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Opportunities for Utilizing Polysomnography Signals to Personalize Obstructive Sleep Apnea Subtypes and Severity

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Abstract

Obstructive Sleep Apnea (OSA) is a heterogeneous sleep disorder with many pathophysiological pathways to disease. Currently, the diagnosis and classification of OSA is based on the apnea-hypopnea index, which poorly correlates to underlying pathology and clinical consequences. A large number of in-laboratory sleep studies are performed around the world every year, already collecting an enormous amount of physiological data within an individual. Clinically, we have not yet fully taken advantage of this data, but combined with existing analytical approaches, we have the potential to transform the way OSA is managed within an individual patient. Currently, respiratory signals are used to count apneas and hypopneas, but patterns such as inspiratory flow signals can be used to predict optimal OSA treatment. Electrocardiographic data can reveal arrhythmias, but patterns such as heart rate variability can also be used to detect and classify OSA. Electroencephalography is used to score sleep stages and arousals, but specific patterns such as the odds-ratio product can be used to classify how OSA patients responds differently to arousals. In this review, we examine these and many other existing computer-aided polysomnography signal processing algorithms and how they can reflect an individual's manifestation of OSA. Together with current technological advance, it is only a matter of time before advanced automatic signal processing and analysis is widely applied to precision medicine of OSA in the clinical setting.

Keywords

obstructive sleep apnea; physiological signals; polysomnography; precision medicine

1. Introduction

The momentum for Precision Medicine comes from advances in the collection and storage of big data, including clinical, behavioral, anthropometric, molecular, imaging and physiological data, as well as advances in software that can process this large amount of data using model-free unbiased predictive analytics. The use of averages and summary-based analyses limit the application of scientific knowledge gained from clinical trials because it inherently discounts the effect within the individual. Currently, a paradigm shift is underway: the accumulation of high-resolution biological data and the utilization of computational tools developed decades ago has led to Predict-Prevent-Personalize-Participate medicine or "P4 medicine" (Lim *et al* 2017, Pack 2016). However, large-scale individual-oriented data has yet to be implemented, including that for Sleep Medicine.

Obstructive Sleep Apnea (OSA) is a prevalent sleep disorder characterized by the partial (hypopnea) or complete (apnea) cessation of airflow as a consequence of upper airway obstruction that causes repetitive respiratory pauses during sleep and arousals. Subsequently, this affects sleep architecture and whole body oxygenation, which leads to molecular, immunological, physiological and clinical consequences (Cowie 2017). OSA is a highly heterogeneous disorder in that there are many pathways that to cause OSA. These pathways include varying degrees and combinations of restrictive craniofacial structures, soft tissue fat deposition related to obesity, rostral fluid shift during sleep, airway collapsibility, arousal threshold, negative pressure reflex response and overall loop gain of the ventilatory control system (Pack 2016, Eckert *et al* 2013). Different pathways may result in one OSA patient having a respiratory event associated with a low arousal threshold, sleep fragmentation and excessive daytime sleepiness, while another patient has a long respiratory event with significant desaturations. Although patients with OSA are often combined into a single group when assessing associations to clinical outcomes, a more accurate assessment might be done if OSA patients were subtyped into groups based on distinct clinical (Ye *et al* 2014) or polysomnographic manifestations (Zinchuk *et al* 2018). The lack of more accurately characterizing the heterogeneity of OSA could explain the lack of reproducibility when assessing genetic associations, outcomes and treatment response, as well as finding biomarkers. Hence, a more accurate classification and utilization of OSA subtypes using symptoms, polysomnographic characteristics, biological and other clinical information (Ye *et al* 2014, Zinchuk *et al* 2018) will help clarify underlying pathophysiology of OSA within an individual.

For almost 20 years, the AASM manual has maintained standards for signal collection and updated definitions based on evidence and new technology (American Academy of Sleep Medicine 1999). In scoring polysomnographic data for OSA, we have largely used a single metric, the apnea-hypopnea index (AHI), to diagnose and classify severity. Although other parameters such as the oxygen desaturation index (ODI), percentage time below 90% oxygen saturation, cardiorespiratory coupling, respiratory arousal threshold, arousal index, and wake after sleep onset have often been better associated with outcomes of interest (e.g. excessive sleepiness, hypertension and cardiovascular disease) (Ren *et al* 2016, Martynowicz *et al* 2017, Beaudin *et al* 2017, Trimer *et al* 2014) they are not routinely utilized in clinical practice nor have been integrated into disease classification (American Academy of Sleep

Medicine 1999). Despite the weak correlation between AHI and clinical presentation, clinical consequences, and response to treatment, we continue to diagnose and classify OSA severity based solely on the AHI. While computer-aided signal-processing algorithms of PSG physiological signals have been helpful to inform an individual's phenotype and pathway to OSA (Eckert *et al* 2013), they have not been widely accepted, integrated or commercialized for clinical use. This suggests that there is a disconnect between what is technically feasible today (i.e. modern applications of signal processing algorithms) and clinical utility.

In this review, we will assess the broad range of physiological PSG signals that are routinely being collected and its potential to help us understand the heterogeneity of OSA subtypes in leading to a more personalized approach to sleep medicine (Figure 1). We will also discuss how a more detailed examination of physiological information can lead to a more accurate description of OSA diagnosis, prognosis, clinical consequence, and response to different treatments (Table 1). Finally, we will discuss algorithms and analytical strategies developed for these physiological signals, as well as proven data-driven approaches that could identify OSA subgroups.

2. Overview of Polysomnographic Physiological Signals in OSA

Polysomnography (PSG) is the main tool for diagnosing a broad range of sleep disorders. It is a multi-sensor method characterized by the simultaneous recording of airflow (thermistors, nasal air pressure sensors), blood oxygen levels (pulse oximeter), respiratory effort (respiratory inductance plethysmography), electrical activity of the heart (electrocardiogram [ECG]), brain (electroencephalogram [EEG]), eyes (electrooculogram [EOG]), and skeletal muscle (electromyogram [EMG]). Other sensors usually include body position, and on occasion video and audio monitoring. The PSG performed in a sleep laboratory has been used for decades and is the gold-standard for diagnosing OSA (Lyons *et al* 2017). In addition, by standardizing signal acquisition and processing, laboratories are able to build on top of each other's knowledge to describe normal and disturbed sleep physiology, especially in OSA. The AASM Scoring Manual Version 2.4 recommends technical specifications, terminology and rules for scoring sleep and respiratory events in polysomnography recordings (Berry *et al* 2017). Thus, today, a large repository of standardized physiological signal data has been stored and could potentially undergo modern signal processing techniques to better characterize OSA. In the next three sections, we describe in more detail the technical aspects of respiratory, cardiac and brain PSG signals and the clinical relevance of applying modern signal processing techniques to these signals. In the last section, we describe novel applications and analytical approaches that have been developed with the intent to use PSG signals to better characterize OSA subtypes and severity.

3. Relevance of PSG respiratory signals in OSA

Respiratory events during sleep are a partial or complete absence in airflow or air pressure detected by oronasal thermal sensor and nasal pressure sensor. These events are usually associated with drops in peripheral oxygen saturation levels measured by a pulse oximeter

(Allen 2007). While a 3-4% drop in oxygen saturation is the minimum desaturation to define a hypopnea, it is common for severe OSA patients to have larger drops. The origin of respiratory events (central or obstructive) can be determined by measuring respiratory effort using respiratory inductance plethysmography. A number of physiological features are known to occur in response to respiratory events, such as drops in oxygenation, changes in heart rate variability, and arousals (assessed by abrupt changes in the EEG (Roebuck *et al* 2014)). Although the immediate consequences of these repetitive and intermittent drops in oxygen saturation throughout the night is not yet clear (Ayappa *et al* 2005), they have been associated with carotid wall thickening and plaque occurrence (Baguet *et al* 2005), excessive daytime sleepiness (Jacobsen *et al* 2013), cancer progression (Cao *et al* 2015), and neurobehavioral and autonomic alterations (Idiaquez *et al* 2014). This suggests that in addition to duration of the respiratory event, other physiological parameters such as the magnitude of oxygen desaturation may contribute to OSA subtypes, severity and consequences.

Currently, the diagnosis and severity of OSA is determined primarily by the number of respiratory events detected during the sleep study, as measured by the AHI (Berry *et al* 2017). However, this metric poorly correlates to clinical consequences and may oversimplify the complexity of the disorder (Zinchuk *et al* 2017). Therefore, the current definition of flow limitation and duration of apnea and hypopnea events may not fully characterize the physiological consequences of respiratory events. Incorporation of other important features that reflect the respiratory event such as respiratory event duration, magnitude of the oxygen desaturation, arousal threshold, sleep fragmentation and sympathetic activation may better characterize physiological consequences of a respiratory event. In addition, the comprehensive characterization of the obstructive breathing, combined with its associated outcomes (i.e. arousals and oxygen desaturations) might improve the understanding of the pathophysiological role of the respiratory event (Arnardottir and Gislason 2016). While it would be time-consuming and inaccurate to score all of these features visually, with the assistance of computer auto-scoring, we propose that a combination of many respiratory physiological signals might better inform OSA diagnosis and treatment and provide better projective information.

OSA is in part due to craniofacial skeletal and/or soft tissue abnormalities such that the pharyngeal airway is compromised and collapses (Dempsey *et al* 2002). OSA treatment has mostly relied on Continuous Positive Airway Pressure (CPAP), which keeps the entire upper airway open (Edwards *et al* 2016) or a specific site of collapse (Ng *et al* 2006). Although CPAP has high efficacy, it is limited by patient adherence and therefore other individualized treatment options are desirable (Carberry *et al* 2017). Although there are a number of longstanding and emerging alternative treatment options for OSA, such as mandibular advancement devices (Kuhn *et al* 2017) and hypoglossal nerve stimulation (Mwenge *et al* 2015), they are usually not universally efficacious like CPAP. It is possible that information from the PSG respiratory signals could better define who will benefit from specific alternative therapies.

For example, a study that measured upper airway collapsibility using pharyngeal critical closing pressure (Pcrit) found that measures of peak and mid-inspiratory flow were useful

predictors of active Pcrit (with dilator muscle influence) (Azarbarzin *et al* 2017b). This study also demonstrated a potential use of airflow measurements on PSG to glean additional information about upper airway collapsibility in a noninvasive way. Although the study uses pneumotachography to measure airflow, a follow up study suggested that it can be feasible to adapt the algorithm for nasal pressure signals from the PSG and hence for use in routine clinical studies (Azarbarzin *et al* 2017a).

Another example is using PSG inspiratory flow signals to predict OSA treatment. One study identified seven unique inspiratory shapes that were different between two groups of OSA patients (postmenopausal women and post-uvulopalatopharyngoplasty men) and a control group (Aittokallio *et al* 2001). Separately, another study associated inspiratory flow shapes with site of pharyngeal collapse confirmed by endoscopy (e.g. soft palate vs epiglottis) (Genta *et al* 2017). This could be helpful in identifying who might benefit from hypoglossal nerve stimulation (Strollo *et al* 2014) treatment. Together, these data suggest that inspiratory flow shapes could be used as a tool to predict which OSA treatments (e.g. oral appliances, specific surgeries) is the most effective to target specific regions of upper airway collapse within an individual with OSA.

Currently, in-laboratory studies with complicated instrumentation are required to obtain physiological information to tailor alternative OSA therapies(Azarbarzin *et al* 2017b, Aittokallio *et al* 2001, Genta *et al* 2017). However, obtaining physiological information from readily available PSG signals are emerging (Azarbarzin *et al* 2017a). These can be based to tailor therapy for specific individuals with OSA. For example, sedatives can be helpful in individuals with a low arousal threshold to maintain stable breathing during sleep (Eckert *et al* 2011, Carter *et al* 2016). While traditional methods of determining arousal threshold are mostly used in a research setting, a low arousal threshold has been correctly predicted in 84% of patients based on 3 variables from clinical sleep studies (AHI <30, nadir oxygen saturation >82.5%, and fraction of hypopneas >58.3% (Edwards *et al* 2014). This also led to methodological advancements in the prediction of arousal threshold using only PSG signals, and suggesting its use in a clinical setting (Sands *et al* 2018). Another example is that supplemental oxygen can blunt the ventilatory response in individuals with high loop gain during sleep (Wellman *et al* 2008). Again, traditional methods of determining loop gain is used only in research settings, but algorithms have been developed to derive loop gain from PSG signals (Terrill *et al* 2015). Further studies that relate physiological signals to clinical responses will help clinicians tailor treatment in the individual with OSA.

3.1 Automated processing of respiratory signals.

In designing automatic signal processing algorithms to detect respiratory events most of the time one or more of the PSG sensor signals is employed to identify patterns within a defined epoch. A typical epoch length is 30-60 seconds, which is a tradeoff between longer epochs favoring better detection rates (e.g. more signal is available), and shorter epochs allowing better time resolution of the events. As the epoch is generally longer than the minimum length of an event (10 seconds), epoch based processing of events do not necessarily identify all events individually. However, automated detection of respiratory events can still form an estimated AHI by using regression to establish a relationship between the epochs per hour

and the AHI. Research groups have designed many automatic algorithms for processing PSG signals to identify respiratory events (refer Roebuck et al., 2014 (Roebuck *et al* 2014) for a comprehensive review). Table 1 represents a list with the best validated respiratory signal features that have been used to characterize OSA to date.

Electrocardiography (ECG) derived respiratory signals.—First considered in 1984 (Guilleminault *et al* 1984), the ECG has been used to identify apneic epochs (Penzel *et al* 2002, Moody *et al* 2000). With optimal signal processing, respiration can be extracted out of the ECG signals with a reasonable degree of reliability and this can be valuable information when studying patients with OSA (Langley *et al* 2010). Extracting out respiration from the ECG signal is possible by three mechanisms. First, the physical effect of respiration causes displacement of the ECG electrodes on the chest relative to the heart resulting in a change of the cardiac vector thereby altering the amplitude of the ECG (Pall*ás-Areny *et al* 1989). Second, ventilation changes the volume of air within the lung, which alters the electrical impedance of the thorax and the amplitude of the ECG signal (Hahn *et al* 1995). Third, respiration causes heart rate variability (HRV) such that the R-R interval on an ECG is shortened during inspiration and prolonged during expiration (Eckberg 2003). Algorithms that detect sleep apnea from the ECG use heart rate variability and ECG derived respiration, can thus successfully estimate AHI (de Chazal *et al* 2003). Another algorithm combined the ECG signal with pulse oximetry and further improved the detection of respiratory events (de Chazal *et al* 2009).

Photoplethysmography (PPG) derived respiratory signals.—The PPG signal is derived from the optical pulse oximeter signal using time-varying measurements of blood volume in the tissue at the measurement location. Thus, the PPG waveform reflects the heart pumping blood to the periphery (fingers), which is influenced by breathing. During inspiration, the pressure in the thorax becomes more negative thereby decompressing the heart in the process, resulting in a decreased stroke volume and decreased blood volume to the periphery. During expiration, the pressure in the thorax becomes less negative thereby compressing the heart in the process, resulting in an increased stroke volume and increased blood volume to the periphery. Collectively, PPG baseline and amplitude signal fluctuates in the low frequency region, and this corresponds to the breathing rate (Meredith *et al* 2012, Nitzan *et al* 1994, 1996). Due to the relative low cost of a pulse oximeter, PPG has become an interesting alternative tool for OSA screening (Romem *et al* 2014) that is easily implementable in mobile applications (Garde *et al* 2015, Behar *et al* 2015) or portable devices (Bilgin *et al* 2016). We anticipate that the widespread use of these applications with other PSG-derived physiological signal data might inform diagnosis, prognosis and personalized clinical management of OSA patients, as further elaborated in the following sections.

Microphone and Video.—Audio recordings are inexpensive and non-invasive tools used to identify snoring and other disordered breathing events by using sound analysis methods. A recent study supports the use of audio signals to provide insights about the level of airway obstruction, by discriminating normal breathing, apneas and hypopneas (Halevi *et al* 2016). Video recordings supplements PSG to confirm sleep behavior, but may also be used to gain

information about respiration during sleep. Thirty-minute video recordings can be useful to screen children at home for OSA, with an 84% agreement with PSG and 94% sensitivity to diagnose OSA (Sivan *et al* 1996). A limitation of traditional videography is that blankets, bedclothes and a dark sleep environment may obscure relevant information and severely limit visual analysis. Therefore, thermal/infrared cameras have been used to assess sleep and respiration rate (Sivan *et al* 1996, Bennett *et al* 2015). One thermal method is the use of pixel color around the nostril and using post-processing video magnification to ascertain variations in breathing rates (Bennett *et al* 2015). This promising thermal method was validated against respiratory inductance plethysmography and could be used for apnea detection (Bennett *et al* 2015). Another thermal method used whole body motion to classify normal breathing, apneic events, and deep breathing using thresholds and had a high (94%) accuracy to detect apnea when validated against the PSG (Wang *et al* 2014). Therefore, by combining audio and video analysis with other physiological signals in the PSG, we expect to significantly improve OSA detection. Combined with readily available mobile health devices, tools can be developed for large-scale application and potentially widespread OSA screening in populations with poor access to care.

4. Relevance of PSG cardiac signals in OSA

Although the AASM Scoring Manual Version 2.4 (Berry *et al* 2017) only recommends a single modified electrocardiograph (Lead II) to score cardiac events, it is a rich source of data to assess underlying autonomic activity and cardiovascular physiology in OSA subtypes especially when combined with PPG (Gesche *et al* 2012). Known cardiac consequences of OSA include hypertension (Peppard *et al* 2000, Beaudin *et al* 2017), myocardial ischemia (Morra and Roubille 2017) and atrial fibrillation (Gami *et al* 2007), making the investigation of cardiac signals critical to the work up of OSA. Although OSA is a well-established risk factor for cardiovascular disease and death (Punjabi *et al* 2009, Shah *et al* 2010, Yaggi *et al* 2005), this association is largely based on the AHI as a single metric of OSA severity (Zinchuk *et al* 2018). But the AHI does not reflect cardiac pathophysiological effects, this is another opportunity to more accurately assess associations between OSA and cardiovascular outcomes.

4.1 Automated processing of cardiac signals.

OSA patients have marked changes in cardiovascular and respiratory regulation in response to respiratory events and this is the basis of automatic cardiac signal processing techniques to identify cardiac pathology. While automated processing of cardiac signals has not yet been applied clinically, we anticipate that when combined with other physiological signals, will be able identify patients at higher risk of cardiovascular morbidity and mortality. For example, we can quantify cardiac and autonomic function in subjects with OSA by measuring different aspects of heart rate variability and cardiorespiratory coupling to classify cardiovascular consequences. Table 1 represents a list with the best validated ECG signal features that have been investigated in OSA to date.

Heart rate variability (HRV).—While HRV is a normal physiological event in response to the sympathetic and parasympathetic nervous system, as well as the sleep-wake cycle,

(European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996) an abnormal HRV occurs when the heart is no longer able to respond appropriately due to cardiac pathology. In OSA, HRV has a remarkable and characteristic pattern described as cyclical variation of heart rate (Guilleminault *et al* 1984). During an obstructive apnea event, cyclical variation of the heart rate is bradycardic during a respiratory event and tachycardic during recovery breaths (Guilleminault *et al* 1984). Consequently, methods to automatically identify apnea events from the ECG signal can be developed (Penzel *et al* 2016). A recently developed algorithm used only ECG recordings during sleep and extracted features from HRV and ECG-derived respiratory signals and correlated them to respiratory events (Atri and Mohebbi 2015). Specifically, respiratory events were mapped using image recognition techniques of heart rate and R-wave amplitude based time-frequency maps, and respiratory events were most visible at very low frequencies (VLF) around 0.03 Hz (Atri and Mohebbi 2015).

Pulse Transit Time.—Although blood pressure is a very important cardiac measurement to more directly reflect cardiovascular risk in response to arousals and respiratory events, technological limitations prevent this at present from being obtained continuously and routinely. Recently, surrogate measures of blood pressure were derived from the PPG waveform obtained from pulse oximeters (Gesche *et al* 2012). Pulse transit time (PTT) is an index that reflects variations in sympathetic activity during sleep, peripheral vascular resistance and intrathoracic pressure (Schwartz 2005), and studies have demonstrated that with appropriate calibration, PTT can track relative changes in blood pressure over the course of the night (Gehring *et al* 2018) as well as arousals and respiratory events to characterize sleep structure and fragmentation (Pépin *et al* 2009). In the study by Gehring *et al*, patients with severe OSA presented periods of extremely high systolic blood pressure (superposition) and very low oxygen saturation, suggesting additional evidence for high risk of cardiovascular events during the night (Gehring *et al* 2018).

Nonlinear analysis of inter-beat intervals.—Non-linear detrended fluctuation analysis of heart rate dynamics results in parameters relevant for OSA detection (Bunde *et al* 2000, Penzel *et al* 2003). For example, during slow wave sleep, heart rate shows a strongly short-term correlated behavior whereas during REM sleep it shows a strong long-term correlated behavior, expressed by the parameters alpha-1 and alpha-2. Changes in these parameters can be used to improve detection of sleep apnea severity, as well as estimates of sleep stages (Bunde *et al* 2000) and ECG-derived AHI (Penzel *et al* 2003).

Cardiorespiratory coupling.—Coupling between ECG and respiratory signals reflects an important aspect of cardiorespiratory interaction (Kabir *et al* 2010), where respiration has a strong influence on the cardiovascular system (Dick *et al* 2014). Aspects of cardiorespiratory coupling have been investigated in healthy subjects during sleep (Bartsch *et al* 2007), and studies support a tight relationship between high frequency cardiopulmonary coupling and delta power in the EEG (slow wave sleep) (Thomas *et al* 2014), suggesting that it can be used to measure sleep quality. Patients with severe OSA showed a significant reduction in phase-coupling (Kabir *et al* 2010) (may be an early marker of OSA severity (Sola-Soler *et al* 2015)), and CPAP therapy reverses this abnormal cardiorespiratory

coupling (Chang *et al* 2013). Evidence for short-term consequences of cardiovascular decoupling in patients with OSA, specifically between heart rate and systolic blood pressure, has also been reported in a study that evaluated the effect of CPAP therapy for 3 months on daytime cardiovascular regulation in normotensive and hypertensive patients (Penzel *et al* 2012). These results indicated an effect of CPAP therapy on the baroreflex response in hypertensive patients, while on normotensive patients there were changes in the influence of the systolic blood pressure on the heart rate, from pathological patterns to adaptive mechanisms (Penzel *et al* 2012). However, it is still unclear whether changes in cardiovascular and cardiopulmonary coupling result in long-term effects on cardiovascular outcomes, and studies aimed to address this are warranted. Thus, the relationship between cardiac signals and the pathophysiology of OSA supports the use of analytical tools to better characterize the connection between OSA and cardiovascular consequences.

5. Relevance of PSG EEG signals in OSA

EEG recordings are widely used in sleep medicine because of its ability to detect variations in cortical activity and differentiate wake from different stages of sleep. Guidelines for scoring wake and sleep stages standardize and improve upon previous ad-hoc methods (Rechtschaffen and Kales 1968, Iber *et al* 2007). Because sleep is currently assessed using a visual scoring system, some properties and features of the EEG signal are not used in clinical practice, even though it is routinely collected. Therefore, efforts to further process these stored data will be helpful in better characterizing sleep physiology in patients with OSA.

In OSA patients, respiratory events can terminate with an arousal on EEG, which reflects the respiratory threshold to arouse from sleep (Younes and Hanly 2016). Frequent arousals on EEG have been associated with increased sympathetic activity that extends to daytime, and may explain why some patients with severe OSA have increased daytime sleepiness and hypertension (Slater and Steier 2012, Ren *et al* 2016). Patients with OSA also have more respiratory-induced arousals than controls, and these cause more frequent changes in blood pressure (Bartels *et al* 2016). In addition, it is common for OSA patients to have significant changes in their sleep architecture (e.g. sleep fragmentation, decreased rapid eye movement sleep and slow wave sleep), which is also associated with excessive daytime sleepiness and serious health consequences (Ayas *et al* 2014). Today we have the ability to measure specific EEG features of cortical activity that provide information about clinically relevant OSA subtypes. These novel signal processing techniques provide more details of sleep stages and clinical consequences of OSA such as sleepiness, chronic cognitive changes, metabolic changes and cardiovascular consequences (D'Rozario *et al* 2017).

5.1 Automated processing of EEG signals.

EEG activity during normal sleep remains relatively stable and may be amendable to visual-analog analysis of scoring sleep stages. However, during disrupted sleep, visual-analog analysis may be inadequate to identify and quantify the disruptions without the aid of a computer. To date, there are several digital processing techniques of EEG activity that improve sleep scoring reliability and increases sensitivity to different clinical status (Kubicki

and Herrmann 1996, Penzel *et al* 2007). The use of automated EEG analyses on shorter segments of EEG activity are not constrained by arbitrary definitions of epoch length but at the same time, correlates well to definitions recommended by the task force and can better approximate the effect of OSA on sleep physiology (Malhotra *et al* 2013, Anderer *et al* 2010, Park *et al* 2015, Younes 2017). Automated EEG analyses include the application of spectral analysis, wavelet transformation and combined approaches. Table 1 summarizes the best EEG-derived signals and features relevant to OSA described to date.

Spectral Analysis.—Unlike visual review, EEG spectral analysis relies on computerized identification of discretely defined EEG frequencies. These frequencies correlate with underlying neurophysiological activities known to be associated with sleep, such as slow wave sleep and sleep spindles. Benefits of spectral analysis include the ability to analyze shorter EEG segments, allowing more granular analysis of sleep architecture. The most commonly used applications are the Power Spectral Density (PSD) and the Period-Amplitude Analysis (PAA). While these techniques have been clinically applied in other neurophysiological techniques, they have been largely studied as research tools in PSG, but now should be considered as part of the routine evaluation of sleep disorders in clinical practice, especially for OSA. In the PSD method, the Discrete Fourier Transform (DFT) of a finite epoch is calculated and then power density over that time segment derived. Since sleep stages are defined, in part, by EEG activities of given frequencies, this allows for the quantification of parameters related to sleep stages (Uchida *et al* 1999). The PAA uses a relatively straightforward methodology of measuring waves of varying frequencies based on their periodicity. The ‘half-period’ of a given sinusoidal wave would cross the ‘Zero’ amplitude of an analog EEG recording and could thus be measured in time frequency (Uchida *et al* 1999). Several studies have compared the two techniques in sleep EEG recording (Tan *et al* 2000, Uchida *et al* 1999) and have demonstrated similar results although the PAA requires some additional processing in order to be useful across the typical sleep EEG frequency spectrum. In OSA studies, spectral analysis has been more widely applied to clinical research. Although with limited evidence, severe OSA patients show specific changes in EEG power density when compared to controls (Vakulin *et al* 2016, Xiromeritis *et al* 2011), and these changes have been correlated with worse driving performance in these patients (Xiromeritis *et al* 2011). Thus, this quantitative EEG technique has the potential to provide complementary clinical information to traditional EEG analysis.

Wavelet Transformation.—While PSD can resolve the different frequencies in a given segment reliably, it cannot specify the time location of the frequency within that segment (Ebrahimi *et al* 2008). The Wavelet transformation provides controllable time/frequency trade-off and hence can provide more precise time information particularly for high frequency EEG events. It shows reasonable sleep stage scoring reliability (77.6 to 94.4%) when compared to human scoring (Ebrahimi *et al* 2008, Oropesa *et al* 1999). Additionally, recent studies have demonstrated the use of wavelet transformation to estimate arousal intensity (Azarbarzin *et al* 2014). Figure 2 represents 4 examples of arousals with varying intensities using a scale from 0 (less intense) to 9 (more intense), according to the visual scoring of an expert. The arousal intensity is calculated based on the extraction of wavelet features of arousals that showed the best discrimination between a visually scored arousal, in

a training set of 271. By using the pooled output of different classifiers, any EEG arousal in the PSG could then be classified according to its intensity. This index metric was validated by showing a strong relationship between arousal-related changes and heart rate (Azarbarzin *et al* 2014). Furthermore, these changes in heart rate response to arousal demonstrated a remarkable difference between individuals and have been demonstrated to be heritable in a recent twin study (Gao *et al* 2017). Collectively, these studies support the application of arousal intensity and heart rate response to arousal to further characterize meaningful physiological responses to OSA, as discussed further below.

Cyclic alternating pattern, K-complexes and sleep spindles.—Several other EEG features have been associated with OSA such as cyclic alternating pattern (CAP) (Terzano *et al* 1985), K-complexes (Nguyen *et al* 2016) and sleep spindles (Saunamäki *et al* 2017). Phasic events such as k-complexes, vertex waves, delta-like EEG bursts and short arousals are commonly seen in sleep EEG (Smerieri *et al* 2007). These NREM phasic events have been described to follow a peculiar time organization described as CAP, or sequences of transient electro-cortical events that are distinct from background EEG activity at up to 1-minute intervals (Terzano *et al* 1985). Changes in the CAP rate has been associated with fatigue and sleepiness in adults deemed to have the upper airway resistance syndrome (Guilleminault *et al* 2007). Also, CAP has been reported to improve the accuracy of detecting flow limitation events compared to respiratory-event related arousal in OSA patients (Milioli *et al* 2015), while another study suggested that increases in CPAP pressure should be avoided in non-CAP NREM sleep (Thomas 2002). Larger studies are needed to determine how NREM sleep instability, as represented by CAP, will have clinical utility in the diagnosis and treatment of patients with OSA, and approaches integrating these parameters with other features of EEG are yet to be investigated.

Automated system approaches and novel features.—The use of combined measures to determine sleep physiology is also an area of active research. A combined approach has the benefit of using more advanced processing algorithms as well as utilizing all to better inform about sleep physiology. Since muscle activity, eye movement activity and others signals have a significant relationship to sleep stages, automatic scoring of sleep stages can be performed using chin EMG, EOG and a limited EEG array (Malhotra *et al* 2013). In terms of technical scoring and efficiency, there are several published studies that have demonstrated similar sleep stage and respiratory event scoring outcomes between the combined automated system approach and traditional technologist scoring (Younes *et al* 2016, Malhotra *et al* 2013, Younes *et al* 2015b), suggesting that the field should now move to automated approaches. Recently, this has also been applied to generate and evaluate other novel physiological sleep traits of increasing interest in the field (Amatoury *et al* 2016, Younes and Hanly 2016, Younes *et al* 2015a). Younes et al have defined a continuous measure of sleep-wakefulness state based on the power spectrum patterns of EEG in 3-second epochs and the probability of each pattern occurring in 30-second epochs scored as awake, standardized by the percentage of epochs scored as awake. This metric of sleep-wake state, termed the odds-ratio product (ORP), when calculated in 30-second epochs, was highly correlated to the likelihood of visually scored arousals or awakenings in the following 30-second epoch (Younes *et al* 2015a). Thus, the ORP reflects a continuous measurement of

sleep-wakefulness state. In a follow up study, the ORP in the immediate 9 seconds following arousals/awakening (termed ORP-9) was used to calculate post arousal dynamics of sleep and might better inform how different patients respond to arousal. The ORP-9 metric was associated with sleep depth in patients with OSA as well as the arousal index and AHI (Younes and Hanly 2016). Furthermore, scoring arousal intensity on a scale from 0 to 9, as calculated using wavelet transforms, was associated with respiratory control instability and is being suggested as a distinct pathophysiological trait in OSA (Amatoury *et al* 2016). This suggests that novel quantitative indices of sleep physiology will better represent specific aspects of sleep in OSA and could be leveraged as part of the heterogeneity of this disorder and potentially other sleep disorders (refer to Younes (Younes 2017) for further discussion on these novel indices) Therefore, having valid automated systems with standardized measures will be helpful to discern biologically meaningful subtypes of OSA that are biologically homogenous sharing a similar pathway to disease and treatment.

6. Novel analytical approaches of physiological signals to identify OSA subtypes and severity classification

A substantial amount of data is already being collected during sleep studies and novel analytical tools have already been developed to utilize these data to further describe specific aspects of OSA (Table 1). To date, these novel analytical approaches have largely been reported as secondary outcome variables in observational studies to lend support to specific physiological characteristics of the disease. We argue that these well-studied novel approaches that use widely accepted computational methods should be systematically utilized as primary outcome variables to reveal OSA subtypes, provide a more clinically relevant measure of OSA severity, and help clinicians move towards a more personalized approach to OSA management. Currently, there is an opportunity to explore these already available clinical and physiological data, and evaluate how the development of computational algorithms improves the advance of personalized approaches to manage OSA. Several datasets were made publicly available, mainly through the National Sleep Research Resource (https://sleepdata.org) (Dean *et al* 2016, Zhang *et al* 2018), a National Heart Lung and Blood-funded resource established to improve access to sleep data, including information from overnight physiological signals. Therefore, the combined expertise of clinicians, physiologists, engineers and computer scientists can offer the field all the components to advance Precision Sleep Medicine. This final section describes initial studies that used novel approaches to identify OSA subtypes, and include a brief description of the computational methods that were utilized in these investigations.

While initial efforts to describe clinically meaningful OSA subtypes were done using symptoms assessment, anthropometric and demographic data (Ye *et al* 2014, Keenan *et al* 2018, Kim *et al* 2018), the use of physiological signals from the PSG is still in its infancy. Two general types of analytical methods could facilitate the integration of these different sources of data in OSA: unsupervised and supervised. Unsupervised models can identify patterns in data that could potentially discover clinical insights not previously recognized. Methods like latent class analysis, K-means clustering and principal component analysis have been extensively used in the medical fields, and have provided support for the existence

of different OSA subtypes (Zinchuk *et al* 2018, Ye *et al* 2014, Keenan *et al* 2018, Kim *et al* 2018). A recent retrospective study using conventional summary indices from the PSG and other demographic data found that OSA patients were grouped into seven different clusters by using unsupervised methods (Zinchuk *et al* 2018). These clusters, named 'mild', 'periodic limb movements of sleep', 'NREM and arousal', 'REM and hypoxia', 'hypopnea and hypoxia', 'arousal and poor sleep' and 'combined severe' were distinguished by a number of polysomnographic features and were associated with a combined outcome of cardiovascular risk, while conventional AHI measured severity were not. Interestingly, the 'periodic limb movements of sleep', 'hypopnea and hypoxia' and 'combined severe' clusters showed benefit of CPAP therapy on subsequent cardiovascular events compared to non-users while other groups did not exhibit such benefits (Zinchuk *et al* 2018) This study supports the notion that combining several different physiological aspects are more likely to identify OSA subtypes that exhibit cardiovascular benefits from CPAP therapy.

Supervised classification machine learning methods require labeled data to train predictive models that are further tested on an independent set of data. These approaches include logistic regression, support vector machine, classification and regression trees, and random forests. Usually, a number of metrics for classification performance are calculated and evaluated, so the researcher can assess the accuracy of the predictive model. Recently, these methods are becoming more popular to help predict OSA diagnosis and severity using different types of clinical and anthropometric features (Liu *et al* 2017, Bozkurt *et al* 2017, Lee *et al* 2009). An important issue when applying supervised machine learning methods is the balance between accuracy (i.e. how well the model performs) and model generalizability (i.e. how the model is applicable in a dataset that was not used to build the model). One factor that substantially affects these parameters is the feature selection strategy, or the way variables are selected as input in the prediction models. One study assessed different feature selection and classification methods to spectral and nonlinear traits extracted from oxygen saturation and PSG recordings, applied to OSA diagnosis (Alvarez *et al* 2013). The authors found that the combination of forward stepwise feature selection with logistic regression had the best performance using four features (83.2% validation accuracy), and the combination of a genetic algorithm with support vector machine had the best generalizability using 7 features (84.2% validation accuracy). Other methods evaluation studies have been conducted (Al-Angari and Sahakian 2012, Nemati *et al* 2014) and suggest that further optimization of feature selection algorithms might improve classification of OSA diagnosis and severity.

While these methods have been applied to inform OSA risk and severity, the studies are very heterogeneous in terms of sample size, input variables, model selection and definition of outcome and severity. To our knowledge, there are no studies attempting to combine more than one set of input variables (e.g. physiological and craniofacial) efficiently. Also, other factors such as ethnicity and genetic background are still not incorporated into OSA risk and severity. Based on the existing literature, we need more studies to explore OSA classification based on all aspects of the disease to increase our ability to better characterize the heterogeneity of this disorder.

7. Conclusion and future directions

This review highlights the extensive amount of available physiological PSG data that has yet to be incorporated into clinical practice. Use of the AHI limits our ability to advance precision medicine of OSA, as it does not reflect the heterogeneity of OSA. Advanced signal-processing methods and data analysis has been used to help subtype OSA, but only in the research setting. In the near future, respiratory, cardiac and EEG signals will undergo automated analyses, further standardizing PSG scoring, and provide, in addition, a rich set of reliable features that can more accurately describe OSA pathophysiology within an individual patient. Large, international consortia provide an ideal platform to collect standardized clinical, behavioral, anthropometric, molecular, imaging and physiological data on an ethnically diverse group of OSA patients. This, combined with advanced signal-processing methods and modern data analysis algorithms, have the promise to transform the way we manage OSA patients.

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Abbreviations List

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
CAP	cyclic alternating patterns
CPAP	continuous positive airway pressure
DFA	detrended fluctuation analysis
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyogram
EOG	electrooculogram
FFT	fast Fourier transformation
HF	high frequency
HRV	heart rate variability
LF	low frequency
NED	negative effort dependence

NN50	Number of pairs of adjacent NN intervals differing by more than 50 ms
NREM	non-rapid eye-movement
ODI	oxygen desaturation index
ORP	odds-ratio product
OSA	obstructive sleep apnea
PAA:	period-amplitude analysis
Pcrit	pharyngeal critical closing pressure
pNN50	NN50 count divided by the total number of all NN intervals
PPG	photoplethysmography
PSG	polysomnography
PTT	pulse transit time
REM	rapid eye-movement
RMSSD	square root of the mean squared differences of successive NN intervals
SDNN	standard deviation of NN intervals
SDSD	standard deviation of differences between adjacent NN intervals
SpO2	peripheral oxygen saturation
TST	total sleep time
ULF	ultra low frequency
VLF	very low frequency

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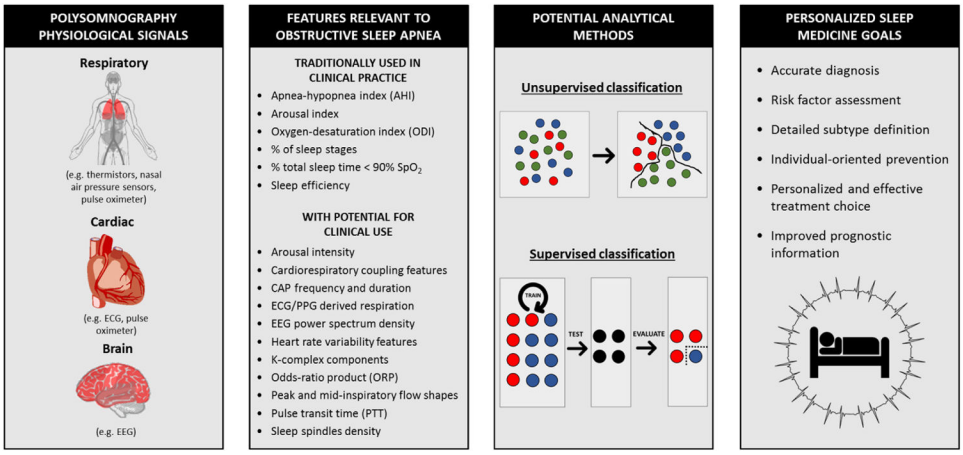

Figure 1:

Summary of polysomnography physiological signal features relevant to obstructive sleep apnea, potential analytical approaches and the goals of understanding these data towards personalized medicine for this disorder. Abbreviations: CAP: cyclic alternating pattern; ECG: electrocardiogram; EEG: electroencephalogram; SpO2: oxygen saturation; PPG: photoplethysmography. Some illustrations used with permission and adapted from (Petryszak *et al* 2016)

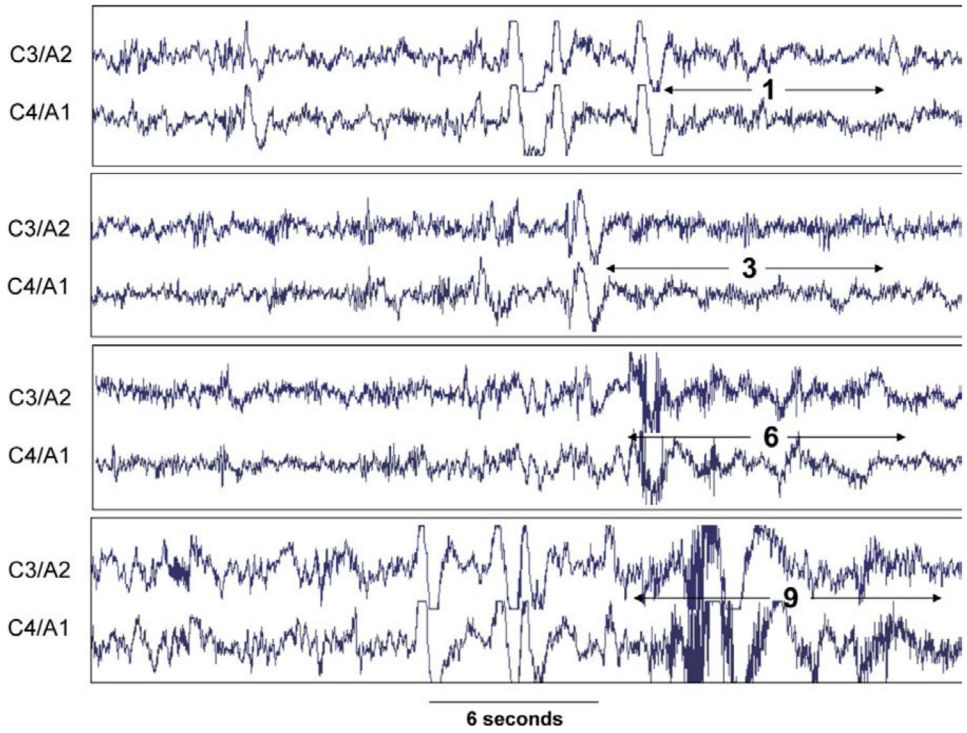

Figure 2.

Examples of arousal with different intensity scales (0-least intense to 9-most intense) in the same patient. C3/A2 and C4/A1 are central electroencephalograms. Figure used with permission (Azarbarzin *et al* 2014)

Table 1:

Detailed summary of polysomnographic physiological features that can be applied to better characterize obstructive sleep apnea subtypes.

	Feature	Main PSG sensor	Description	Effect on OSA	References
Traditionally used in clinical practice	AHI	Thermistors, nasal air pressure, and pulse oximeter	Average number of apnea and hypopnea events per hour of TST.	Current index used to classify OSA severity; increased in more severe patients.	(American Academy of Sleep Medicine 1999, Ho *et al* 2015)
	Arousal index	EEG	Number of identified arousals per hour of sleep, as defined by AASM. Can be a measure of sleep fragmentation.	Increased in more severe OSA.	(American Sleep Disorders Association 1992)
	ODI	Pulse oximeter	Average number of desaturation episodes per hour of total sleep time. Desaturation usually defined as 3 or 4% decreases from baseline.	Alternative metric associated with OSA severity; it is increased in more severe patients.	(Svanborg *et al* 1990, Dawson *et al* 2015)
	Percentage of sleep stages	EEG	Proportion of total sleep time spent on sleep stage N1, N2, N3 and REM.	More severe OSA patients spend more time in REM than slow wave sleep and in light sleep than awake.	(Iber *et al* 2007, Ratnavadivel *et al* 2009, Bianchi *et al* 2010)
	Percentage of TST with SpO_2 <90%	Pulse oximeter	Measure of time with low levels of peripheral oxygen saturation (<90%). Can be a measure of degree of hypoxia and desaturation.	Direct relationship with the duration and severity of hypoxia in patients with OSA.	(Bostanci *et al* 2015)
	Sleep efficiency	EEG	Ratio of total sleep time to time in bed. Indicates how much of the recording time spent on bed was scored as sleep.	Usually decreased in more severe OSA, but with controversial results.	(Ng and Guan 2012, Iber *et al* 2007, Ratnavadivel *et al* 2009, Bianchi *et al* 2010)
With potential for clinical use	Arousal intensity	EEG	Intensity of EEG arousal detected and quantified using discrete wavelet transform.	Associated with increased heart rate response to arousal and respiratory control instability in OSA.	(Azarbarzin *et al* 2014, Amatoury *et al* 2016)
	Cardiorespiratory coupling features	ECG, respiratory inductance plethysmography	Influence of respiration on heart rate. Include % of synchronized time per unit of sleep time and average duration of synchronization.	Percentage of synchronization decreases and average duration increases in severe OSA.	(Sola-Soler *et al* 2015)
	CAP phases frequency and duration	EEG	Number/duration of CAP A-phases subtypes (A1, A2, A3) per unit of sleep time. CAP represents a marker of NREM sleep instability.	Associated with inspiratory flow limitation, poor response to CPAP therapy, fatigue and sleepiness.	(Guilleminault *et al* 2007, Bosi *et al* 2018, Gupta and Shukla 2018)
	ECG/PPG-derived respiration features	ECG and pulse oximeter	Mean respiratory rate, respiratory frequency and respiratory power spectrum density. Used for apnea detection and ECG-derived AHI calculation.	Mostly used to help automatic classification of respiratory events in patients with OSA.	(Pallás-Areny *et al* 1989, Penzel *et al* 2002, de Chazal *et al* 2009)

Feature	Main PSG sensor	Description	Effect on OSA	References
HRV features	ECG	Linear, nonlinear, spectral and wavelet characteristics of ECG. These include mean RR interval, SDNN, RMSSD, SDSD, NN50, pNN50, DFA alpha1, DFA alpha2, entropy, ULF, VLF, LF, HF, Allan factor.	Patients with OSA have changes in specific features of HRV that indicate autonomic dysfunction.	(European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996, Aeschbacher *et al* 2016)
K-complex components and distribution	EEG	Signal characteristics and frequency of K-complexes per unit of sleep time.	Mild airflow limitation, such as in OSA, increases K-complex frequency and amplitude.	(Nguyen *et al* 2016)
ORP	EEG	Continuous measure of sleep-wakefulness state based on power spectrum patterns of EEG.	ORP in the immediate 9 seconds following arousals (ORP-9) was associated with sleep instability in OSA.	(Younes *et al* 2015a, Younes and Hanly 2016)
Peak and mid-inspiratory flow shape features	Nasal air pressure	Indicate aspects of pharyngeal narrowing and site of collapse. Features include negative effort dependence (NED, percent reduction in inspiratory flow between peak and plateau).	Lower NED indicates tongue-related obstruction and severe indicate epiglottis collapse. Can guide therapy choice.	(Genta *et al* 2017, Azarbarzin *et al* 2017a, 2017b)
PTT	Pulse oximeter	PPG-derived index that reflects peripheral vascular resistance and intrathoracic pressure. Can estimate blood pressure, respiratory effort and arousal index.	Severe OSA patients have more periods of ≥ 10 mmHg increases in baseline systolic blood pressure.	(Gehring *et al* 2018, Pépin *et al* 2009, Schwartz 2005)
Sleep EEG power spectrum density	EEG	Power density and ratios of discretely defined EEG frequencies (e.g. delta, theta, alpha, beta), calculated from short sleep EEG epochs.	Increased delta and theta power in more severe OSA. Increased beta power in NREM and delta power in REM sleep, and correlation with worse driving performance.	(Xiromeritis *et al* 2011, Vakulin *et al* 2016)
Sleep spindles density/frequency	EEG	Number of sleep spindles (high-frequency and short EEG oscillations emerging mostly during NREM sleep) per unit of sleep time	Reduced with more severe OSA and increased after CPAP treatment	(Himanen *et al* 2003, Carvalho *et al* 2014, Yetkin and Aydogan 2017)

AASM: American Academy of Sleep Medicine; AHI: apnea-hypopnea index; CAP: cyclic alternating patterns; CPAP: continuous positive airway pressure; ECG: electrocardiogram; EEG: electroencephalogram; HF: high frequency; HRV: heart rate variability; LF: low frequency; NED: negative effort dependence; NN50: Number of pairs of adjacent NN intervals differing by more than 50 ms; NREM: non-rapid eye-movement; ODI: oxygen desaturation index; ORP: odds-ratio product; OSA: obstructive sleep apnea; pNN50: NN50 count divided by the total number of all NN intervals; PPG: photoplethysmography; PSG: polysomnography; PTT: pulse transit time; REM: rapid eye-movement; RMSSD: square root of the mean squared differences of successive NN intervals; SDNN: standard deviation of NN intervals; SDSD: standard deviation of differences between adjacent NN intervals; SpO_2: peripheral oxygen saturation; TST: total sleep time; ULF: ultra low frequency; VLF: very low frequency