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Review article

Etiologies of insomnia in Parkinson's disease – Lessons from human studies and animal models

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ABSTRACT

Sleep disorders are integral to Parkinson's disease (PD). Insomnia, an inability to maintain stable sleep, affects most patients and is widely rated as one of the most debilitating facets of this disease. PD insomnia is often perceived as a multifactorial entity – a consequence of several of the disease symptoms, comorbidities and therapeutic strategies. Yet, this view evolved against a backdrop of a relative scarcity of works trying to directly dissect the underlying neural correlates and mechanisms in animal models. The last years have seen the emergence of a wealth of new evidence regarding the neural underpinnings of insomnia in PD. Here, we review early and recent reports from patients and animal models evaluating the etiology of PD insomnia. We start by outlining the phenomenology of PD insomnia and continue to analyze the evidence supporting insomnia as emanating from four distinct subdivisions of etiologies – the symptoms and comorbidities of the disease, the medical therapy, the degeneration of non-dopaminergic cell groups and subsequent alterations in circadian rhythms, and the degeneration of dopaminergic neurons in the brainstem and its resulting effect on the basal ganglia. Finally, we review emerging neuromodulation-based therapeutic avenues for PD insomnia.

1. Prevalence and clinical manifestations of PD insomnia

Sleep symptoms are highly prevalent in idiopathic Parkinson's disease (PD) and some of them even precede the hallmark motor symptoms. Insomnia is the most common sleep symptom in PD, affecting 60% of all patients (De Cock et al., 2008; Gjerstad et al., 2007; Kryger et al., 2017), which is significantly more than in age-matched controls (Tandberg et al., 1998). The term insomnia usually refers to difficulties in sleep initiation, sleep maintenance, or awakenings which occur earlier than desired (Stefani and Högl, 2020; Zuzuárregui and Ostrem, 2020). Insomnia in PD predominantly expresses as poor sleep maintenance and early awakenings (Gros and Videnovic, 2020; Marinus et al., 2018; Tholfsen et al., 2017), is usually present early in the course of PD (Garcia-Borreguero et al., 2003; Tholfsen et al., 2017) and becomes more common (Xu et al., 2021) and severe (Gjerstad et al., 2007; Tholfsen et al., 2017; Zhang et al., 2020) with increasing disease duration. Insomnia was shown to increase the risk of cognitive decline (Stavitsky et al., 2012) and mental illness (Rutten et al., 2017; Suzuki et al., 2009). It is consistently reported by patients to exert a substantial negative impact on their health-related quality of life (Duncan et al., 2014; Forsaa et al., 2008; Shafazand et al., 2017; Shearer et al., 2012), and was rated as one of the most bothersome PD symptoms in a population of advanced PD patients (Politis et al., 2010).

2. Sleep architectural changes in PD insomnia

In clinical practice and research, insomnia is evaluated subjectively through questionnaires, individually or jointly with other sleep symptoms, or objectively using polysomnography. Polysomnography refers to a number of measures, mostly EEG, EMG and EOG, which are used to determine the stages of the vigilance cycle, namely wakefulness, REM (rapid eye movement) sleep and non-REM sleep. Non-REM sleep breaks

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down into N1 which is a transitional and relatively shallow sleep stage, N2, which constitutes most non-REM sleep time, and deeper slow wave sleep (SWS, or N3).

Patients with PD experience changes in sleep macro-structure and sleep micro-structure (Stefani and Högl, 2020). Sleep macro-structure usually refers to the overall architecture of sleep and the relative predominance of the different sleep stages. A systematic review and meta-analysis of studies using polysomnography in PD patients reported decreases in total sleep time, SWS, REM sleep and sleep efficiency, which is the fraction of sleep out of total night time. Also, it revealed an increase in REM sleep latency and wakefulness after sleep onset, demonstrating that sleep is poor in both amount and quality (Zhang et al., 2020). Fig. 1 shows an exemplary hypnogram from a healthy non-human primate and a hypnogram from the same animal after the induction of experimental Parkinsonism that was associated with severe insomnia. Note the fragmentation of non-REM sleep as well as the decrease in SWS and frequent awakenings.

Sleep micro-architecture refers to finer details of the EEG, and specifically its spectral components. In an early study, the power spectrum of non-REM sleep EEG was found to contain significantly less power in the 0.78–1.2 Hz range (low-delta or slow oscillation, characteristic of deeper sleep) and non-significantly more sigma range (12–16 Hz) power in drug-naïve patients relative to age-matched controls. Interestingly, this EEG spectral signature paralleled a trend toward increased wakefulness and decreased sleep efficiency and SWS (Brunner et al., 2002). An increased EEG sigma power in de novo patients was then corroborated by a more recent work (Margis et al., 2015). Another work reported increased sleep spindle duration and peak to peak amplitude (but decreased spindle density, i.e. number of spindles per minute), as well as a trend toward decreased sleep efficiency, in PD patients vs. controls (Christensen et al., 2015). As sleep spindles are ~1 s EEG events in the 10–16 Hz range, the increase in spindle amplitude and duration and the increased EEG sigma power may represent two sides of the same coin.

An early destabilization of non-REM sleep in PD patients was also suggested by analysis of cycling alternating pattern (CAP) sequences in the EEG. CAP sequences are repetitive clusters of stereotyped EEG activity (phase A) superimposed on theta/slow oscillation background activity (phase B), lasting 2–60 s. Phase A activity breaks down into different subtypes, representing varying degrees of desynchronization (phase A1 represents a relatively synchronized sequence, while phase A3 represents a desynchronized sequence). The more desynchronized the activity is, the more it is taken to represent bouts of arousal within sleep. Thus, non-REM sleep instability is indicated by an increase in overall CAP rate, i.e. the total time of CAP sequences during sleep, and especially by a decrease in synchronized A1 sequences (Parrino et al., 1998). In a study utilizing CAP measures to evaluate early changes in sleep micro-architecture, PD patients exhibited overall increased wakefulness after sleep onset and a decrease in SWS and sleep efficiency. While in all PD patients CAP rates were increased and A1 phases were decreased, when the analysis was broken down to early vs. late PD patients, early PD patients did not exhibit changes in macro-architecture, but only an increase in CAP rate and a decrease in A1 phases (Priano et al., 2019). Thus, micro-architectural changes could represent the first signs for the destabilization of slow EEG rhythms, predicting later changes in SWS and sleep efficiency.

3. Etiologies of PD insomnia

The etiology of insomnia in PD is multifactorial. This is a reflection of the fact that PD is a complex and multifaceted pathological process that results from several degenerative processes diverging in anatomic location and timing in the disease natural history. The next section provides a wide account of the etiologies of insomnia in Parkinson's, discussing data from human patients as well as from animal models of PD. We divide the etiologies of insomnia to four different groups (Fig. 2). First, we describe the relationship between PD insomnia and the symptoms and comorbidities of PD. This section deals with the motor symptoms, the mental comorbidities of PD (depression, anxiety, and hallucinations), its non-insomnia sleep-wake comorbidities (REM sleep behavior disorder and restless legs syndrome) and finally nocturnal non-motor symptoms (nocturia and nocturnal pain). Next, we evaluate the possible contribution to insomnia of the medical therapy of PD. We then address the degeneration of non-dopaminergic cell groups in the brain (namely orexin, serotonin, noradrenaline, histamine and acetylcholine) and a possible involvement of the circadian system. Finally, we review a possible contribution to insomnia by dopaminergic denervation. In this last section, we briefly handle a possible role for the basal ganglia (BG) in sleep maintenance, discuss the mechanisms through which

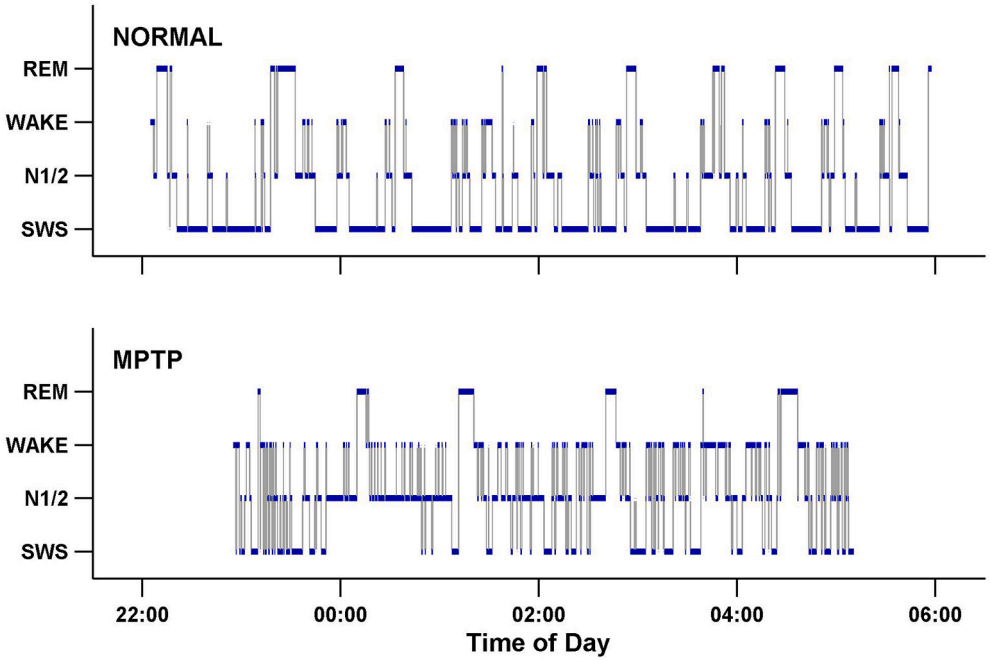

Fig. 1. Example of a normal hypnogram (top) and a hypnogram after MPTP intoxication in a primate model of Parkinson's disease (bottom).

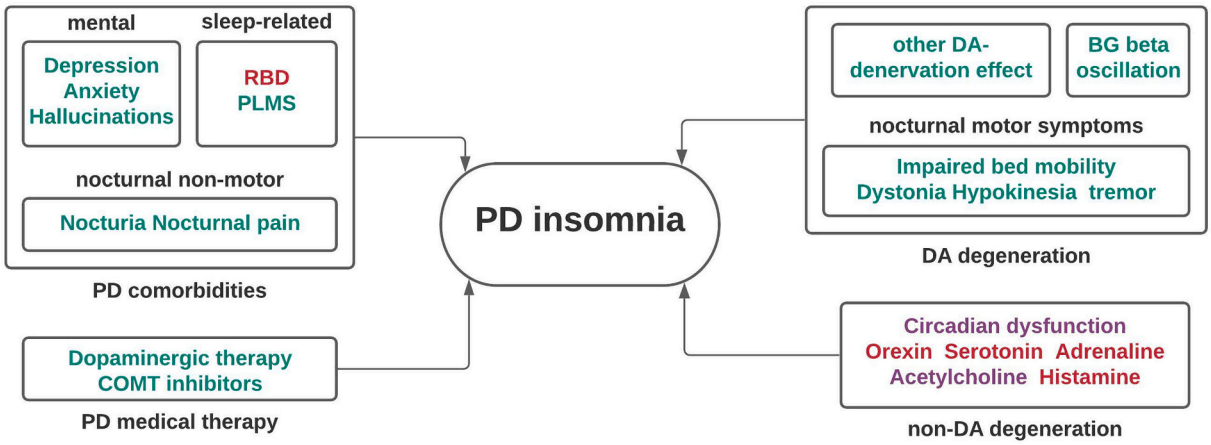

Fig. 2. Etiologies of PD insomnia. The different etiological factors are grouped into subdivisions and marked according to the strength of evidence relating them to PD insomnia. Green represents probable association, red represents lack of evidence for association and purple represent a probable relationship that has not yet been convincingly demonstrated. BG, basal ganglia; COMT, catechol-*O*-methyltransferase; DA, dopamine; PD, Parkinson's disease; PLMS, Periodic leg/limb movements; RBD, REM sleep behavior disorder. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dopaminergic denervation might affect insomnia and present emerging techniques using BG neuromodulation to ameliorate PD insomnia.

3.1. PD symptoms and comorbidities

PD is hallmarked by its waking motor symptoms, some of which may persist into sleep. Further, PD is comorbid with a number of conditions, which may independently interfere with sleep initiation or maintenance. These may be grossly divided into three divisions - mental comorbidities, accompanying sleep-wake disorders and nocturnal non-motor symptoms.

3.1.1. PD nocturnal motor symptoms

Classical results point to an attenuation of PD tremor (Stern et al., 1968) and rigidity (Arnaldi et al., 2016) during sleep. Nevertheless, some of the motor symptoms in PD are reflected in altered movements during sleep – nocturnal hypokinesia (Louter et al., 2012), early-morning dystonia (Dhawan et al., 2006; Muntean et al., 2016) and impaired bed mobility (Xue et al., 2018), which could result from increased muscle rigidity in comparison to normal sleep. Further, tremor itself attenuates during sleep, but is still present in nocturnal waking bouts (Muntean et al., 2016). A questionnaire-based study found that self-reported nocturnal hypokinesia was correlated with lower self-reported sleep quality (Louter et al., 2012). Impaired bed mobility in PD was associated with significantly lower sleep efficiency and total sleep time (Louter et al., 2013; Xue et al., 2018). In another study, fluctuations in the severity of motor symptoms (a result of dopaminergic treatment) were significantly correlated with complaints of difficulty falling asleep, increased nocturnal wakefulness, early awakenings and obtaining too little sleep (Zhu et al., 2016). Significant direct support to a possible contribution of nocturnal motor symptoms to insomnia comes from the finding that subthalamic nucleus (STN) deep brain stimulation (DBS) during sleep is associated with an improvement of subjective sleep quality (Baumann-Vogel et al., 2017) and reductions in insomnia and sleep fragmentation in PD (Baumann-Vogel et al., 2017; Zuzuárregui and Ostrem, 2020).

Notably, some reports examining the correlation between subjective or objective insomnia measures (e.g., sleep latency, total sleep time, sleep efficiency) and general measures of PD motor disability, like the motor section of the unified Parkinson's disease rating scale (UPDRS) or the Hoehn and Yahr score, returned negative results (Diederich et al., 2005; Gjerstad et al., 2007; Tholfsen et al., 2017; Xu et al., 2021). This may suggest that the degree of motor disability during wakefulness and during sleep may not necessarily be highly correlated for all patients.

3.1.2. Mental comorbidities of PD

3.1.2.1. Depression and anxiety. PD is associated with a host of neuropsychiatric disorders, including depression and anxiety, psychosis and hallucinations (Aarsland et al., 2009). Clinically significant depression, predominantly mild, is reported in 35–42% of PD patients (Reijnders et al., 2008; Slaughter et al., 2001), making depression substantially more prevalent in PD patients than in age-matched controls or in the general population (Rutten et al., 2017). Anxiety affects 30–40% of PD patients (Aarsland et al., 2009). Follow-up studies indicate depression as a strong and consistent risk factor for the development of insomnia in PD (Gjerstad et al., 2007; Tholfsen et al., 2017; Zhu et al., 2016). Similarly, baseline anxiety symptoms were also predictive of future insomnia (Rutten et al., 2017). Depression and anxiety are also correlated with concurrent poor sleep quality (Borek et al., 2006; Caap-Ahlgren and Dehlin, 2001; Ratti et al., 2015). Interestingly, the female sex has also been identified as a risk factor for insomnia in PD (Gjerstad et al., 2007), but this is probably also due to the fact that the female sex is an independent risk factor for depression (Marinus et al., 2018).

Depression and anxiety are independently related with insomnia in the general population (Ohayon and Roth, 2003), and insomnia is a hallmark complaint needed for diagnosis in depressive disorders (Marinus et al., 2018). In a meta-analysis of polysomnographic studies assessing sleep disturbances in numerous mental conditions unrelated to PD, major depression was found to be associated with decreased sleep efficiency, longer sleep onset latency, increased number of awakenings, longer duration of stage N1 sleep and shorter duration of N2 and SWS (Baglioni et al., 2016), which also characterize the polysomnographic picture in PD insomnia.

Whether or not the Parkinsonian condition itself is synergistic with depression or anxiety in driving insomnia is hard to disambiguate. In one study, Kay and colleagues show that shorter self-reported total sleep time on the Pittsburgh Sleep Quality Index (a questionnaire that subjectively assesses sleep quality over a 1-month period) was associated with depression severity in early-stage PD patients, but not in matched controls. However, the association between actual insomnia severity and depression severity was not different between groups (Kay et al., 2018). A direct causal contribution for affective disorders in PD insomnia is hard to establish due to the fact that this connection is probably bidirectional (Rutten et al., 2017), and owing to the lack of satisfactory animal models for psychiatric comorbidities in PD.

3.1.2.2. Hallucinations. Hallucinations, predominantly visual, are the

most common psychotic symptom in PD (Aarsland et al., 2009). Affecting as many as 30% of patients receiving dopaminergic treatment (Graham et al., 1997), hallucinations are commonly regarded as a complication of medical therapy. However PD hallucinations are also suggested to result from α-synuclein related degenerative processes in the brain (Onofrj et al., 2007). Hallucinations often occur at night (Aarsland et al., 2009) and are correlated with worse sleep quality and more severe sleep disturbances (Gama et al., 2015). Alterations in dream content are also relatively common during chronic dopaminergic treatment (Sharf et al., 1978), and were found to be strongly correlated with sleep fragmentation (Pappert et al., 1999). As before, any causal relationship between insomnia and night-time hallucinations or altered dream content is probably bidirectional and complicated by other sleep disorders common in PD, such as REM sleep behavior disorder (Onofrj et al., 2007).

3.1.3. Non-insomnia sleep disorders in PD

3.1.3.1. REM sleep behavior disorder. REM sleep behavior disorder (RBD) is characterized by a loss of muscle atonia and the onset of complex motor behavior (vocalization, laughing, crying and limb movements that may reflect dream contents and can be violent) during REM sleep. RBD is strongly associated with synucleopathies in general and with PD in particular (St Louis et al., 2017). A meta-regression analysis reported a pooled RBD prevalence of 42.3% in PD patients (Zhang et al., 2017). Furthermore, RBD is a strong predictor of PD years to decades after its diagnosis: nearly 97% of RBD patients convert to an α-synuclein neurodegenerative disease after 14 years of follow-up, and most converters develop PD (Galbiati et al., 2019). Vocalizations and movements that may even lead to injury appear as natural candidates to accelerate insomnia, both directly and indirectly through patient and partner anxiety. However, a systematic review of polysomnographic studies assessing PD patients with and without RBD detected no difference in polysomnographic measures other than a slight increase in REM sleep percentage in PD + RBD patients (Zhang et al., 2020). Indeed, insomnia in PD is usually discussed in the context of non-REM sleep, so a sleep disorder involving REM sleep is not likely to represent a central driver for PD insomnia.

3.1.3.2. Restless legs syndrome and periodic limb movements. Restless legs syndrome is defined as an urge to move the legs, usually accompanied or triggered by uncomfortable or unpleasant sensations in the legs. To meet criterion, these symptoms must 1) occur predominantly during rest or inactivity, 2) be partially or totally relieved by movement, and 3) occur primarily in the evening or night (Sateia, 2014). Periodic leg or limb movements during sleep (PLMS) are repetitive and stereotyped limb movements, usually of the big toe, the ankle, or the knee, that occur during sleep. They are not unique to patients with RLS, but were shown to carry a genetic risk for RLS (Högl and Stefani, 2017). PD patients receiving therapy (in contrast to de novo PD patients) are probably more prone to RLS (Trenkwalder et al., 2016), and PD is also associated with an increased frequency of PLMs per hour during sleep (PLM index) (Zhang et al., 2020). Further, in a small group of PD patients, the number of PLMS was negatively correlated with the degree of dopamine transporter binding in the striatum (Happ et al., 2003), suggesting an association between PLM and dopaminergic degeneration. A meta-analysis of polysomnographic studies in PD revealed that an increase in PLM index is associated with a decrease in SWS and an increase in the more superficial sleep stage, N1, speaking in favor of a possible involvement of PLMS in PD insomnia (Zhang et al., 2020).

3.1.4. Nocturnal non-motor symptoms

3.1.4.1. Nocturia. Nocturia refers to the increased need to wake up in order to pass urine during the night (Mantovani et al., 2018). Usually cited by patients as one of their most common non-motor symptoms, most works report its prevalence in PD patients to exceed 60% (Barone et al., 2009; Cheon et al., 2008; Martinez-Martin et al., 2007; Vaughan et al., 2013). Nocturia is generally more common in men and in older patients, and increases with disease duration and severity. It is probably multifactorial, stemming from a variety of PD- and non-PD-related symptoms, like detrusor muscle hyperactivity, benign prostatic hyperplasia (BPH) and polyuria (increased urine production) (Barone et al., 2009; Chahine et al., 2017).

One study evaluated the association between nocturia and polysomnographic measures in PD patients. The majority of patients had two or more episodes of nocturia per night, and nocturia was independently associated with decreased sleep efficiency and total sleep time in PD patients. Further, the self-reported bother associated with nocturia was found to predict lower total sleep time and sleep efficiency within the group of patients with 2–3 episodes of urine passing per night (Vaughan et al., 2013). Similar results were reported also in a non-PD population of older adults (Parthasarathy et al., 2012), suggesting that this effect is not unique to PD. Further, PD is associated with increased urinary frequency and urgency also during daytime (Verbaan et al., 2007), suggesting that the above relationship is not specific to sleep. Nevertheless, judging by the relative high prevalence of nocturia in PD patients, it is probable that it constitutes a major independent factor in disrupting sleep in PD.

3.1.4.2. Nocturnal pain. Pain is highly prevalent in PD, affecting two thirds of patients and mostly bearing a musculoskeletal character and centering on the lower limbs (Broen et al., 2012). Mao and colleagues reported that PD patients with pain (not necessarily nocturnal) were more likely to report insomnia than PD patients with no pain or controls (Mao et al., 2015). Further, patients who specifically reported nocturnal pain had higher Parkinson's Disease Sleep Scale-version 2 (PDSS-2) scores, but this subjective score jointly evaluated insomnia along with other sleep symptoms (Martinez-Martin et al., 2019).

3.2. PD pharmacological therapy

Dopaminergic and other treatment is prescribed to PD patients from an early stage of their disease. The different medications have varying effects on the sleep-wake cycle, and some of them are implicated in insomnia.

Dopaminergic medication is associated with excessive daytime sleepiness and sleep attacks in a dose-dependent manner (Wallace et al., 2020). It was also identified to constitute an independent factor associated with insomnia in PD (Tholfsen et al., 2017; Zhu et al., 2016). A meta-analysis of random control trials examining the effect of various medications on subjective insomnia (not necessarily in PD) implicated levodopa, the dopaminergic agonists ropinirole, rotigotine, pramipexole, and lisuride, and the catechol-*O*-methyltransferase (COMT) inhibitor tolcapone with insomnia. However, when only data obtained from PD patients was considered, only pramipexole and tolcapone were significantly and consistently associated with insomnia (Doufas et al., 2017). A different meta-analysis of trials assessing the safety of several types of PD medications found an insomnia odds ratio of 1.59 for COMT inhibitors vs. placebo and of 1.28 for dopamine agonists vs. placebo (Stowe et al., 2010). However, significance was not reached for the dopamine agonist case. Finally, a systematic review and meta-analysis of studies using polysomnography in PD patients reported that increased levodopa equivalent dose (LED) was associated with increased wakefulness after sleep onset and decreased total sleep time (Zhang et al., 2020).

The time in which the drug is being taken relative to sleep also seems to be important: when taken within 4 h of sleep, greater LEDs were associated with subjective and objective insomnia in early stage PD patients (Chahine et al., 2013). A possible strategy to benefit from the

advantages of therapy in alleviating motor symptoms without suffering its sleep-destabilizing effects could thus be to use dopaminergic drugs earlier in the day (Chahine et al., 2017). However, this may also negatively affect sleep through decreased control over the motor symptoms.

Indeed, the association between PD treatment and insomnia is probably not straight-forward. A direct causal relationship between PD therapy and insomnia is complicated by at least three factors. First, insomnia itself is multifactorial, and a single medication could differently affect it through dissociable mechanisms, e.g., an ameliorating effect through decreasing motor symptoms, and an aggravating effect through increasing hallucinations (Chaudhuri et al., 2006) or nocturia (Uchiyama et al., 2009). Second, dopaminergic neuromodulation in the brain is complex, involving several different pathways and distinct types of receptors (Monti et al., 2016). It is probable that dopaminergic signaling in different synaptic pathways (i.e., mesolimbic vs. nigrostriatal) has non-overlapping effects on sleep and alertness (Rye and Jankovic, 2002). Exogenous administration of dopaminergic therapy circulating through the blood and the CSF is obviously blind to this complexity. Third, a single therapeutic agent could have a different effect in lower vs. higher doses (Chahine et al., 2017; Lagos et al., 1998).

3.3. Degeneration of non-dopaminergic pathways

The pathological correlate of the motor symptoms of PD is the progressive and irreversible degeneration of dopaminergic neurons in the midbrain substantia nigra pars compacta (SNc) due to the deposition of α-synuclein immunopositive Lewy neurites and Lewy bodies. This results, through dopaminergic denervation of the BG and the resulting disruption of their normal physiology, in rigidity, bradykinesia, resting tremor and postural instability (Poewe et al., 2017). However, the multitude of non-motor symptoms prevalent in PD, some uncorrelated in severity and natural history with the motor symptoms, attests to a significantly wider underlying degenerative process. Indeed, alongside the midbrain, the neurodegenerative process in PD encompasses the medulla oblongata and pons, the basal forebrain, the hypothalamus and the neocortex, as well as neurons outside the CNS (Braak et al., 2003). Sleep is orchestrated by neuromodulatory groups located in some of these structures, and their degeneration could constitute an independent cause for insomnia in PD.

3.3.1. Orexin

Some of the sleep symptoms in PD, namely excessive daytime sleepiness, alterations in REM sleep (RBD and sleep-onset REM periods), and nocturnal sleep fragmentation, resemble those found in narcolepsy. Narcolepsy results from the degeneration of orexin neurons in the lateral hypothalamus (Arnulf et al., 2000a; Fronczek et al., 2007; Thannickal et al., 2007). Indeed, a post-mortem study revealed that relative to matched controls, PD patients had less orexin neurons and decreased orexin levels in the CSF and in the prefrontal cortex. Further, the presence of Lewy bodies was verified in the hypothalamic orexin cell area in PD patients (Fronczek et al., 2007). Finally, the loss of orexin neurons in PD brains was correlated with the clinical stage of PD (Thannickal et al., 2007) and so was the decrease in CSF orexin levels (Drouot et al., 2003).

Orexin neurons project to the monoaminergic and cholinergic cell groups of the arousal systems, are mostly active during waking, and are hypothesized to reinforce arousal and stabilize wakefulness (Saper et al., 2005). Rodent experiments demonstrated that the knock-out of orexin neurons results in the fragmentation and destabilization of sleep and wakefulness (Chemelli et al., 1999; Diniz Behn et al., 2010; Mochizuki et al., 2004). The mechanism by which intact orexinergic signaling might contribute to sleep stability was postulated to be an indirect one, via an increase in homeostatic sleep drive due to consolidated daytime wakefulness (Saper et al., 2005).

Works trying to validate the association between CSF orexin levels in PD patients and their sleep disorders have produced inconclusive results. One study reported a correlation between objective sleepiness and decreased CSF orexin levels (Wienecke et al., 2012). In other works, lumbar CSF orexin levels in PD patients, some of which had excessive daytime sleepiness, were not lower than control values (Baumann et al., 2005; Compta et al., 2009; Overeem et al., 2002; Ripley et al., 2001; Yasui et al., 2006). It is possible that the difference stems from a ventricular vs. lumbar CSF origin. However, lumbar CSF orexin levels were undetectable in narcoleptic patients (Ripley et al., 2001), suggesting that lumbar CSF levels are an accurate measure for orexinergic neuronal activity. At any rate, none of the above studies correlated orexin levels with insomnia or sleep fragmentation. A recent study reported increased plasma orexin levels in PD insomnia (Huang et al., 2021), making the putative relationship between orexinergic neuronal loss and insomnia in PD even less straight-forward.

Rodent works examining sleep/wakefulness alterations in animals that underwent combined dopaminergic and orexinergic lesions do not support a direct role for orexinergic neuronal loss in insomnia when an additional dopaminergic deficit is present. Oliveira and colleagues used 6-hydroxydopamine (6-OHDA) lesions in the dorsal striatum to achieve a marked midbrain dopaminergic lesion and a modest lateral hypothalamic orexinergic lesion, with no substantial change in the time spent in wakefulness or non-REM sleep (Oliveira et al., 2018). In another experiment, rats were fed pellets made from Cycad seed flour, that was associated with the development of Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex in humans, possibly due to the presence of a phytosterol neurotoxin (Shen et al., 2010). In rats, cycad flour consumption elicited both motor and non-motor Parkinsonian symptoms, but not ALS symptoms. Pathologically, it was associated with a progressive nigrostriatal dopaminergic (Shen et al., 2010) and orexinergic degeneration (McDowell et al., 2010). The lesioned rats showed changes in wakefulness and non-REM sleep during the active phase but not during the quiescent phase of their vigilance cycle (McDowell et al., 2010), arguing against a dopaminergic/orexinergic involvement in nocturnal insomnia.

3.3.2. Serotonin

Serotonergic innervation from the brainstem raphe nucleus is postulated to promote wakefulness (Monti, 2011). A meta-analysis of reports utilizing positron emission tomography (PET) imaging of the serotonin transporter to study serotonergic innervation in PD reported a decrease in serotonergic activity in PD relative to controls (Pagano et al., 2017). Serotonin transporter availability in the raphe nuclei has been shown to be lower already in early stages of PD (Qamhawi et al., 2015) and to decrease progressively over the natural history of the disease (Pasquini et al., 2020). However, in none of these works was serotonergic denervation reported to associate with any sleep symptoms. Importantly, one recent work did report a correlation of serotonin loss in the striatum, raphe and hypothalamus with the severity of sleep symptoms. However, these symptoms were assessed using a general score that jointly evaluated a number of PD sleep disorders, including insomnia, RBD, restless legs syndrome, vivid dreaming and excessive daytime sleepiness (Wilson et al., 2018). Similarly, another study found a correlation between α-synuclein pathology in the raphe nuclei and disturbed sleep, but evaluated sleep symptoms generally and was not specific to insomnia (Kalaitzakis et al., 2013). This relationship was not unique to the raphe nuclei: similar correlations were found with α-synuclein pathology in the locus coeruleus (see below), amygdala, and hypothalamic, cortical and thalamic regions, exemplifying the complexity of sleep symptoms in PD and the probable lack of one underlying cause.

3.3.3. Noradrenaline

Another source of widespread wakefulness-reinforcing innervation is the locus coeruleus (LC) (Saper et al., 2005; Szabadi, 2013). Noradrenergic neurons in the LC are affected early in the PD-related neurodegenerative process (Braak et al., 2003; Del Tredici et al., 2002). Imaging studies correlated the degree of noradrenergic deficit in PD either with

sleep symptoms generally (Kalaitzakis et al., 2013) or with RBD symptoms, rather than insomnia (Sommerauer et al., 2018). Evidence connecting loss of noradrenergic signaling with non-REM sleep microstructure are rare: A recent work reported decreased CAP rate (suggesting less sleep fragmentation, rather than the expected increased fragmentation. See Section 2 above) in PD patients which was correlated with the degree of noradrenergic dysfunction. This micro-architectural sleep change was found in the absence of a difference in polysomnographic sleep macro-parameters (Doppler et al., 2021). These results might suggest that LC degeneration is associated with a decreased ability to drive micro-arousals rather than stabilize sleep. In accordance with these findings, a transgenic mouse model expressing human α-synuclein specifically in the LC has reported an increase in sleep latency. This effect was normalized by adrenergic receptor antagonists, suggesting that the behavioral phenotype resulted from enhanced noradrenergic neurotransmission, rather than noradrenergic degeneration (Butkovich et al., 2020). In summary, the above results do not draw a causal connection between noradrenergic degeneration in PD and insomnia.

3.3.4. Histamine

Histaminergic neurons of the tuberomammillary nucleus (TMN) in the posterior hypothalamus target the cortex, BG and thalamus, as well as structures orchestrating sleep and wakefulness in the brainstem, basal forebrain and hypothalamus. Exerting an excitatory input that is highly specific to wakefulness, they are strategically positioned to drive cortical activation (Lin et al., 2011). Indeed, a large body of work demonstrates their role in maintaining normal wakefulness (Lin, 2000; Parmentier et al., 2002). Although Lewy bodies and Lewy neurites are found in the TMN in PD, neuronal histamine production is not affected by PD (Shan et al., 2012), histaminergic neurons themselves do not appear to degenerate (Nakamura et al., 1996) and the level of histamine synthesis, as judged by the mRNA levels of the rate-limiting enzyme, L-histidine decarboxylase, is not different between PD and controls (Garbarg et al., 1983). We are not aware of data relating changes in histamine levels in PD with insomnia.

3.3.5. Acetylcholine

Pedunculopontine nucleus (PPN) and laterodorsal tegmental (LDT) nucleus cholinergic neurons are active during wakefulness and REM sleep, as reported by recent works employing electrophysiology and calcium imaging (Boucetta et al., 2014; Cox et al., 2016). They are postulated to support these states of cortical arousal through their thalamic projections which regulate cortical activity (Chambers et al., 2020). However, rather than a tonic increase in firing during wakefulness and REM sleep, they display transient increases in firing around brain state transitions, suggesting that cholinergic firing may not be necessary for the maintenance of arousal (Kroeger et al., 2017; Mena-Segovia and Bolam, 2017). Cholinergic projections also promote muscle atonia during REM sleep through their projections to the subcoeruleus dorsalis and nucleus reticularis gigantocellularis neurons (Chambers et al., 2020).

PPN neurons are also subject to degeneration in PD (Rinne et al., 2008), and cholinergic loss was reported to associate with RBD in this disease (Kotagal et al., 2012). Along the same lines, a case report of three RBD patients found improvement of RBD symptoms on donepezil, an acetylcholine esterase inhibitor (Ringman and Simmons, 2000). PPN-DBS was reported to increase REM sleep in PD patients. It also had a subjective and objective beneficial effect on sleep fragmentation, increasing sleep efficiency (in an additive manner over STN-DBS) and stage N2 and decreasing awakenings (Alessandro et al., 2010; Peppe et al., 2012). However, it is hard to discern whether these effects are mediated through the PPN cholinergic cells. The possible contribution of a PPN lesion to sleep fragmentation in PD was evaluated in the MPTP-treated macaque model of PD by Belaid and coworkers. MPTP intoxication resulted in a decrease in REM sleep, as well as a decrease in SWS and increase in awakenings, similarly to PD insomnia. An additional acute cholinergic PPN lesion induced a transient increase in sleep fragmentation and a decrease in sleep efficiency and REM sleep. These effects were transient, and in a few weeks sleep efficiency and nocturnal awakenings improved relative to the post-MPTP state (Belaid et al., 2014). Further work in animal models is needed to more directly investigate a possible relationship between cholinergic degeneration in PD and insomnia.

Emerging from the above mentioned results and considerations is the notion that the orexinergic, serotonergic, noradrenergic, histaminergic or cholinergic neuronal degenerative processes cannot fully account for insomnia in PD. Rather, these pathological changes are probably related to other sleep disorders, such as excessive daytime sleepiness and RBD.

3.3.6. Melatonin and circadian rhythms

Sleep fragmentation and increased wakefulness after sleep onset, which are defining hallmarks of insomnia, along with excessive daytime sleepiness, could represent an underlying circadian defect. Indeed, PD patients exhibit alterations in the 24-h daily profiles of other behaviors, not related to sleep (Fifel, 2017). These alterations include flattening of diurnal motor patterns in patients with severe PD (Van Hilten et al., 1993), increased variability in rest-activity rhythms within individual days (Whitehead et al., 2008) and increased between-day variability in the timing of daily life activities (Santiago et al., 2010). Physiologically, the circadian dysfunction in PD manifests in changes in cortisol basal level and rhythms (Hartmann et al., 1997) and in altered rhythms of blood pressure and heart rate, to mention a few examples (Fifel, 2017).

However, the suprachiasmatic nucleus (SCN), which orchestrates the innate circadian rhythms and entrains them to the external daily light/dark phases, is relatively spared by the Parkinsonian degenerative process (Langston and Forno, 1978) and so is the pineal gland, that secretes melatonin (Critchley et al., 1991). Consistently, the daily profile of melatonin secretion was similar between non-medicated PD patients and controls (Bolitho et al., 2014; Bordet et al., 2003). On the other hand, circadian melatonin secretion could be affected by dopaminergic therapy, possibly through a pineal gland- or SCN-mediated dopaminergic effect (Fifel, 2017). MPTP-intoxicated non-human primates showed intact rhythms in a normal day/light regime, but displayed severely disturbed locomotor rhythms when exposed to constant light, suggesting that in this animal model the normal circadian rhythm is more dependent on environmental timing cues (Fifel et al., 2014).

Thus, although mechanistic evidence is currently lacking, it is plausible that PD patients indeed suffer from alterations in innate circadian rhythms. It is also conceivable that insomnia and excessive daytime sleepiness, due to the lack of consolidated sleep and wakefulness, could further destabilize the circadian rhythms in patients, and that the disorganized circadian activity itself could in its turn worsen insomnia.

3.4. Degeneration of dopaminergic pathways

The degeneration of midbrain SNc neurons and the resulting dopaminergic denervation of the basal ganglia (BG) is widely regarded as the defining pathological alteration in PD and the root cause of its motor symptoms. However, as evidence regarding the role of BG circuits and dopaminergic networks in sleep regulation accumulates over the past years, a possible contribution for BG pathology to PD sleep symptoms is postulated and studied. This section will discuss recent work focusing on the effect of BG lesions and dopaminergic denervation on sleep in PD patients and in animal models of PD. The contribution of the motor symptoms to PD insomnia is discussed in Section 3.1.1. above.

3.4.1. Basal ganglia involvement in sleep maintenance

Neurons in most BG structures change their firing rates and patterns across the different stages of sleep (Mahon et al., 2006; Mizrahi-Kliger et al., 2018; Urbain et al., 2000). This is true for BG input structures like the striatum and STN, for the GPe (Globus Pallidus, external segment), a

central structure in the BG network, and for the BG output structures (the SNr, Substantia Nigra pars reticulata and GPi, Globus Pallidus, internal segment). Generally, firing rates and cFos expression are higher in the BG during wakefulness and REM sleep than during non-REM sleep (Mizrahi-Kliger et al., 2018; Vetrivelan et al., 2010).

A series of lesion experiments suggested that intact BG structures are needed for the maintenance of wakefulness and sleep. Gerashchenko and colleagues elicited insomnia with increased locomotion in rats using a lesion of the SNr (a BG output structure) and SNc (Gerashchenko et al., 2006). Qiu and coworkers showed that bilateral ibotenic acid lesions in the caudate-putamen in rats resulted in reduced wakefulness and in fragmentation of sleep-wake behavior, while lesions of the accumbens core and GPe resulted in increased wakefulness and a decrease in non-REM sleep bout duration. The relatively minor effects of STN and SNr lesions prompted them to suggest that the BG might modulate sleep through a cortico-striato-pallido-cortical loop (Qiu et al., 2010). A later work from the same group showed that unilateral high-frequency DBS of the GPe in rats increased non-REM and REM sleep (Qiu et al., 2016b). Finally, optogenetic or chemical inhibition of BG output neurons in the SNr in mice greatly decreased sleep, indicating the importance of their endogenous spiking activity in sleep generation (Lai et al., 2021; Liu et al., 2020).

Huntington's disease (HD), which is associated with the degeneration of striatal medium spiny neurons, is also associated with sleep abnormalities. Like PD, sleep impairments are significantly more common in HD patients than in controls, reaching a prevalence of 58% (Aziz et al., 2010), and insomnia is a very common complaint, shared by most patients (Arnulf et al., 2008). A recent systematic review and meta-analysis of polysomnographic data from HD patients reported decreased sleep efficiency and SWS, and increased N1 sleep and wakefulness after sleep onset, some of which were correlated with disease severity (Zhang et al., 2019). Given that the BG represents the major brain area where the two divergent pathological pathways of PD and HD converge, the similarity in the polysomnographic signatures of insomnia in these two diseases is consistent with a direct involvement of BG in sleep maintenance.

3.4.2. Direct effect of the dopaminergic denervation

The finding that intact BG circuits are important for sleep integrity does not in itself indicate that BG dopaminergic innervation is needed to maintain sleep or that the lack thereof triggers insomnia. A first indication for the role of dopaminergic innervation of the BG in the vigilance cycle is the finding that striatal dopamine concentrations (Ghosh et al., 1976), as well as dopamine receptor binding (Lim et al., 2011; Volkow et al., 2008, 2012), change following sleep deprivation.

A possible contribution of SNc degeneration to PD insomnia is suggested by studies using chemical or anatomic lesions of the SNc in animal models. The 6-OHDA rodent model of PD uses direct, usually unilateral, injection of the 6-OHDA toxin, generating reactive oxygen species through inhibition of mitochondrial function and resulting in the death of cells having dopamine transporters (De Castro Medeiros et al., 2019). This results in an extensive SNc cell loss modeling unilateral severe PD. Due to the relatively specific nature of the lesion, this model allows a direct interrogation of the role of SNc neurons, unlike other models where many cell groups and structures are affected.

Works in rats showed that 6-OHDA lesions of the SNc or its afferents to the striatum produced severe sleep fragmentation and increased wakefulness in the inactive phase of the circadian rhythm (Ciric et al., 2019; Oliveira et al., 2018; Qiu et al., 2016a; but see Vo et al., 2014). In one study, subsequent optogenetic stimulation of dopaminergic terminals in the striatum served to increase total sleep and delta power (Qiu et al., 2016a). This was not reproduced in a 6-OHDA lesion of the ventral tegmental area (VTA), the source of mesolimbic and mesocortical dopaminergic innervation (Sakata et al., 2002), or when 6-OHDA was injected to the ventricle (Monti et al., 1999), suggesting that the increase in wakefulness is dependent specifically on an SNc defect. A study using injections of the neurotoxin hypocretin2-saporin into the VTA and SNc of rats showed that only after SNc injections (and the resulting local dopaminergic degeneration) was quiescent-phase insomnia attained (Gerashchenko et al., 2006). A dedicated study designed to examine the role of VTA in the vigilance cycle reported increased VTA activity predominantly during wakefulness and demonstrated that these neurons are necessary for arousal (Eban-Rothschild et al., 2016). Finally, a different model for dopaminergic denervation, utilizing subcutaneous rotenone (a mitochondrial complex-I inhibitor) injections to model PD through SNc degeneration, reported increased wakefulness and decreased SWS during the inactive phase in rats (Yi et al., 2007). However, it is likely that lesions achieved with systemic injections are less region-specific, making it harder to parse out the exact effect of dopaminergic innervation on sleep stability. Taken together, these reports suggest that dopaminergic innervation of the striatum, originating specifically from SNc, is needed for sleep maintenance in the quiescent phase of the vigilance cycle in rodents.

Genetic models of Parkinson's disease in rodents usually produce inconsistent results in relation to insomnia. This is probably due to the relative variation in the underlying modeled pathological process (α-synuclein overexpression, mitochondrial dysfunction etc.) (De Castro Medeiros et al., 2019).

Systemic intoxication of non-human primates with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in marked midbrain SNc dopaminergic denervation and relatively severe Parkinsonism, along with a degeneration of other cell groups. Shown to replicate the major biochemical, pathological, and clinical signs of PD (Fox and Brotchie, 2010), the MPTP primate model is therefore regarded a leading model for idiopathic PD. The effect of MPTP intoxication on the vigilance cycle in rodents is inconclusive (Laloux et al., 2008; Lima et al., 2007; Monaca et al., 2004; Revishchin et al., 2016). However, in primates it results in nighttime insomnia which is very similar to that of the human disease, involving delayed sleep onset, severe sleep fragmentation and decreased SWS and sleep efficiency (Barraud et al., 2009; Belaid et al., 2015; Mizrahi-Kliger et al., 2020), further supporting the importance of intact dopaminergic transmission to sleep stability.

3.4.3. Basal ganglia-mediated effect of the dopaminergic denervation

The mechanisms through which dopaminergic denervation of the BG might contribute to PD insomnia are still obscure. The presence of a seemingly appropriate pathological model for PD in an animal whose sleep architecture (Toth and Bhargava, 2013) and BG anatomy (Hardman et al., 2002) bear major similarities to humans have prompted us to use the vervet MPTP model to seek a neural correlate for PD insomnia. In a recent work, we found that severe insomnia was associated with synchronized beta oscillations in the BG and cortex (Mizrahi-Kliger et al., 2020).

Beta oscillatory activity (11–30 Hz) is prominent in the STN, pallidum and cortex of PD patients (Brown, 2003) where it correlates primarily with akinesia and rigidity during wakefulness (Kühn et al., 2006; Neumann et al., 2016) and is responsive to dopaminergic therapy as well as STN-DBS (Kühn et al., 2008). During wakefulness, beta oscillations are synchronized across the STN, pallidum and cortex, and they are hypothesized to drive akinesia and rigidity through disruption of normal cortical and brainstem activity (Hammond et al., 2007; Turner and Desmurget, 2010). Beta oscillations during different sleep stages were reported in STN field potentials of PD patients in a few studies (Christensen et al., 2019; Thompson et al., 2018; Urrestarazu et al., 2009), but without demonstration of a relationship between beta activity and insomnia. In one study investigating subthalamic field potentials, beta band activity during REM sleep was significantly higher than during non-REM sleep, and wakefulness beta levels were higher than overall sleep levels (Thompson et al., 2018), opposing previous findings suggesting a significant increase of REM sleep beta power as compared to waking beta power (Urrestarazu et al., 2009).

Beta oscillation is also a prominent hallmark of BG neuronal activity

in the MPTP model of PD, and it associates with severe motor symptoms (Deffains et al., 2016). Varying across species, the beta frequency band in MPTP-intoxicated primates overlaps the low beta band seen in PD patients and spans the 10- to 17-Hz range (Moran et al., 2012). In primates with severe insomnia, prominent beta activity in the STN, GPe and GPi field potentials was found during non-REM sleep. Markedly coherent within and between BG and cortex, beta oscillations were associated with a decrease in BG and cortical slow oscillatory activity, characteristic of deep sleep. Finally, beta activity preceded spontaneous awakenings and overall correlated with decreased non-REM sleep, increased wakefulness and increased awakening frequency (Mizrahi-Kliger et al., 2020). These results lend weight to the hypothesis that slow oscillation in the BG during sleep could be important for sleep maintenance, and suggest that the onset of synchronized beta oscillation in the BG during sleep might disrupt slow oscillatory activity in the BG and cortex and thus contribute to insomnia.

Further support to the hypothesis relating increased beta activity and decreased slow oscillatory activity with disrupted non-REM sleep comes from PD patients. As reviewed earlier, non-REM sleep in PD patients is associated with a decrease in low delta (corresponding to the slow oscillatory range) and an increase in sigma range (12–16 Hz) power (overlapping the 10–17 Hz low beta range). In some works this was even shown to parallel a trend toward decreased SWS and sleep efficiency, and increased wakefulness after sleep onset (Brunner et al., 2002; Christensen et al., 2015). These results, highlighting the critical role of desynchronization of slow oscillatory activity in PD, were reported in patients in the early stages of their disease (Priano et al., 2019). Thus, although MPTP intoxication represents a relatively severe form of Parkinsonism, it replicates well the core alterations in sleep micro- and macro-architecture that are integral to PD insomnia, irrespective of disease severity.

4. Neuromodulatory effect of DBS on sleep physiology in PD

STN-DBS has been associated with an improvement of subjective sleep quality (Baumann-Vogel et al., 2017) and reductions in insomnia and sleep fragmentation in PD (Baumann-Vogel et al., 2017; Zuzuárregui and Ostrem, 2020). The improvement in insomnia following DBS stimulation was observed both when DBS was compared to a group receiving medical therapy (Jost et al., 2021) and within the same patients, in ON vs. OFF stimulation regimes (Arnulf et al., 2000b). Post-surgery improvement in sleep quality remained clinically stable for up to 48 months (Georgiev et al., 2021; Jost et al., 2021). How DBS leads to improved sleep quality is still a matter of debate. It is well known that STN-DBS specifically reduces BG beta oscillation that has been related to clinical motor improvement in PD (Kühn et al., 2008; Quinn et al., 2015). While most studies were conducted in acute peri-operative recordings, this could also be shown in chronic recordings using sensing-enabled implantable devices (Feldmann et al., 2021; Kehnemouyi et al., 2021; Neumann et al., 2016). Thus, it could be hypothesized that enhanced beta band activity in the cortico-BG network is also related to insomnia and its reduction not only reduces awake bradykinesia but improves sleep by restoring a more physiological sleep pattern.

It is prudent to remember that the above works showing correlation between increased nocturnal beta oscillation in the BG or cortex (via EEG) and PD insomnia (Brunner et al., 2002; Christensen et al., 2015; Mizrahi-Kliger et al., 2020) may also be consistent with an alternative explanation, relying on the persistence of the waking motor symptoms into non-REM sleep. Beta during sleep might alternatively represent muscle rigidity that by itself causes a constant irritation preventing deep sleep, and not through beta-mediated reduction of slow oscillatory activity. To test a possible contribution of muscle rigidity to insomnia, we used the root mean square of the trapezius EMG signal as a corollary for muscle rigidity (Duval et al., 2002). In this dataset no correlation between the trapezius tone and cortical or BG beta activity during non-REM sleep was found, and no correlation was found between the trapezius tone and polysomnographic sleep measures (Mizrahi-Kliger et al., 2020). However, the possibly dissociable roles of enhanced beta oscillations and nocturnal motor deficits in insomnia should be disentangled using invasive BG recordings, EMG recording from additional muscles and an analysis of the correlation between muscle activity patterns and bed turns or awakenings.

Animal models have helped to explore the functional role of abnormal BG activity patterns in PD. However, the primate MPTP model of Parkinson's disease has its limitations with regard to PD insomnia. Mainly, it results in a relatively severe Parkinsonian state that does not necessarily model the pathogenesis of insomnia in the human disease. Further, MPTP intoxication is not specific to midbrain dopaminergic neurons, and could result in toxic injury to other brain structures involved in sleep regulation (Pifl et al., 1991) or the circadian rhythm (Fifel et al., 2014), that are not part of the pathogenesis of PD. Finally, neural activity in the BG in human patients is usually affected by long-term dopaminergic therapy, which is not captured by the MPTP model. However, the stark similarities between the sleep micro- and macro-architecture changes elicited by MPTP intoxication and those in PD, as well as its established pathological and clinical relevance to the human disease, mark this model as an appropriate one to elucidate the mechanisms of insomnia in PD. Future studies, utilizing for example chronic low-dose MPTP models or α-synuclein genetic models, will yield further insights into sleep pathophysiology in PD. Unlike the acute MPTP model, these techniques may be used to more closely model the relatively slow-paced dopaminergic degeneration characteristic of idiopathic PD, and would allow the close monitoring of the onset of insomnia and its neuronal correlates.

Insomnia and sleep disorders crucially contribute to PD patients' impaired quality of life. Our understanding of the long-term neuromodulatory effects of DBS on sleep electrophysiology and circadian rhythmicity in PD patients is only partial. To our knowledge, field potential data recorded concurrently with active STN-DBS stimulation during sleep is currently not available. With the novel BrainSense technology, chronic electrophysiological recordings have become easily accessible, and first recordings revealed that stepwise stimulation induces beta band suppression, correlated with motor improvement (Feldmann et al., 2021). Long-term electrophysiological biomarker analysis will increase the understanding of the patterns underlying sleep disorders and their modulation through neurostimulation. To mention one example, given that different frequency bands behave differently during sleep, a few groups explore the possibility of sleep staging based on field potentials from perioperative recordings with externalizations (Chen et al., 2019; Christensen et al., 2019; Thompson et al., 2018). On the other hand, sleep-stage related changes in beta power could be a challenge for adaptive DBS (aDBS), e.g., they could make it harder for a stimulating algorithm to rapidly adjust to changing beta levels during night-time arousals (Little and Brown, 2020). In the first available aDBS algorithm using an implantable pulse generator (IPG), the long-term biomarker analysis is limited to an investigator-selected peak frequency window of 5 Hz. As to date, the main focus of aDBS lies on motor symptoms and this peak is usually set to beta band peak power. While first preliminary long-term recordings reveal circadian oscillatory patterns in the beta band, it remains to be explored whether these changes correlate with the degree of insomnia, whether they might be modulated through stimulation or dopaminergic medication, and whether technical specifications of the sensing-enabled IPG contribute to the observed rhythmicity.

5. Summary and conclusions

Insomnia is a highly common and debilitating non-motor symptom of PD. Data acquired over the last decade from controlled human studies and animal models of the disease suggests that insomnia results from several unnecessarily related pathological pathways characteristic of PD. First, the mental, sleep-wake and nocturnal non-motor

comorbidities of PD represent highly plausible contributing factors, although most of the existing evidence is correlative and not causal. This is probably due to the lack of appropriate animal models that specifically and individually capture and isolate each of these factors, dissecting their unique contribution to insomnia. Second, randomized controlled trials advocate for a role of the PD medical therapy in driving insomnia. Finally, a possible role for dopaminergic degeneration is supported by extensive work done in rodents and in non-human primates. The dopaminergic degeneration probably drives insomnia both through the resulting motor symptoms of the disease persisting through non-REM sleep and through the dopaminergic denervation of the BG. One emerging mechanism through which this could occur is the onset of synchronized beta oscillation and a parallel decrease in slow oscillatory activity during non-REM sleep, recorded both in patients and in non-human primates with Parkinsonian insomnia. With the increasing availability of chronic electrophysiological data from patients, sleep-specific changes in beta oscillatory activity will have to be considered to achieve personalized neuromodulation.

Declaration of Competing Interest

None.

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