeneration and the clinical presence of PD. The mechanisms contributing to the progression of PD can be as variable as the disease itself.[28]

2.2.2 Neuromelanin

The two hallmarks of PD are αsyn aggregates and neuromelanin (NM). Interaction between αsyn and oxidative stress form a vicious circle, where oxidative stress induces αsyn aggregation, which in turn increases oxidative stress [29] leading to neurodegeneration, i.e. progressive loss of NM containing dopaminergic neurons in the substantia nigra pars compacta. NM is the dark insoluble macromolecule that confers the pigment to monoaminergic basal ganglia, e.g. substantia nigra and locus coeruleus. Pigmentation of substantia nigra, accumulation of NM, initiates very early in life, approximately at 3 years of age.[30] The role of NM is unclear. NM is supposed to protect intracellularly by binding toxic metabolites, such as oxidized dopamine, metabolites of dopamine, and metals, and by acting as an antioxidant. According to antipodean hypothesis, NM is toxic to DA neurons, by inhibiting proteasomes function, and catalyzing the production of free radicals by reaction with hydrogen peroxide.[31] NM and αsyn form another vicious circle, which results in the death of dopamine neurons in PD. Firstly age-related accumulation of NM induces αsyn expression and aggregation, then αsyn promotes the biosynthesis of NM by increasing the levels of cytosolic dopamine.

NM can be released by damaged or dying neurons into the extracellular space, where NM activates microglia by producing a variety of neurotoxic and proinflammatory factors. The microglia-based neuroinflammation plays another important role in dopaminergic neurodegeneration in PD.[32] Thus NM has a dual role in the pathogenesis of Parkinson's disease. In the early stages, NM synthesis and metal-chelating properties act as a protective mechanism. Once these systems have been exhausted, the pathogenic mechanisms destroy NM-harboring neurons, with consequent leakage of NM which in turn activate microglia.[33]

2.2.3 Inflammatory and autoimmune mechanisms

There is accumulating evidence for an immunogenic role of NM in PD pathogenesis. NM triggers maturation of dendritic cells which are heterogenous antigen-presenting cells of the immune system that play an important role in the initiation of innate and adaptive immune responses. Activated dendritic cells migrate from the brain into the cervical lymph node where they present the potential (auto-) antigens to T and B cells. This autoimmune response against NM would be directed against NM-rich cells in the brain, leading to dopaminergic cell death. This auto-aggressive loop would be enhanced by a NM-triggered activation of microglia.[34] Autoantibodies directed at antigens associated or related to PD pathogenesis have been identified in PD patients, including antibodies directed at melanin[35], and αsyn[36].

Microglia, approximately 0.5-16.6% of the adult human brain, perform when activated dynamic cellular functions that include synaptic plasticity, cleaning of cellular debris, neuronal support through the production of growth factors, wound healing through alternative activation, and innate immune defense. Activated microglia monitor the brain environment by interpreting and processing through pattern recognition receptors. The SN pars compacta ganglia are densely rich with microglia, rendering them potentially more susceptible to the effects of sustained inflammation in PD.[37] The direct stimulation of microglia by environmental toxins or endogenous proteins enhance and amplify neuronal damage and it seems that this, in turn, induces more widespread damage to neighbouring neurons (reactive microgliosis).[38] Instead of talking about neuroinflammation, the proper term in the context of aging would be microglial senescence, which in humans progresses to an advanced, pathological level, called dystrophy, that can be directly associated with neurodegeneration. Diseased microglia are incapacitated cells, not aggressors, but victims of free radical damage like all cells.[39] So, microglial overactivation initiated by early immunological insult or direct injury to neurons might be propagated and potentially amplified throughout the course of neurodegenerative disease, driving the continuous and cumulative loss of neurons over time.
2.2.4 Oxidative stress

Together with progressive neuron damage, inflammation, and microglial overactivation, oxidative stress is present in the development of PD. Oxidative stress defines a disequilibrium between the levels of reactive oxygen species (ROS) produced and the ability of a biological system to detoxify the reactive intermediates. The brain consumes about 20% of the oxygen supply of the body, and a significant portion of that oxygen is converted to ROS by dopamine metabolism, mitochondrial dysfunction and neuroinflammation.[40]

Dopamine is an unstable molecule that undergoes auto-oxidation to form dopamine quinones and free radicals.[41] Mitochondrial dysfunction is mainly characterized by the generation of ROS, a defect in mitochondrial electron transport complex enzyme activities, ATP depletion, caspase 3 release and depletion of mitochondrial DNA. Environmental toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat, induce dopaminergic neuronal death through direct inhibition of mitochondrial complex I activity. Mutant proteins from PD-related genes elicit diverse mitochondrial dysregulation and subsequently cause neuronal degeneration. Nevertheless, the exact process by which the mitochondria become dysfunctional in PD remains to be determined.[42] Later on depolarized mitochondria may undergo fission and mitochondria-associated autophagy (mitophagy), a degradation by autophagosomes fused with lysosomes.[43]

ROS can be generated through direct interactions or by indirect pathways involving the activation of enzymes such as nitric oxide synthase (NOS) or NADPH oxidases. The NOX family of NADPH oxidases is comprised of seven transmembrane proteins that oxidize intracellular NADPH/NADH, causing electron transport across the membrane and the reduction of molecular oxygen to superoxide. Neuronal NOX2 has been implicated in neuronal apoptosis, learning and memory, long-term potentiation, and in neuronal myelination signals. Microglial NOX2 is involved in host defense, proliferation, and regulation of cell signaling via redox signaling mechanisms. Microglial NOX2-induced neurotoxicity is believed to occur through two mechanisms: the production of extracellular ROS that directly damages neurons and intracellular signaling that primes microglia to enhance the pro-inflammatory response and propagate neurotoxicity.[44] The ubiquitin-proteasome system is the main pathway through which cells degrade and remove damaged and unwanted proteins. The proteasome is considered as a defense mechanism, since degradation for example defective mitochondria lessens the threat of oxidized proteins forming toxic aggregates. As αsyn is a substrate of this proteasome, oxidatively damaged αsyn aggregates impair this function.[45]

2.2.5 The role of autophagy in PD – genetic perspective

Keeping in mind that only a minority of PD is due to genetic factors, results from genetic studies show that dysregulated autophagy may play a causal role in the pathogenesis of PD. The LBs comprise of a plethora of protein constituents that include several PD-linked gene products. Identification and functional characterization of several genes, including αsyn, parkin, DJ-1, PARK1 and LRRK2, implicate aberrant protein and mitochondrial homeostasis as key contributors to the development of PD, with oxidative stress likely acting an important nexus between the two pathogenetic mechanisms.[46] LBs consist of 90 components which can be grouped into 13 functional groups, i.e. structural elements like αsyn and neurofilaments, αsyn binding proteins, synphilin-1-binding proteins, ubiquitin protein system (UPS) -related proteins, autophagosome-lysosome system, aggresome-related proteins, stress response-related proteins, signal transduction-related proteins, cytoskeletal proteins, mitochondria-related proteins, cell cycle proteins, cytosolic proteins and immune-related proteins.[47] Eucaryotic cells have several complex machineries to destroy faulty proteins. Coupling of chaperone and UPS provides an efficient way to remove the misfolded proteins by the proteasome. However, e.g. under conditions of cellular stress, the capacity of these proteolytic systems may be exceeded, and degradation of aggregated proteins happens via autophagy-lysosome system. Proteasome-independent ubiquitination acts as a cargo selection signal to autophagy. Macroautophagy is characterized by the formation of a unique double-membrane organelle called autophagosome. In microautophagy, lysosomes engulf cytoplasmic materials by inward vagination of the lysosomal membrane. Thirdly, the proteins can be removed via chaperone-mediated autophagy.[48] Failure in one of these highly conserved cellular homeostatic processes can precipitate protein aggregation, LB formation and subsequent cell death in affected neurons.[49] Virtually all the major PD-associated gene products are directly or indirectly related to the autophagy-lysosome axis. Autophagic degradation of mitochondria is called mitophagy. Mitochondria provide 90% of the energy in cells through oxidative phosphorylation, involve calcium homeostasis and regulation of apoptosis.[48] Mitochondrial dysfunction has
a major role in pathogenesis of PD. Deficits in mitochondrial complex I activation, increased oxidative stress and aging associated damage to mitochondrial DNA are known to dominate as key mitochondrial alterations associated to PD.[50] Parkin and PINK-1 are recruited to impaired mitochondria and promote mitophagy.[51] Key components of autophagy and mitophagy overlap, and whether LB biogenesis represents a cytoprotective or pathogenic mechanism in PD remains to be debatable.

Autophagy is described as a double-edged sword, since both reduced and excessive autophagy can be detrimental. Rapamycin,[52], which is an inhibitor of mTOR (a serine/threonine protein kinase regulating cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription), trehalose,[53], an mTOR-independent autophagy activator, and latrepirdine,[54], a neuroactive compound known to enhance cognition, neuroprotection and neurogenesis, induce all the reduction of αsyn in an autophagy-dependent manner. Autophagy induction by these compounds could prevent the accumulation of αsyn. On the other hand, MPP+,[55], a neurotoxin metabolite of MPTP, accumulation of iron,[56], mutant αsyn overexpression[57] can result in aberrant activation of autophagy. In these cases, autophagy is harmful to dopaminergic neurons. AMP-activated protein kinase (AMPK) is a key regulator of energy homeostasis switching the cell from an anabolic to catabolic mode. AMPK can regulate mitophagy and autophagy, and overexpression of AMPK increases cell viability after exposure to MPP+. Metformin, a direct activator of AMPK, reduced the risk of PD in a diabetic population.[58] Antidiabetic glitazone, a peroxisome proliferation-activated receptor gamma agonist, is also associated with a reduction in incidence of PD.[60] The mechanism could be that peroxisome proliferator-activated receptor gamma is an inducer of apoptosis and an inhibitor of autophagy.[61]

2.3 Sleep theory

Sleep remains the only universal behavior known to biology with no clear consensus regarding a fundamental underlying function. “Che vi sia ciascun lo dice, dove sia nessun lo sa” (“that there is one they all say, where it may be no one knows,” Wolfgang Amadeus Mozart and Lorenzo da Ponte [1790]. Così fan tutte).

2.3.1 Energy hypothesis of sleep-wake control

The energy requirements of the brain are quite high relative to other organs, with the brain accounting for approximately 20% of the body’s resting metabolism despite only constituting 2% of body mass.[62] The magnitude of cerebral metabolic rate of oxygen decreases 25% in NREM deep sleep, which normally constitutes only about 20 percent of total sleep, as compared to the rate of wake state. [63] Benington et al postulated in 1995 that during wakefulness, adenosine increases and astrocytic glycogen decreases reflecting the increased energetic demand of wakefulness. As glycogenolysis can be initiated more rapidly than increased transport of glucose from plasma, cerebral glycogen is the only significant energy reserve in the brain, located almost entirely in astrocytes. NREM sleep is essential for resplenishment of cerebral glycogen stores that are depleted during waking.[64] This hypothesis of glycogen and adenosine has turned out to be an oversimplification. In addition, energy-related pathways are involved in transitioning the brain from the metabolically-deplete catabolic state of wakefulness to the metabolically-replete anabolic state of sleep. These pathways include the unfolded protein response, the electron transport chain, NPAS2, AMPK, the astrocyte-neuron lactate shuttle, production of ROS and uncoupling proteins.[65] Sleep is a stage of synthesis which necessarily answers the insult of wakefulness. In animal models, 3,988 genes in the cerebral cortex and 823 genes in the hypothalamus alter expression patterns between sleep and sleep deprivation. Over 2000 genes in the cerebral cortex and 400 genes in the hypothalamus were defined as sleep specific. The largest categories of overrepresented genes increasing expression with sleep were those involved in biosynthesis and transport.[66]

Current evidence suggests that there is no rigid association in vivo among changes of oxygen consumption, glucose combustion, and blood flow in the human brain. The claim that increased blood flow must occur simply to satisfy the demands for oxygen and glucose during neuronal excitation therefore is simplistic. The main sites of energy transformation are the mitochondria, which provide over 90% of cellular ATP.[67] Evidence of mitochondrial dysfunction in the pathogenesis of PD first emerged in the 1980’s when drug abusers developed an acute and irreversible parkinsonian syndrome after using MPTP. Abundant evidence from three decades research supports the view that mitochondria play a quite upstream role in sporadic neurodegenerations.[68]
According to the energy allocation model, a universal sleep function is to shunt waking energy utilization toward sleep-dependent biological investment. Sleep–wake cycling downregulates specific biological processes in waking and upregulates them in sleep, thereby decreasing energy demands imposed by wakefulness, reducing cellular infrastructure requirements, and resulting in overall energy conservation. In an energy allocation economy, the currency is energy.\[69\]

2.3.2 Sleep – garbage truck of the brain

In fast synaptic transmission, the exocytotic fusion of a vesicle with the presynaptic membrane releases thousands of neurotransmitter molecules that diffuse into the synaptic cleft, a small fraction of which encounter and bind to specific sites on their receptors in the postsynaptic membrane. Reuptake mechanisms eliminate 99.9% of these neurotransmitters preventing their local accumulation. However, in the vicinity of a neurotransmitter specific synapse, other neurotransmitters escape reuptake and accumulate in brain interstitial fluid (ISF).\[70\] The clearance of ISF with its constituent proteins and other solutes not absorbed across postcapillary venules to a sink for brain extracellular solutes, i.e. the cerebrospinal fluid (CSF), during awake periods has been shown to be extremely slow. Some 10–30% of the total CSF flow is thought to be associated with the bulk flow of ISF, while the majority of CSF is produced by the choroidal epithelium.\[71, 72\]

Subarachnoid CSF cycles through the brain interstitial space. CSF enters the parenchyma along paravascular spaces that surround penetrating arteries, and ISF is cleared along paravenous drainage pathways, which were named glymphatic system. Astrocytic water channels link paravascular and interstitial bulk flow. Deletion of astrocytic aquaporin-4 (AQP4) water channels reduced clearance of exogenous β-amyloid by 65%, suggesting that its impairment may contribute to the mis-accumulation of other soluble proteins known to involve with neurodegenerative conditions.\[73\]

The pathogenesis of PD may be governed by a prion-like mechanism of endogenous misfolding and templated corruption of disease-specific proteins. A proportion of these cytosolic proteins are released into the interstitial space in the brain, suggesting that extracellular disposal routes may also eliminate waste.\[74, 75\]

Evolutionary origin of “need to sleep” suggests, that sleep provides regular periods in which the rate of clearance of solutes from the ISF is greatly increased, during which synaptic transmission is significantly reduced, of sufficient duration to ensure the elimination of potentially toxic metabolites -the very results of a working brain- from the ISF.\[76\]

The interstitial space in the waking brain is only 14% of brain volume, but increases by over 60% in natural sleep or anesthesia to 23% of the brain volume. The flow of CSF through the interstitial space is reduced during waking to only 5% of the flow found in sleep. The brain switches into a functional state that facilitates the clearance of degradation products of neural activity that accumulate during wakefulness.\[77\] Possibly the accumulation of metabolites, such as adenosine during waking, forced by the constricted interstitial space, drives the switch to sleep state.\[78\]

After ISF is drained through the glymphatic system, subsurface system of drains continues in meningeal lymphatic vessels lining the dural sinuses. There are both initial and collecting afferent lymphatic vessels. Fluid enters throughout initial lymphatics via openings between button- and zip-like junctions which open and close without disrupting junctional integrity, into collective vessels.\[79, 80\] In addition to draining ISF, cells can travel through meningeal lymphatic vessel into the deep cervical lymph nodes.\[81\]

2.3.3 Astrocytes and sleep

The synaptic homeostasis hypothesis proposes that the fundamental function of sleep is the restoration of synapses, which is challenged by synaptic strengthening triggered by learning during wake and by synaptogenesis during development, i.e. plasticity.\[82\] A few hours of wake and chronic sleep restriction, defined as 70% of sleep loss, bring astrocytic processes closer to the synaptic cleft and increase the available astrocytic surface in the neuropil (i.e. astrocyte neuron metabolic unit). Wake-related changes in synaptic strength likely reflect an increased need for glutamate clearance. Instead during sleep, the reduced astrocytic coverage may favor glutamate spillover and increased glymphatic flow, thus promoting neuronal synchronization during NREM sleep.\[83\] In astrocytes, the number of 396 wake genes uniquely expressed during waking drastically outnumbered the 55 sleep-associated genes. As a comparison, oligodendrocytes have similar numbers of both sleep and wake genes. The model thus posits that changes in glial gene expression, morphology, and physiology may modulate synaptic transmission to promote sleep.\[84\]

Santiago Ramón y Cajal was the first to propose a direct involvement of astrocytes in neuronal function. He hypothesized, in 1895, that astrocytes retract their processes during wakefulness to allow normal synaptic transmission. During sleep, he reasoned, astrocyte processes invade the synapse to block synaptic transmission.\[85\] The long-held
belief that brain information processing is an exclusive function of neurons is erroneous. Glia cells account for approximately 85% of cells of the human neocortex. Astrocytes, macroglial cells, greatly outnumber neurons, often 10:1 and occupy 25% to 50% of brain volume.[86] They are essential for normal synaptic function and maintenance, instrumental in expression, storage and consolidation of synaptic information from individual synapse to global neuronal networks.[87]

Astrocytes have a neuroprotective role in PD. Glial fibrillary acidic protein (GFAP) is an intermediate filament protein localized to astrocytes. Although its precise contributions to astroglial physiology and function are unclear, it is upregulated following injury and astrogliosis. Both the number of astrocytes and GFAP expression are increased in PD. The increase in antioxidant glutathione-peroxidase-containing astrocytes correlate inversely with the severity of dopaminergic cell loss, while the presence of asyn-positive astrocytes correlate with nigral neuronal cell death. Exposing nitric oxide to astrocytes increases the release of glutathione (the main antioxidant of the brain) from astrocytes to neurons, thereby making them less susceptible to reactive nitrogen species, oxidative stress.[88] MPP+ (MPTP metabolite) induces negative effects in astrocytes, such as loss of viability, impairment of energetic metabolism of mitochondria, ROS generation and decrease in the glutamate clearance by astrocytes.[89] Deep-brain stimulation, which relieves the symptoms of PD, probably acts on astrocytic calcium waves that coordinate the activity of large populations of neurons controlling movement.[90]

2.3.4 Locus coeruleus and sleep

The locus coeruleus (LC) is a major wakefulness-promoting nucleus located in the upper dorsolateral pontine tegmentum, giving rise to fibres innervating extensive areas throughout the neuraxis. The efferent output of LC consists of noradrenergic projections, which inhibit GABAergic neurons in basal forebrain (to promote wakefulness) and ventrolateral preoptic area of the hypothalamus (to maintain arousal), excite serotonergic neurons of the dorsal raphe nucleus (the regulation of the sleep-wakefulness state), inhibit and excite two subpopulations of cholinergic neurons in pedunclulopontine and laterodorsal tegmental nuclei (active during both wakefulness and REM sleep). The afferent input to LC includes orexin system of lateral hypothalamic/perifornical area (suppression of REM sleep and increase of wakefulness), histaminergic neurones of tuberomamillary nucleus (increase of wakefulness), the cholinergic neurones of pedunculopontine and laterodorsal tegmental nuclei (active during either wakefulness or REM sleep), dopaminergic and glycnergic neurones in the ventral periaqueductal grey matter (PAG) (increase of wakefulness), and GABAergic neurones in the rostral medulla (active during REM sleep). The transition into REM sleep, a flip-flop switch, is a reciprocal connection of REM-off neurons in the ventrolateral PAG inhibiting REM-on neurons in subcoeruleus and vice versa.[91]

The duration of PD correlates to neuronal death in LC, where it is also more severe than in SN pars compacta. LC cell loss in PD is about 83% compared with age-matched controls.[13] The formation of the Lewy neurites and bodies are seen in LC before any pathology occurs in SN.[92] PD is also associated with morphological changes, such as changes in size and shape of the pre- and postsynaptic components, polymorphism of the synaptic vesicles and marked morphological alterations of the mitochondria, to the surviving neurons in the LC.[93] It has been hypothesized that deficits in noradrenergic LC may underlie the progression of PD. LC noradrenaline depletion caused a 61.2% dopamine depletion in the nigrostriatal pathway and denervation of locus coeruleus noradrenergic terminals induced partial dopaminergic neurodegeneration and parkinsonian symptoms. Thus LC has both neuromodulatory and neuroprotective effects on these dopaminergic neurons.[94] Sleepiness, the incidence of dementia, depression and anxiety in PD results from the reduction in LC activity due to the neurone loss.[95]

2.4 Epidemiology

PD is considered to be the second most common neurodegenerative disease after Alzheimer’s disease.[96] The problems in epidemiological research on PD start with the definition of diagnosis. Clinical criteria at best lead to a diagnosis of probable PD, while post mortem confirmation is required for a diagnosis of definite PD. Only 76% of the cases with the clinical diagnosis of PD were confirmed at autopsy with accepted neuropathological criteria, i.e. nigral Lewy bodies.[97] The knowledge of order in which motor and non-motor symptoms appear, disease progression and responsiveness to levodopa therapy are important to distinguish PD from other neurodegenerative disorders and frequently present conditions such as arthritis or neuropathy, that may resemble some of the cardinal signs or affect
their presentation.[98] Door-to-door surveys show higher prevalence rates as they screen all participants and find new diagnoses than record-based studies.[99]

In the EUROPARKINSON collaborative study, the overall prevalence of PD in the age group of 65 to 69 years was 0-6% increasing to 3.5% in the age group of 85 to 89 years. Prevalence was similar in men and women, and 24% of the subjects with Parkinson's disease were newly detected through the surveys.[100] The Finnish prevalence of PD was 166 per 100 000 population in 1992.[101] In a prospective 23-year cohort study of 22,000 male physicians aged 40-84 years at baseline, the incidence rate of PD was 121 cases/100,000 person-years. Age-specific incidence rates increased sharply beginning at age 60 years, peaked in those aged 85–89 years, and declined beginning at age 90 years. Mortality-adjusted lifetime risk in men from ages 45 to 100 years was 6.7% (95% CI 6.01% to 7.43%).[102] Another lifetime risk estimate for PD is 2.0 and 1.3% for men and women, respectively.[103]

Both prevalence and incidence rates in Asian populations seem to be lower. In Asian countries, the age-standardized prevalence reported in door-to-door surveys ranged from 16.7 to 176.9 per 100 000, and in the record-based surveys, the standardized prevalence per 100 000 was 35.8 to 68.3. The prevalence of PD in door-to-door surveys is reported as 101.0 to 439.4 per 100 000 in non-Asian countries, and in the record-based surveys 61.4 to 141.1, respectively. The standardized incidence rates from two Asian record-based studies were 6.7 and 8.3 per 100 000 person-years, as compared to 6.1 to 17.4 per 100 000 person-years in Western countries. The male/female ratios for Asian PD incidence ranged from 1.0 to 1.2, which was lower than those reported worldwide (range, 0.7 to 2.4).[104] Estimates of PD incidence have varied widely depending on nationality, sex, population age distribution, and case ascertainment methods.[102] The worldwide incidence of PD is 16 to 19/100,000/year.[105]

### 2.4.1 Epidemiological risk factors and protective factors of Parkinson’s disease

Because the pathogenesis of PD remains unknown, the role of the environment as a putative risk factor has gained interest. However, the available epidemiologic literature on environmental agents has its problems. Although the majority of PD cases are diagnosed in the elderly population, the exposure could have occurred years or decades before the resulting effect. This long latency period makes it difficult to track exposures before the outcome in a longitudinal fashion. Only few groups have conducted longitudinal studies of this type, and most investigators have used a case-control study design that examines cases after diagnosis. Their major limitations are recall and selection. Ecologic studies have limitations with the inability to characterize exposure data to individuals, i.e. too broad exposure definition, use of proxy respondents, lack of dose-response data or intensity of exposure, misclassification, non-persistent exposure, peak exposure or accumulation of low-level exposure not captured, existence of an earlier critical window.[106]

#### 2.4.1.1 Pesticides

Substantial numbers of epidemiologic studies have been executed on PD and exposure to pesticides, herbicides, and fungicides. The meta-analysis of 46 studies found a positive association with PD and insecticides (summary risk ratio=1.50, 95% CI 1.07 to 2.11), and herbicides (1.40, 1.08 to 1.81), but not with fungicides (0.99, 0.71 to 1.40).[107] Farming occupation and farm residence are related to pesticide exposure. Another meta–analysis found a combined OR of 1.56 (95% CI, 1.18–2.07) for rural living, 1.42 (95% CI, 1.05–1.91) for farming and 1.26 (95% CI, 0.97–1.64) for well-water consumption.[108]

Paraquat is one of the most commonly used herbicides worldwide. It does not act by direct inhibition of complex I, but generates reactive oxygen species (ROS) by redox cycling and it is very likely that such a mechanism is responsible for effects on dopaminergic neurons. Rotenone, a naturally occurring compound in the roots and leaves of several plant species, has been used extensively as an insecticide and as a piscicide to kill fish. It is a well-known, high-affinity, selective inhibitor of mitochondrial complex I. In 110 PD cases and 358 controls, PD was associated with paraquat (OR = 2.5; 95% CI, 1.4–4.7 and with rotenone (OR = 2.5; 95% CI, 1.3–4.7).[109] Both paraquat and rotenone have been used in experimental toxic models of PD in animal studies, but models have shown contradictory results, variable cell death and loss of striatal dopamine content.[110]

Association studies between PD and other environmental agents, including organochlorines, organophosphates, and carbamates, show limited epidemiological evidence and chronic animal-based, laboratory-based research is mostly lacking.[111] Du et al examined microstructural changes in SN in 12 asymptomatic agricultural workers with chronic pesticide exposure, 12 idiopathic PD subjects and 12 healthy controls. The first group had extensive histories of
chronic, multiple pesticide exposure, several of whom were professional pesticide applicators, and especially with a history of paraquat exposure. In diffusion tensor imaging, this group showed a significantly lower fractional anisotropy value in SN compared to controls (p=0.022), but not to PD subjects.[112]

2.4.1.2 Heavy metals and solvents

Metals have long been thought to play a role in PD. Iron accumulation occurs in the substantia nigra either as a result of PD or as a contribute to the pathogenesis of PD. Disruption of mitochondrial iron transport system involving transferrin and transferrin receptor in the rotenone model, and also in idiopathic PD, leads to transferrin and iron accumulation in SN.[113] Thus the role of iron in PD is unlikely due directly to environmental or dietary factors.

Manganese is the 12th most abundant element in the earth’s crust and is an essential element for human biology. Elevated manganese exposures can occur in miners and welders, and during the chemical manufacture of maneb fungicide. Manganese is a form of atypical parkinsonism with nigrostriatal pathway spared, unresponsiveness of L-Dopa, neurodegeneration of globus pallidus, and absence of Lewy bodies.[111] The epidemiological evidence of Pb association with PD is more consistent because the accumulative lifetime exposure can be estimated. Pb exposure significantly decreases the dopamine release and D1 receptor sensitivity post-synaptically. The cumulative exposure to Pb increased the risk of PD (OR=3.21, 95%CI 1.17 to 8.83) in 330 PD patients vs.308controls recruited from 4 clinics for movement disorders in Boston, MA area.[114] There is no consistent evidence of the association with PD and copper, aluminium, mercury, or zinc.[106]

Solvents are known to cause injury to the peripheral nervous system, injury to the eyes, and cerebellar atrophy in CNS. Being lipophilic they can easily cross blood brain barrier. Trichloroethylene (TCE) has been used for many years in food industry, as a grain fumigant, a caffeine extractant, and as a dry cleaning solvent, although replaced in the 1950s by tetrachloroethylene. TCE replaced earlier anesthetics chloroform and etherin the 1940s, but was itself replaced in the 1960s in developed countries with the introduction of halothane. The proposed mechanism is inhibition of mitochondrial complex I. So far, as the toxicology findings in rats with TCE have all come from one group in the same institution, confirmation by other research groups is warranted.[115] Limited epidemiologic studies suggest an association between exposure to other solvents and PD. There are claims of an increase of PD for occupations involving hydrocarbon or wood preservative exposure, working with wood or in other forms of construction.[106] At the moment there is no consistent evidence from either the toxicological or epidemiologic perspective that any specific solvent or class of solvents is a cause of PD.[116]

2.4.1.3 Nutrition

Examination of dietary factors in PD has received less attention compared to other environmental exposures. However, several dietary habits have been shown to modify the risk of developing PD. Current data on a role for vitamins A, B6, B9, B12, and C in PD development is extremely limited and questionable.[117, 118] The data for a protective or preventative role of vitamins D and E appears to be stronger than other vitamins. Vitamin D plays a role in regulating Ca2+ homeostasis and if disrupted, SN pars compacta dopaminergic neuron loss is accelerated. A systematic review and meta-analysis, including 1008 PD patients and 4536 controls, concluded that subjects with vitamin D deficiency [25(OH)D level <50 nmol/l] have an increased risk of PD (OR=2.2, 95% CI 1.5 to 3.4).[119] Vitamin E with its chain-breaking capabilities in biological membranes, prevents induced oxidative damage by trapping reactive oxyradicals. A meta-analysis of eight epidemiological studies showed a protective effect against PD in humans with moderate intake of vitamin E (OR=0.81, 95% CI 0.67 to 0.98).[120]

The most common groups of polyphenols in human diet are flavonoids, which can modulate oxidative-related enzymes and regulate mitochondrial function in neurons pointing to a potential protective role of flavonoids in PD. In a large prospective study of 129617 participants, where 805 subjects (0.6%) developed PD during 20 years, the top 5 major flavonoid rich foods were examined in relation to PD risk. Total flavonoid intake, the highest vs lowest quintile, was associated with a significantly lower PD risk in men (OR=0.60, 95% CI 0.43 to 0.83) but not in women (OR=1.01, 0.70 to 1.44). In the analyses of flavonoid subclasses, greater intake of berries, which are rich in anthocyanins, but not of tea, red wine, and orange/orange juice, were significantly associated with a lower risk of developing PD (0.76, 0.61 to 0.96).[121] Tea (rich in catechins, flavonols, theaflavins and thearubigins) consumption has been proposed as a promising lifestyle choice that may slow age-related deficits and neurodegenerative diseases. Consumption of tea ≥ 3
cups per day delayed age of motor symptoms onset of PD by 7.7 years.[122] In an Asian population, intake of black tea (OR=0.58, 95% CI 0.35 to 0.97), and Japanese and Chinese teas (0.59, 0.45 to 0.995) reduced the risk of PD.[123] Several epidemiological studies have identified dietary components as impacting the risk of developing PD. Total fat intake in general is not related to the risk for PD [124], but the intake of polyunsaturated fats appeared to be protective [125]. In a meta-analysis of nine studies, PD was inversely associated with α-linolenic acid (an omega-3 fatty acid found in seeds, nuts, and many common vegetable oils) (OR=0.81, 95% CI 0.68 to 0.96).[126] Omega-3 deficiency causes alteration of the dopamine mesocorticolimbic pathway, which is anatomically relevant to PD.[127] The traditional Mediterranean diet (i.e., high intake of vegetables, fruits, and olive oil; moderate intake of fish; low intake of meat; and a regular but moderate consumption of wine during meals) may be protective against the development of PD (OR=0.86, 95%CI 0.77 to 0.97) and delay PD age at onset.[128]

2.4.1.4 Coffee, smoking and alcohol consumption

Caffeine is an inhibitor of the adenosine A2 receptor which improves motor deficits in a mouse model of PD. This protection of dopaminergic neurons is supposedly related to removal of tonic inhibition by adenosine on dopaminergic neurotransmission. In a follow-up study for 30 years, nondrinkers of coffee had an increased risk of PD associated to nondrinkers of coffee compared to drinkers of coffee (≥28 oz per day, i.e. 8 dl brewed coffee) (OR=5.1, 95% CI 2.1 to 12.3).[129] A recent meta-analysis of 10 prospective studies confirmed the inverse association between use of caffeine and PD (0.67, 0.57 to 0.80).[130] Although numerous epidemiological studies have shown a reduced risk of PD among cigarette smokers, the underlying biological basis for the association is poorly understood. Proposed mechanisms include smoke stimulating dopamine release through nicotine, inhibiting free radical damage through carbon monoxide, and inhibiting of monoamine oxidase to protect against neuronal damage. In a large meta-analysis based on 44 case control studies and 4 cohort studies on the relationship between smoking and the risk of PD conducted in 20 countries between 1968 and 2001, a pooled relative risk of 0.59 (95% CI, 0.54-0.63) was calculated for ever smokers, and a relative risk of 0.39 (0.32 to 0.47) for current smokers.[131] Alcohol drinking is one of common lifestyle choices that can have significant effect on the development of PD. Compared to nondrinkers, daily alcohol drinkers had an almost 5-fold increase and daily green tea drinkers a 2-fold increase in association with hyperuricemia.[132] Urate is an effective antioxidant, free radical scavenger, iron chelator and ascorbate stabilizer. High plasma urate levels are known to slower PD progression.[133] PD patients have a significantly lower plasma uric acid level than the controls.[134] Beer, but not wine or liquor, contains a large amount of purine, which may work synergistically with ethanol to augment plasma urate. Epidemiological evidence shows that beer drinking is a protective factor (1 drink per day, OR=0.79, 95% CI 0.68 to 0.92) while liquor consumption is a risk factor (≥2 drinks per day, 1.35, 1.02 to 1.80).[135]

2.4.1.5 Brain-gut axis (BGA) and microbiota

The current data suggest that the underlying neurodegenerative process in PD affects the central (CNS), autonomic (ANS) and enteric nervous systems (ENS). LC has close connections with the Barrington nucleus that sends descending projections to the sacral parasympathetic command of the distal colon and bladder functions. The direct neural communication between gut and brain occurs via the vagal nerve.[136] Braak et al proposed that PD might originate outside of CNS, caused by a yet unidentified pathogen that is capable of passing the mucosal barrier of the gastrointestinal tract and, via postganglionic enteric neurons, entering the central nervous system along unmyelinated praeganglionic fibers generated from the visceromotor projection cells of the vagus nerve.[25] α-Syn in PD may self-propagate and spread progressively between interconnected brain regions via a cell- to-cell transmission mechanism. The direct experimental evidence show that α-syn can be transported via the vagal nerve to the CNS after the injection into the intestinal wall of adult rats.[137] PD may start in CNS and then spread toward ENS, or vice versa. The pathology can arise in both places with different time courses. α-Syn within ENS is not necessarily a pathological sign since it occurs regularly in adults with increasing age. Both central and peripheral derangements cause gastrointestinal dysfunction, which is present in over 80% of PD subjects. Gastrointestinal dysfunction includes constipation that occurs early in PD course and may predate motor features by several years.[138] Gut microflora are able to stimulate directly afferent neurons in ENS, to synthesize neurotransmitters and neuromodulators, and to upregulate local and systemic inflammation due to lipopolysaccharides (LPS). Activation of
the peripheral immune systems exacerbates the discordant central inflammatory response in aged or genetic predisposed brains. LPS may be seen as an environmental trigger which causes neuro-inflammation and α-syn misfolding to potentiate each other.[139] Interaction between microflora and GBA is bidirectional. GBA alters immune function, motility, intestinal permeability, and production of mucus and biofilm.[140] Clinical evidence of microbiota GBA interactions comes from the association of dysbiosis with central nervous disorders and functional gastrointestinal disorders, such as irritable bowel syndrome and PD.[141] The most compelling evidence of a GBA microflora interaction is the observation of the often dramatic improvement in patients with hepatic encephalopathy, after the administration of oral antibiotic neomycin.[142]. However, the causal relationship between the microbiota changes and the pathogenesis of PD remains unclear.

2.4.1.6 Nanocarriers and PD

The nanoneuromedicine is a broad area of research with enormous potential to address the malfunction of the nervous system. Nanoparticles, i.e. molecules that are smaller than 100 nm in size and endowed with special properties, cross easily the blood–brain barrier into the nervous system and retain the ability to achieve targeted delivery to appropriate brain or spinal cord subregions.[143] Nanodelivery of dopaminergic agonists improve brain uptake and reduce side effects associated with these compounds. As levodopa exhibits low oral bioavailability (30%) and very low brain uptake due to its extensive metabolism in the peripheral circulation, intranasal delivery of levodopa nanoparticles via the olfactory route and the trigeminal nerves is a promising novel drug delivery system.[144] Other targeting molecules include antioxidants, peptides, and neurotrophic factors per se or in combination.[145] Nanotoxicology is a new branch of toxicology that addresses the adverse human and environmental health effects associated with nanoparticles.[146, 147] Nanoparticles enter the brain primarily by inhalation, specifically by crossing into the brain through the olfactory nerves. In an animal model, manganese nanoparticle exposure was neurotoxic to dopaminergic neurons by inducing oxidative stress, modulating mitochondrial function and mediating the release of a number of proapoptotic factors to initiate the apoptotic cell signaling cascade.[148] Similar findings have been reported for copper oxide nanoparticles and the copper compound Casiopeina III-ia.[149]

2.5 Genetics and epigenetics

2.5.1 Multiple-hit hypothesis

Instead of the old stochastic acceleration hypothesis in which ageing (i.e. aging is the main risk factor for PD) directly sensitizes the dopamine system, recent investigation favours the multiple-hit hypothesis for PD. Collectively, the aging process, genetic mutation, and/or dysregulation of certain gene expression serve as a “priming” stimulus for microglia, and upon secondary stimulation (e.g., environmental toxin or viral infection), the primed microglia release excessive quantities of proinflammatory cytokines driving neurodegeneration.[139] After the antioxidant cellular defense systems are overwhelmed, initiation of mitochondrial dysfunction, iron accumulation or inflammation will induce or enhance the others through the generation of a synergistic self-feeding cycle that in time will end in apoptotic neuronal death. It is unclear why SN neurons are so particularly prone to carry-on this positive feedback loop.[150] The two-hit (neuroinflammation and mutant α-syn overexpression) progressive animal model was developed to mimic PD multifactorial etiology. The key features of PD were replicated in LPS-injected (inflammogen lipopolysaccharide) α-syn transgenic mice, but not in NS-injected (normal saline) transgenic mice or in LPS-injected wild-type mice, indicating synergistic effects of environmental stress and genetic predisposition in the pathogenesis of PD. Authors claim that persistent neuro-inflammation bridges α-syn pathologic alterations and progressive neurodegeneration in mediating chronic PD progression.[151] Systematic review of animal experiments ends in conclusion that peripheral inflammatory stimuli cause microglial activation. The mechanisms connecting systemic inflammatory challenge and microglial activation remain unclear, but the normal aging process is an important intrinsic factor inducing microglial senescence.[152]

2.5.2 Genetics

Current assumption is that 90% of PD cases are sporadic and cannot be attributed only to genetic factors.[153] A fraction of PD occurrence has a clear familial inheritance. At least 16 loci (designated as PARK1 to PARK16) and 11 genes have been associated with PD onset. The identification of genes such as SNCA or PARK1 encoding for α-syn (maybe involved in the regulation of dopamine release and transport), LRRK2 or PARK8 encoding for LRRK2 (or
network hubs were mostly related to compensatory responses to proteotoxic stress (one of these hubs was PARK14), in LC-PD (LC in PD patients) network hubs were linked to neuroprotection and brain homeostasis, although in the context of repairing/compensating various PD-associated cellular injuries, and in SN-PD (SN in PD patients) network the hubs displayed a very different landscape: six out seven hubs were associated with neurodegenerative processes. These results were compatible with the caudo-rostral model of PD progression.[157] Network medicine is sketched as “think globally, act locally” in pursuit of a comprehensive view of complex diseases. These are typically caused by combinations of molecular turmoil that might vary strongly in different patients, yet dysregulate the same component of a cellular system leading to the same phenotype.[158] A systems-based approach (using microarray, RNAseq, and label-free quantitative mass spectrometry on the same tissue samples) was used to reveal underlying transcript and proteomic changes common among unique brain regions affected during PD disease pathogenesis. Analysis of gene expression and proteomics revealed functionally connected pathways which correlated with the disease progression in SN, striatum, and cortex with increasing degrees of αsyn pathology in PD. Microarray and RNAseq experiments showed causal changes related to oligodendrocyte function and synaptic vesicle release. Massive cell death was not the driving force.[159]

### 2.5.3 Epigenetics

Epigenetics is referred to all changes in gene function that are mitotically and/or meiotically heritable and which do not entail a change in DNA sequence. Mechanisms comprise histone variants, posttranslational modifications of amino acids on the aminoterminal tail of histones, and covalent modifications of DNA bases.[160] A short exposure to environmental factors, such as metals and pesticides, prenatally or early in life could be memorized through epigenetic mechanisms long after the chemical trigger is gone. This could increase the vulnerability to effects of a second environmental factor (two-hit model).[161] PD could be initiated in utero according to Barker hypothesis for chronic diseases [162], and aging is only a time period where the second interaction happens. The role of DNA methylation and its links to PD pathogenesis is currently unclear. Hypomethylation of SNCA gene (the gene coding for αsyn) may be involved in the increased αsyn production via structural changes or overexpression of the protein, leading to protein aggregation or via impaired gene expression.[163] Mitochondrial toxins, like MPTP, paraquat, rotenone, or those overexpressing human αsyn, have revealed that aggregated αsyn translocates into the nucleus interacting with histones and inhibiting histone acetylation.[164] The histone deacetylase (HDAC) inhibitor protects dopaminergic neurons from αsyn toxicity by promoting inclusion formation, i.e. cytoprotective form, and decreasing the amount of αsyn oligomers (αsyn monomers are nontoxic).[165] The application of HDAC inhibitor (Trichostatin A which is an anti-cancer drug) was able to block the mitochondrial fragmentation, which is an early event during MPP+ induced neuronal apoptosis.[166] HDAC inhibitors therefore could provide potential therapeutic agents for neuroprotection in different neurodegeneration diseases.[167] Another epigenetic change in PD happens in microRNAs (miRNAs) which are a group of small noncoding RNAs that bind to the target mRNAs and mediate their posttranscriptional regulation leading to either degradation or translational inhibition, depending on the degree of sequence complementarity. A miRNA profiling of PD brains identified early downregulation of miR-34b/c which modulate mitochondrial function.[168] The use of complementary and alternative medicine (CAM) modalities has been proposed as an explanation to lower frequency of PD in Asia compared to the Western world. These can be divided into the following groups: 1) natural
products such as herbals, vitamins, minerals, and probiotics; 2) mind and body practices such as acupuncture, massage, meditation, movement therapies, relaxation techniques, tai chi, and yoga; 3) alternative systems such as traditional Korean or Chinese medicine, Ayurvedic medicine, and homeopathy. Despite centuries of experience using CAM, there is insufficient clinical evidence that any of these can improve motor function or delay disease progression in PD.[169]

2.6 Etiology

As molecular mechanisms involved in PD are still unclear, etiology is still under debate. Different causative monogenetic mutations likely explain only a small proportion of all PD patients and about 90% of cases are sporadic.

2.6.1 MPTP as a cause of Parkinsonian syndrome

MPTP was discovered by accident, when in 1982 an unfortunate, but fortuitous, accident happened in San Francisco. Four young drug users developed a rapidly progressive parkinsonian syndrome traced to intravenous use of a street preparation of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), an analog of the narcotic meperidine (Demerol). The “new” synthetic heroin contained a contaminant 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP).[170] The first hint however was obtained already in 1979 when a drug abuser had taken a batch that had been hurriedly prepared, injecting the derivative MPTP. Severe parkinsonian syndrome clinically indistinguishable from PD responded to levodopa. Postmortem examination showed severe loss of dopaminergic SN neurons.[171] MPTP is a lipophilic protoxin which crosses the blood brain barrier rapidly. Then it is converted by MAO-B into an intermediary called MPDP+. This intermediary undergoes rapid and spontaneous oxidation to MPP+, which is the toxic moiety. MPP+ is released into the extracellular space and taken up by the dopaminergic neurons. When MPP+ is taken up it triggers the production of ROS. Another mechanism of action of MPP+ is inhibition of complex I in the mitochondrial electron transport chain. This produces reduced availability of cellular ATP and a raise in ROS activity. Both mechanisms promote activation of cell death pathways. MPTP causes both acute and progressive cellular death but not LB bodies. Nowadays MPTP animal model is used to study central motor effects in PD. Unlike previous models of Parkinson’s-like syndrome, MPTP produces not only slowness of movement, paucity of movement, and rigidity, but also tremor. MPTP animals improve when given levodopa and have side effects of chorea with larger doses, similar to what happens to in people with PD.[172]

2.6.2 Could PD be an autoimmune/ inflammatory disease?

The evidence that viruses or other contaminating agents may be a cause of PD relates to the findings of coincident cases of PD which lie outside of the expected. PD clusters, i.e. the spatial and temporal pattern of excessive disease occurrence, indicate an important role for environmental causation in Parkinson disease. Clustering, or a cohort exposure phenomenon, has been reported in in residents of Israeli kibbutz’s[173], in a television crew, in a group of college teachers, and in garment workers of a manufacturing factory.[174] PD was associated with teaching (OR 2.50, 95% CI 1.67-3.74) and occupation in healthcare services (OR 2.07, 95% CI 1.34-3.20), and the increased risk supported the respiratory infection hypothesis.[175] Long considered to be an immune-privileged site because of the presence of the blood brain barrier and the lack of a lymphatic system, it is now accepted that the brain is fully capable of mounting an inflammatory response. The offending agent, e.g. MPTP, causes a long lasting immune response in the brain that persists many years after the insult has resolved[176], leading to a “hit and run” mechanism where the original insult is no longer present but the secondary sequelae, such as inflammation derived oxidative stress and cytokine dependent toxicity contributing to nigrostriatal pathway degeneration, persists. Neuro-inflammation in PD brains at autopsy is merely the end result of phagocytic microglia scavenging dead or dying dopaminergic neurons.[177] Over fourteen different viruses (e.g. influenza, Coxsackie, Japanese encephalitis B, western equine encephalitis, herpes and HIV) have been associated with both acute and chronic parkinsonism.[178] Influenza A virus was the etiological agent of the 1918 H1N1 pandemic. There are periodic exchanges of influenza virus genes or whole viruses between species, giving rise to pandemics in humans. The targets of neurovirulent influenza A virus are the SN, ventral tegmental area in the brainstem and the hippocampus.[179] In an animal model, cell counts of dopaminergic neurons in the SN 60 days after H5N1 infection demonstrated a 17% loss of dopaminergic neurons. The observed 17% reduction alone is not sufficient to cause PD, but it may make the brain more susceptible, especially in combination with other.
factors such as genetic, other environmental triggers, or simply old age. Influenza virus is supposed to enter the CNS via the olfactory epithelium (olfactory nerve), orofacial mucosa (trigeminal nerve) and digestive system (vagus nerve).

2.7 Symptoms in PD

For nearly 200 years the diagnosis of PD has remained essentially a clinical one, and it is important to recognize the symptoms and signs suggesting a parkinsonian syndrome. In the PD–UK PDS Brain Bank diagnostic criteria, the cardinal motor symptoms of PD include bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following: (i) 4–6 Hz rest tremor, (ii) muscular rigidity and (iii) postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction. There are fifteen exclusion criteria for PD, e.g. (vi) more than one affected relative and (viii) strictly unilateral features after 3 years, and eight supportive criteria for PD (three or more required for diagnosis of definite PD), e.g. (v) Excellent response (70–100%) to levodopa.

However, PD is a multifaceted disorder comprised of both motor and non-motor symptoms at all stages of the disease. The Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) is the most commonly used scale to assess the severity of PD symptoms. It has four parts: Part I (non-motor experiences of daily living nMEDL), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). nMEDL evaluates complex behaviors (Part 1A) completed by rater and other behaviors (Part 1B) completed by patient. Part 1A includes questions about cognitive impairment, hallucinations and psychosis, depressed mood, anxious mood, apathy and features of dopamine dysregulation syndrome. Part 1B includes questions about sleep, daytime sleepiness, pain and other sensation, urinary problems, constipation problems, lightheadedness on standing, and fatigue. E.g. question 1.7 Sleep problems is asked as “Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.” The five alternatives for the responses are: 0) normal, 1) slight, 2) mild, 3) moderate, and 4) severe.

2.7.1 Non-motor symptoms in PD

The non-motor symptoms (NMSs) of PD, often overshadowed, constitute a major clinical challenge. The NMSs of PD, including neuropsychiatric, cognitive, gastrointestinal and sensory, are observed not only in later stages but also in the early stages of PD. The NMSs seem to be present at onset, while some, like anxiety and depression can precede the motor symptoms, often by many years. The prevalence of NMS increases from 21% at the time of PD diagnosis to 88% after 7 years of disease duration. Some 90% have at least one NMS, whereas 10% of PD patients exhibit five NMSs.

2.7.1.1 Scales of Non-motor symptoms

In order to enhance the recognition of the non-motor symptoms in PD domain-specific instruments have been developed: 1) the Scales for outcomes, i.e. cognition, sleep, autonomic and psychiatric complications, in Parkinson’s disease (SCOPA) 2) the self-rated Non-Motor Symptoms Questionnaire (NMSQuest) with 30 items that detects the presence of non-motor symptoms and 3) the Non-Motor Symptoms Scale (NMSS) for the evaluation of severity and frequency of various domains of non-motor symptoms. The NMSQuest provides a comprehensive symptom assessment strategy of NMS in PD. NMSQuest is a screening tool designed to draw attention to the presence of NMS and initiate further investigation. Frequencies of 30 items varied from 4.9% (Bowel incontinence) to 66.7% (nocturia). E.g. Hallucinations occurred in 19.5% of PD patients, sad/blues in 44.7%, anxiety in 39.9%, daytime sleepiness in 28.4%, insomnia in 40.6%, intense vivid dreams in 30.9%, Acting out during dreams in 32.5% and RLS in 37.4%, respectively.

Among the 166 consecutive PD patients attending the outpatient clinic for PD, correlation between NMSQuest total score and duration of the disease was significant ($r=0.282; p=0.000$). Disease severity was not significant, e.g. daytime sleepiness 7.7% (H&Y 1-2) vs 9.6% (H&Y 3-4) $P=0.761$, insomnia 23.1% vs 34.6% $P=0.180$, vivid dreams 23.1% vs 21.2% $P=0.841$, RBD/acting out during dreams 26.9% vs 30.8% $P=0.706$, restless legs 24% vs 40.4% $P=0.041$, respectively.
The NonMotor Symptoms Scale (NMSS) is a clinically validated instrument that comprehensively assesses the burden of 30 NMS relevant in PD. [191, 192] It calculates a score for each NMS as a function of severity and frequency to reflect its burden. It is suitable for assessing a wide range of NMS and evaluating which ones clinically manifest differentially in PD patients. To date, there exist few case-controls studies using the NMSS to compare the NMS burden between PD patients and healthy controls. [193, 194] The overall NMS burden was significantly greater in non-demented PD patients compared to age- and sex-matched healthy controls, and increased NMS burden in PD applied to all domains of the NMSS, in line with previous studies. [195]

NMSS contains the following four questions on sleep and fatigue:

A) Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading).
B) Does fatigue (tiredness) or lack of energy (not slowness) limit the patient’s daytime activities?
C) Does the patient have difficulties falling or staying asleep?
D) Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?

Severity is defined as 0 =None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient. Frequency is scored as 1 = Rarely (<1/wk), 2= 1x /wk, 3=2-6x/wk, 4=every day. Multiplication of severity and frequency gives finally the total score of sleep/fatigue domain with values from 0 to 48 points.

It has been reported that non-motor symptoms of PD are not identified by neurologists in over 50% of consultations and sleep disturbance in particular is not recognized in over 40% of PD patients. [196, 197] A 15-year follow-up study of patients with PD reported that the NMS that did not respond to dopamine therapy (e.g. dementia, sleep disruption) were “more disabling than end-of-dose failure or dyskinesia” and were the major cause of morbidity and mortality. [198] These data confirm that the total burden of NMS is likely to be more important than the motor symptoms in determining the quality of life across all stages of PD. [199]

2.7.1.2 Sleep scales in PD

The Parkinson’s disease sleep scale (PDSS) [200] tried to provide a holistic and clinical assessment of the complex etiology of sleep problems in PD. The PDSS is a visual analogue scale addressing 15 items: overall quality of the sleep (1), sleep onset and maintenance insomnia (2-3), nocturnal restless leg syndrome (4-5), nocturnal psychosis (6-7), nocturia (8-9), nocturnal motor symptoms (10-13), sleep refreshment (14) and daytime dozing (15). The total PDSS score was associated with a longer PD duration, depression, and complications in the dopaminergic treatment (dyskinesia, wearing off). [201] In 2010, the movement disorder society recommended the use of PDSS, the SCOPA-sleep and the Pittsburgh sleep quality index (PSQI) for rating overall sleep problems. The Epworth sleepiness scale (ESS), the inappropriate sleep composite score (ISCS) and the Stanford sleepiness scale (SSS) were suggested for rating daytime sleepiness. [202]

The PDSS-2 is a revised version of PDSS, where daytime sleepiness (item 15) was replaced by a sleep apnea syndrome screening question (“Did you wake up at night due to snoring or difficulties with breathing?”). Visual analogue scale was changed to categorical answers, from 0 (never) to 4 (very frequent). [203] The PDSS-2 total score was correlated with impaired quality of life and motor impairment [203], and with the PSQI, ESS, Beck depression Inventory -II, Parkinson Fatigue scale, PDQ-39 summary index, all of the PDQ-39 domains and Unified Parkinson's Disease Rating Scale part III [204]. The factor analysis of PDSS-2 has derived three subscales: 1) motor problems at night (items 4-6, 12-13), 2) PD symptoms at night (items 7, 9, 10-11, 15), and 3) disturbed sleep (items 1-3, 8, 14). Limitations in PDSS-2 are still that RLS is screened with two questions (items 4-5) and RBD with one question (item 6: “Did you suffer from distressing dreams at night?”).

2.8 Sleep disturbances in PD

Sleep disorders were significant predictors of increased sleep complaints (difficulty falling asleep, frequent awakenings during the night, and early morning awakenings), depressive symptoms (Beck BDI-II), lower quality of life (PDQ-19), increased fatigue (MFSI-SF), and poorer cognition (MoCa). Results revealed a relationship between the number of sleep disorders (=RBD, RLS, PLM, OSA) per patient and reports of NMS (NMSQuest 30-item questionnaire). [205]
Sleep disturbances occur in 49 to 75% of PD patients.[206-208] In two multicenter observational studies of non-motor symptoms in PD, prevalence of clinically significant insomnia was 37 to 39%, EDS 21 to 23%, RBD 22 to 30%, RLS 15 to 16%, and intense dreaming 10.3%, respectively.[209, 210] According to estimates of sleep disorders in PD, 32 to 67% complained of difficulty falling sleep, 39 to 88% reported frequent awakenings during the night, and 23% reported early morning awakenings.[211, 212]

2.8.1 Insomnia

Insomnia is defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment.(ICSD-3) Individuals who report insomnia symptoms, i.e. problems with sleep initiation, sleep maintenance, early morning awakenings, and the subjective feeling of non-refreshing nocturnal sleep, in the absence of daytime impairment are not regarded as having an insomnia disorder. Daytime symptoms include fatigue, decreased mood or irritability, general malaise, and cognitive impairment.

Previous insomnia nosology promoted the concept that insomnia should be dichotomized to give a primary sleep disorder or a result of secondary form of sleep disturbance due to psychiatric, medical, or substance abuse disorder. However, in clinical practice differentiation among primary and secondary subtypes is impossible. Even when insomnia follows secondarily another clinically significant condition, it may develop an independent course over time and can stay put even though the primary clinical condition yielded to adequate treatment. Therefore, insomnia is now viewed as a comorbid disorder that warrants separate concern.

Likewise, subtyping of primary insomnia to psychophysiological insomnia, idiopathic insomnia, inadequate sleep hygiene, and paradoxical insomnia is no longer relevant. Experience has shown that there are no patients who exclusively meet the diagnostic criteria of any of these subtypes. There are now only three categories of insomnia: chronic insomnia disorder, short-term insomnia disorder (i.e. clinically significant sleep dissatisfaction or waking impairment without minimal frequency and duration criteria of chronic insomnia disorder), and other insomnia disorder (i.e. rare cases with insomnia symptoms to warrant clinical attention who fail to meet criteria for short-term insomnia disorder).

In the ICSD-3 criteria A–F must be met for Chronic Insomnia Disorder: (A) difficulties initiating sleep, maintaining sleep, waking up earlier than desired, resistance to going to bed, or difficulty of sleeping without caregiver intervention. (B) fatigue/malaise; attention, concentration, or memory impairment; impaired social, family, occupational, or academic performance; mood disturbance/irritability; daytime sleepiness; behavioral problems; reduced motivation/energy/initiative; proneness for errors/accidents; or concerns about or dissatisfaction of sleep. (C) sleep complaints are not explained by inadequate opportunity or circumstances for sleep. (D) symptoms occur at least 3 nights per week. (E) symptoms occur at least 3 months. (F) symptoms occur at least 3 months. (G) symptoms occur at least 3 months. (H) symptoms occur at least 3 months. (I) symptoms occur at least 3 months. (J) symptoms occur at least 3 months. (K) symptoms occur at least 3 months. (L) symptoms occur at least 3 months. In the ICD-10 [213] criteria (A) includes difficulties falling asleep, maintaining sleep or non-refreshing sleep. (B) Symptoms occur on at least 3 nights per week and for longer than one month. (C) The sleep problems cause marked personal distress or interference with personal functioning in daily. Noteworthy differences between ICSD-3 and ICD-10 criteria are the lack of waking up earlier than desired (criteria A) in ICD-10 and duration of disorder from one to three months. In the DSM-V criteria [214] waking up earlier than desired (criteria A) and duration of disorder at least 3 months are the same as in ICSD-3 criteria, but non-restorative sleep (criteria B in ICSD-3) is lacking. In spite of detailed instructions none of these classification systems define the frequency of maintaining sleep symptom. Chronic insomnia disorder is more common in women, and it is most likely due to age-related deterioration in sleep continuity. Disorder occurs in about 10% of the population, and transient insomnia symptoms in 30 to 35% of population. (ICSD-3 ref) In PD as mentioned before, prevalence of clinically significant insomnia is 37 to 39%. The problem with sleep initiation in PD patients is as frequent as in healthy elderly people, i.e. 32%. But sleep fragmentation (38.9 vs. 12%) and early morning awakenings (23.4 vs. 11.0%) are more common in PD. [211]

2.8.2 Excessive daytime sleepiness and fatigue

Excessive daytime sleepiness (EDS) is a common, approximately 15%, complaint among subjects aged 60 years and older. For men, EDS (defined as the Epworth Sleepiness Scale ≥10) increases with age from 5.1% for the age group 20-29 years to 29.0% for the age group ≥80 years. Likewise for women, the prevalence of EDS increases from 14.7% to 17.0%, respectively.[215] Also, fall rate elevates through age from 0.47 falls/year for those aged 70-74 years to 1.21 for
those 80 years and older. Men with falls, but not women, have an elevated death risk (OR 3.2; 95% CI 1.7 to 6.0).[216] Functional lower-extremity weakness (OR 1.66; 95% CI 1.20 to 2.29)[217] and impaired balance (2.44; 1.18 to 4.28) are the two most accurate singular predictors of fall risk [218]. However, in both sexes EDS (ESS≥10) is a significant independent risk factor for falls at least once in the past 12 months; men (OR 1.52; 95% CI 1.14 to 2.03)[219] and women (2.05; 1.21 to 3.49)[220].

The subjective EDS (ESS>10) occurs in 50 to 57% of patients with PD.[221, 222] Multiple sleep latency test (MSLT) is the gold standard to evaluate objective daytime sleepiness in central hypersomnia. Self-reported EDS (ESS>10) in PD yielded a sensitivity for MSLT below 8 minutes of 19.4%, and a specificity of 91.7%, with corresponding positive and negative predictive values of 66.7 and 56.9%, respectively. The poor correlation between ESS and MSLT means that these two measurements explore different components of sleepiness. At the moment, there is no good method to explore objective EDS in PD.[223] In another study, Arnulf et al found no correlation between MSLT score and polysomnographic parameters, such as total sleep time, sleep efficiency, arousal index, apnea-hypopnea, or periodic movement indices.[224] Therefore, there must be other factors, not only the quality of nighttime sleep, responsible for daytime sleepiness. The total dopaminergic drug dose is probably the best predictor of daytime sleepiness in PD.[222, 225] Sleep latency is correlated to subjective EDS (ESS>10) and objective EDS (MSL in MSLT <5min), and the amount of REM to objective MSL, whereas severity of PD (Hoehn and Yahr stage or UPDRS III) had no significant association to either EDS.[222] Also reduced activity of daily living most likely causes subjective EDS per se.[226] Yet today, reasons to EDS in PD remain still controversial.

Symptoms of fatigue include asthenia, debility, general physical deterioration, lethargy, and tiredness. The prevalence of substantial fatigue lasting six months or longer in middle-aged general population is 18.3%, and 1.4% of these with excessive tiredness attributed their symptoms to the chronic fatigue syndrome (i.e. 0.12% in the whole population).[227] In healthy elderly population, restricting fatigue, defined as staying in bed for at least half the day and/or cutting down on one's usual activities because of fatigue for at least 3 consecutive months, occurred in 31.1% of men and in 42.1% of women.[228] Although the prevalence of fatigue in PD is approximately 33 to 58%[229], there is no universally accepted definition of fatigue in PD. Fatigue is a subjective experience; what one person finds difficult to live with, another might better cope with. Several screening scales are available, but none meets the criterion of sensitivity to change in a study of PD.[230] Only the Parkinson Fatigue Scale (PFS-16), a 16-item scale patient-rating the physical aspects of fatigue and their impact on patient’s daily functioning,[231] is specific to PD.[232] Approximately one-third of patients with PD have distressing fatigue (PFS-16 ≥ 3.3), which is significantly associated with depression (Beck Depression Inventory. OR 3.137; 95% CI 1.228 to 8.012) and sleep disorders (PDSS. 1.833; 1.018 to 3.199), women (1.781; 1.026 to 3.092), and UPDRS total score (1.039; 1.018 to 1.059).[233] The Multidimensional Fatigue Inventory (MFI)[234] tries to measure independently five dimensions of fatigue, i.e. general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. In PD, physical fatigue and mental fatigue are independent symptoms needing separate assessment and treatment.[235]

### 2.8.3 Circadian disorders

The circadian timing system comprises an endogenous oscillator, i.e. the master circadian clock, in the hypothalamic suprachiasmatic nuclei (SCN), an entrainment agent and pathways that couple the internal clock to rhythms in physiology and behavior.[236] Entrainment (input) agents are primarily visual cues of light and darkness that are communicated along a pathway from the eyes to SCN. Other cues, that can influence the clock’s timing, include meals and exercise schedules. Glutamate is the main signal for photic entrainment. Coupling (output) pathways from SCN project primarily to nuclei within the hypothalamus.[237] In addition to the aforementioned circadian process, a homeostatic process monitors and responds to the quality and quantity of prior sleep and wakefulness. Melatonin and cortisol profiles are used as endocrine parameters to surrogate the central clockwork in vivo. In humans, chronotypes differ considerably. Extreme morning-types differ more than 8 hours from evening-types. Approximately 25% of the middle-aged working adults are “larks”, and 26% “owls”, respectively.[238] Subtypes of circadian rhythm sleep disorders are delayed sleep phase disorder, advanced sleep phase disorder (i.e. a person is “morning type” who goes to sleep and wakes up earlier than most people), jet lag disorder, shift work disorder, irregular sleep-wake rhythm, and free-running (non-entrained) type.

In PD, patients receiving dopamine therapy have a phase-advanced and amplitude-decreased melatonin rhythm.[239] The dopaminergic therapy delays sleep onset time relative to onset of melatonin secretion.[240] PD patients have a
sustained elevation of serum cortisol levels, reduced circulating melatonin levels, and altered peripheral clock gene expression.[241] Videnovic et al also reported a 4-fold reduction of melatonin secretion in PD patients, and PD patients with EDS had a significant 2.5-fold reduction in the melatonin rhythm amplitude compared with PD patients without EDS.[242] These data shows that alterations in the circadian system play some part in disturbing sleep in PD. Though, it is not known whether the alterations in peripheral circadian markers reflect a dysfunctional central clock. These findings can also mirror dysfunctional entrainment or coupling pathways of SCN. It is somewhat surprising that there are no reports on morningness/eveningness in PD.

2.8.4 Sleep disordered breathing

In epidemiologic studies, the prevalence of obstructive sleep apnea (OSA) defined at an apnea-hypopnea index (AHI) ≥5 is 22% in men and 17% in women. Only a part of subjects with OSA have symptoms of daytime sleepiness. OSA syndrome (OSAS), defined as AHI ≥5 and excessive daytime sleepiness, occurs in 6% of men and in 4% of women.[243] Since the prevalence of OSA increases with age and obesity, due to population aging and current obesity epidemic the reported prevalence rates of OSA have been increasing. The overall prevalence of mild to severe SDB (AHI ≥5) was 26% (95% CI 24 to 28) among general American population 30–70 years of age, moderate to severe SDB (AHI ≥15) was 10% (8 to 11), respectively.[244] The community-based Sleep Heart Health Study showed the prevalence of OSA steadily increasing with age and reaching a plateau after the age of 60 years.[245] Aging is per se associated with a decrease in the quality of sleep, and SDB, i.e., obstructive, central or mixed sleep apneas, may further disrupt the sleep architecture in older subjects. The apnea and hypopnea events of sleep-disordered breathing (SDB) have substantial immediate effects, such as intermittent hypoxia, fragmented sleep, and exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure. These in turn evolve into hypertension (OR 1.65 to 4.47 with OSA subjects with AHI ≥5 and ≥15)[246], coronary heart disease (OR 1.5 to 1.8, respectively)[247] and stroke (OR 3.30 with OSA subjects with AHI >36)[248], mild cognitive impairment or dementia (OR 1.85. AHI ≥15)[249], depression (OR 2.2. OSA diagnosis following PSG)[250] and PD (OR 1.84)[251].

Risk for SDB can be evaluated with two validated questionnaires.[252] The self-administered Berlin Questionnaire (BQ), consisting of ten symptom-items in three categories related to the risk of having SDB, predicts PSG-proven SDB (AHI >5) with a sensitivity of 68 to 86% and a specificity of 49 to 77%.[253] The sensitivity of the STOP-BANG (snoring, tiredness, observed apnea, and high blood pressure (STOP) and body mass index, age, neck circumference, gender (Bang)) questionnaire has a sensitivity of 82% and specificity of 48% (AHI >5).[255] Pulmonary function abnormalities in PD, such as subclinical upper airway obstruction due to rigidity and hypokinesia affecting the upper airway, restrictive lung disease, autonomic dysfunction and kyphoscoliosis reducing lung volumes, have been hypothesized to predispose patients to OSA.[257] High risk for SDB, assessed by BQ, was apparent in 49.3% of the PD patients and 34.8% of the controls (OR 2.81).[258] Retrospective clinical and polysomnographic study of PD patients showed SDB in 48% (AHI ≥5) and in 25% (AHI ≥15), wherefrom 12% had central SDB predominance and 88% obstructive SDB predominance.[259] However, selection of patients for PSG on the basis of sleepiness may have lead to overestimation of the overall frequency of SDB in PD. In another PSG study, the prevalence of OSA was 27% in PD patients, who did not display more sleep hypoventilation, stridor and abnormal central sleep apnea than in-hospital controls.[260] At the moment there is no conclusive evidence to support the relation between PD and the prevalence of OSA. A recent meta-analysis of five eligible studies showed a significant negative association between PD and the prevalence of OSA (OR 0.60, 95% CI 0.44 to 0.81). These results are primarily due to the lower BMI of PD patients when compared with the general population controls.[261]

2.8.5 Restless legs syndrome

Patients with restless legs syndrome (RLS) have complaints of odd sensations deep in their legs. From a historical point of view, already in 1685 the English physician and anatomist Sir Thomas Willis did pay attention to these symptoms. It took nearly 300 years, before the formal diagnostic criteria start with the seminal monograph “Restless Legs” by Karl-Axel Ekbom in 1945.[262] The disorder is now referred as RLS or as Willis-Ekbom disease (WED). Ekbom described the essential features in 1960. The first formal diagnostic definition saw daylight in 1979 with the publication of Diagnostic Classification of Sleep and Arousal Disorders, and the first official operational diagnostic criteria in 1990 (ICSD-1). A broad international consensus was achieved in 1995, when The International RLS Study Group (IRLSSG)
established “four minimal criteria” for RLS/WED that remain to this day the core of diagnosis. The next improvement was the replacement of confusing "motor restlessness" criterion by “urge to move” criterion. These criteria were published in 2003 as the “NIH/IRLSSG criteria”. The latest IRLSSG Consensus Diagnostic Criteria for RLS/WED (2012) has the same four essential criteria, except that they formalize the need to do a proper differential diagnosis and exclude mimics.[263] Four essential clinical features of RLS/WED are:

1. Urge to move the legs usually accompanied or caused by uncomfortable sensations in the legs
2. Worsening of symptoms during times of rest or inactivity
3. Partial or total relief of symptoms by movement
4. Symptoms only occur or are worse in the evening or night

The exclusion of mimics is important to the accurate diagnosis of RLS, since the specificity of the 4 criteria is 84%.[264] Common mimics include leg cramps, positional discomfort, local leg injury, arthritis, leg edema, venous stasis, peripheral neuropathy, radiculopathy, habitual foot tapping/leg rocking, anxiety, myalgia, drug-induced akathisia. Less common are myelopathy, myopathy, vascular or neurogenic claudication, hypotensive akathisia, orthostatic tremor, painful legs, and moving toes. RLS/WED may also involve other body parts, including the hips, trunk, and even rarely the face. Arm involvement is reported in 21–57% of cases. The symptoms may occur only unilateral, or are predominant in arms with little or no involvement of the legs. Thus the final diagnosis is confirmed by matching the patient’s history and symptoms with the IRLSSG diagnostic criteria, accompanied by the exclusion of secondary conditions.

RLS lacks a biomarker. Therefore, the recommended diagnostic instruments are the Hening Telephone Diagnostic Interview (HTDI) (2008), the Cambridge-Hopkins diagnostic questionnaire for RLS (CH-RLSq) (2009), and the RLS Diagnostic Index (RLS-DI) (2009).[265] A single question for screening RLS is: ‘When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?’[266] A conservative estimation of the prevalence is 2.4% for primary RLS and 1.5% for primary RLS sufferers (symptoms ≥2 per week with moderate-to-severe distress). Only 33% of the patients had a physician diagnosis of RLS.[267] A majority (85%) of patients with RLS report disturbances in sleep onset, sleep maintenance, and total sleep time. RLS is a circadian disorder with symptoms culminating between midnight and 2 am.[268] Although exact pathophysiology of RLS remains unknown, dopaminergic dysfunction and brain iron deficiency have long been regarded as the key culprits.[269]

The significance of RLS in PD is controversial. Idiopathic RLS (iRLS) and PD are likely to be distinct entities.[270, 271] The prevalence of RLS symptoms in PD ranges from 11 to 24% in Europe.[272, 273] PD patients with RLS (PD-RLS) had a lower prevalence of family history of RLS, higher age at onset of symptoms, poorer response to dopaminergic treatment, and smaller periodic limb movements index measured by polysomnogram than in iRLS subjects.[274] Subjects with iRLS had SN hypoechogenicity assessed by transcranial brain sonography, while subjects with RLS-PD had typical SN hyperechogenicity seen in PD.[275]

In a prospective longitudinal cohort study of male health professionals aged 40 to 75 years, frequent RLS (symptoms ≥15 times per month) was associated with higher risk of PD within 4 years of follow-up (OR=2.77, 95% CI 1.08 to7.11) but not within full 8 year follow-up, suggesting that RLS was an early feature of PD, not a risk factor.[276] This data support the hypothesis that PD-RLS is a different entity from iRLS. On the other hand, in previously unmedicated early PD patients derived from a population-based incident cohort, the frequency of RLS in PD did not differ from controls. Instead the leg motor restlessness (LMR), defined as urge to move the legs, though not fulfilling the minimal RLS criteria, occurred with a near 3-fold higher risk (OR=2.84, 95% CI 1.43 to 5.61) Authors conclude that LMR and RLS can either be two different entities, or represent overlapping features within the same spectrum of motor restless id PD.[277] RLS occurring in these patients could be related to dopaminergic therapy for PD.[278] Sometimes long-term treatment with dopaminergics leads to the problematic complication of augmentation, a phenomenon in which the medication induces a worsening of symptoms beyond the level of severity that was experienced when the medication was first given.[279] Whether PD-RLS exists ipso facto, or possibly results from dopaminergic augmentation is a recent matter of debate if RLS improves with reducing dopamine drugs, then it is the case of augmentation. LMR patients can go on to develop full diagnostic criteria of RLS. LMR of PD could be like mild cognitive impairment in relation to AD. [280]
2.8.6 Narcolepsy like syndrome

Diagnostic ICSD-3 criteria of narcolepsy type 1 (narcolepsy with cataplexy) consist of two criteria. The patient must have daytime sleep attacks. Secondly the patient has both cataplexy and short sleep latency on daytime MSLT with two or more sleep onset REM periods, or reduced CSF hypocrein-1 concentration. Patient of narcolepsy type 2 (narcolepsy without cataplexy) has also daytime sleep attacks and the same MSLT findings as in narcolepsy type 1. Additionally, CSF hypocrein-1 is not changed, cataplexy lacks, and hypersomnia is not explained by other causes, such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.[281]

In PD, sleep attacks (i.e. sleep episodes without prodroma) occur infrequently.[282] Dozing off unexpectedly can be used as rude estimate of sleep attacks. The prevalence of sudden onset of sleep while driving is 3.8%, after the diagnosis of PD.[283] On MSLT, 39% of the PD patients with excessive daytime sleepiness show a specific narcolepsy-like phenotype (sleep latency lesser than 10 minutes, and two or more sleep-onset REM periods).[224] Bliwise et al examined REM sleep during daytime Maintenance of Wakefulness Testing (MWT) and polysomnography in 63 patients with early or mid-stage PD. MWT was performed a full-day test that consisted of four opportunities for naps, each 40 minutes long, during which the entire period was recorded, regardless of whether sleep occurred. The sleep efficiency was calculated as the proportion of the 40 minutes in which the patient was asleep. Two thirds of patients had naps without REM with SE 19%, whereas 16% of participants had one REM (SE 41%) and 17% had two or more REMs (SE 47%), respectively. In 74% of daytime nap opportunities, the REM period occurred within 15 minutes of the first 30 second epoch of sleep.[284] CSF hypocretin-1 levels are not reduced in PD.[285] Cataplexy-like symptoms have not been reported to occur in PD.[286] Hallucinations occur in 59% of narcolepsy type 1 patients, in 28% of narcolepsy type 2 patients, and in 26% of PD patients, respectively. Compared to PD group, hallucinations in narcolepsy are less often minor, and more often auditory.[287] Shortly, narcolepsy-like symptoms in PD resemble symptoms in narcolepsy type 2.

2.8.7 Parasomnias

The three states of human consciousness are wake, NREM sleep, and REM sleep. Under normal physiologic conditions with homeostasis and circadian rhythm these states are stable and predictable. However, if sleep-wake cycle oscillates the state of consciousness can enter into a temporary unstable state of dissociation. Sleep and wake change from distinct dichotomous states to a spectrum of states. Disorders of arousal are an admixture of wake and NREM sleep, and RBD of REM sleep coupled with either wake or NREM sleep, respectively.

2.8.7.1 REM sleep parasomnias

Parasomnias, undesirable physiological events, are defined as state dissociations that can occur in any stage of sleep, or during transitions to and from sleep. According to the latest classification (ICDS-3) there are listed ten core categories of parasomnias. The first three sleep disorders are classified as REM sleep parasomnias, namely REM sleep behavior disorder (RBD), recurrent isolated sleep paralysis, and nightmare disorder.

Isolated sleep paralysis is a hypnopompic period accompanied by terrifying hallucinatory phenomena, whereas in narcolepsy and familial sleep paralysis, the episodes are more hypnogogic. During a discrete period of time lasting approximately four minutes voluntary muscle movement is inhibited, yet ocular and respiratory movements are intact and one’s sensorium remains clear. Lifetime episodes of sleep paralysis are a fairly common experience with 7.6% occurrence of the general population.[288] The etiology of isolated recurrent sleep paralysis is unknown. Nightmare or dream anxiety attack is a disturbing mental experience that usually awaken the dreamer from REM sleep. For three hundred years, from about 1450 to 1750, these false ideas, i.e. incubus, vampire, werewolf, devil and witchcraft were fused together and reached their acme of importance. Then in 1753 Bond's An Essay on the Incubus or Nightmare, the essential three components were stressed: (1) agonizing dread, (2) a sense of oppression or weight at the chest that interferes with respiration, and (3) a conviction of helpless paralysis. The scientific name for this condition, nightmare denoted a lewd demon who visits women at night, lies heavily on their chest and violates them against their will. These visitors of women were called Incubi (French follets; Spanish duendes; Italian folletti; German Alpen); those of men were called Succubi (French soulièves). The belief that sexual intercourse can occur between mortals and supernatural beings, is one of the most widespread of human beliefs.[289] The sexual theory of the nightmare was
significant in the development of psychoanalysis. However, the historical roots of this particular conception are too numerous to allow of their being traced here. The Finnish prevalence of frequent nightmares is 4.2%, and occasional 40.0%, respectively. The frequent nightmares correlate to advancing age. The sex difference of nightmare prevalence is age-dependent. While young women reported nightmares significantly more often than young men, this difference disappears at approximately age 60 years for both frequent and occasional nightmares. The finding that women have a higher dream recall frequency in general does not explain why men report more nightmares as they age. High levels of androgens could act as a protective factor against nightmares explaining part of the of the sex difference. [290]

RBD is discussed separately.

2.8.7.2 NREM parasomnias

The NREM parasomnias are disorders of arousal from NREM sleep, with impaired sleep–wake transitions that can result in activation of physiologic systems. The four NREM parasomnias are sleepwalking, confusional arousals, sleep terrors and sleep related eating disorder which may occur when the transition from slow-wave sleep to wakefulness is disrupted. Partial or total amnesia for the episode is present, and parasomnia usually occurs during the first third of the major sleep episode. The prevalence of sleepwalking occurs up to 4.3% in adults, confusional arousals among adults up to 4.2%, night terrors in 1% of elderly people over 65 years. [291] Two pathological processes lead to disorders of arousal. First, phenomena such as sleep deprivation, circadian misalignment and sedative hypnotic medication, that deepen sleep and enhance sleep inertia promote NREM parasomnias by impairing otherwise normal arousal mechanisms. Second, conditions such as pain, noise, and RLS/PLM, which cause repeated cortical arousal lead to NREM parasomnias through sleep fragmentation. Obstructive sleep apnea and orexin dysfunction can act in both ways. [292]

The sleep walking begins with an abrupt onset of motor activity arising out of slow wave sleep during the first 1/3 of sleep. Episodes generally last less than 10 min. There is a high incidence of positive family history. Injuries and violent activities have been reported during sleepwalking episodes but generally individuals can negotiate their way around the room. The eyes are usually wide open during an episode with a confused “glassy” stare, in contrast to RBD where the eyes are usually closed during an episode. The episodes are four to nine times more common in patients with Tourette syndrome or migraine headaches. Somnambulism may be associated with abnormalities of the metabolism of serotonin. [293] Of 165 consecutive patients with PD seen for 2 years, 6 patients with adult-onset sleep walking were identified giving the 3.6% prevalence of sleep walking in PD. [294] The neural mechanisms underlying this condition remain poorly understood. Using functional neuroimaging with SPECT during wakefulness, adult sleepwalkers have decreased regional brain perfusion in the in posterior association cortices, namely the inferior temporal cortex bilaterally, after sleep deprivation. That being said, the exact contribution of the inferior temporal cortex to the pathophysiology of sleepwalking remains unclear. [295]

In confusional arousals individual is disoriented in time and space, with slow speech, diminished mentation, and poor reactivity to environmental stimuli; attempts to awaken the person are often unsuccessful and may be met with vigorous resistance. There is prominent anterograde and retrograde memory impairment. Most episodes last from a few to 15 minutes. [293] A case report describes an epilepsy patient who underwent a personalized investigation in which intracerebral implanted electrodes were used to define the epileptogenic area for surgical purposes. During an episode of confusional arousal, the motor and cingulate cortices were precociously activated (allowing motor output), while the frontoparietal associative cortices continued to maintain a sleep pattern. Since some brain networks can exhibit sleep patterns while others exhibit wake-like activities, one may speculate that typical features of the confusional arousal could be explained as an activation of amygdalo-temporo-insular areas disengaged from the prefontal emotional activation control cortex paralleled by the deactivation of the hippocampal and frontal associative cortex (annesia for the event). [296]

Sleep terrors are characterized by a loud piercing scream or cry for help, intense autonomic activation (e.g., tachycardia, tachypnea, flushing of the skin, diaphoresis, mydriasis) inconsolability, and overwhelming anxiety or acute panic. Facial expressions often reflect intense fear. These reactions may be followed by agitated motor activity such as hitting the wall or running about as if reacting to imminent danger. Attempts to escape from bed can result in harm to the patient or others. Historically, they were confused with nightmares. Gastaut and Broughton (1965) first observed polysomnographically that sleep terrors were not associated with REM sleep but rather occurred suddenly during SWS. Sleep terrors can be readily distinguished from sleep walking and confusional arousals in children but not as easily in
adults, who show considerable overlap among the disorders of arousals as well as between these disorders and RBD.
Parasomnia overlap disorder should be diagnosed if sleep terrors or sleep walking occur with RBD. [293]
Sleep related eating syndrome consists of recurrent episodes of involuntary eating and drinking during arousal from
sleep with problematic consequences. Level of consciousness during these episodes ranges from partial consciousness
to dense unawareness typical of somnambulistic episodes. On the other hand, the night eating syndrome shows
hyperphagia episodes at full arousal from nocturnal sleep without accompanying amnesia. Self-reported prevalence of
night time eating in a large community study was 1.6% among young women. [297] The prevalence rate of sleep related
eating disorder in narcolepsy patients with cataplexy (32%) [298] and in RLS patients (33%) [299] is similar. These
findings tentatively attribute to an underlying common abnormality in dopaminergic metabolism. The nocturnal eating
could be viewed as a non-motor feature of restless legs syndrome. [299] This parasomnia is also different from binge
eating disorder described as part of impulse control disorder in PD patients. Patients with binge eating have
uncontrollable consumption of food throughout the day, but have full consciousness during eating. The prevalence of
binge eating disorder in PD is 4.3%. [300]

2.8.7.3 Other parasomnias

The third category of parasomnias classified as “other parasomnias” include sleep-related dissociative disorder, sleep
enuresis, exploding head syndrome, and sleep related hallucinations. In sleep-related dissociative disorder, a dreamlike
mentation emerges during waking consciousness thereby causing dissociative symptoms with experience of
depersonalization or amnesia. Patient's clinical features may support a specific dissociative disorder subtype diagnosis
associated with sleep-related episodes, specifically dissociative identity disorder, dissociative fugue, or dissociative
disorder NOS. Psychogenic non-epileptic seizures (pseudoseizures) can be characterized by their dissociative nature.
Although pseudoseizure patients usually experience amnesia for the period of an attack, it is yet controversial whether
their memories can be recalled under hypnosis with the hypothesis that amnesia is of psychogenic origin. [301]
Sleep enuresis is characterized by recurrent involuntary urination during sleep that occurs at least twice a week, for at
least 3 consecutive months. Three factors are considered important in the pathogenesis of bedwetting, i.e. disorders of
arousal from sleep, nocturnal polyuria (a delay in achieving the circadian rise in arginine vasopressin), and reduced
nocturnal bladder capacity. [302] In community-dwelling older adults aged 65 to 79 years, the prevalence of nocturnal
enuresis was 2.1%. [303] In comparison with enuresis, nocturia (i.e. voids at least 2 times per night) occurs in about
40% of men and in 25% of women at the age group 60 to 69 in Finland. [304]
Exploding head syndrome is a rare phenomenon characterized by a sense of explosion in the head, confined to the hours
of sleep, which is harmless but very frightening for the sufferer. The phenomenon was reported initially in 1920s and
coined in 1980s. [305]
Sleep-related hallucinations are hallucinatory experiences, principally visual, that occur at sleep onset (hypnagogic
hallucinations) or on awakening from sleep (hypnopompic hallucinations). In general population, the prevalence is 37%
for hypnagogic hallucinations, and the equivalent reported prevalence for hypnopompic hallucinations is 13%. [306]
Sleep-related hallucinations are often vivid and terrifying, and are also recalled clearly; they are not perceived as
dreams. Complex nocturnal visual hallucinations represent a well-defined syndrome characterized by nocturnal visual
hallucinations that occur upon waking during the night. The hallucinations seem to occur immediately after an arousal
from NREM sleep. [307] Night time hallucinations in PD is a poorly described condition. There seem to be three
mechanisms underlying complex visual hallucinations: 1) Epileptic hallucinations are probably due to a direct irritative
process acting on cortical centres integrating complex visual information. 2) Visual pathway lesions cause defective
visual output and may result in hallucinations from defective visual processing or an abnormal cortical release
phenomenon. 3) Brainstem lesions appear to affect ascending cholinergic and serotonergic pathways, and may also be
implicated in PD. From these mechanisms the third is often associated with sleep disturbances. [308] Predictors of visual
hallucinations in PD patients are supposedly sleep disorders and visual disturbances. [309] In a 10-year longitudinal
study of patients with PD, the prevalence of hallucinators increased from 33% at baseline to 63% at 10 years. In
contrast to hallucinations, sleep abnormalities varied in their progression over time. At baseline, 81% had at least 1
sleep abnormality (sleep fragmentation 58%, vivid dreams/nightmares 43%, daytime sleepiness 36%, and acting out
dreams 12%). At the end of 10 years, the only significant increase related to acting out dreams: 12% at baseline and
33% at 10 years. [310] As sleep fragmentation or vivid dreams/nightmares and hallucinations in PD seem to have
different pathophysiologic aberrations, sleep problems and hallucinations are now considered as completely separate
issues. [311]
2.8.7.4 Isolated motor phenomena and symptoms of sleep

Additionally to these, parasomnias may be due to drug, other substance, or medical condition. Among isolated motor phenomena and symptoms of sleep are sleep talking, sleep bruxism, and nocturnal sweating. Somniloquy or sleep talking is now coded among isolated symptoms, “apparently normal variants and unresolved issues”, given its high frequency of occurrence in normal sleep or within parasomnias such as sleep walking and RBD or obstructive sleep apnea. Somniloquy is reported by 24% of normal adults without apparent sex difference. In general, 20–25% of speech are associated with REM sleep and 75–80% with NREM sleep. There is a strong association between sleepwalking, night terrors, and somniloquy.[307] Somniloquy may be a prodrome of RBD.[312] Sleep-dependent memory consolidation has been studied in RBD patients. After a learning episode, memory consolidation occurs during sleep. Procedural memory predominantly benefits from REM sleep whereas hippocampus-dependent declarative memory benefits particularly from NREM sleep. The main hypothesis states that the neural traces encoding newly acquired information are reshaped and strengthened via reactivation processes during sleep. Over 60% of RBD patients talk in their sleep, and the learned material could be orally reprocessed during sleep talking. The consolidation of verbal declarative memory was found to occur normally during sleep in patients with RBD. [313] In sleep medicine, bruxism has been described as a sleep related movement disorder, associated with simple repetitive movements and transient arousals during sleep. In dentistry, sleep bruxism has been described as a parafunctional activity associated with clenching, bracing, and grinding of the teeth. The prevalence of reported sleep bruxism in adults is 8%, declining from childhood (14%) to persons over age 65 years (3%).[314] The bruxism is not probably associated with PD[315], but perhaps more likely with RLS[316] or cranial-cervical dystonia[317].

In sleep hyperhidrosis, more commonly known as “night sweats”, profuse sweating occurs during sleep and requires the patient to change the bedclothes. The classification is no longer in the group of miscellaneous secondary parasomnias. Hyperhidrosis is estimated to affect about 3% of the general population affecting both men and woman equally.[318] The pathophysiology of hyperhidrosis is poorly understood, however, dysfunction of the sympathetic nervous system is postulated. The “Harlequin syndrome” is an autonomic syndrome where there is a sudden appearance of flushing or sweating limited to one side of the face.[319] Lombardi et al has reported two patients with Harlequin syndrome and sleep disorders (sleep paralysis, disorder of arousal, hypnagogic hallucinations, and RBD) in the form of overlap parasomnia syndrome.[320]

2.8.8 REM Sleep Behavior Disorder

2.8.8.1 Diagnosis of RBD

The clinical features of RBD consist of a history of recurrent nocturnal dream enactment behavior. The primary aspects of dream enactment behavior can be divided to abnormal vocalizations, abnormal motor behavior, and altered dream mentation. The vocalizations in RBD tend to be loud and suggest unpleasant dream mentation. Shouting, screaming, and swearing are common, and are often described as being very unlike the typical soft-spoken nature of the person's tendency to speak during wakefulness. The motor activity often begins with some repetitive jerking or movements, followed seconds later by more dramatic and seemingly purposeful activity such as punching, flailing as if to protect oneself, running, jumping out of bed. It is during these behaviors that injuries to patients and their bedpartners can occur. Most patients view their dreams as nightmares, and the dream content often involves insects, animals, or people chasing or attacking them or their relatives or friends; the patient is almost always the defender and not the attacker. Many patients are able to recount the content of their dreams upon being awakened at the time of the behavior. The vocalizations and behaviors that are exhibited are strikingly consistent with the content of the dreams later reported by the patient -- the behaviors mirror the dream content.[321] The characteristic electrophysiologic finding in patients with RBD is REM sleep without atonia. The SINBAR Group (Sleep Innsbruck Barcelona) published normative values for EMG detection in RBD and suggested that using a polysomnography montage quantifying “any” (either tonic or phasic twitching) EMG activity in the mentalis muscle and phasic twitching EMG activity in right and left flexor digitorum brevis muscles in the upper limbs with a cutoff of 32%, using 3-sec miniepochs, or 27%, using 30-sec epochs. These cutoff values are the same for the idiopathic form of
RBD and RBD in the setting of PD, in regards to distinguishing RBD patients from controls. Polysomnograms performed to diagnose RBD typically include EEG leads to rule out seizure activity. Definition of REM sleep without atonia (RSWA) includes aforementioned EMG findings. Propable RBD is a clinical diagnosis with a history of recurrent abnormal and disruptive sleep behavior with injuries or the potential for injury. The definitive RBD diagnosis consists of the presence of RSWA and propable RBD, and the absence of EEG epileptiform activity during REM sleep. The frequency of dream enactment behavior also varies widely from every night (presumably during most or all episodes of REM sleep) to no more than one night per month. Also clustering occurs, with RBD occurring nightly for a week and then going months with little or no RBD, and then RBD occurring frequently some time later. It is not known why the frequency varies so broadly.

2.8.8.2 Screening questionnaires of probable RBD

Several RBD questionnaires have been developed to screen RBD. The term of probable RBD can be used when questionnaires are shown to be adequately sensitive and specific for RBD based on PSG validation. Stiasny-Kolster et al. developed REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), which is a 10-item patient self-rating questionnaire (maximum total score of 13 points) with a cutoff of five points, yielded a sensitivity of 96% and a specificity of 56%.

The RBDSQ-HK questionnaire, a self-administered (by patient and/or bed partner), comprised 13 questions which are all assessed on lifetime occurrence and recent 1-year frequency. Additionally, seven questions (Q6–Q12) were weighted due to the clinical importance of behavioral manifestations of RBD, and the total score had a range from 0 to 100. The best cut-off score for the overall RBDSQ-HK questionnaire (18/19) gave the sensitivity of 82% and the specificity of 87%.

Mayo Sleep Questionnaire (MSQ), a 16 item measure to screen for the presence of RBD and other sleep disorders, includes a core question on recurrent dream enactment which yielded the sensitivity of 98% and the specificity of 74%. Four additional sub-questions on RBD and one question on obstructive sleep apnea improved specificity.

The REM Sleep Behavior Disorder Single-Question Screen (RBD1Q) consists of a single question, answered "yes" or "no," as follows: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?" The sensitivity was 94% and the specificity of 87%.

The Innsbruck RBD inventory (RBD-I) consists of five questions: 1) Do you dream of violent or aggressive situations (e.g., to have to defend yourself)? 2) Do you scream, insult, or curse during your sleep? (Note: this does not include normal sleep talking.) 3) Do you move out of your sleep and occasionally perform "flailing" or more extensive movements? 4) Have you ever injured or nearly injured yourself or your bed partner while you were sleeping? 5) Are the above-described movements out of your sleep occasionally or always in line with the content of your dreams? (items 2, 3, 4) The cutoff of 0.25 (number of positive symptoms divided by number of answered questions) yielded the sensitivity of 91% and the specificity of 86%. Frauscher et al evaluated also the diagnostic value of a single, "yes" or "no" answer, RBD summary question: "Do you kick or hit during your sleep because you dream that you have to defend yourself?" (German: "Kommt es vor, dass Sie, während Sie schlafen, um sich treten bzw. schlagen, weil Sie träumen, sich zur Wehr setzen müssen?"). The sensitivity of RBD summary question was 74%, whereas and specificity was 93%.

All these questionnaires are excellent screening tools for detecting the presence or absence of RBD. The high sensitivity values probably reflect the rather unique features of RBD.

2.8.8.3 Epidemiology of RBD

There is no solid data on the prevalence of RBD The only published epidemiologic data on parasomnias in the general population with relevance to RBD found 0.8 to 2% reported histories of sleep-related injury or violent behaviors during sleep. From these participants 0.38 to 0.5% reported features highly suggestive of RBD. These two studies have thus formed the basis for the current estimated prevalence of RBD. Most patients with RBD are male. Onset of symptoms varies widely, although most develop symptoms in the 40-70 age range.
2.8.8.4 Etiology of RBD

The brainstem nuclei that control REM sleep are often involved early in the natural history of synucleinopathies (i.e. Parkinson’s disease, dementia with Lewy bodies, multiple system atrophy, and pure autonomic failure). The premotor interval between the onset of RBD and the parkinsonian triad of resting tremor, bradykinesia, and cogwheel rigidity varies from months to decades.[321] Different case series all demonstrate that 18 to 38% of idiopathic RBD patients convert to a synucleinopathy disorder 5 years after the diagnosis of iRBD[330-332], the 10-year risk was 41 to 76%, and the 14-year risk was 52 to 91%[331, 332], respectively.

As idiopathic RBD can last up to 20 years without other neurologic symptoms[333, 334], it is still speculative whether all or only some of RBD patients represent a manifestation of an early neurodegenerative disorder. RBD has been associated with other non-synuclein neurodegenerative etiologies, such as tauopathy related parkinsonian syndromes (Progressive supranuclear palsy, Guadaloupean parkinsonism), TDP-43opathies (frontotemporal dementia, amyotrophic lateral sclerosis), amyloidopathies (AD), spinal cerebellar ataxia type 3 and Huntington’s disease.

However, these conditions are not typically preceded by RBD but instead develop RBD coincidentally or later on during the progress of disease. Also, the prevalence rates of these conditions are much lower as compared to synuclein disorders.[292]

RBD has also been associated with impaired orexin function. Up to 50% of narcolepsy patients also have RBD symptoms. Orexin, a neuropeptide secreted from the lateral hypothalamus promotes state (wake, NREM, REM) stability and prevents frequent transitioning. When deficient, such as in narcolepsy, REM-wake instability arises with wake-like motor activity in parallel to REM dream mentation.[335]

RBD can be induced by toxic effect. Many serotonergic agents, as well as excessive alcohol and caffeine us, have long been noted to acutely precipitate or exacerbate RBD. Implicated medication classes include: tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors, serotonin-specific reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and an and an acetylcholinesterase inhibitor.[336] The diversity of pharmacological mechanisms confirms that various pathways can lead to RBD. In animal models, both toxic effect of MPTP to dopaminergic neurons[337] and impaired glycine and GABA-A activity[338] triggers RBD.

RBD has occasionally been associated with local lesions from various vascular, demyelinating, and traumatic etiologies. Cranial imaging typically demonstrates pontine tegmentum pathology.[339]

2.8.8.5 Pathogenesis and pathophysiology of RBD

Although many specifics are unknown, a dysfunction of one or several neuronal pathways in the brainstem probably causes the pathogenesis of RBD.[340] The main component of the REM-generating circuit, the subcoeruleus nucleus (SubC), is localized at the mesopontine junction, medial to the trigeminal motor nucleus and ventral to the LC. TheSubC is composed of cells that are predominantly active during episodes of REM sleep. Another component of the REM-generating circuit is located in the medulla. The dorsal GABAergic paragigantocellular reticular nucleus (DPGi) is also REM-active and inhibits wake-promoting areas producing REM sleep. DPGi inhibits the LC, dorsal raphe (DR), and part of the ventrolateral periaqueductal gray (vLPG). GABAergic neurons of the vLPG region are divided into two subpopulations – REM-active and REM-inhibiting. REM-active neurons of vLPG silence wake-promoting neurons of the LC and DR. The transition into REM sleep is induced, when both direct cholinergic activation (i.e. cholinergic neurons of the laterodorsal (LDT) and pedunculo-pontine tegmentum (PPT)) and GABAergic inhibition activate SubC. Descending SubC projections recruit both GABA and glycine neurons in the ventromedial medulla (VMM) and spinal cord motoneurons, which causes atonia of skeletal muscles in REM sleep. Both GABA and glycine inhibition of motoneurons are required. Abnormal activation of this circuit leads to cataplectic attacks in awake narcoleptic patients, and abnormal deactivation leads to over-expression of motor activity during REM sleep both in sleeping narcolepsy and RBD patients.

The mutual interaction between brainstem structures (i.e., the SubC, PPT/LDT, vLPG and DPGi) constitute the REM-generating network. In summary, the most important nucleus is glutamatergic SubC which is the central part that coordinates the entrance, maintenance, and exit from REM sleep.

In addition to the brainstem, hypothalamic and forebrain structures project to and influence the core of the REM sleep circuit. Melanin-concentrating hormone (MCH) neurons of the lateral hypothalamus (LH), GABAergic neurons of the basal forebrain (BFB) and GABAergic neurons of the extended ventrolateral preoptic area (eVLOP) are REM-active.
At the moment we know much too little how these different brain regions interact and we lack the information why these circuits are vulnerable to degeneration or pathological recruitment. The link between the limbic system and REM sleep circuits is not yet examined. Pharmacological studies show that GABAA receptor agonism and antagonism of the amygdala decrease and increase (respectively) REM sleep, application of serotonin during NREM sleep produces rapid transitions into REM sleep, and cholinergic excitation increases the frequency of REM episodes.[341] There is minimal direct evidence to implicate the substantia nigra or dopaminergic dysfunction in RBD pathophysiology.[321] However, the strong association between RBD and synucleinopathies, data on lower brainstem structures being commonly affected in synucleinopathies, and data on MPTP destroying selectively dopaminergic neurons in the substantia nigra causing clinically progressing Parkinson syndrome suggest that the dopamine dysfunction may also be involved in the pathophysiology of RBD.
3. AIMS OF THE STUDY

Albeit sleep is affected in over 50% of PD patients, sleep disorders are often omitted from analyses of PD’s putative risk factors, pathophysiology and clinical course. The objective of the present study is to demonstrate the clinical significance of sleep that has long been overshadowed by motor and other non-motor signs. In the following examples sleep disorders are divided in six:

Parasomnias have gained a lot of interest since the discovery of synucleinopathies, e.g. PD and RBD. Up to 38% of patients with idiopathic RBD convert to synucleinopathies. Parasomnia overlap syndrome is a rare disorder including RBD and sleepwalking. However, classification of parasomnias consist also other states of consciousness. We wanted to examine the relationships between RBD and other parasomnias and isolated sleep symptoms. (Publication I)

Enigma of RBD associating both with PD and narcolepsy deserves to be studied in more detail. Cataplexy like symptoms have not been reported to occur in PD. Hallucinations occur in 59% of narcolepsy type 1 patients, in 28% of narcolepsy type 2 patients, and in 26% of PD patients, respectively. Could PD patients with narcolepsy like symptoms resemble narcolepsy type 2 patients? (Publication II)

Literature on RLS and PD is colossal, but despite of all work done the debate continues whether RLS is a predictor of later PD, augmentation of dopaminergic medication, or distinct of PD. Are idiopathic RLS and RLS in PD different entities with the same clinical phenotype? (Publication III)

Insomnia is the most common sleep complaint of PD patients. While data on why we need to sleep is slowly expanding, a question arises: what insomnia does to a PD patient? Detailed reports of insomnia symptoms in PD would be helpful to throw light on the matter. (Publication IV)

In sleep medicine, the sleep is described in more detail than just included in categories of sleep disorders. In PD studies, sleep is much too often only a footnote in scales of non-motor symptoms. Descriptive features of sleep in PD are a build bridge between the two science approaches. (Submitted manuscript V)

Sleepdisordered breathing can cause hypertension, coronary heart disease, stroke, cognitive impairment, and depression. PD patients are known to have respiratory problems, dysphagia. Cough and swallowing dysfunctions, choking and gasping are symptoms in OSAS. We tried to find a short clinical questionnaire to address these questions in PD. (manuscript VI)
4. SUBJECTS AND METHODS

4.1 Subjects

Altogether 1500 patients with PD were randomly selected from the registry of the Finnish Parkinson Association including 5373 PD patients from the total of 10000-12000 Finnish PD patients. We computed random numbers, based on the registration number in the registry. This allowed us to have a representative sample of all subjects in the registry. After an initial selection we found that forty-nine subjects were either deceased or hospitalized (unable to answer), two were relatives of Parkinson’s patients, one had dystonia without Parkinson’s disease and one was a healthy person. These persons were excluded and the remaining number of eligible patients was 1447. A new questionnaire was sent to those participants who did not respond within three months. The patients were defined as having Parkinson’s disease, a) if their diagnosis had been confirmed by a neurologist and b) they used a typical antiparkinsonian medication. Due to the nature of a questionnaire study, most likely subjects with a cognitive dysfunction, e.g. patients with Lewy body disease, were among non-responders.

4.2 Methods

The structured questionnaire with 207 items included questions derived from the Basic Nordic Sleep Questionnaire (BSNQ).[342, 343] The basic five alternatives for the responses were: 1) “never or less than once per month”, 2) “less than once per week”, 3) “on 1–2 days per week”, 4) “on 3–5 days per week” and 5) “daily or almost daily”. The time frame was the past three months.

Insomnia symptoms [difficulty initiating sleep (DIS), disrupted sleep (DS), nocturnal awakenings during the night (NAW), early morning awakenings (EMA) and non-restorative sleep (NRS)] of BNSQ were assessed on a five-point frequency scale.

In the ICD-10[213, 344][212, 343][213] criteria A-C must be met for Chronic Insomnia Disorder:

A. Difficulties falling asleep, maintaining sleep or non-refreshing sleep
B. Symptoms occur on at least 3 nights per week and for longer than one month
C. The sleep problems cause marked personal distress or interference with personal functioning in daily living.

In the ICSD-3[345] criteria A includes difficulties initiating sleep, maintaining sleep or waking up earlier than desired, criteria B symptoms occur at least 3 nights per week and for at least 3 months, and criteria C fatigue/malaise, impaired social/family/occupational/academic performance, mood disturbance/irritability, or daytime sleepiness, respectively. In the DSM-V[344][343][342][342](American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington) criteria A-B are the same as in the ICSD-3, criteria C the same as in ICD-10, respectively. Difficulty of maintaining sleep is defined as waking up on at least 3 nights per week (DS).

In our study persons were defined as having insomnia if criteria A-C were met:

A. they had at least one of the following symptoms:
   a. difficulties falling asleep on at least 3 nights per week
   b. waking up too early at night without being able to sleep again on at least 3 nights per week
   c. waking up at least 3 times per night on at least 3 nights per week
   d. unrefreshing (non restorative) sleep during at least one month
B. they had suffered from insomnia at least for one month, and the sleep disturbance affected negatively their social life, working life or leisure time.

Maintaining sleep was defined using two insomnia symptoms i.e. DS and NAW as it is much too common to wake up once a night due to nocturia.[346] Sleep maintenance insomnia (SMI; criterium A.c. of the ICD-10) was evaluated asking two questions as “How often weekly have you awakened at night during the past three months?” and “If you use to wake up during night, how many times do you usually wake up during one night?” : 1) “usually I don't wake up at night”, 2) “once”, 3) “2 times”, 4) “3-4 times”, 5) “at least 5 times”. The sum of the questions was named as Sleep Maintenance Insomnia Index (SMII) giving a score from 2 to 10. SMI occurred when index was at least 8.

Questionnaire included a question whether a diagnosis of RLS was made by a physician. Otherwise, RLS was defined using the old international 4-item definition criteria.[347] The fifth essential criteria excludes RLS mimics.[263] Some
motor- and non-motor sensory fluctuations in PD could mimic RLS causing overestimation of RLS frequency. This limitation comes from conducting this study by a mailed questionnaire with no face to face interview with a sleep specialist. The questionnaire included six separate questions of RLS symptoms, two questions of their current unpleasantness for pain and urge to move limbs, circadian occurrence and occurrence in the family. Alternatives to unpleasantness were: 0) “not at all”, 1) “a little”, 2) “somewhat”, 3) “plenty” and 4) “very much”. Discomfort of RLS symptoms was the sum of two questions (score 0-8). Severity of RLS was defined as none (score=0), mild (1-2), moderate (3-4), severe (5-6) and very severe (7-8).

The REM Sleep Behavior Disorder (RBD) Screening Questionnaire (RBDSQ) is a patient self-rating instrument with ten questions (yes/no) assessing various aspects of sleep behavior.[323] RBDSQ as a screening tool for secondary RBD among PD patients has been validated (the cut-off value is 6 points, with a sensitivity of 0.842 and a specificity of 0.962).[348]

Fatigue was asked as “Do you feel fatigued during daytime at least 3 days per week?”

The presence of obstructive sleep apnea (OSA) was asked separately with a question: “Have you had breathing pauses (sleep apnea) at sleep (have other people noticed that you have pauses in respiration when you sleep)?” The occurrence of sleep-disordered breathing (SDB) was evaluated with two questionnaires and with questions from BNSQ. The Berlin Questionnaire consists of 10 questions in three categories. The first category includes five questions on snoring and/or apnea, and the second category three questions on daytime somnolence. Each category is positive if the patient is symptomatic in ≥2 questions for ≥3 times a week. The third category has two questions on the presence of hypertension and/or obesity (BMI > 30 kg/m2) and will be considered positive with each of these questions being positive. Two or more positive categories indicate a high likelihood of SDB.[253] The STOP-Bang Questionnaire consists of four STOP-questions (yes/no), i.e. snoring, daytime somnolence, apnea and hypertension, and of four Bang-questions (yes/no), i.e. obesity (BMI > 35 kg/m2), age (> 50 years), neck size (≥43 cm for men, ≥41 cm for women) and male gender. For general population, high risk of SDB occurs with ≥5 positive questions, or with ≥2 positive STOP questions and one positive question obesity/neck size/male gender.[255] Thirdly SDB was defined with questions derived from the BNSQ. If the answer to the question ‘Do you snore when sleeping?’ (Ask others if you are not sure) was ‘no’, sleep apnea was considered to be unlikely. If the answer was ‘yes’ then the following additional questions were addressed: (1) ‘How often do you snore?’; (2) ‘How does your snoring sound like? (Ask others if needed)’; and (3) ‘Have you noticed (or have others noticed) respiratory pauses when you sleep?’. SDB was considered quite probable, if snoring was frequent (≥3 nights weekly) and either of the following items was positive: (1) snoring is loud and irregular, with occasional respiratory pauses and/or stertorous breathing; (2) respiratory pauses occurring weekly. Otherwise SDB was considered to be unlikely.[349]

Sleepiness and overall narcolepsy symptom severity were ascertained with the Epworth Sleepiness Scale (ESS)[350] and the Ullanlinna Narcolepsy Scale (UNS)[351], and the Skogby Excessive Daytime Sleepiness Index (SEDS)[343]. In all cases, higher scores indicated greater sleepiness and worse narcolepsy symptom severity. In 5-item SEDS, a cut point of 16 out of 25 points, and in 8-item ESS, a cut-point of 11 out of 24 points are commonly used as an indication of excessive daytime sleepiness. In our experience, mentally fatigued people (often depressive) usually do not have high scores in the ESS as opposed to sleepy patients with, say, sleep apnea or narcolepsy. An 11-item UNS-score varies between 0 and 44 points. An UNS score >14 indicates narcolepsy. In the current study, a subject was considered as having suspected narcolepsy (NARC) if UNS ≥14 and ESS ≥11 simultaneously.

Intense dreaming was defined as recalling dreams nightly.

About different other parasomnias and isolated symptoms the questionnaire included 11 items including: nightmares, night terrors, sleep walking, enuresis, hallucinations, sleep talking, sleep bruxism and nocturnal sweating. Hallucinations were separated in four different questions: 1) hallucinations during evening when awake, 2) hallucinations at the moment of falling asleep, 3) hallucinations at the moment of awakening and 4) hallucinations during night. The time period was last year. In these questions a sixth response alternative was given by separating 0) “never” from 1) “less than once per month”. In the study, other parasomnias and isolated symptoms were asked separately as “How often during last year you have had this disturbance?”

The health-related quality of life was evaluated either by the Euroqol (EQ-5D) questionnaire and visual-analog scale (VAS)[352] or by the standardized World Health Organization Well-being Questionnaire (WHO5)[353] or by self-rated health (SRH). The quality of life is considered poor if the VAS value is less than 60[354] or WHO-5 score is less than 52[355]. SRH was ascertained by one question with six alternative responses: “Would you say your health in general is excellent, very good, good, poor, very poor, or extremely poor?” As a categorical outcome, we estimated the probability that a survey participant reported that his or her overall health was either “good” or “poor.”
Depression was evaluated using an easy screening method for general practice, i.e. Rimon's Brief Depression Scale (score 0–21), since it does not include any question about sleep. The limit for depression is 11. \[356-358\] Anxiety was asked as “Do you have a general feeling of anxiety, that causes you, e.g., to rise up frequently from chair or bed, to walk, to move or massage or stretch your legs, or to take warm or cold shower?” Subjective negative stress was asked as “Do you suffer from stress a lot or very much?”

Comorbidities were asked with yes/no questions, e.g. pulmonary disease as “Do you have asthma or other lung disease?” Definition of anosmia was a subjective inability to perceive odor, constipation as infrequent bowel movements (≤3 times per week), and nocturia as frequent urgency to urinate during night (≥3 times a night). Patients were defined physically inactive (i.e. exercise <2 hours weekly), if they reported to either walk or jog or run less than 2 hours in a week. If the patients reported either that they had no rest tremor or that rest tremor had started later than bradykinesia or rigidity, they were defined as having an akinetic-rigid subtype of PD.

 Separate conversion factors for antiparkinsonian drugs were used to calculate a total daily levodopa equivalent dose (LED). \[359\] Annual increase of LED was calculated as a measure of progress rate of hypodopaminergic motor symptoms or signs in PD. Usage of prescriptive sleep medication was considered as regular usage, if usage happened at least 3 nights per week. The dominating drugs in this class are zopiclone, zolpidem, and temazepam.

Sleeping difficulties included short, long and poor sleep, sleep deprivation, disrupted night sleep, and difficulties to fall asleep. Time in bed was based on the time participants went to bed until the moment of getting up the next morning. If they took naps every day, one hour was added to time in bed. Short and long sleep durations were defined as a sleep duration of 6 hours or less and 9 hours or longer, respectively. The sleep duration of more than 6 hours to less than 9 hours was used as the reference. The following equation was used to calculate sleep efficiency (SE): 100 * total sleep time (TST) / time in bed. Poor sleepers had SE ratio below 80%. Need of sleep was asked as “How many hours and minutes would you sleep if you could sleep as long as you wanted?” Equation to calculate sleep deprivation was: need of sleep-TST. Subjects were defined to have sleep deprivation if sleep deprivation was over 60 minutes. Sleep latency was ascertained by the categorical question “How quick do you fall asleep?” Alternatives for responses were: 1) “over 40 minutes”, 2) “31 to 40 minutes”, 3) “21 to 30 minutes”, and 4) “10 to 20 minutes”, and 5) “under 10 minutes”.

Participants were defined to have difficulties to fall asleep, if sleep latency exceeded 30 minutes. Wake after sleep onset (WASO) was defined as the amount of time spent awake after sleep had been initiated and before final awakening. Subjects had disrupted night sleep if WASO exceeded 30 minutes.

4.3 Statistical methods

All statistical analyses were conducted using Stata 12.0 (Copyright 1985–2011 StataCorp LP). Quantitative values were expressed as medians, means, standard deviations and ranges. The normality of the distributions was tested with the Shapiro–Wilk normality test. For continuous variables parametric (Student's t-test) or nonparametric methods (Mann–Whitney U-test) were used depending of the distribution. Categorized values were expressed in numbers and percentages and analyzed by the Pearson's chi-square test and Fisher's exact test. Values of P < 0.05 were considered statistically significant. Logistic regression analysis was used to compute odds ratios (OR) and their 95% confidence intervals (CI). Examples of predicted probabilities were computed with the prvalue command of the STATA. With the prvalue the predicted probability of having sleep disorder can be computed, when the other characteristics of the defined model are known. In case of rare events, such as narcolepsy, CIs were computed using Poisson distribution. The ethical permission was obtained from the local ethical committee and the study was conducted according to the declaration of Helsinki.
5. RESULTS

The response rate was 59% (N=854), and of these 77% returned fully answered questionnaire (N = 661). In this cohort, the mean age of the responders was 68.8 years (SD 8.5; median 69 years; range 41–89), and 55.6% of them were male. Obesity (body mass index >25) occurred in 61.4% of the participants, increased waist circumference in 59.9% of men (>100cm) and in 51.6% of women (>90cm), and hypertension in 33.4%, respectively. The mean duration of Parkinson’s disease was 6.1 years (SD 5.0; median 5). The total daily levodopa equivalent dose (LED) could be estimated in 590 subjects. Altogether total daily LED was 601mg (95% CI 573mg to 630mg). Annual increase of LED was 141mg/year (SD 111; median 113). An akinetic-rigid subtype of PD was found in 38.3% of the participants. Quality of life measured using EQ VAS was poor (<60) in 46.0% of patients (364/792) (42.5% to 49.4%), and using WHO5 (<52) in 45.0% (359/798) (41.5% to 48.4%). Answers indicating depression (depression scale>10) were found in 20.9% (20.2% to 26.0%) of the subjects (188/813), daytime sleepiness using ESS (>10) in 30.2% (241/797) (27.0% to 33.4%) and using SEDS (>15) in 46.1% (325/705) (42.4% to 49.8%), and fatigue in 43.9% (351/800) (40.4% to 47.3%).

5.1 Parasomias and isolated sleep symptoms

Intense dreaming occurred in 14.5% of the subjects, and RBD according to the questionnaire study 39.0% (258/661 PD patients). REM sleep parasomnia (weekly nightmares), NREM sleep parasomnias (at least weekly occurring night terrors and sleep walking), other parasomnias (at least weekly enuresis and hallucinations), and isolated sleep symptoms (at least weekly nocturnal sweating, bruxism, and sleep talking) were all, i.e. as each and every one and as a group, significantly related to RBD. RBD without coexisting other parasomnias or isolated sleep symptoms was rare (35/661 PD patients; 5.3%). In other words 86.4% (223/258) of the PD patients with RBD had at least one other parasomnia or some isolated sleep symptoms as mentioned above. Association of RBD with sleepwalking (parasomnia overlap disorder) was found in 1.7% (95% CI 0.7% to 2.6%) of all participants. Sleepwalking at least once weekly was reported by only one (0.2%) PD patient without RBD, while it was reported by 11 (4.3%) of the 258 patients with RBD (P<0.001). Although 45/114 (39.5%) of the PD patients with weekly nightmares had also hallucinations, 69/114 (60.5%) were not hallucinating. On the other hand, in the group of the PD patients with weekly hallucinations 45/101 (44.6%) had weekly nightmares and 56/101 (55.4%) did not have weekly nightmares. At least weekly occurring bedwetting (21.0%) was more common in women (27.4%) than in men (15.6%) (P<0.001). On the other hand, nocturia (the need to get up to urinate at least three times during the night; 15.9%) was more common in men (20.2%) than in women (10.7%; P=0.001). Patients with parasomnias, other than RBD, or isolated sleep symptoms did not differ from the others in the quality of life measures neither in the depression scores.

The adjusted logistic regression analysis showed that at least weekly occurring nightmares (OR 12.5; 95% CI 5.3 to 29.7), hallucinations (OR 5.1; 95% CI 2.1 to 12.4), sleep talking (OR 11.6; 95% CI 5.9 to 22.8), male gender (OR 1.9; 95% CI 1.1 to 3.1), and restless legs syndrome (OR 4.7; 95% CI 1.7 to 13.2) associated statistically significantly with the presence of RBD. The final model was computed by limiting the number of items to seven factors. The reason for this model was to select only factors that can be obtained quickly during a clinical interview and examination. This model can be used in clinical practice in the estimation of predicted probability of RBD. As an example of predicted probabilities: 99.3% of male PD patients , aged 75 years, with sleep talking, nightmares, hallucinations, RLS, and enuresis have RBD. Using the results of the adjusted logistic regression analysis, we composed a new short questionnaire to detect possible RBD. The sum of questions gender (male=1), nightmares and sleep talking gives a score from 0 to 11. This screening questionnaire (Male/nightmare/ST), with the cut-off value is 5 points, has a sensitivity of 60.2% and a specificity of 94.3%.

5.2 Narcolepsy like symptoms

Occurrence of narcolepsy-like symptoms (UNS ≥14) was 11.0% (95% CI 8.6 – 13.5), weekly daytime sleep attacks was 13.8%, and cataplexy symptoms ever 22.2% (monthly 2.9%). Daytime sleepiness (ESS >10) was reported in 30.9% of patients. Answers indicating hallucinations before going to bed in the evening were found in 6.1% of the subjects, hypnagogic hallucinations in 4.0%, hypnopompic hallucinations in 3.4%, and hallucinations during night in 8.3%,
respectively. The PD subjects with NARC (UNS≥14 and ESS>10) tended to have a higher usage of levodopa compared to the rest of PD subjects. Adjusted for age, sex, disease duration and levodopa, there appeared more RBD, all types of hallucinations, daytime sleepiness, fatigue, insomnia, and intense dreaming in the PD with NARC group.

Cataplexy symptoms occurred in 43.1% of subjects (25/58) with PD and NARC. Thus, the prevalence of suspected narcolepsy with or without cataplexy was 9.3% (95% CI 7.0 – 11.6). The prevalence of narcolepsy with cataplexy was 4.0% (95% CI 2.5 – 5.6) and the prevalence of narcolepsy without cataplexy was 5.3% (95% CI 3.5 – 7.0). RBD occurred more often in subjects with cataplectic symptoms than in those without any history of cataplexy. Two patients with Parkinson’s disease had been diagnosed, based on sleep studies, of having narcolepsy. This gives a minimum prevalence of 0.32% (Poisson 95% CI 0.04 – 1.16) corresponding to 320 per 100 000 (40 – 1160 per 100 000) patients with Parkinson’s disease. Both were men, aged 73 and 77 years. Neither of them had unambiguous history of cataplexy, as asked by UNS, but otherwise their symptoms fitted with narcolepsy with severely disturbed night sleep. The younger man had also a positive history of RBD (RBDSQ=7) and a history of hypnagogic hallucinations fitting with narcolepsy. Age at the time of PD diagnosis was 63 and 72 years, and their UNS-values were 14 and 16, respectively. Both men had ESS-value 16.

5.3 RLS

Previous diagnosis of RLS made by a physician occurred in 6.0% (49/812) of the participants (95% CI 4.4% to 7.7%). Occurrence of RLS (constellation of the four IRLSSG criteria) was found in 20.3% (117/577) of PD subjects. The PD subjects with RLS tended to have an earlier diagnosis of PD and a longer disease duration. The frequency of RLS was 18.1% “never or less than once per month”, 24.1% “less than once per week”, 20.7% “on 1-2 days per week”, 18.1% “on 3-5 days per week” and 19.0% “daily or almost daily”. Severity of RLS was none in 1.7% of participants with RLS, mild in 16.2%, moderate in 42.7%, severe in 23.9% and very severe in 15.4%. The frequency and severity of RLS were highly correlated (chi square 172.6; P=0.000).

Number of six different RLS symptoms were 1.6 (95% CI 1.4 to 1.7) in PDw/oRLS, and 4.8 (4.6 to 5.0) in PD with RLS. Likewise discomfort of RLS symptoms (score 0-8) were 2.0 (1.8 to 2.2) and 4.5 (4.2 to 4.9). The circadian rhythm differed between groups. The unpleasantness was found during 7.00-12.00 a.m. in 17.2% of PD-non-RLS group and in 14.5% of PD-RLS group (P=0.492), during 1.00-6.00 p.m. in 22.9% and in 16.2% (P=0.118), during 7.00-12.00 p.m. in 34.6% and in 68.4% (P<0.000), and during 1.00-6.00 a.m. in 22.2% and in 54.7% (p<0.000). A total of 39.3% of RLS patients (46/117) experienced RLS suffering (discomfort score ≥5). Occurrence of OSA was 76.5% in RLS-sufferers and 22.5% in RLSL-non-sufferers (OR 6.4, 95%CI 1.9 to 21.3, P=0.002), depression 54.3% and 45.7% (2.3, 1.04 to 5.2, P=0.041). Otherwise no significant differences were found in RLS-sufferers compared to RLS-non-sufferers.

Adjusted for age, sex, and disease duration, there appeared more daytime sleepiness (SEDS>15), fatigue, insomnia, SMI, intense dreaming, and low quality of life in the PD with RLS group.

In PD with RLS group, 70.1% (82/117) answered to the question at which age RLS symptoms had begun. An estimate of early onset RLS prevalence was 4.2% (17/404 patients [i.e. 70.1% of the current cohort of 577 patients]; RLS symptoms onset ≤45 years) in this cohort of PD patients. Likewise an estimate of late onset RLS prevalence can be calculated as 16.1% (65/404 patients; RLS symptoms onset >45 years). PD with RLS onset ≤45 years was more hereditary than PD with RLS onset >45 years (64.7% vs. 22.4%; P<0.001). The PD with RLS onset >45 years group used more often levodopa and MAO-inhibitors medication (Levodopa and MAO-inhibitors combined 17.6% vs 46.1%; p=0.033). Adjusted for age, sex, and disease duration, this difference in medication remained significant (OR 4.7; 95% CI 1.18 to 19.0).

From the subgroup of secondary RLS an estimate of drug-naïve RLS prevalence was 5.4% (22/404 patients; RLS symptoms onset before PD diagnosis). The prevalence of RLS in PD patients could have been the result from the confounding medication in 10.4% (43/404 patients; RLS symptoms onset after PD diagnosis). In drug-naïve patients, RLS symptoms onset was 6.3 years (95% CI 9.6 to 3.1) before PD diagnosis compared to the latter group 4.6 years (3.0 to 6.3) after PD diagnosis. The duration of RLS symptoms were 11.0 years (7.7 to 14.3) and 5.1 years (1.9 to 8.2). In the analyses, drug-naïve RLS had a shorter duration of PD (4.7 years; 95% CI 3.2 to 6.2) than secondary RLS with confounding medication group (9.7; 6.3 to 13.1) (P=0.022). Otherwise there were no significant differences between these groups.
5.4 Insomnia

When the participants had suffered from insomnia at least for one month, the prevalence of insomnia ICD-10 was 47.9%, insomnia ISCD-3 43.4% and insomnia DSM-V 38.6%. Prevalence of chronic insomnia disorder was 36.9% (95% CI 33.3-40.5). DIS (≥3 evenings per week) was present in 18.0% (95% CI 15.1-20.9), DS (≥3 nights per week) in 81.5% (78.5-84.4), NAW (≥3 times per night) in 31.3% (27.8-34.8), EMA (≥3 mornings per week) in 40.4% (36.8-44.1) and NRS (at least during the last month) in 38.5% (34.8-42.1) of the respondents. The PD subjects with chronic insomnia disorder tended to have a younger age, female predisposition, longer duration of PD, and different mood and health related quality of life.

DIS occurred in 22.0% of women and in 14.6% of men (Chi square 6.2; P=0.013), nocturia (≥3 times per night) in men 19.8% and in women 11.5% (Chi square 8.6; P=0.003). NAW occurred in patients with younger age (<67 years).

Duration of PD, annual increase of LED or akinetic-rigid subtype did not differ between groups. Poor quality of life, depression and anxiety were associated with all types of insomnia complaints.

In PD patients with chronic insomnia disorder, fatigue and depression were experienced in 44.6% (40.9-48.4) and in 23.8% (20.6-27.0). Heart disease occurred in 54.5% of subjects with NRS (Chi square 12.7; P<0.001), hypertension in 22.6% of subjects with DIS (Chi square 4.8; P=0.029) and in 44.8% of subjects with NRS (Chi square 5.9; P=0.015), chronic low back pain in 40.0% of subjects with NAW (Chi square 4.8; P=0.028) and in 50.4% of subjects with NRS (Chi square 8.2; P=0.004).

The total daily levodopa equivalent dose (LED) could be estimated in 85.6% of subjects (N=590/689). Altogether total daily LED was 601mg (573mg to 630mg). Annual increase of total daily LED was 141mg (131mg to 152mg).

Dopamine agonist LED was 219mg (193mg to 245mg) in PD patients without DIS and 142mg (77mg to 206mg) in PD patients with DIS (P=0.030). MAO inhibitor LED was 85mg (79mg to 92mg) and 92mg (89mg to 95mg) (P=0.029), and total daily LED 578mg (539mg to 617mg) and 658mg (602mg to 713mg) (P=0.019), respectively. Otherwise antiparkinsonian medication or annual increase of LED had no significant effect on chronic insomnia disorder or insomnia symptoms.

Regular usage of prescriptive sleep medication (≥3 nights per week) occurred in 16.9% (95% CI 14.0 to 19.7) in all PD patients, in 9.7% (6.9 to 12.5) in PD patients without insomnia and in 29.2% (23.5 to 34.9) in patients with insomnia ICD-10 (P<0.001). Patients with DIS, EMA or NRS used hypnotics more often than others.

In the logistic regression analyses, poor quality of life correlated significantly with chronic insomnia disorder (OR 2.0; 95% CI 1.3 to 3.2), NAW (2.3; 1.3 to 4.0) and NRS (3.1; 2.0 to 4.9), anxiety with NAW (2.3; 1.3 to 4.1), heart disease with NRS (OR 2.2; 95% CI 1.2 to 4.3), nocturia with DIS (2.8; 1.3 to 5.7), DS (11.6; 1.5 to 87.2) and NAW (60.0; 23.8 to 157.7), fatigue with EMA (OR 1.7; 95% CI 1.1 to 2.6) and NRS (2.1; 1.3 to 3.3), RBD with DS (2.7; 1.4 to 5.0), RLS with chronic insomnia disorder (1.9; 1.1 to 3.3) and DIS (2.6; 1.4 to 5.2), ESS with chronic insomnia disorder (2.9; 1.7 to 4.9), and narcolepsy with DIS (0.2; 0.05 to 0.83).

5.5 Sleeping difficulties and health-related quality of life

TST was 7.4 hours (SD 2.0; median 7), need of sleep 7.9 hours (SD 1.4; median 8), and SE 87.0% (SD 12.7; median 90). Long sleep (≥9 h) occurred in 26.2% of all participants, short sleep in 32.5% (≥6 h), poor sleep (SE <80%) in 21.2%, sleep deprivation (≥60 minutes) in 33.8%, disrupted sleep (WASO >30min) in 47.4%, and difficulties to fall asleep (sleep latency >30 minutes) in 12.2%, respectively. Poor SRH and poor quality of life (WHO5 <52) occurred in 44.4% and in 43.3% of all participants.

Men were more often long sleepers, and they had more often disrupted sleep. Women tended to have poor sleep, sleep deprivation, and difficulties to fall asleep. There was no difference by gender in short sleep, SRH, or poor quality of life (WHO5 <52).

In the logistic regression analyses, long sleep correlated significantly with depression (OR 2.46; 95% CI 1.43 to 4.24), subjective negative stress (4.50; 1.82 to 11.12) and fatigue (2.04; 1.25 to 3.31), short sleep with use of hypnotics (OR 1.87; 95% CI 1.15 to 3.02), excessive daytime sleepiness (ESS >10) (1.94; 1.31 to 2.87) and poor quality of life (WHO5 <52) (1.52; 1.04 to 2.23), poor sleep with use of hypnotics (OR 2.68; 95% CI 1.54 to 4.66) and RLS (1.86; 1.07 to 3.22), sleep deprivation inversely with age (OR 0.92; 95% CI 0.89 to 0.94) and male gender (0.45; 0.29 to 0.70), directly with chronic low back pain (OR 1.88; 95%CI 1.06 to 3.32), use of hypnotics (2.74; 1.59 to 4.71), excessive daytime sleepiness (ESS >10) (2.25; 1.41 to 3.60), OSA (2.58; 1.64 to 4.06) and poor quality of life (WHO5 <52) (2.21; 1.41 to 3.47). SRH correlated significantly with lack of exercise (OR 2.45; 95% CI 1.57 to 3.82), chronic low back pain...
(2.30; 1.36 to 3.90), depression (3.91; 2.26 to 6.79), subjective negative stress (9.21; 2.54 to 33.44), fatigue (2.54; 1.66 to 3.87) and OSA (1.70; 1.13 to 2.55), poor quality of life (WHO5 < 52) with age (OR 1.03; 95% CI 1.01 to 1.06), akinetic-rigid subtype (1.49; 1.01 to 2.22), depression (2.97; 1.78 to 4.95), subjective negative stress (5.40; 1.90 to 15.34), fatigue (2.73; 1.83 to 4.09) and sleep deprivation (2.48; 1.57 to 3.92).

Proportion of variations in these models remained low, i.e. pseudo R2 was 0.1395 in long sleep, 0.0496 in short sleep, 0.0454 in poor sleep, 0.2002 in sleep deprivation, 0.2288 in SRH, and 0.1743 in poor quality of life (WHO5 <52). No significant correlations were found between disrupted sleep and variables. Anxiety, age and gender adjusted; correlated with the difficulties to fall asleep (OR 1.84; 95% CI 1.09 to 3.11).

5.6 SDB

Previous diagnosis of OSA made by a physician was in 4.5% (37/828) of subjects (95% CI 3.1% to 5.9%), and OSA with one question in 14.9% (12.3% to 17.4%). The occurrence of SDB was 43.3% (38.7% to 48.2%) with the Berlin Questionnaire, 26.3% (21.5% to 31.1%) with the STOP-Bang Questionnaire, and 22.1% (18.3% to 26.0%) with questions derived from BNSQ (SDB-BNSQ), respectively. Berlin and STOP-Bang Questionnaires and SDB-BNSQ correlated with each other. With Berlin Questionnaire, 46.8% of patients with SDB had also SDB with STOP-Bang Questionnaire (p<0.001), and 36.6% with SDB-BNSQ (p<0.001), with STOP-Bang Questionnaire, 77.9% of patients with SDB had SDB with Berlin Questionnaire, and 55.8% with SDB-BNSQ (p<0.001), and with SDB-BNSQ, 73.9% of patients with SDB had SDB with Berlin Questionnaire, and 71.6% with STOP-Bang Questionnaire, respectively. OSAS defined as SDB with Berlin Questionnaire and ESS>10 occurred in 16.1% of the participants. Likewise, the frequency of OSAS defined with STOP-Bang Questionnaire was 13.3%, and with SDB-BNSQ 10.4%, respectively.

Gender, BMI, waist circumference in women, ESS (>10), fatigue, narcolepsy like symptoms (UNS >14), RBDSQ (≥6), nightmares, night terrors, sleep walking, enuresis, hallucinations, nocturnal sweating, bruxism, sleep talking, depression, SRH, anxiety, subjective negative stress, pulmonary disease, chronic low back pain and nocturia (≥3 times per night) associated with SDB-BNSQ. Variables significantly associated with SDB-BNSQ in bivariate analyses were used in multiple regression analyses with SDB-BNSQ as the dependent variable. In the final age-adjusted logistic model, SDB-BNSQ correlated significantly with UNS (>14) (OR 2.8; 95% CI 1.5 to 4.4), weekly nightmares (2.5; 1.4 to 4.3), nocturnal sweating (1.8; 1.1 to 2.8), sleep talking (2.1; 1.2 to 3.5), male gender (2.4; 1.5 to 3.7) and pulmonary disease (2.0; 1.1 to 3.6). For example, 89.4% of male PD patients with narcolepsy like symptoms, nightmares, night sweats, sleep talking and pulmonary disease have SDB.

In an additional analysis, 11.1% of PD patients had both weekly nightmares and sleep talking. Coincident nightmares and sleep talking correlated, age and gender adjusted, significantly with RBD (OR 18.1; 95% CI 7.03 to 46.6) and SDB-BNSQ (2.65; 1.40 to 4.98)
6. DISCUSSION

6.1 Parasomnias and isolated sleep symptoms

Except for RBD, nightmares and hallucinations, there seems not to exist previous systematic studies about the occurrence of other parasomnias in patients with PD. The main findings of the present study was the prevalent combination of other parasomnias and isolated sleep related symptoms with RBD symptoms in PD patients. Isolated RBD (RBD without any other parasomnia) was rare. Originally, parasomnia overlap disorder (POD) refers to a sleep disorder characterized by the association of RBD with NREM-sleep parasomnia (SW) in the same patient.[360] The previous reports on parasomnias, other than RBD, among PD patients have been small. Of 165 consecutive patients with PD seen for 2 years, 6 patients with adult-onset SW were identified.[294] Night walking was also reported in 10 of 93 patients with RBD of different origin, including PD. Five of these 10 patients had underlying neurodegenerative diseases, and two patients with SW had confusional arousals during the video-PSG indicating the parasomnia overlap syndrome. The authors discuss the possibility, that all 10 patients with SW represent this overlap disorder.[361] Parasomnias may be explained on the basis that wakefulness and sleep are not mutually exclusive states, and abnormal intrusion of wakefulness into non-REM (NREM) sleep produces arousal disorders, and intrusion of wakefulness into REM sleep produces recurrent isolated sleep paralysis, nightmare disorder and RBD.[362] These undesirable emotional or physical events that accompany sleep are inappropriate for the time of occurrence but may seem purposeful or goal directed. They occur more commonly in children and decrease in frequency in the adult population. However, their occurrences may increase in neurologically affected adults.

According to Bjorvatn and collaborators the prevalence of at least weekly occurring parasomnias in adults are: sleep walking 0.6% (95% CI 0.2-1.1), sleep talking 6.3% (4.7-7.7), sleep terror 1.0% (0.4-1.6), nightmares 2.8% (1.8-3.9).[363] In patients with PD (present study) the respective prevalences were: sleep walking 1.9% (0.8-3.0), ST 21.7% (18.5-24.9), night terrors 3.9% (2.4-5.5) and nightmares 17.2% (14.3-20.2). Our finding is that 3.8% of patients with PD without RBD see frequently nightmares, which is similar to the prevalence of nightmares in general population. The prevalence of nightmares is much more common (38.3%) in PD patients with RBD. The logistic regression analysis showed both nightmares and hallucinations to have independent and significant associations with RBD. However, 60.5% of nightmare PD patients did not have hallucinations and no association with RBD. They were more often women. The sex difference in the prevalence of nightmares may be contributed by the higher rate of dream recall in women.

Previous studies have shown, that the prevalence and severity of hallucinations significantly increase with the duration of PD, and that the nightmares have no predictive influence on the future development of hallucinations.[310] Using the UPDRS I sub score, item 2 (thought disorder) the frequent hallucinations have been estimated to occur in 18% of Parkinson´s patients with Parkinson´s disease.[364] On the other hand, previous epidemiological studies have not made the distinction according to the presence of RBD. RBD has been found to associate with cognitive impairment and predict development of dementia in PD.[365] The association of cognitive status and other parasomnias was not possible to evaluate in this questionnaire study.

Enuresis in children is defined in DSM-IV as repeated voiding of urine in the bed at least twice per week for at least three consecutive months. Nocturnal incontinence occurs in 1% of young adults, with rates being higher in males. Infrequent bedwetting (only once or less a week) in children is six times more commoner than enuresis.[366] In our series, weekly occurring bedwetting was more common among females, and nocturia occurred more often with males. Enuresis nocturna may be classified as a parasomnia but bedwetting/ nocturia/ incontinence may also be a manifestation of autonomic dysfunction. Their differentiation from each other is very difficult in a questionnaire study. Occurrence of bruxism in patients with PD has not been reported. As the prevalence of tooth grinding decreases linearly with age, SB is not associated with PD but perhaps more likely with RLS.[316, 367] The prevalence rate of idiopathic night sweats in adult population has not been reported.

Our study has its limitations. Only a questionnaire was used and it is possible that the sample includes besides idiopathic Parkinson’s disease also some other patients using PD medication e.g. patients with Lewy Body Dementia or other types of Parkinsonism. As subjects with significant cognitive dysfunction may be missing, our results cannot be generalized to PD patients with serious memory complaints. As concerns RBD our data is also based on the questionnaire and we do not have polysomnographic confirmation of the disorder. Because of the large number of participants and the fact that the participants were from different parts of Finland, we did not have sufficient funding to
include polysomnography. There might also be some under-reporting as parasomnias may not be detected among persons, who sleep alone. Also some symptoms, such as sleep talking, are often under-reported. Patients with Parkinson’s disease have many non-motor symptoms that can act as mimics of parasomnias and isolated sleep symptoms. A thorough interview with each subject made by an experienced sleep researcher should be done to differentiate mimics from true findings.

6.2 Narcolepsy like symptoms

In the adult Finnish (Caucasian) population, the prevalence of narcolepsy with cataplexy has been estimated to be around 0.026%.[351] Narcolepsy with cataplexy is associated with the HLA DQB1*06:02 allele in more than 95% of patients.[281, 368] In Finland 25 to 30% of the general population carry this HLA subtype. If 2% of the middle-aged general population has PD, the random association of narcolepsy and idiopathic PD in a given patient can be estimated to be about 5 in 1 million people. In our study the prevalence of narcolepsy-like symptoms (with UNS ≥14) in PD is around 11% and the prevalence of suspected narcolepsy (UNS≥14 and ESS≥11) was 9.3%. The prevalence of an earlier diagnosis of narcolepsy in patients with Parkinson’s disease was 0.32%. These figures indicate that narcoleptic symptoms and also narcolepsy is more common in patients with Parkinson’s disease than in general population. The sensibility and specificity of the UNS is good, but unfortunately we were not able to perform sleep studies systematically for all subjects with suspected narcolepsy (polysomnography and MSLT). Two patients have been diagnosed with narcolepsy but it is possible that also some other patients would have had pathological PSG and MSLT studies. Thus, our figure is an underestimation from the true prevalence.

It is known that CSF-levels of hypocretin decrease with the severity of PD and low levels of hypocretin may explain the high prevalence of narcolepsy with cataplexy like symptoms. Our figures are in accordance with the results of Christine et al.[369] They found three cases of narcolepsy in a population of 1152 patients with PD. We are not aware of any previous epidemiological studies showing that PD would be more common in patients with narcolepsy than in general population. The prevalence of previously diagnosed narcolepsy was 10 times higher in our Parkinsonian population than in the Finnish general population.[351] The lower 95% CI falls inside the 95% CI of the earlier Finnish figures, but because our prevalence figure is an underestimation we are pretty sure that narcolepsy is more common in Parkinson’s disease than in general population. A common denominator could be RBD, which is a known risk factor for Parkinson’s disease and it is also commonly present in patients with narcolepsy.[370] We need further studies in populations of narcolepsy patients to find out the incidence of Parkinson’s disease in those populations. As our study was cross-sectional we cannot say anything about the incidence. Narcolepsy with cataplexy is associated with low CSF levels of hypocretin and CSF-hypocretin levels are also lowered in Parkinson’s disease.[371] We hypothesize that in most cases the symptoms of narcolepsy are probably secondary to Parkinson’s disease, and possibly to decreased level of hypocretin (at least in narcolepsy with cataplexy). The other possibility would be that patients with narcolepsy and cataplexy with low levels of hypocretin would develop Parkinson’s disease but no prospective studies have shown this so far.

Parkinson’s disease is a progressive neurodegenerative disease but there is no evidence that narcolepsy would be neurodegenerative.[281] Contrary to PD, narcolepsy usually does not become worse with time. On the contrary the symptoms of narcolepsy are most severe when the symptoms start in childhood or adolescence and they usually alleviate in older age. Narcolepsy without cataplexy (Nw/oC) is a more heterogeneous group, whereas narcolepsy with cataplexy (N-C) forms a more uniform entity with a specific HLA association and low CSF hypocretin. The DQB1*06:02 frequency is found only in 40 to 60% of Nw/oC patients.[372] Nw/oC occurs in 20% of adult narcolepsy patients[373] with usually normal hypocretin-1 levels. In this group, the diagnosis can accurately be made with polysomnography followed by an multiple sleep latency test (MSLT), and it can be diagnosed only when 2 or more sleep onset REM periods (SOREMP) on the MSLT are observed. The pathogenesis of the Nw/oC group remains less clear. Medications used in PD, especially dopamine agonists[374], have been associated with sleepiness, and this may explain partly our findings of sleepiness. However, use of dopamine agonists did not explain occurrence of narcolepsy or narcolepsy with cataplexy.

In PD patients with excessive daytime sleepiness, hallucinations and SOREMP, lumbar hypocretin-1 levels have been reported to be normal.[285] High levels of ventricular hypocretin-1 may be associated with RBD.[375] This raises a question, whether PD-NC without cataplexy (conversely to idiopathic narcolepsy patients with cataplexy who have low lumbar hypocretin levels) have more RBD symptoms. Our finding contradicts this hypothesis, and according to our results RBD associates mainly with presence of cataplexy.
Hallucinations are dreams, usually frightening, that intrude on wakefulness. Their prevalence and severity significantly increase with the duration of PD.[310] Psychosis in long-standing PD is diagnosed if hallucinations or delusions are present. In a prospective study with 59 PD patients, the presence of psychosis had no significant effect on the development of dementia in 26 months follow-up.[376] Furthermore, clinicopathological analysis show different underlying pathologies between hallucinations and dementia.[377] Previous epidemiological studies have not reported together narcolepsy like symptoms, hallucinations and RBD in the same patient population. It is not known whether narcolepsy in PD also predicts diminishing mental processing. The different states of living (wakefulness, NREM sleep, and REM sleep) are not reciprocally exclusive. These states may exist in various combinations. Narcolepsy is an intrusion of REM sleep into wakefulness. Sleep attacks can also be intrusions of NREM stage 1 and 2 sleep into wakefulness.[378] Cataplexy attacks are usually associated with emotions such as laughing.[281, 379] Among healthy people 9.2 to 16.5% may experience sometimes symptoms resembling cataplexy.[380, 381]

6.3 RLS

The age of onset of RLS is known to vary widely from childhood to more than 80 years of age.[382] The prevalence of RLS in adults is around 3% in people aged 18 to 29 years and 10% in those aged 30 to 79 years.[383] In patients with PD symptoms of RLS symptoms have been reported to follow PD diagnosis in 68-82% of PD patients.[384] In our study the prevalence of early onset RLS was 4.2% and prevalence of late onset RLS was 16.1%. In this study, onset of RLS symptoms followed PD diagnosis in 52.4% of all RLS patients and in 66.2% of the late onset RLS patients. Women are two times more likely than men to have RLS in the general population.[385] We found the same ratio in PD patients, as early onset of RLS occurred more often in women (70.6%) than in men (29.4%). This ratio is not statistically significant (N=577, male 52.2%; chi square 3.63 χ<0.057) (N=404, male 52.2%; chi square 3.70 χ<0.055). However, extrapolating to all responders (with incompletely answered questionnaire) gender difference becomes significant (N=577, male 52.3%; chi square=3.89 χ<0.049). In previous studies on PD patients, this typical gender distribution has not been described.[273, 277, 278] Likewise, we found no gender difference in all RLS patients (N=577) or in late onset RLS patients (N=65). About 50 percent of people with primary are familial.[386] In PD patients, a familial trait seems to be more common if RLS onset happens ≤45 years.[387] These findings are consistent with our result. A familial occurrence of RLS was found in 64.7% of the early onset RLS. Symptoms of RLS are known to respond dopaminergic drugs in both idiopathic RLS and PD. Treating RLS patients, augmentation has been reported less frequently with dopamine agonists 27%[388] than with levodopa 82%[389]. The more frequent symptoms of RLS in PD patients with longer dopaminergic could be the result of the same augmentation mechanisms which are not fully known. Our finding of medication difference between early onset vs late onset of RLS groups contradicts the hypothesis that RLS and PD are two different entities that just happen to occur simultaneously, as there was no medication difference between secondary drug-naive RLS group (RLS onset before PD diagnosis) and possible confounding medication RLS group (RLS onset after PD diagnosis). Without high doses of dopaminergic medication the prevalence rates of secondary RLS with PD would probably have been higher. Could it be that at least in some patients symptoms of RLS may be considered as non-conventional symptoms of PD? If this is the case, it does not fit with the iron hypothesis of PD (accumulation of iron in the striatum) and RLS (lack of CNS iron).

Previous reports on the frequency and severity of symptoms of RLS in PD are rare. In a series of 29 PD patients with RLS, frequency of RLS was reported as 17% “at least once a year but less than once a month”, 24% “2 to 4 times a month” and 10% “6 to 7 times a week”. The severity of RLS, measured with IRLSSG rating scale, was estimated as moderate in 19% of participants, severe in 19% and very severe in 4%.[390] In our series of 117 PD patients with RLS, the weekly frequency of RLS was 81.9%. The degree of difficulty was moderate in 42.7%, severe in 23.9% and very severe in 15.4%. All in all, the dopaminergic medication had no soothing effect on the frequency and severity of RLS in PD patients. The severity of RLS has been correlated to depressive symptoms.[390] Quality of life, as measured with Parkinson’s Disease Questionnaire (PDQ-39), is not affected by RLS.[384] Excessive daytime sleepiness, as measured with ESS, is not shown to correlate with RLS.[384, 387] Some specific sleep scales for PD populations find more sleep complaints in PD patients with RLS than in PD patients without RLS. The relationship between PDSS and RLS remained still significant when item on nocturnal restlessness was removed from the analysis.[391] In the current study, there appeared more daytime sleepiness (SEDS>15), other sleep complaints and low quality of life in the PD-RLS group.
6.4 Insomnia

The prevalence rates of insomnia complaints and insomnia disorder vary considerably, depending on how insomnia is defined. The PD sleep scales (PDSS and PDSS-2), the Pittsburgh sleep quality index (PSQI) and the SCOPA-sleep (SCOPA) have been recommended as an assessment of global sleep quality in PD.[202] Previous studies on PD patients have reported the prevalence of insomnia symptoms[391, 392] or insomnia according to one compound question[209, 393] or sub threshold insomnia[394]. Insomnia is known to overlap with multiple medical problems and comorbid sleep disorders.

In our study, chronic insomnia disorder insomnia occurred in 36.9%. DS and EMA were the most common insomnia symptoms. Difficulties in sleep initiation were not overpresented among PD patients. Occurrence of chronic insomnia disorder increased with the duration of PD, but not with the progression rate of hypodopaminergic motor symptoms, i.e. annual increase of LED, or age. In the logistic regression models the most significant predictor of NAW and DS was nocturia, which must be considered when treating insomnia in PD.

In the Priamo observational study on PD patients, the prevalence of insomnia symptom with a dichotomous (yes/no) question was 37%.[209] The problems with sleep initiation were equally frequent among PD patients (31.8%) and healthy elderly people (22.0%).[211] Sleep fragmentation (38.9% vs. 12%) and early awakenings (23.4% vs. 11.0%) are more common in PD.[211] The prevalence of insomnia defined with one compound question was 54 to 60% over an eight-year period in a prospective study, but there was no linear increase over eight-year follow up period. DS occurred in 23.2 to 44.4% of patients with PD, and EMA in 19.0 to 23.9%, respectively.[392] Frequency of at least sub threshold insomnia in PD patients (Insomnia severity index ≥8) was 48%.[394] Frequency of insomnia symptoms according to Parkinson Disease Sleep Scale (PDSS) (questions 2 and 3) was 25% in a community based study of PD outpatients.[391]

How does the prevalence of insomnia in patients with PD relate to other populations? The overall prevalence of insomnia symptoms, e.g. DIS, DS, EMA and NRS, occurring at least three nights per week is reported to be 25 to 38% of general adult population.[395] In FINRISK 2012 Study, the prevalence of insomnia complaint according to one question was 19%.[396] In a cross-sectional representative population –based Health 2000 Survey in Finland, insomnia according to one compound question occurred somewhat in 27% and much or very much in 17% of general population aged 55 years and older.[397] In a large telephone interview of 155 877 participants, sleep disturbance among American general population was evaluated with one compound question (trouble falling asleep or staying asleep or sleeping too much). Sleep disturbance (complaints ≥6 days over the last 2 weeks) generally declined across the life span (from the 18-24 age group to the 80+ age group: women 25.1% to 17.7% and men 18.1% to 15.4%).[398] The diagnosis of insomnia disorder according to DSM-V or ICD-10 requires also daytime impairment, and with this definition the prevalence rates of insomnia decrease to about 10 to 12% in general adult populations in Nordic countries of the Arctic Circle.[395, 399, 400] In the general Finnish adult population study, DIS was 11.8% (CI 9.8 to 13.9), DS 31.7% (28.7 to 34.5), EMA 11.0% (9.1 to 13.0) and NRS 7.9% (6.3 to 12.0).[395] A population based survey in Sweden showed the prevalence of both DIS and DS to be at 10.7%. A combination of these two symptoms was 24.6%.[400] The prevalence of insomnia symptoms in both studies did remain comparable between age groups from 18 to 100 years.[395, 400]

Most but not all epidemiologic evidence suggests a female predisposition of insomnia.[401] There is a significant overlap between insomnia and multiple medical problems. A history of heart disease, hypertension, diabetes, stomach ulcers, arthritis, migraine, asthma, COPD, neurological problems (including epilepsy or stroke), or menstrual problems is associated with a higher prevalence of insomnia.[402] Persons with hypertension, migraine, or neurological problems had significantly higher sleep latency (adjusted for age, gender, and AHI) than those without these disorders.[402] In the current study, DIS occurred in 22.0% of women and in 14.6% of men (P=0.013). Our results show more heart disease with NRS, hypertension with DIS and NRS, chronic low back pain with AND, NAW and NRS.

Fatigue was experienced in 22.3% in the whole general population, in 25.6% of subjects with DIS, in 22.2% of subjects with DS, in 22.0% of subjects with EMA, and in 34.6% of subjects with NRS.[395] In PD, estimated prevalence of fatigue is 28 to 58%.[403] The prevalence of fatigue is consistent with our result. Fatigue in PD was more common with DS and EMA than with general population.

DSM-IV mental disorders, such as bipolar or depressive or anxiety or adjustment disorders, were experienced in 17.0% in the whole general population, in 17% of subjects with DIS, in 20% of subjects with DS, in 18% of subjects with EMA, and in 15% of subjects with NRS.[395] Mallon et al found depression DSM-IV to occur in 10% of general population, and in 40% of participants with insomnia.[400] In PD, clinically significant depressive symptoms are
present in 35%. Schneider et al found minor depression or dysthymia (WHO-5 <52) in 35% of patients with PD.[404] This is in accordance with our results. In a recent Swedish survey in general population, around 20% of insomnia patients used sleep medication regularly (≥3 nights per week).[400] Likewise in the current study, 29.2% of PD patients with chronic insomnia disorder used hypnotics regularly.

6.5 Sleeping difficulties and health related quality of life

Sleeping difficulties were common among the PD patients in this study. Long sleep and sleep deprivation differed from each other both in age and gender. Depression, subjective negative stress and fatigue occurred with long sleep. On the other hand, poor WHO5 and ESS occurred with short sleep and sleep deprivation. Use of hypnotics occurred with short sleep, poor sleep and sleep deprivation.

Approximation of different sleep parameters in a questionnaire study gives not as accurate measurements as objective measuring with actigraphy or polysomnography in sleep lab. However, there are few studies that have compared subjective and objective measures of sleep in patients with chronic disease. In PD patients, subjective SE correlated with SE measured in sleep lab with polysomnography.[405] In an actigraphy study of PD patients, subjective TST in sleep log did not differ from objective measurement of TST.[406] Compared with the standard overnight polysomnography, actigraphy with appropriate scoring parameters give reliable estimates of mean values for TST, SE and WASO in participants with mild to moderate PD. Sleep onset latency could not be accurately measured with actigraphy.[407] Objective measurements in PD patients show TST as 4.7 to 6.8 hours, sleep latency as 18 to 20 minutes, SE as 64 to 80% and WASO as 57 to 106 minutes.[394, 406-408] Our findings in subjective questionnaire were 7.4 hours, 15 minutes, 87% and 37 minutes, respectively.

Polysomnography studies. Patients with PD showed reduced subjective sleep and quality of time awake[405], and reduced SE[241, 405, 409] compared with the controls. TST is reduced[405, 409], or unchanged[241]. Sleep latency is prolonged.[241, 409] WASO is increased.[409] PD duration has been shown to correlate with sleep latency, and to correlate inversely with TST and SE.[410] Parts I-III of the UPDRS scores correlated with TST, SE and WASO.[409] Actigraphy studies. PD patients had reduced[406] or unchanged[411] SE, reduced[406] or unchanged[411] TST and more fragmented sleep[406] than controls. Differences with sleep latency[406] and WASO[406, 411] were not significant. Breen et al reported that apart from later sleep onset time, there were no actigraphy differences in nocturnal motor activity between patients with PD and controls.[241]

The movement disorder society recommended three scales for rating overall sleep problems to screen and to measure severity, i.e. the PD sleep scale (PDSS), the Pittsburgh sleep quality index (PSQI) and the SCOPA-sleep. Poor sleep quality as measured with PDSS related with part IV of the UPDRS (complications of therapy) but not with Parts I-III of the UPDRS or polysomnographic parameters (including SE, TST, sleep onset latency and WASO)[409] or SE[241]. In contrast to this, Gomez-Esteban et al found PDSS correlated with UPDRS I (mental state), III (motor conditions) and IV.[412] PDSS showed no significant relationship with duration of PD[413] nor with PD severity in a community-based study of medicated patients[391]. However, the PSQI score was found to be an independent risk factor for diminished HRQL in PD (PDQ-39 score).[241] HRQL was correlated with scores from PDSS,[414] Screening scales (PDSS, PSQI or SCOPA-sleep) help to rate overall sleep problems in PD, and they give some measurement of severity, but they give little or no information on different sleep difficulties other than actual sleep disorders. E.g. HRQL in long sleepers is more specific than HRQL with low PDSS score. It is more practical to evaluate long, short, poor sleepers, and patients with sleep deprivation, difficulties to fall asleep, and disrupted sleep in separate subgroups.

Studies that examine the relationship between different sleep disorders in PD and HRQL are rare. In a series of 86 PD patients, presence of comorbid RBD (RBDSQ or EMG score ≥ 10% during overnight PSG) and RLS (4-item criteria) were factors of lower quality of life (PDQ-39)[415], but OSA (AHI ≥ 10 during PSG) was not[205]. Knowledge how sleeping difficulties other than specific sleep disorders occur with low HRQL is mostly lacking.

6.6 SDB

In polysomnographic (PSG) studies of PD patients, mild SDB (AHI >5) occurs in 43% to 60% of the participants[259, 416-418], and moderate-to-severe SDB (AHI >15) in 15% to 28%[224, 259, 416-419], respectively. However, selection of patients for PSG on the basis of sleepiness may have led to an overestimation of the overall frequency of SDB in PD. In another PSG study, the prevalence of OSA was 27% in PD patients, who did not display more sleep hyperventilation, stridor and abnormal central sleep apnea than in-hospital controls.[260] A meta-analysis of five
eligible studies with a total of 322 PD patients showed a significant negative association between PD and the prevalence of OSA. These results were primarily due to the lower BMI of PD patients (BMI = 24.9) when compared with the general population controls (28.4 in 6361 controls).[261] PSG, the gold standard diagnostic procedure to OSA diagnosis, is time-consuming and costly. Therefore, screening tests have been developed to identify high-risk patients who should undergo sleep studies. In the elderly population, 31.4% of the subjects were in an OSA high-risk group according to the BQ. Among BQ categories, snoring correctly classified 61% of the sample.[420] In a general population of the Sao Paulo Epidemiologic Sleep Study, the STOP-Bang questionnaire showed that 53.6% of volunteers had high risk for OSA.[421] High risk for SDB, assessed by BQ, was apparent in 49.3% of the PD patients and 34.8% of the controls (OR 2.81).[258] In PD population, BQ has a sensitivity of 72% and a specificity of <60%, and STOP-Bang questionnaire of 75% and of <44% (AHI >15), respectively.[422] The Berlin and STOP-Bang questionnaires are comprised of questions on daytime somnolence, obesity and hypertension. However, in PD population, OSA does not contribute to severity of sleepiness[224], weight loss is associated with the disease progress[423], and loss of sympathetic nerves and subsequent failure of baroreflex are supposed to cause orthostatic hypotension[424]. SDB-BNSQ evades these detriments, as it uses only questions on snoring/apnea. In a representative nationwide cohort of 5177 Finnish adults aged ≥30 years, SDB-BNSQ occurred in 7.6% of the participants, and it was an independent predictor of cardiovascular events.[349] In the current study, SDB-BNSQ occurred in 22.1% of PD patients.

Both PD and OSA are said to be associated with abnormalities of the flow-volume loop in many patients.[425] In a group of PD patients without clinical signs or symptoms suggesting respiratory problems, 82% of the subjects had upper airway obstruction (UAO) or a combination of decreased effective muscle strength and possible UAO.[257] An obstructive airway disease occurs in 31% of the PD patients, and 28% of the patients have a restrictive dysfunction.[426] Both obstructive and restrictive dysfunction is related to disordered motor control of respiratory musculature. Hypothetically, the depletion of the chemosensitive glutaminergic neurons in the dorsolateral pons encompassing the nucleus of tractus solitarius and surrounding reticular formation and the ventrolateral medulla in PD may trigger the impairment of respiratory muscle control.[427, 428]

The diminished strength of respiratory muscles, hypokinesia and UAO can lead to retention of secretion and possible subsequent infection. Respiratory problems are a major cause of death in PD.[429] The pathogenesis of respiratory infections is due to the presence of dysphagia with silent aspiration or aspiration without an appropriate cough response.[430] Cough and swallow dysfunctions are coordinated to minimize the risk of aspiration, and both voluntary cough[431] and swallowing[432] are impaired in PD. Dysphagia in PD may be caused by central nervous system, i.e. degeneration of the cholinergic neurons in the pedunculopontine tegmental nucleus or Lewy-type synucleinopathy, or peripheral upper aerodigestive tract changes, i.e. Lewy-type synucleinopathy in sensory nerve terminals.[433] Classic symptoms in OSAS include choking or gasping at night.[434] Gasping has been described as snoring, gurgling, moaning, snoring, agonal or labored breathing. Choking occurs when pharyngeal phase of swallowing is impaired. Chronic cough affects 9% to 33% of the adult population[435], and 44% of patients with chronic cough in a community-based pulmonary practice have OSA defined with PSG[436].

Except for motor fluctuations due to long-term treatment with levodopa most PD patients develop nonmotor fluctuations. Among the most common dysautonomic fluctuations are drenching sweat (64%), dyspnea (40%), dysphagia (40%) and stridor (21%).[437] In our study, nocturnal sweating occurred weekly in 31.1% of the participants and it associated significantly with SDB (OR 1.8; 95% CI 1.1 to 2.8). Frequent nocturnal sweating occurs in 31.1% of OSA patients and in 11.1% of controls in the general population.[438] Prepubertal children with NREM parasomnias, i.e. night terror and sleepwalking, are frequently accompanied by SDB (58.3%) during slow-wave sleep.[439] In our study of PD patients, both nightmares (OR 2.5; 95% CI 1.4 to 4.3) and sleep talking (2.1; 1.2 to 3.5) were significantly associated with SDB independent of age, gender and RBD. Arnulf et al examined with PSG and multiple sleep latency tests 54 PD patients, who experienced OSA (20%) and narcolepsy-like phenotype (39%), but the relationship between two sleep disorders was not discussed.[224]
7. CONCLUSIONS

In Parkinson’s disease, there seems to be a significant overlap of RBD and other parasomnias and isolated sleep symptoms. Thus, if a patient with PD complains of at least weekly occurring parasomnias (nightmares and sleep talking, or sleepwalking), a clinician should suspect a possibility of RBD and consider further sleep studies in order to confirm the diagnosis.

Narcolepsy-like symptoms including daytime sleepiness, cataplexy and hallucinations are common in patients with Parkinson’s disease. Also the prevalence of narcolepsy seems to be higher in patients with Parkinson’s disease than in general population. However, there is no indication at the moment that narcolepsy patients would have an increased risk of PD. These symptoms are most probably secondary for the Parkinson’s disease. In other words narcolepsy-like symptoms are common but also narcolepsy is roughly about ten times more frequent in PD than in general population. In patients with PD early onset of RLS resembles idiopathic RLS with typical gender distribution and familial trait. Late onset RLS, with an onset after age of 45 years, is more common regardless of dopaminergic medication. The pathophysiology of RLS in PD patients may differ from that of idiopathic RLS in non-PD patients.

Insomnia symptoms including difficulty of initiating sleep, disruptive sleep and non-restorative sleep are common in patients with PD. Also the prevalence of insomnia diagnosis seems to be higher in patients with Parkinson’s disease than in general population. Both insomnia disorder as defined by the classification systems, and also the symptoms of insomnia rarely occur per se without other simultaneous sleep disorders or other comorbid medical conditions. Today the mechanistic pathways in chronic insomnia are still under debate, so it is not possible to say exactly about the association or direction of causality between insomnia and such co-occurring conditions as e.g. depression.

In PD, disrupted sleep and both short and long sleep are common. On the other hand only about 12% have difficulties to fall asleep. Poor health-related quality of life of the PD patients is associated with sleeping difficulties except long sleep. The long sleeping patients are often depressive, stressed and fatigued. More attention should be given to sleep and also the quality of sleep should be taken into consideration.

SDB is a serious medical condition that coincides with PD. On this questionnaire approach, self-reported SDB using only questions on snoring/apnea was accompanied by pulmonary disease, narcolepsy like symptoms, nightmares, sleep talking and nocturnal sweating. The pathophysiology of SDB in PD patients may differ from that of idiopathic OSA in general population.

This has been a cross-sectional questionnaire study that can at best propose new associations, and prospective follow-up studies are needed to study the clinical significance of sleep disorders and sleeping difficulties in PD.
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62


65


