UNRAVELING SLEEP AND ITS DISORDERS USING NOVEL ANALYTICAL APPROACHES

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PUBLISHED IN: Frontiers in Neuroscience

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88976-323-8
DOI 10.3389/978-2-88976-323-8

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UNRAVELING SLEEP AND ITS DISORDERS USING NOVEL ANALYTICAL APPROACHES

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Citation: Hornero, R., Gozal, D., Kheirandish-Gozal, L., Gutiérrez-Tobal, G. C., eds. (2022). Unraveling Sleep and Its Disorders Using Novel Analytical Approaches. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-323-8

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frontiers | Frontiers in Neuroscience

EDITORIAL
published: 18 May 2022
doi: 10.3389/fnins.2022.924359

Editorial: Unraveling Sleep and Its Disorders Using Novel Analytical Approaches

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Keywords: sleep apnea, cardio-pulmonary coupling, insomnia, sleep deprivation, sleep disruption, depression

Editorial on the Research Topic

Unraveling Sleep and Its Disorders Using Novel Analytical Approaches

Despite significant and meritorious research efforts over the last decades, the functions and evolutionary determinants of sleep remain one of the mysterious and relatively unexplored dimensions of physiology (Krueger et al., 2016). The recipe for deciphering such an attractive challenge in biology and medicine most probably includes ingredients such as unraveling the complexity of brain functioning during sleep (Olbrich et al., 2011), the specific roles of sleep in coordination of other body systems (Penzel et al., 2016), or defining the specific cellular and system-related pathways that regulate or are regulated by sleep. In addition, the already established and novel techniques and technological tools aiming to explore sleep-related systems, e.g., electroencephalogram (EEG), magnetoencephalogram, positron emission tomography, functional magnetic resonance image (fMRI) and several others in the case of the brain, have their own limitations and advantages (Huster et al., 2012).

This Research Topic aimed to be an overarching framework and instigator for those sleep-related studies presenting novel conceptual approaches and disruptive ideas in the field. Manuscripts submitted for this special issue represent high scientific contributions to this topic. The only drawback in the Editors' opinion is that most of the studies focused on sleep disorders rather than on deep and sophisticated analyses of physiological sleep. This Research Topic might however stimulate further research in this direction.

Among the studies finally incorporated to the Research Topic, four of them focused on sleep apnea and cardio-pulmonary coupling, four additional articles focused on insomnia, sleep deprivation, and micro-sleep episodes, one focused on sleep disruption and, finally, another one focused on depression. Consistent with these topics, we have organized the rest of the document in four sections.

SLEEP APNEA AND CARDIO-RESPIRATORY COUPLING DURING SLEEP

The first study we present is an excellent example of the close relationship between sleep research and the emerging technologies and analytical techniques. Kelly et al. used at-home recordings of overnight mandibular movements to validate an automated machine-learning approach based on random forest aimed at diagnosing sleep apnea in adult subjects. Very high accuracy performances

OPEN ACCESS

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *20 April 2022*
Accepted: *04 May 2022*
Published: *18 May 2022*

Citation:
Gutiérrez-Tobal GC, Kheirandish-Gozal L, Gozal D and Hornero R (2022) Editorial: Unraveling Sleep and Its Disorders Using Novel Analytical Approaches. Front. Neurosci. 16:924359. doi: 10.3389/fnins.2022.924359

were reported for several apnea-hypopnea cutoffs, thus highlighting the approach as a promising alternative to the standard and labor-intensive diagnostic methodologies.

Karhu et al. explored further on the implications of the oxygen desaturation episodes in the context of sleep apnea evolution. They analyzed 805 adults with mild sleep apnea from the well-known Sleep Heart Health Study to show how the characteristics of the episodes, rather than their counts number, may be predictive of sleep apnea worsening 5 years later.

Gutiérrez-Tobal et al. analyzed the overnight electroencephalogram (EEG) from 294 children to find sleep apnea-related effects, including cognitive implications. A correlation network analysis on spectral features from the EEGs, clinical variables, and cognitive scores unraveled both general patterns and specific associations that showed severity-dependent sleep apnea features.

Finally, Al Ashry et al. presented a very interesting review on cardio-pulmonary coupling during sleep. They showed how distinct patterns are observed in the cardio-pulmonary spectrogram, built with heart rate variability and derived respiratory signals, according to different sleep stages, sleep apnea endotypes and phenotypes, insomnia, and other sleep-related conditions.

Insomnia, Sleep Deprivation, and Micro-Sleep Episodes

Vaziri et al. presented a "Hypothesis and Theory" article regarding insomnia. Particularly, they propose a novel conceptual framework for the cognitive implications of insomnia in a search for more personalized clinical interventions. The authors argue that their methodology could pave the way to conceptual frameworks for other cognitive problems.

Xu et al. combined fMRI data, a network centrality analysis, and machine learning (support vector machines) to predict sleep deprivation vulnerability. They report remarkable results in the task while pointing out the brain regions that contribute the most to such susceptibility in performance.

Another sleep deprivation study is presented by Xiong et al.. The authors evaluate the effect of the arousal enhanced drug Modafinil to mitigate the cognitive decline after sleep deprivation. They used a rat model to report that the drug suppresses neuronal pyroptosis and inflammation associated to sleep deprivation.

Finally, a study on micro-sleep episodes detection is presented by Malafeev et al.. The authors used a combination of deep-learning techniques (convolutional neural networks and recurrent neural networks) to identify episodes of wakefulness, micro-sleep episodes, micro-sleep candidates, and drowsiness on the EEG and electro-oculogram of 76 patients with excessive daytime sleepiness. Micro-sleep episodes and wakefulness were reported to be highly separable, while significant overlap of these with micro-sleep candidates and drowsiness were also shown.

Sleep Disruption

A very interesting review on new approaches to improve sleep disruption definitions is presented by Lechat et al.. They start by pointing out the limits of current standards and then go over some of the latest discoveries and techniques that have helped gain insights into sleep disruption. The authors highlighted alterations in EEG (in slow waves, K-complexes, or sleep spindles), oxygen saturation (hypoxic burden), and other respiratory signals (low arousal threshold, high loop gain, etc.), while acknowledging automatic processing techniques such as spectrogram, signal coupling measures, and environmental factors.

Depression

A study on the brain activity alterations during sleep caused by depression is presented by Lian et al.. The authors analyzed the sleep EEG of 25 healthy controls and 26 depressed patients using symbolic phase transfer entropy as a measure of effective connectivity between electrodes, within the common spectral bands, and in the different sleep stages. Results reported show how the main way of information transition during sleep is attenuated in depressed patients.

Altogether, these 10 studies underline the impact of sleep in our lives, the need for increasing the research efforts on this topic, as well as on how to develop and apply new powerful tools to do it.

AUTHOR CONTRIBUTIONS

GG-T, LK-G, DG, and RH reviewed the submissions, wrote the editorial, and approved it for publication. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Ministerio de Ciencia, Innovación y Universidades and the European Regional Development Fund (FEDER) under projects PID2020-115468RB-I00, and PDC2021-120775, by the European Commission and FEDER under project Análisis y correlación entre el genoma completo y la actividad cerebral para la ayuda en el diagnóstico de la enfermedad de Alzheimer (Cooperation Programme Interreg V-A SpainPortugal POCTEP 20142020), and by CIBER-BBN (ISCIII), cofunded with FEDER funds. DG was supported by the United States National Institutes of Health AG061824, and by Tier 2 and TRIUMPH grants from the University of Missouri.

ACKNOWLEDGMENTS

The editors want to thank the excellent work of authors and reviewer of the submitted manuscripts.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 24 March 2021
doi: 10.3389/fnins.2021.564098

Automatic Detection of Microsleep Episodes With Deep Learning

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Brief fragments of sleep shorter than 15 s are defined as microsleep episodes (MSEs), often subjectively perceived as sleepiness. Their main characteristic is a slowing in frequency in the electroencephalogram (EEG), similar to stage N1 sleep according to standard criteria. The maintenance of wakefulness test (MWT) is often used in a clinical setting to assess vigilance. Scoring of the MWT in most sleep-wake centers is limited to classical definition of sleep (30 s epochs), and MSEs are mostly not considered in the absence of established scoring criteria defining MSEs but also because of the laborious work. We aimed for automatic detection of MSEs with machine learning, i.e., with deep learning based on raw EEG and EOG data as input. We analyzed MWT data of 76 patients. Experts visually scored wakefulness, and according to recently developed scoring criteria MSEs, microsleep episode candidates (MSEc), and episodes of drowsiness (ED). We implemented segmentation algorithms based on convolutional neural networks (CNNs) and a combination of a CNN with a long-short term memory (LSTM) network. A LSTM network is a type of a recurrent neural network which has a memory for past events and takes them into account. Data of 53 patients were used for training of the classifiers, 12 for validation and 11 for testing. Our algorithms showed a good performance close to human experts. The detection was very good for wakefulness and MSEs and poor for MSEc and ED, similar to the low inter-expert reliability for these borderline segments. We performed a visualization of the internal representation of the data by the artificial neuronal network performing best using t-distributed stochastic neighbor embedding (t-SNE). Visualization revealed that MSEs and wakefulness were mostly separable, though not entirely, and MSEc and ED largely intersected with the two main classes. We provide a proof of principle that it is feasible to reliably detect MSEs with deep neuronal networks based on raw EEG and EOG data with a performance close to that of human experts. The code of the algorithms (https://github.com/alexander-malafeev/microsleep-detection) and data (https://zenodo.org/record/3251716) are available.

Keywords: microsleep episodes, excessive daytime sleepiness, drowsiness, deep learning, machine learning

OPEN ACCESS

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *20 May 2020*
Accepted: *03 March 2021*
Published: *24 March 2021*

Citation:
Malafeev A, Hertig-Godeschalk A, Schreier DR, Skorucak J, Mathis J and Achermann P (2021) Automatic Detection of Microsleep Episodes With Deep Learning. Front. Neurosci. 15:564098. doi: 10.3389/fnins.2021.564098

INTRODUCTION

Excessive daytime sleepiness (EDS) is a common complaint of many patients (Harrison and Horne, 1996; Hara et al., 2004; Ford et al., 2015; Hayley et al., 2015) and also reported by the general population when sleep is chronically curtailed. Accurate diagnosis of the underlying disorders often requires objective evaluation of nocturnal sleep and daytime sleepiness in these patients. State of the art methods to evaluate sleepiness are the Multiple Sleep Latency Test (MSLT) (Carskadon, 1986) and the Maintenance of Wakefulness Test (MWT) (Mitler et al., 1982).

Microsleep episodes (MSEs) are considered to be an objective sign of excessive daytime sleepiness (EDS) (Hertig-Godeschalk et al., 2020). The MWT is the primarily used test to quantify the ability to maintain wakefulness despite the presence of increased sleep pressure subjectively perceived as EDS.

In most of the studies, the latency to sleep stage N1 or any other stages of sleep is used as a definition for objective sleepiness (Correa et al., 2014; Sauvet et al., 2014; Sriraam et al., 2016). However, it is well accepted that signs of sleepiness appear much earlier, not only in the EEG but also in behavioral changes and performance lapses.

Therefore, more sensitive and systematic, but still practically useful definitions of objective sleepiness are needed. The recently developed Bern continuous and high-resolution wake-sleep (BERN) scoring criteria for assessing the wake-sleep transition zone represent such an approach (Hertig-Godeschalk et al., 2020). The criteria were developed for visual scoring of MSEs as short as 1 s, which is time consuming. Moreover, no generally accepted scoring criteria exist so far. Thus, tools for automated analysis of such data would be very useful for both clinicians and researchers in order to reduce the workload and the subjectivity of scoring.

In a study subsequent to the development of the BERN scoring criteria, we developed algorithms for machine learning based automatic detection MSEs using manually engineered features mainly derived from spectral information of the electroencephalogram (EEG) (Skorucak et al., 2020b).

Another interesting approach was taken by authors of the Vigilance Algorithm Leipzig (VIGALL) (Olbrich et al., 2012). They established scoring criteria for 7 vigilance stages (1 s resolution; from fully awake to sleep) and developed an algorithm for the automatic scoring of these stages.

The aim of this work was to implement a deep learning approach using raw data as input. We think that such an algorithm resembles human scoring, which is mainly based on visual pattern recognition. It has also been shown that deep learning methods perform better than classical machine learning (ML) methods on various types of data (Goodfellow et al., 2016), including EEG data (Davidson et al., 2006; Tsinalis et al., 2016; Supratak et al., 2017; Chambon et al., 2018; Malafeev et al., 2018). Automatic sleep classification has been extensively developed mainly due to the advantages in machine learning, and especially in deep learning (Tsinalis et al., 2016; Supratak et al., 2017; Chambon et al., 2018; Malafeev et al., 2018; Fiorillo et al., 2019; Mousavi et al., 2019).

Our Contribution

We developed several artificial neural networks, which work with raw data as input and compared their performance with the inter-rater agreement of two experts. Note that inter-rater agreement was computed only for five recordings, which were scored by two different experts from the same sleep center. It is also important to note that the selection of the recordings for double scoring was not totally random: only recordings containing MSEs were randomly selected for double scoring. Our networks showed similar agreement to a human expert as the inter-rater agreement between two human experts. We also performed visualization of the hidden representation of the data by one of the networks, the one performing best, using a t-distributed stochastic neighbor embedding (t-SNE) method (van der Maaten and Hinton, 2008).

MATERIALS AND METHODS

Data

MWT data from 76 patients with EDS recorded at approximately 15:00 were retrospectively analyzed. The suspected diagnosis widely varied between patients (**Table 1**) and included sleep apnea, narcolepsy, idiopathic hypersomnia, non-organic hypersomnia, and insomnia (Skorucak et al., 2020b). Patients were not stratified into subgroups because only few patients were available with a certain suspected diagnosis due to their low prevalence. Among other data, recordings included EEG, electrooculogram (EOG), and video recordings of the face (Hertig-Godeschalk et al., 2020; Skorucak et al., 2020b). Electrophysiological signals were sampled at 200 Hz [band pass filter 0.3–70 Hz; 50 Hz notch filter; RemLogic^{TM} (Embla Systems LLC)] and exported in the European data format (EDF) for post processing.

MSEs were visually scored by a sleep expert using both occipital EEG derivations referenced to contralateral mastoid electrodes (i.e., channels O1M2 and O2M1), two EOG channels, both referenced to the left mastoid electrode (i.e., channels E1M1 and E2M1), and video recordings of the face. Video recordings were not used for automatic detection algorithm, only EEG and EOG data were considered. MSEs were defined as 1–15 s in duration with a clear slowing in the EEG resulting in a theta dominance resembling non-rapid eye movement (NREM) sleep stage 1 (N1), while at least an 80% eye closure was observed in the video recording. MSEs were typically preceded by slow eye movements, visible in the EOG. Apart from clear wakefulness and MSEs, two poorly defined EEG patterns were categorized as microsleep episode candidates (MSEc; not fulfilling all of the criteria for a MSE, e.g., eyes were closed less than 80%) and episodes of drowsiness (ED; even more vague, not clear wake or MSE or MSEc) (Hertig-Godeschalk et al., 2020). Approximately 2/3 of the recordings were checked by another expert and differences were resolved by discussion. The beginning and the end of each episode was marked continuously, i.e., with the resolution of the recording (1/200 s).

Each MWT lasted 40 min and was supposed to be terminated earlier if consolidated sleep occurred (Hertig-Godeschalk et al., 2020; Skorucak et al., 2020b). However, if the technician missed

TABLE 1 | Demographics, diagnosis and fraction of time spent in the four stages of patients contributing to the training, validation, and test set: total number of patients (N), number of males/females, mean age and standard deviation, number of patients with a suspected diagnosis of sleep apnea, idiopathic hypersomnia, non-organic hypersomnia, narcolepsy, insomnia, EDS with unclear cause, excessive tiredness, and others, and the fraction of time spent in wake, MSEs, MSEc, and ED.

	Training	Validation	Testing
N	53	12	11
Male/Female	35/18	6/6	9/2
Age (mean ± SD years)	45.99 ± 18.17	44.64 ± 20.56	44.92 ± 14.48
Sleep apnea	20	0	3
Idiopathic hypersomnia	2	1	1
Non-organic hypersomnia	1	0	0
Narcolepsy	4	1	1
Insomnia	1	0	0
EDS with unclear cause	18	4	4
Excessive tiredness	2	3	2
Others	5	3	0
Fraction of time in			
Wake	0.89	0.85	0.91
MSEs	0.08	0.09	0.05
MSEc	0.01	0.01	0.01
ED	0.02	0.05	0.03

terminating the recording, data from the entire recording were used for training, validation and testing (i.e., also including sleep episodes lasting longer than 15 s; basically, sleep stage N1) to obtain as much data as possible as the fraction of time covered by MSEs is small (5–8%; **Table 1**). In total, 1,262 MSEs and segments of sleep were scored.

Preprocessing

The signals were bandpass filtered with a Fourier filter in the band 0.5–45 Hz (FFT of EEG followed by setting of frequencies < 0.5 Hz and > 45 Hz to 0 and then performing an inverse FFT). This step is considered as signal conditioning and is necessary for the application to future data that are recorded with different devices. We still refer to it as raw data as no features were derived for the classification.

For each training sample, we used one occipital EEG derivation and two EOG channels. The EEG derivation for each training sample was chosen randomly out of two derivations (O1M2 or O2M1) and we assigned the corresponding scoring. Thus, we effectively doubled our training set by using both EEG channels as independent signals. Since both EEG signals were similar and most of MSEs were observed in both channels simultaneously we did not gain completely new examples by this procedure, but it served as data augmentation. Data augmentation is commonly referred to slight changes to the data, such as additional noise, cropping or warping. It helps to avoid overfitting of the networks (Perez and Wang, 2017). Video recordings were not used for automatic classification. For the validation and testing we detected the events using only EEG channel O1M2, the two EOG channels (E1M1 and E2M1), and the corresponding expert scoring.

ML Methods

Many pattern recognition problems are easy to solve for a human expert (for example object recognition in images), but it is incredibly hard to define explicit decision rules for such tasks. Machine learning methods are proven to be very efficient for pattern recognition tasks (Murphy, 2012; Bishop, 2016; Goodfellow et al., 2016), including EEG data (Davidson et al., 2006; Tsinalis et al., 2016; Supratak et al., 2017; Chambon et al., 2018; Malafeev et al., 2018; Stephansen et al., 2018; Phan et al., 2019). The idea behind machine learning is to let the algorithm learn the patterns in the data. This can be achieved either in a supervised way, i.e., when there are labels attached to each datapoint, or an unsupervised way, when there are no labels and the algorithm should find the structure in the data on its own. A typical example of unsupervised learning is clustering (Xu and Wunsch, 2005), and the most common example of supervised learning is classification (Bishop, 2016). In this work, we are aiming to detect MSEs. This problem can be solved in different ways. For example, one can solve it as object detection problem (Dalal and Triggs, 2005; Girshick, 2015; Ren et al., 2015; Liu et al., 2016; Redmon et al., 2016), where the objects are MSEs. Since the MSEs are not overlapping it can also be considered a segmentation problem. Further, we can also represent it as a classification problem for every sample, i.e., we classify each sample of a recording as one of the four classes: wake, MSE, MSEc or ED. We have chosen to use the classification approach.

Classification

We developed and implemented automatic classification algorithms (supervised learning) based on a Convolutional Neural Network (CNN) (LeCun and Bengio, 1995). Such a network uses small filters, and every layer of the network has its own set of filters. Each filter is convolved with an input to the layer, i.e., the filter is moved across the input and a similarity measure is computed for every position and stored in a new matrix. Matrices corresponding to all filters are stacked together and this stack is the input for the next layer. We used small filters based on empirical knowledge. Further, it was shown that deep networks with small filters perform best (Simonyan and Zisserman, 2014). We applied a small number of filters in the first layers of the network and more filters in later layers. This is a common approach used in computer vision (Simonyan and Zisserman, 2014). Filters in the first layers have a small receptive field and usually detect simple patterns, thus, there is no need for many filters in the first layers. The layers located deeper have larger receptive fields, thus they detect more complex patterns, and it makes sense to increase the number of filters to extract the maximal amount of information from the signal. It is common to use the number of filters equal to a power of two. We used a similar approach and choose the number of filters as in our previous EEG analysis paper (Malafeev et al., 2018). Also the same ladder of convolutional layers was used in Simonyan and Zisserman (2014) and other works on computer vision. The number of layers was chosen such that the last layer's receptive field covers the whole input window.

Since we wanted to assign a label to each sample of the signal, we ran the classification algorithm on a sliding window. The stride of the sliding window was equal to the segmentation resolution, i.e., one sample. We could have used a larger stride and predicted a label not for every sample but for example every 100 samples. Resolution would be lower, but computational expenses would be reduced, and the algorithm would be faster. However, we wanted to avoid coarsening of the expert's segmentation resolution (please note that this was done for CNN-LSTM network architecture; see below). Our CNNs predicted the label for the central point of each window. We could minimize the fringe effect in this way, i.e., the different amount of information available at the edge and in the middle of the window. The amount of information available at the edge is lower than in the middle, thus, we chose to work with a sliding window. The idea of using a convolutional neural network on a sliding window is illustrated in **Figure 1A** and its structure in **Figure 2A**.

We also implemented a combination of convolutional and recurrent neural networks (RNN; **Figure 1B**) to test whether performance could be considerably improved as RNN take into account the temporal structure of the data (Hochreiter and Schmidhuber, 1997). We wanted the network to see a certain window, it can be achieved either by using a CNN with large input size or a combination of CNN and LSTM. In the latter case we have an input window size with a much smaller number of parameters. We first processed the signals with a CNN with a 1 s window. The windows were overlapping, and the stride was equal to 50 samples (0.25 s). We chose relatively large stride to speed up this network. As a consequence of the large stride, we predicted the label every 50 samples, and the resulting resolution of the prediction was lower than the resolution of the other networks used. We do not think this is a problem since the MSEs are 1–15 s long by definition. Next, we used a recurrent neural network, namely a long-short term memory (LSTM) (Hochreiter and Schmidhuber, 1997) network. The LSTM network received the vectors resulting from the CNN as input (**Figure 2B**) and the output was a sequence of labels (MSE, Wake, ED, or MSEc). Each label was assigned to the center of the corresponding CNN window.

Most of our networks were convolutional networks working with a sliding window (CNN) and one network was a combination of convolutional and LSTM networks (CNN-LSTM network).

Architecture of the Networks

Figure 2 (A: CNN and B: CNN-LSTM) illustrates the network architectures.

Raw EEG and EOGs (in μV) served as the input data for CNNs and they were divided by 100 and clipped to the range $[-1; 1]$ to keep weights and gradients small. For CNN-LSTM network similar procedure was performed, however, we first added 100 to the signals, divided them by 200 and clipped them in the range $[0; 1]$. In the first layer of the network, we added some Gaussian noise ($SD = 0.0005$) to increase robustness of the network to noise.

Convolutional blocks are the basic parts of the networks. They are composed of convolution followed by batch normalization, activation and max-pooling, i.e., filtering, non-linear activation and reduction of the size of the tensors (**Figure 2** and **Table 2**).

We first explored different network configurations based on our previous experience with sleep stage scoring (Malafeev et al., 2018) and decided to investigate the ones finally implemented in detail. However, the parameter space is infinite, and we do not claim that our choice is the best one. Some of the blocks were repeated many times because we want to make the network deep and would like to end up with a vector of size 1 in the temporal dimension (i.e., the receptive field of the last layer covers the whole input window) and a large size in the dimension of the filters (that these filters can contain large amount of information about the input window). Thus, some of the blocks are repeated different number of times depending on the size of the sliding window, i.e., for each doubling of the window size, we repeated the block one more time to increase the depth of the network accordingly: 3 times for 2 s, 4 times for 4 s, 5 times for 8 s, 6 times for 16 s, and 7 times for 32 s windows. In the end we applied 5 different window sizes. We limited the length of the sliding window to the range of 2–32 s because we explicitly did not want the networks to learn MSE duration criteria, only the underlying EEG patterns. For practical applications, duration criteria can easily be applied *post hoc*. We also tested a network (16 s long window) with a single EEG channel as input instead of an EEG channel stacked together with the two EOG channels. To account for the imbalance between the stages (**Table 1**), weights inversely proportional to the frequency of a class were generally applied. To test for the impact of the weighting, an additional network (16 s long window) was trained with equal weights. This resulted in seven CNN networks and one CNN-LSTM network, in total 8 different network configurations to explore.

The notations used in **Figure 2** and the corresponding parameters are summarized in **Table 2**. For the parameter values applied see the corresponding values in **Figure 2**.

Performance Evaluation

There are several methods to evaluate the performance of a classification algorithm. The simplest one is to find the proportion of correctly classified examples, a metric called accuracy. While it might be a good measure when we have nearly the same number of examples of each class, it is a very poor measure in case the dataset contains predominantly examples of one class. In our case the most frequent class was wakefulness. Imagine that 90% of the data is labeled as wakefulness, then a classifier, which labels all the data as wake would result in 90% accuracy, but such a classifier would be useless.

One can compute measures such as sensitivity and specificity. These measures consider both true positive and true negative results. In this case we need two numbers to characterize an algorithm. However, it is more convenient to have a single number to measure performance. Many different single-number measures exist but they always capture only partial information about the quality of an algorithm.

We used Cohen's Kappa (Cohen, 1960) to measure the quality of the algorithms. This measure compares the output of the classifier with one that would give random answers with the

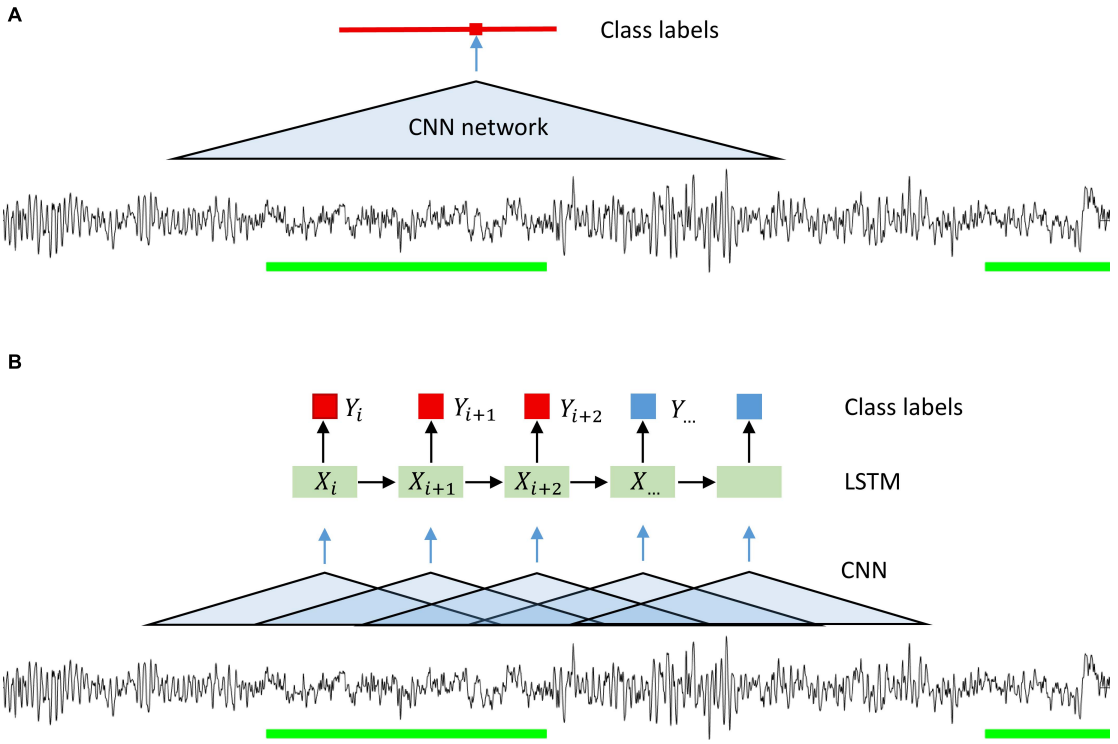

FIGURE 1 | Illustration of the idea behind the segmentation (classification) with a CNN **(A)** and CNN-LSTM **(B)** network. A sliding window was used in the case of CNN only networks. Microsleep episodes were inferred corresponding to the middle of the window on every step (sampling resolution). In case of CNN-LSTM network a sequence of overlapping windows (classified by a CNN) with the stride of 0.25 s inferring microsleep corresponding to the middle window in the sequence (LSTM classification). Thus, the resulting resolution of the detection was 0.25 s. Green bars: scored MSEs; red bar in **(A)** classified MSE; red and blue squares in **(B)** classification of a sample or window.

probabilities of classes taken according to the proportion of examples of a corresponding class in the original data.

The main disadvantage of Cohen's Kappa is the fact that if our data contains only one class, kappa will be equal to zero. For example, a kappa for a particular subject who was always awake, and the algorithm correctly classified the entire recording as wake will be equal to zero. This would indicate a very bad performance, despite the fact, that such a segmentation is correct.

There are two important aspects regarding the computation of Cohen's Kappa in this work. First, we could not compute kappa for each patient since in some recordings not all classes were present. Thus, we concatenated all the recordings and then computed kappa resulting in an overall performance. As a consequence, error bars are not available. Second, we computed kappa for each class separately. To compute kappa for a particular class k, we assigned the labels of the examples of the class k to 1 and all other labels to 0 and then computed kappa. We repeated this step for each class.

Training, Validation, and Testing

As mentioned above, our data comprised 76 MWT recordings, one recording per patient. The data was split into three parts: 70% training (n = 53), 15% validation (n = 12), and 15% testing (n = 11). Only the best performing network was additionally evaluated using the test dataset. The demographic data, diagnosis and fraction of time spent in the four stages of the patients contributing to the three parts are provided in **Table 1**. Most of the time the patients were awake (85–91% of the time) and in 5–9% of the time MSEs occurred.

We used the Keras package (v 2.2.0) (Chollet Fao, 2015) with the Tensorflow (v 1.8.0) (Abadi et al., 2016) backend to train the networks and Python 3.5.2 to run the scripts. Data conversion and filtering was performed with Matlab 2018b.

We trained the networks using the Adam (Adaptive momentum estimation) optimization algorithm (Kingma and Ba, 2014) with Nesterov momentum (Nesterov, 1983) (Nadam in Keras with the default parameters, learning rate 0.002). For the CNN-LSTM network gradient clipping at a value of the gradient norm equal to 1 was applied.

The batch size (stack of input windows) for CNN networks was equal to 200 and 128 for CNN-LSTM network. The input windows were selected randomly for each batch without repetitions.

We trained every CNN network for 3 training iterations and the CNN-LSTM network for 8 iterations. Here we use the term training iteration instead of commonly used training epoch because epoch is reserved for scoring epoch in the literature on sleep analyses. It appeared that the performance reached its maximum already after only one training iteration and did not improve further. This is not surprising given that our dataset

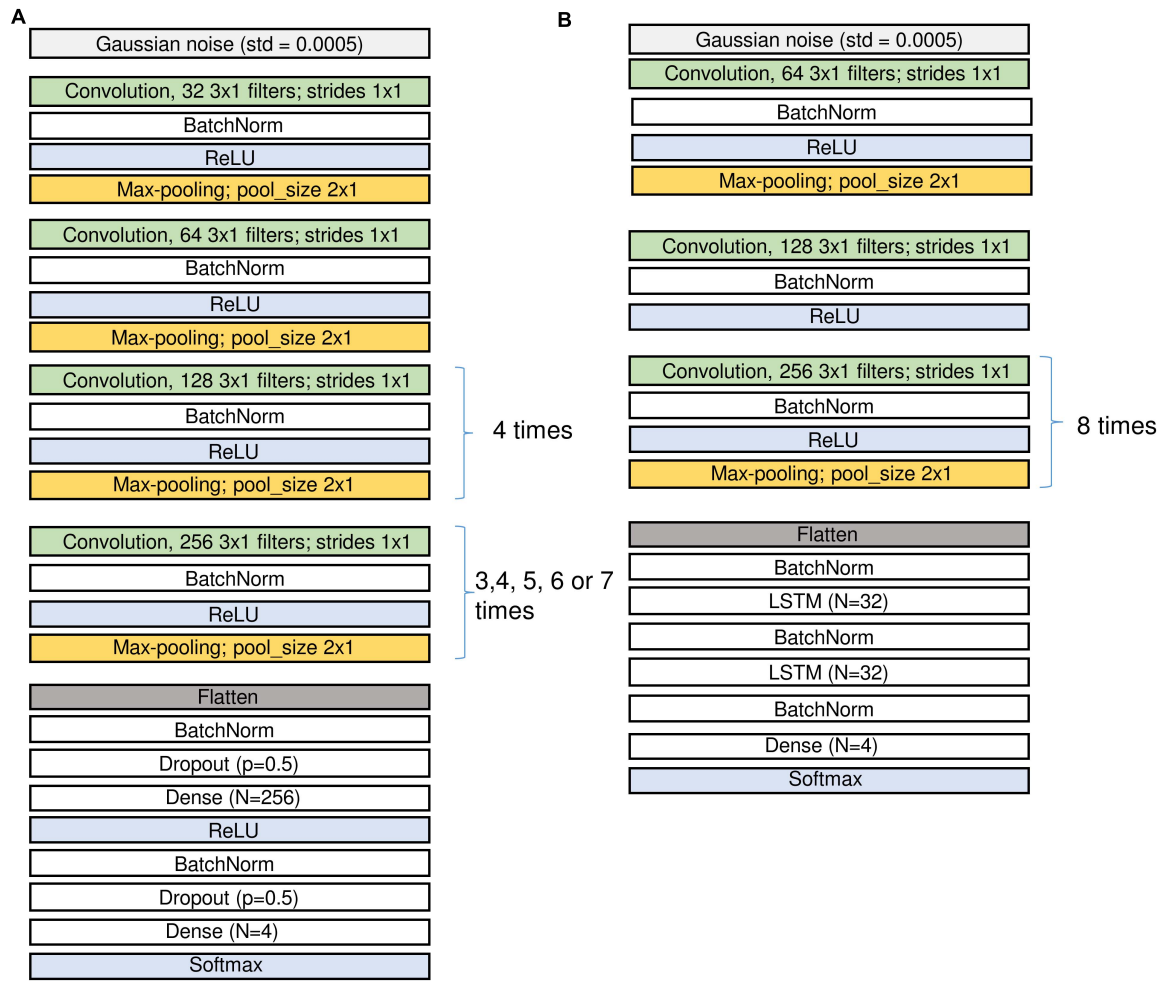

FIGURE 2 | Structure of the CNN **(A)** and the CNN-LSTM **(B)** networks. Input is on top, output at the bottom. Since we applied several configurations of the CNN networks the repetitions of the last convolutional and pooling blocks were different. The number of channels in the input may differ for the networks using either an EEG and two EOG channels or a single EEG channel only. See sections "Architecture of the Networks" and "Materials and Methods" and **Table 2** for the description of the different layers.

included a frame for every sample of the signal. It produced a lot of redundant data because the frames corresponding to consecutive samples differ only in the first and the last values and thus are almost identical. Thus, our networks were able to converge within one training iteration.

Visualization

Our data contained 4 classes defined by an expert and it was interesting to see how they are represented in the feature space. We took the best performing network (with 3 input channels and a 16 s window) as we used it for solving the classification problem and added one more convolutional layer with 64 filters of size 3. The reason to use an additional layer was to reduce the size of the resulting feature vector. We used the output of the last convolutional layer as a feature vector. The length of the vector was 64, which is large. Thus, it was not realistic to look at the data points in this 64-dimensional space. Fortunately, there are many dimensionality reduction methods available. We have chosen the t-distributed stochastic neighbor embedding (t-SNE) (van der Maaten and Hinton, 2008) to project the data into a 2D space. This mapping preserves the distance ratios between the data points. In this way we can see whether separable clusters of data points exist. It should, however, be kept in mind that this mapping is reflecting the representation of the data by the network (internal representation) and not any sort of ground truth. Thus, the visualization might differ if another network structure is employed.

RESULTS

How Our Algorithms Performed in Classification

Detection of the different classes in one recording with one of the networks (CNN 16s) and the corresponding expert scoring are illustrated in **Figure 3**. A good match between the algorithm

TABLE 2 | Description of the different layers and notions used in the architecture of the networks (**Figure 2**).

Layers	Description
Convolution, N 3 × 1 filters; strides 1 × 1	Convolutional layer (LeCun and Bengio, 1995) with N filters of size 3 × 1, i.e., one-dimensional filters of the length 3 and the convolution had a stride of length 1. The weights of convolutional filters were initialized with a Glorot normal distribution (Glorot and Bengio, 2010)
BatchNorm	Batch normalization is a way to speed up training and regularize the network (Ioffe and Szegedy, 2015)
ReLU	Rectified linear unit (Hahnloser et al., 2000), a non-linear activation function. It makes the activations of a network sparse and prevents vanishing of the gradients (Hahnloser et al., 2000)
Max-pooling; pool_size 2 × 1	Max-pooling layer (Fukushima and Miyake, 1982) with pooling size 2. It takes a maximum out of every 2 elements of a tensor. Thus, the size of the resulting tensor will be reduced by a factor of 2. Max-pooling allows us to reduce the size of the vector, retain most useful information and it also has the property of shift invariance
Flatten	Layer which resizes the input tensor and produces a one-dimensional vector with the same number of elements
Dropout (p = q)	Dropout layer (Srivastava et al., 2014). It switches off a fraction q of the neurons in the previous layer in the training phase. Dropout is a good way to regularize the networks, i.e., prevent overfitting (Srivastava et al., 2014)
Dense (N = n)	Densely connected layer with n neurons
Softmax (N = n)	Densely connected layer with n neurons and a special activation function which produces a probability distribution with n values (Bishop, 2016). The sum of these values is equal to 1, n is equal to number of classes we want to predict (in our case it was 4) and every output value is the probability that the sample belongs to the corresponding class
LSTM (N = n)	Long short-term memory layer (Hochreiter and Schmidhuber, 1997) with the size of hidden states equal to n. It has a memory and can use information about the past to make decisions in a current timepoint

*For the parameters applied see the corresponding values in **Figure 2**.*

and the expert scoring for wakefulness and MSEs can be seen, but the detection of MSEc and ED was not successful. Performance of the network on the other patients in the validation dataset are illustrated in **Supplementary Figure S1** and of patients of the test set in **Supplementary Figure S2**.

Our algorithms resulted in Cohen's Kappa coefficients close to the ones resulting from the scoring of two experts (5 recordings were scored by two experts; **Figure 4**). Importantly, our algorithms did not produce any substantial amount of false positive MSE detections in most of the recordings (except one recording). A small number of false positives (high precision) is especially important for recordings, which do not contain any MSEs.

Cohen's Kappa of the algorithms and of the inter-rater agreement was good for MSEs and wakefulness (∼0.7), but negligibly low for MSEc and ED (<0.1). The results for the different network configurations are illustrated in **Figure 4** and summarized in **Table 3**. We suggest that the CNN with a 16 s window is an optimal network, as we did not observe any further improvement with a 32 s window (**Figure 4** and **Table 3**).

The agreement between the experts for MSEc was higher than the agreement between the algorithm (CNN 16 s) and an expert (MSEc—0.04). Kappa for ED was the same (0.06) when computed between experts and between the algorithm and an expert. Cohen's kappa for both MSEc and ED was very low (<0.1) for both interrater comparison and the comparison of an algorithm with an expert. Such level of agreement is negligible (McHugh, 2012). There were five recordings in the validation dataset which contained a very small amount of MSEs or none at all (**Supplementary Figure S1**). The CNN with a 16 s window detected a substantial amount of false positive MSEs in one of the patients (recording uXdB).

The performance of MSE detection with the best of our CNNs was slightly better than the one with the CNN-LSTM architecture. It might be due to different resolution of detection. We cannot be sure that this result would hold if the temporal resolution had been the same. The quality of segmentation was dependent on the length of the window. We think that the optimal length of the window is 16 s since we did not see further improvements with a 32 s long window. The network with uniformly weighted classes (CNN 16s_u; **Figure 4**) did not perform better than the ones with balanced weights. The CNN which did not use the ocular channels as an input, i.e., used only a single EEG channel as input, performed worse than a similar network with three input channels (1 EEG and 2 EOG). This suggests that ocular channels contain information important for the MSE detection, most likely slow eye movements, eye blinks and saccades.

We evaluated only the best (optimal) performing algorithm, the CNN with a 16 s window with the test dataset. Evaluation resulted in the following Cohen's kappa values: W—0.59; MSE—0.69; MSEc—0.05; ED—0.11. These results were very close to the ones resulting from the validation dataset (**Table 3**), and thus suggest, that there was no substantial overfitting to the validation dataset. Again, we observed no substantial false positive MSE detections in the test dataset, except for one recording (patient f8H5; **Supplementary Figure S2**). Overall, there were six recordings with no or very little MSEs in the test dataset and five of them were scored nearly perfectly by the algorithm (CNN 16s). Moreover, the recordings with a substantial amount of MSEs were scored with very high quality (**Supplementary Figure S2**).

Why Did the Algorithm Not Perform Equally Well for All Classes?

Visualization (t-SNE) and analysis of the internal representation of the data in our network (CNN 16s) revealed as expected for the training data of artificial neural networks, that in the representation of training data all four stages form clearly

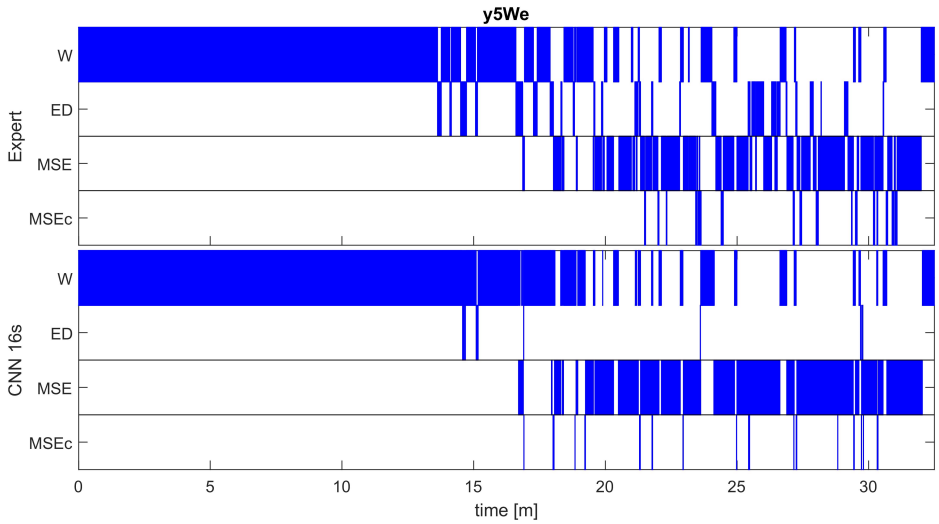

FIGURE 3 | Expert (top) and automatic soring with one algorithm (CNN with 16-s window; bottom) of an MWT (40 min) in one patient of the validation set (patient y5We). A good match between the algorithm and an expert scoring for wakefulness (W) and microsleep episodes (MSE) are evident, but a poor match for episodes of drowsiness (ED) and microsleep episode candidates (MSEc). Scoring was performed with the resolution of one sample; for the illustration, we coarsened the result to a resolution of 0.5 s (100 samples), i.e., the most frequent class within an interval was plotted. Results for other patients of the validation set are illustrated in **Supplementary Figure S1**, those of the test set in **Supplementary Figure S2**.

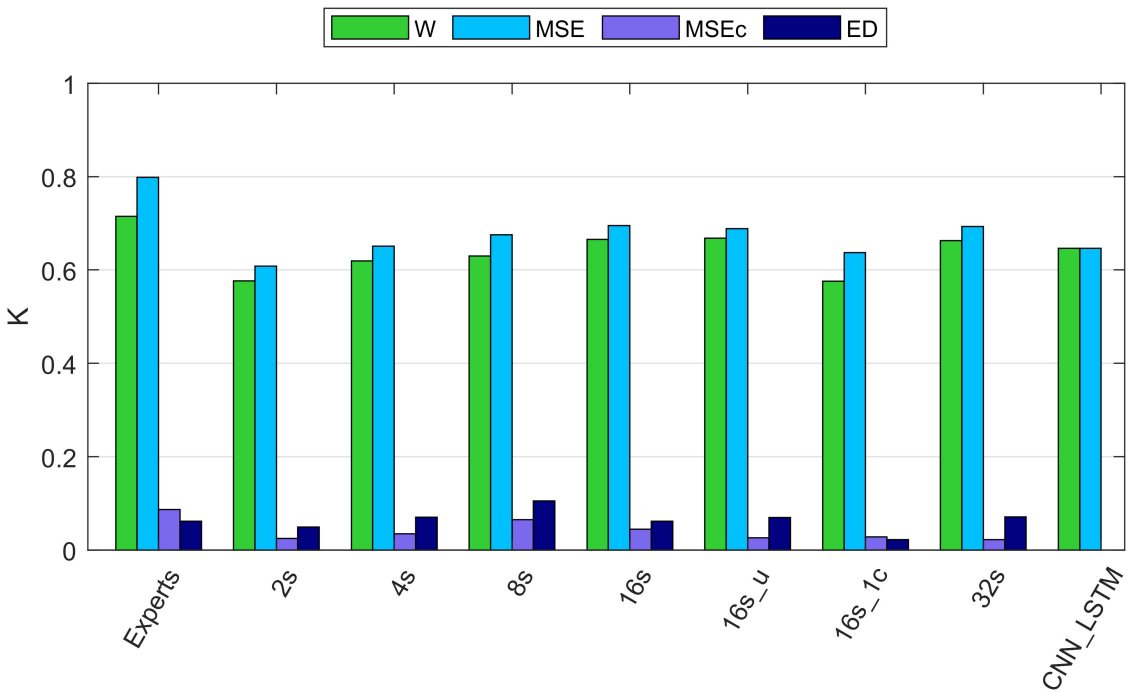

FIGURE 4 | Cohen's kappa of different algorithms along with the agreement between two experts. W, wakefulness; MSE, microsleep episodes; MSEc, microsleep candidates; ED, episodes of drowsiness. Experts: agreement between two experts computed based on five recordings containing MSEs. 2–16s: comparison between one expert and convolutional neural networks (CNNs) with window lengths 2, 4, 8, and 16 s. 16s_u: CNN with a 16s window and uniformly weighted classes. 16s_1c: CNN with 16s window and only one EEG channel as input. 32s: CNN with a 32s window. CNN_LSTM: CNN combined with a long-short term memory (LSTM) architecture; it has only two classes because this network was trained to detect only MSEs, everything else was considered as wakefulness. If not mentioned otherwise, one occipital EEG channel and two ocular channels served as input for the networks. Kappa of the neural networks was computed using the validation dataset (12 recordings). The data of all recordings were concatenated to estimate the overall kappa.

TABLE 3 | Cohen's kappa computed on the validation dataset (n = 12) using different network architectures.

	W	MSE	MSEc	ED
Experts	0.71	0.80	0.09	0.06
2s	0.58	0.61	0.02	0.05
4s	0.62	0.65	0.03	0.07
8s	0.63	0.67	0.07	0.11
16s	0.67	0.69	0.04	0.06
16s_u	0.67	0.69	0.03	0.07
16s_1c	0.58	0.64	0.03	0.02
32s	0.66	0.69	0.02	0.07
CNN_LSTM	0.65	0.65		

*See **Figure 4** for the meaning of the network labels.*

separated clusters except for very few data points (**Figure 5A** and **Supplementary Figure S3**). However, in the representation of validation data generally the four classes are not separable. In most cases there were two clear clusters representing wakefulness and MSEs with a smooth transition between them (**Figure 5B** and **Supplementary Figure S4**). However, most MSEc and ED were on the interface between these two classes, which explains why they cannot be reliably identified by the algorithm. In some cases (**Supplementary Figure S3**; patient IhpU), we observed not only a cloud of MSEs, which was connected with the cloud of wakefulness but additionally a second clearly separable cluster. This distinct cluster may not represent MSEs but sleep episodes longer than 15 s which were marked as microsleep by the expert (see section "Discussion").

DISCUSSION

Our algorithms reliably identified MSEs and wakefulness with a performance close to a human expert and did not produce any substantial amount of false positive MSEs detection in recordings of patients, indicating that reliable automatic MSE detection is feasible based on raw EEG and EOG data recorded during the MWT in a clinical setting. In one of the recordings (uXdB; **Supplementary Figure S2**) we observed a considerable amount of false positive MSE detections. We do not yet have an explanation why this happened. Visual inspection of recording uXdB revealed that it was quite noisy. Thus, it would make sense to test the algorithm on more data, especially noisy ones to check if noise poses a problem for the algorithm.

We provide a proof of principle that reliable automatic detection of MSEs using raw data is feasible and of a high quality. The performance of the CNN with a 16 s window on validation and test data was very similar indicating that there was no substantial overfitting, and the algorithm performs well independent of any disorder or medication. However, we would need more recordings double scored by independent experts, and overall larger datasets to draw a final conclusion. Further, evaluation of the algorithms on data of healthy subjects and subjects recorded in a driving simulator should be performed (Skorucak et al., 2020a).

Performance of our raw data based approach was similar to the feature-based ones (Skorucak et al., 2020b). The feature-based algorithms of Skorucak et al. (2020b) detected only bilateral occurring MSEs, i.e., MSEs occurring in both occipital EEG channels simultaneously and was not trained to detect MSEc and ED. It is easier to detect MSEs occurring bilaterally (i.e., in two channels) than detecting them based in a single channel. Moreover, the feature-based algorithms worked with a 0.2 s resolution, and the subdivision into training and testing data sets were different, i.e., randomization of individuals was different and there was only a test set (no subdivision into validation and test). Thus, a direct comparison of the algorithms must be made with care. The feature based artificial neural network (Skorucak et al., 2020b) detected wake and MSEs with kappa values of 0.65 and 0.75, respectively (recalculated as described in "Performance evaluation"). The same algorithm applied to MWT recordings of healthy subjects after sleep deprivation (Skorucak et al., 2020a) revealed kappa values of 0.61 and 0.65, respectively. Taken together, with our approach (best performing 16-s network) we achieved a similar performance (validation: 0.67 and 0.69; testing: 0.59 and 0.69). In the feature-based approach (Skorucak et al., 2020b), EEG recordings had first to be cleaned of electrocardiography (ECG) artifacts to be able to reliably classify the data as the features were mainly derived from EEG spectra. Human scorers, however, were not distracted by these artifacts. Similarly, our raw data based approached worked well without prior ECG artifact removal. Generally, we expect that raw data based algorithms would be more robust and better transferable to other datasets and might be better suited for on-line processing.

Performance of the CNN algorithms depended on the length of the sliding window. We think that 16 s is an optimal window size because we did not observe further improvement with a 32 s compared to a 16 s window. Even the network with a 2 s long window performed reasonably well. This is an interesting observation because an expert needs to see 10–20 s of the signals to score MSEs. Further, training with a 16-s window and weights inversely proportional to the stage prevalence or with equal weights resulted in the same performance (**Figure 4** and **Table 3**) indicating that the low prevalence of MSEs (**Table 1**) was not an issue; MSEc and ED could not be detected with both weightings.

One EEG and two EOG channels served as input of the classifiers, except for one case. Classification based on a single EEG derivation (16s_1c) worked well, suggesting that the occipital EEG contains substantial information to score MSEs at least for our conservatively defined MSEs as short as 1 s (Hertig-Godeschalk et al., 2020). Nevertheless, a similar network, which used also EOG signals as input, performed better. This was expected since the eye closure is a criterion for expert scoring. Moreover, eye blinks or saccades might be correlated with wakefulness providing additional information for the algorithm.

Borderline segments between clear wakefulness and MSEs that were particularly difficult to score were categorized as MSEc or as ED (Hertig-Godeschalk et al., 2020) in the BERN microsleep scoring criteria. Both, experts and algorithms performed bad in scoring these borderline segments (**Figure 4** and **Table 3**). After visualizing the internal representation of the data in the

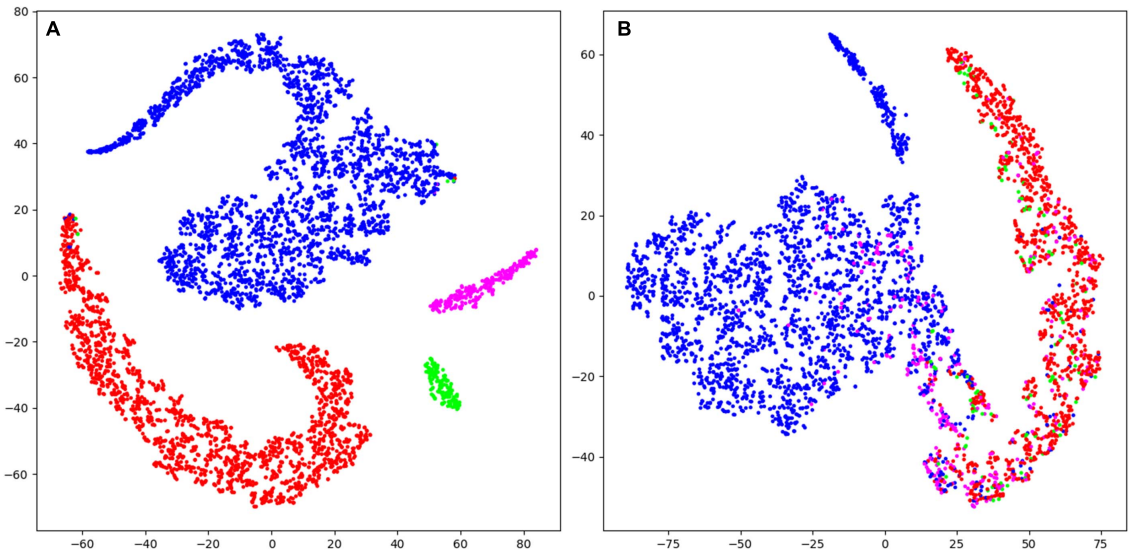

FIGURE 5 | T-distributed stochastic neighbor embedding (t-SNE) was used to illustrate the data and their classification mapped into a 2D space (last layer of the CNN 16s; arbitrary units). **(A)** Mapping of training data (patient Nzhl). All stages form clearly separated clusters except for very few data points as expected for the training data of artificial neural networks. **(B)** Mapping of validation data (patient y5We; same data as in **Figure 3**). Basically, two large clusters corresponding to W and MSE are visible which do not completely separate. MSEc and ED do not form clusters and are not separable from W and MSE. Thus, it illustrates why our algorithms could not score MSEc and ED reliably. Wakefulness (W): blue; microsleep episodes (MSE): red; microsleep episode candidates (MSEc) green; episodes of drowsiness (ED): magenta. For the convenience we illustrated only every hundredth datapoint (sample). Please note that this figure only shows the internal representation of the data in this specific network. Further data are illustrated in supporting information, for training and validation separately (**Supplementary Figures S3**, **S4**).

neural network we came up with a hypothesis why this might be the case (**Figure 5** and **Supplementary Figures S3**, **S4**). Visualization (t-SNE) of the internal representation of the data in one of the networks (CNN 16 s) revealed that generally the 4 classes were not completely separable. In most cases there was a smooth transition between the clusters of wakefulness and of MSEs (**Figure 5B** and **Supplementary Figure S4**). Most MSEc and ED were at the interface between MSE and wake and overlapped with them considerably. This explains why they cannot be reliably identified neither by the algorithm nor by an expert. Thus, in contrast to MSEs, MSEc and ED are currently far from being practically applicable. Please note that this visualization only reflects representation of the data in the particular neural network. For other networks the representation might be different.

In some cases (**Supplementary Figure S3**; patient IhpU), we observed not only a cluster of MSEs, which was connected with the cluster of wakefulness but also a second clearly separable cluster of MSEs. These distinct clusters may not represent MSEs, but sleep episodes longer than 15 s (stage 1), which were marked as MSEs by the expert as the occurrence of consolidated sleep was missed by the technician and the recording continued leading to MSEs lasting longer than 15 s. Note, that we observed such a cluster only in the training dataset. We did not observe this in the validation dataset but observed several clusters of points marked as wakefulness **Supplementary Figure S4**.

Cohen's kappa was somewhat higher for the inter-rater agreement. However, it is important to note that the interrater agreement was assessed on only five recordings, which were not selected completely randomly. The experts randomly selected only recordings, which contained MSEs. Moreover, the experts were trained in the same laboratory and the second expert checked the scoring of the first one for about 2/3 of the recordings.

Our CNNs performed classification for every sample, thus the detected episodes are likely to be fragmented. This issue can be easily solved with median filtering or splitting the results into consecutive intervals and assigning the most frequent class to all samples in the corresponding interval. We used latter approach for the visualization in **Figure 3** using 0.5 s long intervals. Additionally, classification was performed based on a sliding window shifted by one sample.

The use of occipital EEG channels was based on clinical experience since features of the MSEs are often best visible in this brain region (Hertig-Godeschalk et al., 2020). In particular, the alpha rhythm observed during rest with eyes closed is best observed over occipital brain areas. Further, the transition to sleep is accompanied by a slowing of the EEG, i.e., a loss of alpha activity and a shift to theta activity which again is best seen in occipital derivations (Hertig-Godeschalk et al., 2020). Given the local aspects of sleep, future development of algorithms should take other brain regions into account.

As a result of this work, we provide a proof of principle that reliable automatic MSE detection with deep neuronal networks working with raw EEG and EOG data as input is feasible with a quality close to the one of human experts. Deep neural networks

may also be used as a tool to visualize data and thus, foster their interpretation and gain new insights.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: MWT data and the corresponding scoring are available in the Zenodo repository https://zenodo.org/record/3251716 (doi: 10.5281/zenodo.3251716). The code of our algorithms is available at https://github.com/alexander-malafeev/microsleep-detection.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by KEK Bern (KEK-Nr. 308/15). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM developed and programmed the algorithms and conducted the analysis. AM and PA wrote the manuscript. AH-G, DS, and JM brought in longstanding expertise with microsleep episodes in patients, collected the data and performed visual scoring. JS provided her expertise with the data (scripts, demographics, and performance of previous algorithm). PA, JM, and DS organized funding. All authors commented on the manuscript, proposed corrections, and agreed on the final version of the manuscript.

FUNDING

This work was supported by the Swiss National Science Foundation (grant 32003B_176323), nano-tera.ch (grant 20NA21_145929), the Clinical Research Priority Program "Sleep and Health" of the University of Zurich, and the Swiss Commission of Technology and Innovation (CTI; grant 17864.1 PFLS-LS). NVIDIA Corporation provided us a GPU in the framework of academic grants.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.564098/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 28 April 2021
doi: 10.3389/fnins.2021.657126

Longer and Deeper Desaturations Are Associated With the Worsening of Mild Sleep Apnea: The Sleep Heart Health Study

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OPEN ACCESS

Edited by:
Gonzalo C. Gutiérrez-Tobal, Centre for Biomedical Network Research (CIBER), Spain

Reviewed by:
Daniel Álvarez, University of Valladolid, Spain
Frederic Roche, Université Jean Monnet, France

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *22 January 2021*
Accepted: *17 March 2021*
Published: *28 April 2021*

Citation:
Karhu T, Myllymaa S, Nikkonen S, Mazzotti DR, Töyräs J and Leppänen T (2021) Longer and Deeper Desaturations Are Associated With the Worsening of Mild Sleep Apnea: The Sleep Heart Health Study. Front. Neurosci. 15:657126. doi: 10.3389/fnins.2021.657126

Study Objectives: Obesity, older age, and male sex are recognized risk factors for sleep apnea. However, it is unclear whether the severity of hypoxic burden, an essential feature of sleep apnea, is associated with the risk of sleep apnea worsening. Thus, we investigated our hypothesis that the worsening of sleep apnea is expedited in individuals with more severe desaturations.

Methods: The blood oxygen saturation (SpO_2) signals of 805 Sleep Heart Health Study participants with mild sleep apnea [5 $\leq$ oxygen desaturation index (ODI) $<$ 15] were analyzed at baseline and after a mean follow-up time of 5.2 years. Linear regression analysis, adjusted for relevant covariates, was utilized to study the association between baseline SpO_2-derived parameters and change in sleep apnea severity, determined by a change in ODI. SpO_2-derived parameters, consisting of ODI, desaturation severity (DesSev), desaturation duration (DesDur), average desaturation area (avg. DesArea), and average desaturation duration (avg. DesDur), were standardized to enable comparisons between the parameters.

Results: In the group consisting of both men and women, avg. DesDur (β = 1.594, p = 0.001), avg. DesArea (β = 1.316, p = 0.004), DesDur (β = 0.998, p = 0.028), and DesSev (β = 0.928, p = 0.040) were significantly associated with sleep apnea worsening, whereas ODI was not (β = −0.029, p = 0.950). In sex-stratified analysis, avg. DesDur (β = 1.987, p = 0.003), avg. DesArea (β = 1.502, p = 0.024), and DesDur (β = 1.374, p = 0.033) were significantly associated with sleep apnea worsening in men.

Conclusion: Longer and deeper desaturations are more likely to expose a patient to the worsening of sleep apnea. This information could be useful in the planning of follow-up monitoring or lifestyle counseling in the early stage of the disease.

Keywords: sleep apnea, intermittent hypoxemia, hypoxic burden, desaturation, progression, risk factor, oxygen saturation, disease worsening

INTRODUCTION

Sleep apnea is a common nocturnal breathing disorder in which breathing is interrupted numerous times during sleep. These interruptions are usually associated with transient drops in blood oxygen saturation (SpO_2) and/or arousals from sleep. The apnea–hypopnea index (AHI) is the most widely used parameter in sleep apnea diagnostics and is derived from polysomnography (PSG) (Kapur et al., 2017). However, PSG is a labor-intensive and expensive method and experienced technicians are required to set up and monitor patients during in-laboratory PSGs or instruct patients using in-home PSG equipment. Therefore, alternative recording setups containing fewer channels have been developed (Krishnaswamy et al., 2015). The oxygen desaturation index (ODI), determined from the SpO_2 signal, could be alternatively used as a parameter in sleep apnea screening (AASM, 1999). The ODI is a good AHI predictor due to its high correlation (Tsai et al., 1999). Furthermore, the AHI and ODI can be accurately determined from the SpO_2 signal using neural networks (Nikkonen et al., 2019). Therefore, screening of sleep apnea and monitoring of disease progression could be based on a simple and low-cost pulse oximetry measurement.

Male sex, obesity, and older age are known risk factors for sleep apnea (Young et al., 1993; Young et al., 2004). In addition, neck circumference (NC) (Ahbab et al., 2013; Caffo et al., 2010) and the neck circumference/height ratio (NC/H) (Davies et al., 1992; Ho et al., 2016) are independent risk factors for sleep apnea. However, assessing the risk of sleep apnea progression by body mass index (BMI), NC, age, snoring, and/or upper airway structure is challenging. For example, both positive (Redline et al., 2003; Tishler et al., 2003; Lin et al., 2015) and negative (Sforza et al., 1994; Pendlebury et al., 1997; Berger et al., 2009) results on whether the BMI is a factor for sleep apnea worsening have been reported. Similarly, there are conflicting results about whether higher baseline ODI values are associated with an expedited worsening of sleep apnea (Sforza et al., 1994; Lin et al., 2015).

Patients with mild sleep apnea are not systematically treated, especially if symptomless, despite being the most prone to the worsening of the disease (Sforza et al., 1994; Berger et al., 2009). Moreover, even though the severities of individual respiratory events vary within mild sleep apnea patients (Kulkas et al., 2013a,b) and are generally associated more strongly with severe health consequences than the AHI (Muraja-Murro et al., 2013, 2014), the severity of individual events are ignored in current sleep apnea diagnostics. To address these shortcomings, we have introduced novel SpO_2-derived parameters (Kulkas et al., 2013a) to quantify the severity of the hypoxic burden and physiological stress experienced by a patient. An elevated hypoxic burden has been associated with several sleep apnea-related comorbidities (Stone et al., 2016; Azarbarzin et al., 2019, 2020), while the AHI and ODI have not. Therefore, novel parameters considering the severities of individual desaturation events could describe the true severity of sleep apnea better than the AHI and ODI (Otero et al., 2012; Kulkas et al., 2013a). However, it is unknown whether mild sleep apnea patients with deep and long desaturations have an elevated risk of expedited worsening of the disease. We hypothesize that mild sleep apnea patients with severe desaturations at baseline experience an expedited worsening of sleep apnea severity. To investigate this, we evaluated the effect of baseline hypoxemia markers on the progression of mild sleep apnea in 805 Sleep Heart Health Study participants.

MATERIALS AND METHODS

Dataset

The Sleep Heart Health Study (SHHS) is a multicenter cohort study implemented by the National Heart, Lung, and Blood Institute to determine the consequences of sleep-disordered breathing, such as cardiovascular diseases (CVD). The SHHS dataset is available through the National Sleep Research Resource (Quan et al., 1997; Zhang et al., 2018; The National Sleep Research Resource, 2021). Participants were recruited from nine existing parent cohort studies and provided informed consent for data collection. Successful baseline PSG examination was performed for 6,441 participants between 1995 and 1998, who met the following inclusion criteria: (1) age $\geq$40 years; (2) no history of sleep apnea treatment; (3) no tracheostomy; and (4) no current home oxygen therapy. The follow-up PSG was performed between 2001 and 2003 for 3,295 participants who were not treated for sleep apnea with positive continuous airway pressure, oral device, or oxygen therapy 3 months prior to the follow-up PSG. Due to the sovereignty issues with one of the parent studies (Strong Heart Study), data from approximately 600 participants are not available. Moreover, due to data corruption over time, data have been lost from a few participants. Therefore, 5,793 baseline and 2,651 follow-up PSGs are available; out of these, 2,647 participants have both recordings available. More details on the SHHS dataset are available elsewhere (Quan et al., 1997; Redline et al., 1998; Dean et al., 2016).

Polysomnography and Covariates

In-home PSGs were performed with Compumedics P-series portable monitors (Abbotsford, Australia) (Quan et al., 1997; Redline et al., 1998). The finger pulse oximeters (Nonin XPOD model 3011, Minneapolis, MN, United States) were used to record SpO_2 with a 1-Hz sampling frequency. Mercury gauge sensors were used to record the body position during sleep. Total sleep time was determined based on 30-s epochs in which the sleep stage was scored as non-rapid eye movement sleep (N1, N2, or N3) or rapid eye movement sleep (REM).

Each PSG recording was supplemented with a sleep habits questionnaire, medical history, medication usage, blood pressure, and anthropometric measurements. NC was measured just below the laryngeal prominence. The existence of hypertension was defined if the systolic blood pressure was $\geq$140 mmHg, diastolic blood pressure was $\geq$90 mmHg, or medication for hypertension was in use. At the medical history interview, history of CVD, consisting of myocardial infarction, heart failure, stroke, coronary angioplasty, and coronary artery bypass graft, was inquired. In addition, the existence of diabetes was defined based on self-reported diabetes status and usage of insulin or oral hypoglycemic agents.

Oxygen Desaturation Parameters

Oxygen saturation signals were reanalyzed due to known issues of data corruption and loss of scored event data in the SHHS (The National Sleep Research Resource, 2021). To improve data consistency, desaturations were automatically re-scored using Noxturnal software (version 5.1.19824, Nox Medical, Reykjavík, Iceland). The scoring criteria for desaturations were: (1) minimum of 3% drop in the SpO_2 signal; (2) minimum event duration of 3 s; (3) maximum plateau duration of 45 s; and (4) values lower than 50% were considered as artifacts (no desaturations were scored in these parts of the signal). The maximum plateau duration denotes the maximum period within the desaturation event during which the SpO_2 signal values do not change. If this period is exceeded, the end point of the desaturation is determined to be the starting point of the plateau. It was observed that the software started automatic event scorings systematically one data point too early, and thus, this was corrected in the parameter calculations. To validate the accuracy of the automatic scorings, 30 SpO_2 signals were randomly selected from the available SHHS dataset of 8,444 recordings and scored manually. Correlations and Bland–Altman plot agreements between manual and automatic scorings of the desaturation events were calculated. In addition to the ODI, novel SpO_2 signal-based parameters consisting of desaturation severity (DesSev), desaturation duration (DesDur), average desaturation duration (avg. DesDur), and average desaturation area (avg. DesArea) were calculated (**Table 1**; see Kulkas et al., 2013a). These parameters describe the hypoxic burden by taking into account the duration and depth of the desaturation events.

Sleep Apnea Severity Classification

The severity of sleep apnea was determined based on the ODI 4% criterion for several reasons. First, only desaturation events fulfilling the minimum transient drop of 4% were included in the analysis as the 4% criterion was considered more reliable than the 3% criterion, as the desaturations were scored automatically and separately from respiratory events. Second, the ODI is known to be a good predictor of AHI (Tsai et al., 1999; Chung et al., 2012; Fabius et al., 2019). Third, originally apneas and hypopneas were scored based on the thermistor, respiratory belts, or some combination of them (The National Sleep Research Resource, 2021). Therefore, scored respiratory events are not in line with the current standards. In addition, the hypoxic burden is an important feature of sleep apnea pathophysiology (Dempsey et al., 2010), and thus, the usage of ODI in the assessment of sleep apnea severity can be justified. In the present study, the term "progression" refers to a change in ODI (either an increase or a decrease) between the two PSG recordings, whereas "worsening" refers to an increase in ODI.

Out of the 2,647 participants with both PSG recordings, 832 had mild sleep apnea ($5 \leq \text{ODI} < 15$) at baseline, from which 27 were excluded due to the missing covariate data. Therefore, 805 (441 men and 364 women) participants were included for further analyses (**Table 2**). The results utilizing the ODI 3% criterion are presented in **Supplementary Tables 1–5** and **Supplementary Figure 1**.

TABLE 1 | Descriptions and formulas of desaturation parameters.

Parameter	Description	Formula
ODI (1/h)	Average number of desaturation events per hour of sleep	$\frac{n_{\text{desat events}}}{\text{TST}}$
DesDur_i (s)	Desaturation duration of a single desaturation event	$t_2 - t_1$
DesArea_i (s%)	Desaturation area of a single desaturation event	$\int_{t_1}^{t_2} \text{SpO}_2\,(t)\ dt$
DesSev (%)	Total desaturation area normalized with total sleep time	$\frac{\sum_i \text{DesArea}_i}{\text{TST}}$
DesDur (%)	Total desaturation duration normalized with total sleep time	$\frac{\sum_i \text{DesDur}_i}{\text{TST}} \times 100\%$
Avg. DesArea (s%)	Average area of individual desaturation events	$\frac{\sum_i \text{DesArea}_i}{n_{\text{desat events}}}$
Avg. DesDur (s)	Average duration of individual desaturation events	$\frac{\sum_i \text{DesDur}_i}{n_{\text{desat events}}}$

$n_{\text{desat events}}$ is the number of desaturation events and TST is the total sleep time. t_1 and t_2 denote the start and end time points of a single desaturation event, respectively, in the SpO_2 signal. ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events.

Statistical Analysis

The statistical significance of the differences in the demographic and desaturation parameters between the baseline and follow-up were evaluated within men and women using the Wilcoxon signed-rank test, and between men and women with the Mann–Whitney *U* test and Chi-squared test for continuous and categorical variables, respectively. Linear regression was used to investigate the association between the baseline desaturation parameters and the progression of mild sleep apnea with and without covariate adjustment. Change in the ODI between the PSG recordings was used as a continuous dependent variable. Baseline BMI, change in BMI during the follow-up, age, NC/H, the existence of hypertension, diabetes, and CVD, percentage of time slept in the supine position, percentage of time slept in REM, change in the time slept in REM between the PSGs, and follow-up time were used as covariates in the adjusted models. Desaturation parameters at baseline were standardized to enable comparisons between parameters. Thus, regression coefficients (β values) correspond to the expedited increase in ODI between the PSG recordings that were associated with a one standard deviation (SD) change in the desaturation parameter values at baseline. In addition, we investigated whether the desaturation parameter values at baseline differed between the participants whose sleep apnea severity remained in the healthy-to-mild state (i.e., $\text{ODI} < 15$) and the participants whose disease worsened to moderate ($15 \leq \text{ODI} < 30$) or severe ($\text{ODI} \geq 30$) sleep apnea during the follow-up. Finally, to address the possibility of selection bias, we investigated whether there were differences in the baseline parameter values between the participants with mild sleep apnea who underwent only baseline PSG and those with both PSGs. Analyses were conducted in MATLAB® (version 2018b, MathWorks, Natick, MA, United States). To address the multiple comparisons,

due to five investigated desaturation parameters, a Bonferroni-corrected p-value threshold of <0.01 was used to indicate statistical significance, whereas p-values < 0.05 were considered as nominal evidence.

RESULTS

During the follow-up, the ODI, DesSev, and DesDur values increased for both sexes ($p < 0.001$), whereas avg. DesArea decreased ($p < 0.001$ for men, $p = 0.004$ for women) (**Table 2**). The increase in ODI ($p = 0.002$), DesSev ($p = 0.002$), and DesDur ($p < 0.001$) was greater in men than in women.

Linear regression analyses revealed that the baseline ODI was not associated with the worsening of mild sleep apnea either in the unadjusted or in the adjusted model (**Table 3**). However, in men and in the group consisting of both sexes, all novel desaturation parameters were significantly ($p < 0.05$) associated with sleep apnea worsening in the unadjusted models. In the covariate-adjusted models for the group consisting of both sexes, avg. DesArea ($p = 0.001$) and avg. DesDur ($p = 0.004$) were significantly associated with sleep apnea worsening by fulfilling the Bonferroni-corrected threshold, while DesSev ($p = 0.040$) and DesDur ($p = 0.028$) reached the limit of nominal significance. Moreover, in men, avg. DesDur was associated with sleep apnea worsening at the Bonferroni-corrected threshold ($p = 0.003$), while avg. DesArea ($p = 0.024$) and DesDur ($p = 0.033$) reached nominal association. Overall, in men and in the group consisting of both sexes, a one SD unit increase in avg. DesDur resulted in the greatest expedited increase in ODI during the follow-up (i.e., largest β values), followed by avg. DesArea.

Men and women whose mild sleep apnea worsened to moderate sleep apnea during the follow-up had significantly higher ODI ($p < 0.001$ for men, $p = 0.008$ for women), DesSev ($p < 0.001$ for men, $p < 0.001$ for women), and DesDur ($p < 0.001$ for men, $p < 0.001$ for women) at baseline compared to the participants who remained in the healthy-to-mild state (**Table 4**). Similar findings were observed in men ($p < 0.001$ for ODI, DesSev, and DesDur) and women ($p < 0.001$ for ODI, $p = 0.001$ for DesSev, and $p = 0.001$ for DesDur) whose mild sleep apnea worsened to severe sleep apnea during the follow-up. In addition, avg. DesArea ($p < 0.001$) and avg. DesDur ($p = 0.021$) were significantly higher at baseline in women whose disease worsened to moderate sleep apnea. The only statistically significant difference between the participants who worsened to moderate sleep apnea and those who worsened to severe sleep apnea was observed in ODI ($p = 0.039$) in the group consisting of both sexes.

No statistically significant differences in the baseline desaturation parameters were observed between the participants with mild sleep apnea who underwent only baseline PSG and those who underwent both PSGs (**Table 5**).

The automatic scoring of the desaturation events was very well in line with the manual scoring. For all five desaturation

TABLE 2 | Demographic, anthropometric, and desaturation parameter values for men and women participants with mild sleep apnea at baseline and after a mean follow-up time of 5.2 years.

Parameter	Men			Women		
	Baseline	Follow-up	Change during the follow-up	Baseline	Follow-up	Change during the follow-up
Number of patients, *n*		441			364	
Follow-up time (years)		5.2 (0.3)			5.2 (0.2)	
Age (years)	64.1 (9.7)	69.4 (9.5)[a]	5.2 (0.6)	65.0 (10.3)	70.1 (10.2)[a]	5.1 (0.6)[b]
BMI (kg/m^2)	28.9 (3.7)	29.0 (4.0)	0.1 (1.7)	29.7 (5.7)	29.5 (5.9)	−0.2 (2.4)
TST (h)	6.0 (1.0)	6.0 (1.2)	0.0 (1.2)	6.1 (1.1)	6.2 (1.2)	0.1 (1.3)
Supine time (%)	23.3 (0.0–52.9)	25.0 (8.0–55.0)	1.9 (38.8)	32.7 (1.1–63.6)[b]	36.0 (12.3–60.8)	2.6 (44.0)
NC (cm)	40.9 (3.0)	40.7 (2.9)	−0.2 (2.3)	35.8 (2.9)[b]	35.7 (3.1)	−0.1 (2.2)
NC/H (%)	23.5 (1.8)	23.6 (1.8)	0.1 (1.4)	22.3 (1.9)[b]	22.5 (2.0)[a]	0.2 (1.4)
REM (%)	19.6 (5.9)	19.6 (6.6)	0.0 (7.8)	19.7 (6.9)	20.1 (6.7)	0.4 (8.4)
Hypertension, *n* (%)	219 (49.7)	252 (57.1)		203 (55.8)	216 (59.3)	
Diabetes, *n* (%)	42 (9.5)	n.a.		29 (8.0)	n.a.	
CVD, *n* (%)	74 (16.8)	107 (24.3)		25 (6.9)[b]	43 (11.8)	
ODI (1/h)	8.7 (6.8–11.5)	16.4 (10.3–25.1)[a]	10.6 (14.5)	8.0 (6.3–10.7)[b]	13.0 (7.9–20.4)[a]	7.4 (11.3)[b]
DesSev (%)	0.27 (0.11)	0.58 (0.55)[a]	0.31 (0.52)	0.24 (0.11)[b]	0.44 (0.34)[a]	0.19 (0.31)[b]
DesDur (%)	8.3 (2.9)	17.1 (12.3)[a]	8.8 (11.6)	7.4 (2.8)[b]	13.4 (9.1)[a]	6.0 (8.6)[b]
Avg. DesArea (s%)	107.2 (29.6)	103.2 (30.0)[a]	−3.9 (32.0)	100.9 (29.9)[b]	96.7 (28.2)[a]	−4.1 (27.2)
Avg. DesDur (s)	31.8 (6.8)	31.5 (6.8)	−0.3 (7.4)	29.9 (6.9)[b]	30.0 (6.6)	0.1 (7.1)

Data are presented as means and standard deviations for normally distributed variables, as medians and interquartile ranges for non-normally distributed variables, and as n and percentages for categorical variables. BMI, body mass index; TST, total sleep time; NC, neck circumference; NC/H, neck circumference/height ratio; REM, rapid eye movement sleep; CVD, cardiovascular disease (consisting of heart failure, stroke, myocardial infarction, coronary artery bypass graft, and coronary angioplasty); ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events; n.a., not available. [a]Statistical significance ($p < 0.05$) between baseline and follow-up measurements was determined with Wilcoxon signed-rank test. [b]Mann–Whitney U and Chi-squared tests were used to compare the baseline parameter values for continuous and categorical variables, respectively, and changes in the parameter values during the follow-up between the sexes.

parameters, the correlations between the manual and automatic scorings were excellent ($\rho \geq 0.94$), the median differences in the parameter values were minimal (**Table 6**), and agreements in the parameter values were strong (**Figure 1**).

DISCUSSION

In this study, we investigated whether the desaturation parameters at baseline were associated with the worsening of mild sleep apnea. We provide novel evidence showing that especially avg. DesDur and avg. DesAreas are associated with the expedited worsening of sleep apnea. Notably, the baseline ODI values did not appear to be associated with the worsening of mild sleep apnea. These findings suggest that a detailed analysis of the oxygen desaturation signal that considers the morphology of the desaturation events is relevant in the risk assessment of sleep apnea progression. More importantly, this study focused on patients with mild sleep apnea as these patients are not systematically treated especially when symptomless. Therefore, our results implicate that mild sleep apnea patients with deeper and longer desaturation events might benefit from regular follow-up monitoring.

Previously, Lin et al. (2015) demonstrated that baseline ODI is a significant predictor of the worsening of sleep apnea, which is partially contradictory to our findings. On one hand, it represents the same biological concept where increased nocturnal hypoxemia is a predictor of disease worsening. However, based

TABLE 3 | Linear regression analyses for the estimation of mild sleep apnea progression based on the desaturation parameter values at the baseline.

	Unadjusted			Adjusted[a]		
	β	SD error	*p*-value	β	SD error	*p*-value
ODI (1/h)						
Men	0.705	0.691	0.308	0.021	0.646	0.974
Women	−0.079	0.593	0.894	−0.246	0.614	0.688
Both	0.519	0.466	0.266	−0.029	0.458	0.950
DesSev (%)						
Men	1.652	0.687	0.017	1.169	0.644	0.070
Women	0.616	0.592	0.299	0.447	0.595	0.453
Both	1.378	0.464	0.003	0.928	0.450	0.040
DesDur (%)						
Men	1.948	0.685	0.005	1.374	0.644	0.033
Women	0.473	0.592	0.425	0.278	0.599	0.643
Both	1.518	0.463	0.001	0.998	0.453	0.028
Avg. DesArea (s%)						
Men	1.506	0.688	0.029	1.502	0.661	0.024
Women	0.988	0.590	0.095	0.951	0.593	0.110
Both	1.428	0.464	0.002	1.316	0.454	0.004
Avg. DesDur (s)						
Men	1.914	0.685	0.005	1.987	0.661	0.003
Women	0.986	0.590	0.096	0.888	0.603	0.142
Both	1.696	0.463	<0.001	1.594	0.458	0.001

β values correspond to the expedited increase in ODI between the PSG recordings that is associated with a one standard deviation change in the desaturation parameter values at the baseline. Standard deviations for men, women, and the group consisting of both sexes were respectively: for ODI = 2.8, 2.7, and 2.7; for DesSev = 0.11, 0.11, and 0.12; for DesDur = 2.9, 2.8, and 2.9; for avg. DesArea = 29.6, 29.9, and 29.9; and for avg. DesDur = 6.8, 6.9, and 6.9. ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events. [a]Adjusted for age, body mass index, change in body mass index during the follow-up, neck circumference/height ratio, the existence of hypertension, diabetes, and cardiovascular diseases (consisting of heart failure, stroke, myocardial infarction, coronary artery bypass graft, and coronary angioplasty), percentage of time slept in the supine position, percentage of time slept in rapid eye movement sleep, change in rapid eye movement sleep between the polysomnography recordings, and follow-up time.

TABLE 4 | Desaturation parameter values at baseline in participants whose sleep apnea severity remained in the healthy-to-mild state (ODI < 15) and in those whose disease worsened to moderate (15 ≤ ODI < 30) or severe (ODI ≥ 30) sleep apnea during the follow-up.

	ODI < 15	15 ≤ ODI < 30	ODI ≥ 30
ODI (1/h)			
Men	7.9 (6.3–10.3)	9.7 (7.1–12.0)[a]	9.9 (7.5–12.2)[a]
Women	7.5 (6.1–9.8)	8.5 (6.4–10.9)[a]	9.8 (7.6–12.0)[a]
Both	7.8 (6.2–10.0)	9.2 (6.8–11.7)[a]	9.9 (7.5–12.2)[ab]
DesSev (%)			
Men	0.24 (0.11)	0.29 (0.11)[a]	0.31 (0.13)[a]
Women	0.22 (0.10)	0.27 (0.12)[a]	0.29 (0.13)[a]
Both	0.23 (0.10)	0.28 (0.11)[a]	0.30 (0.13)[a]
DesDur (%)			
Men	7.5 (2.7)	8.8 (2.8)[a]	9.3 (3.1)[a]
Women	6.8 (2.7)	8.0 (2.8)[a]	8.6 (3.0)[a]
Both	7.2 (2.7)	8.4 (2.8)[a]	9.0 (3.1)[a]
Avg. DesArea (s%)			
Men	104.0 (28.1)	110.7 (31.7)	108.2 (28.2)
Women	96.5 (28.7)	108.4 (31.5)[a]	101.5 (26.9)
Both	100.2 (28.6)	109.7 (31.6)[a]	106.1 (27.9)[a]
Avg. DesDur (s)			
Men	31.3 (6.9)	32.4 (6.9)	32.2 (6.5)
Women	29.1 (6.8)	31.3 (7.4)[a]	29.9 (5.0)
Both	30.2 (6.9)	31.9 (7.1)[a]	31.5 (6.1)

Data are presented as means and standard deviations for normally distributed variables and as medians and interquartile ranges for non-normally distributed variables. Mann–Whitney U test was used to determine the statistical significance ($p < 0.05$) between the participants who remained in the healthy-to-mild state ($n_{Men} = 206$, $n_{Women} = 209$) and those who worsened to moderate ($n_{Men} = 158$, $n_{Women} = 119$) or severe ($n_{Men} = 77$, $n_{Women} = 36$) sleep apnea ([a]) and between participants who worsened to moderate sleep apnea and those who worsened to severe sleep apnea ([b]). ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events.

TABLE 5 | Comparison between participants with mild sleep apnea at baseline who participated only to the baseline PSG and those who participated also to the follow-up PSG.

	Participants with only baseline PSG	Participants with both PSGs	*p*-value
n (men, women)	871 (458, 413)	805 (441, 364)	
Age (years)	67.0 (10.7)	64.5 (10.0)	<0.001
BMI (kg/m^2)	29.0 (5.0)	29.2 (4.7)	0.083
Supine time (%)	22.9 (0.0–58.9)	26.6 (0.1–57.2)	0.421
NC (cm)	38.7 (3.9)	38.6 (3.9)	0.604
NC/H (%)	23.1 (1.9)	22.9 (1.9)	0.177
REM (%)	18.6 (7.1)	19.7 (6.4)	0.015
Hypertension, *n* (%)	557 (63.9)	422 (52.4)	<0.001
Diabetes, *n* (%)	91 (10.4)	71 (8.8)	0.260
CVD, *n* (%)	159 (18.3)	99 (12.3)	0.001
ODI (1/h)	8.6 (6.6–11.0)	8.4 (6.5–11.0)	0.636
DesSev (%)	0.26 (0.12)	0.26 (0.12)	0.739
DesDur (%)	7.9 (3.0)	7.9 (2.9)	0.859
Avg. DesArea (s%)	104.3 (32.7)	104.3 (29.9)	0.765
Avg. DesDur (s)	30.8 (7.2)	31.0 (6.9)	0.406

Values are presented as means and standard deviations for normally distributed parameters, as medians and interquartile ranges for non-normally distributed parameters, and as n and percentages for categorical variables. Statistical comparison of the observed differences between the populations was investigated with Mann–Whitney U test for continuous variables and with Chi-squared test for categorical variables. BMI, body mass index; NC, neck circumference; NC/H, neck circumference/height ratio; REM, rapid eye movement sleep; CVD, cardiovascular diseases (consisting of myocardial infarction, heart failure, stroke, coronary angioplasty, and coronary artery bypass graft); ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events.

TABLE 6 | Automatically and manually scored oxygen saturation signal-derived parameters were highly similar and strongly correlated.

Parameter	Automatic scorings	Manual scorings	Difference	Spearman's correlation
ODI (1/h)	3.6 (2.0–11.1)	3.7 (2.0–11.1)	0.0 (0.0–0.2)	1.00
DesSev (%)	0.09 (0.05–0.32)	0.08 (0.06–0.32)	0.00 (−0.01–0.00)	0.98
DesDur (%)	3.1 (1.6–10.1)	2.9 (1.2–9.8)	0.0 (0.0–0.3)	0.98
avg. DesArea (s%)	90.6 (76.3–118.6)	94.2 (73.1–121.1)	−1.8 (−5.3–1.1)	0.95
avg. DesDur (s)	28.7 (24.2–34.8)	28.5 (22.8–35.3)	−0.4 (−1.2–0.4)	0.94

For this analysis, 30 oxygen saturation signals were randomly selected from the Sleep Heart Health Study dataset of 8,444 available recordings. Values are presented as medians (interquartile range). Statistical significance ($p < 0.05$) of the observed difference between the scorings was investigated with Wilcoxon signed-rank test (no statistically significant differences were observed). ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events.

on the present results, the ODI alone might not be a robust marker for assessing the progression of mild sleep apnea; a more detailed morphological assessment of individual desaturation events could provide more accurate estimates. Furthermore, the opposing findings could be partly explained by differences in the study populations and the lengths of the follow-up periods. Our study population size is significantly larger than that in the study by Lin et al. (n = 805 vs. n = 50), and we had a longer follow-up period (5.2 vs. 3 years). In addition, their study population consisted of patients who were suffering from more severe sleep apnea at baseline (ODI mean ± SD = 20.8 ± 13.4), whereas we focused only on patients with mild sleep apnea. Nevertheless, the present results are consistent with other previously reported findings (Sforza et al., 1994) with a similar follow-up period (5.7 years), but with a small population (n = 32) of patients with more severe sleep apnea (mean AHI = 52.2 at baseline).

Moreover, it has been shown that AHI does not change over time (mean follow-up period of 5.1 years) in severe sleep apnea patients, and the ones whose AHI increased have initially mild or moderate disease (Berger et al., 2009). It was suggested (Berger et al., 2009) that this is due to the ceiling effect of sleep apnea. Another explaining factor could be the "regression toward the mean" phenomenon, where initially extreme AHI values get closer to the mean at the follow-up measurement, and *vice versa*. Therefore, it seems that it is highly dependent on the severity of sleep apnea whether baseline ODI or AHI values can be used in the risk assessment of sleep apnea progression; thus, the generalization of our findings should be done with caution.

We observed that mild sleep apnea patients with longer and deeper desaturations experience an expedited worsening of the disease. However, in the sex-stratified analyses, significant findings were observed in men when the ODI 4% criterion was used, whereas the associations were stronger in women with the ODI 3% criterion (**Supplementary Material**). In addition, we noted that men had more severe desaturations than women, which is supported by previous studies (Ware et al., 2000; Schwartz et al., 2008; Peppard et al., 2009). Therefore, it could be speculated that the 4% criterion might be too strict to assess the progression of sleep apnea severity in women. Furthermore, the ODI values increased, while the avg. DesArea decreased for both sexes during the follow-up. Thus, our findings suggest that individuals whose desaturation events are more severe at baseline develop more of these less severe events. Azarbarzin et al. have also shown that the severity of hypoxic burden predicts cardiovascular mortality (Azarbarzin et al., 2019) and incident heart failure (Azarbarzin et al., 2020). Therefore, the nocturnal hypoxic burden seems to play a potential prognostic role in the worsening of sleep apnea and the development of related comorbidities.

The present study has limitations. First, the desaturations were autoscored using a commercial software without further manual adjustment by specialists. However, the correlations and agreements between the subset of manual and automatic scorings were excellent and the median differences minimal (**Table 6** and **Figure 1**). Therefore, we were convinced that the used automatic desaturation scoring methods can be assumed to be valid. New scoring was required since part of the manually scored desaturation events had been lost due to the SHHS data corruption over time (The National Sleep Research Resource, 2021). Moreover, there are no current standardized criteria

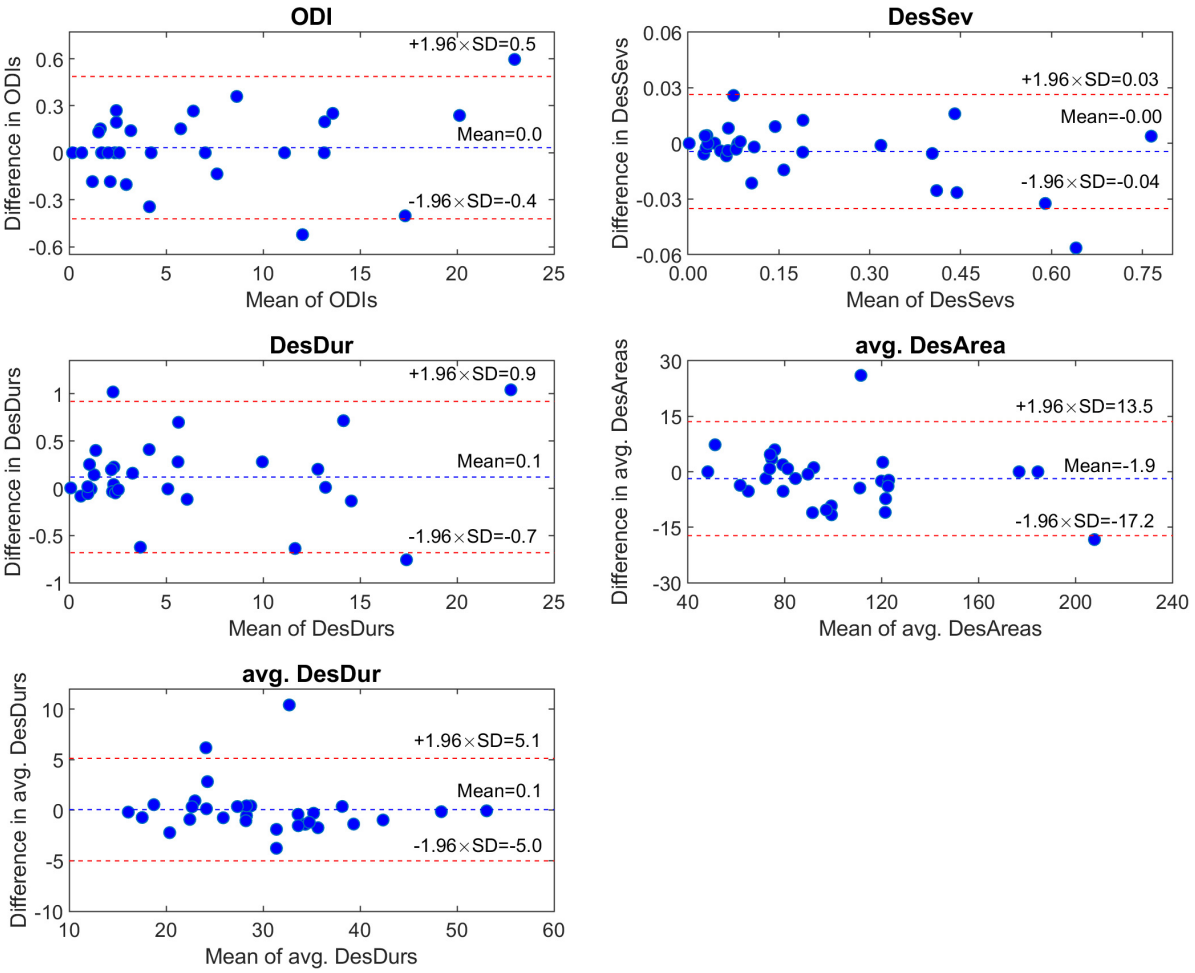

FIGURE 1 | Comparison of automatically and manually scored desaturation parameter values of 30 randomly selected oxygen saturation signals using Bland-Altman plots. ODI, oxygen desaturation index; DesSev, desaturation severity parameter; DesDur, desaturation duration parameter; avg. DesArea, average area of individual desaturation events; avg. DesDur, average duration of individual desaturation events.

for scoring desaturation events, in addition to a minimum transient drop of 3 or 4% in the SpO_2 signal. For example, the minimum or the maximum durations of the desaturation events are not specified in the rules of the American Academy of Sleep Medicine (AASM), unlike in the case of hypopneas and apneas (Berry et al., 2017). Furthermore, no instructions for the maximum duration of the plateau in the middle of the event exist. In this study, a minimum event duration was set to 3 s and a maximum plateau duration set to 45 s based on visual inspection in which this criterion was observed to be appropriate. However, no fine-tuning to obtain an optimized desaturation scoring criterion was performed. With a shorter plateau length, some of the events might not have filled the minimum rule of transient drop in the SpO_2 signal, or one longer event might have been split into multiple shorter events. In contrast, with longer plateau criteria, short events could fuse into a longer one. All these aspects affect the number (ODI) and severity (novel parameters) of the events and, therefore, the determined parameter values. Furthermore, we decided to use the 4% criterion for our primary analysis as, without associating desaturation events to the respiratory events, the 3% criterion was assumed to be too sensitive.

Apnea–hypopnea index was not used for the severity categorization in this study because the scoring criteria have changed since the apneas and hypopneas were originally scored in the late 1990s and early 2000s. The biggest difference is in the channels used for hypopnea scoring. At the time the recordings were conducted, hypopneas could have been scored based on signals from the thermistor, respiratory belts around the thorax or abdominal region, or some combination of them (The National Sleep Research Resource, 2021). The current AASM recommendation for apnea scoring is an oronasal thermal airflow sensor, while a nasal pressure transducer is recommended for hypopnea scoring (Berry et al., 2017). Moreover, in addition to the desaturation events, the Noxturnal software is capable of scoring apneas and hypopneas automatically. However, the accuracy of the detection of hypopnea and apnea events without manual adjustment was found to be insufficient, and manual

re-scoring of the massive SHHS dataset was not feasible. Furthermore, the oximetry used in the SHHS data acquisition differs from the current clinical recommendations. For example, the oximetry used in the SHHS utilized a sampling frequency of 1 Hz, while the current minimum recommendation for routine clinical recordings is 10 Hz (Berry et al., 2017). However, the use of a sampling frequency of 1 Hz can be considered sufficient as it has been shown not to affect the accuracy to detect sleep apnea (Nigro et al., 2011).

Using the ODI to characterize the severity of OSA has certain limitations. As the SpO_2 is not a direct measure of breathing, the ODI cannot be used as a direct measure of the frequency of respiratory events. In addition, the ODI cannot distinguish between obstructive and central respiratory events. Furthermore, no standardized criteria exist to score desaturations, as discussed above. The ODI can also potentially underestimate the AHI, as hypopneas can be scored with an association to desaturation or arousal (Berry et al., 2017). In addition, apneas can be scored without desaturation or arousal, or multiple respiratory events can be associated with a single desaturation. However, using the ODI for the severity categorization is adequate as it has been shown that only 6.3% of apneas are not associated with desaturations and 4.7% of desaturations are not associated with respiratory events (Fabius et al., 2019). Thus, misclassification due to unmatched events can be assumed to be minor.

Another limitation is the potential influence of night-to-night variability in the assessment of sleep apnea severity. It has been shown that there is significant intra-patient variability in the AHI between two consecutive nights (Roeder et al., 2020). However, no such night-to-night variability was observed at the group level (Roeder et al., 2020). Therefore, it is likely that such variations are averaged out in our relatively large study population. Finally, the study population was relatively old and could be enriched with participants with CVD, due to the study design of the SHHS, thus potentially causing selection bias.

Our present findings give a new perspective on the risk assessment of whether mild sleep apnea will worsen over time. The consideration of individual desaturation event severities could be an additional tool in the planning of regular follow-up monitoring, initiation of treatment, or lifestyle counseling. With these preventive actions, sleep apnea worsening could be slowed or prevented earlier. Adequate management of mild sleep apnea patients with severe desaturation events could further lower the risks of sleep apnea-related comorbidities and generally improve the quality of life. However, regular monitoring of all mild sleep apnea patients would be complicated and expensive with the current diagnostic methods (i.e., polysomnography). In addition, treating a large number of mild sleep apnea patients would be costly while not providing significant benefits for many of the patients, thus being a waste of resources. Therefore, using novel SpO_2-derived parameters in the risk assessment of sleep apnea worsening and planning of the follow-up monitoring and interventions could be a practical approach. This would allow cost-efficient regular monitoring of sleep apnea using a simple pulse oximeter often included, e.g., in many consumer-grade wearable devices. This could also enable reducing the effect of night-to-night variability on sleep apnea severity estimation (Stöberl et al., 2017; Roeder et al., 2020), allowing more reliable diagnosis and prognosis.

CONCLUSION

The present results indicate that, in the risk assessment of mild sleep apnea worsening, the severity of the desaturation events is more useful than the exact number of the events. Based on the present findings, sleep apnea can be understood as a progressive disease, and many of the mild patients develop more severe disease in 5 years.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: National Sleep Research Resource: https://sleepdata.org/datasets/shhs/. Access to the full Sleep Heart Health Study data was granted by the National Sleep Research Resource as a part of Mazzotti's proposal (agreement #2731).

ETHICS STATEMENT

Each patient/participant provided written informed consent and the study protocol was reviewed and approved by the institutional review boards of each participating site of the Sleep Heart Health Study (SHHS). Participating institutions in the Sleep Heart Health Study are (https://sleepdata.org/datasets/shhs/pages/full-description.md): Boston University, Case Western Reserve University, Johns Hopkins University, Missouri Breaks Research, Inc. New York University Medical Center, University of Arizona, University of California at Davis, University of Minnesota – Clinical and, Translational Science Institute, University of Washington.

AUTHOR CONTRIBUTIONS

TK contributed to the study design, data analysis, and interpretation, and wrote the manuscript. SM contributed to the study design and writing of the manuscript. SN contributed to the writing of the manuscript and data analysis. DM contributed to data interpretation and writing of the manuscript. JT and TL contributed to the study design, data interpretation, and writing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by the Academy of Finland (decision numbers 313697 and 323536), the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (projects 5041767, 5041768, 5041770, 5041781, 5041787, 5041794, and 5041797), Business Finland

(decision number 5133/31/2018), The Research Foundation of the Pulmonary Diseases, Tampere Tuberculosis Foundation, Orion Research Foundation, Instrumentarium Science Foundation, Finnish Anti-Tuberculosis Association, Päivikki, and Sakari Sohlberg Foundation, and The Finnish Cultural Foundation—North Regional Fund. This manuscript was supported by the American Academy of Sleep Medicine Foundation (194-SR-18) and the NHLBI (P01HL094307).

ACKNOWLEDGMENTS

The Sleep Heart Health Study (SHHS) was supported by the National Heart, Lung, and Blood Institute cooperative agreements U01HL53916 (University of California, Davis), U01HL53931 (New York University), U01HL53934 (University of Minnesota), U01HL53937 and U01HL64360 (Johns Hopkins University), U01HL53938 (University of Arizona), U01HL53940 (University of Washington), U01HL53941 (Boston University), and U01HL63463 (Case Western Reserve University). The National Sleep Research Resource was supported by the National Heart, Lung, and Blood Institute (R24 HL114473 and RFP 75N92019R002).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.657126/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 07 June 2021
doi: 10.3389/fnins.2021.660365

Classifying Vulnerability to Sleep Deprivation Using Resting-State Functional MRI Graph Theory Metrics

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Sleep deprivation (SD) has become very common in contemporary society, where people work around the clock. SD-induced cognitive deficits show large inter-individual differences and are trait-like with known neural correlates. However, few studies have used neuroimaging to predict vulnerability to SD. Here, resting state functional magnetic resonance imaging (fMRI) data and psychomotor vigilance task (PVT) data were collected from 60 healthy subjects after resting wakefulness and after one night of SD. The number of PVT lapses was then used to classify participants on the basis of whether they were vulnerable or resilient to SD. We explored the viability of graph-theory-based degree centrality to accurately classify vulnerability to SD. Compared with during resting wakefulness, widespread changes in degree centrality (DC) were found after SD, indicating significant reorganization of sleep homeostasis with respect to activity in resting state brain network architecture. Support vector machine (SVM) analysis using leave-one-out cross-validation achieved a correct classification rate of 84.75% [sensitivity 82.76%, specificity 86.67%, and area under the receiver operating characteristic curve (AUC) 0.94] for differentiating vulnerable subjects from resilient subjects. Brain areas that contributed most to the classification model were mainly located within the sensorimotor network, default mode network, and thalamus. Furthermore, we found a significantly negative correlation between changes in PVT lapses and DC in the thalamus after SD. These findings suggest that resting-state network measures combined with a machine learning algorithm could have broad potential applications in screening vulnerability to SD.

Keywords: sleep deprivation, vulnerability, functional magnetic resonance imaging, machine learning, psychomotor vigilance task

OPEN ACCESS

Edited by:
Leila Kheirandish-Gozal, University of Chicago, United States

Reviewed by:
Kai Yuan, Xidian University, China
Yi Zhang, Xidian University, China

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *29 January 2021*
Accepted: *12 May 2021*
Published: *07 June 2021*

Citation:
Xu Y, Yu P, Zheng J, Wang C, Hu T, Yang Q, Xu Z, Guo F, Tang X, Ren F, Zheng M and Zhu Y (2021) Classifying Vulnerability to Sleep Deprivation Using Resting-State Functional MRI Graph Theory Metrics. Front. Neurosci. 15:660365. doi: 10.3389/fnins.2021.660365

INTRODUCTION

Cognitive ability and healthy brain function rely on sufficient sleep, during which metabolic waste products are cleared away (Xie et al., 2013; Fultz et al., 2019). Lack of sleep, however, can impact nearly all aspects of cognitive and emotional function, including attention, working memory, and affect (Durmer and Dinges, 2005). Notably, functional magnetic resonance imaging (fMRI) studies

measuring blood oxygen level–dependent (BOLD) signals have demonstrated that sleep deprivation (SD) is associated with widespread brain network alterations (Chee and Chuah, 2008). These include changes in interhemispheric connectivity (Zhu et al., 2016, 2020), connectivity between the thalamus and prefrontal cortex (Shao et al., 2013), and compromised anti-correlation between the Default Mode Network (DMN) and dorsal attention network (Kaufmann et al., 2016).

While cognitive deficits have been well documented and reliably related to SD, large inter-individual differences in cognitive deterioration after SD have been noted (Hudson et al., 2020). For some cognitive domains, such as sustained attention, SD-induced differences in performance are stable within a given individual even when assessed months or years apart (Rupp et al., 2012). Previous studies have indicated that differences in the vulnerability/resistance of individuals to SD-induced deficits in cognition and performance are trait-like (Van Dongen et al., 2004). Thus, the underlying mechanisms of these individual differences are a current research focus. For instance, many recent brain imaging studies have attempted to identify the neural correlates of vulnerability/resistance to SD. Using the hierarchical regression model, our previous study found that the white matter integrity of the upper longitudinal tract fibers connecting the frontal and parietal lobes was negatively associated with individual differences in psychomotor vigilance task (PVT) performance after SD (Zhu et al., 2017). Another study found that stronger anti-correlations among several networks (such as between DMN and Attention networks) during rested wakefulness could predict the vulnerability of PVT performance during SD (Yeo et al., 2015).

However, as traditional approaches are based on average estimates of differences at the group level, a reliable predictive marker of cognitive vulnerability to SD has been elusive. The translational applicability of such data to clinical practice should be based on inferences at the individual rather than group level. With recent advancements in the field of machine learning, such as the support vector machine (SVM) model, a multivariate pattern recognition machine learning (ML) technique especially well-suited for discriminating high-dimensional rsFC fMRI data, measurements derived from fMRI combined with artificial intelligence algorithms have led to improvements in diagnoses, classification, and treatment outcome prediction for a range of situations (Zhao et al., 2018; Liu et al., 2020). Furthermore, multivariate machine learning techniques are more sensitive to differences that are subtle and spatially distributed because they consider inter-regional correlations, which might be undetectable using group comparisons (Liu et al., 2020). Because SD is associated with widespread changes in functional networks, graph-based measurements of network organization, such as degree centrality (DC) (Wang et al., 2011), might have potential in predicting vulnerability to SD-induced deficits in function.

In the current study, we adopted supervised machine learning-based SVM algorithms to investigate whether baseline resting wakefulness (RW) DC measures could predict inter-individual differences in PVT lapses after SD. We hypothesized that the baseline DC in hub regions of the DMN, frontal-parietal network, and thalamus could be used to accurately classify participants as vulnerable or resistant to SD.

MATERIALS AND METHODS

Subjects

This study was approved by the clinical trial ethics committee of Xijing Hospital at the Air Force Medical University. Written informed consent was obtained from each subject prior to the study. All participants were recruited via advertisements distributed in the local community. The exclusion criteria were as follows: (1) having a history of alcohol or drug abuse; (2) having a history of psychiatric or neurological illness; (3) sleep disorders; (4) sleep later than 24 o'clock or get up earlier than 5 o'clock; and (5) claustrophobia. The Pittsburgh sleep quality index (PSQI) was used to evaluate sleeping quality (Guo et al., 2016), and subjects who scored more than five points on the PSQI test were also excluded. Hence, the final sample comprised 60 participants.

Study Procedure

All subjects were asked to make three visits to the laboratory. During the first visit, they were briefed about the study protocol and signed the informed consent form. All subjects agreed to undergo an MRI scan after normal sleep and after 24 h of SD, which occurred on the last two visits to the laboratory. To minimize the influence of the scanning sequence on the experimental results, the experimental condition in the last two visits was presented in a pseudo-random order. The interval between these two visits was at least 1 week. The SD process began at 8:00 AM on 1 day and ended at 8:00 AM on the following day. During SD, the participants could read books or use their mobile phones. The SD took place in a room with standard light (340 lux) and the temperature was maintained at approximately 23°C. No snack food was given after midnight. The entire SD process was monitored by two researchers to prevent the subjects from falling asleep. All of the MRI scans were scheduled between 8:00 AM and 10:00 AM.

Psychomotor Vigilance Task

A 10-min PVT was used in the current study (Basner and Dinges, 2011). The PVT task was rendered using E-prime (version 3.0) software. During the task, participants were asked to focus on a blank box in the middle of a computer screen. A millisecond counter then began to scroll at a random interval of 2–10 s. The participants were required to press the space bar to stop the counter as quickly as possible. Reaction time was displayed for 1 s as feedback so that the participants could monitor their performance. Reaction times longer than 500 ms were recorded as a lapse in performance (Zhu et al., 2017). The participants completed 10 min of the PVT every hour from 8:00 PM to 6:00 AM.

MRI Data Acquisition

MRI data were collected using a GE Discovery MR750 3.0T scanner with a standard 8-channel head coil at Xijing Hospital. The subjects were instructed to lie quietly on the scan flatbed,

wear earplugs, open their eyes, stay awake, and try to avoid sleeping (Song et al., 2020). Cotton pads and tape were used to minimize head motion. During each scan, the subjects were reminded via a microphone to stay awake, and the heart and respiratory rates of the subjects were recorded. Resting-state functional images were collected via an axial gradient-echo EPI sequence with the following parameters: TR/TE: 2,000/30 ms, FOV: 240 × 240 mm^2, matrix size: 128 × 128, slices: 45, and a total of 210 volumes. The structural MRI data were obtained using a sagittal 3D Bravo T1-weighted scan sequence with the following parameters: TR/TE: 8.2/3.2 ms, FOV: 256 × 256 mm^2, matrix: 256 × 256, slice thickness: 1.0 mm, slices: 196.

MRI Data Analysis

The fMRI data were preprocessed using Data Processing and Analysis for Brain Imaging (DPABI)[1] with the statistical parameter mapping software package (SPM12)[2] and the Resting-State Functional MR imaging toolkit (REST)[3] (Yan et al., 2016). First, the initial 10 volumes were discarded to stabilize the signal. Then, the remaining 200 volumes were realigned to the first volume after correcting for the differences in acquisition times, during which the mean frame-wise displacement (FD) was calculated. Data were excluded if head motion exceeded 2 mm and 2°. Two participants were excluded because of heavy head motion. The effects of nuisance signals and head motions (Friston-24 model) were also regressed out. Then, the diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) tool was used for normalization (Asami et al., 2012), and the normalized data were finally band-pass filtered (0.01–0.08 Hz).

Degree Centrality

The correlation matrix was obtained by calculating the Pearson correlation coefficient between the time course of one voxel within the predefined gray matrix mask and the time courses of all other voxels. Then, an undirected adjacency matrix was obtained by eliminating the weak correlation caused by noise through threshold processing of each correlation item at $r > 0.25$. Finally, z-score maps were obtained by converting the individual voxel-wise DC. The z-score maps were registered with 3-mm^3 cubic voxels into the MNI space using the transformation information obtained from DARTEL and smoothed using a kernel of 6 mm.

Statistical Analysis

Demographic data were analyzed using IBM SPSS Statistics (IBM SPSS Statistics for Windows, version 18.0, IBM Corp.). For detection of between-group differences in DC, the General Linear Model (GLM) with a paired t-test (resting wakefulness (RW) vs. SD) was used to identify regional DC changes. The threshold for significance was $P < 0.05$, corrected with the false discovery rate (FDR) criterion. The mean FD calculated during the preprocessing step was accounted for by including this term as a covariate. The differences between RW and SD were binarized as a mask for further machine learning analysis.

Support Vector Machine Analysis

Trait-like individual differences in vulnerability to SD were defined using the same methods stated in our previous study (Zhu et al., 2017). Vulnerability to SD was computed on the basis of the extent of change in the number of lapses in each individual after SD. The participants were then ranked from highest to lowest per the vulnerability value. Finally, the participants were categorized into a vulnerability group and a resilience group.

The SVM was applied using the Pattern Recognition for Neuroimaging Toolbox (PRoNTo)[4] to investigate whether the DC during RW could classify vulnerability to SD (Schrouff et al., 2013). In the first step (feature selection) the feature vector encoded the pattern of baseline DC values masked by the aforementioned mask. Feature selection comprised identifying brain regions that were expected to differ between the two sub-groups. These procedures were processed in the "Prepare feature set" program. In the second step, Leave-one-out cross-validation (LOOCV) was used to evaluate the performance of the classifier (Liu et al., 2020). In LOOCV, data from one subject was used as test data and the classifier is trained on the remaining dataset. These procedures were processed in the "Specify model" program. Next, once the SVM algorithm had been established, a 1,000-times permutation test was used to evaluate the performance of the SVM model. The corresponding accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve were obtained. One advantage of the PRoNTo is that the weight map can be built at the voxel level. According to the contribution in the classification model, the region contributions can be ranked and presented for illustration. Finally, for each region, we used Pearson correlation to examine the associations between the changes in DC and PVT lapses using SPSS. Correction for multiple comparisons was accomplished using the FDR criterion ("mafdr" script implemented in MATLAB) (Zhu et al., 2019).

RESULTS

A total of 58 subjects successfully completed the SD experiment. Sleep diaries and Actiwatches confirmed that all subjects normally had good quality, habitual sleep. On the basis of the differences in the PVT lapses between the SD and RW conditions, subjects were divided into a vulnerable group and resilience group. The average number of PVT lapses for each group was 8.47 and 1.69, respectively. As expected, significant differences in PVT lapses were found between the two groups ($t = 5.39$, $p < 0.001$). No significant differences were found for gender, age, body mass index, or objective sleep measures observed via Actiwatches. Detailed sleep information is listed in **Table 1**.

A paired t-test was used to investigate the significant changes in DC measures after SD. As shown in **Figure 1**, we observed significantly increased DC within the bilateral inferior temporal

[1] http://rfmri.org/dpabi

[2] https://www.fil.ion.ucl.ac.uk/spm/

[3] http://www.restfmri.net

[4] http://www.mlnl.cs.ucl.ac.uk/pronto

TABLE 1 | Demographic characteristics, objective sleep measures, and PVT performance.

	Vulnerable	Resilience	*p*-value
Gender (male/female)	15/14	15/14	1
Age (years)	22.4 ± 1.9	22.2 ± 1.6	0.43
Body mass index	23.7 ± 2.8	23.5 ± 2.3	0.81
Objective sleep characteristics from Actiwatch			
Time of falling asleep	00:05 ± 0:22	00:06 ± 0:27	0.86
Number of wakening each night	27.2 ± 6.4	27.4 ± 6.8	0.94
Sleep duration all night	6:45 ± 1:10	6:43 ± 1:25	0.91
Night sleep durations before work days	6:27 ± 0:52	6:25 ± 0:59	0.94
Night sleep durations before free days	7:06 ± 1:18	7:01 ± 1:19	0.83
Sleep efficiency in%	84 ± 2.8	83 ± 2.2	0.31
Sleep latency in minutes	16.6 ± 13.8	16.4 ± 14.3	0.84
PVT performance			
Number of lapse	8.47 (6.01)	1.69 (3.15)	<0.001

Values represent mean ± SEM (n = 58); PVT, psychomotor vigilance task.

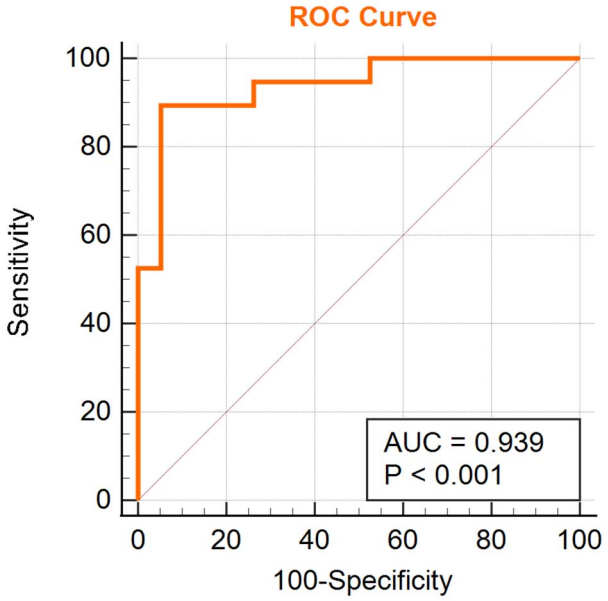

FIGURE 2 | ROC curve of the classifier.

gyrus, left insula, left inferior frontal gyrus, and bilateral precentral gyrus. We found significantly reduced DC within the bilateral cerebellum, thalamus, putamen, middle occipital gyrus, and right supramarginal gyrus.

We obtained an accuracy of 84.75% with a sensitivity of 82.76% and specificity of 86.67% for classification of the two groups. The area under the curve was 0.939 (**Figure 2**). The brain regions that contributed most to the classification are shown in **Figure 3** and listed in **Table 2**. The top 10 regions were the right supplementary motor area, right cerebellum, left inferior occipital gyrus, left precentral gyrus, left supramarginal gyrus, left thalamus, left middle temporal gyrus, left inferior parietal lobule, right middle frontal gyrus, and right middle occipital gyrus; their corresponding discriminative weights are also listed in **Table 2**.

Finally, the mean DC changes (SD-RW) within each region were extracted and plotted against the changes in PVT lapses. We found a significantly negative correlation with the left thalamus (see **Figure 4**).

DISCUSSION

Using a multivariate pattern classification method, the present study demonstrates that degree centrality derived from fMRI data collected during RW can be used to classify subjects on the basis of whether they are vulnerable or resilient to SD. With excellent

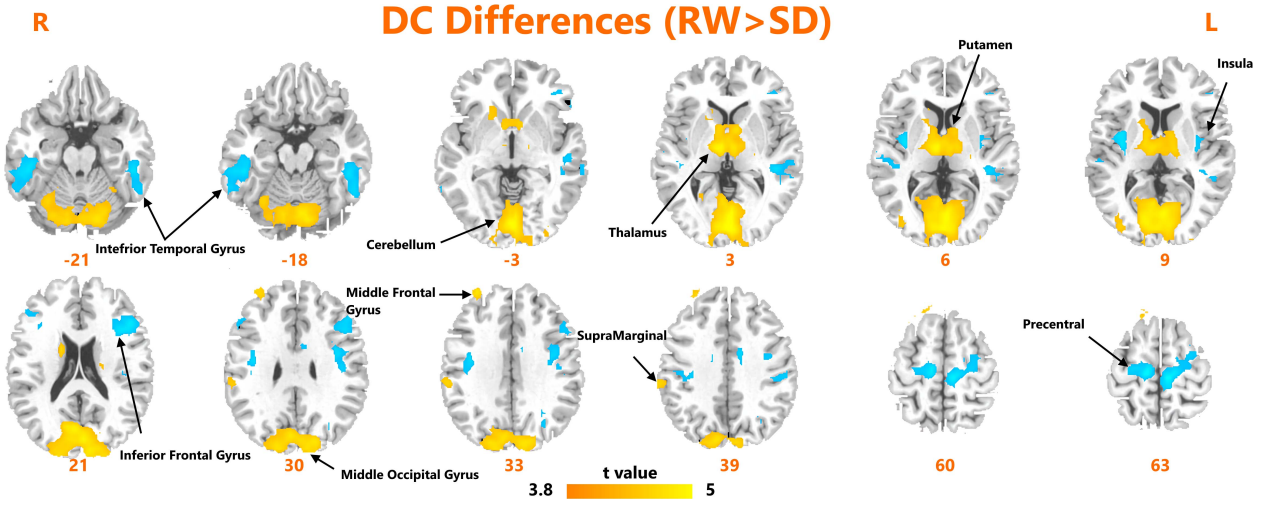

FIGURE 1 | Areas of significant degree centrality differences between resting wakefulness state and sleep deprivation state.

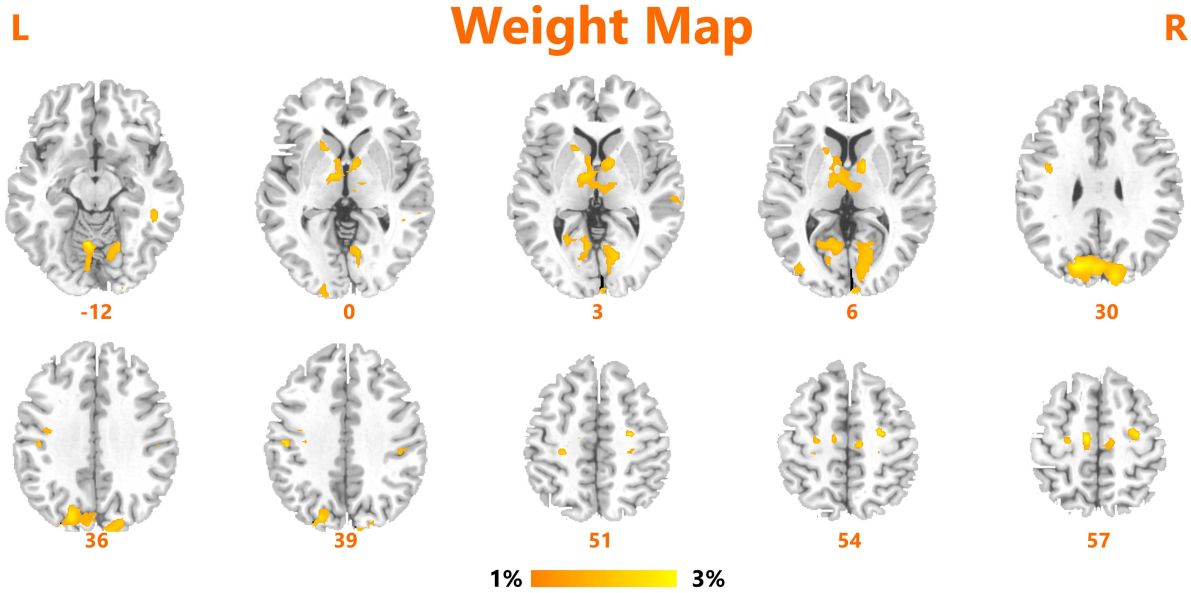

FIGURE 3 | Brain regions of interest that contributed mostly to the accurate classification.

accuracy, the brain regions that showed the most discriminatory power were mainly located within the sensorimotor network (SMN), DMN, and thalamus. Furthermore, we found a significant negative correlation between the changes in PVT lapses and DC in the thalamus after SD. These findings suggest that graph-theory-based measures, such as DC, combined with machine-learning algorithms, can help to predict vulnerability to SD.

Because SD has become very common in contemporary 24/7 society, efficient screening for resilient and vulnerable people has social significance. Although previous studies have used baseline measures of psychomotor vigilance and the drift diffusion model to classify vulnerability to SD (Patanaik et al., 2014), the accurate classification rate was around 77–82%, which was less than satisfactory. Vulnerability to SD has been shown to be stable and trait-like, with characteristic neural correlates that have been identified. Therefore, neuroimaging data combined with state-of-the-art artificial intelligence algorithms might enable greater classification performance. Our results verified that SD leads to significant DC reductions in the cerebellum, thalamus, and putamen. This indicates that functional connections within subcortical regions are compromised, which is consistent with

TABLE 2 | The top ten ranked regions that contributed mostly to the classification.

Brain regions	Cluster size	Peak coordinates (MNI)			Discriminative weight (%)
		X	*Y*	*Z*	
Supplementary motor area R	290	9	−15	57	5.02
Cerebellum R	1402	6	−63	−12	3.84
Inferior occipital gyrus L	46	−21	−99	−12	3.81
Precentral gyrus L	80	−24	−12	51	3.53
Supramarginal R	92	48	−24	36	2.98
Thalamus L	403	−12	−3	6	2.58
Middle temporal gyrus L	88	−63	−27	0	2.44
Inferior parietal lobule L	21	−42	−30	39	2.31
Middle frontal gyrus R	21	24	−21	54	2.22
Middle occipital gyrus R	92	36	−84	3	1.85

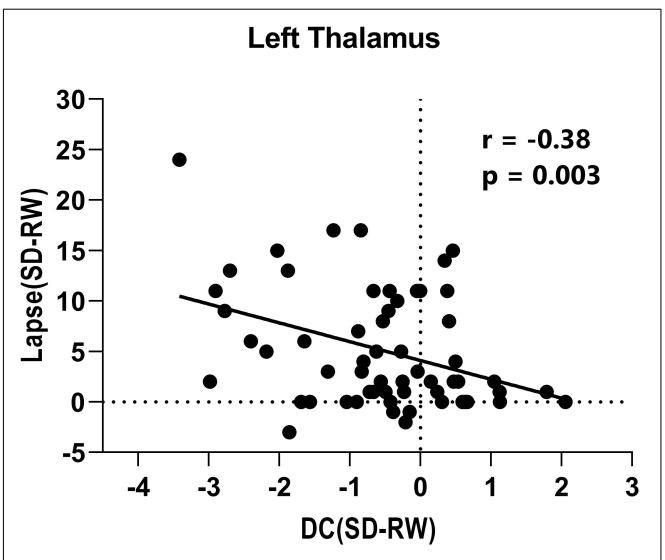

FIGURE 4 | Correlation between change of lapse of psychomotor vigilance task and change of degree centrality within left thalamus.

previous studies (Nechifor et al., 2020). A significant increase in DC was mainly found within the SMN and DMN, which suggests that SD affects lower functional network segregation and higher network integration (Yu et al., 2017).

The brain regions that contributed most to the classification model include the supplementary motor area, middle temporal gyrus, and middle frontal gyrus, which are core regions of the DMN. The DMN is more active during passive tasks than during externally orientated tasks, and has been extensively examined in SD research (Gujar et al., 2010). Furthermore, the anti-correlation between sub-networks of the DMN and frontal-parietal networks subserves working memory performance during the mid-point of night in the regular biological sleep cycle (Zhu et al., 2019). These consistent findings highlight the role of the DMN in predicting vulnerability to SD.

Apart from that related to the DMN, another interesting finding of the present study is that the thalamus also exerts an important role in modulating SD vulnerability. The thalamus is one of the core network brain regions that subserves vigilant attention in humans (Avanzini et al., 2000). Previous studies have indicated that the thalamus is involved in sensory gating and attentional modulation by acting as a bridge between sensory perception and cognition (Saalmann and Kastner, 2011). Increased thalamus activation has been frequently reported in SD studies (Hershey et al., 1991; Gent et al., 2018). However, the activity pattern in the thalamus has been found to be correlated significantly with mean melatonin levels, and therefore, the thalamus is modulated more by circadian rhythms than by sleep debt (Muto et al., 2016; Zhu et al., 2020). Previous studies have indicated that SD vulnerability is stable after total SD or short periods of sleep restriction, suggesting that SD vulnerability is not solely modulated by sleep debt (Van Dongen et al., 2004; Rupp et al., 2012). The common patterns found in thalamus activity and vulnerability to SD, coupled with the discriminative weight and negative correlation found in the current study, imply that baseline activity within the thalamus has broad potential applications in screening for SD vulnerability.

Several limitations are present in the current study. First, the sample size was relatively small. However, we selected the SVM algorithm for classification because it has good efficiency when used with small sample sizes. Second, although it is possible that micro-sleep occurred during the SD period, two research assistants were present to prevent subjects from falling asleep, so this is unlikely. Furthermore, the subjects were required to stay awake and keep their eyes open during the scanning procedure, and their heart rate and breathing frequency were collected concurrently to verify that they were not asleep.

CONCLUSION

Our study demonstrates that graph-theory-based DC measures combined with machine learning algorithms have the potential to predict vulnerability to SD. Brain regions within the SMN, DMN, and thalamus contributed most to the accurate classification model. Future studies may benefit from the integration of white matter connectivity or other imaging modality measurements.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Committee of Xijing Hospital at the Air Force Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YX, PY, and JZ performed all data analysis and wrote the manuscript. YZ and MZ raised the conception of the study. XT, CW, and FR contributed to the collection of MRI data. ZX, TH, QY, and FG contributed to the manuscript revision. All authors read and approved the submitted version.

FUNDING

This study was financially supported by the National Natural Science Foundation of China under grant 81801772.

ACKNOWLEDGMENTS

We thank Sydney Koke, MFA, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript. All volunteers are thanked for their participation of the study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

HYPOTHESIS AND THEORY
published: 22 July 2021
doi: 10.3389/fnins.2021.628836

Conceptual Framework for Insomnia: A Cognitive Model in Practice

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OPEN ACCESS

Edited by:
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Reviewed by:
Vincenzo Natale, University of Bologna, Italy
Maria Paola Mogavero, Istituti Clinici Scientifici Maugeri (ICS Maugeri), Italy

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *13 November 2020*
Accepted: *03 June 2021*
Published: *22 July 2021*

Citation:
Vaziri Z, Nami M, Leite JP, Delbem ACB, Hyppolito MA and Ghodratitoostani I (2021) Conceptual Framework for Insomnia: A Cognitive Model in Practice. Front. Neurosci. 15:628836. doi: 10.3389/fnins.2021.628836

Insomnia is a widespread neuropsychological sleep-related disorder known to result in various predicaments including cognitive impairments, emotional distress, negative thoughts, and perceived sleep insufficiency besides affecting the incidence and aggravation of other medical disorders. Despite the available insomnia-related theoretical cognitive models, clinical studies, and related guidelines, an evidence-based conceptual framework for a personalized approach to insomnia seems to be lacking. This study proposes a conceptual cognitive framework (CCF) providing insight into cognitive mechanisms involved in the predisposition, precipitation, and perpetuation of insomnia and consequent cognitive deficits. The current CCF for insomnia relies on evaluative conditional learning and appraisal which generates negative valence (emotional value) and arousal (cognitive value). Even with the limitations of this study, the suggested methodology is well-defined, reproducible, and accessible can help foster future high-quality clinical databases. During clinical insomnia but not the neutral one, negative mood (trait-anxiety) causes cognitive impairments only if mediating with a distorted perception of insomnia (***Ind-1*** = 0.161, 95% CI 0.040–0.311). Further real-life testing of the CCF is intended to formulate a meticulous, decision-supporting platform for clinical interventions. Furthermore, the suggested methodology is expected to offer a reliable platform for CCF-development in other cognitive impairments and support the causal clinical data models. It may also improve our knowledge of psychological disturbances and complex comorbidities to help design rehabilitation interventions and comprehensive frameworks in line with the "preventive medicine" policies.

Keywords: cognitive model, insomnia, evaluative conditional learning, mediator model, distorted perception, appraisal, valence, conceptual cognitive framework

INTRODUCTION

Behavioral sleep disturbances are classified into various types of insomnia, excessive daytime somnolence (EDS), sleep phase disorders, and parasomnias. These are potentially rooted in psychophysiological, cognitive, emotional, and behavioral abnormalities resulting in impaired sleep efficacy, disintegrated sleep cycles, and/or arousal instability (Cormier, 1990; Sateia, 2014). Insomnias are characterized by poor subjective sleep quality, difficulty in falling asleep and maintaining sleep at bed-time, wakes after sleep onset (WASO), or unprompted early morning awakening. The consequent diurnal symptoms may then present as inadequate cognitive functions, declined cognitive aptitude, fatigue, hampered productivity, depression or irritability, impaired decision-making, low motivation, and mood dysregulation (Mai and Buysse, 2008; Nami, 2014).

Recently, cognitive-vulnerability models, which theoretically justify the interrelation between sleeplessness and mood dysregulation or cognitive insufficiencies, have drawn the attention of the research community. When insomnia becomes a chief complaint, the vicious cycle of insomnia-anxiety-insomnia starts to emerge. Undeniably, affective dysregulation, impulsivity, restlessness, EDS, disrupted vigilance, and cognitive decline are some consequences of long-term sleep insufficiency in many instances (Nami, 2014).

Among the theoretical and cognitive-computational models related to insomnia, the cognitive vulnerability model for insomnia induced mood disturbances (CVMIMD), the sleep-specific cognitive vulnerability (SSCV), the behaviorally induced insufficient sleep syndrome with restricted and extended sleep opportunity (BIISS-RESO), and the global cognitive vulnerability to insomnia (GCVI) (Bei et al., 2015) are the main highlights. These models are addressed subsequently.

Cognitive Vulnerability Model for Insomnia Induced Mood Disturbances

From the neurocognitive standpoint, the prefrontal cortex (PFC), which plays a pivotal role in affect-regulation and cognitive-control, develops intensely throughout the neurodevelopment phase and adolescence owing to neuroplasticity. When the hypnic tone is decreased either due to poor sleep hygiene or socio-behavioral and psychophysiological stressors, a proposed explanation is the activation of PFC's maladaptive processes as a potential neurocognitive mechanism underlying the affective consequences of insomnia and inefficient sleep, in general (Freeman et al., 2005).

The body of psycho-behavioral and neurocognitive empirical evidence describing the precise mechanisms that underlie the link between insomnia and negative mood is thin. However, subjective sleep insufficiencies and dysregulated mood observations exhibited more robust relationship as compared to objective findings from polysomnography or even full-setup sleep electroencephalography data. This points to the fact that psychological factors that hinder sleep efficiency might play significant roles in justifying the sleep-mood crosstalk. Yet some of these insomnia-related cognitive vulnerability factors are now acknowledged as erroneous beliefs, cognitive biases, and thought patterns that increase the likelihood of the predisposed individuals toward psychopathology (Freeman et al., 2005).

Sleep Specific Cognitive Vulnerability

In some instances, the erroneous beliefs and attitudes represent exclusive sleep-related problems in which case, the distressing worries related to insomnia-continuation are usually evaluated using the dysfunctional beliefs and attitudes about sleep (DBAS) Scale. Harvey's cognitive model (Harvey, 2002) described the impact of the DBAS-related cognitive vulnerability on insomnia complaints. According to this model, insomniacs are generally worried about poor sleep and its daytime consequences, and such strong, negatively toned thoughts trigger selective attentional-emotional bias, wherein individuals over-monitor their sleep-related threat cues. Previous investigations proposed a strong connection between DBAS and poor sleepers, which happens to play a key role in DBAS-driven disturbances in sleep perception and sleep safety behaviors such as napping (Harvey, 2002).

Behaviorally Induced Insufficient Sleep Syndrome With Restricted and Extended Sleep Opportunity

This condition refers to a typical complaint reported by the patients as "*at nights I cannot sleep, in the morning, I cannot wake up*." Habitual sleep episodes are usually shorter (confirmed by history, sleep log, or actigraphy) for patients experiencing initial or maintenance insomnia compared to the normative values from age-adjusted groups. Such patients also report sleep-inertia in the morning and complain about EDS for a minimum of 3 months before the interview. However, they tend to sleep considerably longer on weekends or during vacation. In general, the reported objective sleep efficiency as detected by polysomnography is below 80%, besides the mean initial nocturnal sleep latency which takes a longer time, more than 45 min. Also, these patients report repeated WASOs (Bastien et al., 2008).

Global Cognitive Vulnerability to Insomnia

Cognitive vulnerability is defined as global when the dysfunctional beliefs and attitudes are general and not necessarily focused on a distinct behavioral or experiential

Abbreviations: ABM, attentional bias modification; BIISS-RESO, behaviorally induced insufficient sleep syndrome with restricted and extended sleep opportunity; CAAP, conscious attended awareness perception; CBT, cognitive-behavioral therapy; CBT-I, cognitive-behavioral therapy for insomnia; CCF, conceptual cognitive framework; CEOF, Centro Especializado de Otorrinolaringologia e Fonoaudiologia; CS, conditioned stimulus; CVMIMD, cognitive vulnerability model for insomnia induced mood disturbances; DBAS, dysfunctional beliefs and attitudes about sleep; ECL, evaluative conditional learning; EDS, excessive daytime somnolence; GCVI, global cognitive vulnerability to insomnia; Ind, Indirect; MBCT, mindfulness-based cognitive therapy; MSQ, mini-sleep questionnaire; MSQ-R, mini-sleep questionnaire result; PFC, prefrontal cortex; SSCV, sleep-specific cognitive vulnerability; STAI, state-trait anxiety inventory; US, unconditioned Stimulus; WASO, wakes after sleep onset.

area. According to Beck's cognitive model, psycho-traumas in the early years of life combined with a complicated past can foster negative attitudes and biases concerning both self, world and the future. Such beliefs yield maladaptive schemas that may trigger cognitive vulnerabilities and negative tendencies based on depression later in life (Beck, 2008). A few studies on GCVI suggest strong links between sleep predicaments (mainly insomnias) and negatively toned cognitive constructs. For instance, complaints of chronic insomnia in young adults were found to be associated with anxiety and depression-related cognitive factors (Alfano et al., 2009). In the same vein, Sadler et al. (2013) claimed hopelessness, a global cognitive-vulnerability factor in older adults, can amplify the effects of insomnia on depressive symptoms (Sadler et al., 2013).

The various types of insomnia (more than 10) require personalized treatment approaches. Some of the broadly described types include adjustment insomnia, drug or substance-induced insomnia, comorbid insomnia, onset insomnia, middle insomnia, late insomnia, conditioned, or psychophysiological insomnia, behavioral insomnia of childhood, idiopathic insomnia, paradoxical insomnia, and sleep hygiene insomnia (Dzierzewski et al., 2018). Based on the severity of sleep insufficiency, we have categorized insomnia patients into Neutral (with a mild to moderate perception of sleep difficulties) and Clinical (with a severe perception of sleep difficulty) types.

Gross (1998) designed the *modal model of emotion* as a conceptual framework to illustrate how emotions can be generated and evolve over time. The emotion-generation process begins with internal or external goal-relevant situations that draw attention to specific features of the situation, appraisals emerge to make meaning of the situation resulting in multi-faceted emotional responses and feedback to modulate the current situation perpetually. Collectively, the modal model reflects the dynamic nature of the emotions and suggests possible emotion-regulation strategies comprising of situation selection, situation modification, attention deployment, cognitive change, and response modulation (Gross, 2013).

To the best of our knowledge, the aforementioned studies have little mention of causality (mediation) relationships, which can easily mislead interpretations of the findings. Thus, necessitating the design of an approach to conceptualize these theories and hypotheses. A novel insomnia theoretical-conceptual framework would enable the drawing of data models for testing mediational relationships between independent variables and outcomes within retrospective studies. Besides, it may also help suggest research strategies and predictions designing prospective studies on insomnia. The present study aims to fill this void in the literature by proposing and validating a novel conceptual cognitive framework (CCF) for insomnia in light of the above-mentioned models. The CCF illustrates how cognitive processes and their interactions can generate annoyance-distress reactions, which in turn, lead to the development or maintenance of insomnia. The insomnia numerical model is also demonstrated through multi-mediatory (causality) modeling approaches.

PROPOSED CONCEPTUAL COGNITIVE FRAMEWORK

Fundamental Ideas and Postulations of the Conceptual Cognitive Framework

- Conceptual cognitive framework aims at illustrating the interaction between cognitive processes that cause annoyance-distress reactions in insomnia.
- Conceptual cognitive framework rests mainly on evaluative conditioning, assuming a conscious attended awareness perception (CAAP) to both unconditioned stimulus (US) and conditioned stimulus (CS), and their contingencies essential for attitude formation.
- Either or both, cognitive-value and emotional-value, can cause annoyance; however, they can also affect each other merely through annoyance. Furthermore, annoyance distorts the corresponding perception of sleep quality by affecting cognitive and emotional values.
- Lower levels of cognitive-emotional values such as those encountered in the Neutral stage might generate annoyance, yet not sufficient enough to trigger distress reactions. Consequently, annoyance and distress are considered two different concepts in the current framework.
- Cognitive processes for sleep-initiation and sleep-maintenance difficulties are presumed to occur analogously.

Hypothetically, CCF compartments include situation, attention bias, cognitive value (arousal), emotional value (valence), annoyance-distress reaction, and distorted perception. The proposed CCF aims at illustrating how the interaction among cognitive processes contributes to distress reactions.

This paper focuses on insomnia experienced before sleep, and the associated "situation" is restricted to the night-time silence period. According to the CCF, when insomnia-related stimuli capture attentional resources, either directly or through corresponding cognitive and emotional values, distress is triggered resulting in a distorted perception. Distress, in turn, feeds back and influences the situation. Similarly, distress reaction fuels back corresponding cognitive and emotional values. The proposed CCF is illustrated in **Figure 1**.

Toward providing a proof of concept for the proposed CCF, we primarily present some supporting evidence from the Insomnia literature.

COMPARTMENTS AND COGNITIVE PROCESSES

Situation

Nighttime silence in the pre-sleep period can facilitate CAAP of internal (body sensation or thoughts) and external (environmental sounds, light, and heat) stimuli. Bootzin and Rider (1997) noted that "bedtime may often be the first quiet time during the day available to think about the day's events and

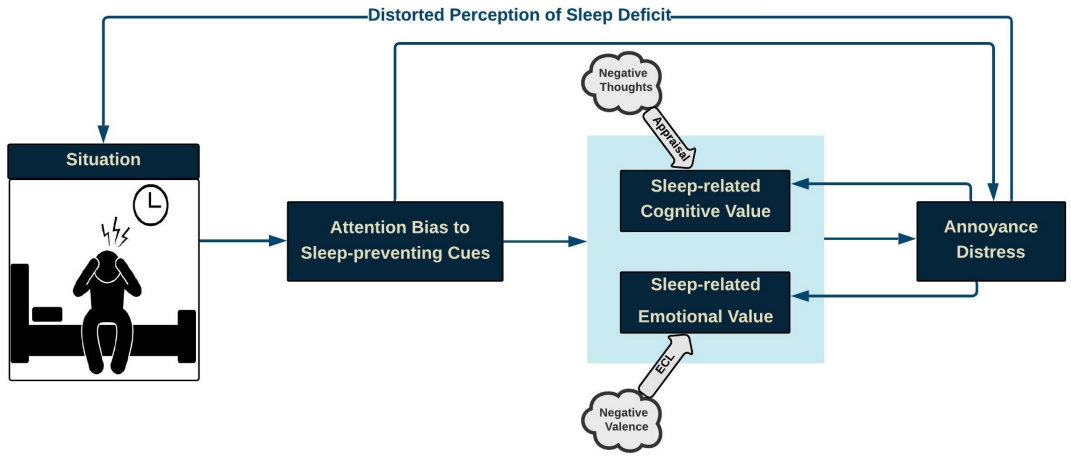

FIGURE 1 | Conceptual Cognitive Framework of Insomnia: During the pre-sleep situation, when attentional resources are captured by insomnia-related stimuli, either directly or through insomnia-related cognitive and emotional values, distress is triggered, thus resulting in a distorted perception of sleep quality, which, in turn, worsens the sleep-initiation process. Likewise, insomnia distress strengthens the negative cognitive-emotional value of difficulty in sleep.

to worry and plan for the next day." Therefore, bed and bedtime tend to be cues for arousal rather than for sleep.

Attention Bias

Consciously attended internal and external stimuli develop an individual's predictions and expectations from the pre-sleep situation. Therefore, an attention bias takes place if any novelty or change occurs in the features of such stimuli (Horstmann and Herwig, 2016). Similarly, Roberts et al. (2013) have supported the notion that "discrepancy between an expectation and upcoming stimuli can bias attention" (Horstmann and Herwig, 2016). Additionally, emotion-laden or threat-related stimuli would be prioritized over other stimuli leading to an attentional bias. The same rationale applies to cognitive theories of anxiety disorders (Beck and Clark, 1997), according to which prioritized attention-allocation to threat cues would trigger the development and maintenance of anxiety (Dalgleish and Watts, 1990). Threat cues for patients with insomnia might be related to sleep quality (arising secondarily to bodily sensations such as palpitation, muscle tension, or attention bias toward noises outside and inside the house), which impairs the process of falling asleep.

One of the commonly used paradigms for experimental assessment of attentional bias is the Dot-Probe task. In this, a pair of stimuli (e.g., words or pictures) are presented simultaneously at different locations (up/down or top/bottom) on the screen. The stimuli pair disappear after a fixed time window and a probe appears in the location of emotional (congruent presentations) or neutral (incongruent presentations) stimuli. Subjects are asked to detect and respond to the location of the probe as fast as possible, and the attentional bias is measured through their reaction time in responding to the probe location. A faster probe detection for congruent trials is believed to indicate vigilance, and a slower probe detection for the incongruent trials is suggestive of difficulty in disengaging attention from emotional stimuli (Koster et al., 2004).

Several studies have investigated the impact of the emotional-attentional bias on sleep-related threatening cues through different attentional paradigms, including Dot-probe (MacMahon et al., 2006; Jansson-Fröjmark et al., 2012), flicker (Jones et al., 2005), Posner (Woods et al., 2009), emotional Stroop (Barclay and Ellis, 2013), and eye-tracking (Woods et al., 2013). Most of these studies have endorsed the notion that poor sleepers display attentional bias to sleep-related cues compared with controls. Jansson-Fröjmark et al. (2012) used a dot-probe task to demonstrate that individuals with primary insomnia had a considerably prolonged reaction-time when shifting attention away from insomnia-associated pictures paired with neutral pictures, in comparison to neutral-neutral paired picture presentations as control. Their findings suggest that insomniacs have more difficulty in shifting attention away from insomnia-related stimuli, but are not more vigilant to those stimuli than normal sleepers (Jansson-Fröjmark et al., 2012). However, results reported by Spiegelhalder et al. (2010) yielded no statistically significant preferential attentional-allocation to sleep-related stimuli. Inconsistent results from studies on insomnia may have emerged due to confounding factors and possible bias, impeding their methodologies and study design.

Emotional Value

The emotional value gets shaped through the evaluative conditional learning (ECL) mechanism which plays a crucial role in liking and disliking stimuli (Ghodratitoostani et al., 2016a,b). Based on ECL, neutral stimuli (CS) can obtain either positive or negative valence after being repeatedly paired with emotion-laden stimuli (US) (De Houwer et al., 2001). Valence represents emotional states varying along a spectrum, ranging from positive to negative feelings with a neutral center-point (Bradley and Lang, 1994). Based on the CCF, CAAP of both CS and US, and their contingencies are required at the time of EC-learning formation. Additionally, evaluative conditioning is an accumulative procedure through which different valenced

USs can add to CS valence after being repeatedly paired (Stahl and Unkelbach, 2009). Therefore, EC-learning is resistant to extinction so that neither individual CS/US presence alone, nor pairing CS with different USs would cause the extinction of previously shaped evaluative conditioning (De Houwer et al., 2001). Applying the CCF, the ECL mechanism suggests that the negative valence of other USs fuels a negative sleep-related emotional-value leading to annoyance or distress reaction. Different negative USs can also frequently get paired with internal (bodily sensations) and external (environmental sounds, light, or heat) sleep-preventing stimuli. Thereafter, attending to sleep-preventing cues alone might trigger distress reactions due to the learned USs' valence.

Cognitive Value

The cognitive value related to internal and external stimuli is built through an appraisal process. This process initiates when the meaning of an object or event is evaluated in a particular situation according to pre-existing beliefs, desires, and intentions (Scherer et al., 2001). However, not all information but that relevant to individuals' concerns (Frijda, 1987), can trigger a cognitively aroused state followed by the appraisal. Accordingly, attention bias to sleep-preventing cues (as concern-relevant stimuli) can trigger a cognitively aroused state with subsequent appraisals about insomnia, "*I am never going to get to sleep*," "*I am not coping with the amount of sleep I get*," and "*I am going to lose my job*" (Harvey, 2002). Negative thoughts through this appraisal mechanism further fuel the negative sleep-related cognitive value, leading to annoyance or distress reaction.

Self-reported questionnaires are widely used for collecting patients' thoughts and beliefs about events, situations, or objects that require conscious appraisals of conditions, and their corresponding consequences. Pre-Sleep Arousal Scale (Nicassio et al., 1985), Sleep Disturbance Questionnaire (Espie et al., 1989), and DBAS Scale (Morin, 1993) are commonly applied for assessing thoughts and beliefs related to insomnia. The latter is greatly helpful in clinical practice since it distinguishes salient irrational, and often emotionally loaded thoughts that disturb sleep onset. Nicassio et al. (1985) and Lichstein and Rosenthal (1980) evaluated the intensity of cognitive and somatic arousal at bedtime through the Pre-Sleep Arousal Scale and reported cognitive arousal was more strongly associated with sleeping difficulty. Similarly, Espie et al. (1989) used the Sleep Disturbance Questionnaire and observed "*My mind keeps turning things over*" and "*I am unable to empty my mind*" were the most often endorsed statements among insomniacs (Espie et al., 1989).

Several authors have assessed characteristics of pre-sleep thoughts in terms of content (Harvey, 2000; Wicklow and Espie, 2000), frequency (Barclay and Gregory, 2010), and valence (Kuisk et al., 1989). For instance, Wicklow and Espie (2000) conducted an experimental study on people with clinically significant sleep difficulties using audiotape to record their pre-sleep thoughts and wrist-actigraphy to obtain sleep patterns. The authors indicated that the more frequent thoughts were related to "rehearsing, planning and problem-solving" and "sleep and its consequences," which strongly correlated with unpleasant emotions and could predict objective sleep latency. Contrarily, Barclay and Gregory (2010) observed that the orientation of catastrophic thoughts in poor sleepers may not be necessarily sleep-specific, instead it was linked to a general tendency to be in an iterative manner regardless of the content or emotional valence. Sleepers were asked to catastrophize their thoughts into three topics namely sleep quality, current personal worries, and hypothetical positive topics. Poor sleepers exhibited greater catastrophic thoughts on every single topic in comparison with good ones, however, no difference was observed in occurrence of catastrophic worry about each topic among poor sleepers. Davey and Levy (1998) suggested that the tendency for repetitive thinking in insomniacs is similar to that of worriers who hold dysfunctional beliefs about the benefits of worrying. In other words, insomniacs believe the ongoing worry helps them find solutions and prevent adverse outcomes. Using DBAS, Morin et al. (1993) reported that not only excessive cognitive activity, but the valence of thoughts also plays a crucial role in provoking emotional reactions to sleep impairment.

Annoyance-Distress Reaction

Consistent with many cognitive-behavioral studies, the CCF suggests that negative appraisals of insomnia trigger the annoyance-distress reactions. According to the cognitive model of insomnia, excessively negative thinking in the pre-sleep time provokes autonomic arousal, and emotional distress (Harvey, 2002). Tang and Harvey (2004a) have reported that the manipulation of psychological and physiological arousal produces adverse effects on the perception of sleep quality. For illustrative purposes, Baglioni et al. (2010) presented five blocks showing neutral, negative, positive, sleep-related negative and sleep-related positive pictures to evaluate the psychophysiological reactivity to emotional stimuli, both related and unrelated to sleep, in people with primary insomnia and normal sleepers. facial electromyography, heart rate, and cardiac vagal tone were recorded during the picture presentation. The insomnia group indicated an enhanced physiological "craving" response for positive sleep stimuli (e.g., picture of a person asleep in bed), prolonged physiological arousal in response to all stimuli, and increased subjective arousal for negative sleep stimuli (e.g., picture of a person lying awake in bed) when compared to normal sleepers (Baglioni et al., 2010).

Distorted Perception

According to the CCF, valence and cognitive-arousal as two components of emotion can affect patients' judgment about sleep quality perception. The following findings lend support to this proposal.

Yoo and Lee (2015) explored the effect of modulating arousal and valence on time-perception in subjects with social anxiety, comparing the time duration of the presented stimuli with the standard duration in training sessions. The perceived duration of negative-stimuli against positive-stimuli was longer with high arousal, but shorter with low arousal levels, suggesting that modifications in the type and magnitude of both valence and arousal modulate time-perception (Yoo and Lee, 2015). This may also be analogous to the distortion in sleep quality-perception in insomniacs.

Using self-reported subjective sleep quality, Tang and Harvey (2004a) observed that experiencing anxious cognitive and physiological arousal in the pre-sleep period resulted in the perception of a longer sleep-onset latency and shorter total sleep time. Moreover, actigraphy results showed contradictions to the reported subjective sleep quality, thus corroborating distorted perception (Tang and Harvey, 2004a).

On the contrary, Herbert et al. (2017) inspected the psychophysiological predictors of subjective/objective sleep discrepancy in Total Sleep Time (Manconi et al., 2010) and Sleep Onset Latency (Herbert et al., 2017) indices among poor sleepers. They reported that excessive pre-sleep cognitive activity and lower mood at the awakening time of the following day are predictors of distortion in time estimation.

Hypotheses of Conceptual Cognitive Framework

The primary speculation was that the CAAP of internal and external sleep-preventing stimuli captures attentional resources preferentially and triggers the appraisal process, ending with annoyance and distress in the pre-sleep situation. A secondary hypothesis was that intermittent distress experienced in the Clinical stage leads to a misperception about sleep quality.

We applied the multi-mediation insomnia model based on clinical data toward putting the CCF into practice and provide supporting evidence for the proposed causality relationship between the cognitive processes in different stages of insomnia.

METHODS

For the CCF assessment, data were collected from the participants of (1) a randomized crossover three-session double-blind study and (2) an observational prospective cohort study. Both studies were approved by the Ethics Committee for Analysis of Research Projects, Specialized Center of Otorhinolaryngology and Speech Therapy, Hospital das Clínicas de Ribeirão Preto, University of São Paulo, Brazil (HCRP no 55716616.1.1001.5440, and HCRP no 09813519.1.0000.5440; internationally registered with U1111-1236-5441). All participants gave written informed consent.

Two-hundred fifty-three participants (123 female, 130 male) aged 27–72 years (54.43 $\pm$ 10.31 years) were recruited for this study. Before the sessions in both studies, participants filled up a Portuguese version of a battery of questionnaires that included (a) a six-item state-trait anxiety inventory (STAI) (Gorenstein and Andrade, 1996) for measuring the presence and severity of anxiety symptoms in the current moment (State anxiety) and a generalized predisposition to be anxious (Trait anxiety), and (b) a mini-sleep questionnaire (MSQ) (Falavigna et al., 2011), i.e., a short screening for sleep disturbances in clinical populations for the assessment of insomnia and sleep difficulties (**Table 1**). **Table 1** shows the items selected from each questionnaire for the development of the insomnia Mediator-Causality model.

TABLE 1 | List of selected questions from state-trait anxiety inventory (Gorenstein and Andrade, 1996) and mini-sleep questionnaire (Falavigna et al., 2011) for each model's component.

Questionnaire	Items	Model Component
State-Trait Anxiety Inventory (STAI)	**St-Q2.** I am tense	State Anxiety-Negative items [STAI-1N]
	St-Q4. I feel nervous	
	St-Q6. I am worried	
	Tr-Q2. I worry too much over something that really doesn't matter	Trait Anxiety Negative items [STAI-2N]
	Tr-Q4. I get in a state of tension or turmoil as I think over my recent concerns and interests	
	Tr-Q5. I feel nervous and restless	
Mini-Sleep Questionnaire (MSQ)	**MS-Q1.** Difficulty falling asleep	Insomnia Perception Factors [Ins_Per]
	MS-Q2. Wake up and do not go back to sleep	
	MS-Q3. Use of sleeping pills	Confounding Factors [MSQ_Cof]
	MS-Q4. Sleep during the day	
	MS-Q6. Snore	Physiological Factors [MSQ-Phy]
	MS-Q7. Wake up and go back to sleep	
	MS-Q10. Restless sleep	
	MS-Q5. Waking up tired in the morning	Insomnia Consequences [MSQ_Conq]
	MS-Q8. Wake up with a headache	
	MS-Q9. Tiredness for no apparent reason	

Pre-processing of the Data

The data were anonymized to ensure blinding. Initially, those with missing values were omitted, which resulted in 112 and 134 session-wised questionnaires from the first and second studies, respectively. The datasets were then aggregated and segmented based on the insomnia severity stage. For insomnia, scores of the MSQ-questionnaire lower than 30 (MSQ-R $<$ 30; mild to moderate sleep difficulties) were labeled as Neutral insomnia, and MSQ-R $\geq$ 30 (severe sleep difficulty) were denoted Clinical insomnia (Natale et al., 2014). Such segmentations provided two sub-datasets (Neutral Insomnia, and Clinical Insomnia) for the statistical analysis. **Figure 2** illustrates the correlation matrix of the variables in the mediator model.

Statistical Analysis

Every segment of the dataset was tested for multicollinearity/autocorrelation by the Durbin-Watson test and showed independence in residuals in general. SPSS v.26 and PROCESS macro (Hayes, 2017) were used for the data analysis. Within the macro, customized models and 5.000 bias-corrected bootstrap samples were set for all tests with the fixed random-seed ("*12020*"). A 95% confidence level was chosen, with significance at for $P < 0.05$ was set. A hierarchical regression analysis investigated the evidence for insomnia CCF within the data-segments, and multiple mediation models were constructed for determining the mediating effects of insomnia-related cognitive items and emotional factors for insomnia. PROCESS macro generated standard errors, *P*-values, and confidence intervals for direct effects, as well as bootstrap confidence intervals for conditional indirect effects.

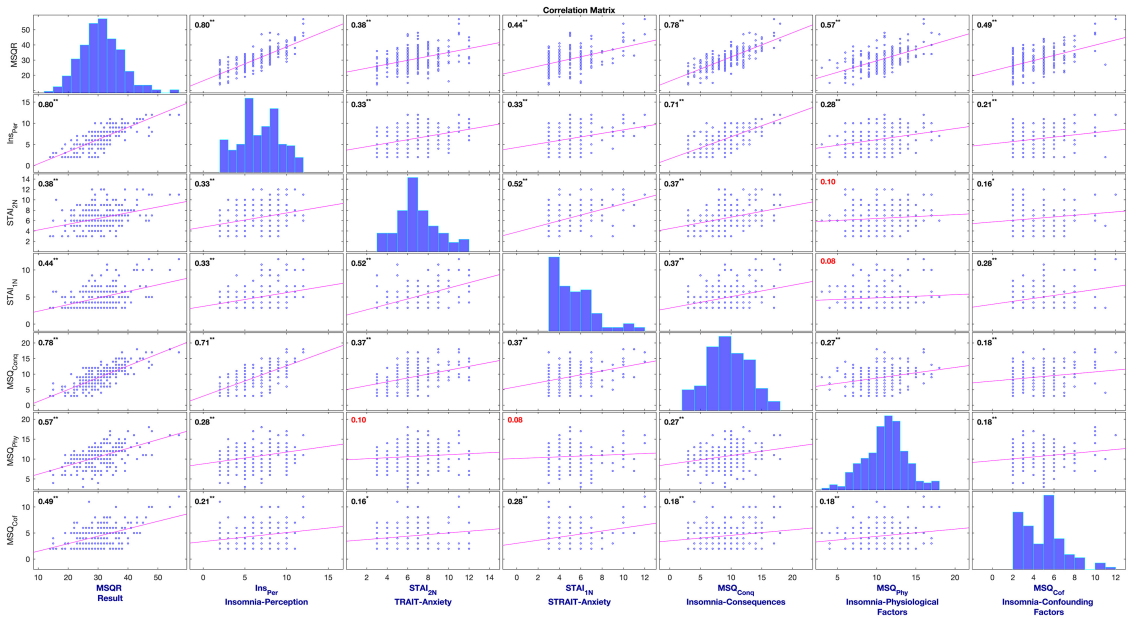

FIGURE 2 | Correlation Matrix of variables used in the multi-mediation model of insomnia to support CCF of insomnia.

Datasets and analyzed details are available on "Zenodo" repository with the DOI: http://doi.org/10.5281/zenodo.4145224.

Fundamental Ideas and Postulations for Mediator Models

- Insomnia-perception-factors (Ins_Per) variable contains difficulty in sleep initiation and maintenance.
- The employed dataset was unable to test hypotheses related to the distorted perception of sleep quality.

Proposed Mediator Model

The insomnia mediator model aims to illustrate that negative *trait-anxiety* can affect the perception of deficits in sleep quality. Concurrently, *Insomnia-perception-factors* can directly or through *state-anxiety* affect *insomnia consequences*. The insomnia model is depicted in **Figure 3**.

Several studies introduced trait-anxiety as an important predisposing factor for both the development and maintenance of insomnia (Sadigh et al., 2014; Bavafa et al., 2018; Lauriola et al., 2019). Harvey (2002) argued that anxious individuals tend to interpret ambiguous situations in a threat-related fashion which, in turn, promotes over-thinking about sleep-related threat cues. This process maintains individuals in a cognitively aroused state which is in contradiction to the relaxed state needed for getting to sleep (Harvey, 2002; Lancee et al., 2017a).

RESULTS

Multi-mediation regression analysis with the conventional least-squares method revealed that trait-anxiety can only indirectly influence the insomnia consequences. As shown in **Figure 3** and **Table 2**, in the full-dataset, trait-anxiety can lead to insomnia consequences through either insomnia perception, or cascade mediators from insomnia perception to state-anxiety. The 95% confidence interval of bootstrap results revealed "***Ind-1***" [$I_{01} \times I_{10} = 0.303$] and "***Ind-2***" [$I_{01} \times I_{12} \times I_{20} = 0.025$] were significantly different from zero (0.183–0.432) and (0.006–0.057), respectively, but there was not enough evidence for trait-anxiety ($I_{c'} = 0.088$, $P = 0.32$) that might directly lead to insomnia consequences.

According to **Table 3**, trait-anxiety in the Clinical insomnia segment leads to insomnia consequences only through insomnia perception. The 95% confidence interval of bootstrap results revealed a significant difference in "***Ind-1***" [$I_{01} \times I_{10} = 0.161$] different from zero (0.040–0.311), but not in "***Ind-2***." Moreover, there was not enough evidence of trait-anxiety ($I_{c'} = 0.2$, P-value = 0.104) might directly lead to insomnia consequences.

Table 4 shows trait-anxiety neither directly, nor indirectly can lead to insomnia consequences within the Neutral insomnia segment.

Clinical Implications

Insomnia *per se* is a clinical issue with short-term and long-term consequences affecting both physiological and psychological systems. It has been associated (at least partly in terms of duration and severity) with increasing the incidence and worsening the state of many pre-existing clinical conditions (Schutte-Rodin et al., 2008). Hence, the need for formulating a conceptual and concurrently pragmatic framework toward an individualized approach for people suffering from insomnia.

The proposed CCF, together with insomnia mediator models, explained the contribution of cognitive processes to the

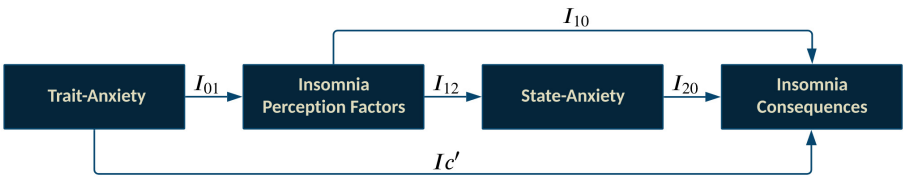

FIGURE 3 | Insomnia mediator model includes the direct effect of trait-anxiety on Insomnia consequences ($I_{c'}$); *Ind-1* [$I_{01} \rightarrow I_{10}$]: Trait-anxiety → Insomnia perception factors → Insomnia consequences;

Ind-2 [$I_{01} \rightarrow I_{12} \rightarrow I_{20}$]: Trait-anxiety → Insomnia perception factors→ State-anxiety→ Insomnia consequences;
Covariates: Confounding factors and Physiological problems.

development and maintenance of clinical insomnia. The CCF proposes the following predictions and target-oriented clinical implications:

Decreasing Attentional Bias

Conceptual cognitive framework predicts that attentional bias modification (ABM) training can decrease the attentional bias to insomnia. In practice, the ABM treatment encourages the insomniacs to shift attention away from the negative sleep-related words toward a neutral one, thus reducing attention bias toward sleep-related threatening cue. Such a simple task enables patients to consciously and repeatedly select unbiased information over negative information, thereby progressively help to develop a tendency to not focus on negative information related to insomnia in their daily life (Clarke et al., 2016).

Milkins et al. (2016) conducted a crossover study in which 18 insomniacs alternatively fulfilled an ABM task and a non-ABM control task before sleep across six successive nights. At nights on which the subjects performed the ABM task, they reported shorter sleep-onset latencies and lower pre-sleep worry, than the nights on which they performed the control task. Likewise, in a parallel design (Clarke et al., 2016), 36 students with sleep

TABLE 2 | Mediator model of insomnia in full-dataset.

Paths and Effects	Coefficient	SE	*t*	LLCI	ULCI
Effect of trait-anxiety on insomnia perception factors (I_{01} path)	0.363	0.074	4.891	0.217	0.509
Covariate: Effect of confounding factors on insomnia perception factors	0.164	0.075	2.194	0.017	0.311
Covariate: Effect of physiological problems on insomnia perception factors	0.219	0.056	3.903	0.109	0.330
Effect of insomnia perception factors on insomnia consequences (I_{10} path)	0.835	0.068	12.308	0.701	0.968
Effect of insomnia perception factors on state-anxiety (I_{12} path)	0.239	0.051	4.709	0.139	0.339
Covariate: Effect of confounding factors on state-anxiety	0.241	0.060	4.015	0.123	0.360
Effect of state-anxiety on insomnia consequences (I_{20} path)	0.292	0.094	3.120	0.108	0.476
Direct effect					
Effect of trait-anxiety on insomnia consequences ($I_{c'}$ path) [*P*-value = 0.32]	0.088	0.089	0.997	−0.086	0.263
Bootstrap results for indirect effects					
Seed number "12020" Bootstrap samples "5000"	**Bootstrap estimate**		**95% confidence interval**		
	Effect	**SE**	**Lower**	**Upper**	
Total indirect effect	0.328	0.072	0.196	0.473	
"***Ind-1***": $I_{01} \rightarrow I_{10}$	0.303	0.064	0.183	0.432	
"***Ind-2***": $I_{01} \rightarrow I_{12} \rightarrow I_{20}$	0.025	0.013	0.006	0.057	

TABLE 3 | Mediator model of insomnia in clinical insomnia segment.

Paths and Effects	Coefficient	SE	*t*	LLCI	ULCI
Effect of trait-anxiety on insomnia perception factors (I_{01} path)	0.223	0.090	2.480	0.045	0.401
Effect of insomnia perception factors on insomnia consequences (I_{10} path)	0.723	0.105	6.863	0.514	0.931
Effect of insomnia perception factors on state-anxiety (I_{12} path)	0.227	0.092	2.456	0.044	0.410
Covariate: Effect of confounding factors on state-anxiety	0.254	0.086	2.950	0.084	0.425
Effect of state-anxiety on insomnia consequences (I_{20} path)	0.230	0.114	2.013	0.004	0.455
Direct effect					
Effect of trait-anxiety on insomnia consequences ($I_{c'}$ path) [*P*-value = 0.104]	0.200	0.122	1.637	−0.042	0.442
Bootstrap results for indirect effects					
Seed number "12020" Bootstrap samples "5000"	**Bootstrap estimate**		**95% confidence interval**		
	Effect	**SE**	**Lower**	**Upper**	
Total indirect effect	0.173	0.078	0.042	0.344	
"***Ind-1***": $I_{01} \rightarrow I_{10}$	0.161	0.069	0.040	0.311	
"***Ind-2***": $I_{01} \rightarrow I_{12} \rightarrow I_{20}$	0.012	0.012	−0.000	0.046	

TABLE 4 | Mediator model of insomnia in neutral insomnia segment.

Paths and Effects	Coefficient	SE	*t*	LLCI	ULCI
Effect of trait-anxiety on insomnia perception factors (I_{01} path)	0.177	0.109	1.622	−0.042	0.396
Effect of insomnia perception factors on insomnia consequences (I_{10} path)	0.881	0.188	4.681	0.503	1.259
Effect of insomnia perception factors on state-anxiety (I_{12} path)	0.095	0.113	0.840	−0.131	0.320
Effect of state-anxiety on insomnia consequences (I_{20} path)	0.370	0.271	1.365	−0.175	0.914
Direct effect					
Effect of trait-anxiety on insomnia consequences ($I_{c'}$ path) [*P*-value = 0.626]	−0.088	0.178	−0.491	−0.446	0.271
Bootstrap results for indirect effects					
Seed number "12020" Bootstrap samples "5000"	**Bootstrap estimate**		**95% confidence interval**		
	Effect	**SE**	**Lower**	**Upper**	
Total indirect effect	0.162	0.126	−0.038	0.456	
"***Ind-1***": $I_{01} \rightarrow I_{10}$	0.156	0.119	−0.039	0.433	
"***Ind-2***": $I_{01} \rightarrow I_{12} \rightarrow I_{20}$	0.006	0.015	−0.007	0.049	

problems underwent ABM or control training sessions across five nights. Compared with the control condition, subjects who underwent ABM training reported less pre-sleep arousal, fell asleep faster, woke less often during the night, reported better overall sleep quality, and had significant reductions in sleep-related anxiety (Clarke et al., 2016). These findings support the above-mentioned proposition.

In contrast, the results of Lancee et al. (2017b) showed no added benefit of the ABM training over the placebo training on sleep-related indices and outcome measures. The authors believe it was probably due to the absence of attentional bias at baseline and hence no change could be deduced after training (Lancee et al., 2017b).

Employing Attention-Distraction Techniques Can Help Deviate Attention From Concerns-Relevant Topics to Neutral Ones

Addressing the issue of attentional bias toward relevant topics, Haynes et al. (1981) observed that engagement with a challenging mental arithmetic problem reduced subjective sleep latency among insomniacs (Haynes et al., 1981). Similarly, practicing crossword puzzles, reading, and listening to audiobooks could provide sufficient distraction so that the patient would no longer attend to or think about their inability to sleep. Troxel et al. (2012) recommended patients should keep doing those activities until they feel sleepy enough to return to bed. And, if they cannot fall asleep after returning to bed, the process should be repeated (Troxel et al., 2012).

Preventing Annoyance and Distress-Reaction

Conceptual cognitive framework draws attention to the crucial role of appraisal and ECL mechanisms in reducing negative cognitive and emotional value.

Cognitive-behavioral therapy (CBT) to reduce the negative cognitive-value related to insomnia

Sleep difficulties are commonly accompanied by dysfunctional beliefs, unrealistic expectations, and worries, which contribute to distress and maladaptive sleep habits producing an anxious state opposite to the relaxation required for sleeping. Therefore, patients' beliefs regarding sleep and insomnia must be explored and attempts be made to change them eventually. Cognitive therapy aims at the identification of dysfunctional beliefs and attitudes related to sleep and their replacement with more adaptive substitutes. Cognitive therapies also address catastrophizing the consequences of poor sleep to help patients reconceptualize the realities of their beliefs, thereby reducing the upcoming distress and arousal that impedes sleeping (Perlis et al., 2006). Through cognitive-behavioral therapy (CBT) a combination of cognitive reconstruction and behavioral techniques are delivered to encourage patients to develop more adaptive coping skills and stop self-criticizing (Perlis et al., 2006). The European guideline for diagnosis and treatment of insomnia (Riemann et al., 2017) recommends CBT for insomnia (CBT-I) as the first-line of treatment for chronic insomnia.

Furthermore, several systematic reviews and meta-analyses (Taylor and Pruiksma, 2014; Mitchell et al., 2019) have reported strong empirical support for CBT-I on different subjective and objective sleep parameters. CBT-I's common approaches for non-comorbid insomnia were cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation. The results indicated that CBT-I improved sleep onset latency, wake after sleep onset, total sleep time, and sleep efficiency. The changes persisted over time alleviating the symptoms (Wang et al., 2005; Trauer et al., 2015).

Mindfulness-based cognitive therapy (MBCT) for reducing the negative cognitive and emotional value related to insomnia

Mindfulness-based cognitive therapy (MBCT), as an emotion-regulation based psychotherapy, is a purposeful and unbiased form of therapy directing attention to the present moment as a way of self-regulation that promotes mind-body relaxation (Ludwig and Kabat-Zinn, 2008). The approach educates people toward changing their relationship with their thoughts and negative emotions. Patients must be aware of their thoughts and are inspired to take a non-judgmental perspective on them rather than a negative, self-referential assessment that intensifies both negative thoughts and emotions (Ludwig and Kabat-Zinn, 2008). In concordance with suggestions put forth by the CCF, Shallcross and Visvanathan (2016) have explained that experiential awareness, attentional control, and acceptance techniques used in MBCT interventions improve rumination, arousal, selective attention, and the distorted perception involved in the development and maintenance of insomnia (Shallcross and Visvanathan, 2016).

The MBCT protocol tailored for insomniacs showed significant pre–post improvements in self-reported total sleep time and various thought-control domains, along with reductions in sleep-related monitoring and worry (Heidenreich et al., 2006). MBCT was also effective for individuals with a history of depression or anxiety accompanied by sleep difficulty or insomnia (Ree and Craigie, 2007; Yook et al., 2008; Britton et al., 2010). Ree and Craigie (2007) reported decreased scores of insomnia severity symptoms lasting for about 3 months with the MBCT. Similarly, MBCT protocol in older adults showed a 14.5% improvement in self-reported sleep problems (Foulk et al., 2014). Self-regulation of attention and orientation to experience to achieve better sleep are the proposed mechanisms of actions for MBCT (Larouche et al., 2014). A recent comprehensive meta-analysis reported significantly improved insomnia symptoms as measured by the Pittsburgh Sleep Quality Index (Wang et al., 2020).

ECL mechanism for modifications in negative emotional-value related to insomnia

Positive emotion-induction techniques can reduce the negative valence of insomnia when paired with positively valenced and high arousal pictures, films (Uhrig et al., 2016), audio (Bergman et al., 2016), music, and video clips (Lazar and Pearlman-Avnion, 2014; Siedlecka and Denson, 2019). Game-like design, app-based format, goggles of virtual reality, or a screen are different ways to present stimuli to provide cost-effective home-based individualized treatments.

Rectifying the Distorted Perception of the Quality of Sleep Deficit

Digital-technology approaches are believed to provide an online measurement of sleep duration and correct the distorted perception of sleep deficit. Since we have established that negative emotions might influence the perception of insomniacs about their sleep deficit, interventions aiming at emotion-regulation or modifications of dysfunctional beliefs may help prevent the formation of the distorted perception. Furthermore, Holter monitoring of rest/activity cycle of sleep, smartphone gadgets (Izmailova et al., 2018), actigraphy, and sleep diary (Tang and Harvey, 2004b) might help insomniacs correct misperception. In contrast, parts of the literature studying the time-perception concept (Thomas and Cantor, 1975, 1976) have revealed that when more information is processed, time is perceived as longer. A high level of cognitive arousal and repetitive thought patterns distorts time perception for insomniacs, leading to an overestimation of sleep onset latency (Tang and Harvey, 2004a). Another implication is that during sleep onset, cognitive arousal maintains an enhanced sensory and memory processing level obscuring the distinction between sleep and wakefulness (Perlis et al., 1997).

Future Trends

The clinical recommendations provided in this paper can be applied separately or in combination, to plan treatment for individuals with insomnia. The CCF builds upon a general assumption that patients should be consciously and actively involved in the rehabilitation process. Subsequently, new treatments can be developed aimed at encouraging patients to be consciously aware of their negative thoughts related to sleep-difficulty and contingencies for intervention. Moreover, the inclusion of surrogate measurements is recommended for guaranteeing the patient's conscious attended-awareness. Collectively, the CCF can provide a decision-support platform for clinicians to deliver more targeted interventions, and eventually, the methodologies suggested can provide a reliable platform to build a CCF for other cognitive disorders and support the causal clinical data models. This novel approach can improve our knowledge of psychological disturbances and complex comorbidities toward the design of rehabilitation interventions and suggestions in line with the "preventive medicine" policies.

Limitation

The CCF of insomnia, its predictions, and the corresponding suggested interventions do not include patients with organic sleep disorders, general cognitive distortion, and psychotic problems. MSQ was obtained from patients with complaints of tinnitus at the clinic during the day, and not before sleep. Despite their importance, daytime cognitive processes were not taken into account in the presented framework. Lastly, to achieve clinical endpoints, repeated measures and longitudinal studies are required to improve predictabilities.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during this study are available from the corresponding author on reasonable request and filling out NEL-Consent redirecting to "Zenodo" with the DOI: http://doi.org/10.5281/zenodo.4145224.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee for Analysis of Research Projects, Specialized Center of Otorhinolaryngology and Speech Therapy, Hospital das Clínicas de Ribeirão Preto, University of São Paulo, Brazil (HCRP no. 55716616.1.1001.5440, and HCRP no. 09813519.1.0000.5440; internationally registered with U1111-1236-5441). All subjects gave written informed consent prior to participation in the study.

AUTHOR CONTRIBUTIONS

ZV: leading author responsible for manuscript development, concept and study design, conceptual modeling participation, and data acquisition in the clinic. MN: collaborating in manuscript development and concept. JL: supervising clinical data acquisition and conceptual development, and collaborating in manuscript development. AD: collaborating in manuscript development and supervising data mining and modeling. MH: monitoring clinical

data acquisition, and collaborating in manuscript development. IG: manuscript development, concept and study design, analogy, numerical methodology design and implementation, and data acquisition, and data pre-processing. All authors read and approved the final manuscript.

FUNDING

This research is part of a Multidisciplinary Cognitive Rehabilitation (MCR) Platform and was supported (Grant number: 2013/07375-0) by Innovation and Diffusion of Mathematical Sciences Center Applied to Industry (CEPID-CeMEAI) of São Paulo Research Foundation (FAPESP). It also supported with Centro de Engenharia Aplicada a Saúde (CEAS) of the University of São Paulo, and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for student's scholarship.

ACKNOWLEDGMENTS

The authors would like to appreciate all efforts of employees and clinicians in CEOF who supported the current study voluntarily.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

REVIEW
published: 07 October 2021
doi: 10.3389/fnins.2021.751730

New and Emerging Approaches to Better Define Sleep Disruption and Its Consequences

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Current approaches to quantify and diagnose sleep disorders and circadian rhythm disruption are imprecise, laborious, and often do not relate well to key clinical and health outcomes. Newer emerging approaches that aim to overcome the practical and technical constraints of current sleep metrics have considerable potential to better explain sleep disorder pathophysiology and thus to more precisely align diagnostic, treatment and management approaches to underlying pathology. These include more fine-grained and continuous EEG signal feature detection and novel oxygenation metrics to better encapsulate hypoxia duration, frequency, and magnitude readily possible via more advanced data acquisition and scoring algorithm approaches. Recent technological advances may also soon facilitate simple assessment of circadian rhythm physiology at home to enable sleep disorder diagnostics even for "non-circadian rhythm" sleep disorders, such as chronic insomnia and sleep apnea, which in many cases also include a circadian disruption component. Bringing these novel approaches into the clinic and the home settings should be a priority for the field. Modern sleep tracking technology can also further facilitate the transition of sleep diagnostics from the laboratory to the home, where environmental factors such as noise and light could usefully inform clinical decision-making. The "endpoint" of these new and emerging assessments will be better targeted therapies that directly address underlying sleep disorder pathophysiology via an individualized, precision medicine approach. This review outlines the current state-of-the-art in sleep and circadian monitoring and diagnostics and covers several new and emerging approaches to better define sleep disruption and its consequences.

Keywords: sleep disordered breathing, sleep apnea, insomnia, circadian rhythm, polysomnography, signal processing, apnea/hypopnea index, precision medicine

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *01 August 2021*
Accepted: *16 September 2021*
Published: *07 October 2021*

Citation:
Lechat B, Scott H, Naik G, Hansen K, Nguyen DP, Vakulin A, Catcheside P and Eckert DJ (2021) New and Emerging Approaches to Better Define Sleep Disruption and Its Consequences. Front. Neurosci. 15:751730. doi: 10.3389/fnins.2021.751730

INTRODUCTION

Sleep, along with diet and exercise, is essential for optimal health and wellbeing. However, globally, nearly 2 billion people are estimated to have one or both of the two most common clinical sleep disorders–sleep apnea (Benjafield et al., 2019) and insomnia (Roth et al., 2011). Most people with sleep disorders remain undiagnosed and untreated, and thus vulnerable to the major adverse health and safety consequences associated with untreated sleep disorders.

Current sleep apnea diagnostic approaches rely on traditional labor-intensive overnight sleep tests and subjective manual scoring approaches developed around the constraints of paper-based methods from the 1960's. This approach, in combination with the advent of continuous positive airway pressure (CPAP) to reverse airway collapse during sleep (Sullivan et al., 1981), led to rapid advances in the modern field of sleep medicine. Although efficacious irrespective of underlying mechanisms, sub-optimal patient acceptance and use of CPAP remain problematic and warrant personalized treatments that better target underlying causal mechanisms. However, traditional sleep assessment methods fail to identify the specific underlying causes and consequences of sleep disorders for individual patients. For example, relationships between perceived sleep quality and/or sleepiness and objective sleep measures derived from traditional gold-standard polysomnography are either absent, weak, or inconsistent (Buysse et al., 2008; Sforza et al., 2015; Adams et al., 2016). In the case of insomnia, diagnosis relies on clinical evaluation since traditional objective sleep measures do not relate to disorder incidence, severity, or recovery. While the gold standard treatment, cognitive behavioral therapy for insomnia (CBT-I) is efficacious for many, it is ineffective or only partially effective for some patients (Trauer et al., 2015). This is potentially because, like CPAP for sleep apnea, CBT-I is a one-size-fits-all treatment regardless of the underlying causal mechanisms (Harvey and Tang, 2003). As such, usual care for sleep disorders typically relies on a trial-and-error treatment approach which often fails to identify the underlying causes of sleep disruption or adequately address patient symptoms and health consequences for which individuals seek treatment. Accordingly, this review focuses on highlighting new and emerging approaches to better define sleep and circadian disruption that underpins sleep disorders based on their underlying pathophysiology and accompanying health impacts.

CURRENT STATE OF THE ART FOR SLEEP RECORDING

Current gold-standard methodology to quantify sleep relies on overnight polysomnographic (PSG) recordings. This includes collection of a wealth of neurophysiological data from electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), body position and movement, and respiratory-related signals including airflow, chest and abdominal motion, and oximetry. These signals are then manually reviewed and analyzed to classify wake, light through to deep non-rapid eye movement (NREM) (N1, N2, and N3), and rapid eye movement (REM) sleep in 30-s epochs. Transient cortical arousals (3–15 s) and longer awakening (>15 s) events are also manually scored on the basis of internationally standardized American Academy of Sleep Medicine (AASM) EEG criteria (Berry et al., 2017).

Traditional polysomnography scoring evolved from observations of behavioral responsiveness changes coincident with changes in EEG patterns of activity at a time when chart recorders necessitated manual scoring, quite literally page-by-30-s-page (Rechtschaffen, 1968). This pattern-matching "bottom-up" approach to sleep medicine was based on the practical constraints with the technology available at the time, rather than being driven by an understanding of underlying sleep neurobiology. Although computerized systems have replaced paper-based recordings, and despite exponential advances in modern computing, sleep medicine remains predominantly based on these manual scoring methods from the 1960s. Manual scoring is labor intensive, and therefore costly, and captures only gross visually discernible EEG features with much poorer time and frequency resolution than is available within the data (**Figure 1**). Thus, EEG scoring into discrete 30-s epochs ignores that wake and sleep are continuous and dynamic states, whereby physiological features within epochs classified as wake can be present during sleep, and vice versa (Prerau et al., 2014; Scott et al., 2020). Manual scoring also has large intra- and inter-scorer variability, which remains problematic in sleep medicine despite AASM scoring criteria updates that attempt to reduce scoring variability (Ruehland et al., 2009; Magalang et al., 2013).

A New Way of Thinking: Top-Down Sleep Signal Features Based on Underlying Neurobiology Rather Than Bottom-Up Measurement Convenience Guided Approaches

Automated sleep scoring methods using advanced signal processing and machine learning approaches to analyze polysomnography signals have been widely developed and can achieve good agreement against consensus-based traditional human scoring (Fiorillo et al., 2019). However, most of the focus has been on reproducing existing manual approaches (Tsinalis et al., 2016; Supratak et al., 2017; Chambon et al., 2018; Olesen et al., 2021). Thus, while these approaches are more standardized and time efficient, the fundamental limitations of traditional sleep metrics remain. Robust evidence to support causal relationships and clinical utility of most existing sleep metrics also remains sparse. Thus, the finer-grained quantifiable features within polysomnography data that may ultimately be more informative regarding underlying sleep mechanisms and quality continue to be largely ignored.

For example, EEG delta waves are tightly coupled in time and precede pulsatile changes in cerebral blood volume and cerebrospinal fluid flow during deep sleep (Fultz et al., 2019). Furthermore, a single night without sleep in healthy volunteers leads to β-amyloid accumulation (Shokri-Kojori et al., 2018). These findings support that delta waves during deep NREM sleep are a major driver of glymphatic clearance of metabolites from the central nervous system (Benveniste et al., 2020; Braun and Iliff, 2020). Wake/sleep transitions, such as potentially fatal microsleeps while driving, and a range of other physiological changes during sleep also occur on shorter timescales than assessed through traditional manual sleep scoring methods. For example, traditional scoring most likely misses potentially clinically informative neurophysiological features of synaptic downscaling, re-organization, memory and learning processes thought to occur during NREM and

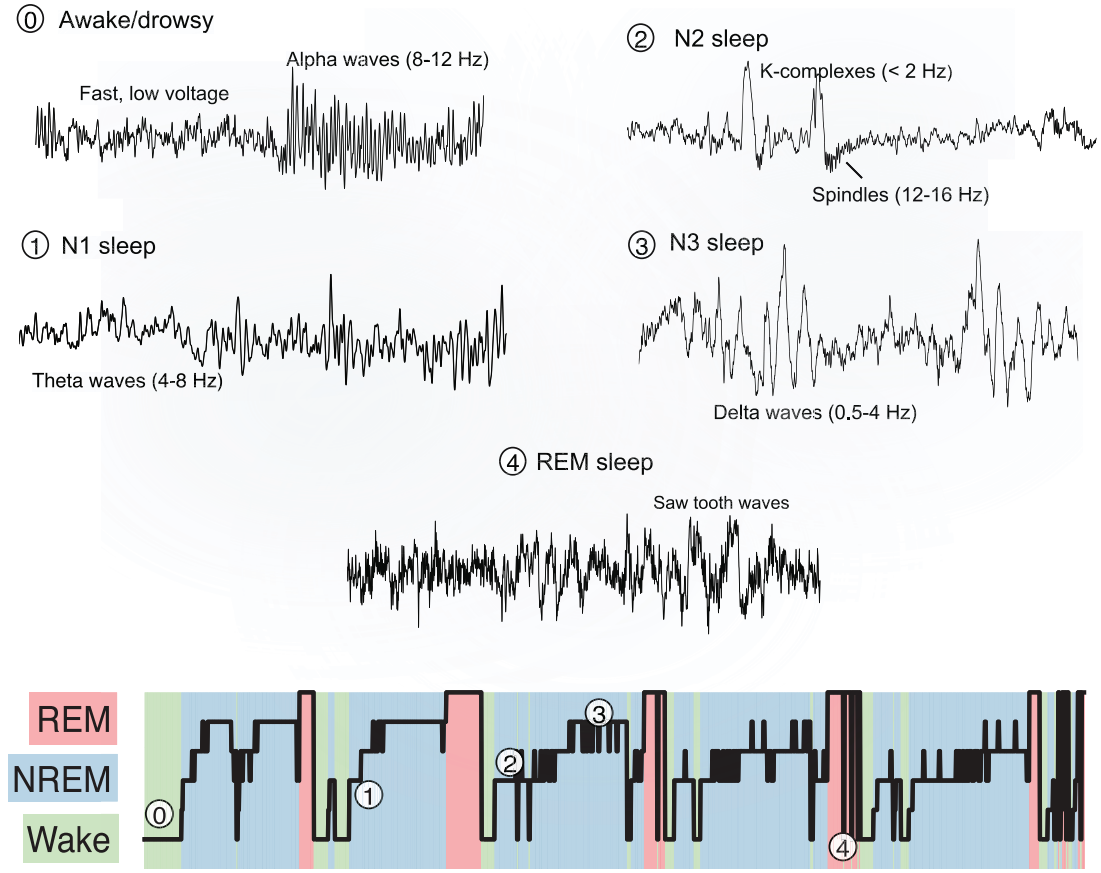

FIGURE 1 | Electroencephalography activity during sleep.

REM sleep (Tononi and Cirelli, 2006). Thus, conventional sleep scoring can only provide relatively superficial insights into brain activity and other physiological changes during sleep that are unlikely to be as sensitive or specific to underlying mechanisms as shorter-time scale features of sleep. Accordingly, a more physiologically guided, top-down measurement approach is clearly needed to provide greater neurobiological insight into sleep health and disease, and how sleep disturbance features relate to clinically relevant outcomes (Léger et al., 2018).

Defining evidence-based electrophysiological sleep markers is important in the age of precision medicine, particularly following rapid growth in minimally intrusive recording and consumer wearable devices that allow for sleep-related monitoring over prolonged periods in the home environment (Liu et al., 2017; Kim et al., 2019). These and other emerging technologies are likely to change many aspects of polysomnography, such as via printed electrodes (Norton et al., 2015) or tripolar concentric ring EEG (Besio et al., 2006), by helping to uncover aspects of sleep health not routinely measured. For example, markers of circadian misalignment are technically difficult to monitor, so remain notably absent from conventional sleep studies. Emerging evidence highlights the potential to estimate circadian phase using non-intrusive physiological data such as skin temperature, heart rate variability and activity (Suárez et al., 2020; Cheng et al., 2021). Blood pressure surges along with vasoconstriction and heart rate responses occur frequently during sleep, especially with swallowing (Burke et al., 2020), but are not currently routinely captured or assessed. Continuous measurement of a range of biomarkers such as cortisol secretion during sleep through skin sensor devices (Parlak et al., 2018) may also have clinical utility.

Together, a range of new and emerging devices could routinely generate large volumes of sleep measurements over extended periods. This approach will require evidence to support clinical use and value, and software tools to assist clinicians to assess, analyze, and interpret sleep-omics (Redline and Purcell, 2021). To increase the uptake of new technologies in research and clinical settings, greater communication between sleep medicine experts and device manufacturers is needed. Rigorous standards for validation and evidence-based advances in medicine are required to ensure that new methods provide clinically useful insights that effectively and cost-effectively improve key patient outcomes (Depner et al., 2020). While not a complete list of all available approaches, the sections below highlight several examples of existing approaches and notable promising new and emerging methods based on underlying pathophysiology/neurobiology to move beyond key limitations of current sleep metrics.

A schematic representation of some of these examples is provided in **Figure 2**.

KEY COMPONENTS OF THE POLYSOMNOGRAPHIC

Electroencephalography

This review focuses on novel sleep metrics derived from EEG collected clinically using routine polysomnography. Other reviews regarding potential neurobiological insights of sleep physiology and circadian rhythms through high density EEG and intra-cranial/depth EEG are available elsewhere (Mosqueiro et al., 2014; Saper and Fuller, 2017; Scammell et al., 2017).

Slow Waves

Slow waves (0.5–4.5 Hz) are the main feature of deep sleep and one of the fundamental electrophysiological features of synchronous neuronal "down states" of relative neuronal inactivity and "up states" as activity resumes (Nir et al., 2011). These waves are thought to play a major role in synaptic recovery and down-scaling to compensate for daily high neuronal activity

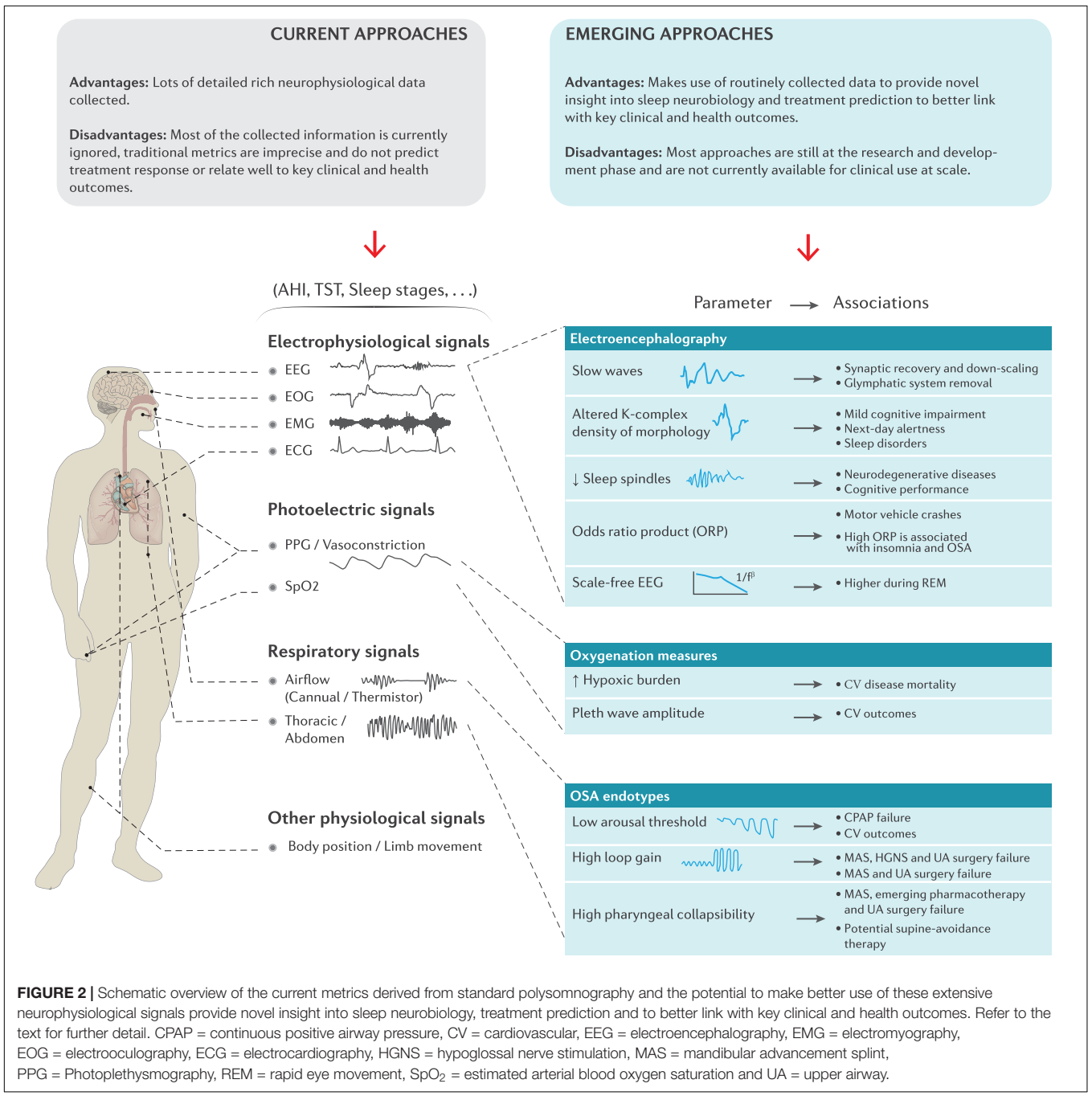

FIGURE 2 | Schematic overview of the current metrics derived from standard polysomnography and the potential to make better use of these extensive neurophysiological signals provide novel insight into sleep neurobiology, treatment prediction and to better link with key clinical and health outcomes. Refer to the text for further detail. CPAP = continuous positive airway pressure, CV = cardiovascular, EEG = electroencephalography, EMG = electromyography, EOG = electrooculography, ECG = electrocardiography, HGNS = hypoglossal nerve stimulation, MAS = mandibular advancement splint, PPG = Photoplethysmography, REM = rapid eye movement, SpO_2 = estimated arterial blood oxygen saturation and UA = upper airway.

and synaptic potentiation during wake (Tononi and Cirelli, 2006) and glymphatic system removal of metabolic waste products from the central nervous system (Benveniste et al., 2020; Braun and Iliff, 2020). Slow waves are ubiquitous during sleep, and decrease in quantity and magnitude with age (Chinoy et al., 2014). Several techniques have been developed to study specific aspects of slow waves, such as slow wave slope, absolute power, amplitude and phase in response to a range of experimental or naturalistic (e.g., aging) conditions (Massimini et al., 2004; Bersagliere and Achermann, 2010; Lazar et al., 2015; Lendner et al., 2020; Djonlagic et al., 2021). For example, the slope of half slow-waves (i.e., the slope between the up- and down-states) and slow wave amplitude/absolute power increase with sleep restriction and decrease with circadian phase, suggesting that sleep need and circadian rhythms have an effect on the shape and distribution of slow oscillations (Massimini et al., 2004; Bersagliere and Achermann, 2010; Lazar et al., 2015). Using the same features, reduced slow oscillations during sleep (low amplitude/absolute power) have recently been associated with poorer cognitive performance on a digit symbol coding test and the Trails B test in a large cross-sectional study of ∼3800 participants (Djonlagic et al., 2021). Many of these tools are available in open-source packages. With standardization, clinical validation and implementation, these novel metrics have substantial potential to provide unique insight into inter-individual vulnerability to specific health consequences in people with sleep disruption (Léger et al., 2018).

K-complexes

K-complexes are a form of isolated slow waves that provide unique insight into sleep stability and sleep disruption. They can occur spontaneously during sleep. However, K-complexes can also provide a sensitive marker of sensory disturbance to noise, respiratory and vibratory stimuli during sleep (Colrain, 2005; Scott et al., 2020; Lechat et al., 2021). Abnormal K-complex morphology (lower amplitude) and lower K-complex density (# per minutes) have been associated with the progression of amnestic mild cognitive impairment (pre-clinical phase of Alzheimer's disease) in ∼70 patients (Liu et al., 2020). Abnormal K-complex morphology has also been associated with greater lapses in next-day alertness as measured using a psychomotor vigilance task (Parekh et al., 2019, 2021). At a population level, cross-sectional studies have suggested that a decrease in K-complex density may be a biomarker of sleep disorders, such as sleep apnea (Lechat et al., 2020). Further evidence regarding the functional significance of K-complexes is still emerging and warrants future investigation. This is likely to be facilitated via recent open-source tool developments (Parekh et al., 2015; Lechat et al., 2020).

Sleep Spindles

Sleep spindles are bursts of 11–15 Hz EEG activity and are another characteristic feature of NREM sleep that may provide a useful biomarker of sleep regulation and cognitive functioning (Diekelmann and Born, 2010; Djonlagic et al., 2021). Sleep spindles are influenced by genetics and vary widely across the lifespan and different demographics (Purcell et al., 2017). Higher spindle occurrence (and density) have been associated with better memory performance and vigilance (Lafortune et al., 2014; Hennies et al., 2016) in cross-sectional studies with moderate sample sizes ($n < 100$). In a clinical population of 47 patients with obstructive sleep apnea (OSA), greater sleep spindle activity was associated with better implicit learning (Stevens et al., 2021). A recent analysis of two large US-cohorts (n∼3800) also supported an association between higher spindle occurrence and spindle power with greater performance on multiple cognitive tests (Djonlagic et al., 2021). In addition, the coupling (proximity and phase differences) between slow oscillations and spindles was also predictive of cognitive performance, further supporting a role of spindles in memory formation (Hahn et al., 2020) and consolidation (Helfrich et al., 2019; Muehlroth et al., 2019). Together, these results may explain, at least in part, the association between abnormal spindle activity during sleep and neurodegenerative diseases such as Alzheimer's disease (Gorgoni et al., 2016) and Parkinson's diseases (Christensen et al., 2015). However, spindle detection is still a challenge and algorithm refinements on public benchmark datasets remain warranted (Warby et al., 2014; Lacourse et al., 2020). Furthermore, recent evidence suggests that the current definition of sleep spindles may be too restrictive and traditionally defined spindles may only be a small subset of a more generalized class of sigma oscillations during sleep (Dimitrov et al., 2021).

Fourier-Based Analysis of Sleep Signals: Quantitative Electroencephalography

Sleep EEG is ideally suited to frequency and time-frequency analysis, since different stages or micro-elements (such as spindles, K-complexes, slow waves) have specific frequency characteristics (Steriade, 2006; Scammell et al., 2017), as shown in **Figure 3**. Power spectral analysis of EEG (sometimes referred to as quantitative EEG [qEEG]) provides a more sensitive and objective marker of neurophysiological features of sleep, some of which may be unique to specific patient phenotypes. For example, several studies have used qEEG to calculate the mean absolute power of given frequency bands (delta, alpha, theta, sigma, and beta), usually averaged over NREM and REM sleep, some of which have been shown to be predictive of insomnia (Krystal et al., 2002; Krystal and Edinger, 2010; Lunsford-Avery et al., 2021; Zhao et al., 2021) and OSA (D'Rozario et al., 2017; Appleton et al., 2019). Emerging evidence also suggests that qEEG markers are associated with vigilance and cognitive performance (Vakulin et al., 2016; Djonlagic et al., 2021; Mullins et al., 2021).

The Odds Ratio Product

The odds ratio product (ORP) is a novel EEG-derived metric that provides a continuous index of sleep depth and alertness (Younes et al., 2015; Younes and Hanly, 2016). ORP is calculated as a ratio of absolute power of different frequency bands over 3-s segments. The ratio ranges from 0 to 2.5, where 0 indicates very deep sleep and 2.5 is wide awake, and correlates well with the visual appearance of EEG across the night (Younes et al., 2015, 2020). ORP derived metrics may be useful for a wide range of clinical applications, such as phenotyping sleep disorders and associated health consequences (Younes and Giannouli, 2020;

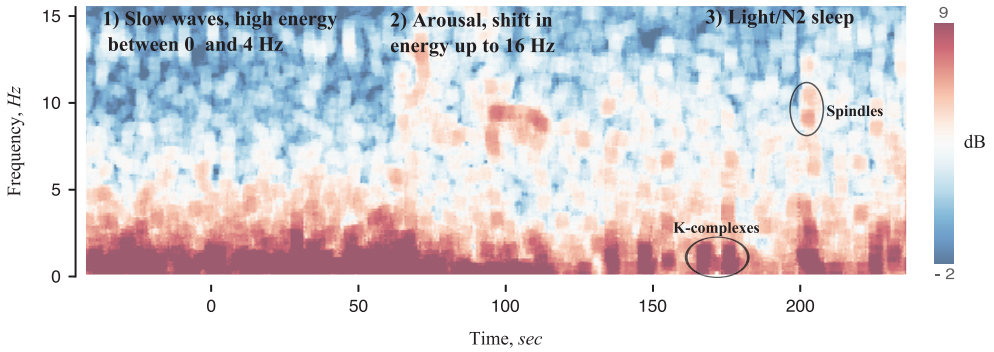

FIGURE 3 | Spectrogram of sleep EEG signals using methods developed in Prerau et al. (2017). A transition from slow wave sleep (1) to N2 sleep (3) with an arousal in the middle (2) is observed. Slow wave sleep is characterized by high absolute power at frequencies less than 4 Hz and very little power at high frequencies, thus making identification of high frequency (8–16 Hz) arousals straight-forward. The transition from arousal to N2 sleep is also very specific, with a reduction in high frequency power, a sparse low frequency burst (likely reflecting K-complexes), sometimes followed by a burst of 12–16 Hz activity.

Azarbarzin et al., 2021; Younes et al., 2021). For example, sleep depth coherence between C3 and C4 channels measured using the ORP is associated with risk of motor vehicle crashes (Azarbarzin et al., 2021). A higher ORP during NREM sleep is also associated with the presence of OSA and insomnia, consistent with a more "alert" brain during NREM sleep in people with OSA and insomnia (Younes et al., 2021).

Scale-Free/Rapid Eye Movement Biomarkers

The scale-free component of neural activity (sometimes called "background brain activity" or "1/f" activity) is a further EEG component that may be an important biomarker of arousal level in human sleep (Lendner et al., 2020). Consistent with neuronal homeostatic and synaptic reorganization activity that takes place during REM sleep, 1/f activity is higher during REM sleep episodes. This observation may be especially important given the lack of targeted metrics designed to capture key physiological features of REM sleep. Eye movements, theta waves and atonia components require further investigation to test for relationships more comprehensively against other markers of REM sleep homeostasis and key clinical outcomes.

A limitation of all current biomarkers is the reliance on traditional manual scoring to express and evaluate summary values against conventional metrics with uncertain relationships with clinical endpoints. For example, absolute delta power, or ORP values, are usually averaged in NREM sleep. Spindles may be only detected in N2 sleep, and K-complex densities calculated in N2 and N3 sleep do not consider fluctuations in neurophysiological features across sleep cycles. EEG dynamics across sleep cycles are highly likely to be regulated by physiological processes such as circadian rhythms, brain metabolism, motor control learning, and memory consolidation processes (e.g., **Figure 4**). While averaging over traditionally scored sleep stages is convenient, it likely masks more subtle and potentially functionally important sleep-dependent changes over both short (<30 s) and longer cumulative time scales (minutes or hours). Secondly, current clinical utility of these biomarkers has mainly been studied cross-sectionally. Thus, well-designed randomized trials to investigate their potential additive benefit

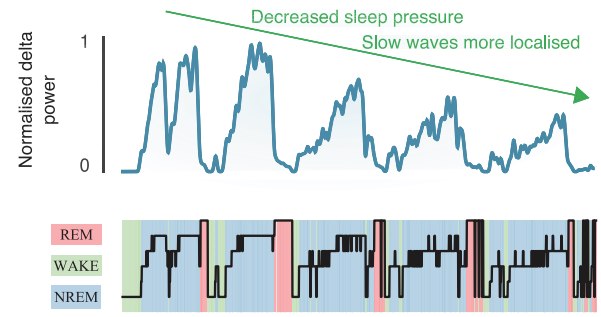

FIGURE 4 | Cyclical variation in delta power across the night.

to sleep disorders management to improve health outcomes is warranted. Thirdly, methodologies used to calculate qEEG, ORP and other more fine-grained EEG elements are not standardized across research groups. Some methods are also not available under common license terms and therefore, independent cross-validation remains challenging.

Oxygenation Measures

Pulse oximeters can continuously and minimally intrusively estimate blood hemoglobin oxygen saturation (SpO_2) and are an almost ubiquitous device in the hospital environment (Jubran, 2004). Overnight pulse oximetry also provides a key requisite measure for the evaluation of sleep apnea (Netzer et al., 2001; Terrill, 2020). Standard traditional time-series measures derived from the oxygen saturation signal include mean and nadir overnight SpO_2, time spent below SpO_2 of 90% and the oxygen desaturation index (ODI), typically calculated as the number of 3 or 4% desaturations below baseline levels per hour of sleep. However, these metrics have their limitations and agreed standards for their calculation remain lacking. For example, the ODI is partly dependent on the criteria used to define SpO_2 dip onsets, offsets, and duration. The ODI also only reflects the frequency of hypoxemic events and fails to reflect the degree and duration of hypoxemia and further oxidative

stress through rapid reoxygenation (Punjabi et al., 2008). The physiological consequence of a 3 or 4% drop is also likely dependent on the baseline saturation level and temporal pattern of desaturation which can vary widely between individuals and comorbidities (Ayache and Strohl, 2018). Nonetheless, worse overnight hypoxemia derived from these traditional metrics has been associated with adverse health outcomes, such as increased blood pressure (Pengo et al., 2016; Su et al., 2021) and more recently atrophy of cortical and subcortical brain areas (Marchi et al., 2020). However, relationships with traditional hypoxia measures and important health/physiological outcomes are often weak, with inconsistent reproducibility between studies and cohorts (Pretto et al., 2014; Baumert et al., 2020; Linz et al., 2020; Terrill, 2020).

Other non-traditional parameters from SpO_2 such as the delta index measures the mean absolute difference between successive points at constant time intervals (Levy et al., 1996; Magalang et al., 2003; Lin et al., 2009), saturation impairment index computed as the time integral over which SpO_2 is below certain threshold levels (i.e., baseline, 90, 80, 70, 60, and 50% saturation) (Kirby et al., 1992), and the hypoxic burden index computed as the area under the time versus desaturation curve ($SpO_2 < 90\%$) divided by total sleep time (Azarbarzin et al., 2019; Baumert et al., 2020) have been derived and used in research settings. Some of these parameters have been associated with important health outcomes. For example, hypoxic burden measures that incorporate frequency, duration and magnitude of hypoxemia have recently been shown to predict cardiovascular disease mortality in different cohorts, whereas traditional PSG metrics such as the AHI and ODI do not (Azarbarzin et al., 2019; Baumert et al., 2020). Quantification of an easily measured index of sleep apnea-related hypoxemia has recently been used to predict incident heart failure (Azarbarzin et al., 2020). Accordingly, there remains considerable scope to better understand the precise mechanisms and characteristics by which hypoxemic and reoxygenation events during sleep contribute to cardiovascular and other end-organ damage, and to derive sensitive metrics to quantify these and other important health consequences. These recent findings highlight the potential for improvement beyond current traditional metrics. Through pulsatile changes in light absorption, oximeters can also provide potentially clinically useful markers of vasoconstriction responses during sleep (Catcheside et al., 2001; Jordan et al., 2003) that may be clinically useful predictors of cardiovascular risk (Hirotsu et al., 2020).

Autonomic Signals

Assessment of autonomic nervous system activity during sleep is facilitated using photoplethysmography and ECG. The use of these signals in sleep medicine including new analytical methods and the potential insights they can provide has been covered in recent in-depth reviews (Fischer and Penzel, 2019; Ucak et al., 2021).

High increases in heart rate following apneic events are associated with 30–60% increases in mortality risk and non-fatal/fatal cardiovascular disease compared to normal heart rate responses (Azarbarzin et al., 2020). New evidence also suggests that heart rate variability during wakefulness could be a useful marker of OSA severity and excessive daytime sleepiness, whereby OSA severity is associated with reduced and less complex dynamics of heart rate variability (Qin et al., 2021). Pulse wave amplitude (a marker of vasoconstriction in the finger) features (e.g., amplitude, frequency) have been associated with hypertension, cardiovascular events and diabetes (Hirotsu et al., 2020). Similarly, a decrease in pulse arrival time (time delay of pulse propagation between two points such as heart and finger) as a result of apneic events, is a predictor of subclinical cardiovascular disease and future cardiovascular events (Kwon et al., 2021). Pulse wave amplitude and heart rate responses are also sensitive markers to sensory disturbances during sleep such as noise (Catcheside et al., 2002; Griefahn et al., 2008) and may therefore provide unique insights into downstream health effect of environmental sleep disturbances.

Signal Coupling and Other Approaches

While an exhaustive list of sleep metrics is not the objective of this review, and recent detailed reviews are available elsewhere (Mendonça et al., 2019; Lim et al., 2020), a few key metrics warrant brief coverage.

Motor system disorders such as periodic limb movement (PLM) and REM sleep behavior disorders (RBD) are associated with adverse outcomes. For example, PLMs are associated with stroke and cardiovascular risk factors in certain patient populations (Lindner et al., 2012). RBD may be an early biomarker of subsequent synucleinopathies such as Parkinson's disease (Claassen et al., 2010) and may increase the risk of stroke (Ma et al., 2017). RBD in people with Parkinson's disease is also associated with faster motor progression and cognitive decline (Pagano et al., 2018). However, diagnosis of motor system disorders can be challenging. For example, screening questionnaires for RBD have variable sensitivity and specificity (Stiasny-Kolster et al., 2007; Li et al., 2010; Boeve et al., 2011). Thus, there is a need for better diagnostic approaches for motor system disorders. These include leg actigraphy for PLMs (Plante, 2014), more standardized quantifiable approaches using EMG signals during polysomnography (Frauscher et al., 2012) and novel 3D video analysis approaches (Waser et al., 2020).

The cyclic alternating pattern (CAP) is an additional sleep scoring system beyond traditional AASM sleep scoring which aims to quantify NREM discontinuity by characterizing phases of activation (A phases) and periods of inactivity (B phases) (Terzano et al., 2001). Automatic methods of CAP scoring have been proposed (Hartmann and Baumert, 2019) and have been applied to study and define NREM instability in large population-based studies (Buysse et al., 2010; Hartmann et al., 2020) and may provide unique insight into sleep neurobiology. CAP and its potential utility is discussed in detail in recent comprehensive reviews (Mendonça et al., 2019; Lim et al., 2020).

Several research groups have investigated the coupling between multiple physiological signals, such as heart rate with respiratory signals (named cardio-pulmonary coupling) (Thomas et al., 2005, 2018; Bartscha et al., 2012; Penzel et al., 2016). Coupling-based analyses have also been applied between sleep EEG and heart rate (Brandenberger et al., 2001). The theoretical concept of coupling-functions between different physiological

systems has been recently generalized under the framework of network physiology (Bashan et al., 2012; Ivanov et al., 2016). A more in-depth review of these techniques and their potential to provide insight into sleep neurobiology and consequences of impaired coupling is available in the literature (Ivanov et al., 2016; Penzel et al., 2016; de Zambotti et al., 2018b).

OSA ENDOTYPES

The underlying causes of the most common sleep-related breathing disorder, OSA, vary considerably between patients. Current evidence indicates that there are at least four key pathophysiological "phenotypes," more recently termed "endotypes," that contribute to OSA pathophysiology (Eckert et al., 2013; Eckert, 2018a; Malhotra et al., 2020). While impaired pharyngeal anatomy is the most influential endotype, the magnitude of impaired pharyngeal anatomy varies widely between patients. In addition, approximately 70% of patients also have one or more non-anatomical endotypes that contribute to their OSA (Eckert et al., 2013; Eckert, 2018a). These include impaired pharyngeal dilator muscle function during sleep, unstable control of breathing (high loop gain) and waking up too easily to minor airway narrowing events during sleep (low respiratory arousal threshold) (**Figure 5**). These advances in knowledge in OSA pathophysiology have major implications for targeted therapy through "precision medicine." For example, detailed physiological studies in which the key OSA endotypes have been quantified and non-CPAP interventions delivered to improve one or more of the non-anatomical treatable traits can reduce OSA severity (Eckert et al., 2011; Edwards et al., 2012, 2016b; Sands et al., 2018a; Aishah and Eckert, 2019; Taranto-Montemurro et al., 2019; Op de Beeck et al., 2021). Identification of patients with a low respiratory arousal threshold endotype may be an important physiological predictor of CPAP treatment failure (Gray et al., 2017; Zinchuk et al., 2021) and the presence of a low arousal threshold endotype is associated with mortality (Butler et al., 2019). Similarly, identification of patients impairment in endotypes such as high loop gain and highly collapsible pharyngeal airways may be important predictors for non-CPAP treatment failure including upper airway surgery, mandibular advancement splint therapy, hypoglossal nerve stimulation, pharmacotherapy (Edwards et al., 2016a; Li et al., 2017; Aishah and Eckert, 2019; Op de Beeck et al., 2021) and potentially positional therapy (Eckert, 2018b).

However, current detailed physiological quantification of OSA endotypes is intrusive and far more complex and time-consuming to perform and analyze than standard polysomnography (Eckert, 2018a). Thus, this approach is impractical for clinical use. Accordingly, novel approaches to estimate the key OSA endotypes have been developed. These include more scalable advanced signal processing techniques (Sands et al., 2018a,b), machine learning approaches (Dutta et al., 2021) and algorithms (Edwards et al., 2014) which simply make better use of the existing rich neurophysiological and respiratory information acquired from diagnostic polysomnography recordings and standard clinical metrics such as age and BMI. Other strategies to estimate specific OSA endotypes include estimates based on a simple intervention during a CPAP titration study (Osman et al., 2020), the therapeutic CPAP level (Landry et al., 2017) and wakefulness upper airway physiology testing (Wang et al., 2018; Osman et al., 2019). These principles and recent proof-of-concept findings have opened multiple new lines of investigation for the development of more clinically feasible and scalable approaches to help better guide targeted therapy and precision medicine for OSA.

CIRCADIAN RHYTHMS

The Need to Assess Circadian Rhythms to Define Sleep Disruption

Aside from advances in PSG sleep and breathing metrics, new approaches are emerging in the assessment of circadian rhythms; another key determinant of sleep and its disorders (Borbély, 1982; Daan et al., 1984). These endogenous rhythms are ubiquitous, with nearly every cell in the human body influenced by a biological "clock." The suprachiasmatic nucleus in the hypothalamus, colloquially termed the "master" clock, governs the timing of many circadian rhythms influential for sleep, including melatonin secretion, core body temperature (Cajochen et al., 2003), gene transcription and translation regulated clock behavior of nucleated cells throughout the body (Kondratova and Kondratov, 2012). Even non-nucleated red blood cells show circadian cycling of redox activity (O'Neill and Reddy, 2011). The effects of circadian rhythms on sleep disruption are most evident in circadian rhythm sleep disorders, such as delayed and advanced sleep-wake phase disorder, shift-work disorder, and non-24-h sleep disorder where the circadian phase (timing relative to clock time), amplitude of the rhythm, and/or period (duration of the circadian cycle) are poorly aligned with wake activities and environmental time cues, leading to disrupted sleep (Micic et al., 2016; James et al., 2017). Fortunately, disrupted circadian rhythms are treatable to improve sleep (Dodson and Zee, 2010).

Given the major role of circadian rhythms in mediating sleep patterns and behavior, methods to assess circadian rhythms across the different manifestations of sleep disruption are likely to be insightful. In chronic insomnia, circadian rhythm factors may importantly contribute to the underlying etiology and pathophysiology (Lack et al., 2008). Chronobiological interventions, such as bright light therapy, have been administered as a stand-alone treatment and combined with CBT-I to moderate effect (Jankù et al., 2020). Circadian rhythms could also play a role in OSA (von Allmen et al., 2018) and comorbid insomnia and OSA (COMISA) (Sweetman et al., 2021). Effects of circadian rhythms on respiratory control (Stephenson, 2003; Yamauchi et al., 2014) and hypoxia (von Allmen et al., 2018) have also been hypothesized and supported by recent evidence of circadian modulation of the key OSA endotypes (El-Chami et al., 2014, 2015; Puri et al., 2020). Circadian rhythms also have an influential effect on metabolism, diabetes, cardiovascular disorders, obesity, and the efficacy of a range of pharmacological

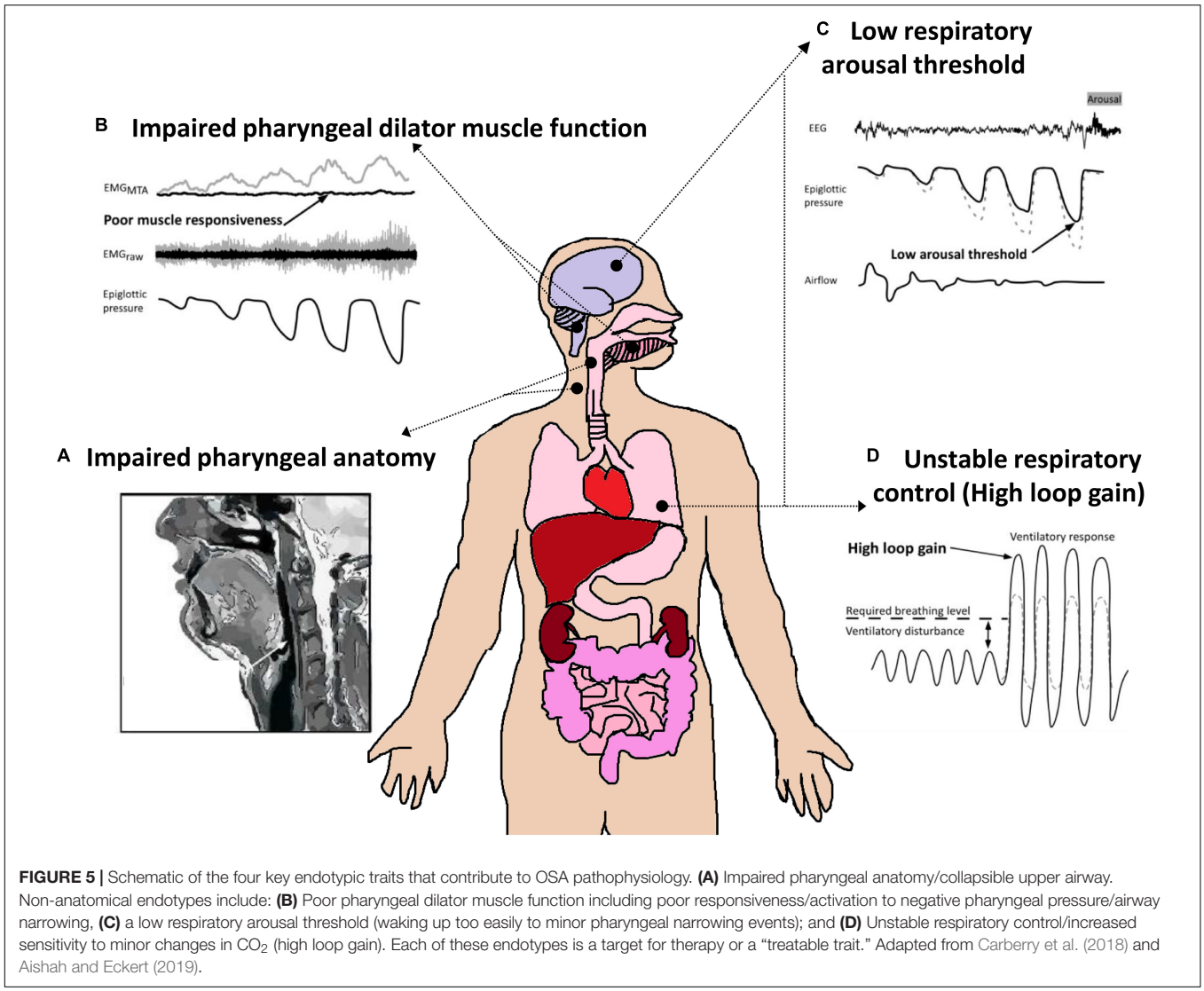

FIGURE 5 | Schematic of the four key endotypic traits that contribute to OSA pathophysiology. **(A)** Impaired pharyngeal anatomy/collapsible upper airway. Non-anatomical endotypes include: **(B)** Poor pharyngeal dilator muscle function including poor responsiveness/activation to negative pharyngeal pressure/airway narrowing, **(C)** a low respiratory arousal threshold (waking up too easily to minor pharyngeal narrowing events); and **(D)** Unstable respiratory control/increased sensitivity to minor changes in CO_2 (high loop gain). Each of these endotypes is a target for therapy or a "treatable trait." Adapted from Carberry et al. (2018) and Aishah and Eckert (2019).

interventions; factors often applicable to sleep disorder cohorts (Guo and Stein, 2003; Frazier and Chang, 2020; Ayyar and Sukumaran, 2021). Therefore, strategies to better define sleep disruption that incorporate circadian rhythm assessments have significant potential to improve diagnostic and targeted therapy outcomes.

Current and Emerging Methods to Assess Circadian Rhythms

The current "gold standard" measure of circadian rhythms is salivary or blood dim-light melatonin onset (Arendt et al., 1985; Benloucif et al., 2008). This method involves measuring the concentration of melatonin (in pmol/mL) via a blood draw or via half-hourly saliva samples for at least 3–4 h before bedtime, under dim-light conditions (light intensity < 10 lux) while the individual remains relatively stationary and avoids consuming food and drinks (Sletten et al., 2018). Samples are processed and analyzed to estimate the clock time of melatonin rise onset (>10 pmol/mL), which is a marker of circadian phase. Another common measure of circadian rhythms in sleep research is core body temperature via an ingestible capsule or rectal thermistor. Frequent sampling of temperature across an extended period (>24 h), where conditions and activities that affect body temperature are controlled (e.g., air temperature, body movement, food consumption, and hot drink consumption), enables assessment of several aspects of the underlying core body temperature rhythm, including circadian phase, amplitude, and period. However, these assessments require carefully controlled laboratory conditions and access to specialized equipment generally infeasible for routine administration outside of circadian rhythm-focused sleep research studies. Fortunately, technologies and analytical methodologies are emerging that promise to facilitate simpler and improved assessments of circadian rhythms.

Emerging methods include advanced monitoring devices and biomathematical modeling to infer circadian rhythm metrics

(Reid, 2019). Newer technologies include skin temperature sensors incorporated into consumer sleep trackers that detect the peripheral temperature rhythm to estimate circadian phase (Hasselberg et al., 2013). Electronic chips that can be implanted in body patches are also being developed to assess the cortisol rhythm via sweat (Upasham and Prasad, 2020), as well as other important clinical indicators such as the cortisol awakening response (Law and Clow, 2020). Rather than direct assessment of circadian rhythms, another approach is to infer circadian timing via the measurement of factors associated with circadian rhythms. Sleep timing data collected from wearable and non-wearable sleep trackers over an extended period are being incorporated into biomathematical models to infer circadian timing, since rest-activity rhythms are highly correlated with circadian timing (Cheng et al., 2021). Light sensors incorporated into newer wearable devices are also being used to infer circadian timing (Stone et al., 2020), since light is the strongest exogenous influencer (zeitgeber) of circadian rhythms. This information, potentially coupled with pupillometry assessment of an individual's retinal responsiveness to light, enables inference of circadian timing, which may be useful for the diagnosis of circadian disruption in sleep disorders. More recent discoveries of genes with circadian oscillations (clock-controlled genes) raises the possibility that certain aspects of circadian rhythms may be amenable to assessment from blood samples (Cogswell et al., 2020). As these newer technologies mature, their implementation in clinical and research practice may result in new discoveries regarding the role of circadian rhythms in sleep disorders and their health-related consequences.

NOVEL MEASURES OF ENVIRONMENTAL FACTORS THAT CAN AFFECT SLEEP

The sleeping environment affects sleep ability, but is minimally assessed in routine clinical practice. Consequently, sleep disruption may be misattributed to endogenous factors alone, ignoring the potential impact of exogenous factors. These include noise, light, temperature, and other factors that impact comfort within the sleep context. In a laboratory environment, these factors are typically well-controlled and designed to be conducive for sleep. However, as the assessment of sleep disruption shifts from the laboratory to the less well-controlled home environment, the assessment and consideration of environmental factors becomes increasingly important to understand mechanisms of sleep disruption.

Potentially the strongest exogenous influencer of sleep is noise, which can adversely affect sleep attainment and

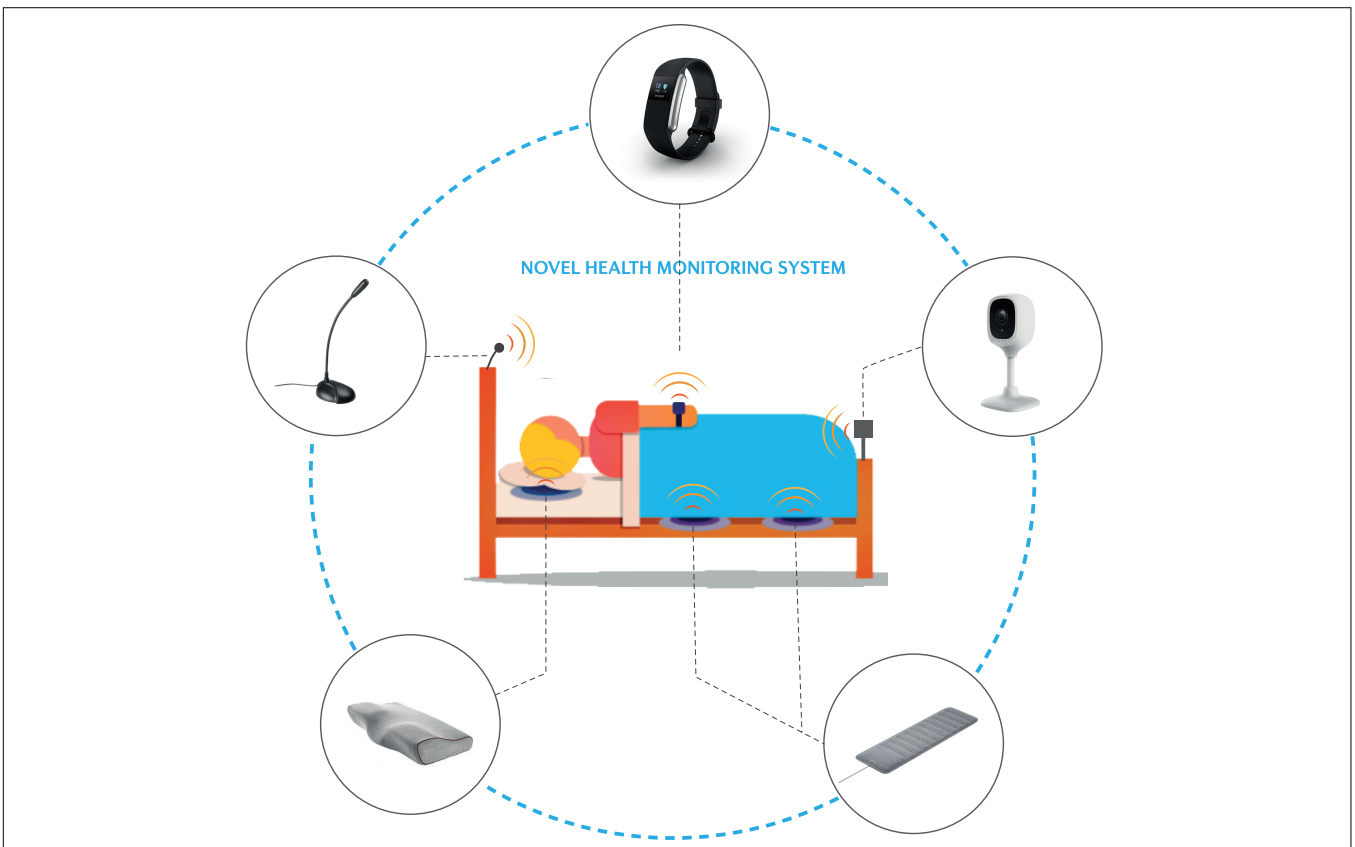

FIGURE 6 | Schematic of novel and emerging approaches to monitor the sleeping environment and track key health measures via "the bedroom of the future." Refer to the text for further detail.

maintenance and fragment sleep to reduce total sleep time and quality (Muzet, 2007; Basner et al., 2014). The most common self-reported outcomes in response to road, rail and aircraft noise exposure are awakenings from sleep, increased sleep latency, and disruption to sleep continuity (Basner and McGuire, 2018). For example, patients in hospital intensive care units consistently rate noise as the most sleep disturbing factor (Freedman et al., 2001; Gabor et al., 2003; Elliott et al., 2013) and polysomnography results indicate poor and fragmented sleep, with a median of only 5 h sleep/24 h, only 3 min of uninterrupted light sleep and almost total abolition of deep and REM sleep (Elliott et al., 2014). However, to date, noise is rarely assessed as a potential sleep disturbing factor in either clinical or home setting contexts. Studies that have investigated the effects of noise on sleep quality have employed generalized metrics that focus on overall noise levels only and/or do not consider specific noise characteristics such as spectral content, time varying noise components, tonality and noise intermittency. These factors are important contributors to noise annoyance (Ioannidou et al., 2016; Schäffer et al., 2016; Oliva et al., 2017), are thus likely to contribute to sleep disturbance, and warrant assessment to better inform clinical decision-making.

SCALABLE APPROACHES TO MEASURE SLEEP INCLUDING MULTI-NIGHT ASSESSMENTS

There are two seemingly opposing challenges regarding sleep monitoring and diagnostics. There is a need for greater in-depth insight into the underlying neurobiology of sleep, yet there is also a need for less intrusive and user-friendly technology. Detailed, in-depth assessments and monitoring approaches as well as smarter use of existing signals and information derived from traditional polysomnography approaches are required to better understand sleep pathology. Yet, given the burden of disease and the scale of sleep disruption in the community, there is also a pressing need for less intrusive sleep tracking technology that can be readily and easily adopted in a home-based setting.

A plethora of technologies have emerged to track sleep in the home setting (**Figure 6**). These include bedside Doppler (Zakrzewski et al., 2015; Tuominen et al., 2019) and instrumented mattresses for ballistographic assessment of heart rate, respiratory rate and body movements/position, which perform relatively well compared to polysomnography and are considerably easier to implement and use (Laurino et al., 2020). Similarly, wearable devices such as smart watches, rings, simplified EEG headbands, and actigraphy devices also provide similar performance in sleep/wake assessment (Griessenberger et al., 2013; de Zambotti et al., 2018a; Arnal et al., 2020; Chee et al., 2021; Scott et al., 2021). Infrared video has also been used to classify body motion to automatically score sleep and wake states (Wang et al., 2013), as well as monitor respiration, head posture, and body posture to detect abnormal breathing (Deng et al., 2018). Together, these devices open new pathways for non-invasive multi-night assessments in various sleep settings to support the clinical diagnosis and management of sleep disorders. This is especially important given that sleep disorder pathophysiology may show large variability between nights (Punjabi et al., 2020), and that variability and irregularity in some sleep components has been associated with downstream effects on health such as cardio-metabolic conditions (Linz et al., 2019a,b; Huang et al., 2020).

FINAL SUMMARY/CONCLUSION

New and emerging approaches to better define sleep and circadian disruption and its consequences offers considerable promise to move beyond the limitations of current sleep metrics and management. To improve outcomes, these approaches need to be underpinned by consideration for underlying neurobiology and will likely require a multisystem approach to capture the diverse impacts that sleep and circadian disruption can have on health and wellbeing. Development of practical, inexpensive methods to assess sleep and circadian disruption, its key contributors, and consequences at scale, including comprehensive, long-term remote monitoring has the potential to transform sleep medicine and management. This includes implementation of precision sleep medicine and targeted therapy approaches.

AUTHOR CONTRIBUTIONS

All authors contributed to drafting and/or revising one or more of the sections of this manuscript, provided feedback on the final version, and agreed to be accountable for the content of the work.

FUNDING

KH was supported by an Australian Research Council Discovery Early Career Researcher Award (DE180100022). AV was supported by a National Health and Medical Research Council (NHMRC) of Australia Career Development Fellowship (1159499). DE was supported by a NHMRC of Australia Senior Research Fellowship (1116942) and an Investigator Grant (1196261). BL was supported by the Nick Antic Sleep Research Scholarship from Flinders Foundation. This was an investigator-initiated, non-commercially funded study.

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Conflict of Interest: DE has a Collaborative Research Centre (CRC-P) Grant, a consortium grant between the Australian Government, Academia and Industry (Industry partner: Oventus Medical) and has research grants and serves as a consultant for Bayer and Apnimed. AV has received research grant funding and equipment from ResMed and Philips Respironics. PC has received research funding from Defence Science and Technology and received research grant funding and equipment from Philips Respironics. The funders Philips Respironics, ResMed, Oventus Medical, Bayer, Apnimed were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neuroscience

ERRATUM
published: 18 November 2021
doi: 10.3389/fnins.2021.804589

Erratum: New and Emerging Approaches to Better Define Sleep Disruption and Its Consequences

*Frontiers Production Office**

Frontiers Media SA, Lausanne, Switzerland

Keywords: sleep disordered breathing, sleep apnea, insomnia, circadian rhythm, polysomnography, signal processing, apnea/hypopnea index, precision medicine

An Erratum on:

New and Emerging Approaches to Better Define Sleep Disruption and Its Consequences
by Lechat, B., Scott, H., Naik, G., Hansen, K., Nguyen, D. P., Vakulin, A., Catcheside, P., and Eckert, D. J. (2021). Front. Neurosci. 15:751730. doi: 10.3389/fnins.2021.751730

Due to production errors, several corrections were omitted.

In "Key Components of The Polysomnographic," "K-Complexes," the sub-title should be "K-complexes."

In "Key Components of The Polysomnographic," "Sleep Spindles," a sentence appears as follows: "In a clinical population of 47 patients with Obstructive sleep apnea (OSA) Headers are correct Confirmed, greater sleep spindle activity was associated with better implicit learning (Stevens et al., 2021)." This should instead read as follows: "In a clinical population of 47 patients with obstructive sleep apnea (OSA), greater sleep spindle activity was associated with better implicit learning (Stevens et al., 2021)."

In "Circadian Rhythms," "The Need to Assess Circadian Rhythms' to Define Sleep Disruption," a sentence appears as follows: "Chronobiological interventions, such as bright light therapy, have been administered as a stand-alone treatment and combined with CBT-I combined with CBT-I to moderate effect (Jankù et al., 2020)." This should instead read as follows: "Chronobiological interventions, such as bright light therapy, have been administered as a stand-alone treatment and combined with CBT-I to moderate effect (Jankù et al., 2020)."

The publisher apologizes for this mistake. The original version of this article has been updated.

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OPEN ACCESS

Approved by:
Frontiers Editorial Office, Frontiers Media SA, Switzerland

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *29 October 2021*
Accepted: *29 October 2021*
Published: *18 November 2021*

Citation:
Frontiers Production Office (2021) Erratum: New and Emerging Approaches to Better Define Sleep Disruption and Its Consequences. Front. Neurosci. 15:804589. doi: 10.3389/fnins.2021.804589

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 03 November 2021
doi: 10.3389/fnins.2021.644697

Pediatric Sleep Apnea: The Overnight Electroencephalogram as a Phenotypic Biomarker

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: 21 December 2020
Accepted: 07 October 2021
Published: 03 November 2021

Citation:
Gutiérrez-Tobal GC, Gomez-Pilar J, Kheirandish-Gozal L, Martín-Montero A, Poza J, Álvarez D, del Campo F, Gozal D and Hornero R (2021) Pediatric Sleep Apnea: The Overnight Electroencephalogram as a Phenotypic Biomarker. Front. Neurosci. 15:644697. doi: 10.3389/fnins.2021.644697

Pediatric obstructive sleep apnea (OSA) is a prevalent disorder that disrupts sleep and is associated with neurocognitive and behavioral negative consequences, potentially hampering the development of children for years. However, its relationships with sleep electroencephalogram (EEG) have been scarcely investigated. Here, our main objective was to characterize the overnight EEG of OSA-affected children and its putative relationships with polysomnographic measures and cognitive functions. A two-step analysis involving 294 children (176 controls, 57% males, age range: 5–9 years) was conducted for this purpose. First, the activity and irregularity of overnight EEG spectrum were characterized in the typical frequency bands by means of relative spectral power and spectral entropy, respectively: δ_1 (0.1–2 Hz), δ_2 (2–4 Hz), θ (4–8 Hz), α (8–13 Hz), σ (10–16 Hz), β_1 (13–19 Hz), β_2 (19–30 Hz), and γ (30–70 Hz). Then, a correlation network analysis was conducted to evaluate relationships between them, six polysomnography variables (apnea–hypopnea index, respiratory arousal index, spontaneous arousal index, overnight minimum blood oxygen saturation, wake time after sleep onset, and sleep efficiency), and six cognitive scores (differential ability scales, Peabody picture vocabulary test, expressive vocabulary test, design copying, phonological processing, and tower test). We found that as the severity of the disease increases, OSA broadly affects sleep EEG to the point that the information from the different frequency bands becomes more similar, regardless of activity or irregularity. EEG activity and irregularity information from the most severely affected children were significantly associated with polysomnographic variables, which were coherent with both micro and macro sleep disruptions. We hypothesize that the EEG changes caused by OSA could be related to the occurrence of respiratory-related arousals, as well as thalamic inhibition in the slow oscillation generation due to increases in arousal levels aimed at recovery from respiratory events. Furthermore, relationships between sleep EEG and cognitive scores emerged regarding language, visual–spatial processing, and executive function with pronounced associations found with EEG irregularity in δ_1 (Peabody picture vocabulary test and expressive vocabulary test maximum absolute correlations 0.61 and 0.54)

and β_2 (phonological processing, 0.74; design copying, 0.65; and Tow 0.52). Our results show that overnight EEG informs both sleep alterations and cognitive effects of pediatric OSA. Moreover, EEG irregularity provides new information that complements and expands the classic EEG activity analysis. These findings lay the foundation for the use of sleep EEG to assess cognitive changes in pediatric OSA.

Keywords: sleep apnea, pediatrics, electroencephalography, cognition, correlation networks

INTRODUCTION

Pediatric obstructive sleep apnea (OSA) is not only prevalent among children but also carries a significant risk for long-term morbidities primarily affecting cognitive and behavioral functioning, as well as inducing cardiovascular and metabolic dysfunction (Marcus et al., 2012). OSA-induced night time perturbations such as intermittent hypoxia, hypercapnia, and sleep fragmentation are often accompanied by systemic inflammation and oxidative stress, the latter being implicated in the neurocognitive and behavioral deficits that could hamper their intellectual and emotional development (Marcus et al., 2012; Hunter et al., 2016). Cognitive impairments have indeed been recognized as one of the major morbidities of OSA during childhood, with the most severe patients showing a higher risk of being affected (Hunter et al., 2016). Nevertheless, cognitive testing is not routinely administered to children being clinically evaluated for suspected OSA. Adenotonsillectomy has shown the reversibility of cognitive deficits associated with OSA, as well as improvements in academic results (Gozal, 1998), with suggested neurocognitive enhancements even in mild patients receiving timely treatment (Tan et al., 2017). Hence, objective identification of cognitive impairments in OSA-affected children is of paramount importance to minimize their impact and maximize their reversibility.

Sleep EEG has shown the potential to provide physiologically based cognitive information (Weichard et al., 2016; Brockmann et al., 2018, 2020; Christiansz et al., 2018) that would obviate the need for traditional neurocognitive tests, yet secure an estimate of risk for OSA-associated morbidities. However, all previous studies exploring sleep EEG and cognition focused on very specific EEG attributes, such as spindles or delta activity (Weichard et al., 2016; Brockmann et al., 2018, 2020; Christiansz et al., 2018). Consequently, how OSA alters the overnight electrical behavior of the brain of children, and whether such alterations indicate cognitive deficits, remains unclear. If such were the case, however, the intrinsic informative value of the PSG-derived EEG recordings would add further incentive to the use of PSG since it would provide not only the necessary respiratory information required for clinical treatment decision making but would also provide inferences as to the cognitive susceptibility of the patients, i.e., would enable more personalized approaches. We, therefore, hypothesized that pediatric OSA and its cognitive implications are reflected in a differential behavior of the overnight EEG. Furthermore, the recurrent nature of apneic events suggests an examination in the frequency domain. Accordingly, our main objective was to characterize new relationships between the information obtained from the overnight EEG spectrum, pediatric OSA-related polysomnographic perturbations, and cognitive functions.

To this effect, we extracted information from the conventional spectral bands of 294 EEG recordings from children, not only using the activity-based classic approach (relative spectral power, *RP*) but also the analysis of their irregularity (spectral entropy, *SpecEn*). Connections between these complementary analyses, applied to eight EEG channels, six polysomnographic variables, and six cognitive scores, were assessed using correlation networks, as they allow for an easy visualization of relationships in high-dimensional data and have been successfully used in the study of different pathological conditions (Liu et al., 2009; Barabási et al., 2011; Epskamp et al., 2012; Kwapiszewska et al., 2018; Jimeno et al., 2020). Our analytical approach is expected to identify how EEG activity and irregularity evolve as pediatric OSA worsens, while concurrently assessing their interrelationship with sleep variables and cognitive outcomes.

MATERIALS AND METHODS

Pediatric Cohort and Sleep Studies

Community nonreferral children (169 boys/125 girls, 5–9 years old) were recruited in Chicago, Illinois, after obtaining an informed consent from their parents or legal caregivers in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the University of Chicago (protocol # 09-115-B). Polysomnography (PSG) was conducted using commercial digital equipment and scored according to the recommendations of the American Academy of Sleep Medicine (AASM) (Grigg-Damberger et al., 2007; Iber et al., 2007; Berry et al., 2012). The apnea–hypopnea index (AHI) from PSG was used as the OSA diagnostic standard. AHI common cutoffs were used to split the cohort in three subgroups: controls (AHI $\leq$ 1 event/h, N = 176), mild OSA (1 e/h $\leq$ AHI $\leq$ 5 e/h, N = 98), and moderate/severe OSA (5 e/h $\leq$ AHI, N = 20). Children were recruited from the sleep clinic and the pediatric otolaryngology clinics as well as by flyers posted in the community. Those children who had genetic or craniofacial syndromes and chronic diseases such as cardiac disease, diabetes, cerebral palsy, and chronic lung disease of prematurity or cystic fibrosis were excluded. In addition, any child with a known neuropsychiatric condition or developmental delay was also excluded.

Polysomnographic Variables and Neurocognitive Tests

Six PSG-related variables were included in the study: AHI, respiratory event-related arousals (AR), minimum oxygen saturation value ($Nadir_{SpO2}$), spontaneous arousals (AS), the number of minutes awake after sleep onset (WASO), and the sleep efficiency (SleepEff). AHI refers to the number of apneas and hypopneas per hour of sleep, and was used to establish the presence and severity of OSA (Berry et al., 2012). AR is the number of arousals per hour of sleep caused by abnormal respiratory events, thus, reflecting associated micro sleep disruptions. Respiratory arousals are involved in hypopnea definition, and therefore, they are also related to AHI. $Nadir_{SpO2}$ is the lowest value of oxygen saturation during the night. It is very often associated with the occurrence of desaturations, which are also involved in hypopnea definition. AS is the number of spontaneous arousals. It has been included to contrast the evaluation of AR. Finally, WASO are the minutes awake after sleep onset, and SleepEff is the percentage of minutes spent asleep divided by the total of minutes in bed. Both are associated with macro sleep disruptions.

Six neurocognitive tests were administered to the children under study in the morning immediately after the PSG night (Hunter et al., 2016). Differential ability scales (DAS) is composed of a battery of subtests with ability to measure the performance of several intellectual activities of children in the range 2–17 years (Elliott, 1990b). However, in this study, it was only used as a measure of global intellectual ability by means of a composite score termed "general conceptual ability." It merges the scores from each subtest, with a proper age standardization, showing high agreement with other common general tests (Elliott, 1990a,b). The third edition of the Peabody Picture Vocabulary Test (PPVT3) was used to assess the verbal ability of the children under study (Restrepo et al., 2006). It is a test in which children point to a picture they think that shows a word previously said aloud, i.e., it is focused on receptive verbal skills. The Expressive Vocabulary Test (EVT) is complementary to PPVT3 when evaluating language (Restrepo et al., 2006; Hunter et al., 2016). During EVT, children have to articulate the word representing the image shown in a picture, so it assesses the expressive part of language (Restrepo et al., 2006). The three remaining cognitive tests are included within NEPSY (for A Developmental NEuroPSYchological Assessment) series. Design Copying (DesCop) is intended for measuring visual–spatial processing (Ahmad and Warriner, 2001; Miller, 2007). Children are asked to copy geometrical figures, and credit is given for each partial drawing (Miller, 2007). Phonological processing (PhPro) from NEPSY assesses language in a different way than PPVT3 and EVT. While the last two refer to receptive and expressive language, respectively, PhPro measures the third subcomponent of language, called indeed phonological processing (Miller, 2007). It consists of two parts. In the first one, children have to identify words from word segments using graphic and verbal indications. In the second part, children are required to repeat a word and create a new one from the original. Finally, Tower (Tow) test is the NEPSY variant of the well-known Tower of London. It is intended for assessing executive functions, such as planning or problem solving (Baron, 2018). In less than six movements, children are asked to imitate with real pieces a given state shown in a figure (Miller, 2007).

Signal Acquisition and Analysis

Eight EEG channels referenced to mastoids (F3, F4, C3, C4, O1, O2, T3, and T4) were acquired during PSGs at a sampling rate of 200 Hz (Grigg-Damberger et al., 2007; Iber et al., 2007). Pre-processing consisted of a four-stage methodology: (*i*) re-referencing to the average of the eight EEG channels; (*ii*) stop-band filter in 60 Hz and band-pass filter from 0.1 to 70 Hz using a Hamming window; (*iii*) automatic rejection of artifacts following an epoch-adaptive thresholding approach (Bachiller et al., 2015); and (iv) rejection of first and last parts of the EEG to avoid initial and final awake states.

The Blackman–Tukey method was used to estimate the power spectral density (PSD) of the eight EEG channels from each subject under study. A rectangular nonoverlapping window was used, with a length of 6,000 samples (30 s). The PSDs of the epochs of the whole night were averaged to estimate one PSD for each channel. Then these PSDs were normalized (PSDn) dividing its amplitude values by the total spectral power of the corresponding channel. The relative power (*RP*) and spectral entropy (*SpecEn*) of delta 1 (δ_1: 0.1–2 Hz), delta 2 (δ_2: 2–4 Hz), theta (θ: 4–8 Hz), alpha (α: 8–13 Hz), sigma (σ: 10–16 Hz), beta 1 (β1: 13–19 Hz), beta 2 (β_2: 19–30 Hz), and gamma (γ: 30–70 Hz) were obtained from the PSDn of each channel (Uhlhaas and Singer, 2010). The split of delta is predicated on their different behavioral characteristics during sleep (Benoit et al., 2000), as well as in OSA presence (Gutiérrez-Tobal et al., 2019b). Sigma band was specifically analyzed because of its well-known relationship to sleep spindles (Iber et al., 2007). *RP*s were obtained per convention as it accounts for EEG activity and were computed as the sum of the PSDn amplitude values within each band:

$$RP = \sum_{f=f1}^{f2} PSDn(f) \quad (1)$$

where $f1$ and $f2$ are the limits of each spectral band. *SpecEn* reflects EEG irregularity within these frequencies, regardless of total activity, thus, affording additional useful information (Inouye et al., 1991; Gutiérrez-Tobal et al., 2019a). It was obtained as follows (Inouye et al., 1991):

$$SpecEn = -\frac{1}{\log N} \sum_{f=f1}^{f2} PSDn\left(f\right) \cdot \log\left(PSDn\left(f\right)\right) \quad (2)$$

which is the application of Shannon's entropy equation to the PSDn values within $f1$ and $f2$, with N being the number of values within these limits. As Shannon's entropy represents the uniformity of a given distribution, *SpecEn* quantifies the uniformity of a given spectrum in terms of its peakedness/flatness (Inouye et al., 1991). Consequently, *SpecEn* values equal to 0, the minimum in Equation (2), are reached when a single spectral component is present. This would be the case of a sinusoid in time domain, that is, a completely regular (predictable) signal. In contrast, *SpecEn* values equal to 1, the maximum in Equation (2), are reached when the power of the spectrum is equally distributed among frequencies as in the case of white noise, which is

a completely irregular (unpredictable) signal in time domain (Inouye et al., 1991). According to these features, *SpecEn* should be able to characterize a redistribution of the within-band spectral power caused by OSA regardless of *RP* remaining the same in the given band.

Correlation Network Analysis

Correlation networks are graphs based on pairwise relationships between variables (Borsboom et al., 2011). Such associations are represented as nodes—the variables—and edges—their connections—where the width and color of the later show the intensity of the correlation and its sign (in this study, red/negative and green/positive). The abovementioned six PSG outcomes and six cognitive scores were used as variables along with the activity (*RP*) and irregularity (*SpecEn*) of each EEG channel and band. A total of six correlation networks (three for *RP* and three for *SpecEn*) were dedicated to show the relationships of polysomnographic and cognitive data with the overnight EEG information in each OSA severity subgroup. Accordingly, the first step was to calculate the Spearman's partial correlation (adjusted by sex and age) between all the variables included in the networks to form the corresponding correlation matrices. In order to cope with the different number of subjects in each OSA severity group, the correlation matrices used to estimate the networks were composed after a 1.000-run bootstrap procedure (correlation matrices with 2.5 and 97.5 percentiles are provided in the file "correlation matrices.xlsx" of the **Supplementary Material**). Thus, 1.000 bootstrap samples with 20 subjects from each OSA severity group were used to compute the relationship between each node of each correlation network. The subjects were randomly selected with replacement and uniform probability, and the median value of the 1.000 runs was chosen to build each network. Then, these were obtained using the R package *qgrah* (Epskamp et al., 2012). Particularly, the Fruchterman–Reingold algorithm was applied (Fruchterman and Reingold, 1991), which forced embedded network layouts after 500 iterations. Newman's maximized algorithm was used to conduct a modularity analysis to show possible clusters in the networks (Newman, 2006; Rubinov and Sporns, 2010). It measures the degree in which a network can be divided into different related and nonoverlapping clusters and, at the same time, provides the composition of such clusters (Rubinov and Sporns, 2010), i.e., the nodes assigned to each of them. An ancillary analysis of centrality of the nodes was assessed using *strength*, *closeness*, and *betweenness* (Rubinov and Sporns, 2010), whose results can be seen as **Supplementary Figures**.

Statistical Analysis

Mann–Whitney nonparametric *U*-test was used to evaluate differences between OSA severity groups in age, body mass index, clinical variables, and cognitive scores. Fisher's exact test was conducted to evaluate these differences in sex. Spearman's partial correlation (ρ), adjusted by the sex and age of children, were used in the correlation networks. R package *qgraph* was used to obtain the corresponding network graphs (Epskamp et al., 2012). Only non-negligible absolute correlation values ($|\rho| \geq 0.30$) were shown in the correlation networks (Mukaka, 2012).

RESULTS

Polysomnography Variables and Cognitive Scores

Table 1 shows the summary of the PSG variables and cognitive scores (median and interquartile range) in the 294 subjects divided according to OSA subgroups. Sociodemographic characteristics (age, sex, and body mass index) are also presented. As would be anticipated from the delineation of the groups, AHI, AR, and $Nadir_{SpO2}$ showed statistically significant differences (p-value < 0.05, Mann–Whitney *U*-test) between them, while AS was significantly lower in moderate/severe OSA. All cognitive scores showed a decreasing tendency as OSA severity increases, with DAS, PhPro, and Tow reaching significant differences. No statistically significant differences emerged for age, sex (Fisher's exact test), WASO, and SleepEff.

Averaged Electroencephalogram Spectrum of the Three Obstructive Sleep Apnea Severity Categories

Figures 1A–D show the averaged EEG PSDn's from the three OSA severity degrees considered. First, the normalized spectrum from the eight EEG channels was averaged for each subject. Then, the median and quartile values within each OSA group were obtained for each frequency to be illustrated in the figure. As shown in **Figure 1A**, a peak coherent with the typical slow oscillation (SO) wave from δ_1 gradually decreases in frequency and increases in relative power as OSA severity is higher. In addition, the spectrum from δ_2 onward (except for α band) tends to flatten (notice the scale of the **Figures 1B–D**) with OSA severity, particularly when comparing controls and moderate/severe OSA.

Overall Evolution of the Electroencephalogram Relationships With Polysomnography Variables and Cognitive Scores

The three networks built using the activity of EEG channels (*RPs*) show high relationships within and between spectral bands (**Figures 2A–C**), i.e., a compact behavior in the activity information that reflects its similarity. However, major associations with PSG and cognitive nodes only arise for moderate/severe OSA (**Figure 2C**). In the corresponding irregularity (*SpecEn*) networks (**Figures 3A–C**), the behavior of the EEG nodes progresses from disaggregated by spectral bands (controls) to strong relationships between these (moderate/severe OSA). Similarly, only a few non-negligible relationships arise between irregularity nodes and PSG or cognitive variables in controls, but this behavior disappears as OSA worsens, reaching the maximum correlations in the moderate/severe group. Therefore, in both activity and irregularity networks, the development of OSA increases the absolute correlations between EEG and non-EEG nodes, as well as between EEG nodes from different spectral bands.

TABLE 1 | Sociodemographic data, polysomnography (PSG) variables, and cognitive scores in the three groups.

Data	Controls (*N* = 176)	Mild obstructive sleep apnea (OSA) (*N* = 98)	Moderate/severe OSA (*N* = 20)	$p < 0.05$
Age (years)	6.92 (6.50, 7.42)	6.92 (6.50, 7.42)	6.81 (6.37, 7.29)	n.s
Sex (M/F)	104/72 (59%)	55/43 (56%)	10/10 (50%)	n.s
BMIz	0.65 (−0.11, 1.47)	0.76 (−0.14, 2.04)	1.70 (−0.08, 2.24)	b
AHI (e/h)	0.40 (0.10, 0.60)	1.50 (1.20, 2.20)	9.20 (7.30, 17.20)	a,b,c
AR (e/h)	0.30 (0.05, 0.80)	1.00 (0.40, 2.82)	7.30 (4.88, 9.55)	a,b,c
AS (e/h)	6.70 (4.70, 9.00)	6.60 (4.20, 9.00)	3.10 (1.52, 6.88)	b,c
$Nadir_{SpO2}$ (%)	94.00 (92.00, 95.00)	91.00 (89.00, 94.00)	84.00 (75.00, 87.00)	a,b,c
WASO (min)	45.50 (27.00, 79.50)	37.50 (23.30, 64.30)	41.00 (19.80, 75.40)	n.s
SleepEff (%)	90.60 (84.03, 94.10)	91.00 (85.23, 94.50)	91.00 (85.45, 95.05)	n.s
DAS	101.50 (92.00, 111.50)	100.50 (86.00, 111.00)	97.00 (85.00, 104.00)	b
PPVT3	99.00 (89.50, 110.00)	98.00 (89.80, 109.30)	96.00 (88.25, 101.50)	n.s
EVT	100.00 (89.30, 108.00)	97.00 (85.50, 105.00)	96.50 (91.00, 99.00)	n.s
DesCop	11.00 (8.00, 13.00)	10.00 (7.00, 12.00)	9.00 (7.50,11.00)	n.s
PhPro	10.00 (8.00, 12.00)	9.00 (8.00, 13.00)	7.50 (5.50, 10.00)	b,c
Tow	12.00 (10.00, 14.00)	11.00 (9.00, 14.00)	9.50 (7.00, 11.50)	b,c

AHI, apnea–hypopnea index; AR, respiratory arousal index; AS, spontaneous arousal index; BMIz, standardized body mass index; DAS, differential ability scales; DesCop, design copying; EVT, expressive vocabulary test; $Nadir_{SpO2}$, overnight minimum oxygen saturation value; PhPro, phonological processing; PPVT3, Peabody picture vocabulary test; SleepEff, sleep efficiency, WASO, time awake after sleep onset; Tow, Tower test [a]Controls vs. mild OSA comparison. [b]Controls vs. moderate/severe OSA comparison. [c]Mild OSA vs. moderate/severe OSA comparison. n.s, not significant.

All correlation values between nodes are in the **Supplementary Material** ("correlation matrices.xlsx"), along with the networks corresponding to 95% confidence interval derived from the bootstrap procedure. The most relevant correlation values are also shown in the next sections.

Spectral Band Average Associations With Polysomnography Variables and Cognitive Scores

Figures 4A,B,D,E are radar (spider) charts showing channel-averaged correlations between the EEG spectral bands and the non-EEG variables. As expected, the overall tendency reflects higher absolute correlations with PSG and cognitive variables as OSA severity increases, for both EEG activity (*RP*) and irregularity (*SpecEn*). The tendency is only somehow different for the relationships between *RP* and PSG nodes (**Figure 4A**), where the averaged absolute correlation is generally higher in controls than in mild OSA.

Average relationships between EEG irregularity and PSG variables of mild and moderate/severe OSA are higher than the equivalent for EEG activity, as reflected by the values of the corresponding radar charts (**Figures 4A,D**). The highest absolute averaged correlations, reached in the moderate/severe group, are mainly influenced by EEG activity from δ_1 (0.28), δ_2 (0.31), and β_1 (0.27), and EEG irregularity from δ_1 (0.25), σ (0.31), and γ (0.27).

Relationships between EEG irregularity and activity with cognitive scores are more similar (**Figures 4B,E**), but still more spectral bands show higher averaged correlations in the case of *SpecEn* for both mild and moderate/severe OSA, the latter reaching the maximums values again in δ_1 (0.25) and δ_2 (0.29), and σ (0.25) for EEG activity, and δ_1 (0.30), σ (0.29), and β_2 (0.26) for EEG irregularity.

Radar charts with the relationships between PSG and cognitive variables were also generated for completeness of the analysis and are shown in **Figures 4C,F**. As can be observed, the relationship between PSG variables and cognitive scores also increases with OSA severity.

Modularity Analysis and Specific Relationships

Coherent with its compact behavior, a low number of groups of especially related nodes (termed modules or clusters) were obtained after applying the modularity analysis to the EEG activity networks: five modules for controls, four for mild OSA, and three for the moderate/severe group (**Figures 5A–C**). This was summarized and quantified in the maximized modularity measure that reached very low values, meaning a low expected modular behavior (0.12, 0.14, and 0.07, respectively) (Newman, 2006). Node distribution through modules agrees with the evolution of the relationships of EEG activity and PSG/cognitive variables from controls to moderate/severe OSA, the latter showing a module shared by all non-EEG nodes and the C3 channels of β_2 and γ bands.

The EEG irregularity networks showed a more modular behavior (**Figures 5D–F**). Controls, mild OSA, and moderate/severe OSA showed eight, six, and five modules, respectively, with concordant maximized modularity values (0.35, 0.29, and 0.19) that quantify the vanishing of the clustering tendency. OSA worsening implied modules more shared by EEG and non-EEG nodes, as well as by EEG nodes from different spectral bands because of increased absolute correlations between them. Interestingly, four out of the five modules of moderate/severe OSA (**Figure 5F**) are shared by both EEG and non-EEG nodes. AHI, PPVT3, EVT, and Tow are with all the σ band nodes and most of δ_1. Similarly, AR, DAS, and PhPro are

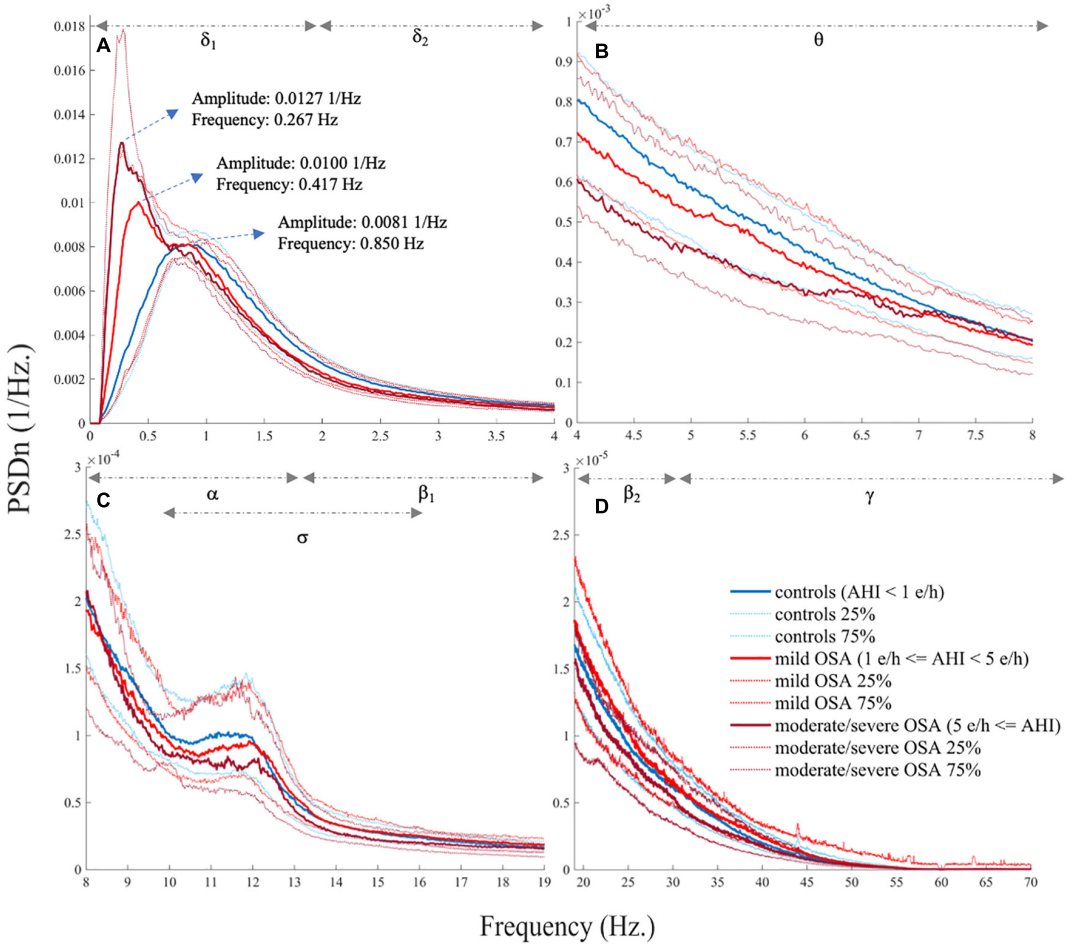

FIGURE 1 | Electroencephalogram (EEG) normalized spectrum (PSDn) averaged for the three obstructive sleep apnea (OSA) severity groups (median, 25%, and 75% quartiles), showing **(A)** δ_1 and δ_2, **(B)** θ, **(C)** α, σ, and β_1, and **(D)** β_2 and γ.

with all θ nodes and one node from δ_1 and δ_2. AS, WASO, and SleepEff are with most of β_1 and β_2. DesCop is with all α and γ nodes and most of δ_2. Finally, $Nadir_{SpO2}$ is the single node of the last module.

Supplementary Figures 1–8 show further assessment on the networks based on stability and centrality measures (Rubinov and Sporns, 2010).

DISCUSSION

The approaches undertaken to process the overnight EEG signal show the overall evolution of the activity (*RP*) and irregularity (*SpecEn*) of the overnight EEG as a function of pediatric OSA severity. Implicitly, we have also assessed the ability of *RP* and *SpecEn* to characterize the effects of pediatric OSA in the sleep EEG, with *SpecEn* being specifically used for the first time toward this goal. As such, current findings obtained using correlation networks unravel the existence of novel specific relationships between both activity and irregularity of the EEG, PSG variables, and cognitive scores in children with OSA. These initial observations open the door to more intense explorative analyses of the PSG as a source of not only clinical information regarding respiratory disturbance but also to provide improved phenotyping of cognitive morbidity in such patients, thereby allowing for tailored and personalized interventions and follow-up.

Electroencephalogram Correlation Networks Evolves With Obstructive Sleep Apnea Worsening

The behavior of the networks showed higher absolute correlations between the nodes as OSA severity increased, regardless of whether these were related to PSG, cognition, or EEG. Such evolution was supported by higher network densities, decreasing number of modules, and lower maximized modularity values. These results support the idea of a gradual pathological expression of OSA in the overnight EEG spectrum, with only the step between controls and mild OSA in the activity networks slightly disagreeing with this general tendency. This *a priori* incongruence might be explained by the AHI range represented

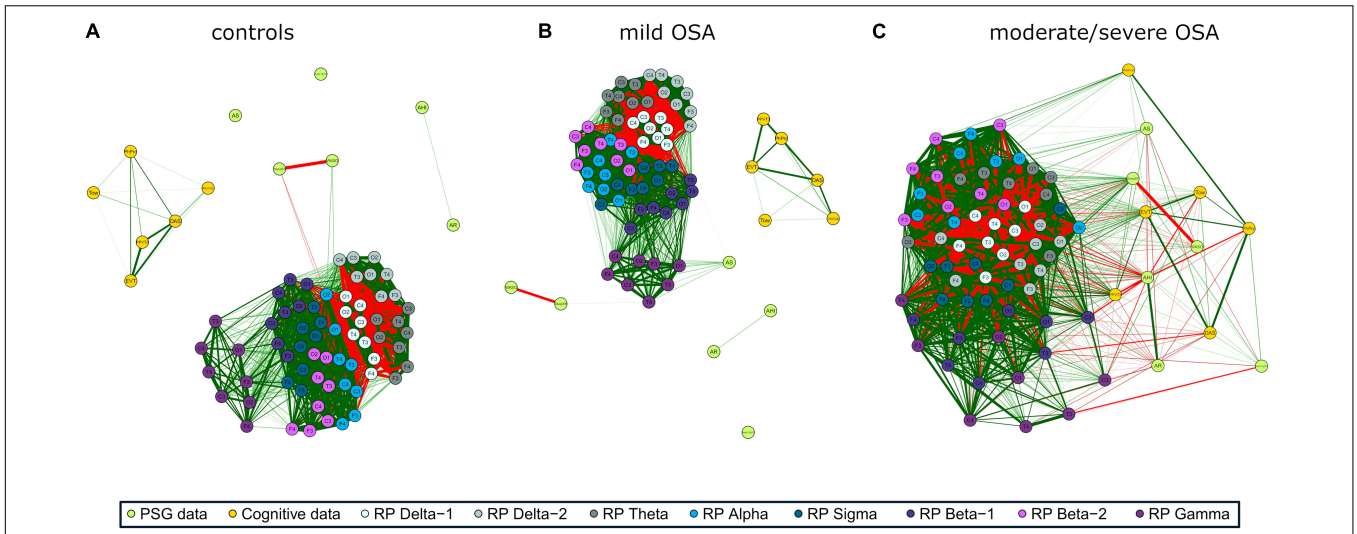

FIGURE 2 | EEG activity (*RP*) correlation networks with polysomnography (PSG) variables [apnea–hypopnea index (AHI), AE, respiratory event-related arousals (AR), minimum oxygen saturation value ($Nadir_{SpO2}$), the number of minutes awake after sleep onset (WASO), and sleep efficiency (SleepEff)] and cognitive scores [differential ability scales (DAS), Peabody Picture Vocabulary Test (PPVT3), Expressive Vocabulary Test (EVT), design copying (DesCop), phonological processing (PhPro), and Tower (Tow)] for **(A)** controls, **(B)** mild OSA, and **(C)** moderate/severe OSA. Wider edges are higher Spearman's correlation absolute values | ρ|, with red color meaning negative correlation and green positive correlation. Solid lines represent | ρ| $\geq$ 0.50.

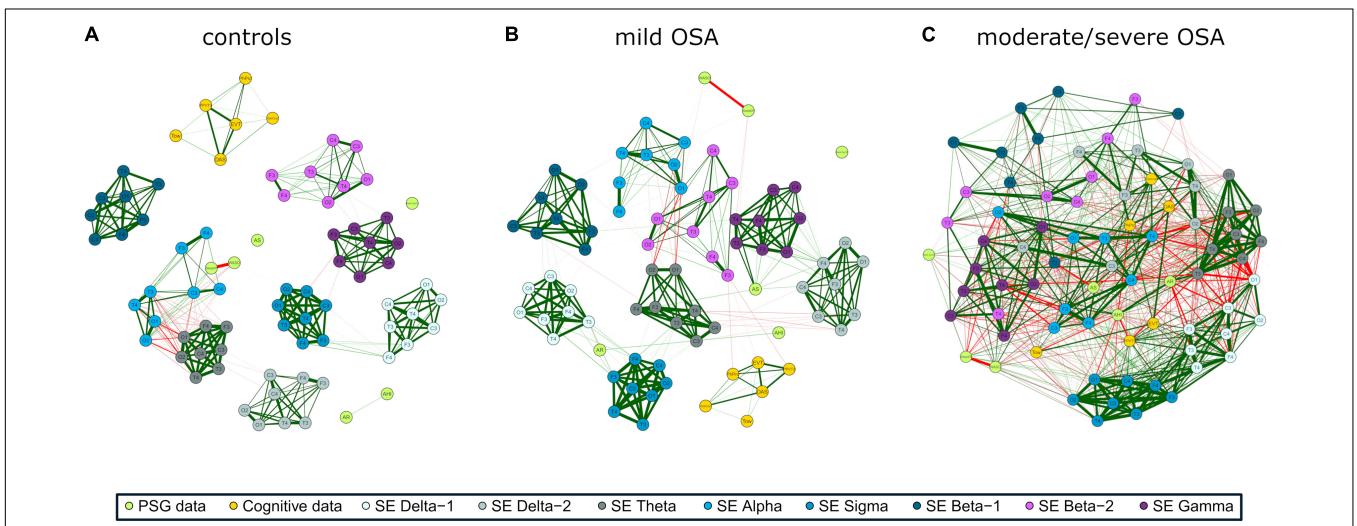

FIGURE 3 | EEG irregularity (*SpecEn*) correlation networks with PSG variables (AHI, AE, AR, NadirSpO2, WASO, and SleepEff) and cognitive scores (DAS, PPVT3, EVT, DesCop, PhPro, and Tow) for **(A)** controls, **(B)** mild OSA, and **(C)** moderate/severe OSA. Explanations regarding the construction of the networks are analogous to those from **Figure 2**.

in our mild OSA group, whose median value (1.5 e/h) is much closer to control threshold (1 e/h) than to the low limit of moderate/severe OSA (5 e/h). This is a potential limitation of our study, whereby the absence of equally distributed AHI values in mild OSA may be hiding higher correlations with the EEG information. However, further investigation would be required to confirm these premises.

Activity *RP* networks were denser and less modular than irregularity *SpecEn* networks. This finding reveals the presence of more similarities among the information offered by *RP* than the corresponding one provided by *SpecEn*, suggesting the representation of a broader variety of information by the latter. However, in both activity and irregularity networks, the information contained in the overnight EEG spectrum became more similar as OSA worsened. Although this effect is clearer for irregularity spectral bands, it is also present in activity ones, which suggests that OSA affects EEG over a wide range. This finding is consistent with recent studies on continuous influence on the EEG of OSA-affected children due to different abnormal respiratory patterns during sleep (Guilleminault et al., 2019).

The moderate/severe OSA group showed the strongest correlations between EEG and non-EEG nodes. This is not

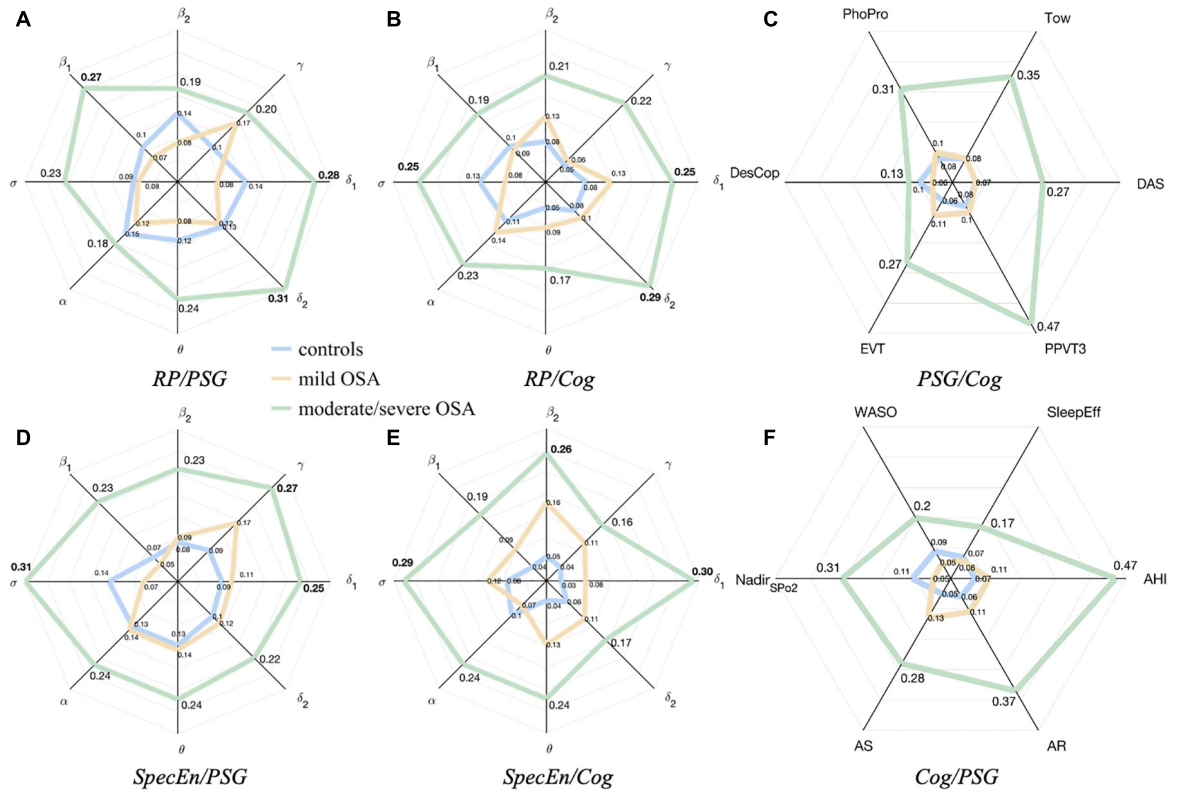

FIGURE 4 | Radar charts summarizing the averaged absolute correlation values between the sleep EEG, the PSG variables, and the cognitive scores. **(A,B)** correspond to relationships with EEG activity (*RP*). **(D,E)** correspond to relationships with EEG irregularity (*SpecEn*). **(C,F)** correspond to averaged correlations of PSG variables with each cognitive score and averages cognitive scores with each PSG variable. The distances from the center represent the average absolute correlations for controls (blue), mild OSA (yellow), and moderate/severe OSA (green).

surprising for the PSG variables, since they either directly reflect pathophysiological events (AHI, AR, and $Nadir_{SpO2}$), or they are indirectly affected by the occurrence of these (WASO, SleepEff, and AS). Regarding cognitive scores, only EEG irregularity in β_2 showed non-negligible (but weak) relationships in networks other than those from the moderate/severe group. The combined indication of these weak associations and the stronger correlations found for the highest severity degree, may be suggesting that sleep EEG does not robustly reflect cognition, in general, at least in an overnight scale, but reflects cognitive alterations in the presence of the most severe degrees of OSA. These results agree with the decreasing tendencies in all our cognitive scores as OSA worsens and the significantly lower values in some of these measures. Our findings also agree with previous reports pointing to a higher risk of cognitive deficits in moderate/severe OSA children (Hunter et al., 2016).

Electroencephalogram Activity and Irregularity Characterize Specific Relationships

Correlation network and modularity analyses highlighted interesting associations of the EEG with PSG and cognitive variables in moderate/severe OSA. EEG δ_1 and δ_2 bands played a key role in both activity and irregularity networks. As reflected in **Figures 2C**, **5C**, activity in these bands was mainly associated with the PSG variables AHI, SleepEff, (δ_1 and δ_2), and AR (δ_2)—absolute correlation through the EEG channels in the ranges 0.35–0.58, 0.26–0.48, and 0.31–0.43, respectively, as well as the cognitive scores PPVT3, EVT, and Tow—ranging 0.30–0.53, 0.31–0.53, and 0.31–0.42. Similarly, irregularity in δ_1 and δ_2 was mainly related to AHI (δ_1), AR (δ_1 and δ_2), and AS (δ_1 and δ_2), ranging 0.41–0.48, 0.31–0.66, and 0.31–0.52, respectively, with δ_1 being also associated with DAS (0.33–0.38), PPVT3 (0.49–0.61), and EVT (0.32–0.54). EEG σ band also exhibited meaningful associations in both networks, with activity being principally related to PSG variables AS (0.19–0.48) and SleepEff (0.11–0.50) and with the cognitive score PPVT (0.31–0.49). Likewise, σ irregularity was mainly related to AHI (0.35–0.58), SleepEff (0.28–0.51), PPVT3 (0.43–0.59), and EVT (0.36–0.46).

Interestingly, EEG irregularity also showed major absolute correlations beyond δ_1, δ_2, and σ: with PSG variables in θ (AHI: 0.30–0.57, AR: 0.46–0.67) and γ (AHI: 0.34–0.61, WASO: 0.40–0.55), and with cognitive scores in β_2 (DesCop: 0.31–0.65, PhPro: 0.32–0.74, Tow: 0.32–0.52). These irregularity further associations reached the strongest correlations of any single EEG node with AHI (0.61), AR (0.67), PhPro (0.74), and Tow (0.52), or were very close to the strongest for WASO (0.57) and DesCop (0.66), which were also obtained using irregularity. The EEG activity nodes, thus, reached

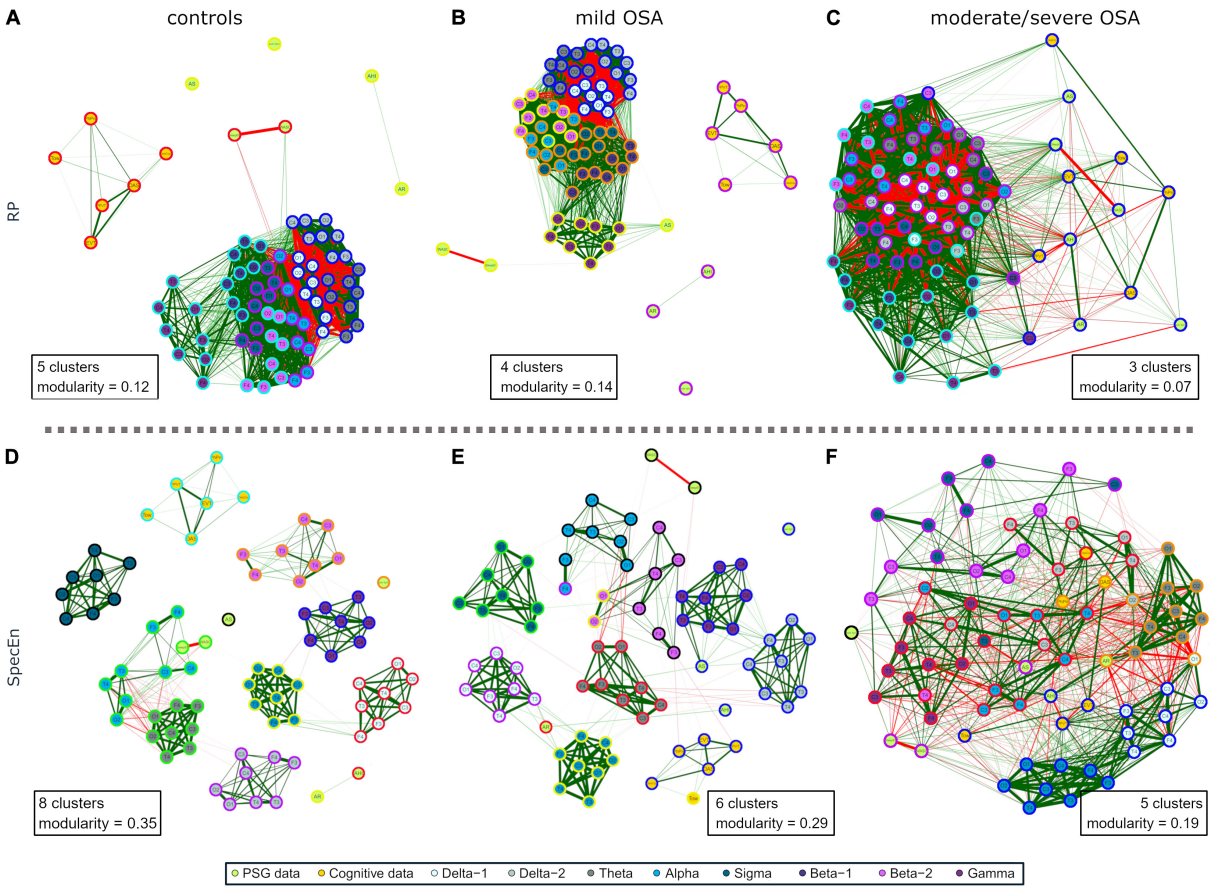

FIGURE 5 | Modularity analysis of the correlation networks of each group using **(A–C)** EEG activity (*RP*) and **(D–F)** EEG irregularity (*SpecEn*). The color of the external circles represents belonging to the same module within each correlation network.

higher maximum absolute correlations with non-EEG variables only in relationships with DAS (0.58) and Nadir$_{SpO2}$ (0.60). This suggests the usefulness of irregularity measured by *SpecEn* to characterize both physiological perturbations and cognitive effects, which adds novelty to the classic activity-based analysis.

Another interesting comparison arose when assessing the maximum absolute correlations found for the PSG variables and cognitive scores in the moderate/severe OSA group. Whereas radar charts (**Figure 4**) showed half of the averaged correlations between PSG/Cog and Cog/PSG higher than those with EEG nodes, only AHI, PPVT3 and Tow reached the highest values in nodes other than *RP* or *SpecEn*. Accordingly, 14, 7, 3, 5, and 14 EEG nodes (either *RP* or *SpecEn*) reached absolute correlations higher than the highest with non-EEG nodes for AR, AS, Nadir$_{SpO2}$, WASO, and SleepEff, respectively. Similarly, 6, 33, 32, and 1 EEG nodes reached absolute correlations higher than the highest with non-EEG nodes for DAS, EVT, DesCop, and PhPro, respectively. Moreover, the maximum absolute values for AHI (0.65 with PPVT3), PPVT3 (0.65 with AHI), and Tow (0.58 with AHI) were almost reached by EEG nodes too (0.61, 0.62, and 0.52, respectively). These figures highlight that the information contained in the EEG reaches a more complete characterization of the cognitive performance than PSG variables in moderate/severe OSA, as well as a more complete characterization of this disease state than cognitive scores. Moreover, in contrast to the PSG variables and cognitive scores, the *SpecEn* and *RP* computing is automated.

Correlation Networks Help Expand Current Knowledge

The found relationship between δ activity and AHI agrees with previous studies reporting differences in slow wave sleep activity (SWS) in OSA-affected children (Bandla and Gozal, 2000; Christiansz et al., 2018). Moreover, we have shown that not only activity in δ but also irregularity in δ, θ, σ, and γ reflects AHI. These bands have been previously associated with arousals and other different wakefulness states (De Gennaro et al., 2001; Scholle and Zwacka, 2001; Cantero et al., 2004; Vanhatalo et al., 2004; Le Van Quyen et al., 2010), suggesting that the most consistent relationships between moderate/severe OSA and EEG activity and irregularity are related to micro and macro sleep disruptions. Coherent with this idea are the also uncovered associations between the EEG information

and AR (δ_1, δ_2, and θ), SleepEff (δ_1, δ_2, θ, σ, and γ), and WASO (γ).

A few studies exist assessing relationships between δ and cognition during sleep in either healthy or OSA-affected children. Weichard et al. (2016) analyzed the EEG of 42 children (13 controls, 15 resolved OSA, and 14 unresolved OSA). They found associations between increased verbal performance and late SWS, which agrees with the relationships of EEG activity in δ_1/δ_2 with PPVT3 (receptive language) and EVT (expressive language) shown in this study. Interestingly, we found stronger relationships between δ_1 and receptive and expressive language using EEG irregularity. Similarly, neither their study nor ours report strong associations of δ activity with DesCop (visual–spatial processing) and PhPro (phonological processing). However, we do expose robust associations of EEG irregularity in β_2 with both cognitive scores. Christiansz et al. (2018) extended the previous work to 72 children and found associations between SWS activity and impaired executive function in OSA presence, showing absolute correlations of 10 different tests in the range 0.33–0.78 (Christiansz et al., 2018). Their observations agree with the non-negligible correlations found between Tow test and δ_1/δ_2 activity of moderate/severe OSA (0.31–0.42). Moreover, our method allowed us to find the strongest correlation with Tow score using β_2 irregularity (0.52).

Brockmann et al. (2018) implemented a different approach by assessing the spindle pattern of 14 controls and 19 mild OSA children. Spindle density was significantly lower in the latter, which also showed associations with Wechsler Intelligence Test for Children total IQ, verbal comprehension, working memory, and processing speed (Brockmann et al., 2018). Spindle frequencies in children ($\approx$10–16 Hz.) are within σ band (Purcell et al., 2017; Markovic et al., 2020), which showed only negligible associations in our mild OSA group. This discrepancy may be due to the different cognitive tests used and that sleep spindles occur mostly in N2 non-rapid-eye movement (NREM) sleep. However, we found some robust relationships between the cognitive scores of moderate/severe OSA with the corresponding σ activity and irregularity values (see "correlation matrices.xlsx"), thus, pointing again to the overrepresented low AHI values in our mild OSA group as the cause for the differences with their results. Brockmann et al. (2020) complemented their previous study by assessing spindle differences in 20 control children and 20 primary snorers, who showed decreased spindle density. This is an interesting finding that agrees with the decreased activity and regularity of our σ band as OSA degree is higher. However, we are precluded from further comparisons since the inclusion of a primary snoring group is both a limitation of our study and a future goal.

Interpretations of the *SpecEn* Characterization on Sleep Electroencephalogram

A preliminary effort focused on the analysis of overnight EEG activity in the context of pediatric OSA (Gutiérrez-Tobal et al., 2019b) laid the foundation for the in-depth evaluation conducted in this study, including the use of *SpecEn*, a wider range of sleep cognitive scores, and common sleep indices from the PSG. As a result, *SpecEn* demonstrated its ability to characterize both PSG variables and cognitive scores, particularly in the case of moderate/severe OSA children, enabling higher absolute correlations than *RP* with most of the non-EEG nodes considered.

According to the correlation network and modularity analyses, the *SpecEn* ability to characterize a wider range of EEG information may underlie these improvements in the strength of the associations identified herein. One reason for such superiority as shown by *SpecEn* may be related to the finite nature of *RP*. Spectrum normalization by its total spectral power is a common tool to avoid the characterization of features different from the object of the study, which, in this case, are the OSA effects on sleep EEG. However, this technique leads to the sum of all *RP*s from the same EEG being 1, thus, providing the *RP* from each spectral band with a competitive essence. Consequently, the *RP* from one spectral band may be related to the others either because a genuine subjacent event is reflected in several spectral bands or, if this shared event does not exist, because an increase in the *RP* of one spectral band means a decrease in the *RP* in the others (to end up with a total sum of 1). This characteristic would also explain the less modular behavior of the *RP* networks. In contrast, the shape of the spectrum (its peakedness or flatness) does not impose the same limitation, since a dominant peak in one spectral band does not imply changes in the occurrence of dominant peaks in other spectral bands. Consequently, one possibility is that *SpecEn* relationships between spectral bands may be reflecting only genuine subjacent events. One example would be the positive relationships between δ_1, σ, and γ found in the *SpecEn* correlation network of controls, which would be coherent with the hierarchical relationships between SO, spindles, and ripples described in the literature (Staresina et al., 2015). Another example in the same network would be the negative relationships found in the occipital channels of θ and α, which are coherent with the transitions between N1 and "wake" stages in which they are involved, respectively (Iber et al., 2007).

Assuming that the *SpecEn* sleep EEG characterization indeed reflects genuine subjacent events, interesting physiological interpretations can be derived from our results. First, as mentioned above, **Figure 1A** shows a decrease in SO frequency with OSA severity. In the control group, SO is located within its normal range: $\approx$0.75 Hz and within (0.55–0.95 Hz) (Achermann and Borbély, 1997). However, the frequency gradually slows down for mild OSA (0.417 Hz) and moderate/severe OSA (0.267 Hz). A progressive increase in the amplitude of the SO peak can be also observed from 0.0081 1/Hz in controls to 0.0100 1/Hz, and 0.0127 1/Hz in mild and moderate/severe OSA. SOs are sleep waves characterized by periods in which cortical and thalamic neurons alternate states of intense synaptic activity, or up states, with the almost complete absence of activity, or down states (Neske, 2016). The functions of SO are still under discussion, but growing evidence suggests that they comprise at least the synchronization of higher frequency oscillations, memory consolidation, and biochemical regulation

of neurons during down states (Neske, 2016). Both cortex and thalamus are involved in SO, the latter playing key roles in generating the up state (i.e., the generation of the oscillation period) and the synchronization of faster oscillations (David et al., 2013; Neske, 2016). It has been also observed that the suppression of the thalamic role leads to a deceleration of the typical SO frequency in rodents, suggesting cortical attempts to mimic the role of thalamus (David et al., 2013; Neske, 2016). Accordingly, our results may be showing that OSA inhibits the role of thalamus in SO, with this inhibition becoming more intense as the illness is more severe. Moreover, the increased normalized power in the corresponding SO frequencies of mild and moderate/severe OSA may be reflecting that more time is spent overnight in these frequencies compared with controls. This increased time could be related to an inefficiency of the cortex when assuming the abovementioned thalamus roles. Concurrently, *SpecEn* in δ_1 may be characterizing an increasing regular behavior of the cortex when trying to compensate the absence of the thalamus as this is more inhibited. Why thalamus function is inhibited with OSA remains unclear. However, it might be related to an increase in the consciousness/arousal degree that would be needed to recover from respiratory events. In the absence of a proper evaluation of this hypothesis, it would be supported by the fact that the cortex activity is increased, as well as by previous studies reporting that the power in δ band is higher and the EEG irregularity is lower when recovering from OSA-related respiratory events (Huang et al., 2018).

A second interpretation can be derived from the flattening experimented in most of the spectral bands beyond δ_1, particularly in the moderate/severe OSA group. A significant increased number of respiratory arousals per hour (see **Table 1**) may be one possible explanation. These EEG events are known to present frequencies in the range of θ, α (except spindles), β_1, β_2, and γ (Iber et al., 2007). They have been also related to some changes in δ band (Bandla and Gozal, 2000; Bruce et al., 2011). Therefore, they can contribute to the spectral power of almost the whole frequency range in a white noise-like behavior. This means that adding these events to the normal EEG could make all its spectral components to be more distributed or flatter, thus, increasing the information similarity among the affected spectral bands. In our study, the meaningful correlations found in all the spectral bands between *SpecEn* and AR make respiratory arousals one of the most central nodes of the moderate/severe correlation network (see **Supplementary Figure 6**), thus, supporting this explanation. In addition, previous works have reported positive correlations between entropy measures on hypnogram and traditional sleep fragmentation measures such as arousal index and sleep efficiency (Kirsch et al., 2012). Another explanation, which does not exclude the previous one, is related to the abovementioned inefficiency of cortex when mimicking the role of thalamus to synchronize higher-frequency oscillations (Neske, 2016). If such synchronization is not properly conducted in moderate/severe patients, a regular behavior is lost (or at least reduced), thus, increasing the EEG irregularity and, consequently, the flatness of the affected spectral components. Further *ad hoc* studies would be required to assess whether any of these two explanations are right.

Finally, to complete the *SpecEn* interpretation, we propose a connection with our cognitive results. A recent systematic review has established speech and language problems in children suffering from OSA (Mohammed et al., 2021). This is aligned with the maximum correlations found between *SpecEn* in δ_1 and PPVT3 (+0.61) and EVT (+0.54) of moderate/severe OSA children, which could be indicating that the impairment of these verbal skills could be measured through the increased regularity (increased peakedness) in this spectral band. Accordingly, the language problems could be somehow associated with the abovementioned thalamus inhibition in SO due to OSA. Interestingly, the third language ability score evaluated in this study, PhPro, was strongly associated with irregularity in β_2 (+0.74), suggesting a different physiological process involved. This idea would be supported by the other correlations found between β_2 and DesCop (+0.65) and Tow (+0.52) scores, which account for visuospatial processing and executive function, respectively. Beta oscillations are common in REM sleep (Vijayan et al., 2017). Although the role of REM sleep and cognition has not been completely delineated, it has been linked to neural network reorganization leading to new neural associations and an increased creativity (Cai et al., 2009; Mason et al., 2021). However, whether these results are associated with altered REM sleep must be further assessed.

Other Limitations and Future Steps

Despite the large database used, the number of moderate/severe subjects is relatively low when comparing with the other groups. We have implemented a bootstrap procedure to account for the median of the correlation distributions and minimize the effect of the imbalance. However, future analyses on children with moderate/severe OSA would improve the statistical power of our results. It would also be very interesting to assess our analyses in symptomatic children referred for clinical evaluation. Moreover, there is substantial skepticism as to the validity of AHI and OSA symptomatology or morbidity (Penzel et al., 2015). This AHI limitation may explain why some cognitive scores do not reach significant differences among our OSA severity groups. The cognitive morbidity of OSA is well established (Gozal, 1998; Marcus et al., 2012; Hunter et al., 2016; Tan et al., 2017; Cardoso et al., 2018), and indeed, all our scores exhibit decreasing tendency as OSA worsens. However, the combination of an unclear association between AHI and OSA symptoms and the assessment of a general community-based nonreferral cohort may have resulted in the inclusion of children with AHI $\geq$ 1 e/h but without any symptoms or morbidity. Another limitation is the specific EEG arrangements we followed. We used the typical EEG channel configuration of sleep studies and the Common Averaged Reference method to minimize the influence of the other channels in each electrode (Cox and Fell, 2020). However, other configurations may lead to different results. On the other hand, we included Nadir_{SpO2} in our analyses because it has been observed that the depth of desaturations is associated with increased OSA-related negative consequences in adults (Kulkas et al., 2013; Karhu et al., 2021). However, it would be an

interesting future goal to assess other oximetric variables such as oxygen desaturation index or hypoxic burden. Similarly, the inclusion of children's subjective sleepiness scores in the analysis could complement our findings. Other interesting future goal would be to analyze the EEG recordings by separating REM and NREM sleep stages. In this study, we have shown that OSA-related changes in EEG were evident even without the labor-intensive task of defining REM and NREM sleep. However, this further analysis would help interpret some of our findings. In addition, it could enhance relationships between cognitive scores and specific EEG information in control subjects. Ultimately, another limitation is the age range of the subjects involved in the study. We have conducted several actions to avoid a bias of our results toward age-related natural brain development. First, the age range is not wide (5–9 years). Second, our control and OSA groups are matched in age. Finally, all the correlations used in the study were controlled for age (and sex). However, EEG changes are present in sleep as a consequence of typical development (Gaudreau et al., 2001; Kurth et al., 2010; Gorgoni et al., 2020), which is the reason why our findings should be evaluated in other age ranges.

CONCLUSION

Pediatric OSA broadly affects overnight EEG and progressively equates the information of its different spectral bands, regardless of whether it refers to activity or irregularity. Such effects on EEG are coherent with the occurrence of micro and macro sleep disruptions. They also reflect cognitive morbidity, particularly in domains involving language processes, visual–spatial processing, and executive function. Sleep EEG irregularity characterizes a wider range of OSA-related information than the classic activity analysis, which results in more numerous and enhanced robustness in their associations with both physiological and cognitive variables. The results from our correlation network approach were coherent with the previous studies, while expanding the knowledge about the EEG classic spectral bands. Thus, our findings illustrate that the EEG spectrum echoes physiological perturbations during sleep and adverse cognitive consequences of pediatric OSA. It may therefore provide a tool to identify children with OSA who are at increased risk of cognitive deficits, thereby enabling a more personalized approach to its evaluation and management.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of restrictions from the ethical committee. The data that support the findings of this study are, however, available on reasonable request from the corresponding authors. Requests to access the datasets should be directed to GG-T, gonzalo.gutierrez@gib.tel.uva.es.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Chicago (protocol # 09-115-B). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GG-T conceptualized and designed the study, analyzed and interpreted data, drafted the initial manuscript, and reviewed the manuscript. JG-P conceptualized the study, analyzed and interpreted data, and contributed to the manuscript editing and reviewing. LK-G conceptualized the study, recruited and diagnosed the subjects, analyzed the data, and reviewed the manuscript. AM-M, JP and DÁ contributed to the data analysis and interpretation, and reviewed the manuscript. FC contributed to the data analysis and interpretation and critically reviewed the manuscript for important intellectual content. DG and RH conceptualized the study, supervised data collection, conducted the data analysis and interpretation, drafted components of the manuscript, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the "Ministerio de Ciencia, Innovación y Universidades" and the "European Regional Development Fund (FEDER)" under projects DPI2017-84280-R, RTC-2017-6516-1, and PGC2018-098214-A-I00, by the "European Commission" and "FEDER" under project "Análisis y correlación entre el genoma completo y la actividad cerebral para la ayuda en el diagnóstico de la enfermedad de Alzheimer" ("Cooperation Programme Interreg V-A Spain–Portugal POCTEP 2014–2020"), and by CIBER-BBN (ISCIII), cofunded with FEDER funds. DG and LK-G are supported by the United States National Institutes of Health grants HL130984 (LK-G) and HL140548 (DG).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.644697/full#supplementary-material

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frontiers in Neuroscience

MINI REVIEW
published: 12 November 2021
doi: 10.3389/fnins.2021.755464

Cardiopulmonary Sleep Spectrograms Open a Novel Window Into Sleep Biology—Implications for Health and Disease

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The interactions of heart rate variability and respiratory rate and tidal volume fluctuations provide key information about normal and abnormal sleep. A set of metrics can be computed by analysis of coupling and coherence of these signals, cardiopulmonary coupling (CPC). There are several forms of CPC, which may provide information about normal sleep physiology, and pathological sleep states ranging from insomnia to sleep apnea and hypertension. As CPC may be computed from reduced or limited signals such as the electrocardiogram or photoplethysmogram (PPG) vs. full polysomnography, wide application including in wearable and non-contact devices is possible. When computed from PPG, which may be acquired from oximetry alone, an automated apnea hypopnea index derived from CPC-oximetry can be calculated. Sleep profiling using CPC demonstrates the impact of stable and unstable sleep on insomnia (exaggerated variability), hypertension (unstable sleep as risk factor), improved glucose handling (associated with stable sleep), drug effects (benzodiazepines increase sleep stability), sleep apnea phenotypes (obstructive vs. central sleep apnea), sleep fragmentations due to psychiatric disorders (increased unstable sleep in depression).

Keywords: cardiopulmonary coupling (CPC), heart rate variability, sleep apnea, stable sleep, insomnia

OPEN ACCESS

Edited by:
David Gozal,
University of Missouri, United States

Reviewed by:
Danny Joel Eckert,
Flinders University, Australia
Boris Heifets,
Stanford University, United States

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *08 August 2021*
Accepted: *08 October 2021*
Published: *12 November 2021*

Citation:
Al Ashry HS, Ni Y and Thomas RJ (2021) Cardiopulmonary Sleep Spectrograms Open a Novel Window Into Sleep Biology—Implications for Health and Disease. Front. Neurosci. 15:755464. doi: 10.3389/fnins.2021.755464

INTRODUCTION

The prevalence of sleep disorders has been increasing over the last two decades (Acquavella et al., 2020). Disorders like insomnia and sleep apnea have a prevalence of as much as 20% in the general population (Franklin and Lindberg, 2015; Acquavella et al., 2020). There is a need for nimble sleep state estimation, diagnostics, and tracking. One approach seeing increasing utilization both in formal medical and consumer wearable devices is through analysis of heart rate and respiration. There is a strong correlation between changes in heart rate variability and sleep during health and disease (Tobaldini et al., 2013). High frequency (HF) components mainly present parasympathetic activity, while low frequency (LF) components is partly a quantitative marker of sympathetic modulation. LF and the LF/HF ratio are high in Wake and decrease in NREM sleep, peaking once more during REM sleep, while HF follows the opposite trend. Deep NREM sleep (N3) typically has the greatest HF power. Sleep disruptive influences such as sleep apnea (Qin et al., 2021; Ucak et al., 2021), insomnia (Spiegelhalder et al., 2011; Dodds et al., 2017; Cosgrave et al., 2021), and depression (Hyunbin et al., 2017; Gao et al., 2019; Eddie et al., 2020) are associated with an increase in the LF components.

Different techniques have been used to assess for such changes one of which is analysis of cardiopulmonary coupling and coherence (CPC) patterns. In this technique a single lead electrocardiogram (ECG) or photo plethysmogram (PPG) is used to extract heart rate variability and ECG or PPG signal derived respiration (EDR/PDR) (Thomas et al., 2005; Hilmisson et al., 2020). Contrary to the stage/grade approach to conventional sleep characterization, CPC analysis based on coupling and coherence provides a novel and complementary view of sleep, that of bistability, which are particularly well defined during NREM sleep. Thus, distinct patterns of CPC are observed: high frequency coupling (HFC) which is associated with stable NREM sleep and low frequency coupling (LFC) which is associated with unstable and often fragmented NREM sleep (Thomas et al., 2005). A third CPC pattern named very low frequency coupling occur in both REM sleep and wake, which may be differentiated by analysis of signal quality and motion artifact (Al Ashry et al., 2021). High and low frequency coupling are mutually exclusive and shift logically with disease states and treatments. For example, there is an increase LFC in patients with insomnia and this can be tracked in the ambulatory setting (Thomas et al., 2017a,b). There is increased LFC during sleep in unmedicated patients with major depression and improvement with therapy of major depression (Yang et al., 2011). Integrating CPC with oximetry allows generating a true FDA approved apnea-hypopnea index (AHI), which shows good correlation with conventional polysomnogram-derived AHI (Hilmisson et al., 2020; Al Ashry et al., 2021).

The overall goal of this article is to review physiological basis, techniques, and applications of CPC spectrograms in sleep in health and disease. There are three aims for this review, to show that—(a) CPC shows a fundamental characteristic of NREM sleep—bimodality, across a number of physiologies; (b) CPC has several uses in sleep apnea care—diagnosis, phenotype, tracking outcomes; (c) CPC can diagnose and track non-apneic sleep fragmentation and medication effects, and should be used in the appropriate clinical context.

PHYSIOLOGY BACKGROUND

Entrainment between heart rate and respiration in humans has been described since the early twentieth century (Galletly and Larsen, 1998). It has been suggested that such synchrony between heart rate and respiration improves pulmonary gas exchange and computational models have shown that healthy cardiopulmonary coupling minimizes the heart workload while maintaining adequate ventilation (Yasuma and Hayano, 2004; Ben-Tal et al., 2012). Such strong cardiopulmonary coupling is seen at its best during deep sleep, sedation, and anesthesia (Dick et al., 2014). There is a critical influence of the autonomic nervous system on cardiopulmonary coupling (Bartsch et al., 2012). Non-rapid eye movement (NREM) sleep is associated with decreased sympathetic activity, a decrease in heart rate, and a decrease of average blood pressure and blood pressure variability in comparison to the wake state (Somers et al., 1993). Respiratory sinus arrythmia is a phenomenon in which the heart rate variability is synchronized beat-to-beat with respiration and is most pronounced during deep NREM sleep (Zemaityte et al., 1984; Yasuma and Hayano, 2004). In contrast, during rapid eye movement (REM) sleep there is dominance of sympathetic control and a burst frequency of sympathetic activity that is actually higher than during wakefulness leading to increases in blood pressure variability and heart rates similar to what is seen during wakefulness (Somers et al., 1993). Using spectral analysis, a frequency of 0.1 Hz and above has been associated with parasympathetic activity dominance and frequencies below 0.1 Hz have been associated with dominance of sympathetic activity (Appel et al., 1989; Cui et al., 2020).

CARDIOPULMONARY COUPLING METHODOLOGY

Cardiopulmonary sleep spectrograms were first obtained from a single lead ECG (Thomas et al., 2005, 2007). ECG-derived respiration (EDR) is obtained either by using R-S wave amplitudes or variations in QRS complexes area (Zheng et al., 2016). Several studies have looked at improving the accuracy of deducing EDR from single lead ECG and reducing noise but is beyond the scope of this paper (Thayer et al., 1996; Leanderson et al., 2003; Liu et al., 2012; Zheng et al., 2016). In parallel to extracting the EDR, ectopic beats are identified and removed and normal sinus—normal sinus (NN) intervals are extracted and outliers are filtered (Thomas et al., 2005). After extracting the N-N interval series on ECG and its associated EDR, the signals are then resampled using cubic splines at 2 Hz. The Fast Fourier Transform is applied to 3 overlapping 512 sample sub-windows within the 1,024 coherence window. The 1,024 coherence window is then advanced by 256 samples (2.1 min) and the calculation repeated until the entire N-N interval/EDR series is analyzed. Thus, the cross-spectral power and coherence of these two signals are calculated over a 1,024 sample (8.5 min) window.

For each 1,024 window the product of the coherence and cross-spectral power is used to calculate the ratio of coherent cross power in the low frequency (0.01–0.1 Hz.) band to that in the high frequency (0.1–0.4 Hz.) band. The logarithm of the high to low frequency cardiopulmonary coupling ratio [log (HFC/LFC)] is then computed to yield a continuously varying measure of cardiopulmonary coupling (Al Ashry et al., 2021). While originally the ECG signal was used as input, any signal or signal set which encodes respiration and heart rate variability may be used to compute the CPC sleep spectrogram. **Figure 1** shows the steps in computing CPC.

DISTINCT CARDIOPULMONARY COUPLING PATTERNS IN SLEEP

Sleep Stages and Cyclic Alternating Pattern

The conventional characterization of sleep stages dictates a "graded" approach to NREM sleep, from lightest (N1) to

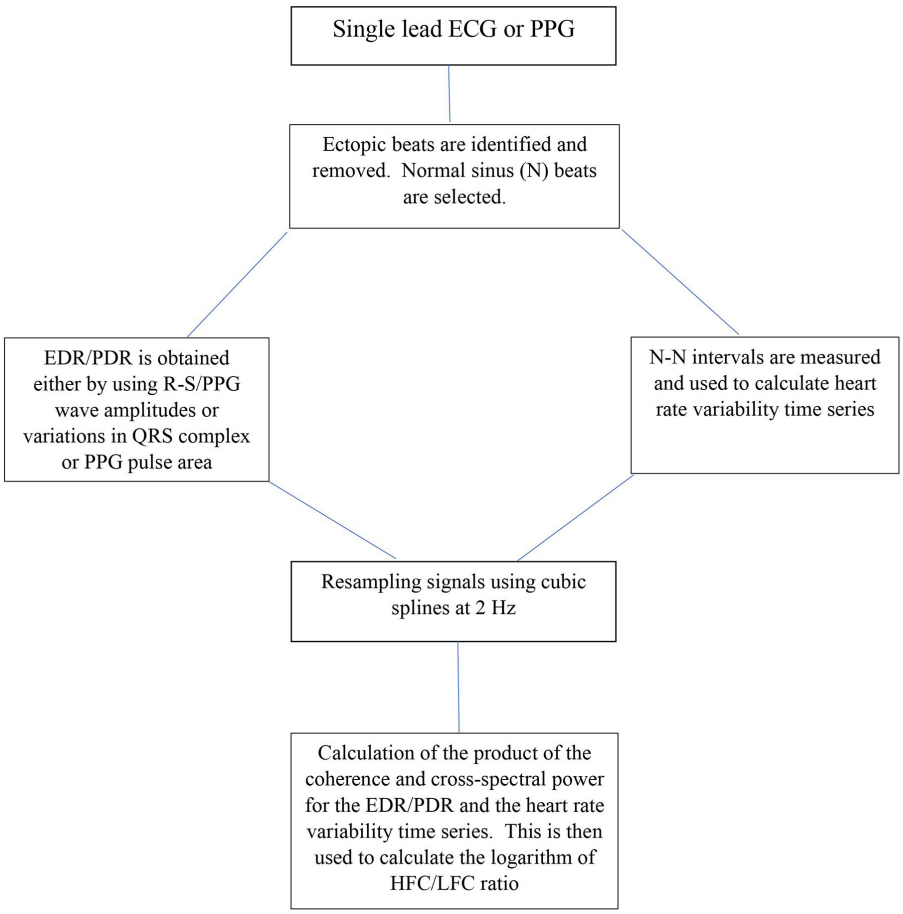

FIGURE 1 | Schematic for CPC analysis. ECG, Electrocardiogram; PPG, Photoplethysmogram; EDR, ECG-derived respiration; PDR, Photoplethysmogram derived respiration R-S and QRS are ECG waveforms; N-N intervals, Normal sinus to normal sinus intervals; Hz, frequency; HFC, high frequency coupling; LFC, low frequency coupling.

deepest (N3). The difference between N2 and N3 are relatively arbitrary, dependent on the proportion of high amplitude slow waves (20% threshold) for a given epoch. However, there is a great variability of depth of NREM sleep, as can be readily objectively demonstrated by techniques such as the Odds Ratio Product (Younes et al., 2015). A unique and key feature of CPC sleep states is poor correlation of HFC and LFC with conventional NREM sleep stages. Thus, in health, the majority if N2 is also HFC, N3 is usually HFC but at times LFC, while N1 is always LFC. There is a moderate correlation with a well-described stability dimension of NREM sleep, Cyclic Alternating Pattern (CAP) (Thomas et al., 2005). CAP is a distinct pattern that can be seen on electroencephalography (EEG) during unstable NREM sleep. High frequency coupling dominates when CAP is sparse or absent, while LFC is reliably associated with CAP. Conventional NREM stage N3 is usually HFC, but so is the majority of healthy N2, where non-CAP periods also dominate. Thus, CAP and CPC capture significantly overlapping domains of NREM sleep stability while both measures correlate only partially with conventional measures of sleep depth.

Slow Wave (Delta) Power

Slow-wave power in the sleep EEG has highly characteristic spatial and temporal evolution patterns across a night. Power in the 1–4 Hz frequencies dominates the first half of the night, but the ebb and flow of slow-wave power continues throughout the night. High frequency coupling strongly covaries with slow-wave power across the whole night, while low frequency power in heart rate variability is inversely related to EEG delta power (Brandenberger et al., 2001; Ako et al., 2003; Thomas et al., 2014). One interesting finding when aligning HFC with delta power is that there is a consistent lag of delta power after HFC where HFC usually precedes an increase in delta power by an average of 6 min, suggesting that subcortical/brain-stem mechanisms may lead large-scale cortical synchrony during sleep (Thomas et al., 2014).

Sleep Blood Pressure

A key dimension of health is a reduction of blood pressure during sleep (blood pressure "dipping"). Sleep blood pressure is known to dip during stage N3, and rise during REM

sleep, yet the majority of sleep is N2, and dipping profiles occupy the entire sleep period, not just N3-enriched zones. This discrepancy has been solved by correlating blood pressure during sleep with stable sleep as determined by CPC (high frequency coupling). Blood pressure dipping occurs only during HFC periods (Wood et al., 2020). In a randomized trial targeting sleep apnea treatment in patients with cardiovascular risk factors, it was shown that those who were treated with CPAP had more HFC during sleep, which was in turn associated with improvement in blood

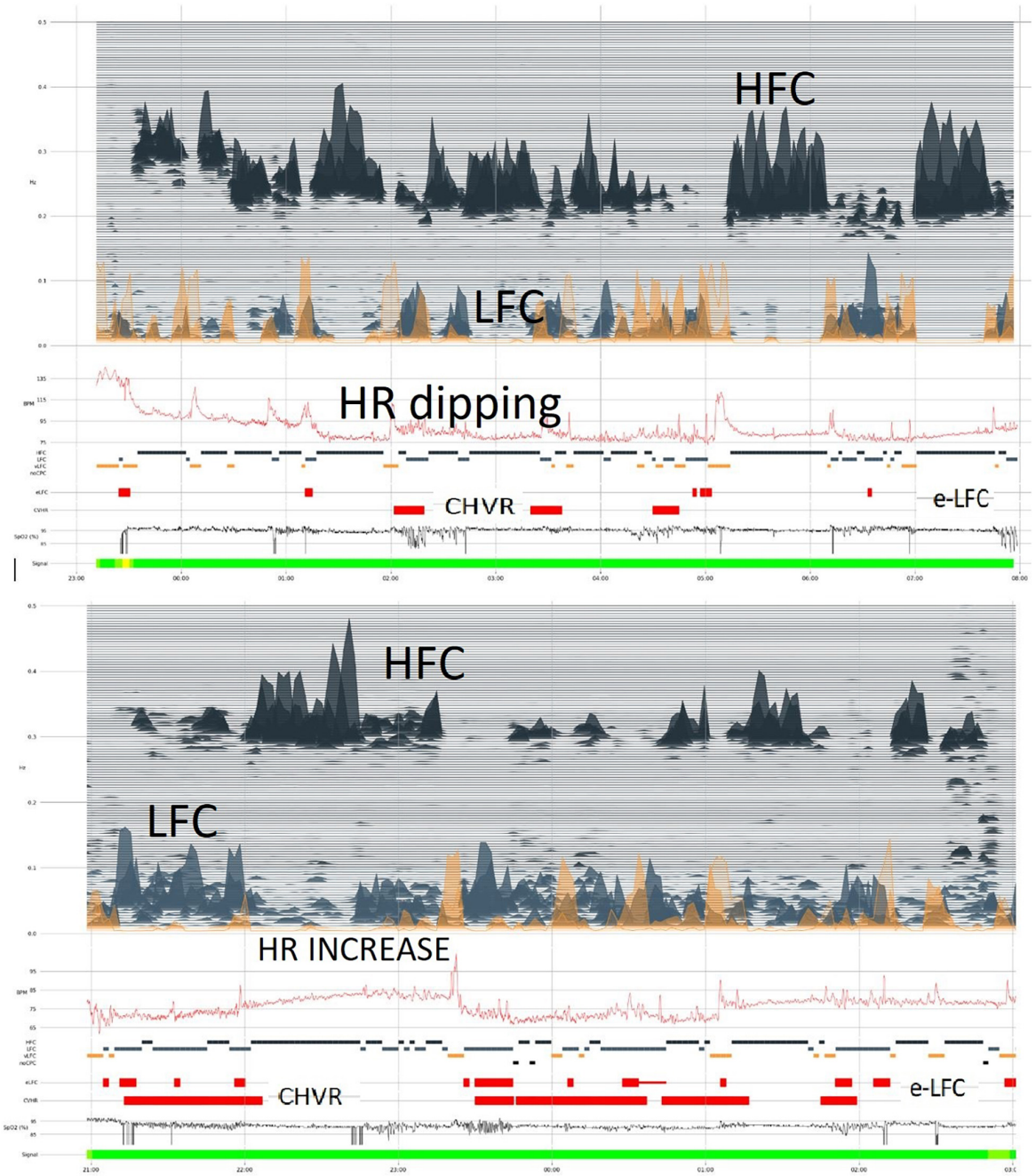

FIGURE 2 | Photoplethysmogram/oximetry-based CPC-heart rate analysis. The oximetry-based analysis provides a full CPC-sleep spectrogram, an apnea-hypopnea index by integrating CPC LFC and oxygen desaturation events, and a profile of heart rate across the night. In the upper segment of the figure, "dipping" of heart rate is noted along with abundant high frequency coupling/stable sleep. In the lower sample, there is less stable state, but the heart rate profile is distinctly abnormal, with an elevation even during stable state. Such relative tachycardia during stable NREM sleep may suggest obstructive hypoventilation. In both examples, oxygen desaturation itself is mild. Stable and unstable sleep (HFC and LFC, respectively) occur intermittently through the night. HFC, high frequency coupling; LFC, low frequency coupling; e-LFC, elevated low frequency coupling; HR, heart rate; CHVR, cyclic heart rate variation.

pressure dipping and mean arterial pressures during sleep (Magnusdottir and Hilmisson, 2018).

Autonomic Regulation During Sleep

There is normally a reduction of the heart rate (HR) during sleep, a HR-dip, which roughly follows the blood pressure dipping pattern. Heart rate during sleep is, however, far simpler to measure than blood pressure and provides a window into cardiovascular health. By aligning heart rate profiles with the CPC spectrogram (**Figure 2**), unique insights and cardiovascular risk profiles are potentially extractable, and can be tracked over time. Normally, HR dipping occurs during HFC periods.

Vertically Integrated Multi-Component Sleep States

Cardiopulmonary coupling analysis established that sleep is bimodal than graded. That is, while conventional NREM sleep stages moves across the N1 to N3 grades, the CPC-spectrogram

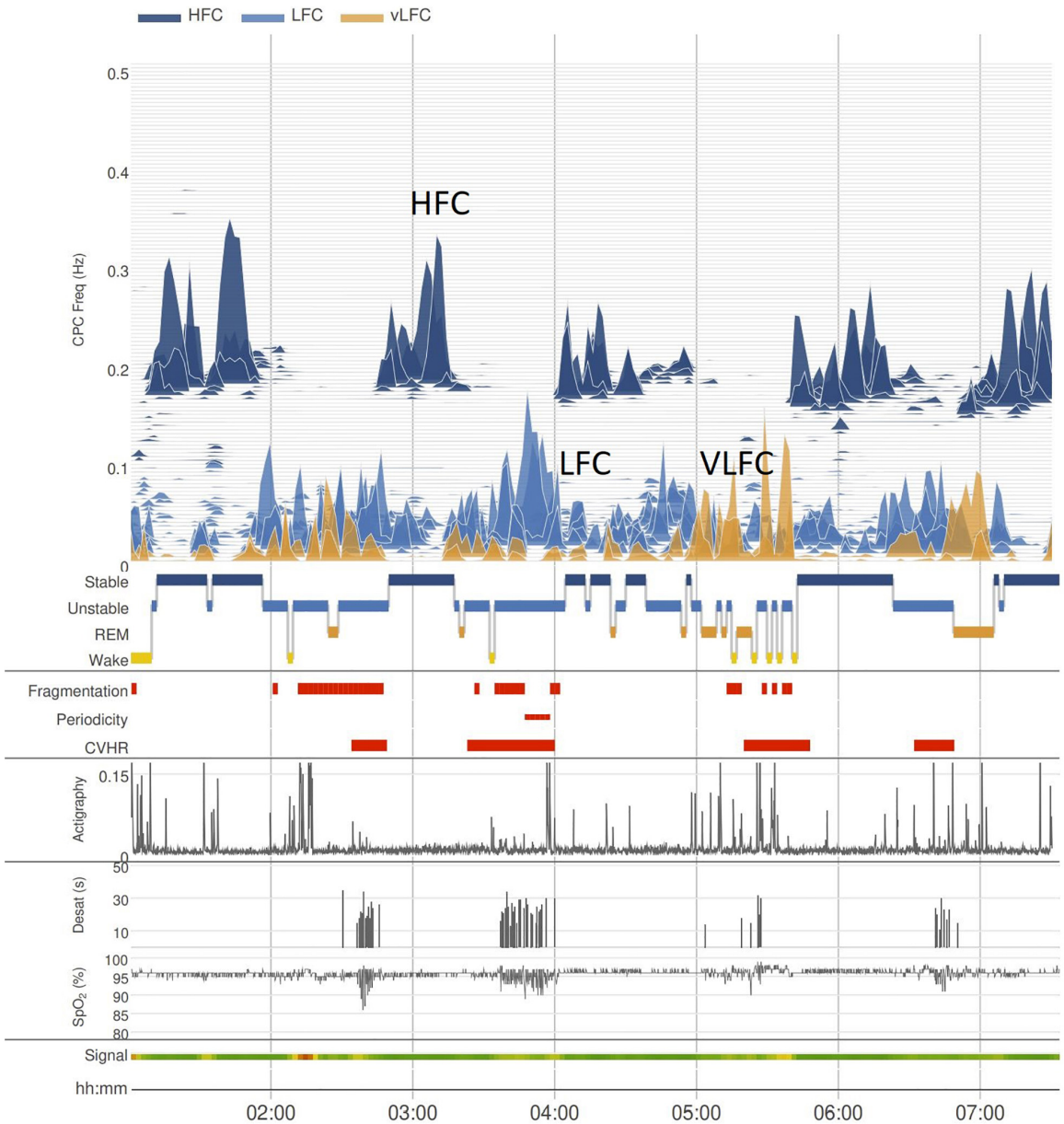

FIGURE 3 | The oximeter-extracted CPC spectrogram. The basic graphical representation of the CPC-spectrogram has high, low, and very low frequency coupling (HFC, LFC, and VLFC, respectively) components. Actigraphy is integrated, and VLFC without movement is considered REM sleep, whereas VLFC with movement is Wake. Cyclic variation of heart rate is also displayed, as well as e-LFC as a measure of sleep fragmentation. The oximeter signal itself provides standard oximetry metrics, such as an oxygen desaturation index. As shows, periods of HFC and LFC alternate throughout the night. LFC, low frequency coupling; VLFC, very low frequency coupling; HFC, high frequency coupling; CHVR, cyclic heart rate variation.

TABLE 1 | Studies that used cardiopulmonary coupling to diagnose and follow treatment response in various sleep disorders.

Study year	Number of subjects	Results
Section A: Studies that used cardiopulmonary coupling analysis to generate automated apnea-hypopnea index		
Roche et al. (2003)	147	Sensitivity of 92.4% and a specificity of 90.1%
Roche et al. (2004)	63	Receiver operating characteristic (ROC) showed area under the curve of 0.848
Vazir et al. (2006)	33	Sensitivity of 85%, specificity of 65%, positive predictive value of 61%, and a negative predictive value of 87%.
Heneghan et al. (2008)	92	Correlation coefficient between the CPC AHI and PSG AHI is: ($r = 0.88$, $p < 0.001$)
Chang (2009)	60	sensitivity of 68.97% and specificity of 100%
Al-Abed et al. (2009)	14	sensitivity, specificity and accuracy were 100.0, 99.9, and 99.9%, respectively
Hayano et al. (2011)	862	Receiver operating characteristic (ROC) showed area under the curve (AUC) of 0.913 for subjects with AHI 15 or higher
Guo et al. (2011)	63 children (mean age 6.2 years; range 2–12 years)	Compared CPC AHI to AHI from portable sleep testing device and found correlation coefficient of 0.70
Liu et al. (2012)	69	Receiver operating characteristic (ROC) showed area under the curve of 0.79 in detecting apneas and hypopneas
Magnusdottir and Hilmisson (2018)	47 subjects with moderate to severe OSA with AHI 15 or higher	Sensitivity 89%, specificity 79%, agreement 85%, PPV (positive predictive value) 0.86, and NPV (negative predictive value) 0.83
Hilmisson et al. (2019a)	42 subjects with moderate to severe OSA with AHI 15 or higher	Sensitivity of 100%, specificity of 81%, and agreement of 93%
Lu et al. (2019)	179	ROC showed AUC 0.79 in mild OSA, 0.79 in moderate OSA, and 0.86 in severe OSA
Hilmisson et al. (2020)	805 children with mean age of 6.8 years	ROC demonstrated strong agreement in all OSA categories: 91.4% in mild OSA; 96.7% in moderate OSA; 98.6% in severe OSA
Ma et al. (2020)	205	Correlation coefficient between the CPC AHI and PSG AHI is: ($r = 0.851$, $p < 0.001$)
Seo et al. (2020)	194	Correlation coefficient between the CPC AHI and PSG AHI is: ($r = 0.973$, $p < 0.001$)
Al Ashry et al. (2021)	833	ROC demonstrated strong agreement in all OSA categories: 98.5% in mild OSA; 96.4% in moderate OSA; 98.5% in severe OSA
Study year	**Number of subjects**	**Results**
Section B: Studies that used cardiopulmonary coupling in phenotyping and following response of treatment of sleep apnea		
Roche et al. (1999)	Cohort of 14 patients with OSA treated with CPAP for 3 months	Follow up PSGs showed that AHI decreased from average of 50 to 2/h and this was associated with significant reduction in the LFC/HFC ratio
Gilman et al. (2008)	Randomized control study in 19 patients with heart failure	The group treated with CPAP for 1 month had significant increase in HFC compared to the group not treated with CPAP
Shiina et al. (2010)	Cohort of 50 patients with AHI > 20/h tested before and after 3 months of CPAP therapy	There was significant decrease in LFC/HFC ratio and C-reactive protein after 3 months of CPAP
Schramm and Thomas (2012)	Case report of patient with mild OSA. Multiple ECG recording nights obtained. No therapy, dental device, oxygen therapy, and positional therapy were compared	HFC/LFC ratio significantly improved on the night of dental device as compared to oxygen therapy and positional therapy.
Lee et al. (2012)	Cohort of 37 children with OSA after adenotonsillectomy	AHI determined by PSG decreased significantly after adenotonsillectomy. This was associated with significant improvement in HFC/LFC ratio
Harrington et al. (2013)	Cohort of 24 patients undergoing CPAP titration PSG for OSA. A successful titration was defined as AHI < 5/h.	HFC was decreased and LFC was increased in subjects with unsuccessful CPAP titrations.
Ramar et al. (2013)	Cohort of 106 patients with complex sleep apnea undergoing ASV titration	No correlation was found between percentage of LFC_{NB} and ASV titration success
Lee et al. (2014)	Cohort of 52 patients with OSA treated with dental devices. PSG and CPC were obtained at baseline and 3 months into treatment	The reduction in AHI as assessed by PSG was associated with increase in HFC and decrease in LFC
Choi et al. (2015)	Cohort of 62 patients with OSA treated with surgery.	36 patients had a successful surgical outcome defined as 50% reduction of AHI to AHI < 20/h and were found to have significant increase in HFC and significant decrease in LFC compared to those who didn't have a successful surgical outcome
Lee et al. (2016)	Cohort of 98 patients with OSA treated with surgery or dental device. PSG and CPC were obtained at baseline and 3 months into treatment	Patients who had > 50% reduction in their AHI 3 months after treatment were found to have significant reduction in LFC and significant increase in HFC

(Continued)

TABLE 1 | (Continued)

Study year	Number of subjects	Results
Cho and Kim (2017)	Cohort of 62 patients tested in the sleep lab for OSA	In those who met criteria for split night the CPAP titration portion was associated with significant increase in HFC and significant decrease in LFC
Chen and He (2019)	Case control study in a pediatric population with OSA. The control group underwent adenoidectomy only whereas the intervention group underwent drug-induced sleep endoscopy (DICE) and tonsillectomy was performed in addition to adenoidectomy if tonsillar obstruction was seen on DICE	Both groups had improvement in AHI as determined by CPC but AHI improvement in the DICE group after 1 year was better as compared to the control group.
Study year	**Number of subjects**	**Results**
Section C: Studies that used cardiopulmonary coupling in sleep disorders other than sleep apnea		
Sforza et al. (2005)	Cohort of 14 patients with periodic limb movements (PLMs) was studied. Periods of PLMs were compared to periods without PLMs	Periods with PLMs were associated with significant increase in LFC compared to periods without PLMs
Thomas et al. (2010)	Prospective case control study. 14 patients with fibromyalgia were compared to 13 matched controls	Elevated-low frequency coupling was significantly increased in Fibromyalgia patients and there was a trend toward less HFC in those patients as compared to controls
Yang et al. (2011)	100 patients with major depression (50 of which were on hypnotics due to insomnia) were compared to 91 healthy subjects	HFC% was significantly lower and LFC% significantly higher in patients with depression not on hypnotics compared to patients with depression on hypnotics and healthy subjects
Chien et al. (2013)	Sleep quality of 156 nurses was assessed using the Chinese edition of Pittsburgh sleep quality index	CPC were analyzed and classified into stable vs. unstable sleep. Patients deemed as poor sleepers according to the Chinese edition of Pittsburgh sleep quality index had a significant inverse correlation with the stable sleep ratio as determined by CPC
Lin et al. (2013)	CPC patterns were studied in 13 medical interns and nights when being on call were compared to nights when they were off duty	HFC% significantly decreased during on call nights when sleep deprivation is expected compared to off duty nights
Schramm et al. (2013)	CPC variables were compared between 50 patients with primary insomnia and 36 good sleepers	Primary insomnia patients had lower HFC%, low HFC/LFC ratio, and higher LFC% when compared to good sleepers
Jarrin et al. (2016)	Single arm cohort study of 65 patients with chronic insomnia before and after 6 weeks of cognitive behavioral therapy	Improvement in sleep parameters were associated with lower HFC% contrary to what would be expected. Study is limited by absence of control arm
Thomas et al. (2018)	CPC variables from 128 nights were collected from10 healthy volunteers and compared to 121 nights in 20 patients with insomnia.	Patients with insomnia had increased LFC specifically increased broad-band LFC (LFC_{BB})
Hilmisson et al. (2019a)	Prospective cohort of 110 patients with chronic insomnia that have been treated with prescription pharmacological agents for > 3 months and not previously tested for OSA. Home sleep testing showed that 25% had moderate to severe OSA coexistent with their insomnia diagnosis.	Patient with insomnia who were found not to have OSA had less percentage of LFC specifically less LFC_{NB} when compared to patients with insomnia who were found to have moderate to severe OSA. There were no significant differences in CPC parameters in patients with insomnia without OSA when compared to patients with insomnia who have mild OSA
Sun et al. (2019)	41 patients with depression studied before and after 2 weeks of antidepressant medications	Increase in HFC was associated with improvement in psychiatric questionnaire scores
Zhang et al. (2021)	CPC variables were compared between 3 groups: 22 insomnia patients with cognitive impairment, 21 insomnia patients with normal cognition, and 15 healthy volunteers	Insomnia patients with cognitive impairment had less HFC and more LFC/HFC ration when compared to insomnia patients with normal cognition and healthy volunteers

shows that NREM sleep has only two distinct and completely non-overlapping forms—stable and unstable (HFC and LFC, respectively), which intermittently switch across the entire night. While N3 dominates in the first half of the night, HFC occurs throughout (**Figure 3**). This bimodality or stability domain is especially clear when incorporating autonomic and respiratory variables with electrocortical activity, specifically, delta power and the < 1 Hz slow oscillation. Stable NREM is characterized by high probability of occurrence of the < 1 Hz slow oscillation, high delta power, non-CAP EEG, stable breathing, blood pressure dipping, strong sinus arrhythmia and vagal dominance, and high frequency CPC. Conversely, unstable NREM exhibits opposite features: a fragmented and discontinuous < 1 Hz slow oscillation, CAP patterns on the EEG, non-dipping of blood pressure, unstable respiration, cyclic variation in heart rate, and low frequency CPC (Wood et al., 2020).

CARDIOPULMONARY COUPLING IN SLEEP APNEA

Diagnosis of Sleep Apnea

Sleep apnea reliably induces strongly coupled low-frequency oscillations in heart rate and respiration. This results in strong ECG or PPG amplitude fluctuations, besides cyclic variation in heart rate, enabling computing an AHI. This computation

requires knowing the number of oxygen desaturation events, the amount of time in coupled low-frequency oscillations, the mean frequency of these computed oscillations, and the total sleep period.

The first step in using CPC for sleep apnea detection involves a second-levels analysis of the LFC zone, where a spectral band designated as elevated-LFC (e-LFC) was found which correlated highly with scored apneas and hypopneas. Within e-LFC, two further patterns were discernable, one with a wide dispersion of coupling spectra and another with a narrow band of coupling spectra (broad and narrow-band e-LFC, or e-LFC_{BB} and e-LFC_{NB}). However, other causes of sleep fragmentation may also cause similar patterns, especially e-LFC_{BB}, a limitation which may be minimized by integrating oxygen saturation fluctuations into the computation. In two recent large studies combining CPC AHI with oximetry desaturation index events in one index have improved the accuracy of derived AHI in comparison to PSG AHI (Hilmisson et al., 2020; Al Ashry et al., 2021). This derived AHI was approved to be equivalent to PSG AHI in adults and children in 2019 by the FDA (K182618).

These LFC_{NB} and LFC_{BB} indices have been used in several studies in the adult and pediatric populations for automated detection of sleep apnea (**Table 1**, section A). There are several advantages for using CPC through wearable devices, especially the current embodiment of a ring-form oximeter, in the sleep apnea population. These include: (1) cost-effective screening of high risk adult and pediatric populations; (2) minimizing patient (wearing) and system (scoring) burdens; (3) detection of expressed high loop gain (central apnea and periodic breathing), which can be a risk stratification approach, as such patients are at risk for treatment-emergent central sleep apnea, reduced adherence to therapy, and persistent respiratory instability during apnea therapy.

Sleep Apnea Treatment Effects

Successful sleep apnea treatment is expected to increase HFC relative to LFC, including following oral appliance therapy and upper airway surgery (Schramm and Thomas, 2012; Lee et al., 2014, 2016; Choi et al., 2015). A similar pattern is noted in pediatric patients with OSA after adenotonsillectomy (Lee et al., 2012; Chen and He, 2019). The same results are seen with CPAP treatment of OSA (Harrington et al., 2013; Cho and Kim, 2017). Successful treatment of OSA with CPAP is associated with improvement in HFC/LFC ratio (Roche et al., 1999; Shiina et al., 2010). Gilman et al. (2008) randomized patients with heart failure (ejection fraction less than 45%) who had moderate to severe OSA to CPAP vs. usual care. After 1 month the CPAP treated group showed an increase in HFC compared to the control group (Gilman et al., 2008). Harrington et al. (2013) looked at CPAP titration studies and defined successful CPAP titration and optimum CPAP pressures as AHI less $\leq$ 5 / h of sleep for 30 min during supine REM; higher HFC was found in successful CPAP PSGs and higher LFC in unsuccessful titrations (Harrington et al., 2013).

Endotyping and Phenotyping Sleep Apnea

Endotypes are the mechanisms which drive pathology, while phenotypes are the expression of these endotypic effects. Multiple driver endotypes are now recognized as important in the pathogenesis of obstructive sleep apnea, including high loop gain, low arousal threshold, airway collapsibility, impaired negative pressure response, and sleep fragmentation resulting in amplified wake-sleep transitional instability (Dutta et al., 2021; Finnsson et al., 2021). Thus, what is considered "obstructive sleep apnea" can be caused by one or more of the above driving mechanisms, which can be classified into anatomical and non-anatomical. High loop gain, reflecting respiratory control instability and an imbalance between input (oxygen and carbon dioxide levels) and output (neural drive to respiratory muscles and upper airway) of the respiratory system, is perhaps the most important non-anatomical endotype. When loop gain is more than 1, self-sustained oscillations are inevitable. The

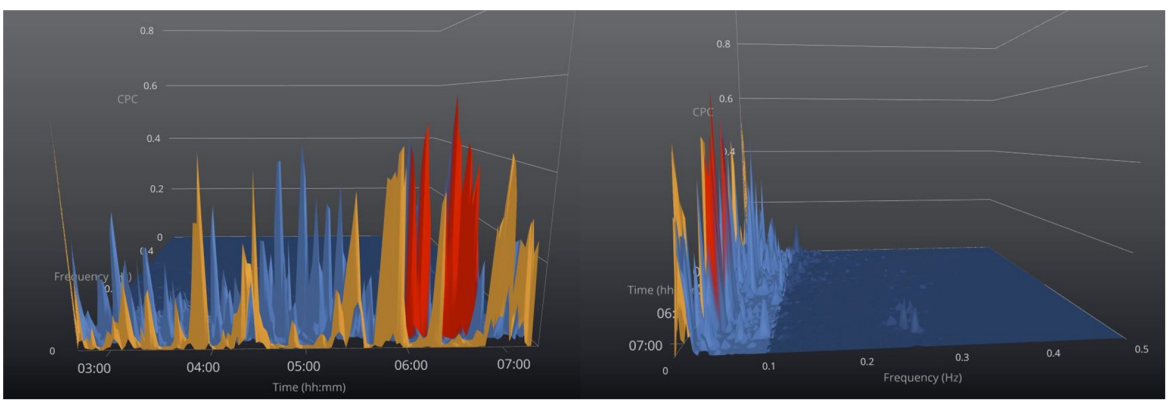

FIGURE 4 | Sleep apnea phenotyping. 3-Dimensional graphical view of the CPC- spectrogram in a patient with severe sleep apnea and no stable (HFC) sleep. Color code: orange = VLFC, blue = e-LFC_{BB} (broadband coupling), and red = e-LFC_{NB} (narrowband coupling). The offset view (right) shows the narrow dispersion of coupling frequencies induced by periodic breathing toward the end of the recording period, while earlier in the night the e-LFC spectra are "broadly dispersed," consistent with predominantly obstructive sleep apnea. On the figure to the right the time axis is cut off and the figure is off set to show the narrow band best.

importance of high loop gain is that treatment failure risk is high and options such as oxygen (Edwards et al., 2016; Sands et al., 2018) and acetazolamide (Edwards et al., 2012) can be beneficial. Though mathematical methods can accurately quantify endotypes, analysis of the expressed phenotypes can also accurately identify sleep apnea with high loop gain.

When high loop gain is manifested, the polysomnographic patterns include classic central sleep apnea, periodic breathing, complex apnea with codominant loop gain and airway pathology, treatment-emergent central sleep apnea, and NREM-dominant obstructive sleep apnea. A common theme across all these conditions is self-similar (metronomic timing, identical morphology of consecutive events) of respiratory abnormality (Oppersma et al., 2021), which induce e-LFC_{NB}, which is a marker of this expressed high loop gain (**Figure 4**; Thomas et al., 2007). In a study of 671 subjects with sleep apnea which compared CPC indices to conventional PSG scoring (Thomas et al., 2007), e-LFC_{NB} was associated with respiratory instability during CPAP titration. Since e-LFC_{NB} is a marker of expressed high loop gain and "central" sleep apnea, Ramar et al. (2013) evaluated if could be used as a marker of adaptive servo-ventilation titration success in 106 patients with complex sleep apnea. Overall ASV titration success as defined as AHI < 10/h on ASV was found in 81% of patients and no correlation was found between percentage of LFC_{NB} and ASV titration success (Ramar et al., 2013). One limitation of this study was the use of opiates, which causes ataxic breathing, and is unlikely to cause the exact self-similarity needed to induce e-LFC_{NB}. **Table 1** (section B) summarizes the studies that used CPC in phenotyping and following response of treatment of sleep apnea.

CARDIOPULMONARY COUPLING IN OTHER SLEEP DISORDERS

CPC has been used to study other sleep disorders beyond OSA. Patients with insomnia have been shown to exhibit increased LFC even in the absence of sleep disordered breathing (Thomas et al., 2018). It appears that LFC_{BB} is the main LFC pattern seen in pure insomnia so the coexistence of LFC_{NB} should raise the suspicion for coexisting sleep apnea (Hilmisson et al., 2019b). Schramm et al. (2013) studied CPC in a group of primary insomnia and compared to a group of good sleepers. They found increased LFC and a lower HFC/LFC ratio among the insomnia group (Schramm et al., 2013). Zhang et al. (2021) studied insomnia patients with cognitive impairment and found decreased HFC indicating predominance of unstable sleep compared to insomnia patients with normal cognition. However, Jarrin et al. (2016) found that improvements in some sleep parameters in insomnia patients subjected to 6 weeks of cognitive behavior therapy was associated with decreased HFC. One of the limitations of this study was absence of control group. A systematic review of cardiovascular autonomic activity in insomnia patients showed that increased LFC/HFC ratio is a consistent finding in those patients (Nano et al., 2017). Similar findings of increased LFC/HFC ratio were also seen in CPC studies of populations with conditions that would predispose them to secondary insomnia/short sleep durations including: sleep deprivation, fibromyalgia, and periodic limb movement disorder (Sforza et al., 2005; Thomas et al., 2010; Chien et al., 2013; Lin et al., 2013).

Since insomnia is common in patients with uncontrolled psychiatric disorders (Sateia and Nowell, 2004); CPC could be used in studying and tracking treatment response in such patients. In comparison to controls, patients with untreated major depression have reduced HFC and increased LFC (Yang et al., 2011). Sun et al. (2019) studied 41 patients with depression and showed that the increase in HFC following 2 weeks of antidepressant medications treatment was associated with improvement in psychiatric questionnaire scores and suggested that this can be used to predict early response to treatment in such patients. **Table 1** (section C) summarizes the studies that used CPC in sleep disorders other than sleep apnea.

CONCLUSION

The CPC sleep spectrogram provides a novel window into sleep physiology and key information about sleep during health and disease. Because such data can be obtained from simple/reduced and even contactless signal acquisition methods, it allows studying sleep in greater numbers, and with greater ease, in a wider range of conditions, with nearly limitless repeatability, than typically possible with traditional polysomnograms or current home sleep apnea testing devices.

AUTHOR CONTRIBUTIONS

HA and RT wrote the manuscript. All authors contributed to study design and the literature search, and revised the manuscript.

FUNDING

RC1HL099749-01 (National Heart Lung Blood Institute, United States) to RT.

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Conflict of Interest: RT has the following disclosures: (1) Patent for a device to regulate CO_2 in the positive airway pressure circuit, for treatment of central/complex apnea. (2) Patent and license for an ECG-based method to phenotype sleep quality and sleep apnea (to MyCardio, LLC, through Beth Israel Deaconess Medical Center). (3) Patent, past consultant—DeVilbiss-Drive, CPAP auto-titrating algorithm. (4) GLG Councils and Guidepoint Global– general sleep medicine consulting.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neuroscience

ORIGINAL RESEARCH
published: 06 January 2022
doi: 10.3389/fnins.2021.736426

Sleep-Dependent Anomalous Cortical Information Interaction in Patients With Depression

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Depression is a prevalent mental illness with high morbidity and is considered the main cause of disability worldwide. Brain activity while sleeping is reported to be affected by such mental illness. To explore the change of cortical information flow during sleep in depressed patients, a delay symbolic phase transfer entropy of scalp electroencephalography signals was used to measure effective connectivity between cortical regions in various frequency bands and sleep stages. The patient group and the control group shared similar patterns of information flow between channels during sleep. Obvious information flows to the left hemisphere and to the anterior cortex were found. Moreover, the occiput tended to be the information driver, whereas the frontal regions played the role of the receiver, and the right hemispheric regions showed a stronger information drive than the left ones. Compared with healthy controls, such directional tendencies in information flow and the definiteness of role division in cortical regions were both weakened in patients in most frequency bands and sleep stages, but the beta band during the N1 stage was an exception. The computable sleep-dependent cortical interaction may provide clues to characterize cortical abnormalities in depressed patients and should be helpful for the diagnosis of depression.

Keywords: sleep, depression, electroencephalography, effective connectivity, delay symbolic phase transfer entropy

OPEN ACCESS

Edited by:
Gonzalo C. Gutiérrez-Tobal, Center for Biomedical Network Research (CIBER), Spain

Reviewed by:
Brian Henry Silverstein, University of Michigan, United States
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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *05 July 2021*
Accepted: *22 November 2021*
Published: *06 January 2022*

Citation:
Lian J, Luo Y, Zheng M, Zhang J, Liang J, Wen J and Guo X (2022) Sleep-Dependent Anomalous Cortical Information Interaction in Patients With Depression. Front. Neurosci. 15:736426. doi: 10.3389/fnins.2021.736426

INTRODUCTION

Depression is a prevalent mental illness with high morbidity and encompasses abnormal performances such as anhedonia, low self-esteem, and even self-mutilation, which is considered the main cause of disability worldwide (World Health Organization [WHO], 2019). Cumulative neuroscience research on resting state and various cognitive tasks have suggested that the dysregulated cortical and subcortical functional network, which is considered to affect brain function integration and information interaction, was found in depressed patients (Furman et al., 2011; de Kwaasteniet et al., 2013; Ma et al., 2021). Moreover, brain activities while sleeping were also reported to be affected by such mental illness (Steiger and Pawlowski, 2019).

Sleep is significant for the regulation of brain function, including the adjustment of cerebral cortex activity to preserve the homeostasis of the functional network (Tononi and Cirelli, 2006;

Krueger et al., 2016). During sleep, brain's response to external stimuli is weakened and, thus, specific spontaneous pathological information of neurological or mental diseases can be observed (Berry, 2012). The majority of studies regarding depression during sleep have investigated the polysomnographic alterations and some typical differences have been found: the longer sleep latency, the decreased sleep efficiency, prolonged first rapid eye movement (REM) stage, and reduced slow wave sleep (Tsuno et al., 2005; Sculthorpe and Douglass, 2010; Murphy and Peterson, 2015). However, scant research worked on exploring sleep functional network of depressed patients. Synchronous likelihood was utilized on sleep electroencephalography (EEG) signals to find that lower mean level of global synchronization was present in depressed patients (Leistedt et al., 2009). According to linear Granger causal analysis, small-world network organization in patients with depression was altered during REM sleep (Hein et al., 2019). Moreover, Zhang B. T. et al. (2020) used connectivity metrics derived from two sleep EEG channels to obtain sound results in depression screening. In light of the existing research background, the special relationship between depression and sleep should not be overlooked. Further investigation on the sleep cerebral functional network of depression may help us more comprehensively understand the pathological mechanism of depression.

In virtue of noninvasive high time resolution, long-range timely recording, and relatively low physiological load, EEG is deemed as an ideal tool for studying cerebral activity during sleep. The current functional network analyses based on cortical EEG include functional connectivity (FC) and effective connectivity (EC), which are both based on the functional properties of the various cortical regions (Friston, 2011; Stam, 2014). FC represents the temporal correlations that imply direct or indirect interactions between brain regions (Cai et al., 2018), whereas EC refers to a kind of directional causal influence that neural masses exert upon each other, which should be more comprehensive to illuminate the cerebral activity (Valdes-Sosa et al., 2011). Currently, informatics methods were widely applied to EC analysis for further directional brain network investigation, and based on which, transfer entropy (TE) was proposed as an EC measure to study the information flow in the cortical network (Vicente et al., 2011). Since the cortical EEG is easily affected by the volume conduction (He et al., 2019), in recent years, constantly improved algorithms have been proposed to reduce this effect on scalp estimates of EC and improve the reliability and stability of the calculations, and related applications on research unveiled anomalous cerebral information interaction in depressed patients. Cukic et al. (2020) applied transfer entropy on resting EEG and found that the frontal, parietal, and temporal lobes of patients are relatively isolated. A more randomized brain network structure was found in patients in accordance with phase transfer entropy analysis (Hasanzadeh et al., 2020). Zhang Y. et al. (2020) used multivariate symbolic transfer entropy to find that the connection strength of patients between the left occipital area and the frontal lobe area under the stimulation of positive and neutral emotional pictures was significantly different from that of healthy controls. Recently, delay symbolic phase transfer entropy (dSPTE), a new extension of TE incorporating the advantages of phase information analysis and symbolic scheme, was proposed to quantify brain activity EC, which has better noise robustness and more accurate identification of EC (Wang and Chen, 2020). With the advantages of nice stability and accuracy, dSPTE was applied in this study to investigate the functional interactive network in depressed patients during sleep.

Studies have implied the cerebral functional asymmetries in depressed patients, and the anomalous functional network may lead to the aberrant symptoms such as abnormal information processing and excessive rumination (Rotenberg, 2008; Bruder et al., 2012). However, insufficient investigations committed to reveal and characterize the asymmetries of cortical information flow in depressed patients during sleep, the topic of which was considered to provide valuable information for the abnormal cerebral function in patients. Moreover, previous studies have tried to explore different inter-regional features to quantify different patterns of cortical information flow, such as left–right index and anterior–posterior rate (Zhou et al., 2020; Ekhlasi et al., 2021; Pan et al., 2021). To discover the difference in sleep-dependent information flow patterns in patients, analysis on various EC asymmetry patterns was included in this research.

In this study, we tried to explore the changes in the interactive functional network in patients with depression during sleep. The information transfer between cortical regions and two information flow patterns (left–right pattern, posterior–anterior pattern) in different sub-bands and sleep stages were considered to analyze the differences between patients with depression and healthy controls. We expect to provide new insights into the understanding of pathological mechanisms in depression.

MATERIALS AND METHODS

Participants

Twenty-five patients with depression and twenty-six age-matched healthy controls were enrolled in our study, and the clinical characteristics of participants are listed in **Table 1**. Patients from Guangdong 999 Brain Hospital were diagnosed

TABLE 1 | Demographic and clinical data for participants.

Variables	Healthy controls	Depressed patients	*p*-value
Age (years)	20 ± 1.50	21.6 ± 7.04	0.947
Gender, male/female	13/13	14/11	0.668
HAMD score	2.08 ± 1.57	25.5 ± 6.28	<0.001
SDS score	40.92 ± 6.99	67.3 ± 9.91	<0.001
Total Analysis Time (min)	458.13 ± 96.84	583.75 ± 55.17	/
NREM1 Time (min)	25.17 ± 12.45	22.89 ± 15.58	0.205
NREM2 Time (min)	181.71 ± 41.39	253.81 ± 82.91	0.001
NREM3 Time (min)	141.21 ± 37.31	146.45 ± 55.56	0.445
REM Time (min)	82.03 ± 22.17	103.22 ± 50.08	0.220
Total Sleep Time (min)	429.40 ± 41.59	526.33 ± 74.11	/

All data are presented as mean ± standard deviation, except for gender. HAMD, Hamilton Depression Scale; SDS, Self-rating Depression Scale. The comparison of gender was assessed with chi-squared test and the other comparisons were assessed using the Mann–Whitney U test.

by two experienced psychiatrists based on criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Patients with depression were also assessed by the Hamilton Depression Scale (HAMD) and the Self-Rating Depression Scale (SDS). The exclusion criteria for patients with depression included the presence of drug abuse, suicide risk, pregnancy, present or history of head injuries, seizures, or epilepsy. Healthy participants were recruited from Sun Yat-sen University and had no history of nerve damage, no family history of psychiatric disorders, no history of sleep disorders, and no history of drug or alcohol abuse. Participants in the experiment were not interfered by medications under the judgment of an experienced clinical psychiatrist, and had not experienced sleep deprivation and other disturbances. This study had the approval of the Ethics Committee of Guangdong 999 Brain Hospital (approval number: 2020-010-059). All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments. All participants voluntarily signed an informed consent form before the experiment and were appropriately remunerated after the experiment.

Polysomnography

All participants underwent overnight polysomnography (PSG) examination using a Compumedics Profusion EEG recording system with Neuvo amplifier, and the recording lasted for 9–10 h. Six scalp EEG channels (F3/M2, F4/M1, C3/M2, C4/M1, O1/M2, and O2/M1) following the 10–20 system were selected for the study at a sampling rate of 500 Hz. The reference electrodes (M1 and M2) were placed on contralateral auricle and a ground electrode was on Fpz according to the recommendation of the American Academy of Sleep Medicine (AASM) criteria (Berry et al., 2017). Moreover, electrooculography, electrocardiography, electromyography, oral and nasal respiratory airflow, chest and abdomen breathing movement, blood oxygen saturation, snoring, leg movement, and body position were also recorded. Sleep stages (REM, N1, N2, N3, and Wake) were then scored by two experienced sleep technicians according to the AASM criteria.

Electroencephalography Signal Pre-processing

The EEG recordings were divided into 30-s epochs for sleep scoring. Segments with obvious artifacts were excluded by visual inspection. Finally, 18,422 segments from depressed patients (694 W epochs, 4,571 R epochs, 421 N1 epochs, 6,973 N2 epochs, and 5,763 N3 epochs) and 18,691 segments from healthy controls (563 W epochs, 2,997 R epochs, 540 N1 epochs, 7,737 N2 epochs, and 6,854 N3 epochs) were obtained. Then, middle 10-s segments from these epochs were extracted for analysis, and a fourth-order zero phase shift Butterworth band-pass filter (0.5–60 Hz) was used to denoise the raw EEG signals.

Directionality Analysis

To determine the directed information flow between cortical regions, dSPTE was estimated based on EEG signals. Under the framework of directional dynamic analysis, TE evaluates the degree of influence of the driving time series on the target one (Schreiber, 2000). Suppose a causal relation between source signal X and target signal Y, uncertainty of the target signal prediction would be reduced when adding both its own past information and that of the source signal:

$$TE_{X\to Y} = \sum P\left(Y_t, Y_{t-\delta}, X_{t-\delta}\right) \log\left(\frac{p(Y_t|Y_{t-\delta}, X_{t-\delta})}{p(Y_t|Y_{t-\delta})}\right)$$

Developed from TE, the dSPTE has better noise robustness and can correctly identify the EC, and its calculation procedure contains phase information extraction, symbolic process, and true delay search. For phase information extraction, a combined Morlet wavelet was used to obtain the instantaneous phase (Liao et al., 2019). The definition of a single Morlet complex wavelet is:

$$\sigma\left(t\right) = \frac{1}{\sqrt{\pi f_b}} e^{2i\pi f_c t} e^{-\frac{t^2}{f_b}}$$

where f_c is the center frequency of the wavelet and f_b is the bandwidth parameter. Then, Morlet complex wavelets with different center frequencies f_n were superimposed to obtain the combined Morlet wavelet, and the f_n can be expressed as:

$$f_n = f_L + n \times \triangle f, n = 0 \ldots N-1$$

where $\triangle f$ was the center frequency spacing of wavelet, and f_L and N were the central frequency of the first wavelet and the number of wavelets, respectively. The combined Morlet wavelet is defined as:

$$\Psi_c\left(t\right) = \frac{1}{C}\sum_{n=0}^{N-1} \sigma_{f_n}\left(t\right) = \frac{1}{C\sqrt{\pi f_b}} e^{-\frac{t^2}{f_b}} \sum_{n=0}^{N-1} e^{2i\pi f_n t}$$

where C is the correction coefficient that makes the amplitude-frequency characteristic passband of the combined wavelet equal to 1. For the EEG signal S(t), its phase information $\varphi\left(\tau\right)$ can be obtained after convoluting with the combined Morlet wavelet. The wavelet coefficient at time τ is defined as:

$$W_S\left(\tau\right) = \int_{-\infty}^{\infty} S\left(t\right) \Psi_C^*\left(t-\tau\right) dt = A\left(\tau\right) e^{i\varphi(\tau)}$$

In this study, the $f_b = 2$ and $\triangle f = 0.05$, and the parameters f_L and N were f_L = 0.5 and N = 70 for delta (0.5–4 Hz), f_L = 4 and N = 80 for theta (4–8 Hz), f_L = 8 and N = 80 for alpha (8–13 Hz), and f_L = 12 and N = 400 for beta (13–32 Hz). Then, we performed a symbolic process based on permutation entropy (Staniek and Lehnertz, 2008), assuming θ_t^x is the phase series extracted from random time series x(t). To better capture the underlying dynamics of the series, the past space state is reconstructed through a time embedding method, so the space state of θ_t^x is approximated as:

$$\theta_t^{xd} = [\theta^x\left(t\right), \theta^x\left(t-l\right), \ldots \theta^x\left(t-(m-1)\,l\right)]$$

where m and l are the embedding dimension and delay, respectively. Then, the values are arranged in an ascending order $[\theta^x\left(t-\left(j_1-1\right)l\right) \leq \theta^x\left(t-\left(j_2-1\right)l\right) \leq$

$\ldots \leq \theta^x\left(t-\left(j_m-1\right)l\right)]$, and the symbol is defined as $S_t^{\theta^x}=[j_1,j_2,\ldots,j_m]$. In this study, m = 5 and l = 62, 31, 19, and 7 were selected for the delta, theta, alpha, and beta frequency bands, respectively (Li et al., 2017; Zubler et al., 2018). For two discrete time series X and Y, the information transfer from X to Y will be the maximal under the real delay (Wang and Chen, 2020). To obtain the optimal dSPTE, the interaction lag parameter μ between the driving and driven systems was set from 1 to 15 to find the optimal dSPTE. The dSPTE is expressed as:

$$dSPTE_{X\to Y}=\sum p(S_t^{\theta^y},S_{t-1}^{\theta^y},S_{t-\mu}^{\theta^x})log\frac{p(S_t^{\theta^y}|S_{t-1}^{\theta^y},S_{t-\mu}^{\theta^x})}{p(S_t^{\theta^y}|S_{t-1}^{\theta^y})}$$

Inter-Regional Effective Connectivity Pattern

Based on the dSPTE, left–right index (LR) and anterior–posterior ratio (AP) were introduced to assess the different information flow patterns in the cortical regions. To obtain these indices, normalized dSPTE was used:

$$ndSPTE_{xy}=\frac{dSPTE_{x\to y}}{dSPTE_{x\to y}+dSPTE_{y\to x}}$$

where $ndSPTE_{xy}$ ranging from 0.5 to 1 means the information flows preferentially from X to Y, and $ndSPTE_{xy}$ ranging from 0 to 0.5 means the reverse situation. For each EEG channel, we averaged its $ndSPTE_{xy}$ with all the other channels to get its regional *ndSPTE* values, which indicated whether the information transmission role of a cortical area was a driver ($0.5 < ndSPTE < 1$) or a receiver ($0 < ndSPTE < 0.5$). LR represented the relative transmission direction of information and the degree of difference in information exchange between the left and right hemisphere (Zubler et al., 2018), which was defined as follows:

$$\mathrm{LR}=\left\{\lambda\frac{ndSPTE_{LR}-ndSPTE_{RL}}{ndSPTE_{LR}+ndSPTE_{RL}}\right\}_{average}$$

where λ = 1, and $ndSPTE_{LR}$ ($ndSPTE_{RL}$) was the normalized dSPTE from left to right (right to left), and was calculated with the electrode pairs of left and right hemispheres, including F3-F4, C3-C4, and O1-O2. LR > 0 indicated the left-to-right hemispheric information flow and *vice versa*. The closer the LR value was to 0, the smaller the difference between inter-hemispheric information flows.

Anterior–posterior ratio (AP) was defined to assess the anterior-to-posterior pattern of the information flow (Numan et al., 2017):

$$\mathrm{AP}=\frac{\left\{ndSPTE_{AP}\right\}_{average}}{\left\{ndSPTE_{PA}\right\}_{average}}$$

where $ndSPTE_{AP}$ ($ndSPTE_{PA}$) was the normalized dSPTE from anterior to posterior (posterior to anterior), and was calculated with the electrode pairs of anterior and posterior regions, including F3-C3, F3-O1, C3-O1, F4-C4, F4-O2, and C4-O2. The information flow direction is anterior-to-posterior, AP > 1, whereas the opposite direction retrieves 0 < AP < 1, and a balanced direction retrieves AP = 1. The closer the AP value was to 1, the smaller the difference between anterior and posterior information flows.

Statistical Analysis

Statistical tests were conducted to address discrepancies in the cortical interactive network between the healthy controls and depression groups during sleep in various frequency bands and researched sleep stages. Since dSPTEs, LRs, and PAs did not satisfy the normal distribution or the variance homogeneity test, a non-parametric test (Mann–Whitney *U* test) was used to test the significant difference ($p < 0.05$ was considered statistically significant). Furthermore, the Friedman test was utilized to test the null hypothesis that the features of EC between different sleep stages were the same, and the Bonferroni correction was conducted to access the stage-dependent significant differences if the Friedman test showed a significant difference ($p < 0.05$). All analyses were performed using IBM statistical software version 22.0.

RESULTS

Information Transfer Across Cortical Regions

The EC networks during sleep were represented by the dSPTE between EEG channels. **Figures 1**, **2** show the EC network of the healthy controls and that of the depressed patients, respectively. Through the color of the arrows, the advantage transfer directions between channels can be obtained. As shown in **Figures 1A**, **2A**, in delta, theta, and beta bands, most information flow between the two channels has an obvious advantage direction, which means the information transfer in one direction was obviously larger than the other.

In terms of the inter-hemispheric information flow, except for the alpha band, the information transfer into the left hemisphere was larger than the other direction. We also observed that the information transition of occipital regions had a uniform directional tendency, except for the alpha band, where the information transferred from occipital regions was larger than the opposite direction.

The information transition of frontal regions also indicated directional tendency, but the results depended on frequency bands and stages. For the low-frequency bands, delta and theta, the information transfer into the frontal regions was larger, but in delta during N3 sleep, this tendency slightly weakened. The information transferred from occipital regions to frontal regions was slightly larger than the other direction during sleep in the alpha band. For the beta band, such tendency differed during various sleep stages. During Wake, R, and N1, the information into frontal regions was larger, but during N3 stages, information transfer from the frontal regions to central regions was larger than the other direction. We also calculated the average dSPTE in the whole cortical network in different sleep stages for

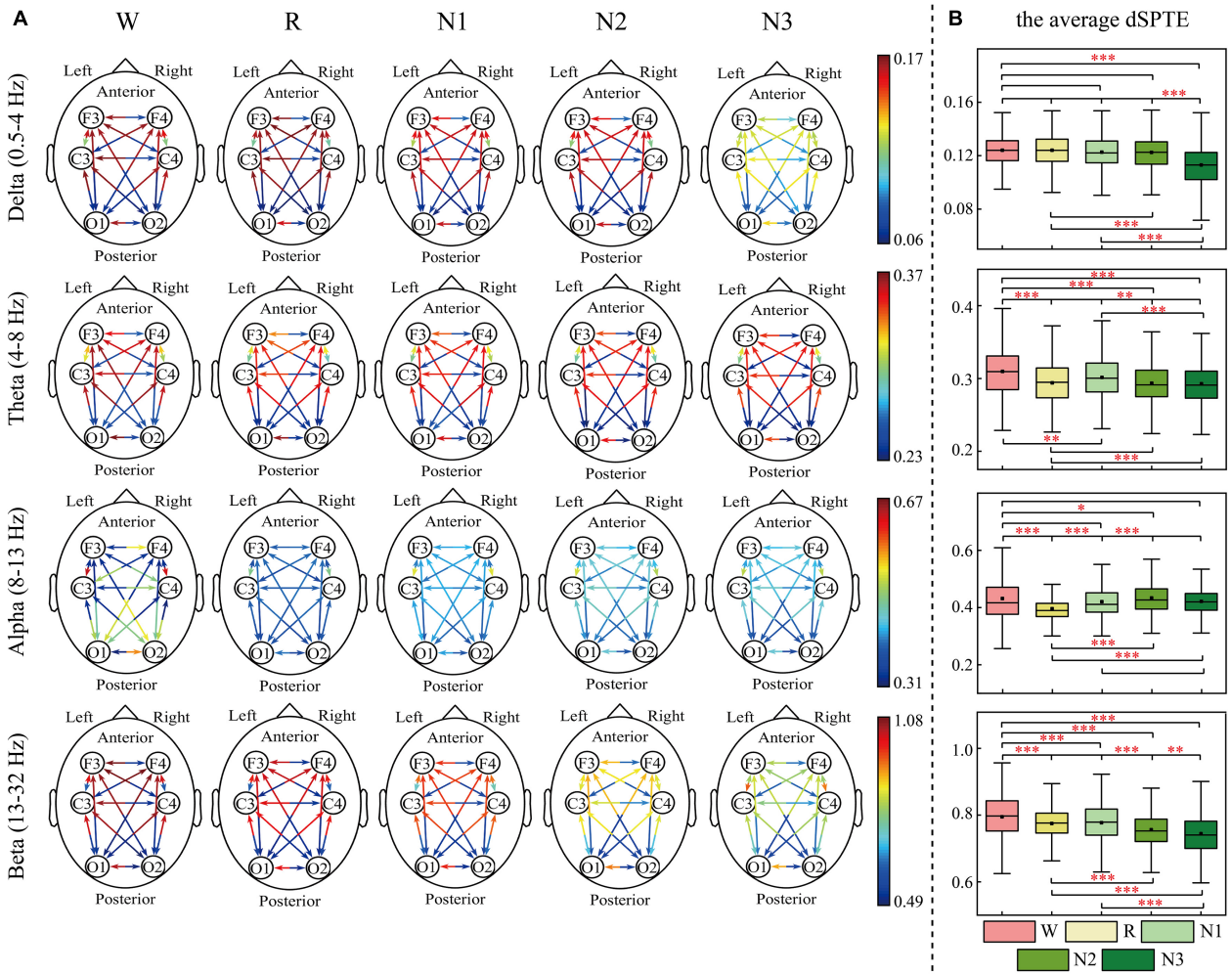

FIGURE 1 | dSPTE of healthy controls during five stages in four frequency bands. **(A)** Overall dSPTE across cortical regions. Each monodirectional arrow indicates the directed influence of one cortical region to another. The warmer the color of the line with the arrow, the stronger the intensity of EC. **(B)** The average dSPTE across six electrodes in five stages. Asterisks denote the significant difference between two stages. *$p < 0.05$, **$p < 0.005$, and ***$p < 0.001$ (Bonferroni correction).

reference (**Figures 1B**, **2B**; the specific values were listed in **Supplementary Table 1**).

Differences in Information Transfer Across Cortical Regions Between Patients With Depression and Healthy Controls

Figure 3 indicates all the significant difference between groups. For delta and theta bands, except for a few compression results, such as the inter-hemispheric information transfer between frontal and occipital regions (O2-F3 and O1-F4), the significant difference weakened the advantage information transfer direction in depressed patients. For example, the advantage direction between F3 and F4 was F4 to F3, but the depressed patients indicated a stronger information transfer from F3 to F4 or weaker transfer from F4 to F3.

For the alpha band, its advantage direction during sleep was not so obvious as other bands. During R and N1 stages, the anterior-to-posterior information flow increased and the opposite information flow decreased, and the information transfer from the left hemisphere increased in patients. However, during N2 and N3 stages, it seemed that the information transfers in the whole cortical network increased in patients, except for O1 to O2. For the beta band, during Wake, R, N2, and N3 stages, the advantage direction weakened in patients like the results of delta and theta bands. However, during N1, these significant differences further enhanced the directional tendency in patients, which may be the result we should notice.

Anterior-to-Posterior Pattern and Left-to-Right Pattern of Information Flow

AP and LR were constructed to summarize the information flow tendency between hemispheres and the anterior–posterior

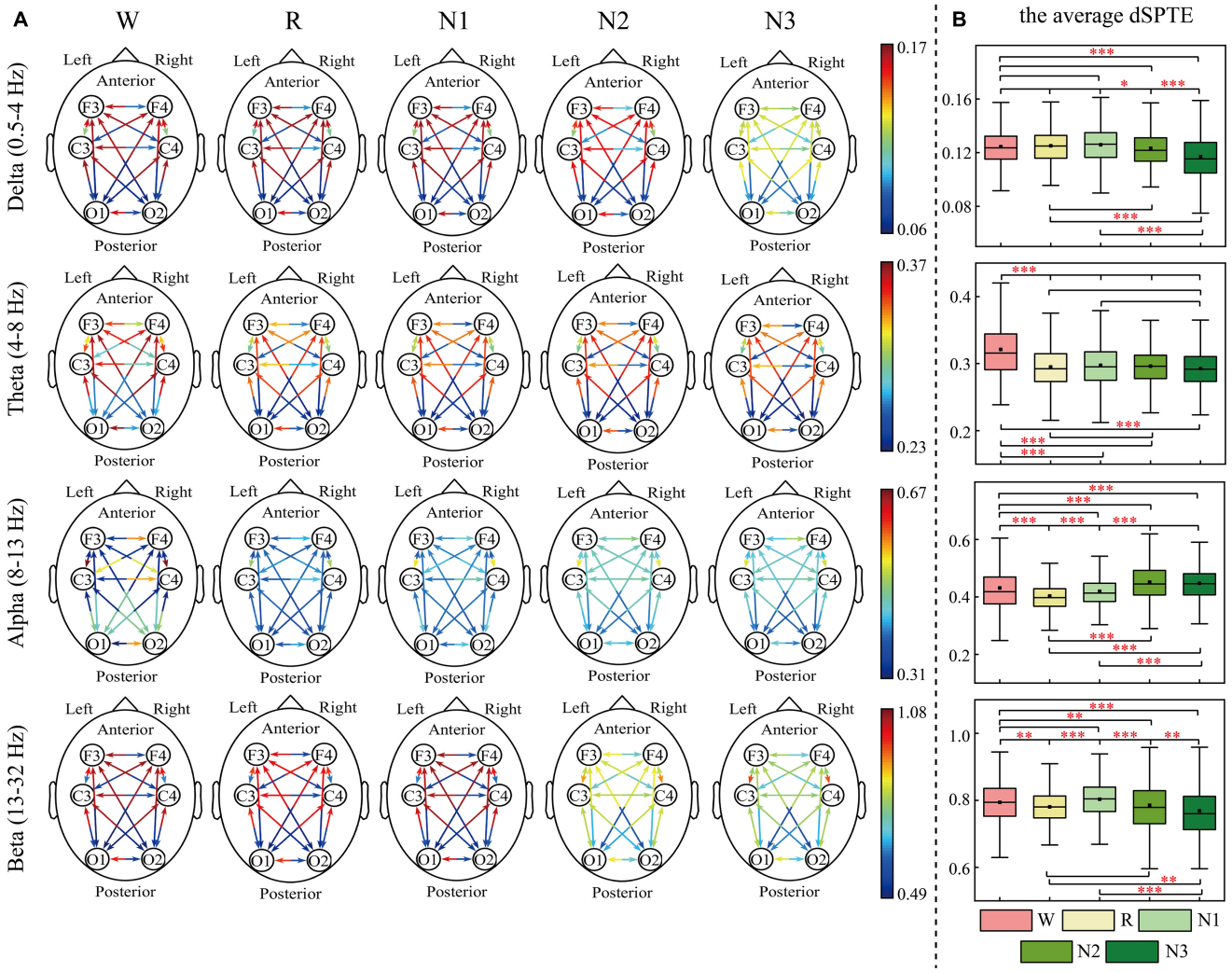

FIGURE 2 | dSPTE of depressed patients during five stages in four frequency bands. **(A)** Overall dSPTE across cortical regions. Each monodirectional arrow indicates the directed influence of one cortical region to another. The warmer the color of the line with the arrow, the stronger the intensity of EC. **(B)** The average dSPTE across six electrodes in five stages. Asterisks denote the significant difference between two stages. *$p < 0.05$, **$p < 0.005$, and ***$p < 0.001$ (Bonferroni correction).

pattern of EC network, the group differences of which are shown in **Figures 4**, **5**, respectively. **Supplementary Figure 1** in the **Supplementary Material** shows the difference in AP and LR values across different sleep stages; the specific values of AP and LR are listed in **Supplementary Table 2**. Except for the alpha band, the other three bands had an obvious hemispheric bias (LR < 0). The overall information flow was from the right to the left cerebral hemispheres, and the information flow tendency was from posterior to anterior (AP < 1). During N3 in delta and during N2 and N3 stages in beta, this hemispheric bias and posterior-to-anterior tendency weakened. During wake in alpha band, this hemispheric bias and anterior-posterior information flow pattern were reversed. The above hemispheric bias and posterior-to-anterior tendency both weakened in patients; the LRs were closer to 0 and APs were closer to 1 in the patient group. With the following exceptions, during the N1 stage, the AP and LR of beta in patients further decreased.

Difference in Regional Information Between Patients With Depression and Healthy Controls

Figure 6 indicates the information transition roles of various cortical regions. Except for the converse results in the wake stage of the alpha frequency band, in most cases, the occipital areas tended to be the sender, whereas the frontal areas were the information receivers. Besides, the right hemisphere showed a stronger information drive than the left hemisphere. These information transition roles slightly weakened in the alpha band during sleep stages and in beta bands during N2 and N3 stages. For delta, theta, and beta bands, the order from receiver to driver

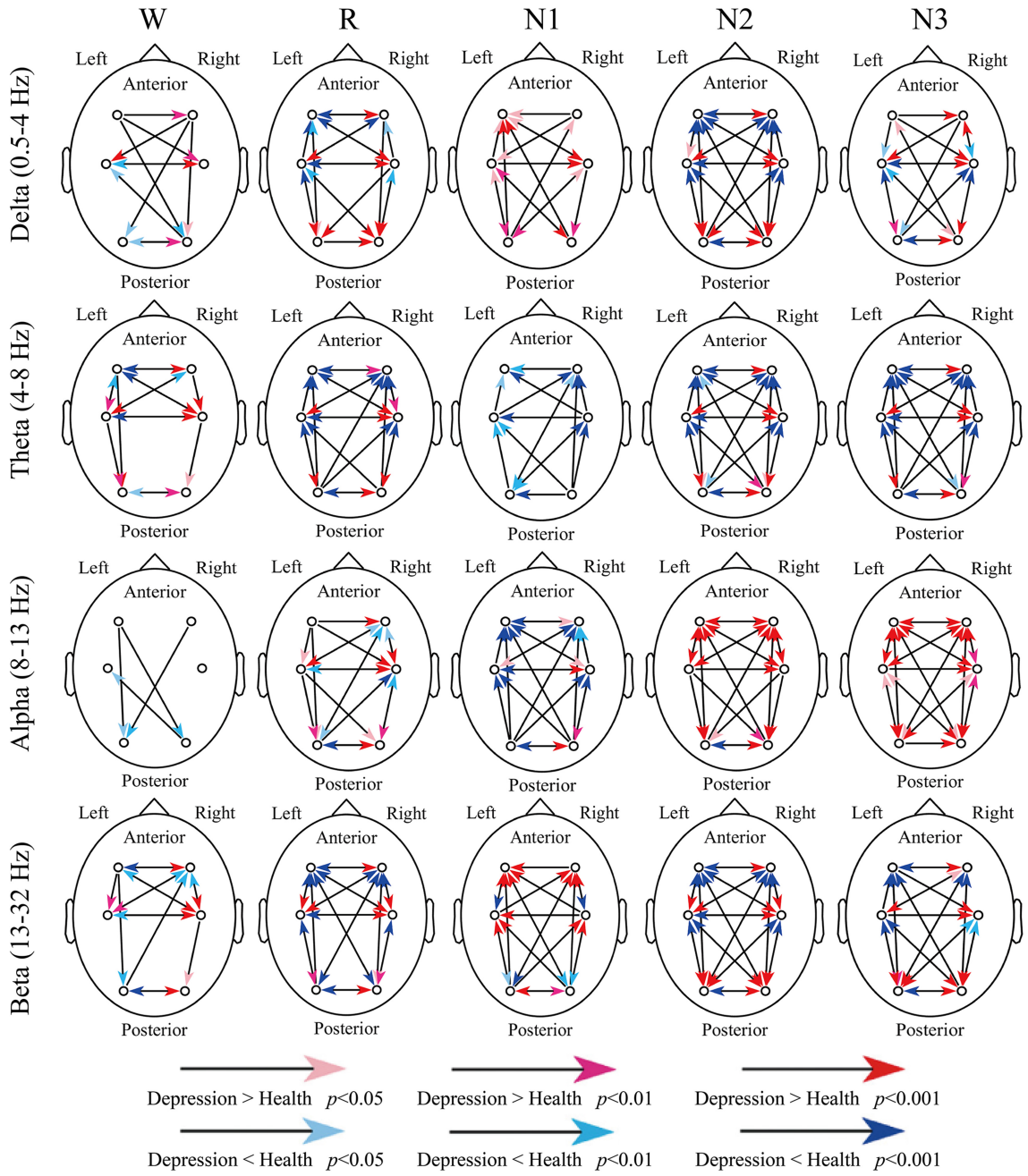

FIGURE 3 | Differences in dSPTE between depressed patients and healthy controls. In each subgraph, the red arrows indicate the significantly stronger flow in depressed patients compared with healthy controls, whereas the blue arrows indicate the opposite condition.

was basically as follows: F3, F4, C3, C4, O1, and O2. C4 was the closest to the balance of information sending and receiving (*ndSPTE* = 0.5). Both groups had the results above.

In regard to the difference between groups, except in beta during N1, nearly all the significant differences made the *ndSPTE* closer to 0.5 in patients. The *ndSPTE* increased in frontal regions and decreased in occipital regions, which meant that the definiteness of role division in cortical regions was weakened in depressed patients. However, decreased *ndSPTE* in frontal regions and increased *ndSPTE* in occipital regions were found in beta during N1, which was an exception.

DISCUSSION

Delay symbolic phase transfer entropy was used to estimate the cortical EC network in patients with depression during sleep. Several features such as LR, AP, and regional *ndSPTE*

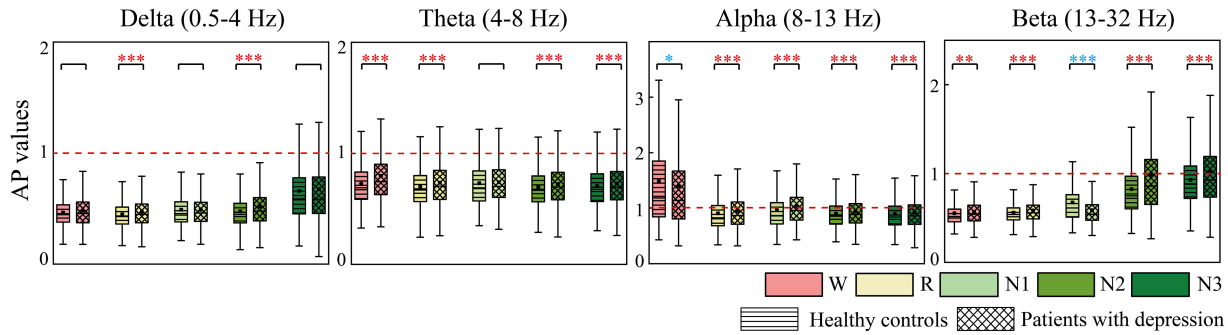

FIGURE 4 | Differences in AP between groups. Red asterisks indicated that the AP of depressed patients significantly increases compared to the controls, whereas the opposite is observed in the other case (blue). *$p < 0.05$, **$p < 0.005$, and ***$p < 0.001$. The red dotted line is the baseline of AP (AP = 1).

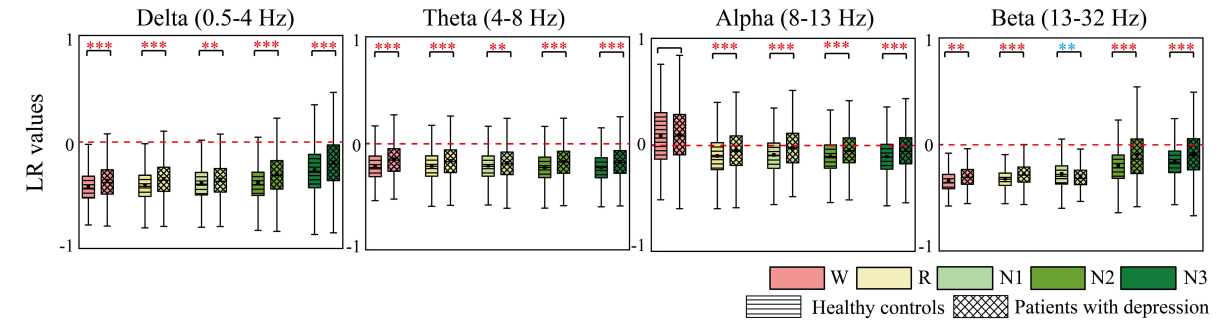

FIGURE 5 | Differences in LR between groups. Red asterisks indicated that the LR of depressed patients significantly increases compared to the controls, whereas the opposite is observed in the other case (blue). * $p < 0.05$, **$p < 0.005$, and ***$p < 0.001$. The red dotted line is the baseline of LR (LR = 0).

were constructed to evaluate the information directions of inter-hemisphere, anterior–posterior, and the roles of information transition of various cortical regions, respectively. We observe obvious information flows to the left hemisphere and to the anterior cortex. For regions, the occiput tended to be the information driver, whereas the frontal regions played the role of the receiver. Such directional tendencies in information flow and the definiteness of role division in cortical regions were both weakened in patients.

Compared with previous studies (Zhou et al., 2020; Pan et al., 2021), our method provided detailed differences in information flow between brain regions, and clearly characterized the role of regions in information transmission (as a receiver or driver). It has been reported that the occipital region and the parietal region are considered to be related to visual information (Heo et al., 2018) and somatosensory information (Fogassi and Luppino, 2005), respectively, while the frontal area has a bearing on senior cognitive functions, emotions, and information integration functions (Fogassi and Luppino, 2005; Alvarez and Emory, 2006). Previous research indicated that the top-down information interaction during sleep was significant for memory consolidation (Axmacher et al., 2009; Miyamoto et al., 2016). The strong forward information flow and the difference in the role of anterior–posterior information communication that we found may reflect the integration and reprocessing of information from the episodic memory during sleep (De Gennaro et al., 2004).

Thanks to the high resolution of dSPTE for information transmission evaluation, we found that the difference in the regional role and in information flow of patients was weaker during sleep compared with healthy controls. Functional research implied that impaired bottom-up limbic cortex regulation led to abnormal mood regulation in patients with depression (Ochsner et al., 2009; Ramasubbu et al., 2014), which may also suggest such abnormal anterior–posterior information interaction in patients. A previous study showed that the information in visual working memory was presented in the occipital, parietal, and frontal cortex (Yu and Shim, 2017). In addition, a physiological study found that increased microRNA-132 levels, which were widely reported in patients with depression, were associated with impaired visual memory (Liu et al., 2016). The anomalous occipital–parietal–frontal information transfer we found may reflect the abnormality of the patient's visual information pathway.

Similarly, such reduction in the difference in information flow was also found between the left and right hemispheres in patients. Studies found that the right hemisphere was regarded as having a relative advantage during sleep, playing a function of vigilance and control of external information (Casagrande and Bertini, 2008b,a). The strong information flow to the left presented in our results may reflect this right hemisphere superiority. Most depressed patients have sleep disorders, such as difficulty in falling asleep, unsustainable sleep, and getting up

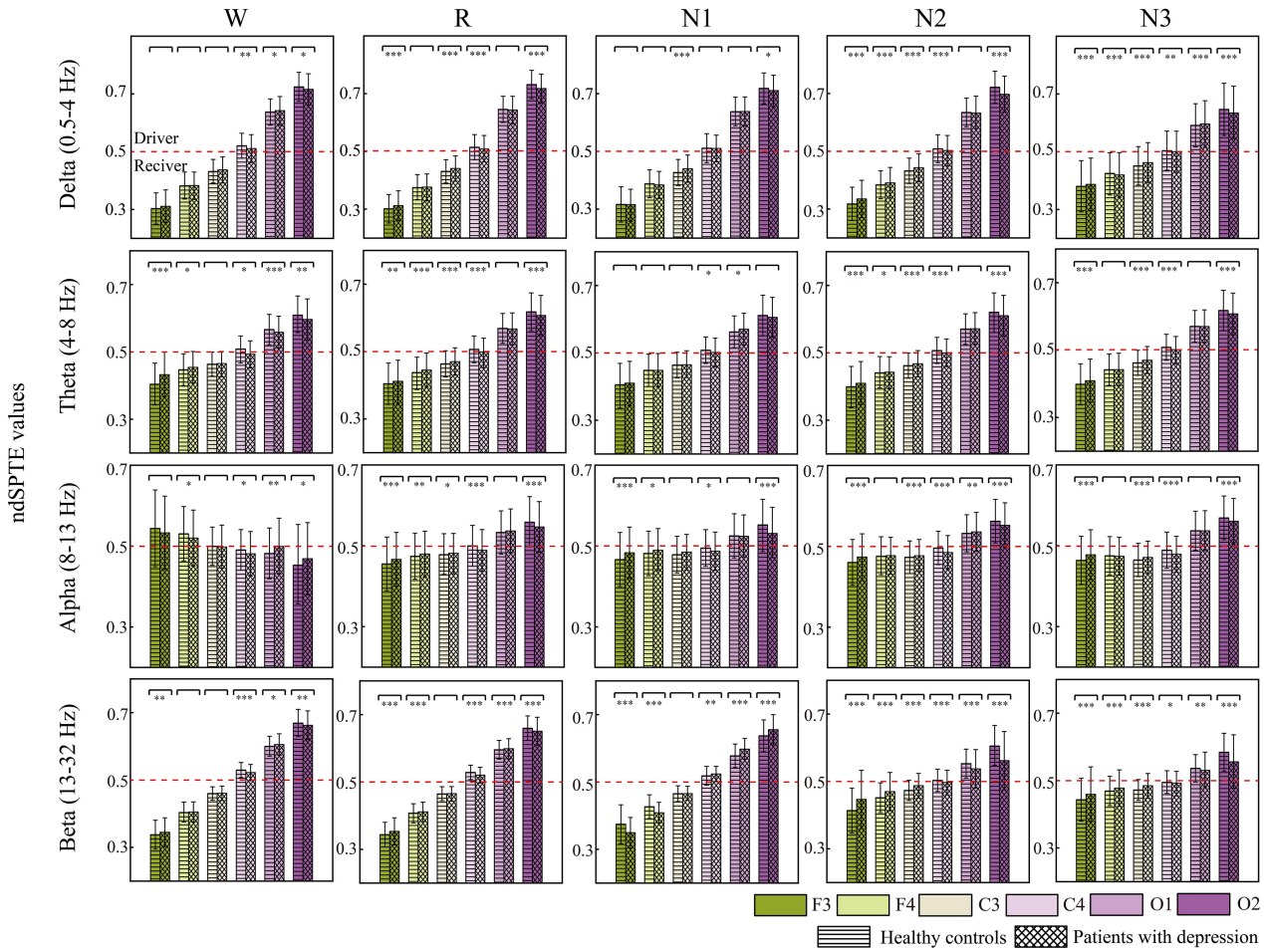

FIGURE 6 | The ndSPTE for each cortical area. The regional ndSPTE represents the information transmission ability of the corresponding cortical area relative to the whole brain. In each subgraph, twelve stacked bars with error bars are included, and six colors represent six cortical locations, and two textures represent two groups. Asterisks denote the significant difference between two groups. *$p < 0.05$, **$p < 0.005$, and ***$p < 0.001$. The red dotted line is the baseline (ndSPTE = 0.5) to distinguish the role of cortical areas in information transmission.

early (Weaver et al., 2018). The weakened role difference between the left and right regions in patients may affect the brain's vigilant and control function of external information during sleep, making it hard for the brain to maintain sleep homeostasis, which may be one of the reasons for sleep disorders in patients with depression.

Different brain regions play their own functions in various functional collaborations (Genon et al., 2018), and the clear distinction between regional roles presented in our results confirms this to a certain extent. Previous studies on sleep brain dynamics found that different brain regions may fall asleep at different speeds and exhibit different sleep intensities, which may reflect the regional function differences in sleep regulation and indicate that the process of sleep is neither spatially nor temporally a uniform state (Vecchio et al., 2017; Fernandez Guerrero and Achermann, 2019). However, we found that the information communication roles of different brain regions in patients tend to be blurred during sleep. Such blurring may reflect the abnormal brain function coordination, which provides possible reasons for the impairments of the ability to process information, emotional regulation, and sleep quality in depressed patients.

In addition, the abnormal change of information flow in N1 of the beta band was found in depressed patients, which may be an important indicator and require further research to investigate.

The present study still has some limitations. The number of participants in this study was relatively small, and the patients we employed were mainly patients with major depression. In order to find an effective characterization of depression, it is necessary to further consider including patients with different severities of depression for research, and explore the relationship between depression scale indicators and EEG characteristics. Moreover, only six EEG channels were included in this study; higher density EEG recording should lead to more accurate results. Due to the spatial limitations of the cortical EEG, in order to further accurately explore the study of sleep brain function in patients with depression, high spatial resolution monitoring methods will be considered in future work. It is

worth noting that our research focuses on the differences in different sleep stages, and the time dynamics of the characteristics throughout the night required further research. We also explored the possible relationship between information flow and brain function, and more experimental exploration and verification are needed in the future. The clinical application value of the features extracted in this work will be further explored in future work. Since depression is also accompanied by changes in heart rate variability (Koch et al., 2019), respiration pattern variability (Zamoscik et al., 2018), and parasympathetic activity (An et al., 2020), research on the multi-physiological system (central nervous system–cardiorespiratory interaction) of depression will be further investigated. Furthermore, although different information theory methods may reach various conclusions, we believe these methods have their respective advantages in tapping different physiological phenomena, and the relations and differences between them need more research.

Overall, the application of dSPTE reveals the information transmission during sleep. Our results mainly include the right-to-left and posterior-to-anterior superiority in information transmission during sleep, and such directional bias of information flow was attenuated in depressed patients. Our findings may provide new insights for understanding the impact of sleep abnormalities on cognitive function and neuropsychiatric deficits in depressed patients, and provide new clues for the quantitative characterization of depression.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because privacy or ethical restrictions. Requests to access the datasets should be directed to YL, luoyuc@163.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Guangdong 999 Brain Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JKL contributed to the design of the study and wrote the first draft of the manuscript. JKL and YL collected the data. JKL, MZ, and JZ performed the statistical analysis. YL, JXL, JW, and XG interpreted the results. All authors provided comments, contributed to manuscript revision, and approved the submitted version.

FUNDING

This work was supported in part by the Science and Technology Program of Guangzhou, China under Grant number 201904010079, in part by the National Natural Science Foundation of China under Grant 82001919, and in part by the De Rucci Healthy Sleep Co., Ltd.

ACKNOWLEDGMENTS

We appreciate the active participation and cooperation of the subjects enrolled in this study. We are also grateful to the sleep technologists for their help.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.736426/full#supplementary-material

Supplementary Figure 1 | Differences in AP and LR within groups across sleep stages. Black asterisks denote the significant difference between two stages. $^{*}p < 0.05$, $^{**}p < 0.005$, and $^{***}p < 0.001$ (Bonferroni correction). The red dotted line is the baseline of AP (AP = 1) /LR (LR = 0).

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Conflict of Interest: The authors declare that this study received funding from De Rucci Healthy Sleep Co., Ltd. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 03 March 2022
doi: 10.3389/fnins.2022.816752

Modafinil Reduces Neuronal Pyroptosis and Cognitive Decline After Sleep Deprivation

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Sleep deprivation (SD) induces systemic inflammation that promotes neuronal pyroptosis. The purpose of this study was to investigate the effect of an antioxidant modafinil on neuronal pyroptosis and cognitive decline following SD. Using a mouse model of SD, we found that modafinil improved learning and memory, reduced proinflammatory factor (IL-1β, TNF-α, and IL-6) production, and increased the expression of anti-inflammatory factors (IL-10). Modafinil treatment attenuated inflammasome activity and reduced neuronal pyroptosis involving the NLRP3/NLRP1/NLRC4-caspase-1-IL-1β pathway. In addition, modafinil induced an upregulation of brain-derived neurotrophic factor (BDNF) and synaptic activity. These results suggest that modafinil reduces neuronal pyroptosis and cognitive decline following SD. These effects should be further investigated in future studies to benefit patients with sleep disorders.

Keywords: modafinil, sleep deprivation, pyroptosis, inflammasome, synaptic plasticity

OPEN ACCESS

Edited by:
David Gozal,
University of Missouri, United States

Reviewed by:
Clementine Puech,
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Junjun Ni,
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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *17 November 2021*
Accepted: *24 January 2022*
Published: *03 March 2022*

Citation:
Xiong X, Zuo Y, Cheng L, Yin Z, Hu T, Guo M, Han Z, Ge X, Li W, Wang Y, Wang D, Wang C, Zhang L, Zhang Y, Liu Q, Chen F and Lei P (2022) Modafinil Reduces Neuronal Pyroptosis and Cognitive Decline After Sleep Deprivation. Front. Neurosci. 16:816752. doi: 10.3389/fnins.2022.816752

INTRODUCTION

Sleep is a universal physiological phenomenon in a variety of mammals, including humans. A large number of studies have shown that a lack of sleep can harm health. In mammals, long-term sleep deprivation (SD) can lead to inattention, emotional instability (Yoo et al., 2007), increased sensitivity to pain (Alexandre et al., 2017), induction of metabolic and cardiovascular diseases (Broussard et al., 2012; Huang et al., 2020), and immune dysfunction (Bryant et al., 2004). In extreme cases, it can lead to death. While the pace of life has increased, a scientific understanding of healthy sleep management is currently lacking. In addition, most people rely on sedatives and sleep drugs. It is true that sleep drugs can effectively improve sleep in the early stage, but their effects continuously decline, leading to a need for increased drug dosage and long-term use, which leads to drug addiction. Thus, drugs that can not only reduce the incidence of adverse reactions during treatment but also help patients recover quickly are needed.

Modafinil is an arousal enhancer originally approved for the treatment of paroxysmal narcolepsy (Bastuji and Jouvet, 1988). Recently, modafinil was shown to be effective in treating Parkinson's disease (Adler et al., 2003), attention-deficit/hyperactivity disorder (Turner et al., 2004), depression, and drug addiction (Martinez-Raga et al., 2008; Kaser et al., 2017). Moreover, modafinil can protect hippocampal neurons by inhibiting excessive autophagy and apoptosis in mice subjected to SD

(Cao et al., 2019). Most recently, the effect of modafinil on changes in lipid composition in the brain was studied in Drosophila melanogaster by mass spectrometry imaging. Modafinil was found to decrease the contents of phosphatidylcholine and sphingomyelin and increase the contents of phosphatidylcholine and PI. It was found that modafinil enhances attention and improves learning, memory, and cognitive function (Philipsen et al., 2021). However, to date, the mode of action of modafinil is not completely clear, and whether modafinil exerts effects similar to those of antioxidants to effectively regulate neuronal inflammation in the brain after SD and modulates neuronal pyroptosis after SD is unknown. Therefore, in this study, we hypothesized that modafinil can alleviate neuroinflammation and cognitive impairment such as learning and memory deficits in mice subjected to SD by inhibiting neuronal pyroptosis.

MATERIALS AND METHODS

Adult male C57BL/6 mice (10 weeks old, weighing 20–25 g) were purchased from the Chinese Academy of Military Sciences (Beijing). All animal husbandry and experimental procedures complied with the newly revised regulations on the management of experimental animals issued by the State Science and Technology Commission on March 1, 2017, and were performed in accordance with a protocol approved by the Animal Protection and use Committee of Tianjin Medical University.

Sleep Deprivation Model

The treadmill SD model selected in this experiment was first established at the United States Naval School of Aeronautics (WEBB, 1957). This method has been continuously improved, and scientists have gradually recognized that the experimental results are relatively reliable and that this method decreases the amount of stress imposed on the tested animals (Xu et al., 2010). This method causes much less damage to animals than a traditional water environment or electrical stimulation. Based on the above factors, the treadmill SD method was used to establish an animal model of acute SD (DB036, Beijing). The treadmill conveyor belt was divided into equal-sized squirrel cages with Plexiglas (30 cm × 30 cm × 40 cm). A fence-type squirrel cage lid that was able to feed and water bottles was fastened to the top of the cage, and the treadmill conveyor belt formed the bottom of the squirrel cage. The mice were given free access to food and water while exercising on the treadmill and housed in a quiet animal room on a 12/12 h light/dark cycle with lights on from 6: 00 to 18: 00 at a temperature of 20–22°C and a humidity of 60–65%. The treadmill speed was set to 2.5 m/min, the running time was 3 s, and the rest time was 12 s. The mice were made to run and stop on a cycle. To study the effect of modafinil on the learning and memory of mice subjected to SD, 36 mice were randomly divided into four groups: the control group, SD group, and SD + modafinil (13 mg kg^{-1}) group. Studies have shown that modafinil can effectively alleviate learning and memory deficits induced by SD in mice at three doses (6.5, 13, and 26 mg kg^{-1}) (Cao et al., 2019). The mice in the control group were not given any treatment, the mice in the SD + modafinil group and Control + modafinil group were given 13 mg kg^{-1} intragastrically, and the mice in the SD group were given the same volume of normal saline for 3 consecutive days as shown in **Figure 1**.

Morris Water Maze Test

The Morris Water Maze (MWM) apparatus used in this experiment consisted of four parts: a circular pool (diameter of 120 cm, height of 50 cm), a circular platform (diameter of 12 cm, height of 30 cm), a behavior tracking system and Morris Water Maze analysis software. The experiment was carried out 1 h after intragastric administration as follows: (1) In the positioning navigation test, the circular pool was divided into four equally sized quadrants (I, II, III, and IV) and the duration of the experiment was 90 s. The circular platform was placed in quadrant I, and then the mice were placed in the water close to the pool wall with their backs to the circular platform. The behavior tracking system was started simultaneously. Morris Water Maze analysis software was used to record the swimming time, swimming distance, and swimming trajectory of the mice in searching for the circular platform over 90 s. If a mouse could not find the target platform within 90 s, it was manually guided to the platform and kept there for 15 s. Each animal was trained four times a day with an interval of at least 30 min between the two sessions for 6 consecutive days. The mice were blow-dried immediately after each training and returned to the cage. SD began on the seventh day and lasted for a total of 3 days, and formal tests were conducted on the 10th day. (2) In the spatial exploration test, the experimental parameters were the same as those used in the positioning navigation test except that the circular platform was removed. The experimenter placed the mice in the water close to the pool wall with their backs to the circular platform. At the same time, the behavior tracking system was activated, and Morris Water Maze analysis software was used to record the number of times the mice crossed the location of the circular platform, the amount of time spent in the target quadrant, the swimming speed, the total swimming distance, and the swimming trajectory over at 90 s. After the last spatial exploration test, all mice were sacrificed for tissue collection.

qRT-PCR

According to the manufacturer's instructions, total RNA was extracted from mouse hippocampal tissue using TRIzol reagent (Invitrogen, Carlsbad, CA, United States). The concentration of RNA was quantified with a NanoDrop ND-2000 spectrophotometer (Thermo Fisher Science). A FastKing RT Kit was used for reverse transcription, and the SuperReal PREMix Plus kit was used for qRT-PCR. The amplification conditions for real-time PCR instrument were 95°C for 15 min and 40 cycles of 95°C for 10 s, and 60°C for 32 s. The data were analyzed by the $2^{-\Delta\Delta Ct}$ method.

Western Blotting

Mouse hippocampal tissues were weighed, and protein extraction buffer was added to each sample at a weight–volume ratio of 1:6 (1 ml RIPA cell lysis buffer was supplemented with 10 μl

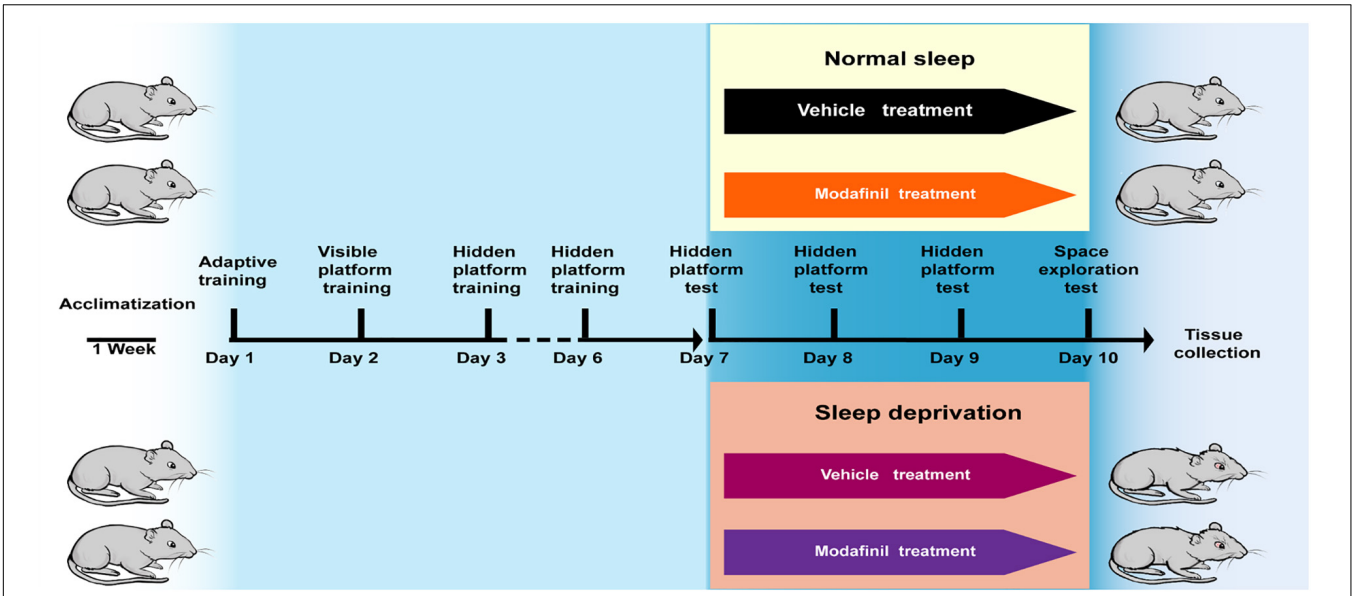

FIGURE 1 | The schematic representation of the experimental design. In the Morris Water Maze (MWM) test, mice were trained for adaptability on the first day, followed by formal training for 2–6 days, positioning navigation testing for 7–10 days (also at the SD stage), and additional space exploration testing after positioning navigation testing on the 10th day. The aim of testing all mice on the morning of day 7 was to exclude those with large individual differences. At the end of the day, they were randomly divided into four groups: the normal group, the Control + MD group, the SD group, and the SD + MD group; subsequently, the sleep deprivation stage was initiated, and the Control + MD group and SD + MD group were treated with modafinil. After the last spatial exploration test, all mice were sacrificed for tissue collection.

PMSF and 10 μl protein phosphatase inhibitor). Then, the samples were homogenized with grinding instrument (KZ-III-F; Servicebio; China). The cleavage product was centrifuged at 4°C and 13,200 × *g* for 20 min, and the supernatant was collected. Finally, the protein concentration was determined with a BCA protein detection kit (Thermo, United States). The proteins were then separated by SDS-PAGE (8, 10, or 12%) and transferred onto a PVDF membrane for 1.5 h, and the membrane was blocked with blocking buffer (TBST buffer containing 5% skimmed milk powder) for 2 h. The membrane was incubated overnight with NLRP1 (1:1,000; ab98181; Abcam), NLRP3 (1:250; PA5-20838; Thermo Fisher Scientific), NLRC4 (1:1,000; 06-1125; MilliporeSigma), GSDMD (1:1,000; ab209845; Abcam), ASC (1:1,000; sc-22514-R; Santa Cruz Biotechnology, Dallas, TX, United States), cleaved caspase-1 (1:1,000; 67314; CST), IL-1β (1:1,000; 12242; CST), IL-18 (1:1,000; ab71495; Abcam), brain-derived neurotrophic factor (BDNF) (11,000; OSB00018G; Thermo Fisher Scientific), β-actin (1:5,000; 4971; CST), and GAPDH (1:5,000; 2118; CST) primary antibodies at 4°C. After being washed with TBST, the membrane was incubated with the respective secondary antibodies. For densitometry, a ChemiDo XRS + imaging system (Bio-Rad, CA, United States) was used. The average pixel density of each band was measured using Quantity One software (Bio-Rad, CA, United States).

Immunofluorescence Staining

The mice were anesthetized by intraperitoneal injection of 5% chloral hydrate. After successful anesthesia, the mice were perfused with 4°C PBS until their livers turned white and then decapitated. After overnight immersion in 4% paraformaldehyde, the mice were fixed and then subjected to gradient dehydration in 15 and 30% sucrose solution. After successful dehydration, the olfactory bulbs and brain stems of the mice were excised, and the brain tissues were embedded in OCT compound. Hippocampal sections were fixed, permeabilized, and incubated with mouse anti-caspase-1 (1:200) and rabbit anti-NeuN (1:200) antibodies at 4°C overnight. The next day, the sections were rinsed with PBS and incubated with a mixture of secondary antibodies (FITC-conjugated goat anti-mouse and TRITC-conjugated goat anti-rabbit) for 1 h at room temperature. Finally, the sections were sealed after incubated with DAPI, and the numbers of cells coexpressing caspase-1 and neurons were counted under an immunofluorescence microscope.

Golgi Staining

A Golgi staining kit (PK401, FD Neuro Technologies, Inc., United States) was used according to the manufacturer's instructions. (1) At least 24 h before brain extraction, equal volumes of solutions A and B were mixed, and the mixture was kept at room temperature. (2) For brain extraction, the mice in each group were decapitated. The blood on the surface of the brain was quickly washed away with double distilled water, and the tissues were soaked in the solution A and B mixture. (3) After the tissues were incubated for 6 h or on the next day, fresh solution A and B mixture was added, and the tissues were incubated in the dark at room temperature for 2 weeks. (4) The tissues were transferred to solution C and placed in a dark environment at room temperature for at least 72 h

(up to 1 week). The solution was replaced once after 24 h. (5) A cryostat was used to cut the tissues into thick 100 μm sections, and then the sections were placed glass slides and dripped with solution C to unfold them. (6) The slices were dried naturally in a dark and dry environment at room temperature. (7) Then the sections were washed twice with double-distilled water for 5 min each. (8) The slices were placed in a 1:1:2 mixture of solution D, solution E, and double-distilled water for 10 min. (9) Then, the slices were washed twice with double-distilled water for 5 min each. (10) The slices were dehydrated successively in 50, 75, and 95% ethanol for 5 min each, and (11) with anhydrous ethanol four times for 5 min each. (12) The sections were cleared in xylene, three times for 5 min each, and (13) sealed with neutral resin, placed in the dark box to dry, photographed, and analyzed. Finally, ImageJ software was used to observe and record the morphology of dendritic spines of hippocampal CA3 pyramidal neurons, record the number and length of dendritic spines, and calculate the density of the dendritic spines.

Statistical Analysis

The statistical analysis of all measurement data was carried out by using GraphPad Prism 7 statistical software, and the data are expressed as the mean ± SD. Groups were compared by one-way analysis of variance (ANOVA) or two-way ANOVA. The significance level was set as $\alpha = 0.05$, and significant differences are expressed as P-values ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$).

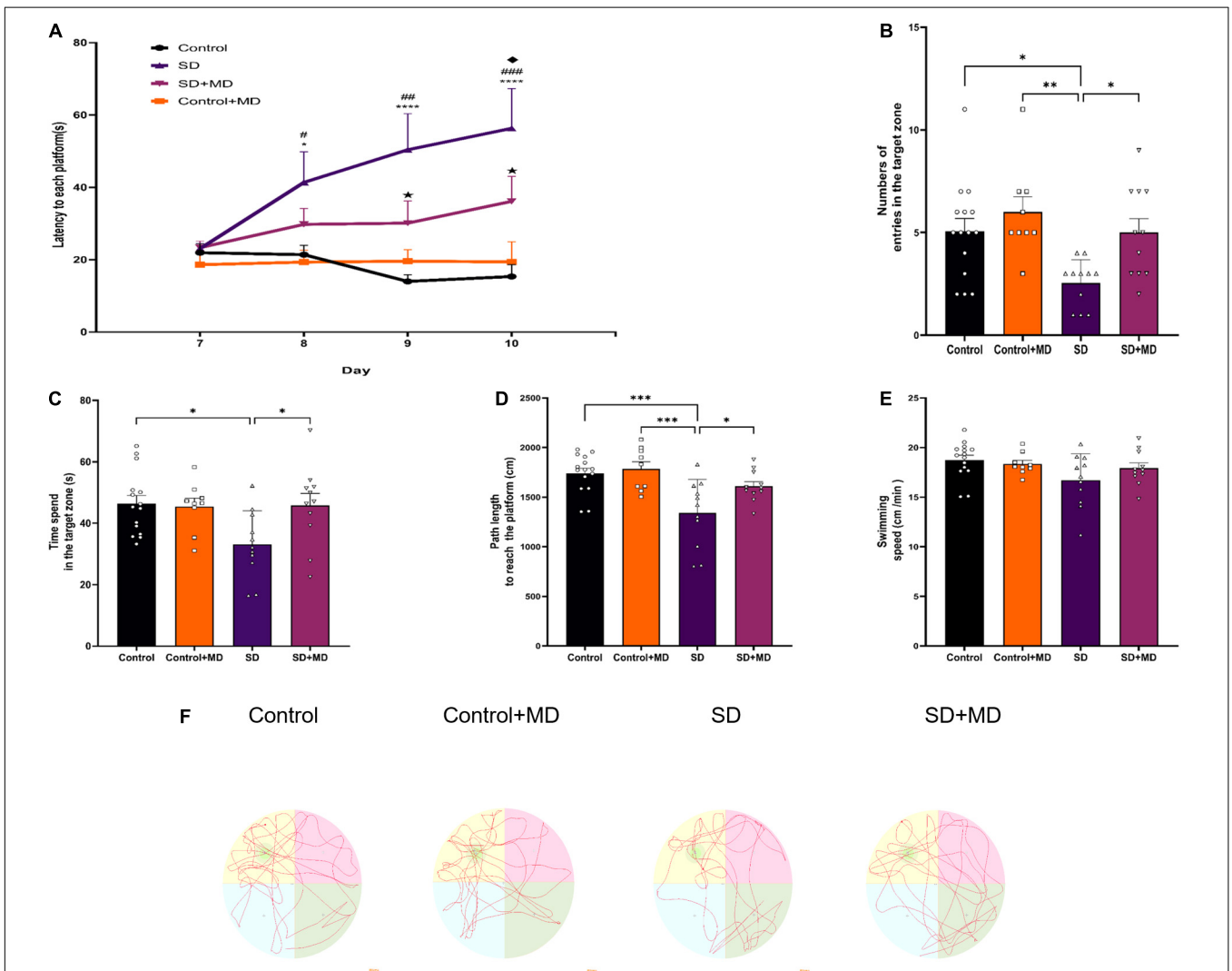

FIGURE 2 | The effect of modafinil on learning and memory of SD. **(A)** The escape latency to reach the platform during the training sessions of the MWM test was detected. $^{*}P < 0.05$, $^{****}P < 0.0001$, significantly different from Control; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, significantly different from Control + MD group; $^{H}P < 0.05$, significantly different from SD group; $^{U}P < 0.05$, significantly different from SD + MD group. **(B)** The number of entries in the spatial acquisition trial was decreased. **(C)** The time spent in the target quadrant in the probe trail was increased by modafinil treatment. **(D)** The swimming path length was recorded after SD. **(E)** There was no significant difference in swimming speed among the four groups. **(F)** Representative swimming tracks of mice after SD for 72 h. All data presented are means ± SD; N = 9–15 mice per group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

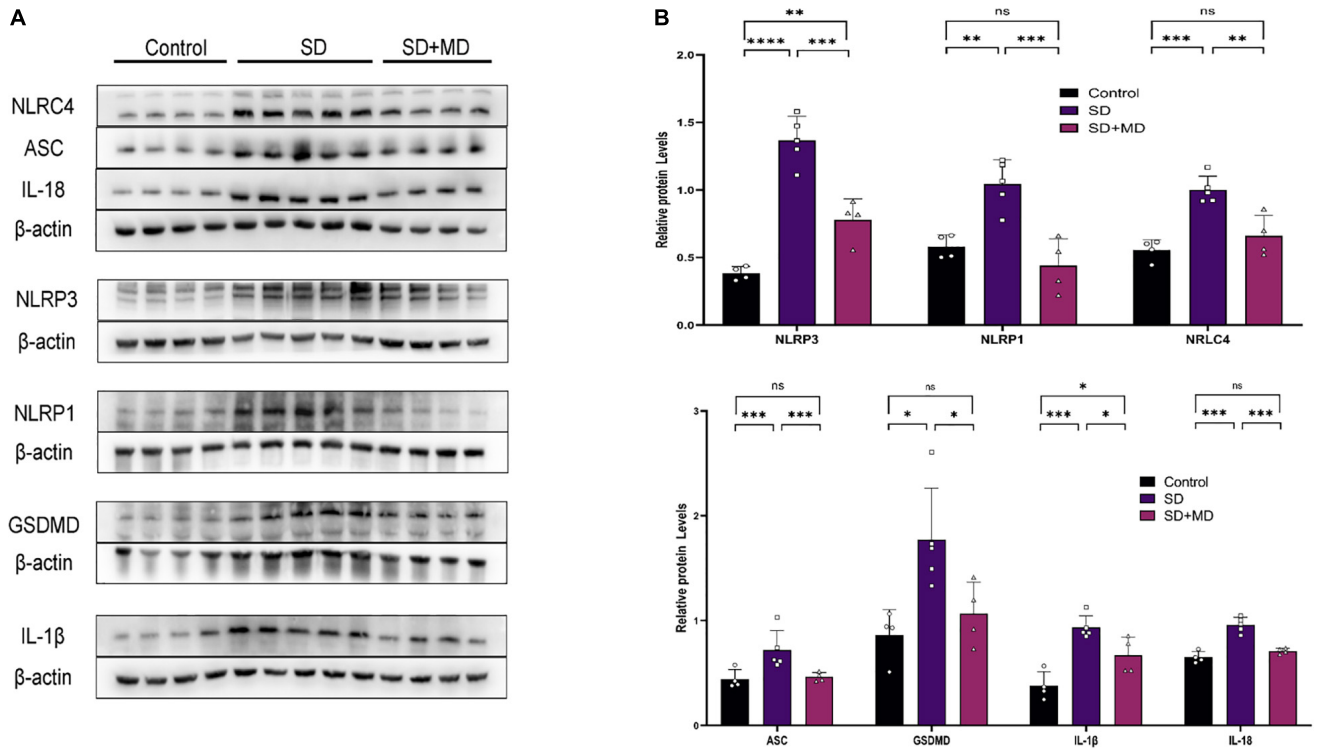

FIGURE 3 | Pyroptosis induced by SD was inhibited by modafinil. **(A,B)** Western blot data showing that modafinil suppressed the increase in the expression of NLRP3, NLRC4, NLRP1, ASC, caspase-1, GSDMD, and the downstream pro-inflammatory cytokines IL-1β and IL-18 in mice subjected to SD. All data presented are means ± SD; N = 4–5 mice per group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

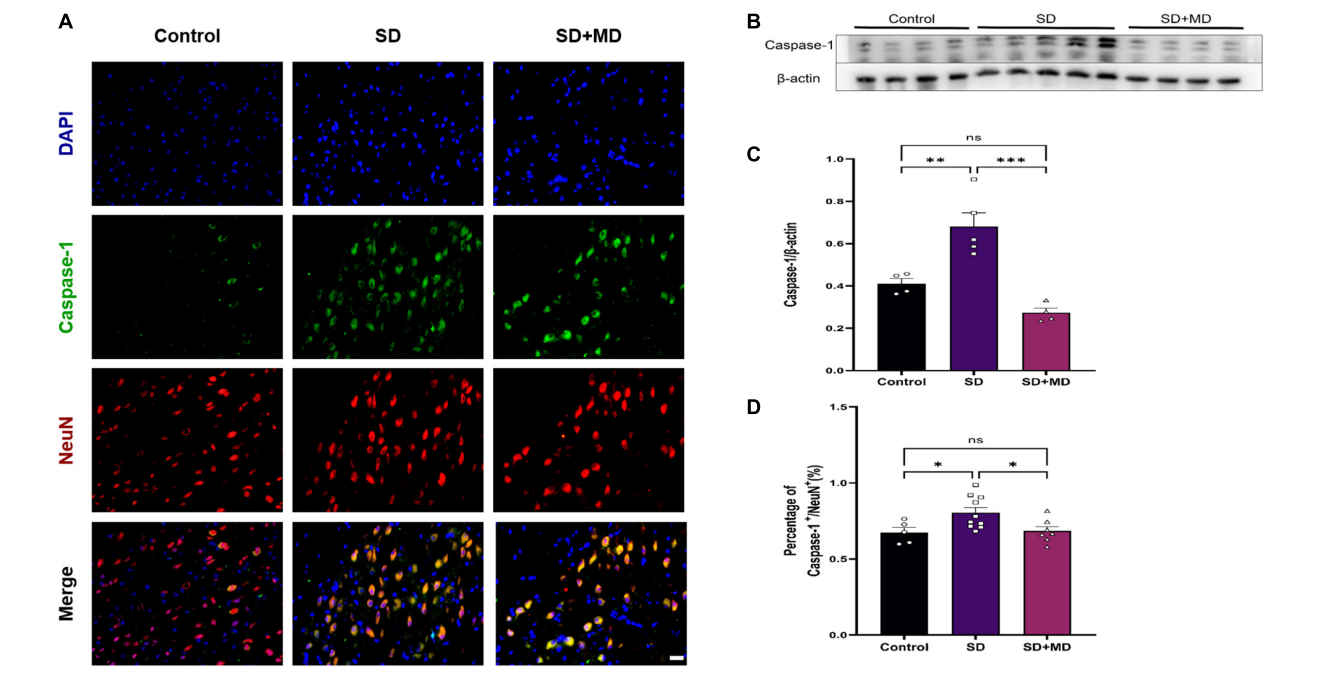

FIGURE 4 | Modafinil decreased the expression of caspase-1 in the hippocampi of mice subjected to SD mice. **(A)** Representative pictures of double staining of caspase-1 and NeuN in the hippocampi of mice obtained by a fluorescence microscope. **(B,C)** Western blot analysis of caspase-1 expression in the hippocampi of mice subjected to SD and treated with vehicle or modafinil. All data presented are means ± SD; N = 4–5 mice per group. **(D)** Immunofluorescence analysis and quantification of the expression level of caspase-1. All data presented are means ± SD; N = 5–10 mice per group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

RESULTS

Modafinil Alleviates Cognitive Impairment in Sleep Deprivation Mice

Before SD, all mice were subjected to the Morris Water Maze. The mice exhibited the same level of performance in the spatial exploration and positioning navigation tests. As shown in **Figure 2A**, modafinil treatment alleviated memory deterioration in mice in the hidden platform test ($P < 0.01$). SD obviously impaired the spatial memory of the mice ($P < 0.001$). As shown in **Figures 2B–E**, after 72 h of SD, the number of times of passing through the hidden platform ($P = 0.0197$), the time of staying in the target quadrant ($P = 0.0176$), and the total distance of swimming ($P = 0.0005$) in the SD group were less than those in the control group. However, after administration of modafinil, the mice in the modafinil group passed through the hidden platform more often ($P = 0.0401$), stayed longer in the target quadrant ($P = 0.0414$), and swam longer ($P = 0.0447$). There was no significant difference in swimming speed among the four groups ($P > 0.05$). The typical swimming trajectories of each group are shown in **Figure 2F**. Interestingly, although there was a tendency of memory enhancement in the Control + MD group compared with the Control group, there was no statistical significance. Therefore, in this study, we focused on the related mechanisms of modafinil in animals with sleep disorders as opposed to in healthy animals.

Modafinil Reduces Pyroptosis in Hippocampus Tissues of Sleep Deprivation Mice

As our understanding of pyroptosis has improved, pyroptosis has been gradually associated with the pathophysiological processes of many diseases. However, there are few reports on the relationship between pyroptosis and SD. In this experiment, the

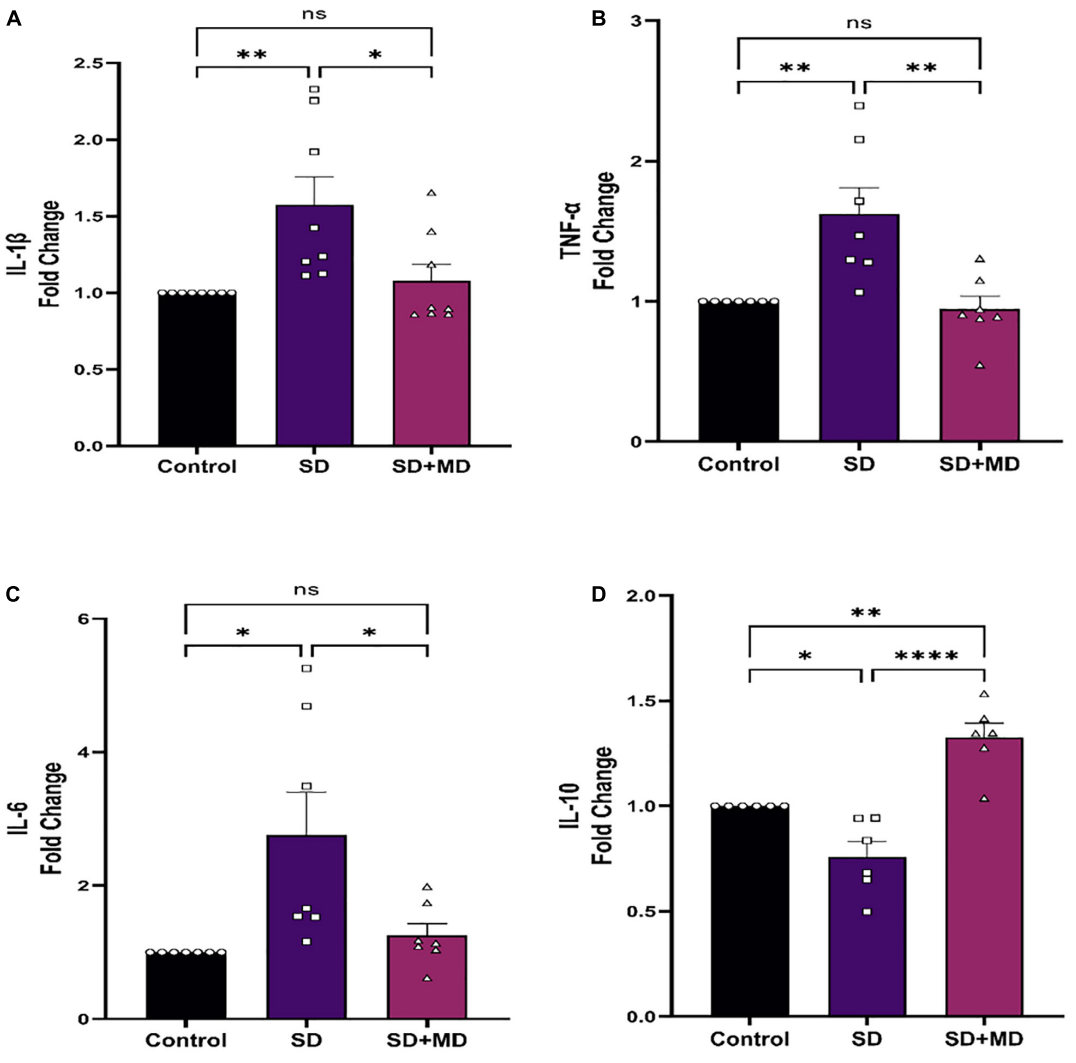

FIGURE 5 | Modafinil altered the expression of inflammatory cytokines in the hippocampi of mice subjected to SD. Modafinil upregulated the expression of IL-1β IL-6 and TNF-α and downregulated the expression of IL-10. All data presented are means ± SEM; $N = 5$–8 mice per group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

expression of many proteins involved in pyroptosis was altered in the hippocampi of SD mice. As shown in **Figure 3**, the expression of NLRP3 ($P < 0.0001$), NLRC4 ($P = 0.0004$), NLRP1 ($P = 0.0048$), ASC ($P = 0.0246$), GSDMD ($P = 0.0125$), IL-1β ($P = 0.0004$), and IL-18 ($P < 0.0001$) in the hippocampus was increased in the SD group compared with the control group. Modafinil antagonizes the effects of SD on the expression of NLRP3 ($P = 0.0003$), NLRC4 ($P = 0.003$), NLRP1 ($P = 0.0007$),

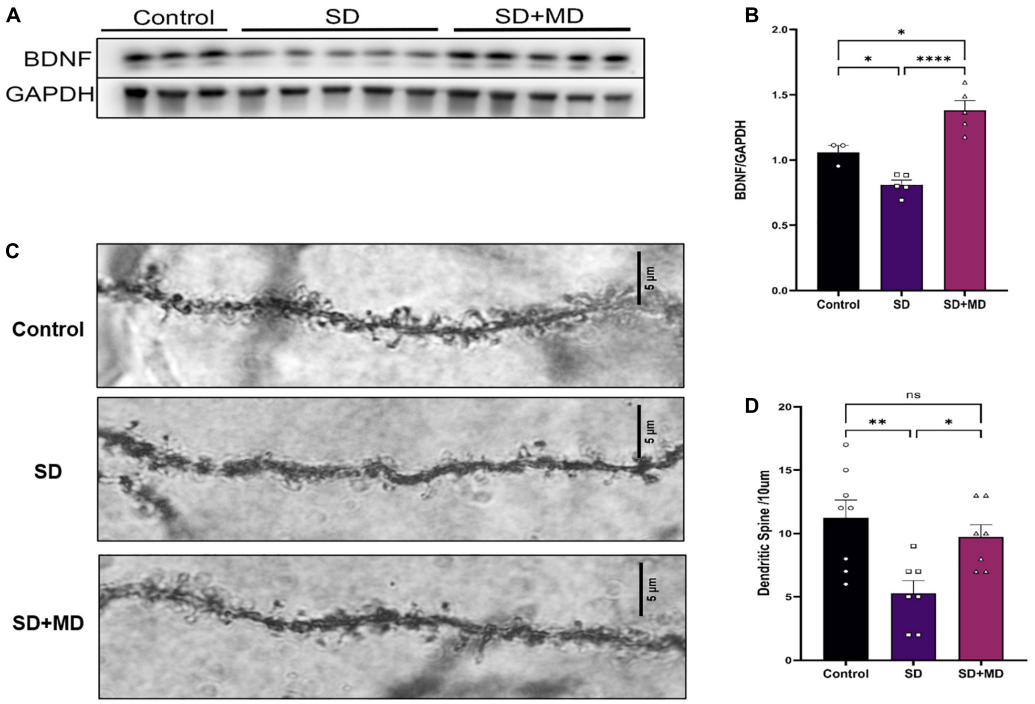

FIGURE 6 | Modafinil decreased BDNF expression and alleviated dendritic spine loss in hippocampal CA3 pyramidal neurons in mice subjected to SD. **(A,B)** Western bot analysis of BDNF expression in the hippocampus. All data presented are means ± SD; $N = 3$–5 mice per group. **(C,D)** The density of CA3 pyramidal neurons, as measured by Golgi staining, was decreased in mice subjected to SD, and modafinil reversed this decrease. All data presented are means ± SD; $N = 7$–8 mice per group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

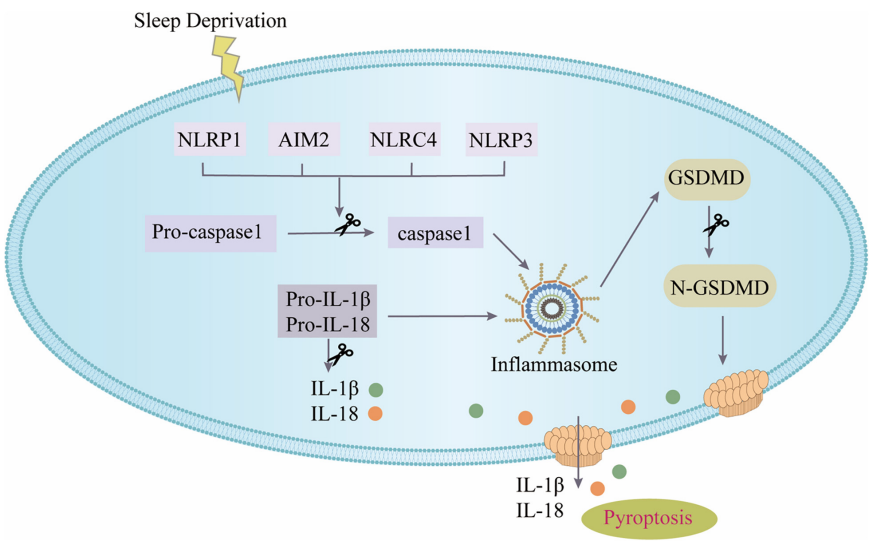

FIGURE 7 | The canonical inflammasome pathway. SD can activate inflammasomes in cells and further recruit ASC and pro-caspase-1 to form inflammasome complex. Active caspase-1 cleaves GSDMD to produce GSDMD pores on the cell membrane; active caspase-1 can activate pro-IL-1β and pro-IL-18, and then IL-1β and IL-18 are released from the GSDMD pores.

ASC ($P = 0.0356$), GSDMD ($P = 0.0468$), IL-β ($P = 0.0428$), and IL-18 ($P = 0.0002$).

Modafinil Alleviates Pyroptosis in Hippocampal Neurons of Sleep Deprivation Mice

We found that the pyroptotic cells in SD model mice were mainly neurons. Next, we evaluated neuronal pyroptosis in mice subjected to SD. Weak caspase-1 immunoreactivity was observed in the normal group, but strong caspase-1 immunoreactivity was observed in the cytosol in mice subjected to SD. The neuronal markers NeuN and caspase-1 were detected by double immunofluorescence. The number of caspase-1-positive neurons in the mouse hippocampus was significantly higher in the group subjected to SD for 72 h than in the control group ($P = 0.0458$). There were significantly fewer caspase-1-positive neurons in the modafinil group than in the SD group ($P = 0.0392$) (**Figures 4A,D**). This finding was consistent with the western blot results. Caspase-1 expression was significantly increased in the SD group ($P = 0.0054$), and modafinil treatment effectively decreased the expression of this protein ($P = 0.0003$) (**Figures 4B,C**).

Modafinil Suppresses Inflammatory Activity in Hippocampus of Sleep Deprivation Mice

In recent years, the relationship between IL-1β, TNF-α, IL-6, and SD has been widely discussed. It was found that the expression of IL-1β and TNF-α in the serum, heart, liver, kidney, and pancreas is significantly increased in mice subjected to SD (Periasamy et al., 2015). There was a significant correlation between the degree of synaptic damage and synaptic transmission. As shown in **Figure 5**, qRT-PCR showed that the expression of IL-1β ($P = 0.0083$) (**Figure 5A**), TNF-α ($P = 0.0043$) (**Figure 5B**), and IL-6 ($P = 0.0119$) (**Figure 5C**) was increased and that the expression of IL-10 ($P = 0.0246$) (**Figure 5D**) was decreased in the hippocampus in mice subjected to SD compared with control mice. Accordingly, modafinil decreased the expression of IL-1β ($P = 0.023$) (**Figure 5A**), TNF-α ($P = 0.0021$) (**Figure 5B**), and IL-6 ($P = 0.0319$) (**Figure 5C**) and increased the expression of IL-10 ($P < 0.0001$) (**Figure 5D**) in the mouse hippocampus after SD.

Modafinil Promotes Brain-Derived Neurotrophic Factor Expression and Synaptic Plasticity in Hippocampus of Sleep Deprivation Mice

Brain-derived neurotrophic factor is thought to be the most important neurotrophin in the central nervous system and is associated with learning and memory (Parkhurst et al., 2013). As shown in **Figures 6A,B**, Western blotting showed that the protein expression of BDNF in the hippocampus was significantly decreased after 72 h of SD ($P = 0.0481$). The protein expression of BDNF in the hippocampus was significantly increased in the modafinil group compared with the model groups ($P = 0.0001$). Similarly, as shown in **Figures 6C,D**, dendritic spines on neurons in the CA3 region of the hippocampus were abundant and highly dense in the control group. The density of dendritic spines on neurons in the CA3 region was significantly decreased in the SD group ($P = 0.0045$). Compared with that in the SD group, the density of dendritic spines on hippocampal CA3 neurons in the modafinil group was increased ($P = 0.0416$).

CONCLUSION

This study focused for the first time on the role and mechanism of pyroptosis mediated by the NOD-like receptors (NLRs) inflammasome in SD as shown in **Figure 7**. The major discoveries are that: (1) modafinil alleviates NLRs inflammasome-mediated pyroptosis in mice subjected to SD; (2) modafinil alleviates inflammation induced by neuronal pyroptosis in mice subjected to SD; (3) modafinil promotes BDNF activation in the hippocampi of mice subjected to SD, which is beneficial for synaptic plasticity; and (4) modafinil improves learning and memory in mice subjected to SD. In summary, targeting the regulation of impaired neuronal pyroptosis and neuroinflammation may be a promising therapeutic strategy for the future treatment of SD.

The term "pyroptosis" was originally to describe a particular type of regulatory cell death (Cookson and Brennan, 2001). That is somewhat similar to apoptosis but is dependent on the inflammatory molecule caspase-1 (Galluzzi et al., 2018). Pyroptosis has been a hot topic in recent years, and an increasing number of studies have shown that it is closely related to a variety of diseases. Pyroptosis is widely involved in intestinal diseases (Bulek et al., 2020), liver diseases (Liu et al., 2020), kidney diseases (Komada and Muruve, 2019), hematological diseases (Johnson et al., 2018), nervous system diseases (Feng et al., 2020), atherosclerotic diseases (Fidler et al., 2021), cancer, and metabolic diseases (Sharma and Kanneganti, 2021). Inflammasome activation is also a key process in severe COVID-19 (Vora et al., 2021). Consistent with previous studies, SD does induce the activation of pyroptosis, but research in this area is relatively insufficient (Fan et al., 2021). Unlike in previous studies, modafinil was able to protect hippocampal neurons by inhibiting excessive autophagy and apoptosis in sleep-deprived mice (Cao et al., 2019). In this study, modafinil inhibited the further activation of pyroptosis and reduced cognitive impairment in sleep-deprived mice. In-depth study of pyroptosis is helpful for elucidating its role in the occurrence, development and prognosis of related diseases and provides new ideas for clinical prevention and treatment.

Early research has shown that modafinil has a variety of positive effects on awakening, movement, and cognitive ability (Minzenberg and Carter, 2008). The new study also found that modafinil enhances attention and improves learning, memory, and cognitive function (Philipsen et al., 2021). At the same time, SD inhibits the expression of BDNF in the hippocampus, which in turn disrupts synaptic plasticity, leading to neurologic decline in the hippocampus and, ultimately, a decline in learning and memory (Zagaar et al., 2016). However, the mechanism has not

been fully identified. In this study, an inflammatory response that inhibited the expression of BDNF and the development of synaptic plasticity in the hippocampus was found to be activated in sleep-deprived mice. Modafinil reduced further inflammation, boosting BDNF activation in the hippocampus and synaptic plasticity in mice. Moreover, behavioral tests showed that modafinil significantly alleviated learning and memory impairment in sleep-deprived mice, possibly through inhibition of neuronal pyroptosis and inflammatory activation.

Studies have shown that skeletal muscle, as an endocrine organ, can release many muscle cytokines during exercise and play an anti-inflammatory role (Hoffmann and Weigert, 2017). As a simple and convenient aerobic exercise, treadmill exercise can inhibit neuroinflammation and microglial activation (Mee-Inta et al., 2019). Treadmill exercise can also prevent inflammation and learning and memory impairment caused by acute SD and reverse the cognitive decline caused by SD (Kojima et al., 2020). In addition, treadmill exercise reduced chronic allergic lung inflammation and airway remodeling in mice (Vieira et al., 2007). Treadmill exercise could increase myeloid-derived suppressor cells (MDSCs) by stimulating the secretion of IL-10 from macrophages through the IL-10/STAT3/S100A9 signaling pathway, thereby achieving heart protection (Feng et al., 2021). Depression symptoms were alleviated by reducing the number of microglia and inhibiting microglial activation and neuroinflammation in the hippocampus. Treadmill exercise lessens hepatic inflammation during non-alcoholic steatohepatitis by reducing the accumulation of hepatic monocyte-derived inflammatory macrophages and bone marrow precursor cells (Fredrickson et al., 2021). Treadmill exercise plays a beneficial role in promoting neurogenesis and functional recovery by activating the CD200/CD200R signaling pathway and improving the inflammatory environment after stroke (Sun et al., 2019). These studies suggest that treadmill exercise has a favorable effect on the balance between pro- and anti-inflammatory and reinforce its potential therapeutic role in reducing the risk of neuroinflammation-related diseases. However, it takes a long time for treadmill exercise to exert its anti-inflammatory effects. In this experiment, intermittent and brief treadmill exercise was mainly used to disturb the sleep of mice, and whether it affected the inflammatory process needs further study.

In conclusion, our study demonstrates that modafinil suppresses neuronal pyroptosis and inflammation following SD. The potential benefit of modafinil in patients with sleep disorders may deserve further investigation in future studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Protection and Use Committee of Tianjin Medical University. Written informed consent was obtained from the owners for the participation of their animals in this study.

AUTHOR CONTRIBUTIONS

PL and YZu were responsible for study design. XX developed methodology. XX, YZu, LC, ZY, TH, MG, ZH, XG, WL, YW, and DW carried out the experiments. FC and QL provided technical support. XX and YZu interpreted the results, performed data analysis, and prepared the figures and tables. XX wrote the manuscript. PL supervised the study. All authors read and approved the final manuscript.

FUNDING

This work was supported by the National Natural Science Foundation of China (Grant Nos. 81772060, 82072166, and 82102318); the Key Projects of Science and Technology support of Tianjin Key R&D Plan (Grant No. 20YFZCSY00030); the Natural Science Foundation of Tianjin (Grant No. 19JCQNJC10200); and the Tianjin Health and Health Committee Foundation (Grant No. KJ20177).

ACKNOWLEDGMENTS

We appreciate Chunsheng Kang, Shu Zhang, Xiao Liu, Hao Liang, Weiyun Cui, and Lei Zhou from Tianjin Neurological Institute for their technical support.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neuroscience

ORIGINAL RESEARCH
published: 15 March 2022
doi: 10.3389/fnins.2022.726880

Diagnosis of Sleep Apnoea Using a Mandibular Monitor and Machine Learning Analysis: One-Night Agreement Compared to in-Home Polysomnography

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OPEN ACCESS

Edited by:
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Reviewed by:
Jitse P. Van Dijk, University Medical Center Groningen, Netherlands
Gonzalo C. Gutiérrez-Tobal, Centre for Biomedical Network Research (CIBER), Spain

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Specialty section:
This article was submitted to Sleep and Circadian Rhythms, a section of the journal Frontiers in Neuroscience

Received: *17 June 2021*
Accepted: *22 February 2022*
Published: *15 March 2022*

Citation:
Kelly JL, Ben Messaoud R, Joyeux-Faure M, Terrail R, Tamisier R, Martinot JB, Le-Dong N-N, Morrell MJ and Pépin J-L (2022) Diagnosis of Sleep Apnoea Using a Mandibular Monitor and Machine Learning Analysis: One-Night Agreement Compared to in-Home Polysomnography. Front. Neurosci. 16:726880. doi: 10.3389/fnins.2022.726880

Background: The capacity to diagnose obstructive sleep apnoea (OSA) must be expanded to meet an estimated disease burden of nearly one billion people worldwide. Validated alternatives to the gold standard polysomnography (PSG) will improve access to testing and treatment. This study aimed to evaluate the diagnosis of OSA, using measurements of mandibular movement (MM) combined with automated machine learning analysis, compared to in-home PSG.

Methods: 40 suspected OSA patients underwent single overnight in-home sleep testing with PSG (Nox A1, ResMed, Australia) and simultaneous MM monitoring (Sunrise, Sunrise SA, Belgium). PSG recordings were manually analysed by two expert sleep centres (Grenoble and London); MM analysis was automated. The Obstructive Respiratory Disturbance Index calculated from the MM monitoring (MM-ORDI) was compared to the PSG (PSG-ORDI) using intraclass correlation coefficient and Bland-Altman analysis. Receiver operating characteristic curves (ROC) were constructed to optimise the diagnostic performance of the MM monitor at different PSG-ORDI thresholds (5, 15, and 30 events/hour).

Results: 31 patients were included in the analysis (58% men; mean (SD) age: 48 (15) years; BMI: 30.4 (7.6) kg/m^2). Good agreement was observed between MM-ORDI and PSG-ORDI (median bias 0.00; 95% CI −23.25 to + 9.73 events/hour). However, for 15 patients with no or mild OSA, MM monitoring overestimated disease severity (PSG-ORDI < 5: MM-ORDI mean overestimation + 5.58 (95% CI + 2.03 to + 7.46) events/hour; PSG-ORDI > 5–15: MM-ORDI overestimation + 3.70 (95% CI −0.53 to + 18.32) events/hour). In 16 patients with moderate-severe OSA (n = 9 with PSG-ORDI 15–30 events/h and n = 7 with a PSG-ORD > 30 events/h), there was an underestimation (PSG-ORDI > 15: MM-ORDI underestimation −8.70 (95% CI −28.46 to + 4.01) events/hour). ROC optimal cut-off values for PSG-ORDI thresholds of 5, 15, 30 events/hour were: 9.53, 12.65 and 24.81 events/hour, respectively. These cut-off

values yielded a sensitivity of 88, 100 and 79%, and a specificity of 100, 75, 96%. The positive predictive values were: 100, 80, 95% and the negative predictive values 89, 100, 82%, respectively.

Conclusion: The diagnosis of OSA, using MM with machine learning analysis, is comparable to manually scored in-home PSG. Therefore, this novel monitor could be a convenient diagnostic tool that can easily be used in the patients' own home.

Clinical Trial Registration: [https://clinicaltrials.gov], identifier [NCT04262557].

Keywords: sleep apnoea, polysomnography, mandibular monitor, in-home diagnosis, one-night agreement, performance, automated machine learning analysis

INTRODUCTION

Obstructive sleep apnoea (OSA) is a major burden worldwide, affecting nearly one billion people (Benjafield et al., 2019; Grote, 2019; Lyons et al., 2020). Alongside symptoms of sleepiness, and impaired memory and mood, untreated OSA is associated with a range of cardiovascular and metabolic morbidities and increased mortality (Knauert et al., 2015; Levy et al., 2015; Reutrakul and Mokhlesi, 2017; Linz et al., 2018). Moreover, the prevalence is set to rise with ageing populations and a global obesity pandemic. Additionally, recent data supporting treatment of mild OSA has created further burden, with over half of patients with OSA experiencing a mild form of the disease (Benjafield et al., 2019; Wimms et al., 2020). Finally, an acute need has arisen to re-evaluate OSA diagnosis and treatment, due to the COVID-19 pandemic, which has reduced resources and increased waiting lists (Patel and Donovan, 2020; Schiza et al., 2021).

Attempts to expand diagnostic capacity in the face of increasing demand have utilised technological advances. In particular, portable monitors have focused on minimally invasive measurements and automated analysis, for ease of use by both patients and staff (Collop et al., 2007). Additionally, the COVID-19 pandemic has resulted in the need for disposable diagnostic monitors that can be used safely in the patients' home, to facilitate remote healthcare pathways (Grote et al., 2020). However, despite the obvious need for new diagnostic tools, monitors must be evaluated for reliability, since issues typically occur in the classification of breathing events as central or obstructive, plus the overall event count, in the absence of sleep monitoring (Randerath et al., 2018).

Mandibular movements (MM) have been established as a surrogate bio-signal for the detection of breathing effort during sleep (Martinot et al., 2015, 2017b, 2020). Analysis of the MM signal has enabled the identification of specific breathing patterns associated with sleep-disordered breathing (Senny et al., 2008; Maury et al., 2013, 2014; Martinot et al., 2017a). MM analysis has also been shown to differentiate between sleep and wake states, allowing for the identification of total sleep time, which may be of value in the calculation of sleep-disordered breathing indices (Senny et al., 2009, 2012; Maury et al., 2014). In a recent study, machine learning was used to homogenise the quality of the scoring of respiratory events, linked with cloud-based data transfer; this automated analysis was equivalent to that of in-laboratory PSG (Pépin et al., 2020).

The aim of the current study was to evaluate the use a novel monitor (Sunrise, Sunrise SA, Belgium) using MM for the diagnosis of OSA in real world conditions. MM and PSG data were recorded simultaneously in the patients' home. MM was analysed automatically and compared to PSG analysed manually by experts at two clinical centres. We hypothesised that the Obstructive Respiratory Disturbance Index (ORDI)(Nordigarden et al., 2011) calculated using MM with machine learning analysis would not be significantly different to the ORDI obtained using manually scored PSG.

MATERIALS AND METHODS

Study Design

A prospective, diagnostic, open study in 40 adult patients referred with a suspicion of OSA to a single centre (Grenoble Alpes University Hospital) was conducted. The study was approved by an independent Ethics Committee (Comité de Protection des Personnes, Sud-Ouest et Outremer III, Bordeaux, France, ID-RCB: 2019-A02965-52) and registered on Clinicaltrials.gov (NCT04262557). All 40 patients were recruited from the Grenoble centre and signed written informed consent. The study was conducted in accordance with Good Clinical Practice, and all applicable laws and regulations. This study followed the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guideline.

Forty consecutive adult patients undertaking a diagnostic home sleep study for suspicion of OSA were invited to participate. Participants had to be able to use portable devices and smartphones. All 40 participants underwent an overnight PSG (the reference method) with simultaneous MM recordings using the Sunrise system (Sunrise SA, Belgium). Two visits were scheduled; the first to verify the eligibility of the patient and to collect baseline data. The second visit was at end of the study, with the patient and clinician, for sharing of the final diagnostic report.

Overnight Sleep Study and Scoring of Polysomnography

In-home PSG was recorded with a portable acquisition system (Nox A1, ResMed, Saint-Priest Cedex, France). Measurements used to determine sleep were electro-oculogram, electroencephalogram, electromyogram, and electrocardiogram. Oxygen saturation was also monitored by

a digital oximeter displaying pulse waveform (Nonin, Nonin Medical, United States). Airflow was measured using nasal pressure associated with the sum of oral and nasal thermistor signals. Respiratory effort was monitored with abdominal and thoracic bands.

Polysomnography recordings were initially scored by experts from the recruiting centre (Grenoble Alpes University Hospital, France). PSG were anonymized, converted in European data format (EDF) and sent *via* a secured platform for blinded scoring to the second reference centre (Imperial College London, United Kingdom). Scoring was performed according to the recommended criteria established by the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated (Berry et al., 2012). Apnoeas were defined as a complete cessation of airflow $\geq$ 10 s and classified as obstructive, central, or mixed according to the presence or the absence of respiratory effort. Hypopneas were scored using the AASM-recommended hypopnoea definition, requiring at least a 30% decrement in airflow lasting 10 s or longer and associated with a decrease of at least 3% in oxygen saturation as measured by pulse oximetry, or an arousal (Berry et al., 2012, 2017). ORDI was defined as the total number of obstructive respiratory disturbances accompanied by respiratory effort divided by the total sleep time (TST) (PSG-ORDI). PSG recordings were analysed blinded to the MM data and the two centres scored the PSG recordings independently.

Obstructive sleep apnoea diagnosis was established according to the third edition of the International Classification of Sleep Disorders (ICSD-3) (Sateia, 2014). Apnoea-Hypopnoea Index (AHI) thresholds of 5, 15 and 30 events/hour were used to define OSA severity levels of mild, moderate, and severe, respectively.

Mandibular Movement Recordings and Description of the Sunrise Monitoring System

The Sunrise monitoring system is a certified medical device used for the diagnosis of sleep apnoea using MM analysis (Sunrise SA, Namur, Belgium). The MMs were monitored using inertial measurement units and data was transferred *via* Bluetooth Low Energy to a smartphone application. For more information on MM analysis see **Appendix**.

Participants first downloaded the application and then performed a device association, before attaching the monitor to their chin, in the mentolabial sulcus. The recorded MM data were automatically transferred from the smartphone to a cloud-based infrastructure at the end of the night. These data were then analysed using a dedicated machine learning algorithm. The algorithm identified obstructive and mixed apnoeas and hypopnoeas, plus respiratory effort–related arousals, through stereotypical MM patterns. Respiratory disturbances were identified by periods of respiratory effort ended by an arousal or an awakening. A full description of the Sunrise System and algorithm have been previously reported (Pépin et al., 2020). The MM-ORDI was defined as the total number of obstructive respiratory disturbances accompanied by respiratory effort divided by the TST, estimated from the Sunrise analytics.

Statistical Analysis

Data analysis was conducted using scientific computing packages (numpy, scipy) in the Python programming language.

Firstly, we evaluated the agreement between the MM-ORDI and the PSG-ORDI. For this, we compared the MM-ORDI with the PSG-ORDI calculated by scorers in Grenoble and in London and we also calculated the combined PSG-ORDI by averaging the ORDI scores from the two centres. Then, we used Pearson's linear correlation matrix and regression plots to evaluate the linear relationship between MM-ORDI and PSG-ORDI. Next, we calculated ORDI Intraclass Correlation Coefficients (ICC) using a 2-way fixed model for single measures (ICC, 3,2) to evaluate the agreement between MM-ORDI and PSG-ORDI. Additionally, we used a complete and groupwise Bland-Altman plot to estimate the 95% limits of agreement and the systematic bias of MM-derived indices compared with their PSG counterparts.

Secondly, we evaluated the diagnostic performance of MM-ORDI for OSA based on receiver operating characteristic (ROC) curves. We performed an area under the curve (AUC), and a *post hoc* analysis to optimise the cut-off points of MM-ORDI for diagnostic decisions, compared with the criterion-standard cut-off values of obstructive PSG-ORDI recommended in ICSD-3 (5 events/hour and 15 events/hour). The optimal MM cut-offs were assessed at the highest value of the Youden index (sensitivity plus specificity minus 1). Finally, we calculated the metrics of clinical utility and accuracy for the optimal detection thresholds and the post-test probability for each cut-off point recommended by the Portable Monitoring Task Force of the AASM (Collop et al., 2007).

Statistical inference was based on null-hypothesis testing at significance threshold of $p < 0.05$.

RESULTS

Participants

Forty participants were recruited to the study and data from 31 participants were included in the analysis. Two participants withdrew, and there were three technical failures of PSG (poor quality signals) and four technical failures of the Sunrise device (Bluetooth connection was lost for three patients and for one patient the Sunrise sensor became disconnected). Participants were 58% men, with a mean (SD) age of 48 (15) years and body mass index (BMI) of 30.4 (7.6) kg/m^2.

Evaluation of the Agreement Between Mandibular Movement Monitoring System and in-Home Polysomnography for Measuring Respiratory Disturbances

The median value of PSG-ORDI, determined by averaging the ORDI scores from the two centres, was 15.45 (IQR: 1.75 to 61.38) events/hour. The median of MM-ORDI was 16.80 (IQR: 3.50 to 42.50) events/hour. Overall, there was a good agreement between

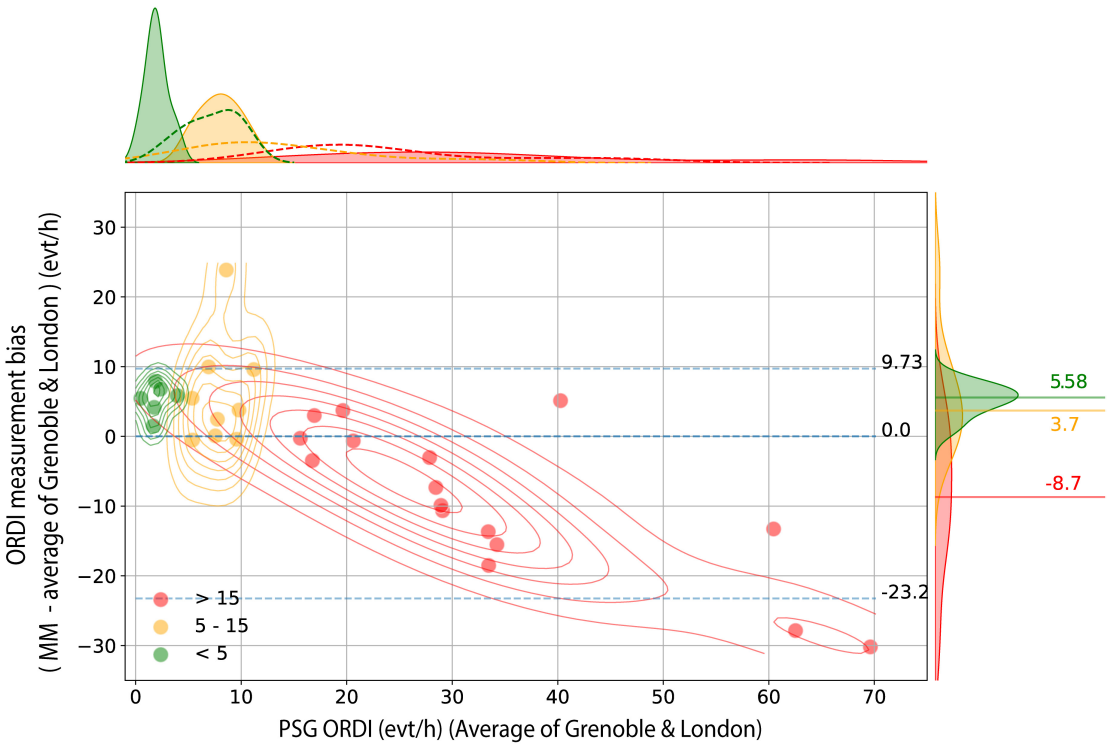

FIGURE 1 | Bland-Altman analysis for MM-ORDI versus average PSG-ORDI. Bland-Altman plot shows the disagreement between average PSG-ORDI and MM-ORDI (y axis) as a function of the average PSG ORDI (x axis), with individual cases stratified into three clinical groups. Bidimensional kernel density estimation plots are superimposed to show the joint distribution of measurement bias within each subgroup. The blue horizontal lines indicate the median, lower and upper bound (5th and 95th centiles) of the measurement bias in the whole sample. The distribution of the disagreement between the two methods, stratified by group, is shown on the right, with three horizontal lines indicating the median bias within each group. MM: mandibular movement; ORDI: obstructive respiratory disturbance index; PSG: polysomnography.

MM-ORDI and PSG-ORDI with a median bias of 0.00 (95% CI −23.25 to + 9.73) events/hour (**Figure 1**). However, there was systematic bias across the disease severity spectrum. In patients with no OSA (<5 events/hour, n = 6) and mild OSA, (5–15 events/hour, n = 9), MM-ORDI over-estimated by a random and normally distributed bias, with medians of + 5.58 (95% CI: + 2.03 to + 7.46) and + 3.70 (95% CI −0.53 to + 18.32) events/hour, respectively. In patients with moderate-severe OSA (ORDI score > 15, n = 16) MM-ORDI underestimated by −8.70 (95% CI −28.46 to + 4.01) events/hour.

Evaluation of the Agreement Between Two Expert Centres for Measuring Obstructive Respiratory Disturbance Index From in-Home Polysomnography

The PSG-ORDI from the two expert sleep centres were: London median 13.60 (IQR: 0.65 to 53.75) and Grenoble 15.9 (IQR: 2.15 to 69.00) events/hour. Overall, the London PSG-ORDI was lower: median −3.40 (95% CI −22.80 to + 14.00) events/hour compared to Grenoble (**Figure 2**). In patients with no OSA (ORDI < 5 events/hour) and those with mild OSA (ORDI 5–15 events/hour) there was a random and low median bias between the two centres of −0.60 (95% CI −2.58 to −0.03). However, in moderate-severe patients with ORDI > 15, the variation became more and unpredictable: mean bias −13.00, varying from −31.36 to + 13.22 events/hour.

There were significant linear correlations and high intraclass correlation coefficients among all the ORDI scores (p-values < 0.001) (see **Appendix**).

Diagnostic Performance of the Mandibular Movement Monitoring System

The ROC analysis at OSA thresholds of 5, 15 and 30 events/hour corresponding to mild, moderate, and severe OSA is shown in **Figure 3**. The AUCs showed high global performance for each threshold; 0.928 (95% CI: 0.84 to 1.0), 0.902 (95% CI: 0.80 to 1.0) and 0.918 (95% CI: 0.79 to 1.0), respectively.

Optimal cut-offs were determined for the MM-ORDI. Mild OSA (PSG-ORDI > 5 events/hour) was detected with an optimal cut-off of 9.53 events/hour with a good balance between sensitivity and specificity (F1 = 0.94, BAC = 0.94). A previously reported cut-off of 7.63 events/hour yielded a high sensitivity, but lower specificity (Pépin et al., 2020). There was good diagnostic agreement for moderate OSA (>15 events/hour) using a cut-off of 12.65 events/hour (F1 = 0.89, BAC = 0.88). This cut-off was the

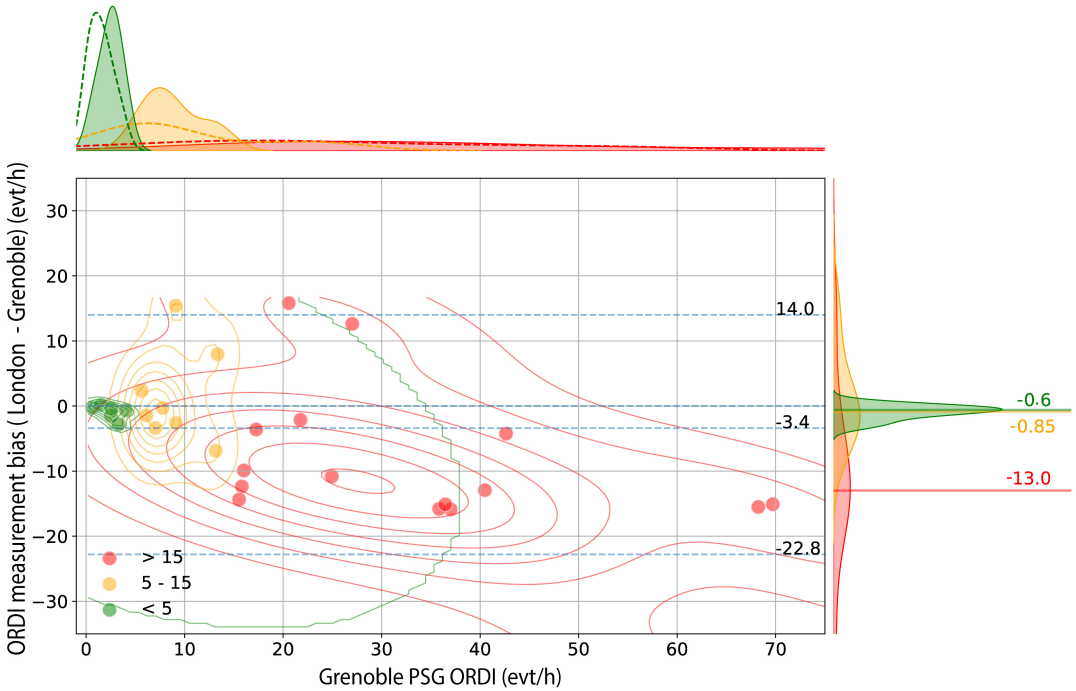

FIGURE 2 | Bland-Altman analysis for London PSG-ORDI versus Grenoble PSG-ORDI. Bland-Altman plot shows the disagreement between average PSG-ORDI (London) and PSG-ORDI (Grenoble) (y axis) as a function of Grenoble PSG-ORDI (x axis), with individual cases stratified into three clinical groups. Bidimensional kernel density estimation plots are superimposed to show the joint distribution of measurement bias within each subgroup. The blue horizontal lines indicate the median, lower and upper bound (5th and 95th centiles) of the measurement bias in the whole sample. The distribution of the disagreement between the 2 methods, stratified by group, is shown on the right, with 3 horizontal lines indicating the median bias within each group. PSG: polysomnography; ORDI: obstructive respiratory disturbance index.

same as observed previously (Pépin et al., 2020). MM-ORDI was also effective for detecting severe OSA (>30 events/hour) at cut-off of 24.81 events (F1 = 0.86, BAC = 0.87). At these cut-offs, the post-test probabilities of obtaining a true positive diagnosis were 100, 80, and 95% respectively (**Table 1**).

DISCUSSION

Our study aimed to answer the question "is the Obstructive Respiratory Disturbance Index (ORDI) calculated using MM with machine learning analysis similar to the ORDI obtained using manually scored in-home PSG?" The main findings of this study are that the use of MM with machine learning analysis to diagnose OSA produced good agreement compared to in-home PSG-derived ORDI. The best agreement was observed at the mild end of the disease spectrum. Additionally, agreement in ORDI, between the MM monitor and in-home PSG, was similar to the agreement for the scoring of PSG between by the two expert centres.

Mandibular movement-derived respiratory disturbance measures and automated analysis demonstrated comparable performances than in-home PSG, suggesting that MM monitoring is an effective and practical way of testing for OSA in the patients' own home. There is an expanding need for simple, automated tools for the diagnosis of OSA that can be used remotely (Randerath et al., 2018). However, it is important for these monitors to be accurate and reliable. Previously, the novel Sunrise device, using MM-derived respiratory disturbance measures and automated analysis, has been shown to have reliable agreement with PSG data recorded in-laboratory (Pépin et al., 2020). The findings of the present study show similar agreement using PSG recorded in the patients' own home. Moreover, the high diagnostic performance, sensitivity and specificity compare favourably with other portable devices for the in-home detection of OSA (Mendonça et al., 2018). The advantages of using home-recorded data include reduced patient stresses, associated with travel and overnight hospital stays, plus a potential reduction in waiting times and clinical costs (Collop et al., 2007). A systematic review is currently underway to determine the cost-effectiveness of limited channel tests compared to laboratory and home PSG in diagnosing OSA (Natsky et al., 2021). Empirical studies support the use of limited channel tests carried out in the patients' own home, suggesting similar efficacy, at lower costs, compared to PSG (Masa et al., 2014; Corral et al., 2017). These advantages of remote data collection, however, are balanced against the risk of technical failure. In the present study there were technical issues with the MM-monitor and smartphone application in 10% of studies, which is comparable to previously reported in-home PSG failure rate of 10–20% (Bruyneel and Ninane, 2014). This may be easily addressed by repeating limited channel studies at home

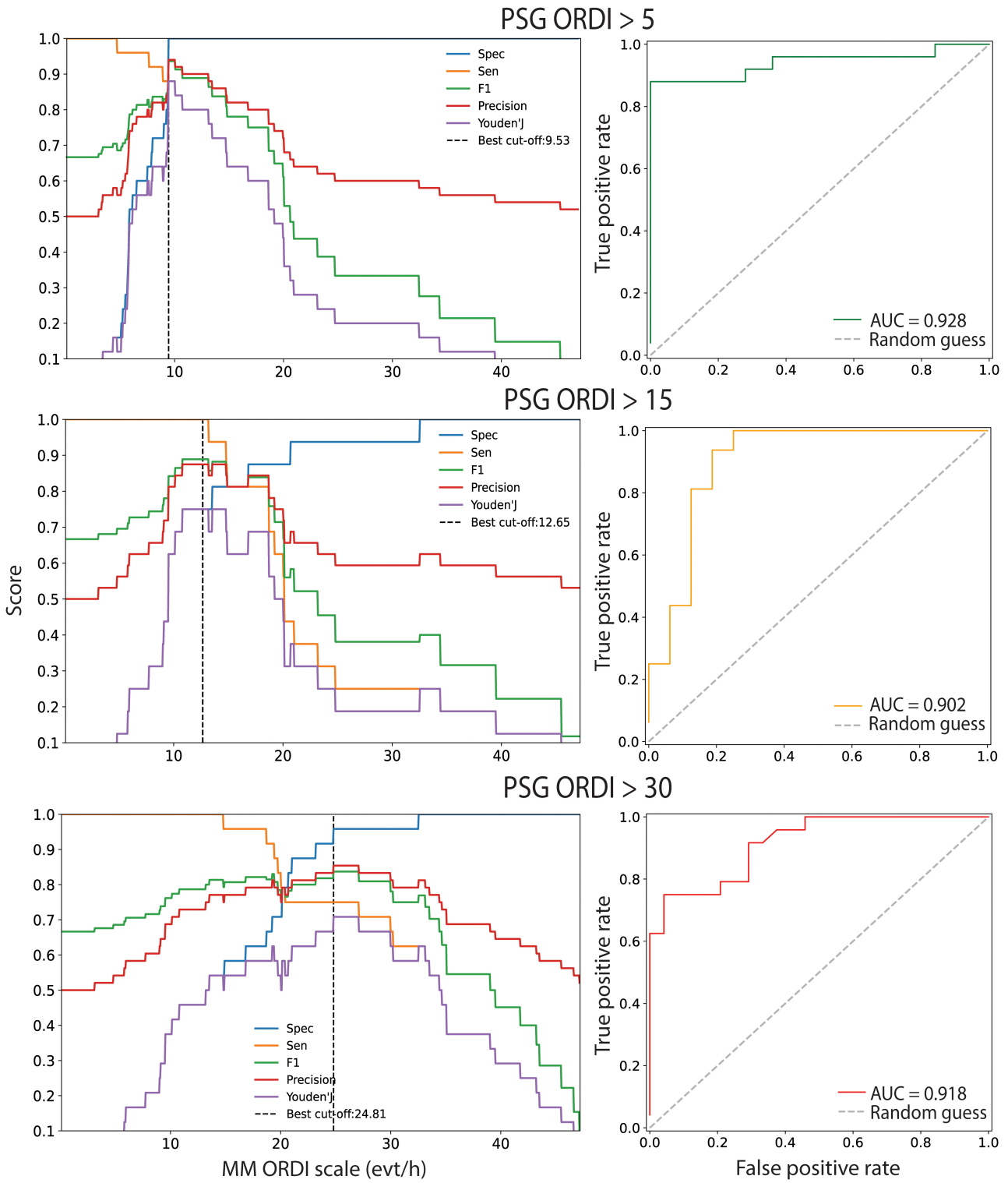

FIGURE 3 | ROC curve analysis for MM-ORDI versus average PSG-ORDI. Cut-off calibration and ROC curves evaluating the global performance of 3 binary classification rules to detect patients with OSA with polysomnography-derived respiratory disturbance index (PSG-ORDI) of at least 5, 15 or 30 events/hour, using MM-ORDI. The 95% CIs of the area under the curve (AUC) were obtained by bootstrapping. The diagonal dotted line serves as a reference and shows the performance if OSA detection was made randomly. ROC: receiver operator characteristic; MM: mandibular movements; ORDI: obstructive respiratory disturbance index; OSA: obstructive sleep apnoea; 95% CIs: 95% confidence intervals; AUC: area under the curve.

over several nights, therefore reducing technical concerns and improving night-to-night variability estimation (Roeder et al., 2020, 2021).

In the current study, comparing PSG scored by experts from Grenoble and London, the ICC was 0.90. The magnitude of this difference was similar to the difference between the ORDI scored by the MM-analysis, compared to the mean ORDI calculated from both the Grenoble and London PSG scoring (ICC 0.85). The manual analysis of PSG data is time consuming. There is also variability between experts, despite the use of standardised scoring criteria. Inter-scorer agreement is generally between 70–80%, however, this figure increases when combined with automated scoring in an auto-edited approach (Magalang et al., 2013; Rosenberg and Van Hout, 2013; Younes et al., 2016). Machine learning for automatic sleep scoring presents many advantages including the removal of the subjectivity and unconscious bias associated with manual scoring. Machine learning algorithms have demonstrated a high level of accuracy and agreement, on average around 85%, between computer and manual scoring (Fiorillo et al., 2019).

Overall agreement between MM-ORDI and PSG-ORDI in the current study was good, with an overestimation of ORDI in mild disease. New technologies that do not use neurophysiological data to identify sleep, typically underestimate respiratory disturbance indices, such as AHI and ODI (Bianchi and Goparaju, 2017). This is due to the number of respiratory events being calculated across the total recording time, rather than total sleep time. Data from the ESADA study, showed that the AHI of patients investigated by polygraphy was approximately 30% lower, compared to patients investigated by PSG (Escourrou et al., 2015). Analysis of MM has previously been shown to reliably detect sleep and wake, which potentially leads to a more accurate calculation of ORDI (Senny et al., 2009, 2012; Maury et al., 2014).

In patients with severe OSA, however, the MM with machine learning analysis underestimated the ORDI. This is similar to results of a previous study, comparing MM analysis to in-lab PSG (Pépin et al., 2020). The scoring discrepancy in more severe OSA patients, may have been due to the use of the 2012 AASM recommended hypopnoea definition (Berry et al., 2012). Specifically, hypopnoeas can be scored when airflow reduction is followed either by a 3% oxygen desaturation, or an arousal from sleep. Therefore, cortical arousals detected by the occurrence of brisk and abrupt MM, typically associated with mouth closure, are reliably scored. However, hypopnoea events scored on PSG due to the presence of a 3% oxygen desaturation, may have been excluded by MM analysis. Ongoing algorithmic developments are likely, specifically to address the scoring of hypopnoeas. In a clinical setting, however, these patients represent the more severe end of the disease spectrum and therefore relatively small differences in ORDI may not impact diagnosis and treatment options, because treatment is usually recommended for patients with moderate-severe OSA (McDaid et al., 2009).

Recently, an international expert group have reinforced the need to move toward outcomes beyond the AHI for the diagnosis and classification of OSA (Randerath et al., 2018). Specifically, they recommend consideration of diagnostic criteria to reflect phenotypic variation. The use of a bio-signal such as MM may provide surrogate sleep data, alongside breathing data to improve the diagnosis of OSA.

TABLE 1 | Diagnostic performance of MM-ORDI versus PSG-ORDI.

	Detecting PSG-ORDI >5 events/hr	Detecting PSG-ORDI >15 events/hr	Detecting PSG-ORDI >30 events/hr
	Optimal cut-off (9.53)	Optimal cut-off (12.65)	Optimal cut-off (24.81)
Sensitivity	0.88	1.00	0.79
Specificity	1.00	0.75	0.96
F1	0.94	0.89	0.86
BAC	0.94	0.88	0.87
Positive predictive value	1.00	0.80	0.95
Negative predictive value	0.89	1.00	0.82
Positive likelihood ratio	Inf	4.00	19.0
Negative likelihood ratio	0.12	0.00	0.22
Youden J index	0.88	0.75	0.75

BAC, balanced accuracy; MM, mandibular movement; ORDI, obstructive respiratory disturbance index; PSG, polysomnography

Strengths and Limitations

This is the first study to compare MM monitoring to PSG recording in the patients' own home. Moreover, the OSA patients were recruited from a clinical referral population, enabling investigation of diagnosis across the disease spectrum. The PSG data was also independently analysed by experts in two centres. However, to fully interpret these data, several limitations need to be considered.

Firstly, the small sample size may have led to a type 2 error. Secondly, the increasing use of technology in healthcare can lead to issues associated with lack of access, either due to reduced internet availability in remote regions, or lack of familiarity e.g. in those who did not use mobile devices when they were younger, or other socioeconomic factors. There were three (7.5%) technical failures due to Bluetooth connection loss in the current study. Refinement of the technology and more access to training may ameliorate some of these issues. However, in-home studies require the ability to understand in-depth instructions, thus information must be given to patients in a clear, concise format (Medicines and Healthcare products Regulatory Agency [MHRA], 2021).

CONCLUSION AND IMPLICATIONS

For future routine clinical practice, MM with machine learning analysis had good agreement with manually scored PSG recorded in the patients' own home and is a promising option for home-based, automated assessment for OSA. Further studies will evaluate the use of the monitor in different care pathways, the patient experience and cost-effectiveness of this new technology. For policy makers, it is time to consider reimbursement and large-scale development of such simplified techniques for sleep apnoea diagnosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Protection des Personnes, Sud-Ouest et Outremer III, Bordeaux, France. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JLP, JBM, and MM contributed to the conception and design of the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RBM and RTe out carried the clinical research and organised the database. NL-D performed the statistical analysis. JK wrote the first draft of the manuscript. RBM and MJF wrote sections of the manuscript. JLP, JBM, MM, MJF, and RTa critically revised the manuscript for important intellectual content. All authors contributed to manuscript revision, read and approved the submitted version.

FUNDING

This work was supported in part by the European Institute of Innovation & Technology, the EIT Health and the French National Research Agency in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) and the "e-health and integrated care and trajectories medicine and MIAI artificial intelligence" Chairs of excellence from the Grenoble Alpes University Foundation. This work was partially supported by MIAI @ Grenoble Alpes, (ANR-19-P3IA-0003).

ACKNOWLEDGMENTS

Imperial College London acknowledge the participation of Ana Gaspar and Marta Vilaca as the expert scorers. Grenoble Alpes University Hospital acknowledge the participation of Corinne Loiodice and Andrew Dawson as the expert scorers.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.726880/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

Machine Learning Analysis

The obstructive respiratory disturbance index (ORDI) was calculated based on a combination of awake/sleep and respiratory effort/arousal/quiet sleep classification tasks. These are handled by stacked classifiers: a binary Random Forest classifier for awake/sleep detection based and a multiclass Random Forest classifier for respiratory effort/arousal/quiet sleep detection based on 30 s epochs.

Input features consisted of a combination of axes of the accelerometer/gyroscope, processing modes (filter with several frequency bands, moving average) and statistical functions. The statistics applied to the above features were tendency toward centrality (mean, median), extreme values (min, max), quartiles, standard deviation, as well the normal standardised version of all above features.

The hyper-parameters of Random Forest classifiers were optimised through a grid-search based 10×10 cross-validation, which aimed to minimise the logarithmic losses. Following hyper-parameters were considered for tuning: tree depth, minimum sample split and tree number.

Choice of the machine learning (ML) approaches:

Machine learning approaches can be classified into 2 main categories: (a) deep learning or (b) conventional methods on structured data, depending on two factors: (1) how to extract input features from the raw signals? and (2) what algorithm should be used?

Based on literature review and previous experiments, there remains uncertainty about the superiority of any specific algorithm among tree-based ensemble algorithms (XGBoost, Random Forest) or deep learning models.

The only advantage of deep learning framework is allowing for automatic feature extraction from raw signal. However, on a well determined problem, with appropriate pre-processing techniques and carefully validated labels, there would be no difference in performance between deep learning and tree-based models.

Instead of using the deep learning models, it was decided to use the features extraction framework, which allows better control and understanding of input data compared to black-box models like convolutional neural networks in deep learning.

Due to the large training data size, complexity of the output and high dimensionality of input features, Random Forest algorithm has been adopted. This algorithm offers several advantages over the classical methods (linear discriminant, support vector machine), including better performance, high efficiency in computation, ability of detecting important features, fast training, and execution speeds. Compared with XGboost, the Random Forest model would have the same level of performance on tabular data, with less complexity in tuning process, as they have less hyper-parameter than XGBoost.

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