Measuring Sleep, Wakefulness, and Circadian Functions in Neurologic Disorders

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KEYWORDS

• Sleep • Wakefulness • Circadian • Stroke • Neurodegenerative disorders • Neuroimmunology • Polysomnography • Sleep architecture

KEY POINTS

- Neurologic disorders impact the ability of the brain to generate sleep, wake, and circadian functions.
- Preexisting or de novo sleep-wake-circadian pathologies are generally underdiagnosed in neurologic patients despite their major impact on onset, evolution, and outcome of neurologic disorders.
- Neurologic disorders are frequently accompanied by sleep-wake EEG changes. Extensive brain damage can lead to the absence of measurable differentiation between sleep and wakefulness (status dissociatus).
- New technologies will facilitate early detection and (long-term) monitoring of neurologic patients and the optimization of their clinical management.

INTRODUCTION

The brain is the organ from which sleep, wakefulness, and circadian functions are generated and ultimately measured. The highly structured and timed transitions between wakefulness, nonrapid eye movement (NREM) sleep, and REM sleep requires an integration of neural networks across many brain structures, including the brainstem, subcortical regions such as the thalamus and hypothalamus, and basal forebrain.

Central nervous system (CNS) lesions underlying neurologic disorders can lead to primary sleep-wake and circadian disorders (SWCD) through lesioning of specific cell types or structures generating or regulating sleep, wake, and circadian functions or through nonspecific lesioning of diffuse neural networks. In addition, SWCD can arise secondarily from complications of CNS lesions such as spasticity, pain, and depression. In many cases SWCD may worsen over time, as in the case of progressive neurologic diseases.

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Finally, SWCD may also represent the first or main manifestation of an underlying neurologic disorder such as dream enactment behavior in Parkinson disease (PD), excessive daytime sleepiness (EDS) in hypothalamic disorders, or insomnia in Alzheimer disease (AD).

Lesions of the various structures that regulate sleep, wake, and circadian functions will lead to specific changes. For example, lesions of the brainstem may affect aspects of REM sleep generation or expression, thalamic lesions can lead to a reduction of spindling, and damage to the suprachiasmatic nucleus may disrupt circadian rhythmicity. These various pathologic manifestations can be measured through subjective assessments, including questionnaires, and objective tools using actigraphy, polysomnography (PSG), or daytime vigilance testing (Fig. 1). The diversity of SWCD in neurologic patients, which may reflect brain damage or other factors such as comorbidities or medication, and their measurement in clinical practice are the subjects of this article.

STROKE

Stroke is one of the leading causes of death and disability worldwide[1] and is often associated with significant changes in sleep-wake electroencephalographic (EEG) architecture and circadian expression.[2,3] In addition, SWCD are also increasingly recognized as stroke risk factors and modulators of stroke outcome.[2,4,5] Therefore, SWCD diagnosis and management should be considered in stroke care pathways.

Subjective Assessments

The simplest way to assess subjective SWCD in patients with stroke is by using structured interview questions. A detailed sleep history addressing sleep habits before and following stroke, including estimated sleep needs (hours per day), can be easily gathered from patients or their relatives, even at hospital admission.[6,7] However, limited studies have assessed subjective sleep duration prestroke and poststroke and heralded conflicting results. A systematic study from our group conducted in 438 patients suggested an increased sleep duration following ischemic stroke with a gradual, but incomplete, return to baseline at 12 months.[8] An increase in sleep duration or need is particularly often found in patients with (bilateral) lesions of the paramedian thalamus.[6,9]

Symptoms such as fatigue, insomnia, and EDS are common after stroke.[10,11] Restless legs syndrome (RLS), in contrast, does not seem to be more prevalent after stroke than in the general population.[12] In a systematic study from our center over a follow-up period of 2 years, fatigue was found in up to 28%, insomnia in 28%, EDS in 14%, and RLS in 9% of patients with stroke (manuscript in preparation).

Sleep questionnaires such as the Epworth Sleepiness Scale, Fatigue Severity Scale, Insomnia

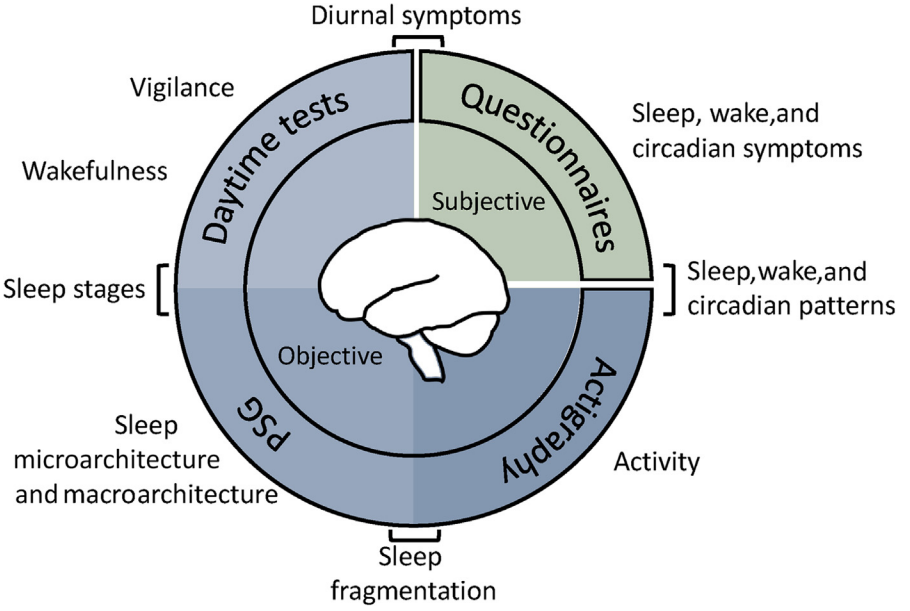

Fig. 1. Measuring sleep-wake and circadian disorders using subjective and objective assessments in neurologic disease.

Severity Index, and the Pittsburgh Sleep Quality Index Questionnaire[9,13,14] can also be used to help investigate specific symptoms of SWCD. It is important to note, however, that validation of these commonly used questionnaires as part of a test battery in patients with stroke is lacking. Moreover, the use of questionnaires for sleep-disordered breathing (SDB) has shown limitations in patients with stroke with their high sensitivity but a rather low specificity.[15] Taken together, although the use of questionnaires validated for the general population may provide potential screening tools for SWCD evaluation, objective assessments remain frequently necessary in a stroke population in which SWCD are highly prevalent.[16]

Objective Assessments

Circadian functions can be assessed using actigraphy. A disruption of circadian rhythmicity, as measured by core body temperature and actigraphy acutely after stroke, correlated strongly with functional outcome 3 months after stroke onset.[17] In addition to estimating macroparameters of sleep-wake rhythms, wearable devices may offer the possibility for long-term home monitoring, allowing the investigation of sleep-wake behavior evolution after stroke, as well as measuring the effect or efficacy of therapeutic interventions (see section 6.2).[18]

In-laboratory PSG demonstrates that sleep macroarchitectural changes following stroke potentially affect all sleep and EEG variables.[2,11] For example, supratentorial stroke may be followed by a reduction in REM sleep in a stroke severity-dependent manner and may persist for months.[19,20] Brainstem stroke lesions affecting the ventrolateral and tegmental areas in the pons can also reduce REM sleep or lead to REM sleep behavior disorder (see later), especially in the case of bilateral lesions.[21] Noteworthy, stroke in these regions may lead to a reduction in NREM sleep even in the absence of subjective sleep complaints.[21]

Thalamic strokes predominantly reduce sleep spindles and deeper NREM sleep stages.[6,9,22,23] Indeed, a reduction in sleep spindles after thalamic and supratentorial strokes[24,25] may occur as a function of lesion size.[19] Moreover, spindle power reduction in the peri-infarct area acutely after stroke is accompanied by a temporarily increased spindle power over the contralesional hemisphere.

In acute and chronic stroke, local slow-wave activity (SWA) is increased over the infarct area and decreased over the peri-infarct area during sleep[25]; this is of interest for different reasons. In a recent study we observed an association between a reduction of the slow-wave slope in patients with thalamic stroke and daytime sleepiness.[26] In addition, SWA is increasingly linked with sleep-related learning and memory,[27,28] processes that could play a role in neuroplasticity after stroke.[5] In support of this hypothesis, optogenetically induced slow waves delivered during sleep were reported to improve functional outcomes in a mouse model of stroke.[29] Together, these data provide a conceptual framework for therapeutic noninvasive neuromodulation approaches targeting (slow wave) sleep after stroke (and overall brain injury).

Only a few studies objectively investigated the impact of stroke on daytime vigilance using the multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT). Sleep latencies were reduced in subcortical stroke,[30] whereas the latencies did not necessarily correlate with subjective measures of EDS in patients with bilateral thalamic lesions.[22] These data reveal potential discrepancies between subjective questionnaires and objective monitoring that may reflect a discordance between perceived alertness and actual waking ability. Such discrepancies can also be observed in the general population[31] and reflect the need for objective assessments of daytime alertness. However, objective testing can be challenging because large supratentorial lesions may also limit the expression of EEG correlates of sleep-wake behaviors (see section Neurodegenerative Disorders).

NEURODEGENERATIVE DISORDERS

Sleep, wake, and circadian disturbances are a common finding in neurodegenerative diseases.[32] As neurodegenerative diseases often affect the neuronal networks underlying the generation of sleep, wakefulness, and circadian timing, standard methods to measure and score sleep and wakefulness are potentially challenging,[33] and this was dramatically documented by Landolt and colleagues[33] in study of patients with sleep-wake disturbances in the course of Creutzfeldt-Jakob disease. Similarly, Santamaria and colleagues[34] emphasized the importance of audiovideographic recordings, including calibration of measured variables with clearly awake periods with major sleep and wake bouts in patients with brain damage.[34]

Subjective Assessments

Up to 60% of patients with AD and 90% of patients with PD suffer from insomnia.[35,36] EDS is also frequent and may affect more than 40% to 50% of both patients with AD and those with PD.[36,37] REM sleep behavior disorder (RBD) is frequent in

PD[38] but rare in AD.[39] In RBD, the complex neural networks controlling muscle atonia or paralysis during REM sleep are disrupted, leading to motor activation during this stage of sleep. If RBD occurs in the context of a neurodegenerative disorder, such as PD, or is triggered by medication, it is classified as secondary RBD. However, if no underlying cause can be identified, it is known as idiopathic RBD (iRBD), which can appear in the prodromal phase of α-synucleinopathies. Finally, RLS is probably more prevalent in patients with PD compared with healthy individuals,[40] and, in patients with AD, RLS may manifest as nighttime agitation.[32]

Several questionnaires for RBD have been developed, including the RBD screening questionnaire (RBDSQ), which is the most commonly used.[38] A meta-analysis of the RBDSQ demonstrated a sensitivity and specificity of 91% and 77%, respectively.[41] However, this questionnaire demonstrated poor sensitivity and specificity in patients with PD.[41] Another problem common to all RBD questionnaires is that some patients are unable to complete the questionnaires, or they live alone and are unaware of their parasomnia. Finally, given the low prevalence of symptomatic RBD in the general population and assuming a questionnaire with a sensitivity and specificity of 90%, only approximately 10% of patients who screen positive will actually have RBD.[38] These and other data suggest the need for comprehensive objective assessments, particularly in patients with neurologic disorders.

Objective Assessments

Actigraphic measurements in patients with AD reveal alterations in sleep-wake patterns with irregular sleep-wake rhythms to a complete reversal of the day/night sleep pattern. Some of these changes can be observed in the prodromal phase of AD.[42] In PD, a loss of stability in the day-to-day rest-activity pattern is associated with impaired cognitive function,[43] whereas reduced circadian rhythmicity may be seen in the prodromal stage.[44] Finally, patients with iRBD show increased probable napping behavior, activity fragmentation, and physical inactivity during the active period. These rest-activity pattern alterations have been associated with an increased risk of phenoconversion to an overt α-synucleinopathy.[45]

Video-PSG assessments in patients with AD reveal reduced sleep efficiency and alterations in sleep macroarchitecture and microarchitecture (summarized in **Table 1**). As neurodegeneration progresses, electrographic features defining NREM stage 2 (N2) may disappear completely, rendering NREM stage 1 (N1) and N2 sleep practically indistinguishable. In this case, indeterminate NREM sleep may be scored.[34] This indeterminate NREM sleep may increase further with the disappearance of the slow waves in later stages of the disease.[46,47]

In patients with PD, the reduction in slow-wave sleep may be associated with increased periodic leg movements in sleep.[48] In addition, lower sigma power in NREM sleep may be predictive for cognitive impairment in PD.[50] In patients with iRBD, smaller densities of fast sleep spindles and larger densities of slow spindles are described.[51]

The diagnosis of an RBD requires the presence of muscle activity during REM sleep (REM sleep without atonia [RSWA]). RSWA shows some degree of night-to-night stability so that a single night of PSG is considered sufficient for the diagnosis of RBD.[38] Obstructive sleep apnea (OSA) is a common comorbidity in AD and PD. Importantly, patients with OSA may show motor events associated with respiratory effort in REM sleep,

Table 1
Microarchitectural and macroarchitectural changes in Alzheimer and Parkinson disease

	Alzheimer disease[46,47]	Parkinson disease[48,49]
Sleep efficiency	↓	↓
Slow wave sleep	↓	↓
REM sleep	↓ episode duration, with EEG slowing	↓
NREM sleep	N1 and N2 become indeterminate, later SW disappear	Lower sigma power
Microarchitecture	↓ frequency and amplitude of spindles and K-complexes	↓ frequency and amplitude of spindles
Sleep latency	↑	↑

Abbreviations: sigma, (12–15 Hz) reflects sleep spindle activity; SW, slow waves.

which can be misinterpreted as RBD, a finding referred to as pseudo-RBD.[52] If RBD is suspected in a patient with OSA, it is recommended to repeat the diagnostic workup after OSA treatment.[38]

When complex neuronal networks involved in the initiation and maintenance of sleep become increasingly impaired, components of different stages may occur together, leading to the so-called state dissociations. With increasing degeneration of these networks, state dissociations may increase in severity, culminating in a status dissociatus, characterized by a complete breakdown of state-determining boundaries.[53] Status dissociatus has been described in patients with α-synucleinopathies, as well as in other neurodegenerative and secondary brain diseases that predominantly affect the thalamus.[53]

Objective measurements using MSLT or MWT often reveal EDS in neurodegenerative disorders. Mean sleep latency was found to be significantly reduced in patients with AD when compared with healthy controls and to correlate with cognitive impairment.[54] Up to 50% of patients with PD suffer from EDS,[55] which is often underappreciated by patients.[37]

NEUROIMMUNOLOGICAL DISORDERS

Many neuroimmunological disorders affect CNS areas involved in regulating sleep, wakefulness, or circadian functions. In the case of narcolepsy type 1, a very specific group of neurons expressing hypocretin (orexin) in the hypothalamus is lost,[56,57] probably secondary to autoreactive CD4+ and CD8+ T cells.[58] Hypocretin neurons are essential for stabilizing the state of wakefulness, so their loss adversely affects the ability to maintain alertness.[57]

In contrast to a specific cell type affected in narcolepsy following a single inflammatory phase, multiple sclerosis (MS) is characterized by intermittent or chronic inflammatory-induced demyelination affecting different neuronal systems. Depending on the extent and localization of the lesions, a diverse range of symptoms can be observed, including SWCD. For example, MS lesions affecting the hypothalamus can result in secondary narcolepsy, whereas spinal lesions may trigger RLS or periodic limb movements in sleep.[59,60]

Subjective Assessments

The cardinal symptom in narcolepsy type 1 is cataplexy: sudden, short episodes with bilateral loss of muscle tone triggered by emotion. Although cataplexy is absent in narcolepsy type 2, all patients with narcolepsy complain of EDS[61] and may report disturbed sleep, episodes of sleep paralysis, and hypnagogic (= while falling asleep) or hypnopompic (= while awakening) hallucinations.[56] Specific questionnaires for narcolepsy, such as the Swiss narcolepsy scale,[62] address this unique constellation of symptoms. In contrast, the Epworth sleepiness scale only assesses the symptom of EDS and shows high mean scores in patients with narcolepsy (17 ± 3 of 24).[61]

Fatigue in MS is found in greater than 85% of patients[63] and can be assessed by the Fatigue Severity Scale or by the Fatigue Scale for Motor and Cognitive Functions questionnaire developed for MS-related fatigue.[64] In contrast to fatigue, EDS is less consistent at the group level in MS, although it still may be present in a substantial subpopulation.[65] Pathologic fatigue and sleepiness in patients with MS was significantly associated with positive screenings for SDB, RLS, and insomnia in a large, questionnaire-based study.[66] Comorbid SDB is present in 12% to 80% of patients with MS, a prevalence likely exceeding that observed in the general population.[59,67] Finally, the prevalence of RLS was reported to be 4 times higher in patients with MS than in the general population.[59,68]

Patients with autoimmune encephalitis commonly suffer from sleep complaints such as insomnia, hypersomnolence, dream enactment behaviors, or frequent arousals.[69] The anti-IgLON5 syndrome is a rare autoimmune disease characterized by sleep-wake disturbances, including insomnia, excessive sleepiness, RBD, SDB, and neurologic manifestations such as bulbar dysfunction and gait and cognitive problems.[70]

Objective Assessments

Sleep-wake examinations involving PSG and MSLT assessments play a critical role for the diagnostic criteria of narcolepsy according to the International Classification of Sleep Disorders, third edition.[71] For example, the PSG may reveal a REM sleep latency within 15 minutes after sleep onset (sleep onset REM) in up to 50% of patients.[56] Furthermore, sleep fragmentation and reduced sleep efficiency are also characteristic for narcolepsy.[56] Current diagnostic criteria of narcolepsy rely on MSLT findings, which should document a mean sleep latency of 8 minutes or less and at least 2 naps with REM sleep.[71]

In patients with MS, PSG may reveal an increased arousal index and reduced sleep efficiency.[72] The MSLT can help to further evaluate sleepiness in patients with MS, for example, to exclude narcolepsy, but robust epidemiologic data on the MSLT in patients with MS are lacking.[59] In autoimmune encephalitis, PSG may show sleep fragmentation, reduced sleep

efficiency, and reduced or absent NREM stage 3 (N3) and REM sleep.[69] In a small study, spindle density was shown to be decreased.[73] Larger systematic studies are needed to assess associations between antibody subtypes and specific sleep disorders and the influence of sleep disorders on the clinical presentation and long-term outcome of patients with autoimmune encephalitis. In the anti-IgLON5 syndrome, the PSG may show an abnormal (undifferentiated) NREM sleep initiation, with sleep-related vocalizations and movements, followed by periods of normal NREM sleep, RBD, and OSA with stridor.[74]

EPILEPSY

Epilepsy is linked in a bidirectional manner to sleep. On the one hand, seizures, antiepileptic drugs, and interictal activity may alter sleep macroarchitecture and microarchitecture. On the other hand, sleep deprivation and comorbid sleep disorders may reduce the seizure threshold and limit its control.[75] Moreover, up to one-half of epileptic patients report sleep complaints.[76,77] Specifically, 52% complain of sleep maintenance insomnia (vs 38% in controls), whereas loud snoring and restless legs symptoms were found to be independent predictors of EDS in patients with epilepsy.[76] Moderate to severe SDB affects up to 26.5% of epileptic patients and may increase seizure frequency.[78] These findings highlight the importance of SWCD diagnosis and treatment in epilepsy management. In addition, several epilepsy syndromes show seizure activity exclusively or predominantly in sleep. These are termed sleep-related epilepsy.

Subjective Measures

A careful clinical history with both patient and witness is critical to correctly diagnose and establish the semiology of the ictal events. The most frequent complaints are EDS and insomnia.[76,79] Specific questionnaires, such as the Frontal Lobe Epilepsy and Parasomnias scale, can help differentiate some forms of epilepsy from disorders of arousal (confusional arousal, sleepwalking and sleep terrors), although the semiological similarities pose diagnostic challenges.

Objective Measures

In case of suspicion of sleep-related epilepsy, objective measurements, such as home video recording and a video-PSG with extended EEG (10/20) montage is recommended.[80,81] PSG recordings in patients with epilepsy may show sleep architectural abnormalities, such as increased number of arousals and increased wake after sleep onset, increased stage shifts, and reduced percentage of REM sleep.[75] Epileptic activity is also specifically affected by sleep stage: interictal and ictal activity are increased predominantly in NREM sleep when compared with REM sleep.[82,83] This association is proposed to be associated with NREM sleep characteristics, that is, increased EEG synchronization that may favor seizure propagation and muscle tone preservation during NREM sleep that allows seizure-related movements to occur.[84]

Although sleepiness is a frequent complaint in patients with epilepsy, objective assessments of vigilance and wakefulness are sparse, showing little correlation between subjective and objective sleepiness.[85]

NEW FRONTIERS FOR MEASURING SLEEP-WAKE AND CIRCADIAN DISORDERS IN NEUROLOGIC DISORDERS

Given the high prevalence of sleep disorders comorbid with neurologic disorders and their impact on the course or presentation of neurologic disease, it is essential to identify and treat SWCD to optimize neurologic management. Future advancements are needed with respect to screening, including questionnaires specifically designed for patients with neurologic disorders. Moreover, future technologies on the horizon may promote new diagnostic and management tools.

Future Role of Questionnaires

Screening tools for individual SWCD disorders are available, including the Epworth Sleepiness Scale[86] to test the propensity to fall asleep, the Fatigue Severity Scale,[87] Insomnia Severity Index,[88] the Single Question for RLS,[89] STOP-BANG score for sleep apnea,[90] and the Swiss Narcolepsy Scale[62] to name a few. However, a fully validated general screening instrument for patients with neurologic disorders is currently missing, making it difficult for neurologists outside of sleep medicine to select the right screening tool. Therefore, a brief domain-based questionnaire might be the future such as a first promising attempt in the SDS-25.[91] The validation of a single, brief questionnaire covering a targeted spectrum of SWCD designed for patients with neurologic disorders remains an area of interest for future research.

Future Frontiers in Sleep-Wake and Circadian Disorders Monitoring

In-laboratory video PSG (ie, a level 1 sleep study) plays a central role in objective clinical sleep

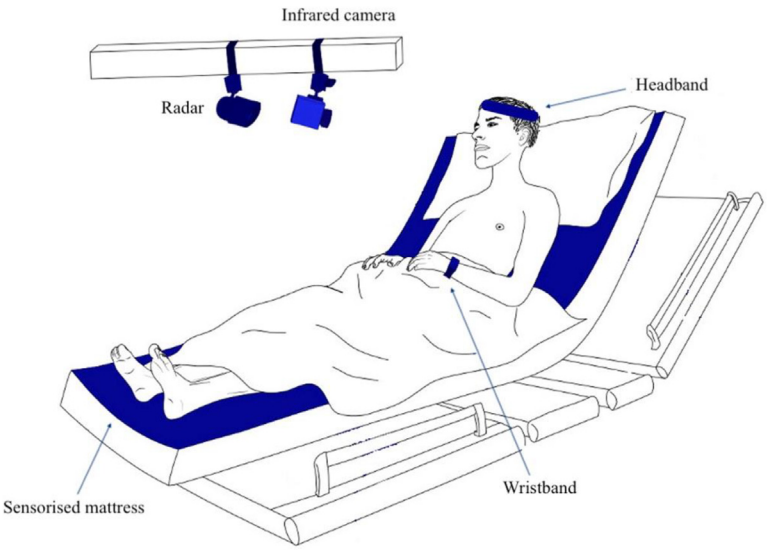

Fig. 2. Example of an unobtrusive sensor network. On top, 2 contactless technologies, radar and infrared camera. The subject lies on a sensorized mattress wearing a smart wristband and an electroencephalographic-based headband.[93]

assessment. Although it is the current gold standard for diagnosis of many SWCD, the unnatural environment and highly obtrusive character of the currently used devices may negatively affect sleep. In addition, this single night snapshot cannot detect periodicities or subtle changes over time as may be anticipated for many chronic or progressive neurologic disorders.

With advances in technology, less obtrusive devices address these issues and allow long-term home monitoring of sleep, wake, and circadian functions. Actigraphy was one of the first wearable devices that could measure several parameters of the sleep-wake rhythm. Novel wrist bands have included additional sensors for measuring heart rate, skin temperature, and electrodermal activity.[92] To record brain activity and derive sleep stages, headbands with dry EEG electrodes have gained popularity over the last years.[93] Even less invasive are contactless technologies to monitor sleep. Here we find sensorized mattresses based on ballistocardiography, which are able to extract body movements, heart rate, and respiratory rate.[94] In addition, bedside radar technology has recently been suggested as a potential future tool for sleep-wake discrimination,[95] sleep stage scoring,[96] and detection of SDB.[97] Although skin temperature changes occur across sleep and wake states, the potential roles of other technologies such as thermal cameras or electrodermal activity remain unclear.

Several studies have shown a high correlation between such wearable and nearable devices and PSG.[98] However, studies mostly compared one single device to PSG in healthy participants. As a result, there is lack of ground truth data on 2 levels: first, each device records specific types of data, but it remains unclear what combination of sensing devices may be optimal. Second, studies are lacking to validate such devices as shown in **Fig. 2** in both medical and home settings with patients with sleep or neurologic disorders. The medical application of currently available commercial smartwatches has been complicated by the lack of harmonization of technologies across devices. However, if these and other wristband devices become validated in the future, the medical setting for clinic investigation will likely shift from an in-laboratory setting to the home environment. Theoretically, a combined sensor network offers the potential for long-term, in-home monitoring with a similar diagnostic efficacy as PSG. At our institution a new unit called NeuroTec was recently inaugurated to test and validate new approaches for wearable and nearable approaches to long-term and home monitoring of SWCD and other disturbances in neurologic patients.[99]

SUMMARY

Neurologic disorders often affect sleep-wake and circadian patterns, either as a primary consequence of brain lesions that disrupt neuronal networks regulating sleep or circadian time or as a secondary consequence of underlying sensory or motor neuropathology. These SWCD may present in diverse ways, ranging from changes to sleep structure or EEG microarchitecture without subjective symptoms up to the complete dissociation of the sleep-wake stages in advanced neurodegeneration. Identifying these symptoms using

both subjective and objective assessments allows inference into the site of the lesion and progression of disease. Importantly, diagnosis and treatment of SWCD can optimize management of neurologic diseases.

The impact of neurologic disorders on SWCD is diverse as can be measured using various methods. Available tools not only provide objective assessments of nighttime sleep but also can provide a long-term view of circadian activity patterns through actigraphy or wearable devices. Moreover, objective daytime testing can measure diurnal symptoms that may result from SWCD. Finally, new technologies may potentially facilitate future long-term monitoring of chronic neurologic patients while retaining a high resolution of recording fidelity, thereby allowing optimization of clinical management and monitoring of treatment efficacy.

DISCLOSURE

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