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The Future of Sleep and Circadian Testing

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I. Introduction

When one writes about the future there is inherent and obvious speculation as no one can, with certainty, predict what will come. That being said, this chapter will reflect a combination of what would seem logical based on the evolving science and what, in the opinion of the author, is needed for the sleep field to grow and prosper. Whether any of this will turn out to be accurate, time will tell.

In looking back over the last 20–30 years, there has been very little actual progress in sleep testing while circadian monitoring has not evolved into the clinical arena at all. That is not to say that the number of sleep laboratories/centers has not multiplied many fold over the last 25 years. That is certainly the case. However, other than transitioning from paper recordings to digital ones, the standard polysomnogram (PSG) remains very much the same over this span of years both in terms of the signals recorded and the methods used to score such records. Why so little progress has been made is arguable. However, at least part of the problem has likely been that standard polysomnography has been increasingly utilized and well reimbursed leaving little motivation to change the status quo. This does not seem to be the case any longer with a number of forces pushing for new methodologies that, in the long run, will benefit both patients and sleep physicians. I will speculate here as to where these changes will take us.

There is not space in this chapter to even attempt to cover all of the changes in sleep/circadian testing that will evolve in the years ahead. This is particularly the case as relates to specific sleep disorders. Thus examples will be given using a single sleep disorder or a single method of testing that could then be extrapolated to other disease processes or approaches to evaluation. Thus no attempt will be made to be exhaustive or comprehensive.

II. Testing in the Sleep Laboratory

A. Sleep Disorders

Current polysomnographic testing in the sleep laboratory has generally yielded diagnostic information and has addressed a relatively limited number of disorders with the vast majority of such testing being conducted to diagnose obstructive sleep apnea. This testing is also used

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for initiation of therapy (CPAP titration) and occasionally to assess therapeutic efficacy (success of upper airway surgery etc). However, standard polysomnography is not realistically used to predict outcomes as current measures of sleep fragmentation and disruption do not predict sleepiness or performance with any degree of accuracy^{1, 2}. Thus the sleep measures resulting from the standard PSG are not commonly used either diagnostically or therapeutically.

In the future, this must change. By the use of shorter duration epochs, computer assessments of EEG frequency, amplitude, and pattern, and both linear and nonlinear dynamic approaches, it seems feasible that more viable measures of both sleep continuity and sleep disruption will emerge. These measures can then be used to assess the impact of a sleep disorder, such as periodic limb movement disorder, on sleep quality or the efficacy of a therapy, such as a hypnotic, on improving sleep. It would be presumptuous to try to outline the methods that will be used to accomplish such quantification of sleep in this chapter. However, without marked improvement in the current measures, home diagnostics (see below) will become the dominant method by which all sleep disorders are diagnosed and followed with little real use for direct measures of sleep. However, if and when such methodologies are developed, it seems likely that:

- A broader range of sleep disorders and totally new disease processes can be identified and diagnosed in the sleep laboratory.
- The effects of a given sleep disorder on sleepiness and performance during wakefulness can be predicted based on the sleep study.
- Follow-up to assess the resolution of an abnormal sleep process or disruptor of sleep will be possible.

B. Phenotyping in the Sleep Laboratory

Although diagnosing a sleep disorder may be sufficiently straight forward that it can be routinely accomplished in the home with relatively few signals, more complex testing in the laboratory may yield valuable additional information that allows for a more sophisticated or individualized approach to therapy. Obstructive sleep apnea (OSA) will be used as the example. There are likely 4–5 anatomic/physiologic traits in a given individual that predict whether that person will have or develop OSA.³ These traits likely vary substantially from one patient to the next meaning that patients may have sleep apnea for quite different reasons. These traits likely include:

- Pharyngeal anatomy (Pcrit, critical closing pressure, Fig. 1)
- Pharyngeal muscle responsiveness during sleep and the ability of these muscles to dilate the airway.
- The arousal threshold to a respiratory stimulus.
- Loop gain, a measure of respiratory control stability (Fig. 2).

When one combines: a) a carefully controlled nasal airway pressure device with the ability to generate both positive and negative airway pressure, b) a smart data acquisition system with well-defined algorithms, and c) real time automated sleep staging, it seems probable that each of these traits could be accurately defined in a single night in a patient with obstructive sleep apnea. Doing so would only be valuable if these measures predicted responses to certain forms of therapy or other outcomes of the disorder. However, individualization of therapy for OSA based on these traits seems quite possible in the relative near future. An easy example would be loop gain. If loop gain is quite high (very unstable ventilatory control) and is the principle cause of the apnea, reducing loop gain could be accomplished with oxygen administration⁴ at

night or daily acetazolamide. Either could well be more easily or better tolerated than many of the currently available therapies.

These same principles may apply to other sleep disorders as well. If insomnia could be more accurately phenotyped allowing for quantitative assessment of hyperarousal, circadian phase (see below), anxiety, or co-morbidities, the entire approach to therapy might change allowing for more focused strategies be they behavioral or pharmacologic. This concept likely applies to primary hypersomnia and central sleep apnea among others.

C. Assessing Psychiatric/Neurological Disease by Monitoring Brain Activity During Sleep

Although virtually all testing currently conducted in the sleep laboratory addresses sleep itself or disorders of sleep, recent work by Giulio Tononi^{5, 6} and his investigative team suggests that sleep may provide an opportunity to examine brain function that is impossible during wakefulness. Using 256 lead EEG and sophisticated signal processing, they have made a number of novel observations. First⁵, they observed that learning is a very focal neurological process that can be monitored during sleep on the night after the learning task. Following a rotation motor learning task with simultaneous PET imaging, the subjects slept with the 256 lead EEG monitoring configuration. The principle observation was increased slow wave activity over the cortical site demonstrated by PET to be involved in the learning process. There was a direct correlation between the increase in slow wave activity and the improvement in the motor task the next day. Dr Tononi interprets the slow wave activity to represent synaptic decompression which is, he believes, one of the fundamental functions of sleep. On a more practical level, however, a fundamental brain function, learning or memory consolidation, could be monitored during sleep.

The second observation using this technique⁶ has even more obvious clinical relevance and addresses the disorder schizophrenia. Currently the diagnosis of schizophrenia is made largely based on clinical criteria without an effective objective test. Using the high resolution 256 lead EEG approach, Tononi and his colleagues examined brain activity during sleep in a group of treated schizophrenic and compared the results to those obtained in healthy controls and subjects with a history of depression. The results showed a significant reduction in centroparietal EEG power from 13.75 to 15.0 Hz in the schizophrenics when compared to both control groups (Fig. 3). They also observed a significant reduction in sleep spindle number, amplitude, and duration in the schizophrenia patients in the same anatomic location when compared to the healthy and depressed controls. No difference in either variable was found between the healthy controls and the depressed subjects. Finally they found that integrated spindle activity provided a greater than 90% ability to separate the schizophrenia patients from both control groups. This would suggest that this approach may be a sensitive and specific method by which to diagnose schizophrenia. A more recent study⁷ assessed the evoked response in the EEG (again using the 256 lead approach) to transcranial magnetic stimulation (TMS) in schizophrenic patients versus healthy controls. As is the previous study, clear differences between groups were evident, particularly in the frontal cortex in the first 100 msec after stimulation. This again suggests the utility of such testing in the schizophrenic population.

Whether this 256 lead EEG approach or others similar to it can be used during sleep to diagnose other psychiatric or neurological disorders is unclear at this time. However, as stated by Dr Tononi, "spontaneous brain rhythms during sleep reflect brain function unconfounded by attention and motivation". Thus it seems likely that this methodology could evolve into a standard clinical tool with the test administered in the sleep laboratory while the results address disorders not classically thought of as relating to sleep.

III Imaging in Sleep Medicine

Predicting the role imaging will take in future sleep testing is difficult but several possibilities seem reasonable. As functional imaging (PET, fMRI, SPECT, etc) evolves improved spatial and temporal resolution, our ability to use these methodologies to precisely evaluate brain activity awake and asleep in patients with a variety of sleep disorders will increase.⁸ An obvious example would be insomnia. Functional imaging could be used to:

- Aid differential diagnosis as different patterns of brain activation may characterize insomnia secondary to hyperarousal⁹ versus depression¹⁰ or other causes.
- Assessment of treatment response by demonstrating changes in regional brain activity awake or asleep in response to a given intervention.
- Select the best pharmacologic agent based on the individual's focus of abnormal brain activity and how this activity is affected by specific drugs.

Thus insomnia patients may well undergo such imaging as the first step in their evaluation for both diagnostic and therapeutic reasons. The other obvious area for future imaging would be the pharyngeal airway in obstructive sleep apnea patients. To date such imaging has been helpful scientifically, but has provided little guidance clinically in the management of the individual patient.¹¹ The problems have been that the images are largely static, cannot reasonably be gathered during sleep, and are quite expensive. However, dynamic MR imaging of the pharyngeal airway during sleep could provide highly useful information regarding site of collapse, extent of collapse (length of collapsing airway segment), and possibly even localized tissue movement/deformation. These results could certainly be used to guide surgery, surgical implants, and possibly other device related therapies. As MR and other dynamic imaging approaches continue to improve, such testing seems possible.

Whether imaging will have a role in the diagnosis or management of disorders such as narcolepsy¹², idiopathic hypersomnia, or movement disorders during sleep¹³ is less clear. However, as the neurobiology of these disorders becomes better understood, a role for functional imaging may emerge.

IV. Circadian Testing

Circadian biology, although quite advanced at the basic science and physiologic level¹⁴, has not found its way into clinical practice in a meaningful way. The main cause for this probably relates, at least in part, to the fact that there is currently no readily available test to define circadian phase. Thus, the only way to identify a circadian abnormality is from the history obtained from the patient. This probably works reasonably well for overt circadian disorders, but many more subtle abnormalities are likely missed. Also, the primary method by which circadian phase can be manipulated or corrected is light¹⁵ which is currently cumbersome to administer. In addition, without clear information on circadian phase, when light should be administered to a given patient is largely guesswork. This speaks to the imperative to develop a clinical test for circadian phase.

In the research setting, circadian phase is most commonly delineated using the dim light melatonin onset (DLMO, Fig. 4).¹⁶ This generally involves the measurement of plasma or salivary melatonin levels every 30 to 60 minutes with the subject lying in dim light or wearing goggles to block light exposure in the relevant wave lengths. As salivary levels are as useful as plasma, there would seem to be no particular reason why a kit could not be developed that would allow for multiple, timed saliva collections which could be sent to a laboratory for subsequent analysis. Whether this evaluation could be best and most reliably accomplished in the sleep laboratory or the home is probably arguable. However, the rapid evolution of such

testing would seem to be an imperative in this field. Once such objective testing becomes available, its use in insomnia patients in whom the cause is not completely clear and in patients with a suspected circadian rhythm disorder both to confirm the diagnosis and to guide the timing of light exposure would seem to be initial logical uses for such an evaluation. Others would likely evolve quickly. Finally, once the circadian phase is known, continuous monitoring of both actigraphy and light exposure would likely allow for the longitudinal monitoring of sleep and circadian phase which could be quite useful in shift workers, some patients with insomnia, and individuals with frequent travel across multiple time zones.

Clinical testing of the circadian period, although not as urgent as circadian phase, will probably also evolve without great difficulty and will likely provide useful clinical information. Knowledge of the circadian period could well explain circadian preference and, in some cases, the cause of a circadian rhythm abnormality. Such information would likely have therapeutic implications as well. Determining the circadian period in a given individual in a research laboratory is a long and laborious process and does not lend itself to clinical utilization.¹⁷ However, individual circadian period may well be determined from dermal fibroblasts using a lentivirally delivered reporter system.¹⁸ The amplitude of the circadian system and its ability to be phase-shifted or entrained to environmental signals may also be assessed in these cells. As a result, a wealth of clinically useful information could well be derived from these cell cultures. If a sleep physician knew the circadian phase, period, amplitude, and susceptibility to phase shifting in a patient with a possible circadian rhythm abnormality, the ability to manage that patient would be immensely improved. Thus, several forms of circadian testing are likely the most near-term and clinically useful new evaluations for the clinical sleep field.

V. Sleep Deprivation and Performance

Acute and chronic sleep deprivation have become increasingly common everywhere and have the potential to not only affect the health¹⁹ and performance²⁰ of the afflicted individual, but also the safety of the sleep deprived person and those around him. The safety issue surrounding this rapidly evolving problem could, at least in part, be addressed by two forms of testing:

- Fitness to perform i.e. monitoring of variables that influence sleep/circadian-based performance prior to a job (work shift) during which vigilance is required.
- A continuous measure of sleepiness or drowsiness.

Fitness to perform monitoring would ideally include measures of previous sleep duration (over a number of nights), time since last sleep (to control for sleep inertia and the duration of the current period of wakefulness), and circadian phase. The vast majority of this information could be obtained from an actigraph worn continuously in combination with one determination of the DLMO as circadian phase is likely to be stable. Algorithms could be then be generated to analyze this information and predict the level of performance or potential for a sleepiness-related error. There is obviously considerable individual variability in nightly sleep need, impact of sleep deprivation on performance, sleep inertia, etc. However, if properly calibrated, fairly simple devices could provide very useful information regarding an individual's ability to perform well in a job requiring sustained attention for a relatively long period of time. Such testing could be accomplished in the very near future.

A continuous measure of sleepiness would also have great value in any job requiring sustained vigilance or outside the workplace while driving. A number of such devices have been developed over the years with quite variable success. An example of such a device would be infrared reflectance oculography which provides a continuous measure of eye lid motion/position from an IR sensor attached to a pair of glasses combined with an algorithm that predicts sleepiness based on eyelid closure and reopening times/variability.²¹ Although certainly not perfect, this particular device has a reasonable ability to detect sleepiness before frank sleep

onset and could be programmed to intervene or alert the individual to prevent an accident or injury. This type of testing would have wide applicability in many setting in which sustained vigilance is required. Programs and devices designed to monitor/document sleep loss and quantify sleepiness as described above, would be best organized, distributed, and interpreted by sleep physicians who understand the strengths and weaknesses of the techniques and can guide their use into appropriate channels. As we become an increasingly 24 hour society, the need for such techniques is likely to be substantial.

VI. Sleep Testing/Screening in the Home

In the years ahead, there is likely to be substantial sleep testing, monitoring, and screening done in the home with a number of examples having already been described above. Home testing not only allows for this assessment in a more natural sleep environment, but in many cases makes it possible to monitor the individual over a number of nights which is likely to provide more complete and representative information. Such testing would likely fall into several categories:

A. Diagnostic Testing

There is already a great deal of sleep apnea diagnostic testing being conducted in the home with most devices utilized in this role simply recording standard respiratory signals with or without some measure of sleep.²² This practice is likely to increase and rapidly become the standard method by which disorders of breathing during sleep are diagnosed. This may be accomplished with sensors attached to the subject as is now generally the case, or by the use of specialized materials placed on the surface of the bed that can detect movement, respiration, and heart rate.²³ Video recording may also have a role in the future. Circadian sleep disorders will likely be diagnosed with actigraphs or easily-utilized monitors of sleep/wake with such testing again being conducted primarily in the home.²⁴ This may or may not always require assessment of the DLMO for which samples could also easily be obtained in the home setting. These approaches apply to insomnia as well. Combined, time-synched, multi-night recordings of EEG and video from the bedroom at home could be quite useful in diagnosing parasomnias, movement disorders, and seizures. Thus most sleep and circadian disorders will likely be diagnosed more conveniently and effectively in the home setting.

B. Sleep Monitoring

In some disorders, with insomnia being an obvious example, monitoring of sleep over a longer period of time (weeks to months) can yield useful diagnostic information or actively assess ongoing therapy. This can be accomplished at this time with actigraphs from which several weeks of sleep/wake information can easily be obtained.²⁵ In time, more complete sleep monitoring with full sleep staging will likely be possible with easily utilized dry electrodes.²⁶ Thus, on a nightly basis, a physician could follow the sleep of his/her patient making interventions as required. Such monitoring devices will likely move into the consumer market as well such that people can follow their own sleep duration and quality adjusting their habits and lifestyles as needed to improve their sleep and subsequently their quality of life. As a result, chronic, home-based sleep monitoring will likely become quite common in the future and will require either individual or algorithmic guidance from the sleep physician.

C. Screening for Sleep Disorders

Active screening for sleep disorders will not likely come into general practice until there is clear evidence that the disorder, if untreated, leads to adverse health consequences and there are acceptable, effective therapies available. The only sleep disorder that could fill both of these criteria in the near future would be sleep apnea. If current and future studies demonstrate an indisputable association between sleep apnea and adverse cardiovascular outcomes²⁷, then

home-based screening would likely evolve rapidly. Such screening could be either home-based monitoring using only a few signals or utilize a biomarker if such a test can be developed. Screening for other sleep disorders seems unlikely in the near future.

VII. Genetic Testing

How genetic testing will be used in the diagnosis and management of sleep disorders is certainly controversial at this time. However, there are a number of possibilities:

- Genetic predisposition to disease is obviously a well established phenomenon and has been demonstrated in humans with narcolepsy and Restless Leg Syndrome (RLS).²⁸ Genes predisposing to parasomnias like sleep paralysis, sleep walking, or the disorder Klein Levin Syndrome seem probable based on existing family studies. Genetic causes for circadian rhythm abnormalities have been demonstrated in a few families.²⁹ Whether these genetic associations are strong enough to have meaningful diagnostic utility is unclear at this time.
- Understanding the pathophysiology of various disease processes (like OSA) will likely result from genetic approaches such as genome-wide association studies.³⁰ Such testing may therefore be able to distinguish the different routes by which an individual develops sleep apnea (see phenotyping above) allowing for different therapeutic approaches based on the phenotypic information.
- The susceptibility to the complications of sleep disorders may also depend highly on individual genetics. An example would be the cardiovascular complications of OSA. As the risk for cardiovascular disease in general is known to have a genetic basis, who develops these complications in OSA is likely genetic as well. Thus, an asymptomatic OSA patient with a high genetic risk for cardiovascular disease might well receive therapy when this would not be the case otherwise.
- Individual susceptibility to important decrements in performance from sleep deprivation may vary substantially based on genetics.³¹ Thus genetic testing could be used to select individuals for jobs during which vigilance is required yet adequate sleep may not always be possible.

Thus genetic testing in sleep medicine may become quite common as will be the case in most areas of medicine.

VIII. Conclusions

Although sleep testing to date has been somewhat limited with a focus on one procedure (PSG) with circadian testing being virtually non-existent, the future possibilities seem promising and exciting. Clinically available methods to define circadian phase and period stand to remarkably improve our ability to care for patients with circadian abnormalities and to lead to a substantially better understanding of these disorders. Improved techniques to measure and quantify sleep itself will not only allow us to more meaningfully assess sleep disruption, but will likely lead to both the recognition of new disorders and better predictions of the outcomes of these disorders. Sleep may also provide a window on the brain allowing for understanding of certain diseases not possible from recordings made during wakefulness. Genetic testing and imaging, now actively used clinically in many fields, needs to evolve in the sleep arena as well providing improved insights into both disease pathophysiology and hopefully new therapies. Thus we have the potential for remarkable advances if we can both recognize these possibilities and not remain mired in the past.

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Figure 1. Maximal airflow ($\dot{V}_{I \max}$) versus nasal pressure (P_N) is shown for a representative OSA patient. The figure demonstrates a P_{crit} of -1.2 cm H₂O (defined by the nasal pressure at which airflow ceases). $\dot{V}_{I \max}$ during tidal breathing at atmospheric P_N is shown by the level of flow at the intercept with the vertical dashed line. Each point represents the mean $\pm$ SD for breaths sampled at each level of P_N shown.³² Published with permission Ref

Figure 2.

Demonstrated is the respiratory control loop the gain of which is referred to as loop gain. The main components are the plant gain (change in PCO_2 per unit change in ventilation, V_e), the controller gain (change in ventilation for each unit change in arterial PCO_2), and the circulatory delay (time for blood to move from the lung to the chemoreceptors (central and peripheral)). Thus a respiratory disturbance will be translated into a respiratory response based on the gain of the loop.

Figure 3.

White Plots: Topographical distribution of the electrodes showing significant power reduction (gray) at 13.75–15.00 Hz in schizophrenia versus comparison and schizophrenia versus depressed but not depressed versus comparison subjects. Color plots: Topographical distribution of mean EEG power at 13.75–15.00 Hz during the first NREM sleep episode in schizophrenia (n=18), comparison (N=17), and depressed (N=15) subjects. Values (color bar) were plotted at the corresponding electrode position (dots) on the planar projection of the scalp surface. The schizophrenia subjects had significantly reduced power in the areas shown while the other groups (comparison and depressed) did not differ from each other.⁶ Published with permission Ref

Figure 4.

Salivary melatonin profiles are shown for 11 subjects. In each the profile was determined on two occasions separated by one week. The two vertical lines represent scheduled, weekday bedtime (23:00 hr) and wake time (07:00 hr). As can be seen, the determinations were quite consistent over time.³³ Published with permission Ref