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Short Communication

ROLE OF OBJECTIVELY MEASURING SLEEP IN DRUG RESEARCH

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ABSTRACT

Sleep quality and duration play an important role for overall health and wellbeing, as it is associated with development of various diseases like cardiovascular disease, diabetes and obesity, making it important in research to have objective information of sleep physiology that either may affect or be affected by sleep. In the past, self-reported habitual sleep quality and duration has been the standard practice in research as a screening method. Although asking about sleep quality and duration seems uncomplicated, subjective questionnaires have been found to have a low correlation with objective measures of sleep.

Until recently it has not been easy or accessible to collect objective data on sleep health. With improvements in sensor technology, now it is possible to apply ambulatory methods available to collect medically relevant physiological bio-signals like ECG that can be automatically analyzed to measure sleep duration sleep quality and sleep pathology providing a unique insight into sleep health.

Keywords: Clinical research; Sleep duration; Sleep quality; Sleep pathology; Cardio pulmonary coupling

INTRODUCTION

The role of sleep and the importance of sleep quality and sufficient sleep duration is increasingly being recognized as critical to overall health and wellbeing. The Nobel Prize in Physiology and Medicine for 2017 places the focus on what the circadian rhythm fundamentally means for our internal body clocks that helps explain the implications ranging

well beyond sleep disorders (https://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html). Sleep loss and sleep disorders have been found to have wide-ranging multi-organ effects on overall health, negatively affecting the cardiovascular system; causing high blood pressure, atrial fibrillation, congestive heart failure, coronary artery disease and stroke; the endocrine system causing impaired glucose tolerance, diabetes and obesity; and affecting mental health causing anxiety and depression (Kurina, LM *et al.*, 2013).

It seems simple enough to ask subjects participating in research about their sleep duration and sleep quality, expecting adult subjects to provide an approximation of how long and how well they slept, yet large differences and inconsistent results have been found between subjective self-assessment and objective measurements (Lauderdale, D, *et al.*, 2008).

Various reasons cause this inaccuracy in peoples' estimates of their sleep duration and sleep quality, causing the realized low correlation between subjective answers and objective sleep measures (Baglioni, C, *et al.*, 2014). Individuals without sleep complaints tend to overestimate their sleep duration while Individuals with insomnia have a tendency to underestimate their sleep duration (Fernandez-Mendoza, J, *et al.*, 2011). Insomnia patients are also often uncertain about their awakenings and co-morbid and undetected sleep apnea has high prevalence in patients previously diagnosed with chronic insomnia (Cronlein, T, *et al*. 2012).

For these reasons subjective patient questionnaires introduce uncertainty that can cause misclassification of groups within study cohorts.

The use of accessible and low-cost ambulatory methods to collect objective and medically relevant physiological signals offers possibilities to collect sleep data over multiple nights to provide comprehensive phenotypic profile on sleep quantity, sleep quality and sleep pathology (Heckman, EJ, *et al.*, 2017 and Thomas, RJ, *et al.*, 2018). Recording sleep for several nights provides information on night-to-night variability within and across individuals, providing a unique insight into research both in health and disease, information that has not been accessible to collect before and at the same time objective information offers both benefits and feedback on effectiveness of the therapy being tested. This ability to measure sleep health objectively, to see its impact on research outcomes should put an end to the era of subjective questionnaires for these purposes.

METHODS TO SCREEN AND DIAGNOSE SLEEP DISORDERS

Sleep Questionnaires

Clinical methods used to screen for sleep disorders have mostly been limited to subjective questionnaires for reasons of convenience and cost. Questionnaires were originally created in a response to a lack of technology available to screen for sleep disruptions and sleep disorders. Sleep questionnaires are based on respondents' own subjective perception of their sleep and even though questionnaires have historically been perceived as accurate enough, when compared to objective physiological data, their results have shown a level of inconsistency to make them unreliable (Westlake, K, *et al.*, 2009 and Pereira, E, *et al.*, 2013). If a questionnaire has a high sensitivity they lack and vice versa, causing them to be inaccurate tools to rely on in isolation. Therefor it is likely that most sleep questionnaires will inaccurately classify a significant proportion of subjects when asked about their sleep duration and quality (Westlake, K, *et al.*, 2009; Pereira, E, *et al.*, 2013 and Bianchi, M, *et al.*, 2011).

Polysomnograpy (PSG)

Polysomongrapy (PSG) is the reference medical test for the diagnosis of obstructive sleep apnea (OSA), the most common sleep disorder breathing (SDB) disorder in adults. PSG tests are however not recommended for adults with insomnia complaints as they are generally diagnosed based on responses to subjective sleep questionnaires (Schutte-Rodin, S, *et al.*, 2008). However, even among individuals who deny symptoms of sleep apnea, more recently published data suggests that OSA and other sleep related breathing disorders, may be an under-recognized cause of insomnia. This co-occurrence of OSA and insomnia requires more comprehensive therapy than each disease in isolation (Bianchi, MT, *et al.*, 2013 and 2016). The recommendation is that individuals with positive results of OSA on sleep questionnaires, needs to be followed up with a diagnostic test for OSA. PSG tests are complicated and challenging to obtain, as the procedure is costly, equipment and labor intensive therefore not available to all at-risk. Due to this complex and labor intensive process PSG studies are not suited for multi-night testing or to track benefit or feedback of efficacy of intervention (Epstein, L, *et al.*, 2009).

Home Sleep Apnea Test (HSAT)

Alternative medical test for diagnosis of OSA in adults with no comorbidities, Home Sleep Apnea Test (HSAT) is an alternative. As HSAT in contrast to PSG do not include electroencephalography (EEG), electrooculography (EOG) or electromyography (EMG) sensors, which are sensored required to identify sleep versus wake, when sleep is measured from the surface of the brain. HSAT are not as challenging to obtain and less expensive than PSG test, but as they only estimate OSA based on the Respiratory Event Index (REI), the sum of apneas and hypopneas divided by total recording time that may include wake as well as sleep periods. HSAT tests may therefor often underestimate OSA severity as they do not record sleep onset, sleep duration, sleep efficiency or wakefulness they have no capabilities of measuring sleep duration accurately and do not measure sleep quality (Shayeb, M, *et al.*, 2014).

CardioPulmonary Coupling (CPC)

One of the ambulatory methods that are now available to easily measure sleep health is based on collecting and analyzing single lead ECG data (Thomas, RJ, 2016 and Magnusdottir, S, *et al.*, 2017). The SleepImage® system (MyCardio LLC, Broomfield, CO) is FDA approved to measure sleep quality and evaluates sleep disorders to inform or drive clinical management. The SleepImage® System uses clinically validated algorithms analyzing single-lead ECG data to provide an objective measure of sleep duration, sleep quality and sleep pathology. The Cardiopulmonary Coupling (CPC) analysis performs as described in detail (Thomas, RJ, 2016; Magnusdottir, S, *et al.*, 2017 and Thomas, RJ, *et al.*, 2014). The SleepImage® wearable sleep data recorder collects a continuous ECG signal. One electrode pad is attached to the device that is then connected to a second electrode using a flexible ECG cable across the chest. Activity and body position is measured by internal accelerometers and gyroscopes and snoring is detected by tissue vibration (Figure 1).

Collected data is uploaded to the SleepImage® secure, cloud-based system for automatic analysis where the Cardiopulmonary Coupling algorithms generate sleep metrics and other physiological data including spectrographic analysis of the sleep period.

Figure 1: SleepImage® Sleep Data Recorder.

The automated CPC data output is presented as the sleep quality index (SQI), providing a summary measure describing sleep duration, sleep stability, sleep fragmentation, and sleep pathology to generate a number between 0 and 100. The Sleep Apnea Indicator (SAI) is an automated measure of Cyclic Variation of Heart Rate (CVHR) during unstable breathing (tidal volume fluctuations in breathing) detecting oscillations in cardiac intervals often associated with prolonged cycles of sleep apnea. Additional physiologic perturbations in the cardiovascular system as a consequence of arousals and/or drops in oxygen saturation are additional indicators for SDB (Thomas, RJ, *et al.*, 2007).

A detailed methodology on the basic algorithms has been published. The technique uses continuous ECG-data collected during sleep that extracts and couples heart rate variability (HRV) and ECG-derived respiration (EDR) to generate frequency maps of coupled autonomic-respiratory oscillations, the ECG-derived sleep-spectrogram (Thomas, RJ, *et al.*, 2016 and 2014). The sleep-spectrogram reveals that non rapid eye movement sleep (NREM) has a bimodal-type structure marked by distinct alternating and abruptly varying periods of high and low frequency CardioPulmonary Coupling (CPC). Stable sleep (high frequency coupling, HFC) occurs during part of stage N2 and all of stage N3 NREM sleep and is associated with periods of stable breathing, non-cyclic alternating pattern (non-CAP) electroencephalogram (EEG) morphology, increased absolute and relative delta power, strong sinus arrhythmia, and blood pressure dipping. Conversely, unstable sleep (low frequency coupling, LFC) is characterized by temporal variability of tidal volumes, cyclic alternating pattern (CAP) EEG morphology, non-dipping of blood pressure and lower frequency cyclic variation in heart rate. Fragmented rapid eye movement sleep (REM) has an LFC signature,

while normal REM sleep and wake show very low frequency coupling signature (vLFC). A subset of low-frequency coupling, termed elevated low-frequency coupling broad-band ($eLFC_{BB}$) defines periods of apneas-hypopneas and elevated low-frequency coupling narrow band ($eLFC_{NB}$) distinguishes between apneas caused by upper airway anatomical obstruction and respiratory dyscontrol (Thomas, RJ, *et al.*, 2007).

Using the Sleep Apnea Indicator (SAI) together with the Sleep Quality Index (SQI), $eLFC_{BB}$ and $eLFC_{NB}$ it is possible to identify the presence and severity of Sleep Disordered Breathing (SDB). It also categorizes SDB as obstructive, central or complex sleep apnea (Magnusdottir, S, *et al.*, 2017 and Thomas, RJ, *et al.*, 2007).

The CPC technique accurately identifies insomnia (Magnusdottir, S, *et al.*, 2017 and Schramm, PJ, *et al.*, 2013) and sleep apnea in adults (Magnusdottir, S, *et al.*, 2017 and Thomas, RJ, *et al.*, 2007) and captures treatment effects in sleep apnea in both adults (Lee, WH, *et al.*, 2017; Choi, JH, *et al.*, 2015 and Lee, WH, *et al.*, 2016) and children (Lee, SH, *et al.*, 2012 and Guo, D, *et al.*, 2011). In this way, the NREM sleep phenotype extends beyond conventional scoring of AHI and its reliance on absolute delta power and SQI may be expected to increase as CVHR and SAI are expected to decrease, as the disease is successfully treated and healthy sleep patterns dominate (Magnusdottir, S, *et al.*, 2017 and Thomas, RJ, *et al.*, 2007).

This simple ambulatory method to identify sleep duration, sleep quality and sleep pathologies will help both researchers and clinicians. It can also provide objective evidence and feedback effectiveness of intervention and can therefore assist in improving both research outcomes and therapy management. Introducing the possibility to track the dynamics of sleep over prolonged periods of time is likely to provide a unique insight into sleep management in health and disease (Figure 2).

CONCLUSION

With advances in sensor technology, ambulatory methods to easily collect bio-signals like ECG are now available providing opportunities and possibilities to collect objective data for multiple nights for assessing sleep duration and sleep quality. Objective sleep data collection may have important implications for both research and clinical understanding of the inter

relationship between untreated sleep disorders and several of the most widely researched chronic conditions like cardiovascular disease, obesity, diabetes and depression.

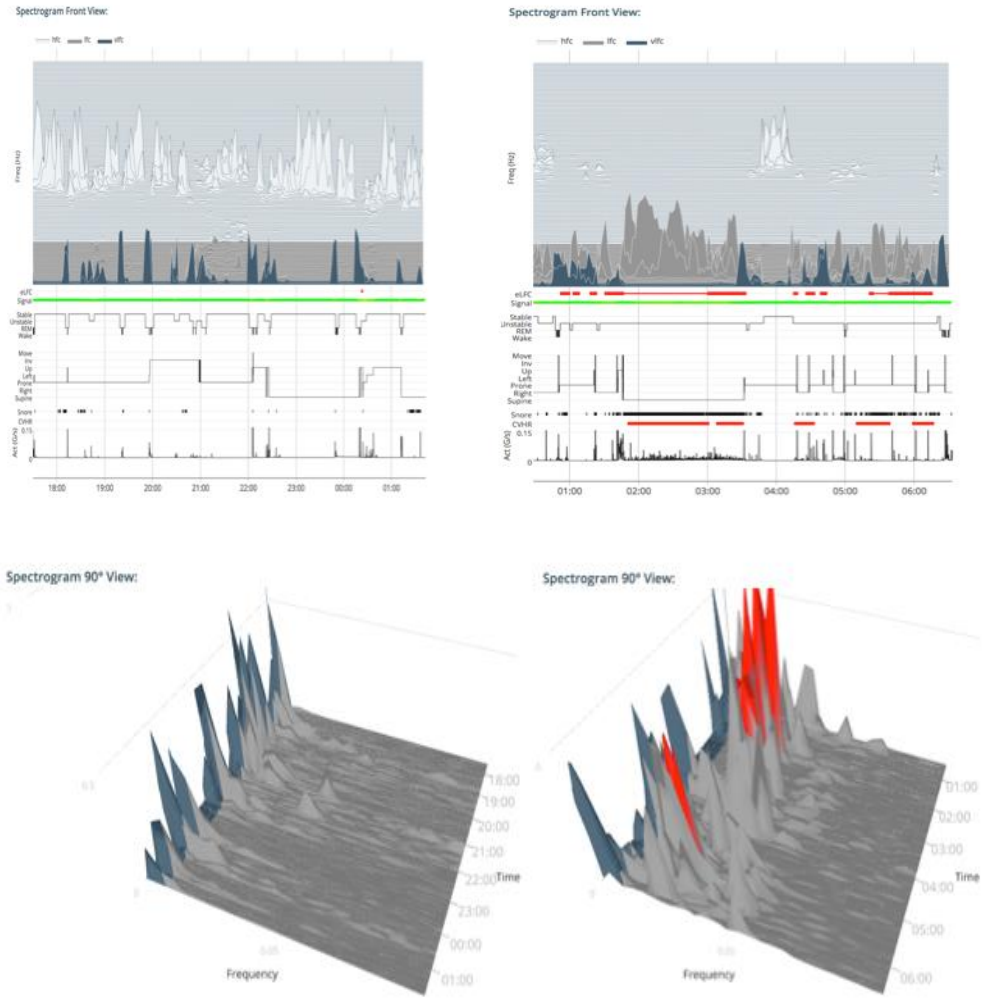

Figure 2: Sleep Spectrograms for a Healthy Sleeper (left) and Unhealthy Sleeper (right). Note the difference between the two with respect to the proportion of the recording spent in HFC and LFC, and increase in both $eLFC_{BB}$ and $eLFC_{NB}$ in the case of unhealthy sleep.

ABBREVIATIONS

Cyclic Alternating Pattern (CAP), Cardiopulmonary Coupling (CPC), Cyclic Variation of Heart Rate (CVHR), Electrocardiogram (ECG), Electrocardiogram Derived Respiration (EDR), Electroencephalogram (EEG), electrooculography (EOG) or electromyography

(EMG) Elevated Low Frequency Broad-band ($eLFC_{BB}$), Elevated Low Frequency Narrow-band ($eLFC_{NB}$), Heart Rate Variability (HRV), High Frequency Coupling (HFC), Home Sleep Apnea Tests (HSAT), Low Frequency Coupling (LFC), Non-Rapid Eye Movement Sleep (NREM), Obstructive Sleep Apnea (OSA), Polysomnography (PSG), Rapid Eye Movement (REM), Respirator Event Index (REI), Sleep Apnea Indicator (SAI), Sleep Quality Index (SQI), Very Low Frequency Coupling (vLFC).

CONFLICT OF INTEREST

Magnusdottir Solveig, MD. MBA: Works as Medical Director for MyCardio LLC and has partial ownership. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the CPC+CVHR algorithms, a method to use ECG to phenotype sleep and sleep apnea, from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

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