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Invited review

Clinical implication of high-density EEG sleep recordings in Parkinson's disease

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ABSTRACT

The diagnosis of Parkinson's disease (PD) is made relatively late in the pathological process, when already most of the dopaminergic synapses have died. The evidence showed that, at the time of the clinical diagnosis, which can be done only after motor symptoms' appearance, the pathogenetic process is too advanced for a potential neuroprotective agent to be efficacious. Thus, the identification of early markers of neurodegeneration would be essential in the fight again the disease. A growing body of literature reported that non-motor symptoms, including sleep disorders, are commonly the earliest manifestation of the disease (i.e. prodromal stage). Furthermore, evidence claimed that these disturbances may have an impact on the progression of the disease itself, possibly altering its phenotype and leading to the emergence of levodopa-induced dyskinesia (LID), a typical treatment-related complication.

The early recognition of subjects at risk of developing PD would offer the opportunity to evaluate the efficacy of possible neuroprotective agents. Additionally, the early identification of sleep alterations, which could possibly be considered an indicator of aberrant brain plasticity and thus be helpful in predicting the emergence of LID, if confirmed, would offer a platform for testing possible sleep targeted therapies able to protect the patients from the development of this treatment-induced condition.

In this review, new techniques for the study of sleep will be addressed, in order to investigate their possible role as diagnostic and prognostic tools in the evaluation of patients suffering from PD.

1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease. It's a slowly progressive highly debilitating disorder mainly affecting the motor system with bradykinesia, resting tremor, rigidity and posture instability (Kalia and Lang 2015). Its progression can be divided into three stages: 1) preclinical stage, where the degenerative process already commenced but neither symptoms or signs are present; 2) prodromal stage, where several symptoms or signs can be observed but they are not sufficient to make a PD diagnosis; 3) clinical stage, where the classical motor symptoms appear and it is possible to make a diagnosis. PD in Western countries affects the 0.5% of the population aged ≥45 years. The prevalence strongly increases across decades with a doubling of the number of patients over the next 30 years affected by this disease, that means more than 12 million patients worldwide by about 2050 (Ascherio and Schwarzschild, 2016). The gold standard treatment for PD is levodopa, a precursor of dopamine, which is well tolerated and allows a satisfactory control of motor symptoms. Nevertheless, three major clinical issues still remain unsolved: 1) the development of preventive strategies targeting the neurodegeneration of dopaminergic neurons at the basis of the disease; 2) the management of long-term treatment-related complications, i.e. levodopa-induced dyskinesia (LID); and 3) the treatment of axial symptoms, which poorly respond, or not respond at all, to levodopa and thus represent a major therapeutic challenge in the management of PD patients.

Concerning the former issue (1), a critical role is played by the early prodromal symptoms. Actually, at the time of motor symptoms appearance, already 70% of dopaminergic synapses are died, and even if a neuroprotective agent would exist, it would be too late to be effective (Maetzler et al., 2009). To identify early markers of neurodegeneration would be a critical step in the fight against the disease.

Sleep disturbances are indeed extremely very common in PD, being often the earliest manifestation of the disease and thus representing the

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most likely candidate for helping in predicting its onset.

Motor symptoms in PD, are in fact often accompanied by sleep disorders, which frequently precede the development of the disease itself. Rem sleep behavior disorder (RBD) and restless leg syndrome (RLS) are two of the most common sleep disturbances, reported to possibly appear before the clinical stage of the disease. Sleep architecture itself has been reported to be altered in PD patients, often experiencing reduced sleep efficiency, increased number of awakenings/arousals and increased wake after sleep onset (WASO). Of note, slow wave sleep (SWS), is dramatically reduced in PD.

Concerning the latter issue (2), no clinically effective medical therapies are able to alleviate LID without worsening parkinsonism and also the serotoninergic receptor agonists, claimed to be drugs against LID (Muñoz et al. 2008), were ineffective (Huot et al., 2011). Preliminary finding from our lab suggested a link between slow wave activity (SWA) alteration and LID development (Amato et al. 2018). Sleep disturbances not only may precede the onset of motor symptoms but, hypothetically, it may have an impact on the progression of the disease itself and it may eventually alter its phenotype. We hypothesize that the relationship between SWA abnormality and LID development may have a causative nature, with the SWA alteration helping in determining the appearance of dyskinetic symptoms. Further studies are needed to better understand the nature of this link. If the disruption of the physiological SWA will be confirmed to have a causative effect on the emergence of LID, early alteration of SWA could be considered a marker for LID development and could thus provide prognostic information. Furthermore, it could pave the way for pioneering SWA targeted therapies in PD.

Polysomnography (PSG) is the gold standard method to study sleep and its disorders. PSG with high-density electroencephalography (hdEEG-PSG) montage are nowadays frequently used to investigate sleep. These systems allow to overcome the low spatial resolution issues, typical of low-density EEG recordings, resulting in a deeper investigation of sleep characteristics.

Aim of this paper is to outline the diagnostic and prognostic value of the hdEEG-PSG in the evaluation of patients suffering with PD.

2. Polysomnography

PSG permits to record simultaneously and continuously multiple physiological parameters during sleep, allowing the identification of sleep stages, the monitoring of body movement and the assessment of cardiopulmonary function. The first whole night electroencephalography (EEG) recording was performed in the late 1930s (Loomis et al., 1937). This recording permitted to distinguish 5 different sleep stages that the authors defined: A (interrupted alpha stage), B (low voltage stage), C (spindles stage), D (spindles plus random stage) and E (random stage). In the early 1950s the electro-oculogram (EOG) was added to the EEG, allowing the definition of rapid eye movement (REM) sleep (Aserinsky and Kleitman, 1953), then, in order to investigate the lack of muscle tone observed during REM sleep, surface electromyographic (EMG) channels were added over the chin. Later, in the 1960s, the discovery of the apnea syndrome, lead to the need of recording respiratory and cardiac channels in order to assess these respiratory events (Jung and Kuhlo 1965). In the 1968, a committee of sleep researchers defined the so called the Rechtschaffen and Kales criteria for recording and scoring sleep stages (Rechtschaffen and Kales 1968). This was a turning point in the history of PSG. Nowadays, in clinical practice a standard PSG includes the recording of several parameters: EOG, EMG of chin and anterior tibialis muscles, oro-nasal airflow (nasal cannula), microphone, thoracic and abdominal effort (piezoelectric strain gauges) and arterial oxygen saturation (pulse oximetry with finger probe). Other parameters could be measured as for clinical recommendation (Fig. 1).

It is performed in a standard sound-attenuated sleep laboratory room. Subjects are usually asked not to drink caffeinated beverages before the beginning of the exam. Lights-off time is possibly based on the individual's usual bed time. Sleep staging is performed by sleep experts according to the standard criteria of the American Association of Sleep Medicine (AASM) (Iber et al., 2007).

2.1. PSG role in detecting sleep disorders appearing before motor symptoms

2.1.1. REM sleep behavior disorders in PD

REM sleep is characterized by fast frequency, low voltage EEG, resembling wake EEG, associated with rapid eyes movements, occurring isolated or in bursts, and lack of muscle tone. The principal brain structures implicated in generating REM sleep are the pons and the midbrain. Indeed, massive lesions of these structures lead to the abolition of REM, whereas selective lesions in smaller portion of these regions can affect it only partially. For instance, damage to small portions of the pons and medulla can lead to REM sleep occurring without the normal lack of muscle tone (Schenkel and Siegel 1989). RBD is characterized by a loss of the normal muscle atonia associated with REM sleep (Fig.2), such that patients seem to 'act out' their dreams.

RBD prevalence in PD is estimated to be over 40% (Zhang et al. 2017), appearing even decades before motor symptoms (Iranzo et al. 2014).

According to the International Classification of Sleep Disorders III (ICSD III), the clinical diagnosis of RBD needs two criteria to be considered: the lack of REM sleep atonia at a whole night PSG recording and an abnormal REM sleep behavior (Schenck and Mahowald 2002; Boeve, 2010). The first criterium is satisfied by the finding of excessive amounts of sustained or intermittent elevations of submentalis muscle EMG tone or excessive phasic submentalis muscle twitching (or upper/lower limbs).

Subjects presenting this disorder can be considered at-risk individuals for developing Parkinson's disease, which makes their early recognition essential in order to have the opportunity to evaluate possible neuroprotective agents for PD. Furthermore, a new diagnosis of RBD should thus be considered as an alarm bell and should lead to the search for existing subtle signs of Parkinson's disease.

2.1.1.1. Quantification of muscle atonia. The lack of muscle tone during REM sleep can be quantified calculating the atonia index (AI), an index defining the amount of muscle tone during REM presented and validated by Ferri et al. (2008). The submentalis muscle EMG activity is filtered between 10 and 100 Hz. A notch filter is also applied. The signal is then rectified. Each sleep epoch considered is then segmented into 1 sec length mini-epoch and a mean amplitude value is obtained. The authors observed that mini-epochs characterized by muscle atonia, presented a mean amplitude value less then or equal to 1 μV, whereas mini-epochs characterized by phasic or tonic muscle activation, presented a mean amplitude value greater than 2 μV. Then, using the values obtained, the authors drew normalized distribution histograms for each sleep stage of the percentage of values in the following 20 amplitude classes, with high values of the first left column of the graph reflecting muscle atonia, and high values of the other columns reflecting instead phasic and tonic muscle activations. Ferri et al. (2008) then defined an index summarizing in a single value the degree of preponderance of the first column in the graphs: AI = amp $\leq$ 1/(100 -1 < amp $\leq$ 2).

AI can go from 0, that means complete absence of EMG atonia, to 1, that means stable EMG atonia throughout the epoch considered.

2.1.2. Restless leg syndrome in PD

RLS is a sleep related movement disorder described by patients as unpleasant or even painful sensations in the legs accompanied by an urge to move them. It's characterized by motor restlessness associated with paresthesias. It has a circadian pattern, occurring mostly during rest, therefore having an impact on sleep, with the patients showing difficulties to fall asleep or in maintaining sleep due to the

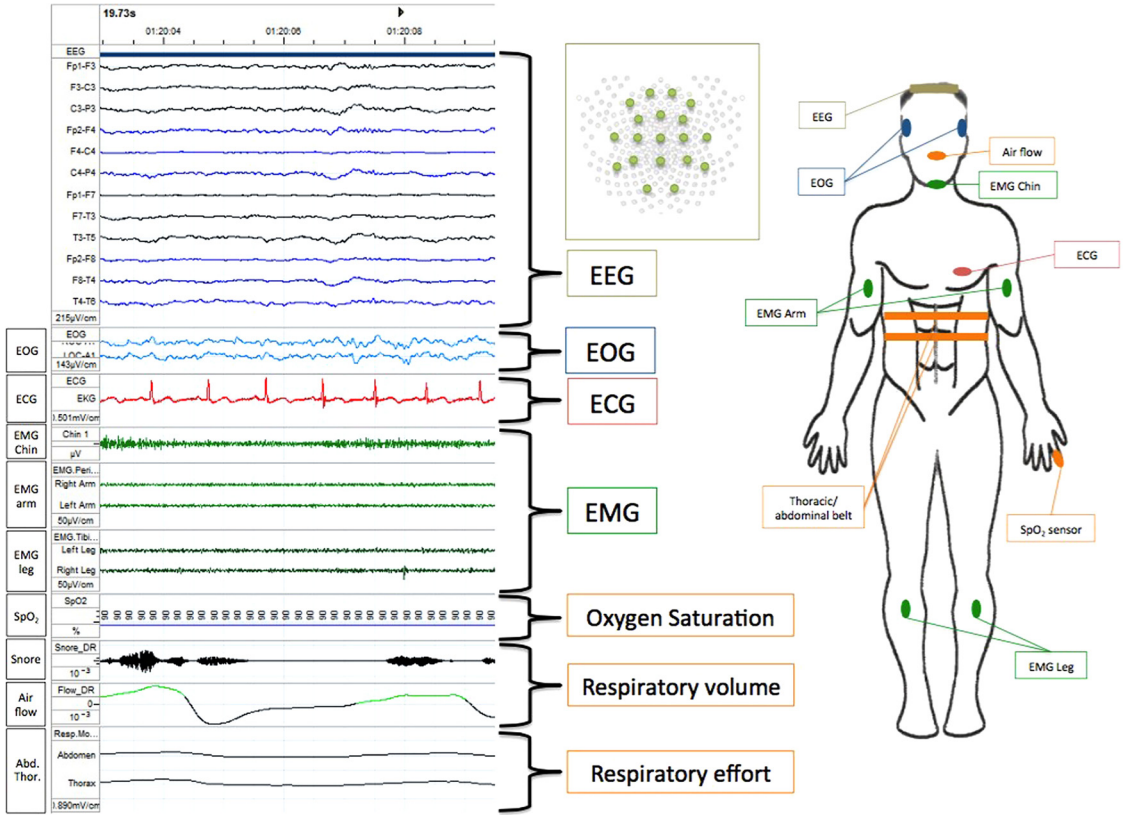

Fig. 1. On the left, PSG traces including an electroencephalography (EEG) low-density montage, electro-oculogram (EOG), electrocardiogram (ECG), electro-myogram (EMG) of chin, arms and legs, arterial oxygen saturation (pulse oximetry with finger probe), oro-nasal airflow (nasal cannula) and thoracic and abdominal effort (piezoelectric strain gauges). On the right, topographical representation showing the locations of each sensor.

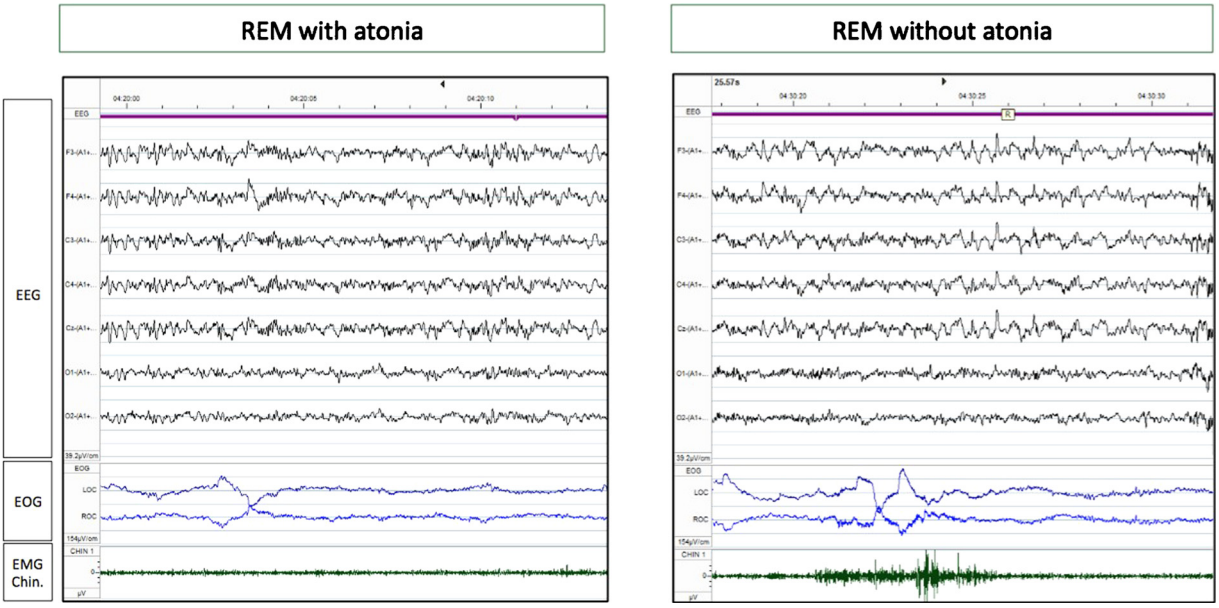

Fig. 2. On the left, an epoch of REM sleep of an healthy subject characterized by the typical low voltage high frequency activity over the EEG channels, rapid eye movements as detected by the EOG and a physiological muscle atonia reflected by the lack of EMG activity at the level of the chin. On the right, an epoch of REM sleep of a RBD patient showing a lack of the physiological muscle atonia as reflected by EMG activity at the level of the chin.

uncomfortable sensations (Ohayon et al., 2012). The responsiveness of RLS symptoms to dopaminergic therapy, a positive familial history of RLS and the presence of periodic limb movements (PLM) during sleep are commonly used as supportive data for diagnosis (Manconi et al. 2007). RLS has been reported to affect 5 to 10 subjects every 100 in the general population (Garcia-Borreguero et al. 2006; Garcia-Borreguero and Williams 2014). Prevalence is much higher in PD, with RLS affecting up to 50% of the patients (Braga-Neto, 2004; Gama et al. 2010). The link between these two pathologies appears even more evident considering the common responsiveness to dopaminergic therapy. In the last two decades a growing body of literature has suggested a common pathophysiology in RLS and PD (Nomura et al., 2006;

Gómez-Esteban et al. 2007; Guerreiro et al. 2010; Verbaan et al. 2010; Azmin et al. 2013; Fereshtehnejad et al. 2015; Ylikoski et al., 2015). Some other studies instead suggested that RLS in PD could be a secondary symptom induced by the disease symptomatology and therapy (Lee et al. 2009; Angelini et al. 2011; Oh et al. 2014). However, a much higher prevalence of PD development in RLS patients has been also documented (Walters et al. 2003; Gao et al. 2010). Although RLS is not yet considered as an established early feature of PD, recent studies pointed in this direction. Indeed, severe RLS symptoms with a frequency > 15 times per months have been reported to be associated with the development of PD in the successive 4 years (Wong et al. 2014). Moreover, a recent case series described several patients presenting with RLS as prodromal symptom of PD (Suzuki et al. 2019). These findings suggest that RLS could represent a possible prodromal symptom of PD. PSG then could play a role in the diagnosis of these patients, eventually being helpful in recognizing individuals that will possibly move forward to the clinical stage.

2.1.2.1. Criteria for recording and scoring PLM. In 2006 and again in 2016, a joint task force of experts on the topic, developed and redefined the criteria for recording and scoring PLM in polysomnogram. The most involved muscle in periodic movement activity during sleep is the anterior tibialis, thus it is recommended to record its activity for this purpose (Fig. 3). A subset of leg monolateral movements, with a length between 0.5 and 10 sec, or bilateral movements, with a length between 0.5 and 15 sec, are considered candidate leg movements (CLM). A leg movement (LM) is defined as an EMG event having an onset characterized by an EMG activity increase greater than or equal to 8 μV above resting baseline, an offset characterized by an EMG activity decrease less than 2 μV above resting baseline and remaining below this threshold for at least 0.5 sec, a duration greater than or equal to 0.5 sec, and containing a period of at least 0.5 sec in which the median EMG amplitude is greater than or equal to 2 μV above resting baseline. CLM will then be evaluated for PLM. An inter movement interval (IMI), representing the time from the onset of CLM(n) to the onset of CLM(n +1), without any non-CLM in between, has to be defined. IMI must have a length greater than or equal to 10 sec and less than or equal to 90 sec for the consecutive CLM to be considered potential PLM. The run must count at least 4 CLM, separated by three appropriate IMI, to be defined PLM. A PLM series is considered terminated when one of the following appears: an IMI longer than 90 sec; a CLM with an IMI shorter than 10 sec; a LM longer than 10 sec.

A more detailed description of the standards for recording and scoring PLM is beyond the scope of this review thus for a more complete treatment of the reader should refer to (Ferri et al. 2016).

2.2. PSG role in detecting early signs of long-term treatment-related complications

2.2.1. hdEEG-PSG

In recent years EEG systems with a much higher number of sensors became available. This kind of montages, including up to 256 electrodes, permitted to overcome the low spatial resolution issues, characterizing low-density EEG recordings (Fig. 4). The introduction of high-density systems was crucial for sleep research, in fact the higher spatial resolution allowed a much more accurate topographical mapping of the main frequency band characterizing sleep. Specific EEG activities during sleep are known. The most prominent is the SWA, dominant during SWS, which is characterized by high amplitude low voltage waves with a frequency ranging between 0.5 and 4 Hz.

The increment in the number of channels used for recording the EEG activity allowed a characterization of the link between SWA and learning. Previous studies using hdEEG-PSG, indeed, showed that learning tasks leaded to the occurrence of a greater amount of SWA over the brain region involved in the task. Moreover, the SWA increase observed during the night following the task was directly correlated with an improvement in the task performance. These local changes in SWA need a sufficient number of channels to be detected. Authors investigated the effect of electrode downsampling on the detection capacity and documented that reducing the electrode number below 100, dramatically decrease the probability to detect local changes in SWA (Lustenberger and Huber., 2012). These findings highlighted the close connection between plastic changes occurring in the brain and the local regulation of SWA (Huber et al. 2004; Huber et al. 2006; Hung et al. 2013).

2.2.2. Slow wave activity and Levodopa Induced Dyskinesia

The ability of the brain to modify its functions in a long-lasting way, through changes at the level of the interneuronal connections, in response to stimulations is called synaptic plasticity.

The interaction with the environment during the waketime leads to synaptic potentiation due to plasticity mechanisms. During sleep neurons have to renormalize total synaptic strength, thus the daytime synaptic upscaling is followed by a sequent selective downscaling process occurring mainly during the first part of the night-sleep. This phenomenon restores the synaptic balance and follows the same trend of the so-called homeostatic process of sleep. The amount of SWA during SWS (SWA-SWS) occupying the first part of the night represents the main electrophysiological marker of the homeostatic process, being enhanced by the duration of wakefulness preceding the sleep occurrence (Fig. 5). By this mechanism, sleep plays a crucial role in neuroplasticity, "restoring neuronal selectivity and enhancing signal-to-noise ratios, leading to the consolidation and integration of memories" (Tononi and Cirelli 2014).

Direct structural visualization studies measured synaptic density and axon-spine interface (contact surface between axonal button and dendritic spine) in the motor and sensory cortices of mice, finding a reduction of synaptic burden after sleep compared to wake, demonstrating that synaptic scale occurs during sleep (De Vivo et al. 2017). Similarly, electrophysiological evidences in humans show that transcranial magnetic stimulation (TMS)-evoked response in the frontal cortex has a progressive increase of slope during wake and returns to baseline levels after one night of sleep recovery (Huber et al. 2007).

Several evidences support the hypothesis that SWA-SWS is crucial

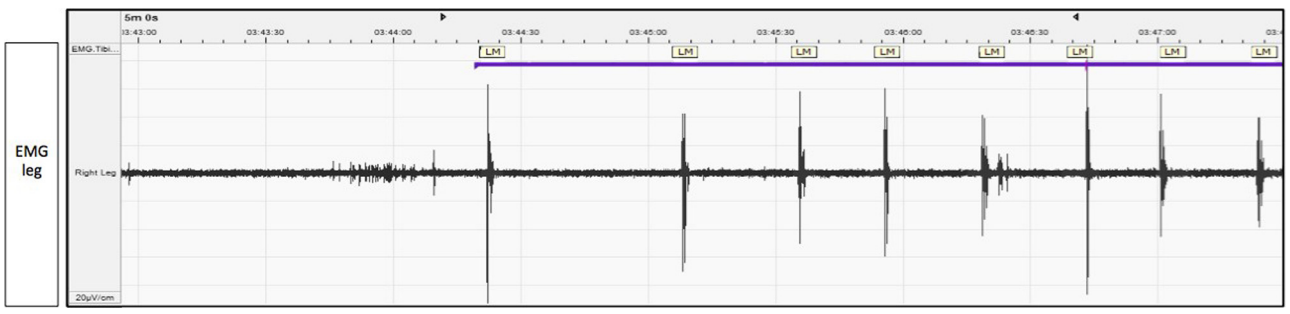

Fig. 3. EMG trace of the anterior tibialis muscles showing a periodic leg movement (PLM).

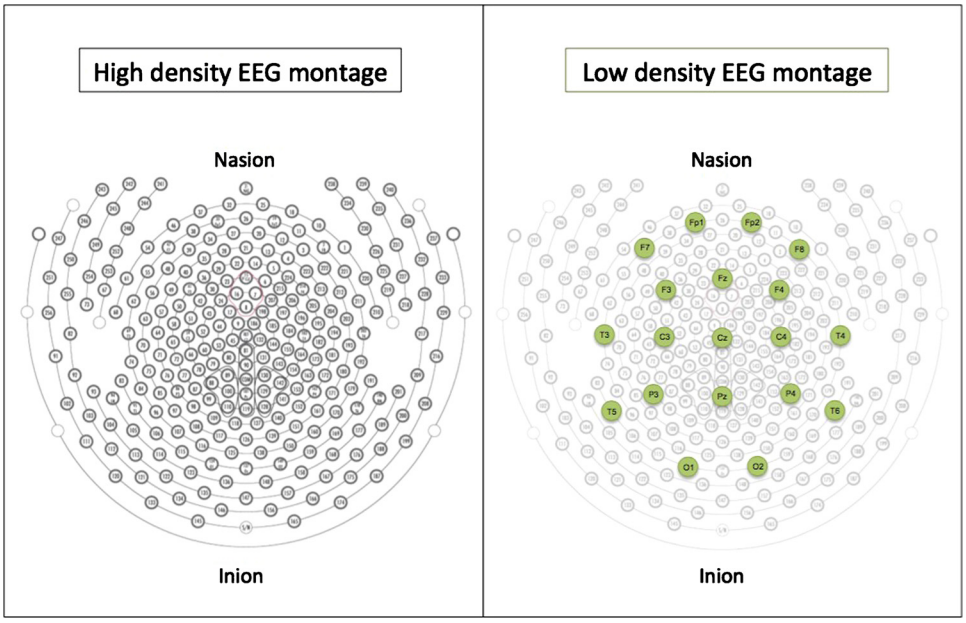

Fig. 4. Topographical representation of the electrodes distribution over the scalp in high-density montage (on the left) and low-density montage (on the right).

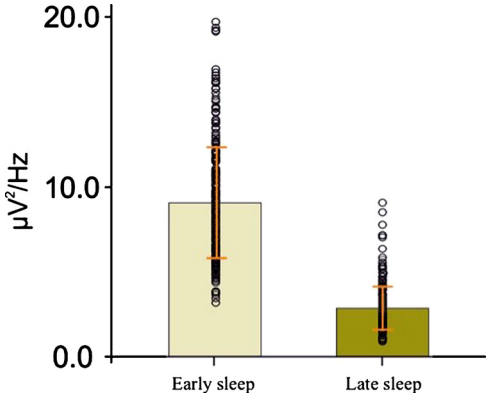

Fig. 5. Graphical representation of the difference in the power of the slow wave activity (SWA) between early and late sleep.

for the restoration of synaptic homeostasis (Tononi and Cirelli, 2003; Tononi and Cirelli 2006; Galati et al., 2018). The increase in synapse formation and strengthening during the wakefulness is optimized during sleep through a global downscaling of all the synapses. Particularly, redundant synaptic connections are erased through the long-lasting burst firing, which is common in SWA during transitions between intracellular up and down states (Nelson and Turrigiano 2008; Tatavarty et al., 2013; Tononi and Cirelli 2014). All the data recognized SWA-SWS as an index as well as a contributor of the downscaling of cortical synaptic strength.

Sleep architecture is well known to be altered in PD patients, frequently showing a reduced amount of SWS (Diederich et al., 2005; Galati et al. 2015; Büchele et al. 2018; Caverzasio et al. 2018).

To investigate sleep alterations in PD is essential in order to evaluate the possible impact of these alterations on the likelihood of developing shortly a long-term treatment-related complications, such as LID.

In both animal models and patients with PD a change in the amount of SWA-SWS has been observed (Galati et al. 2015, Amato et al. 2018). Of note, Schreiner et al. (2019) found that higher amount of SWA had a clear prognostic meaning in terms of slower motor progression in a cohort of PD patients. The amount of SWA-SWS has been reported to be negatively correlated with the duration of the disease and appears to be especially low in PD patients presenting LID (Amato et al. 2018). In patients with LID, also the physiological SWA mediated downscaling process seems to be impaired. Previous findings, in fact, documented a link between SWA mediated synaptic downscaling disruption and the development of LID in PD.

Thus, sleep disturbances appear not only to have a prognostic value in the assessment of PD patients, but, there is a possibility that it might even change the phenotype of this neurological condition leading to the emergence of LID. If this hypothesis will be confirmed by further studies, monitoring the alteration of this physiological process in PD patients, by means of periodic hdEEG-PSG, could be helpful in predicting the emergence of LID and would ultimately offer a platform for testing possible sleep targeted therapies able to protect the patients from the development of this treatment-related complication.

2.2.2.1. Evaluation of SWA parameters reflecting synaptic downscaling. According to the synaptic homeostatic hypothesis (SHY), SWA reflects changes in the synaptic strength (Tononi and Cirelli, 2003; Tononi and Cirelli 2006). This hypothesis, suggesting a link between SWA and plasticity, has been widely supported (Huber et al. 2004; Huber et al. 2007; Mascetti et al. 2013). Several SWA parameters, i.e. the difference between early and late sleep SWA power or the overnight change in the slope of the waves (Achermann and Borbély, 2003; Riedner et al. 2007), have been reported to reflect the synaptic downscaling process.

To investigate these parameters, a whole night hdEEG-PSG has to be recorded. The EEG recording is then off-line band pass filtered, often between 0.5 and 40 Hz, and visually inspected. Bad channels and artifacts are rejected. Sleep staging is obtained according to standard criteria (Berry et al. 2015). Non-rapid eye movement (NREM) sleep episodes are defined. Although the first and the last sixty minutes of NREM sleep are frequently selected for further analysis, we recommend to extract the NREM sleep of the whole night since the population at hand shows a severely fragmented sleep, and this fragmentation could potentially have an impact on the presentation time of the N3 peak, which is the sleep stage showing the greater amount of SWA. After selecting the appropriate part of the recording, a quantitative analysis of the EEG is performed by means of a decomposition method, such as the fast Fourier transform (FFT), used to obtain the frequency components constituting the EEG signal, which is a time-domain signal. The backbone of many technique used to extract frequency information from a time-domain signal is the convolution. The backbone of the

convolution is a basic procedure called dot product, which consists, very roughly, in multiplying each element in vector A by the corresponding element in vector B and then summing all the points. Convolution is a kind of dot product computed repeatedly. It consists in sliding sine waves (known as kernel) of different frequencies (vector A) along the EEG signal (vector B). The result obtained shows how much the signal and the kernel are similar. It is important to opportunely windowing the data when an FFT is applied. A windowing function, for instance a Hanning window, should be applied to minimize the effect of spectral leakage. The FFT indeed assumes the data set to be a continuous spectrum representing one period of a periodic signal, but most of the times the measured signal doesn't contain an integer number of periods. This results in discontinuous endpoints, which appear in the FFT as high frequency components. Thus the spectrum obtained is a smeared version of the actual one that looks like if the energy at one frequency leaks into other frequencies. Multiplying by a window (i.e. windowing) that have an amplitude that smoothly goes to zero at the edges, makes the waveform resulting in a kind of a continuous waveform without discontinuities. It is important also to consider that the FFT needs the signal to be stationary. It is not the case for the EEG signal, whose non-stationarity is due to several reasons, among which the main one is represented by the changes in states of neuronal assemblies. This limitation is overcome by selecting very small epochs, lasting few seconds, along which the parameters of interest show a neglectable variance. The length of the segment is of course a compromise between stationarity and frequency resolution, the latter being defined as 1/n (where n is the length in seconds of the selected epoch). The spectra calculated with the FFT, one for each epoch, will then be averaged. The power value obtained for each channel is then normalized to the average of all channels. Topographical differences in SWA between early and late sleep, reflecting the physiological synaptic downscaling process, are then assessed.

Another reliable measure of this process is the slope of the slow waves, which has been reported to significantly decrease throughout the night. This analysis is performed in the time domain. To assess the slope of the wave, after offline band pass filtering the signal and removing artefacts, half waves, defined as negative deflections between two zero crossing, whose consecutive zero crossings are separated by 0.25 to 1.0 seconds, are selected on each channel. For every half wave, the point in time of the zero-crossings and the peak amplitude are defined. Since, very roughly speaking, the slope is calculated as the rise divided by the run, the amplitude is divided by the time from the zero crossing, obtaining a value representing the slope of the wave. Differences in this parameter between early and late sleep are then assessed.

3. Conclusion

Sleep disturbances are well known to be extremely common in PD. Evidence from a growing number of studies supports the idea of the possible prodromal nature of these disturbances, appearing even decades before the classical motor symptomatology. A major problem in diagnosing PD at the appearance of motor symptoms is that most of the dopaminergic synapses are died at that time and even if a neuroprotective agent would exist, it would be too late to provide any protection against the progression of the disease. To identify early markers of neurodegeneration would be essential in order to see an effect of a possible protective agent. An early recognition of sleep disorders, such as RBD and RLS, would provide a time window to search for early subclinical signs of PD and to test neuroprotective agents. PSG, being a low-cost non-invasive method useful in the diagnosis of sleep disorder, could play an important role at this stage.

PSG could be a crucial methodology to be applied also later on during the course of the disease.

Sleep macrostructure alterations, hugely common in PD patients, leading frequently to an invalidating excessive daytime sleepiness, might eventually have also a negative impact on the disease's phenotype itself, fostering the emergence of complication due to the prolonged therapy. If the link between the amount of SWS -and specifically several parameters of its SWA, such as the power and the slope of the waves- and LID development will be confirmed and the nature of this relationship will be clarified monitoring these sleep parameters could eventually pave the way for exploring SWA enhancing pioneering therapies able to delay the emergence of this invalidating treatment-related complication.

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References

Achermann, Peter, Borbély, Alexander A, 2003. Mathematical Models of Sleep Regulation. Frontiers in Bioscience: A Journal and Virtual Library 8, s683–93.

Amato, Ninfa, Manconi, Mauro, Möller, Jens C, Sarasso, Simone, Stanzione, Paolo, Staedler, Claudio, Kaelin-Lang, Alain, Galati, Salvatore, 2018. Levodopa-Induced Dyskinesia in Parkinson's Disease: Sleep Matters. Annals of Neurology 0 (ja). John Wiley & Sons, Ltdhttps://doi.org/10.1002/ana.25360.

Angelini, Monica, Negrotti, Anna, Marchesi, Elena, Bonavina, Giuseppe, Calzetti, Stefano, 2011. A Study of the Prevalence of Restless Legs Syndrome in Previously Untreated Parkinson's Disease Patients: Absence of Co-Morbid Association. Journal of the Neurological Sciences 310 (1–2), 286–288 Elsevier.

Ascherio, Alberto, Schwarzschild, Michael A, 2016. The Epidemiology of Parkinson's Disease: Risk Factors and Prevention. The Lancet Neurology 15 (12), 1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7. Elsevier.

Aserinsky, Eugene, Kleitman, Nathaniel, 1953. Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, during Sleep. Science 118 (3062), 273–274.

Azmin, Shahrul, Anuar, Khairul, Manaf, Abdul, Nafisah, Wan Yahya, Tan, Hui Jan, Raymond, Azman Ali, Hanita, Othman, Shah, Shamsul Azhar, Norlinah, Mohamed Ibrahim, 2013. Restless Legs Syndrome and Its Associated Risk Factors in Parkinson's Disease. Parkinson's Disease 2013 Hindawi.

Berry, Richard B, Gamaldo, Charlene E, Harding, Susan M, Brooks, Rita, Lloyd, Robin M, Vaughn, Bradley V, Marcus, Carole L, 2015. AASM Scoring Manual Version 2.2 Updates: New Chapters for Scoring Infant Sleep Staging and Home Sleep Apnea Testing. Journal of Clinical Sleep Medicine 11 (11), 1253–1254 American Academy of Sleep Medicine.

Boeve, BradleyF, 2010. REM Sleep Behavior Disorder: Updated Review of the Core Features, the REM Sleep Behavior Disorder-Neurodegenerative Disease Association, Evolving Concepts, Controversies, and Future Directions. Annals of the New York Academy of Sciences 1184, 15–54 NIH Public Access.

Braga-Neto, Pedro, da Silva Júnior, Francisco Pereira, Monte, Francisca Sueli, de Bruin, Pedro FC, de Bruin, Veralice MS, 2004. Snoring and Excessive Daytime Sleepiness in Parkinson's Disease. Journal of the Neurological Sciences 217 (1), 41–45 Elsevier.

Büchele, Fabian, Hackius, Marc, Schreglmann, Sebastian R, Omlor, Wolfgang, Werth, Esther, Maric, Angelina, Imbach, Lukas L, Hägele-Link, Stefan, Waldvogel, Daniel, Baumann, Christian R, 2018. Sodium Oxybate for Excessive Daytime Sleepiness and Sleep Disturbance in Parkinson Disease: A Randomized Clinical Trial. JAMA Neurology 75 (1), 114–118 American Medical Association.

Caverzasio, Serena, Amato, Ninfa, Manconi, Mauro, Prosperetti, Chiara, Kaelin-Lang, Alain, Hutchison, William Duncan, Galati, Salvatore, 2018. Brain Plasticity and Sleep: Implication for Movement Disorders. Neuroscience & Biobehavioral Reviews 86 (March), 21–35. https://doi.org/10.1016/j.neubiorev.2017.12.009.

De Vivo, Luisa, Bellesi, Michele, Marshall, William, Bushong, Eric A, Ellisman, Mark H, Tononi, Giulio, Cirelli, Chiara, 2017. Ultrastructural Evidence for Synaptic Scaling across the Wake/sleep Cycle. Science 355, 507–510.

Diederich, N.J., Vaillant, M., Mancuso, G., Lyen, P., Tiete, J., 2005. Progressive sleep' destructuring' in Parkinson's disease. A polysomnographic study in 46 patients. Sleep Med. 6, 313–318.

Fereshtehnejad, S.-M., Shafieesabet, M., Shahidi, G.A., Delbari, A., Lökk, J., 2015. Restless Legs Syndrome in Patients with Parkinson's Disease: A Comparative Study on Prevalence, Clinical Characteristics, Quality of Life and Nutritional Status. Acta Neurologica Scandinavica 131 (4), 211–218 Wiley Online Library.

Ferri, Raffaele, Fulda, Stephany, Allen, R.P., Zucconi, M., Bruni, O., Chokroverty, S., Ferini-Strambi, L., Frauscher, B., Garcia-Borreguero, D., Hirshkowitz, M., 2016. World Association of Sleep Medicine (WASM) 2016 Standards for Recording and Scoring Leg Movements in Polysomnograms Developed by a Joint Task Force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). Sleep Medicine 26, 86–95 Elsevier.

Ferri, Raffaele, Manconi, Mauro, Plazzi, Giuseppe, Bruni, Oliviero, Vandi, Stefano, Montagna, Pasquale, FERINI-STRAMBI, L.U.I.G.I., Zucconi, Marco, 2008. A Quantitative Statistical Analysis of the Submentalis Muscle EMG Amplitude during Sleep in Normal Controls and Patients with REM Sleep Behavior Disorder. Journal of Sleep Research 17 (1), 89–100 Wiley Online Library.

Galati, S., Song, W., Orban, G., Luft, A.R., Kaelin-Lang, A., 2018. Cortical slow wave activity correlates with striatal synaptic strength in normal but not in Parkinsonian rats. Exp. Neurol. 301 (Pt A), 50–58. https://doi.org/10.1016/j.expneurol.2017.12.004.

Galati, Salvatore, Salvade, Agnese, Pace, Marta, Sarasso, Simone, Baracchi, Francesca, Bassetti, Claudio L., Kaelin-Lang, Alain, Stadler, Claudio, Stanzione, Paolo, Moller, Jens C., 2015. Evidence of an Association between Sleep and Levodopa-Induced Dyskinesia in an Animal Model of Parkinson's Disease. Neurobiology of Aging 36 (3), 1577–1589. https://doi.org/10.1016/j.neurobiolaging.2014.12.018.

Gama, Rômulo L, Távora, Daniel G, Bomfim, Rodrigo C, Silva, Cruiff E, de Bruin, Veralice M, de Bruin, Pedro FC, 2010. Sleep Disturbances and Brain MRI Morphometry in Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy–a Comparative Study. Parkinsonism & Related Disorders 16 (4), 275–279 Elsevier.

Gao, Xiang, Schwarzschild, Michael A, O'Reilly, Eilis J, Wang, Hao, Ascherio, Alberto, 2010. Restless Legs Syndrome and Parkinson's Disease in Men. Movement Disorders 25 (15), 2654–2657 Wiley Online Library.

Garcia-Borreguero, Diego, Egatz, Renata, Winkelmann, Juliane, Berger, Klaus, 2006. Epidemiology of Restless Legs Syndrome: The Current Status. Sleep Medicine Reviews 10 (3), 153–167 Elsevier.

Garcia-Borreguero, Diego, Williams, Anne-Marie, 2014. An Update on Restless Legs Syndrome (Willis-Ekbom Disease): Clinical Features, Pathogenesis and Treatment. Current Opinion in Neurology 27 (4), 493–501 LWW.

Gómez-Esteban, Juan C, Zarranz, Juan J, Tijero, Beatriz, Velasco, Fernando, Barcena, Joseba, Rouco, Idoia, Lezcano, Elena, Lachen, María C, Jauregui, Amaia, Ugarte, Amaia, 2007. Restless Legs Syndrome in Parkinson's Disease. Movement Disorders 22 (13), 1912–1916 Wiley Online Library.

Guerreiro, Tiago Machado, Nishikawa, Danilo Ryuko Cândido, Ferreira, Lis Campos, Aragão de Melo, Hyder, do Prado, Roberto César Pereira, 2010. Restless Legs Syndrome in Parkinson's Disease: Clinical Characteristics and Biochemical Correlations. Arquivos de Neuro-Psiquiatria 68 (6), 869–872 SciELO Brasil.

Huber, Reto, Esser, Steve K, Ferrarelli, Fabio, Massimini, Marcello, Peterson, Michael J, Tononi, Giulio, 2007. TMS-Induced Cortical Potentiation during Wakefulness Locally Increases Slow Wave Activity during Sleep. PLOS ONE 2 (3), e276 Public Library of Science.

Huber, Reto, Felice Ghilardi, M., Massimini, Marcello, Ferrarelli, Fabio, Riedner, Brady A, Peterson, Michael J, Tononi, Giulio, 2006. Arm Immobilization Causes Cortical Plastic Changes and Locally Decreases Sleep Slow Wave Activity. Nature Neuroscience 9 (9), 1169–1176 Nature Publishing Group.

Huber, Reto, Felice Ghilardi, M., Massimini, Marcello, Tononi, Giulio, 2004. Local Sleep and Learning. NATURE 430, 4–7.

Hung, Ching-Sui, Sarasso, Simone, Ferrarelli, Fabio, Riedner, Brady, Felice Ghilardi, M., Cirelli, Chiara, Tononi, Giulio, 2013. Local Experience-Dependent Changes in the Wake EEG after Prolonged Wakefulness. Sleep 36 (1), 59–72 Oxford University Press.

Huot, Philippe, Fox, Susan H, Brotchie, Jonathan M, 2011. The Serotonergic System in Parkinson's Disease. Progress in Neurobiology 95 (2), 163–212 Elsevier.

Iber, C., Ancoli-Israel, S., Chesson, A., Quan, SF for the American Academy of Sleep Medicine, 2007. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine, Westchester, IL.

Iranzo, Alex, Fernández-Arcos, Ana, Tolosa, Eduard, Serradell, Mónica, Luis Molinuevo, José, Valldeoriola, Francesc, Gelpi, Ellen, Isabel Vilaseca, Raquel Sánchez-Valle, Lladó, Albert, 2014. Neurodegenerative Disorder Risk in Idiopathic REM Sleep Behavior Disorder: Study in 174 Patients. PloS One 9 (2), e89741 Public Library of Science.

Jung, Richard, Kuhlo, Wolfgang, 1965. Neurophysiological Studies of Abnormal Night Sleep and the Pickwickian Syndrome. Progress in Brain Research 18, 140–159 Elsevier.

Kalia, Lorraine V, Lang, Anthony E, 2015. Parkinson's Disease. The Lancet 386 (9996), 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3. Elsevier.

Lee, Ji E, Shin, Hae-Won, Kim, Kyung S, Sohn, Young H, 2009. Factors Contributing to the Development of Restless Legs Syndrome in Patients with Parkinson Disease. Movement Disorders 24 (4), 579–582 Wiley Online Library.

Loomis, Alfred L, Newton Harvey, E., Hobart, Garret A, 1937. Cerebral States during Sleep, as Studied by Human Brain Potentials. Journal of Experimental Psychology 21 (2), 127 Psychological Review Company.

Lustenberger, Caroline, Huber, Reto, 2012. High Density Electroencephalography in Sleep Research: Potential, Problems, Future Perspective. Frontiers in Neurology 3, 77 Frontiers.

Maetzler, Walter, Liepelt, Inga, Berg, Daniela, 2009. Progression of Parkinson's Disease in the Clinical Phase: Potential Markers. The Lancet Neurology 8 (12), 1158–1171. https://doi.org/10.1016/S1474-4422(09)70291-1. Elsevier.

Manconi, Mauro, Ferri, Raffaele, Zucconi, Marco, Fantini, Maria Livia, Plazzi, Giuseppe, Ferini-Strambi, Luigi, 2007. Time Structure Analysis of Leg Movements during Sleep in REM Sleep Behavior Disorder. Sleep 30 (12), 1779–1785 Oxford University Press.

Mascetti, Laura, Foret, Ariane, Schrouff, Jessica, Muto, Vincenzo, Dideberg, Vinciane, Balteau, Evelyne, Degueldre, Christian, Phillips, Christophe, Luxen, André, Collette, Fabienne, 2013. Concurrent Synaptic and Systems Memory Consolidation during Sleep. Journal of Neuroscience 33 (24), 10182–10190 Soc Neuroscience.

Muñoz, Ana, Li, Qin, Gardoni, Fabrizio, Marcello, Elena, Qin, Chuan, Carlsson, Thomas, Kirik, Deniz, et al., 2008. Combined 5-HT1A and 5-HT1B Receptor Agonists for the Treatment of L-DOPA-Induced Dyskinesia. Brain: A Journal of Neurology 131 (Pt 12), 3380–3394. https://doi.org/10.1093/brain/awn235.

Nelson, Sacha B., Turrigiano, Gina G., 2008. Strength through Diversity. Neuron 60 (3), 477–482. https://doi.org/10.1016/j.neuron.2008.10.020.

Nomura, Takashi, Inoue, Yuichi, Nakashima, Kenji, 2006. Clinical Characteristics of Restless Legs Syndrome in Patients with Parkinson's Disease. Journal of the Neurological Sciences 250 (1–2), 39–44 Elsevier.

Oh, Yoon-Sang, Kim, Joong-Seok, Park, In-Seok, Song, In-Uk, Son, Young-Min, Park, Jeong-Wook, Yang, Dong-Won, Kim, Hee-Tae, Kwang-Soo, Lee, 2014. Association between Nocturnal/supine Hypertension and Restless Legs Syndrome in Patients with Parkinson's Disease. Journal of the Neurological Sciences 344 (1–2), 186–189 Elsevier.

Ohayon, Maurice M, O'Hara, Ruth, Vitiello, Michael V, 2012. Epidemiology of Restless Legs Syndrome: A Synthesis of the Literature. Sleep Medicine Reviews 16 (4), 283–295 Elsevier.

Rechtschaffen, Allan, Kales, Anthony, 1968. A Manual for Standardized Terminology, Techniques and Scoring System for Sleep Stages in Human Subjects. Brain Information Service. Brain Research Institute. US Dept. of Health, Education, and Welfare.

Riedner, Brady A, Vyazovskiy, Vladyslav V, Huber, Reto, Massimini, Marcello, Esser, Steve, Murphy, Michael, Tononi, Giulio, 2007. Sleep Homeostasis and Cortical Synchronization : III. A High-Density EEG Study of Sleep Slow Waves in Humans. SLEEP 30 (12), 1643–1657.

Schenck, C.H., Mahowald, M.W., 2002. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 25 (March 2), 120–138.

Schenkel, E., Siegel, J.M., 1989. REM Sleep without Flatonia after Lesions of the Medial Medulla. Neurosci Lett 98 (2), 159–165.

Schreiner, S.J., Imbach, L.L., Werth, E., Poryazova, R., Baumann-Vogel, H., Valko, P.O., Murer, T., Noain, D., Baumann, C.R., 2019. Slow-wave sleep and motor progression in Parkinson disease. Ann Neurol. 85 (May 5), 765–770. https://doi.org/10.1002/ana.25459.

Suzuki, Keisuke, Fujita, Hiroaki, Watanabe, Yuji, Matsubara, Takeo, Kadowaki, Taro, Sakuramoto, Hirotaka, Hamaguchi, Mai, Nozawa, Narihiro, Hirata, Koichi, 2019. Leg Restlessness Preceding the Onset of Motor Symptoms of Parkinson Disease: A Case Series of 5 Patients. Medicine 98 (33) Wolters Kluwer Health.

Tatavarty, Vedakumar, Sun, Qian, Turrigiano, Gina G., 2013. How to Scale down Postsynaptic Strength. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 33 (32), 13179–13189. https://doi.org/10.1523/JNEUROSCI.1676-13.2013.

Tononi, Giulio, Cirelli, Chiara, 2003. Sleep and Synaptic Homeostasis : A Hypothesis. Brain Research Bulletin 62, 143–150. https://doi.org/10.1016/j.brainresbull.2003.09.004.

Tononi, Giulio, Cirelli, Chiara, 2006. Sleep Function and Synaptic Homeostasis. Sleep Medicine 10, 49–62. https://doi.org/10.1016/j.smrv.2005.05.002.

Tononi, Giulio, Cirelli, Chiara, 2014. Sleep and the Price of Plasticity: From Synaptic and Cellular Homeostasis to Memory Consolidation and Integration. Neuron 81 (1), 12–34. https://doi.org/10.1016/j.neuron.2013.12.025.

Verbaan, Dagmar, van Rooden, Stephanie M, van Hilten, Jacobus J, Rijsman, Roselyne M, 2010. Prevalence and Clinical Profile of Restless Legs Syndrome in Parkinson's Disease. Movement Disorders 25 (13), 2142–2147 Wiley Online Library.

Walters, Arthur S, LeBrocq, Cheryl, Passi, Vandna, Patel, Shivani, Hanna, Philip A, Cohen, Barry, Wagner, Mary, 2003. A Preliminary Look at the Percentage of Patients with Restless Legs Syndrome Who Also Have Parkinson Disease, Essential Tremor or Tourette Syndrome in a Single Practice. Journal of Sleep Research 12 (4), 343–345 Wiley Online Library.

Wong, Janice C, Li, Yanping, Schwarzschild, Michael A, Ascherio, Alberto, Gao, Xiang, 2014. Restless Legs Syndrome: An Early Clinical Feature of Parkinson Disease in Men. Sleep 37 (2), 369–372 Oxford University Press.

Ylikoski, Ari, Martikainen, Kirsti, Partinen, Markku, 2015. Parkinson's Disease and Restless Legs Syndrome. European Neurology 73 (3–4), 212–219 Karger Publishers.

Zhang, Xiaona, Sun, Xiaoxuan, Wang, Junhong, Tang, Liou, Anmu, Xie, 2017. Prevalence of Rapid Eye Movement Sleep Behavior Disorder (RBD) in Parkinson's Disease: A Meta and Meta-Regression Analysis. Neurological Sciences 38 (1), 163–170 Springer.