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REVIEW ARTICLE

The dynamics of cyclic-periodic phenomena during non-rapid and rapid eye movement sleep

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Summary

Sleep is a complex physiological state characterized by distinct stages, each exhibiting unique electroencephalographic patterns and physiological phenomena. Sleep research has unveiled the presence of intricate cyclic-periodic phenomena during both non-rapid eye movement and rapid eye movement sleep stages. These phenomena encompass a spectrum of rhythmic oscillations and periodic events, including cyclic alternating pattern, periodic leg movements during sleep, respiratory-related events such as apneas, and heart rate variability. This narrative review synthesizes empirical findings and theoretical frameworks to elucidate the dynamics, interplay and implications of cyclic-periodic phenomena within the context of sleep physiology. Furthermore, it invokes the clinical relevance of these phenomena in the diagnosis and management of sleep disorders.

KEYWORDS
biomarkers, cyclic alternating pattern, cyclic-periodic phenomena, heart rate variability, neurophysiology, periodic leg movements during sleep, respiratory-related events, sleep disorders, sleep physiology

1 | INTRODUCTION

Sleep architecture, the intricate organization of sleep stages and their temporal progression throughout the night, is characterized by cyclic alternations between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages. Each of these stages is distinguished by unique electroencephalographic (EEG) patterns, neural activity and physiological processes (Troester et al., 2023). Traditionally, NREM sleep has been perceived as a period of relative quiescence, characterized by reduced arousal thresholds and slower brainwave activity compared with wakefulness. Conversely, REM sleep is associated with heightened brain activity, vivid dreaming and rapid eye movements (Sullivan et al., 2022).

However, sleep research has revealed the presence of intricate cyclic-periodic phenomena occurring within these apparently quiescent sleep stages. These phenomena, which encompass a spectrum of rhythmic oscillations and periodic variations, defy the simplistic view of sleep as a passive state devoid of dynamic activity. Instead, they underscore the dynamic interplay between neural circuits, physiological systems and environmental influences that orchestrate the complexities of sleep regulation.

Among the notable cyclic-periodic phenomena observed during sleep are cyclic alternating pattern (CAP; Parrino et al., 2012), periodic leg movements during sleep (PLMS; Ferri et al., 2016), and respiratory events (Roberts et al., 2022; Waters & Mehra, 2019). These phenomena manifest as rhythmic fluctuations in neural activity, motor behaviour and respiratory patterns, exhibiting distinct periodicities and temporal dynamics. CAP, for instance, comprises alternating phases of EEG arousal and quiescence, reflecting the cyclic modulation of cortical arousal during NREM sleep. PLMS, on the other hand, involve repetitive contractions of leg muscles, often accompanied by cortical arousals and disruptions in sleep continuity. Respiratory events encompass cyclic variations in breathing patterns, including apneas and hypopneas, which arise from the interplay between central respiratory drive, airway patency and ventilatory control mechanisms.

The manifestation of these cyclic-periodic phenomena during sleep underscores the intricate dynamics of sleep regulation, which involve the coordination of multiple physiological processes across various brain regions and neural networks. These phenomena are not isolated events but rather integral components of the sleep architecture, reflecting the adaptive responses of the central nervous system to internal and external stimuli, sometimes referred to as sleep "microstructure", as opposed to sleep stages or "macrostructure".

This narrative review aims to provide an exploration of these cyclic-periodic phenomena, elucidating their manifestation, underlying mechanisms and implications for sleep physiology. By synthesizing empirical findings from diverse research domains, including neuroscience, sleep medicine and computational modelling, this review seeks to offer a comprehensive understanding of the dynamic interplay between neural oscillations, motor behaviour and respiratory dynamics during sleep. Additionally, this review will examine the clinical implications of these phenomena for the diagnosis, management and treatment of sleep disorders, highlighting their potential utility as biomarkers of sleep quality, arousal thresholds and neurophysiological functioning.

In summary, the elucidation of cyclic-periodic phenomena within the sleep architecture, and their difference between NREM and REM sleep, represents a paradigm shift in our understanding of sleep dynamics. By unravelling the complexities of these phenomena, this review aims to contribute to the broader discourse on sleep physiology and neurobiology, possibly inspirating future research endeavours aimed at deciphering the mysteries of sleep regulation and its implications for human health and well-being.

1.1 | Cyclic alternating pattern

The CAP stands out as a notable and recurrent phenomenon discernible especially during NREM sleep, which is characterized by its rhythmic fluctuations in both EEG amplitude and frequency. This cyclic pattern, observed through rigorous sleep monitoring and analysis, unfolds as a dynamic interplay between distinctive phases denoted as phases A and B, each characterized by its unique spectral content and neurophysiological signatures (Ferri, Bruni, et al., 2005; Parrino et al., 2012).

The intricate nature of CAP has been meticulously assessed through systematic research endeavours employing advanced analytical techniques and classification methodologies (Bruni et al., 2009; Ferri, Huber, et al., 2008; Ferri, Rundo, et al., 2007, Ferri, Rundo, et al., 2008; Nasi et al., 2012; Ujma et al., 2018). Through meticulous analysis and classification methodologies, researchers have discerned various subtypes of CAP distinguished by complex spectral features, underscoring the relevance of these patterns in elucidating the underlying mechanisms governing sleep architecture and arousal mechanisms. This comprehensive categorization not only deepens our understanding of the complexities of sleep dynamics but also provides invaluable insights into the neurophysiological underpinnings of CAP.

Moreover, mathematical modelling has emerged as a pivotal tool in further elucidating the periodicity and dynamic characteristics of CAP events. By leveraging sophisticated mathematical algorithms and computational simulations, researchers have been able to unravel the intricate temporal dynamics of CAP, shedding light on their pivotal role in orchestrating sleep regulation and homeostasis (Ferri et al., 2012; Hartmann & Baumert, 2019; Mariani et al., 2011). These mathematical models not only provide quantitative insights into the frequency and duration of CAP cycles, but also offer a deeper understanding of the underlying physiological mechanisms driving these cyclic patterns.

Very interestingly, CAP is practically absent during normal REM sleep during which only isolated and non-periodic arousals can be observed (Parrino et al., 2012; Figure 1). This seems to indicate that during REM sleep the synchronization of the complex neural network supporting CAP slow-wave oscillations (Ferri, Bruni, et al., 2005; Ferri, Rundo, et al., 2005) is not possible. This is further supported by the common observation that when sleep apnea episodes tend to occur during REM sleep, such as in the so-called REM-related obstructive sleep apnea (Rishi & Rishi, 2021), they are associated to CAP almost exclusively composed of fast-wave containing arousals (CAP A3 subtypes; Figure 2).

Thus, the elucidation of CAP dynamics has profound implications for our understanding of sleep physiology and its regulation. By unravelling the intricate interplay between neural oscillations, cortical arousal and sleep architecture, CAP provides a unique window into the complex orchestration of sleep–wake transitions and arousal mechanisms. This deeper understanding of CAP not only enriches our theoretical framework of sleep regulation but also holds promise for the development of novel diagnostic and therapeutic interventions targeting sleep-related disorders aiming at regulating sleep instability, as reflected by CAP.

In summary, 40 years after its discovery (Terzano et al., 1985), the exploration of CAP still represents a pivotal frontier in sleep research, offering profound insights into the intricate dynamics of sleep architecture and neurophysiological functioning.

1.2 | Periodic leg movements during sleep

Periodic leg movements during sleep represent a conspicuous and recurrent phenomenon observed throughout the sleep cycle, predominantly manifesting during the NREM stages (Figure 3). These movements entail rhythmic contractions of the leg muscles. The hallmark of PLMS lies in their periodic nature, characterized by repetitive and stereotypical leg movements occurring at regular intervals

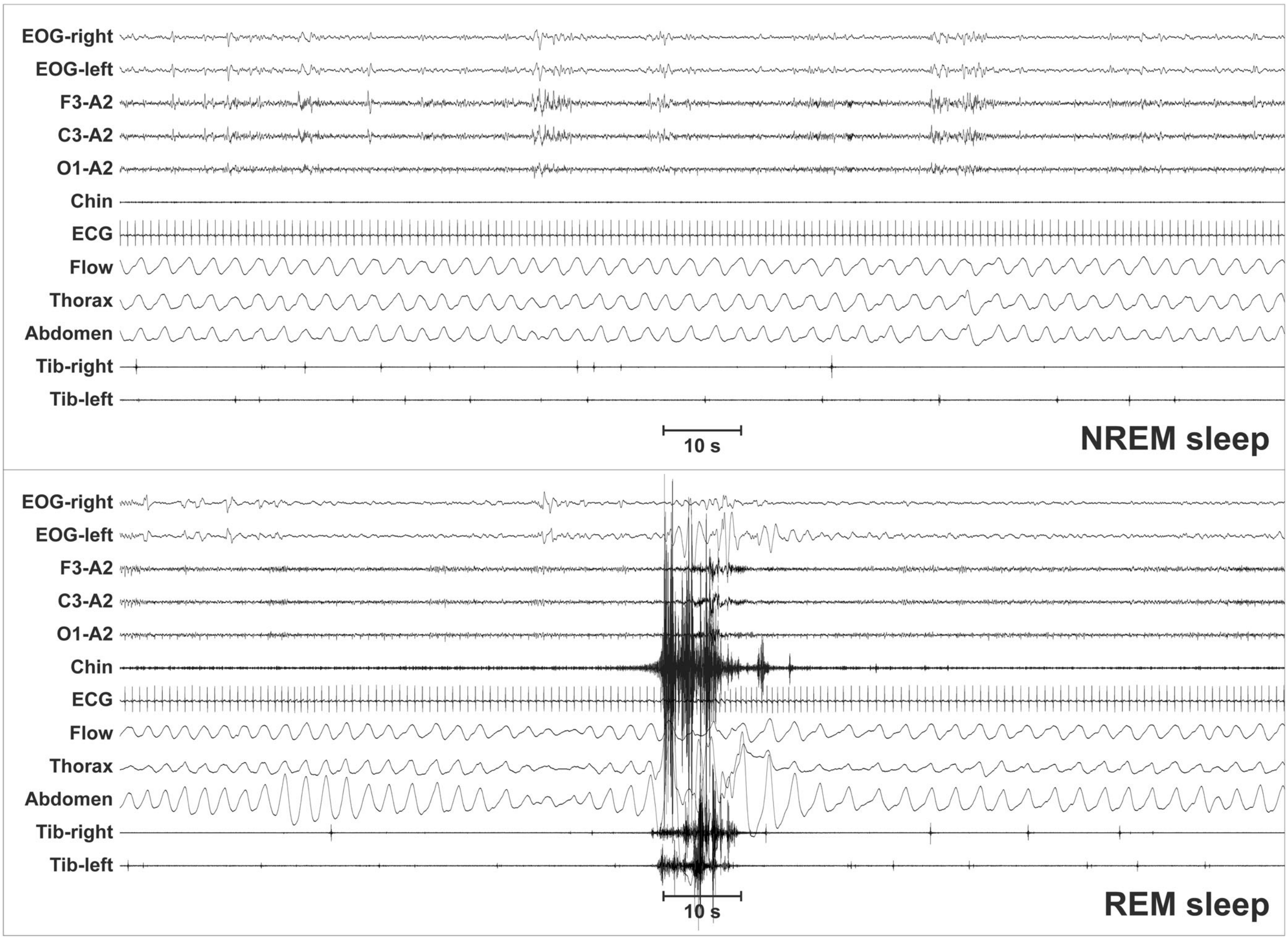

FIGURE 1 Top panel: polysomnographic recording showing a non-rapid eye movement (NREM) sleep period with cyclic alternating pattern (CAP). Bottom panel: polysomnographic recording showing a rapid eye movement (REM) sleep period with a somewhat stable electroencephalographic (EEG) activity interrupted by a large movement involving both tibialis anterior muscles and chin.

during sleep (Ferri et al., 2016). These movements, though seemingly innocuous, often precipitate cortical arousal and transient disruptions in sleep continuity, thereby impinging upon overall sleep quality and the restorative function of sleep (Congiu et al., 2018; Ferri et al., 2017; Figorilli et al., 2017).

The temporal dynamics of PLMS exhibit discernible periodicities and temporal rhythms, reflecting the orchestrated interaction between neural circuits involved in motor control and the regulatory mechanisms governing sleep–wake transitions. The periodic nature of PLMS underscores their integral role in shaping the dynamics of sleep architecture and neurophysiological functioning (Ferri, 2012).

While PLMS may be considered a normal variant in some individuals, their excessive manifestation has garnered attention as a potential marker of underlying sleep disorders, notably restless legs syndrome and periodic limb movement disorder (American Academy of Sleep Medicine, 2023). In these conditions, PLMS are characterized by heightened frequency, intensity and persistence, culminating in significant disruptions in sleep continuity and quality of life.

By quantifying the prevalence and severity of PLMS across different age groups, sexes and clinical cohorts, researchers have sought to delineate the complexity of PLMS pathology and its impact on sleep quality and daytime functioning (Ferri et al., 2018; Ferri et al., 2020; Ferri et al., 2009). Furthermore, advances in diagnostic modalities, including polysomnography and actigraphy, have facilitated the accurate detection and characterization of PLMS, enabling targeted interventions and personalized treatment approaches for individuals affected by PLMS-related sleep disturbances.

Periodic leg movements during sleep predominantly occur during the first hours of sleep (Ferri, 2012; Ferri, Zucconi, Manconi, Bruni, et al., 2006; Ferri, Zucconi, Manconi, Plazzi, et al., 2006), when NREM sleep is predominant, and gradually decrease throughout the night as REM sleep tends to increase. However, not only do PLMS decrease in number, but the overall leg movement activity during sleep shows decreased periodicity in both normal controls and patients (Ferri et al., 2009; Manconi et al., 2007; Figure 3). This, similar to what is observed with the CAP phenomenon, supports the notion that a preserved capability of synchronization of neural

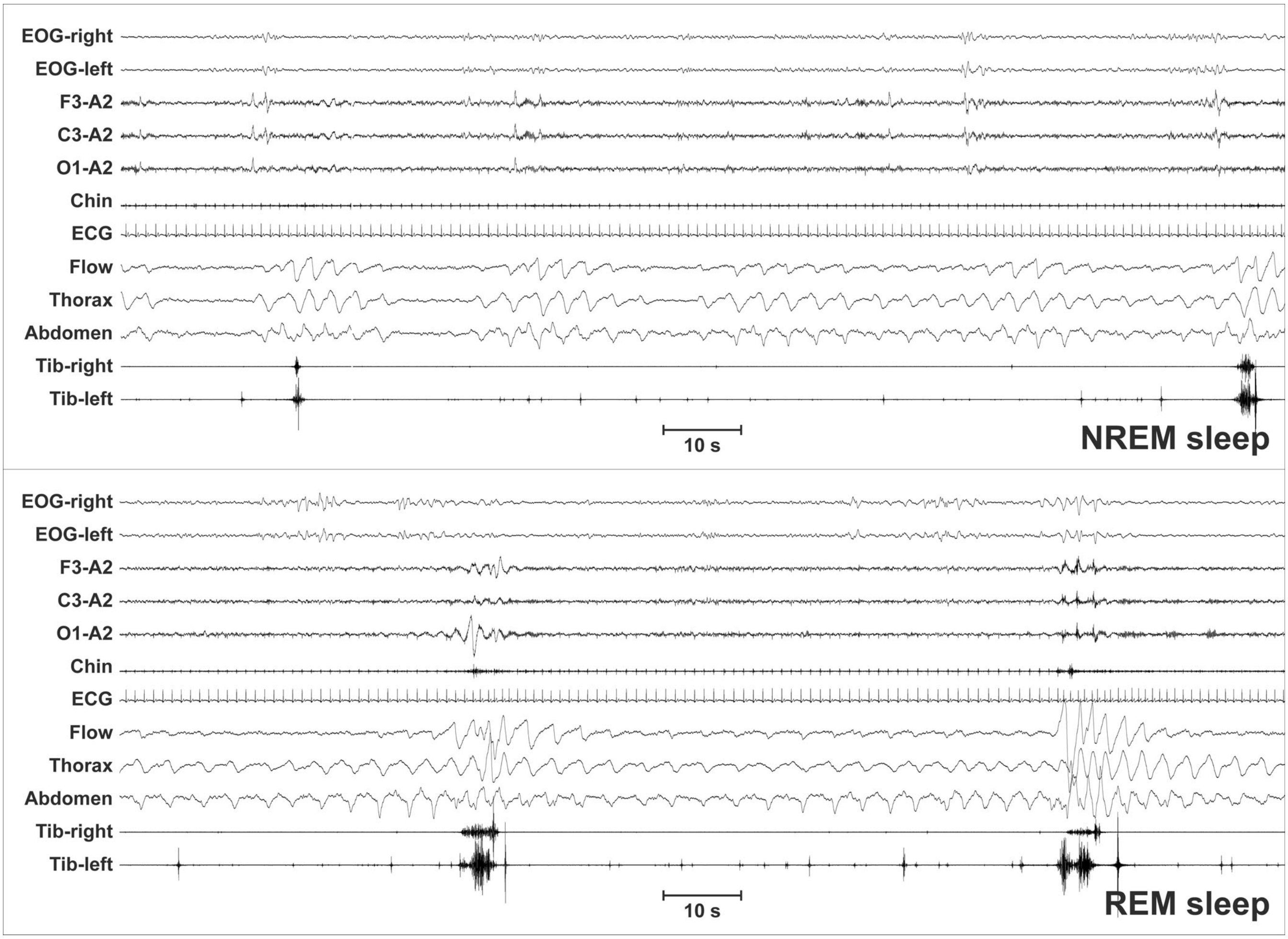

FIGURE 2 Top panel: polysomnographic recording showing a non-rapid eye movement (NREM) sleep period with a sequence of respiratory events associated with cyclic alternating pattern (CAP). Bottom panel: polysomnographic recording showing a rapid eye movement (REM) sleep period with a less regular sequence of apnea events (with a longer period and associated to arousals and leg movements).

circuits is needed for the occurrence of cyclic phenomena, even during REM sleep, which is notoriously inhibited during this stage. The pronounced tendency of PLMS to synchronize with the A phase of CAP (Ferri, 2006; Parrino et al., 1996; Zucconi et al., 2006), additionally supported by the similarity of their time structure (Ferri, Bruni, Miano, Plazzi, et al., 2006; Ferri, Zucconi, Manconi, Plazzi, et al., 2006), indicates that this synchronization is a general phenomenon involving central cortical and subcortical circuits as well as peripheral structures.

In summary, PLMS represent a captivating window into the intricate interplay between motor activity and sleep architecture. While serving as a normal physiological variant in some individuals, the excessive manifestation of PLMS poses significant clinical implications, necessitating comprehensive evaluation and targeted interventions in affected individuals. By unravelling the complex dynamics of PLMS and their impact on sleep health, researchers aim to pave the way for innovative diagnostic and therapeutic strategies tailored to address the multifaceted challenges posed by PLMS-related sleep disorders.

1.3 | Respiratory-related events

Respiratory-related events during sleep, comprising apneas, hypopneas and cyclic variations in breathing patterns, represent a significant category of cyclic-periodic phenomena intricately woven into the tapestry of sleep architecture. These events unfold as disruptive episodes characterized by fluctuations in respiratory airflow and gas exchange, disrupting the regular course of sleep. Concurrently, they often precipitate alterations in EEG activity and perturbations in sleep architecture, reflecting the intricate interplay between respiratory physiology and neural dynamics during sleep (Gnoni et al., 2021; Guilleminault et al., 2007; Terzano et al., 1996).

The duration of an individual apnea or hypopnea event during NREM sleep may vary, but is often shorter on average compared with REM sleep (Oksenberg & Leppanen, 2023). The muscle atonia characteristic of REM sleep can lead to more sustained periods of airway obstruction and respiratory pauses, potentially ranging from several seconds to over a minute or more. These longer periods of airway obstruction in REM sleep may contribute to more significant

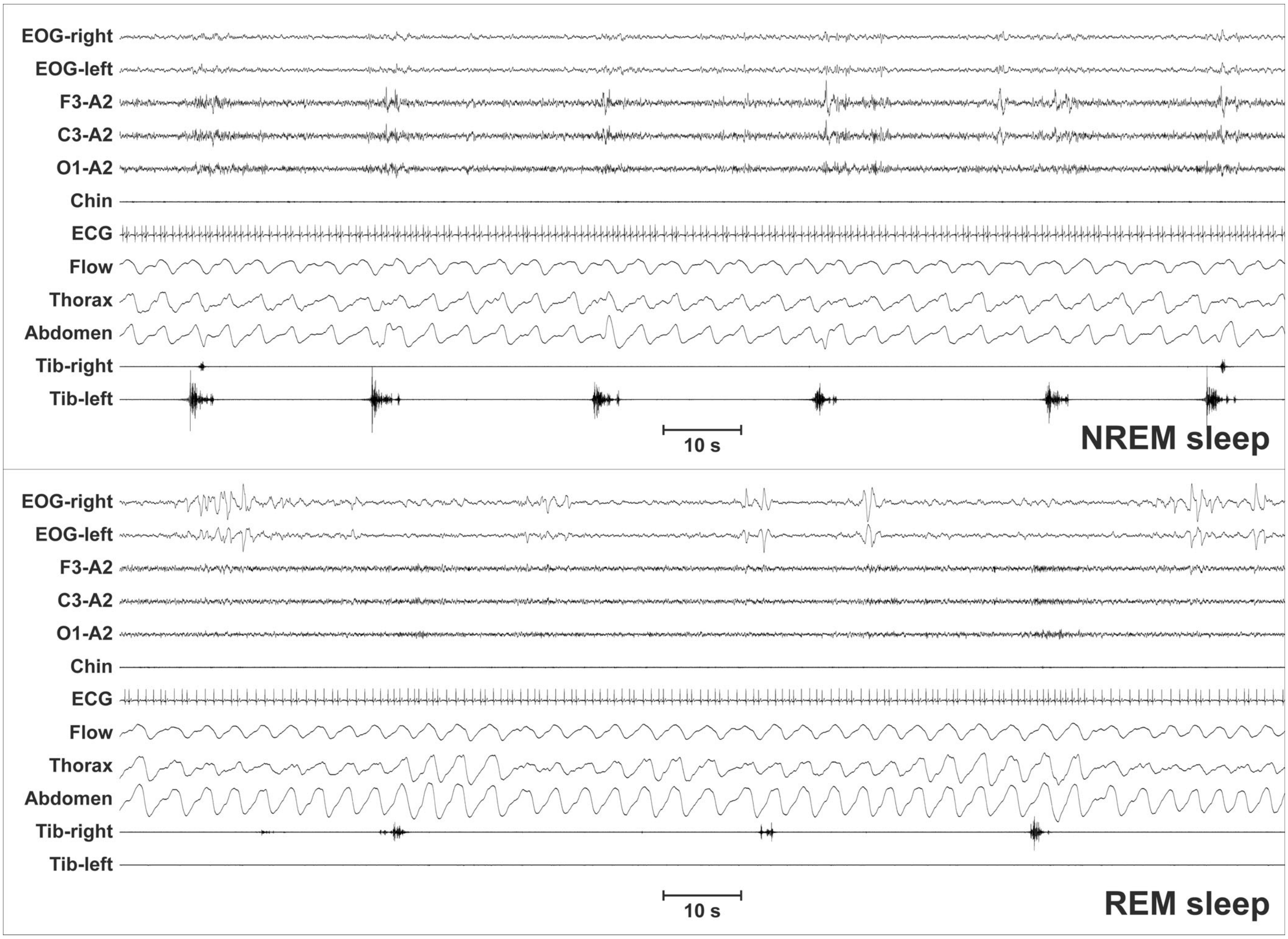

FIGURE 3 Top panel: polysomnographic recording showing a non-rapid eye movement (NREM) sleep period with periodic leg movements during sleep (PLMS) associated with cyclic alternating pattern (CAP). Bottom panel: polysomnographic recording showing a rapid eye movement (REM) sleep period with a less regular sequence of PLMS (with a longer period).

oxygen desaturation and arousal responses than during deep sleep, as the body attempts to restore normal breathing (Leppanen et al., 2018).

These differences in duration are clearly reflected by the respiratory-related leg movements during sleep that, although they can show a periodic course when they are not associated to respiratory events, when are they tend to show a slightly longer typical period (Manconi et al., 2014). This can be interpreted as an effect of the strong drive by the respiratory events able to capture and integrate in their own rhythm that of leg movements; this further confirms the synchronization phenomenon described above encompassing PLMS and CAP and that also involves respiratory events. Finally, not only obstructive events may be involved but also central periodic breathing, such as Cheyne–Stokes respiration (Manconi, Vitale, et al., 2008).

In summary, respiratory-related events represent a pivotal aspect of sleep physiology, intricately intertwined with other cyclic-periodic phenomena in shaping the dynamics of sleep architecture and arousal mechanisms.

1.4 | Heart rate variability

Heart rate variability (HRV) is a marker of autonomic nervous system activity, and reflects the balance between sympathetic and parasympathetic nervous system activity (Task Force of the European Society of Society of Pacing and Electrophysiology, 1996). Physiologically, the patterns of HRV differ between NREM and REM sleep stages (Cajochen et al., 1994). During NREM sleep, HRV tends to be lower compared with wakefulness and REM sleep. The autonomic nervous system is relatively balanced during NREM sleep, with a slight predominance of parasympathetic activity, and reflects a more stable and less dynamic autonomic state, characterized by slower fluctuations in heart rate intervals. This period is typically associated with reduced sympathetic nervous system activity.

During REM sleep, HRV is generally higher compared with NREM sleep and may approach levels observed during wakefulness (Scholz et al., 1997). REM sleep is characterized by increased sympathetic nervous system activity and decreased parasympathetic activity, leading to more dynamic fluctuations in heart rate intervals. The transitions between REM sleep and wakefulness are associated with increased sympathetic activation, which can result in abrupt changes in heart rate and increased HRV. This period is also associated with increased physiological arousal and activity, including changes in respiratory rate and blood pressure, which contribute to the higher HRV observed during REM sleep.

It is important to note that all physiological and pathological phenomena connected to CAP, PLMS and apnea described above are associated with changes in HRV that reflect their different periodicity characteristics during the different sleep stages (Ferini-Strambi et al., 2000; Ferri et al., 2000; Ferri et al., 2021; Ferri, Zucconi, et al., 2007; Penzel et al., 2003; Shiomi et al., 1996) and play an important role in the complex synchronization phenomenon reported above.

2 | CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

A comprehensive grasp of the dynamics and ramifications associated with cyclic-periodic phenomena within sleep physiology holds profound clinical significance in the realm of diagnosing and managing sleep disorders. These phenomena, acting as pivotal biomarkers, offer a window into the intricate landscape of sleep quality, arousal thresholds and neurophysiological functioning, thus furnishing clinicians with invaluable insights into the underlying pathophysiology of various sleep-related conditions.

Cyclic-periodic phenomena, ranging from CAP and PLMS to respiratory-related events and their differential distribution within NREM and REM sleep, serve as sensitive indicators of sleep health and disturbances, offering clinicians a wealth of information to guide diagnostic assessments and therapeutic interventions. By meticulously analysing the temporal dynamics and interplay among these phenomena, clinicians can gain deeper insights into the underlying mechanisms contributing to sleep disorders, facilitating more accurate diagnoses and tailored treatment strategies.

Moreover, it is our opinion that these cyclic-periodic phenomena hold immense potential as prognostic markers, enabling clinicians to predict disease progression, treatment response or long-term outcomes in patients with sleep disorders. By monitoring the fluctuations and alterations in these phenomena over time, clinicians will possibly assess the efficacy of therapeutic interventions, optimize treatment regimens and personalize patient care to maximize therapeutic outcomes (Manconi, Ferri, et al., 2008; Thomas, 2002). However, this needs to be supported by specific future studies.

As the field of sleep medicine continues to evolve, future research endeavours are poised to leverage advanced neuroimaging techniques, computational modelling and personalized medicine approaches to unravel the complexities of cyclic-periodic phenomena and their clinical implications. By harnessing the power of cutting-edge technologies and interdisciplinary collaborations, researchers need to elucidate the underlying neurophysiological mechanisms driving these phenomena, paving the way for innovative diagnostic tools and precision medicine interventions tailored to individual patient needs.

Furthermore, by exploring the intricate interplay between cyclic-periodic phenomena and their impact on sleep physiology, clinicians might develop more targeted and effective therapeutic interventions, ultimately enhancing patient outcomes and quality of life. By embracing a multidisciplinary approach and integrating findings from basic science research with clinical practice, clinicians can unlock new insights into the pathogenesis of sleep disorders and usher in a new era of personalized medicine in the field of sleep medicine.

3 | CONCLUSION

In conclusion, cyclic-periodic phenomena play a crucial role in shaping the dynamics of sleep architecture and neurophysiological functioning. Through systematic analysis and theoretical frameworks, researchers have elucidated the manifestation, interplay and clinical implications of these phenomena within the context of sleep physiology. A comprehensive understanding of cyclic-periodic phenomena holds promise for advancing diagnostic modalities, therapeutic interventions and personalized management strategies for sleep disorders.

AUTHOR CONTRIBUTIONS

Maria P. Mogavero: Writing – review and editing. **Lourdes M. DelRosso:** Writing – review and editing. **Giuseppe Lanza:** Writing – review and editing. **Oliviero Bruni:** Writing – review and editing. **Luigi Ferini Strambi:** Writing – review and editing. **Raffaele Ferri:** Conceptualization; writing – original draft; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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