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Advanced polysomnographic analysis for OSA: A pathway to personalized management?

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ABSTRACT

Obstructive sleep apnea (OSA) is a highly heterogeneous disorder, with diverse pathways to disease, expression of disease, susceptibility to co-morbidities and response to therapy, and is ideally suited to precision medicine approaches. Clinically, the content of the information-rich polysomnogram (PSG) is not currently fully utilized in determining patient management. Novel PSG parameters such as hypoxic burden, pulse transit time, cardio-pulmonary coupling and the frequency representations of PSG sensor signals could predict a variety of cardiovascular disease, cancer and neurodegeneration co-morbidities. The PSG can also be used to identify key pathophysiological parameters such as loop gain, arousal threshold and muscle compensation which can enhance understanding of the causes of OSA in an individual, and thereby guide choices on therapy. Machine learning methods performing their own parameter extraction coupled with large PSG data sets offer an exciting opportunity for discovering new links between the PSG variables and disease outcomes. By exploiting existing and emerging analytical methods, the PSG may offer a pathway to personalized management for OSA.

Key words: machine learning, polysomnography, precision medicine, signal processing, computer-assisted, sleep apnea, obstructive.

INTRODUCTION

There is growing recognition that obstructive sleep apnea (OSA) is a heterogeneous disorder, with variable pathways to disease, expression of disease and response to therapy. The pathways leading to collapse of the airway during sleep include differing combinations of anatomical and neuromuscular factors. Anatomical factors include small airway and excess soft tissue in and around the airway. Non-anatomical

factors during sleep include the ability of the upper airway dilator muscles to respond to respiratory changes, the tendency to wake from increased respiratory drive during sleep (arousal threshold), the response of the respiratory control system to changes in drive (loop gain), high resistance in the nasal airway, rostral fluid shift and the potential for state-related changes in lung volume to influence these factors.^{1–3} Symptoms are highly variable and range from excessively sleepy to asymptomatic. Other individual differences include the effect of OSA on susceptibility to morbidities and the effect of treatment on health outcomes. The variable pathways, symptoms and health outcomes create opportunities for personalized care.⁴

The polysomnogram (PSG), first reported in 1974,⁵ remains the gold-standard diagnostic test. The PSG contains multiple sensors with simultaneous recording of airflow, blood oxygen levels, respiratory effort, electrocardiogram (ECG), electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). Additional sensors include body position, and sometimes video and audio monitoring.

In scoring polysomnographic data, the standard metric used to characterize OSA remains the apnea-hypopnea index (AHI), the sum of the apnea and hypopnea events per hour of sleep. Although used to define OSA severity, this metric poorly correlates to clinical consequences and oversimplifies the complexity of the disorder.⁶ The current definition of flow limitation and duration of apnea and hypopnea events may not fully characterize the physiological consequences of respiratory events.⁷ Better characterization of physiological consequences of a respiratory event may be achieved with additional features such as magnitude of the oxygen desaturation, arousal threshold, sleep fragmentation and sympathetic activation. These consequences can include immediate effects such as hypoxia and arousal or longer term effects such as increased risk of associated co-morbidities.⁸

Hence, the PSG is extremely rich in information and is amenable to more sophisticated analyses. Many other parameters can be derived to potentially characterize OSA in novel and clinically meaningful ways. Examples of other parameters that are better associated with outcomes of interest (e.g. excessive sleepiness,

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hypertension and cardiovascular disease) include oxygen desaturation index (ODI), percentage time below 90% oxygen saturation, cardiorespiratory coupling, respiratory arousal threshold, arousal index and wake after sleep onset.^{9–11} Despite the advantages the parameters may offer, they are not routinely utilized in clinical practice nor have they been integrated into practice guidelines such as the American Academy of Sleep Medicine (AASM) recommendations.^{12,13}

'Personalized' or 'precision' medicine is an approach to health care that recognizes that within a group of patients with the same diagnosis, there are unique subtypes due to individual differences (heterogeneity). Subtype membership has implications for diagnosis, treatment, consequences and prevention of disease. The approach has been expanded into the 'P4 medicine' framework.¹⁴ The four Ps, prediction (of disease risk), prevention (risk prevention strategies), personalized (addressing individual phenotypes) and participation (patient involvement), represent a systems approach to medicine that are enabled by large-scale detailed biological data, sophisticated analytical tools and linkage of patient outcome data. The PSG with its richness of information could be exploited to advance P4 medicine in OSA¹⁵ (Box 1).

The aim of this article is to review recent advances in PSG analysis, with the goal of promoting a shift towards new signal processing and analytical strategies that enable the adoption of precision medicine approaches.

Box 1: Research agenda

- (1) Identify polysomnogram (PSG) phenotypes that link to meaningful clinical outcomes (e.g. symptoms, co-morbidities and treatment outcome). Use large data sets and advanced analytic techniques including minimal preprocessing machine learning algorithms to potentially identify new linkages
- (2) Determine temporal stability of identified phenotypes
- (3) Integrate PSG phenotypes with other phenotypic traits, including risk factors, clinical expression and genetics to determine susceptibility to co-morbidities and treatment outcome

ENHANCED PSG SIGNAL ANALYSIS METHODS

A more nuanced analysis of the PSG can provide additional clinical meaning by providing information such as arousals, magnitude of hypoxia, sleep state and sympathetic bursts.

Electroencephalography

The sleep architecture of OSA patients is commonly different to controls with increased sleep fragmentation, decreased rapid eye movement (REM) sleep and decreased slow wave sleep, which is associated with excessive daytime sleepiness and serious health

consequences.¹⁶ Although manual sleep stage scoring has been the mainstay of EEG processing using 30-s epochs,¹⁷ researchers have sought ways to develop signal processing methods to automate the processing of EEG. These methods provide greater convenience, flexibility and increased linkage to other outcomes than manual scoring. Researchers have achieved further insight by transforming the time domain signals into a frequency representation and looking for discriminating patterns. Frequency representations include the Fourier and Wavelet domains with Wavelets offering a greater diversity of base waveforms than Fourier analysis. Period amplitude analysis is also used for EEG analysis.

By using epochs lengths less than 30 s, the methods can provide more details of sleep stages and clinical consequences of OSA such as sleepiness, chronic cognitive changes, metabolic changes and cardiovascular consequences.¹⁸ Younes *et al.*¹⁹ have defined a continuous measure of sleep-wake state based on power spectral density (PSD) of 3-s epochs of the EEG. By calculating the probability of the patterns of the PSD occurring in 30-s epochs of wake, an odds ratio product (ORP) is formed and provides a continuous measure of the depth of sleep. A later study looked at how the ORP varied after an arousal or awakening.²⁰ The study showed that pattern of sleep recovery appears to be predominantly an intrinsic characteristic of the individual and is highly variable among patients with sleep-disordered breathing. Furthermore, the dynamics of the recovery largely determine average sleep depth and continuity. Identifying patients with a low arousal threshold may help in matching these patients to a targeted therapy such as sedatives.²⁰ Other novel measures that can be derived from the EEG include the arousal intensity²¹ based on the Wavelet transform which was found to be associated with arousal-related tachycardia, with the response found to be highly individual and to be heritable in twins.²² Arousal intensity was also associated with respiratory control instability.²³ As frequent arousals are also associated with hypertension²⁴ and higher levels of daytime sympathetic activity,^{9,25} the ORP and arousal intensity may be a marker of these cardiovascular risk factors.

Another measure is the cyclic alternating pattern (CAP) which is a marker of unstable sleep.²⁶ Changes in CAP have been associated with fatigue and sleepiness in adults with upper airway resistance syndrome²⁷ and therefore may be a PSG marker of this symptom profile. Another study demonstrated that during periods of non-CAP and non-REM (NREM) sleep, pressure increases of continuous positive airway pressure (CPAP) did not improve flow, suggesting that increases in CPAP should be avoided in non-CAP and therefore may have implications for treatment decisions. The CAP detects more flow-limited breaths than using respiratory-related arousals in OSA patients,²⁸ suggesting that CAP may be a better marker to use.

Machine learning (see section below) has been applied to EEG signal processing and provided novel insights. Chambon *et al.* used a convolutional neural network (CNN) to detect the micro-architecture sleep events including spindles, K-complexes and arousals in EEG signals.²⁹ The network achieved better

performance than other state-of-the-art detectors. The intriguing aspect of this study is that the system used unprocessed EEG signals as training data and the convolutional layers automatically identified useful feature for classification of the micro-events. In another study, a feedforward neural network was used to predict a person's age from the sleep EEG,³⁰ with deviation from chronological age being used as measure of 'brain age'. The metric was associated with neurological or psychiatric disease, plus hypertension and diabetes. Brain age index (defined as the difference between brain age and chronological age) from sleep EEG could be a potential biomarker for healthy brain ageing.³⁰

Electrocardiography

OSA is a well-established risk factor for cardiovascular disease and death.³¹ Hypertension,³² myocardial ischaemia³³ and atrial fibrillation³⁴ are established cardiac consequences of OSA. Perhaps, unsurprisingly, exploring this link via the AHI has been relatively unsuccessful³⁵ as the AHI does not capture cardiac-related parameters. The PSG provides signals that provide insight on the cardiovascular system—the ECG, the photoplethysmogram and oximetry.

Heart rate variability (HRV) is a response by the heart to the interactions of the sympathetic and parasympathetic nervous systems on the sinoatrial node and results in small variations in successive R-wave to R-wave (RR) intervals. An abnormal HRV occurs when the heart is unable to respond due to cardiac pathology and/or changes to sympathetic/parasympathetic tone. The cycling of sympathetic/parasympathetic tone during OSA has a unique influence on sleep-time HRV and results in recurring variation of the heart rate.^{36,37} This influence can be detected using time-domain³⁸ or frequency domain methods^{39,40} and is the basis of algorithms for detecting sleep apnea events and estimating sleep apnea severity using the ECG alone.^{41,42} HRV can also be used to make predictions in populations without known cardiovascular disease with low HRV associated with an increased risk of a first cardiovascular event.⁴³

Non-linear detrended fluctuation analysis (DFA) of heart rate dynamics yields further insight on the effect of OSA on cardiopulmonary system.⁴⁴ Long range correlations were found in REM sleep, whereas slow wave sleep showed strong short-term correlation behaviour. Sleep apnea alters the correlations⁴⁴ and hence DFA can be used to estimate sleep stages as well as estimate sleep apnea severity.

During the respiratory cycle, the body-surface ECG is influenced by the mechanics of respiration and this results in a modulation of the ECG amplitude, at the same frequency as the respiratory cycle. The ECG-derived respiration (EDR) signal from a single-lead ECG can be obtained using methods including R-wave area, principal component analysis and amplitude demodulation.⁴⁵ Cardiopulmonary coupling (CPC) is a frequency-based method that captures the phase differences (or degree of coupling) between the EDR and the RR intervals. It reflects the strong influence of respiration on the cardiovascular system. A strong association between delta power in the EEG (slow wave sleep) and

the high-frequency CPC is seen in healthy subjects.⁴⁶ This suggests that CPC can be used as a surrogate measure of sleep quality. It may be a potential marker of OSA severity and successful treatment, as the phase coupling in patients with severe OSA is significantly less than in controls⁴⁷ and CPAP therapy has been shown to strengthen the coupling.⁴⁸

Oximetry

The pulse oximeter is a low-cost and relatively convenient tool for OSA screening⁴⁹ that is easily implementable in portable devices.⁵⁰ A 3% drop in peripheral oxygen saturation is the minimum desaturation to define a hypopnea but it is common to have larger drops. Persistent nighttime oxygen desaturations have been associated with cancer progression,⁵¹ carotid wall thickening and plaque occurrence,⁵² excessive daytime sleepiness,⁵³ and neurobehavioural and autonomic alterations.⁵⁴ This suggests that the magnitude of oxygen desaturation may contribute to OSA subtypes, severity and consequences. In a recent study, the area under the oxygen desaturation curve associated with a respiratory event compared to baseline has been used to measure 'hypoxic burden'. This measure was applied in cohort studies with PSG and long-term follow-up for health outcomes, showing that hypoxic burden, but not AHI, is associated with cardiovascular disease mortality.⁵⁵

The severity of the apnea event (measured as the product of apnea duration and desaturation area) was associated with increased mortality rates for patients with severe OSA.⁵⁶ Weight loss reduced the number of short duration events but did not change the number of longer events leading to the suggestion that the impact of weight loss on OSA reduction may be less previously thought.⁵⁷

Multi-sensor methods

Combining the information from two or more sensors can further exploit the richness of the PSG data as it permits the analysis of cross-sensor information.⁵⁸

The pulse transit time (PTT) is the time difference between signal peaks in the ECG and the photoplethysmogram (PPG) waveforms. The PPG is the unprocessed signal that is used to calculate the oxygen saturation value and provides time-varying measurements of blood volume in the tissue at the measurement location. The PTT can provide a surrogate measure of blood pressure and help identify patients with systolic pressure surges during sleep.^{59,60}

Combining information from the EEG, EOG, EMG, ECG and oximetry sensors was used to develop automated systems for identifying non-apnea arousals (such as respiratory event-related arousals) from the PSG⁶¹ with the best systems achieving an area under the receiver operator curve (ROC) exceeding 0.9. This potentially broadens the use of PSG to automatically detect sleep disturbance in patients who do not have hypopneas/apneas but still have respiratory-related sleep disturbance.

Table 1 Polysomnographic predictors of co-morbidity outcomes

Co-morbidity	PSG predictor	Outcomes
Cardiovascular disease	Sleep fragmentation, autonomic dysregulation, breathing disturbance and hypoxia REM AHI HRV Oxygen desaturations Pulse transit time Hypoxic burden	CVD events and mortality ³⁵ Arterial stiffness, ⁶⁹ carotid wall thickening, ⁷⁰ hypertension ⁷¹ and CVD events ⁷² First CVD event ⁴³ Carotid wall thickening and plaque occurrence ⁵² Night-time systolic blood pressure surges ⁵⁹ CVD mortality ⁵⁵
Neurodegeneration	EEG power spectral analysis Oxygen desaturations	Cognitive impairment and dementia ⁷³ Neurobehavioural changes ⁵⁴
Cancer	Hypoxia and sleep fragmentation	Cancer events and mortality ⁵¹

AHI, apnea-hypopnea index; CVD, cardiovascular disease; EEG, electroencephalogram; HRV, heart rate variability; PSG, polysomnogram; REM, rapid eye movement.

POLYSOMNOGRAPHY AS A WINDOW INTO OSA PATHOPHYSIOLOGY

One of the key drivers of the precision medicine movement is the need for personalized treatment strategies as there are key limitations to the effectiveness of CPAP as the primary therapy in many patients. Some of the endophenotypes of OSA pathophysiology, including instability of ventilatory control, insufficient dilator muscle response and low arousal threshold are amenable to specific treatment strategies. Hence, targeting individual pathophysiology provides a method to tailor therapy to the individual, which may ultimately be more acceptable and more effective. The measurement of these pathophysiological endophenotypes was traditionally performed by intensive physiological experiments involving complex instrumentation including CPAP drops, intramuscular wire electrodes and epiglottic catheters,¹ all of which are prohibitive in routine clinical practice.

Attention has moved to utilizing the clinical PSG for this purpose with development of sophisticated algorithms. Low arousal threshold was correctly predicted in 84% of patients based on AHI, nadir oxygen saturation and hypopnea proportion.⁶² A more sophisticated analysis processed the flow signal during NREM periods to yield a breath-to-breath ventilation time series. This was then further processed to determine the arousal threshold for the patient.⁶³ Other algorithms have been published for measuring loop gain as a measure of ventilatory control,⁶⁴ pharyngeal collapsibility and muscle compensation^{65,66} with strong correlation to values obtained from experimental physiological studies (correlation coefficient: ~0.7). Pharyngeal site of collapse has been predicted from inspiratory flow shape features.^{67,68}

APPLICATION TO MANAGEMENT OF SLEEP-DISORDERED BREATHING

We have detailed enhanced physiological monitoring and data analytical methods. These emerging approaches have the potential to enhance

management of OSA in that clinically useful information, particularly the risk of co-morbidity and individualized treatment outcomes, could potentially be gleaned from clinical sleep studies. Table 1 shows some examples of polysomnographic predictors of co-morbidity outcomes.

Such information would potentially help the clinician decide who needs treatment, and which treatment approach is most likely to be successful, laying the foundation for precision approaches to OSA treatment. While these approaches are still some way from translation to clinical practice, there are some proof-of-concept studies indicating that PSG may soon be able to deliver detailed information to inform precision management.

There is early evidence that PSG algorithms that express different underlying OSA pathophysiology may be utilized to predict response to therapy. Targeting muscle responsiveness through pharmacotherapy, improving ventilatory control using supplemental oxygen or sedative use for raising arousal threshold, has improved OSA in carefully selected patients.¹ Another study used a combination of pathophysiological information (loop gain, collapsibility, muscle compensation and arousability) derived from clinical PSG to predict responders (>50% AHI reduction, 83% accuracy) to oxygen therapy.⁷⁴ Pharyngeal collapsibility and site of collapse also have implication to response to particular therapies, such as upper airway surgery and oral appliances.^{75,76} PSG-based methods may help predict all these outcomes.

Algorithms predicting arousal threshold are applicable to large data sets and are now starting to be applied to large cohorts with PSG. A study of 940 US veterans with OSA identified the low arousal threshold phenotype in 38% and found associations with poorer CPAP usage.³⁵ Hence, these endophenotypes appear to have a role in identifying future management issues.^{66–68,75,76}

In terms of predicting future health risk, there is emerging evidence that better interrogation of the PSG, beyond the AHI, may have predictive utility. At the most basic level, phenotypes such as OSA during REM sleep has specific associations with cardiovascular disease. There is recent recognition that REM AHI (but not NREM AHI) is associated with the presence of

arterial stiffness,⁶⁹ carotid artery intima thickness,⁷⁰ hypertension⁷¹ and cardiovascular events.⁷²

A recent study used a novel application of unsupervised cluster analysis on clinical polysomnography variables.³⁵ This analysis of PSG information from a cohort of 1247 US veterans found no association between AHI and future cardiovascular (CV) events (average 5-year follow-up). However, they did find that three of the seven clusters (labelled 'periodic limb movements of sleep', 'hypopnea and hypoxia' and 'combined severe') predicted the risk of future CV events. This supports the use of discovery approaches for identifying novel information within the PSG.

Future studies of analysis methods used in this manuscript (e.g. hypoxic burden, HRV, PTT, heart rate response to arousal and sleep stage-dependent AHI) may also prove to be useful in future for predicting cardiovascular disease susceptibility.

In addition, some evidence for quantitative analysis of EEG from sleep studies may be indicative of future neurodegenerative disorders. In one cohort of women with no signs of cognitive deficit at baseline, PSG parameters were compared after 5 years as two groups (i) remained healthy and (ii) had developed mild cognitive impairment or dementia. There were no group differences in traditional OSA or sleep architecture measures from polysomnography.⁷³ However, there were differences in EEG absolute and relative power density with higher power values in the impaired group.

KEY ENABLERS FOR THE DEVELOPMENT OF NOVEL ANALYSIS METHODS

To advance efforts in PSG analysis, there are a variety of key enablers that could lead to significant advancements.

Machine learning

Machine learning is a collection of analysis methods that has been highly successful for developing a broad range of systems including medical, security, language processing and economic applications. Methods for machine learning can be divided into two broad groups: supervised and unsupervised learning.

Unsupervised learning draws inferences from data sets without labelled responses. They identify intrinsic groupings in data and have provided evidence of the existence of different OSA subtypes.^{35,77} Supervised classification machine learning methods require labelled data sets to train the prediction models. A standard approach for supervised machine learning methods is to first use a data preprocessing (or feature extraction) step which processes the available signals (e.g. ECG) and determines features from the signals (e.g. heart rate). While a feature extraction step can capture prior clinical experience, it can also be a limiting factor of the system as performance is limited by the discrimination ability of the features.

Convolutional neural networks (CNN) have increased in popularity in recent years as a machine

learning method that requires minimal preprocessing and are well-suited to time series data such as PSG signals. The defining aspect of these networks is that they 'learn' their own features and therefore are not limited by discrimination ability of the hand-engineered features. In other words, by performing their own feature extraction, they are not influenced by prior human knowledge. The disadvantage of these systems is that they may require larger data sets to train than systems processing hand-engineered features.

PSG data may have unknown time difference between important events in the PSG and desired outcomes. Neural networks with a memory capability⁷⁸ such as long short-term memory (LSTM) and residual neural networks are very well suited to this type of data. LSTM networks have been successfully applied to PSG processing and were the enabling technology solutions to the top performing systems in the 2018 Computing in Cardiology Physionet competition of identifying non-apnea arousals from the PSG.⁶¹ They have also been successfully applied to ECG and airflow signals.^{79–81}

Big data

Minimal preprocessing methods such as CNN often have many parameters (current applications can have up to 10⁷ parameters) to be estimated using training data and hence data sets with thousands of examples may be required to adequately train the methods. While a substantial amount of physiological data is routinely collected during sleep studies, it is vastly underutilized for supporting precision medicine approaches.⁷ There are many reasons including varying semantic infrastructure across centres, patient privacy/security concerns and issues with data handling challenges of storing and distributing the data.⁸² Some progress has been made in providing large data sets for use by researchers. The National Sleep Research Resource (<https://sleepdata.org>),⁸² a National Heart Lung and Blood-funded resource, was established to improve access to sleep data including information from overnight physiological signals with data sets up to 5000 nights. This resource has made several data sets publicly available. Another resource is PhysioNet (<https://www.physionet.org/>) which offers free access to large collections of recorded physiological signals including sleep data from approximately 1000 nights.

Linking to health outcomes

Research linking PSG phenotypes to health outcomes is an imperative to enable precision medicine approaches. This may take the form of prospective data collection, preferably on a large scale. Alternatively, data linkage techniques can be used to access the electronic medical record. The linkage of information from multiple administrative data sets enables the construction of chronological sequences of health events and healthcare utilization, which can be linked to PSG signals.

CONCLUSION AND FUTURE DIRECTIONS

OSA is a highly heterogeneous disorder, with diverse pathways to disease, expression of disease, susceptibility to co-morbidities and response to therapy. Hence, OSA is ideally suited to precision medicine approaches. While current clinical assessment relies on the AHI, the metric poorly correlates to clinical consequences and may oversimplify the complexity of the disorder. The PSG is extremely rich in information and parameters such as hypoxic burden, PTT, CPC and the frequency representations of the EEG and HRV can predict a variety of cardiovascular disease, cancer and neurodegeneration co-morbidities. It can also be used to identify key pathophysiological parameters such as loop gain, arousal threshold and muscle compensation which can guide choices on therapy. These parameters can potentially help the clinician decide who needs treatment, and which treatment approach is most likely to be successful, laying the foundation for precision approaches to OSA treatment.

As health informatics has a greater influence on OSA management in the future, we are likely to see the assembling of large, well-coordinated databases of PSG signals from the vast clinical sleep populations available across the world. These databases combined with extensive linkage to the health outcomes will hasten the development of advanced polysomnographic analysis and we anticipate that machine learning methods will play a big role. This will provide the best opportunity for the development and application of precision medicine approaches and help improve individual outcomes and the efficiency of OSA care.

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Abbreviations: AHI, apnea-hypopnea index; CAP, cyclic alternating pattern; CNN, convolutional neural network; CPAP, continuous positive airway pressure; CPC, cardiopulmonary coupling; CV, cardiovascular; CVD, cardiovascular disease; DFA, detrended fluctuation analysis; EDR, ECG-derived respiration; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; HRV, heart rate variability; LSTM, long short-

term memory; NREM, non-REM; ORP, odds ratio product; OSA, obstructive sleep apnea; PSD, power spectral density; PSG, polysomnogram; PTT, pulse transit time; REM, rapid eye movement; RR, R-wave to R-wave.

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