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The neurophysiologic landscape of the sleep onset: a systematic review

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Background: The sleep onset process is an ill-defined complex process of transition from wakefulness to sleep, characterized by progressive modifications at the subjective, behavioural, cognitive, and physiological levels. To this date, there is no international consensus which could aid a principled characterisation of this process for clinical research purposes. The current review aims to systemise the current knowledge about the underlying mechanisms of the natural heterogeneity of this process.

Methods: In this systematic review, studies investigating the process of the sleep onset from 1970 to 2022 were identified using electronic database searches of PsychINFO, MEDLINE, and Embase.

Results: A total of 139 studies were included; 110 studies in healthy participants and 29 studies in participants with sleep disorders. Overall, there is a limited consensus across a body of research about what distinct biomarkers of the sleep onset constitute. Only sparse data exists on the physiology, neurophysiology and behavioural mechanisms of the sleep onset, with majority of studies concentrating on the non-rapid eye movement stage 2 (NREM 2) as a potentially better defined and a more reliable time point that separates sleep from the wake, on the sleep wake continuum.

Conclusions: The neurophysiologic landscape of sleep onset bears a complex pattern associated with a multitude of behavioural and physiological markers and remains poorly understood. The methodological variation and a heterogenous definition of the wake-sleep transition in various studies to date is understandable, given that sleep onset is a process that has fluctuating and ill-defined boundaries. Nonetheless, the principled characterisation of the sleep onset process is needed which will allow for a greater conceptualisation of the mechanisms underlying this process, further influencing the efficacy of current treatments for sleep disorders.

Keywords: Sleep onset; sleep onset period (SOP); neurophysiology

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Introduction

The human brain operates most optimally in meta-states near the critical point of a phase transition between two fundamental and opposing needs: to maintain sensory reactivity to the environment, while promoting recovery and memory consolidation (1-4). While these activities' criticality during awake resting-state has been largely documented, what happens during the course of sleep, and even more pertinently, what happens during sleep onset, is still a matter of discussion. Seminal new work (5-7) suggests that distinct phasic sleep oscillations and microarousals may play a central role. They may act as 'gating and tailoring' power-engines of the sleep-wake-continuum that utilise the brain's arousal circuitry and salience networks and thus represent pivotal adaptive guardians of a restorative sleep (1,8-25).

The latter is relevant because, without sleep or with poor sleep, brain's resilience is decreased, we become tired, irritable, and our brain functions less efficiently (26,27). As restorative sleep underpins physical and mental functioning across the lifespan, understanding which distinct neurophysiologic processes ensure its undeterred progression, and which may underlie the very point of sleep onset, has critical implications for our overall health.

Sleep is a complex and dynamic process (28), which, compared to wakefulness, is subjectively perceived as a reduced responsiveness to environmental stimuli generated by a selective gating of the inputs arriving from the external world (12). The thalamocortical connections modulate the susceptibility of the cerebral cortex to all the activating stimuli; during the sleep onset period (SOP) the generators of cortical electrical activity are modified and shift from the production of low amplitude high frequency electroencephalographic (EEG) activity, a typical expression of the activation of the cortical cells, to the production of high amplitude low frequency EEG activity indicating a widespread synchronization of the cortical cells (12,29).

Traditional view of sleep as a discrete and distinct state from wakefulness has been more recently challenged, and a co-existence of sleep and wake patterns in different cortical and subcortical regions demonstrated (30-32). In this context, it is increasingly clear that the neurophysiologic landscape of a complex and progressive transitory process between wakefulness and sleep may require an authoritative, multimodal parameters definition. Perhaps unsurprisingly, to date, the SOP parameters and biomarkers of non rapid eye movement sleep stage 1 (NREM 1) remain relatively vague and interchangeable across the body of published work (33,34). However, understanding how the sleep onset arises from sleep's basic physiological components has fundamental, and potentially wide reaching translational clinical implications.

Traditionally, neurophysiologic investigations have utilised a consensus-based classification of sleep onset, divided into specific sleep stages (34,35), broadly based on characteristic physiologic patterns as a function of vigilance. Diverse interpretations, however, are often present even in standardised manuals for sleep scoring, further contributing to further fluidity in findings and interpretation of this borderline landscape. For instance, the internationally recognised standard manual for sleep scoring (35) marks the beginning of sleep with the onset of NREM 1, whilst the guidelines for the Multiple Sleep Latency Test (36) in clinical settings guide the scorer to assign one minute of continuous stage NREM 1 to a state of sleepiness. Additional confusion arises when in some studies the first occurrence of a K-complex or sleep spindles, otherwise recognised markers of NREM 2 sleep stage (37,38), are utilised as a marker of the sleep onset.

Nonetheless, several groups have tried to describe more specific spatiotemporal biomarkers of SOP (39). For instance, there have been attempts to develop a specific SO scoring system that subdivides standard scoring stages W, NREM 1 and NREM 2 into nine EEG-based sequential stages (40). Moreover, in a recent study that implemented

Highlight box

Key findings

- Distinct electrophysiological changes across the sleep initiation are defined, including the drop in alpha activity, and in association with the disappearance of slow eye movements prior to sleep onset.
- This process is accompanied by complex cardiovascular, respiratory, and thermoregulatory modifications.

What is known and what is new?

- Sleep onset is a complex and dynamic process, which remains poorly understood.
- The body of research concerning the sleep onset varies not only in wake-sleep state definitions, but also in time referencing, sleep latency, and time interval stipulations.

What is the implication, and what should change now?

- There is an urgent need for an international consensus and characterisation of the sleep onset criteria that will allow for a greater conceptualisation of the mechanisms under-lying this process, further influencing the efficacy of current treatments for sleep disorders.

Table 1 The search strategy and exclusion/inclusion criteria

Items	Specifications
Database	PsychInfo, EMBASE (Ovid), MEDLINE (Ovid)
Search strategy	"sleep* onset" OR "sleep* initiation" OR "wake/sleep transition*")] AND [detect* or assess* or measure* or estimate*
Limits	Year: 1970–2022; species: human; age: >18 years; only in English

*, used with distinctive word stems allows variations of a term with less typing to be retrieved.

large-scale functional magnetic resonance imaging (fMRI) recordings (41) an attempt was made to project the traditional stages of wakefulness and NREM sleep onto a probabilistic map of transitions across global network states (41). These temporally-sensitive analyses revealed that, unlike NREM 2, NREM 1 stage does not correspond to any specific clusters of whole-brain network states, in part owing to its vaguely defined parameters associated with the highest inter-rater scoring discrepancies (41).

In this background, we set out to summarize and analyse the findings of a current body of published work on the SOP, and its abnormalities, across multimodal approaches and methodologies in healthy people and in patients with major sleep disorders (Tables S1,S2). This study was done with the major goal of fostering a more comprehensive understanding of the broad range of paradoxical phenomena that may characterise the very point of the sleep onset transition on the sleep wake continuum. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-325/rc).

Methods

Literature search strategy

The literature search included original studies of human subjects published between 1970–2022. Relevant studies were identified using electronic database searches of PsychINFO, MEDLINE and EMBASE using the following search terms: ["sleep* onset" OR "sleep* initiation" OR "wake/sleep transition*")] AND [detect* or assess* or measure* or estimate*] (*Table 1*). The relevance of the article was initially verified by title and abstract review, subsequently by a further review of each manuscript to ensure they met the inclusion criteria.

Inclusion and exclusion criteria

Full texts of all eligible manuscripts were obtained, and duplicates removed. The following exclusion criteria were applied: participants under 18, non-human studies, interventional studies, studies not in English language, follow-up studies or case reports, studies not published by a peer-reviewed scientific journal, and review articles. All included studies were required to have measured SOP (*Table 2*).

Data extraction and critical appraisal

Two investigators (NB, JR) independently reviewed the abstracts and titles to assess their eligibility. In circumstances where an abstract posed ambiguity in relation to its eligibility, full-text review of the paper was performed. Additional papers were also identified through grey (manual) searches. There were nine disagreements between the reviewers, which were resolved by consensus. Altogether 139 studies of the SOP that fitted our inclusion and exclusion criteria were identified (*Figure 1*, *Tables 1*,*2*). The SOP was investigated with range of methodologies that therefore demonstrate distinct aspect of this dynamic process (see *Figure 2*). Overall, 65 studies the SOP were explored via electrophysiologic, 16 via neuroimaging investigations, 11 via ocular activity investigations, 26 via cardiovascular and respiratory investigations, further nine studies included thermoregulatory investigations, and finally 12 studies also included behavioural measurements (*Figure 3*).

Quality assessment

The quality of evidence and risk of bias were assessed using the Effective Public Health Practice Project (EPHPP) criteria (43). The ratings were subsequently aggregated into a global rating across the three scales of weak, moderate and strong (Table S3). Studies were rated weak due to cross-sectional nature of the study designs. Whilst most studies controlled for at least 80% of relevant confounding variables, moderate ratings were assigned to studies that did not describe blinding. There was no association between global study quality assessment ratings and positivity of findings.

Results

Neurophysiology

The specific spatiotemporal evolution of distinct

Table 2 Search criteria

	Exclusion criteria	Inclusion criteria
Manuscript characteristics	• Interventional studies • studies not in English language • Studies not published by a peer-reviewed scientific journal, conference abstracts and proceedings, unpublished data, preprints, government publications, scientific or case reports, dissertations, and theses, review articles and follow-up studies • Guidelines, statements, and comments • No measurement of the SOP • No reliable and scientifically valid methods of sleep measurements	• Original and peer reviewed research articles • Observational, descriptive, longitudinal, retrospective, cross-sectional, cohort, studies that investigate SOP • Methodologies and samples were well-described (e.g., scoring criteria, modality and measurement of the exact point of SO)
Population's characteristics	• Participants under 18, infants, paediatric • Animal studies	• Healthy controls >18 years of age • Individuals with sleep disorders • Diagnoses made in accordance with DSM-IV, clinical review and laboratory examinations to rule out other medical and psychiatric disorders [Spitzer *et al.*, 1992 (42)]
Study design	RCT; CCT	Appropriate and clinically valid designs to measure the SOP

SO, sleep-onset; SOP, sleep-onset period; RCT, randomized controlled trial; CCT, controlled clinical trial.

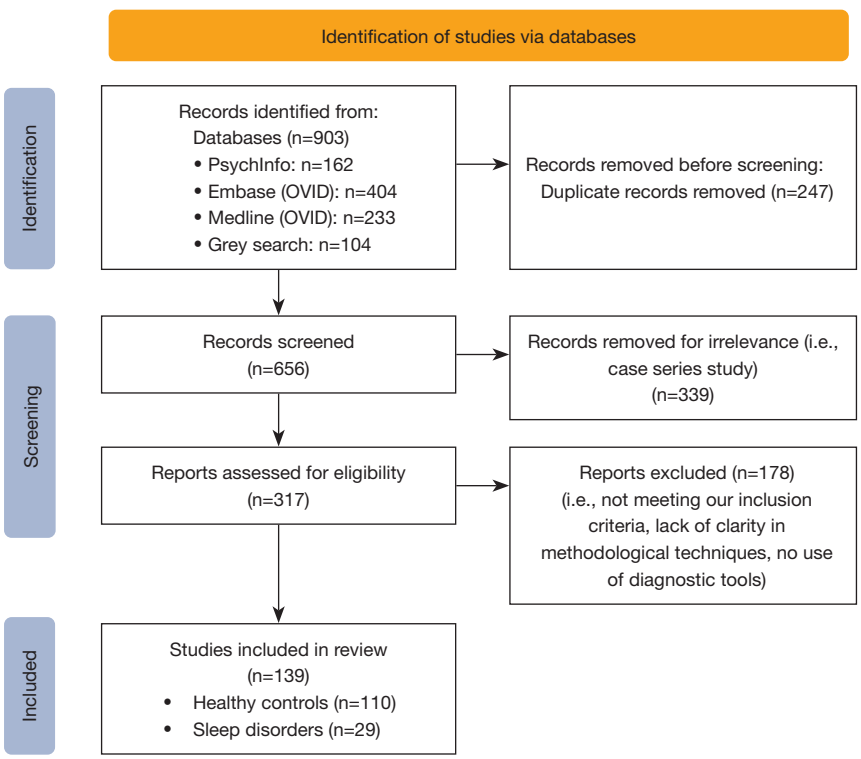

Figure 1 PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

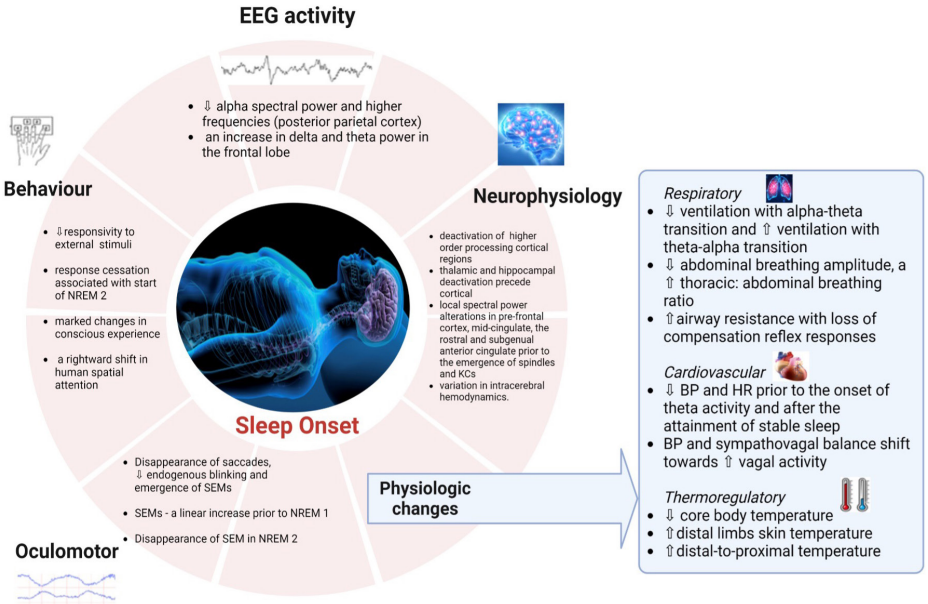

Figure 2 Schematic presentation of physiologic processes during the sleep-onset. EEG, electroencephalographic; BP, blood pressure; HR, heart rate; KC, K-complex; NREM, non-rapid eye movement; SEM, slow eye movement; SO, sleep onset; RT, reaction time.

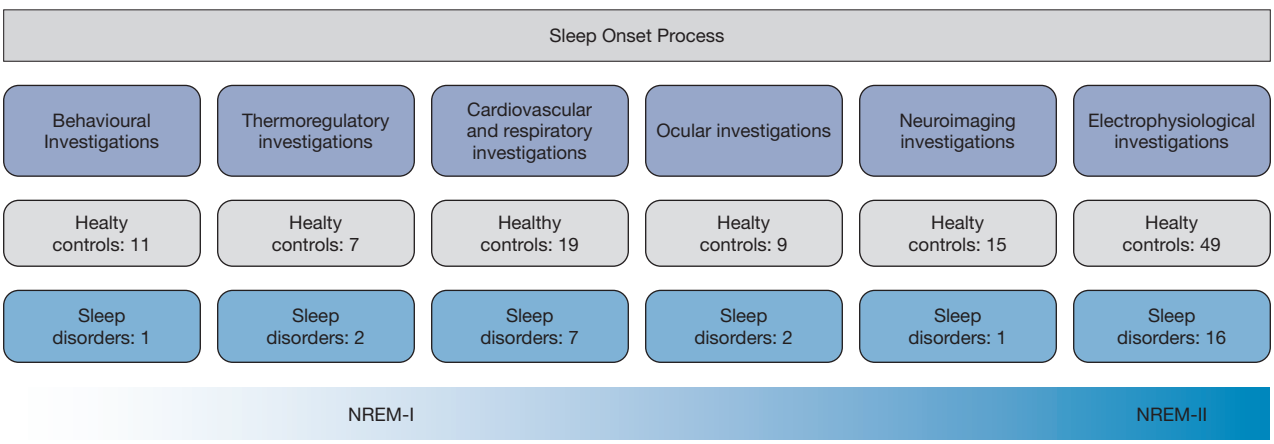

Figure 3 The number of studies identified for Sleep Onset Processes in healthy controls and individuals with sleep disorders. NREM, non-rapid eye movement sleep.

brain rhythms' activity during the sleep initiation has been demonstrated, with overall transition to slower brain rhythms frequencies bands (e.g., from alpha to predominantly theta, delta bands), of higher amplitudes. For instance, a rise of the delta activity (<4 Hz), a biomarker of sleep pressure, has been demonstrated to occur with frontocentral prevalence, just prior to the SOP (44-52). Subsequent to the sleep onset, the generalised enhancement of delta activity has been also shown to occur in the pre-frontal cortex and postcentral gyrus (48,53). Some authors proposed classification of SOP slow waves (and delta activity) into two types representing a "bottom-up" and a "horizontal" cortico-cortical synchronisation process (49). It has been suggested that early slow waves may originate from the sensorimotor and the posteromedial parietal cortex, in contrast to those occurring during late sleep onset, which are characterised with smaller amplitudes and slopes, and that involve circumscribed parts of the cortex, with more evenly distributed origins (49). Overall, there is a progressive decrease in antero-posterior synchrony of

cortical activity within the delta range during SOP (54-56).

In regard to the theta band, a global increase in spectral power of theta activity (5–7 Hz) occurs with an occipital peak, where it replaces the alpha oscillations (38,46-50). This transition is initially observed in precuneus in the superior parietal lobe, followed by the cuneus in the occipital lobe (53). Its spatiotemporal pattern mirrors that observed in the delta band, exhibiting an early frontocentral prevalence (47), however, with the maximum power in the occipital regions following SO (47). Theta modifications in connectivity measures during SO is also in close correspondence with the dynamics described for delta band. The studies consistently demonstrate a decreased antero-posterior coupling (54,56), and the switch to an anterior-to-posterior direction of the information flow (54). The posterior cingulate cortex has been suggested to play a role as a central hub of delta and theta activity that leads to the process of decoupling of the default mode network at SO (57).

Conversely, at SO, alpha band (8–12 Hz) displays two distinct spatiotemporal patterns of activity. Prior to the sleep onset, there appears to be a gradual reduction of the occipital alpha, followed by a post sleep onset increase in frontocentral dominance (45-48,50,52,58,59), with highest values recorded in the precuneus (48,53). At the start of the NREM 2 sleep stage, an increased coherence and effective connectivity along the antero-posterior gradient in the upper alpha sub-band (11–12 Hz) has also been noted (50,54,60), with posterior cingulate cortex being reported as a major driver of the transition (57).

The sigma oscillatory activity (~12–15 Hz) is the predominant rhythm that increases with the beginning of NREM 2 stage of sleep (47). Here, sleep spindles represent one of the important biomarkers of NREM 2 sleep (44), and sigma band maximal increase has been recorded for the centroparietal cortical locations (47), with the parietal lobe and a secondary contribution of the postcentral gyrus, the cuneus, and the lingual gyrus all involved (53). The midcingulate cortex has also been implicated as a fundamental cortical relay hub for spindle synchronisation (57). Early during the sleep onset, spindles appear to be sparse, fast and predominantly local, and in later stages they are progressively slower and more diffuse, widespread and frequent (49).

Only a few studies investigated beta and gamma band's dynamics during the SOP. Overall, a global reduction in both beta (16–24 Hz) (44-49) and gamma (25–40 Hz) power, recognised markers of arousal and motor/cognitive activation, have been observed at SO (49). Beta activity with the most prominent involvement of the parietal and occipital lobes shows a gradual decrease that begins prior to SO and reaches its maximum in temporo-frontal locations (47). It is also noted that cortical activity in beta range does not undergo drastic modifications with respect to connectivity (53) or functional organization of the networks during SOP (61,62). The most salient change appears as an inversion in the direction of the information flow following SO, with beta oscillatory activity propagating from the frontal to the parieto-occipital region (54).

Only several studies investigated distinct electrophysiological properties of SO in patients with sleep disorders (for more details please refer to Table S2). For example, for patients with insomnia, momentary state-switching instabilities were noted using small-epoch scoring, which was otherwise undetected using traditional sleep stages scoring methods (63). Similarly, for patients with insomnia, during the sleep onset, all frequencies below the beta range were shown to have slower rise rates (64-68), with decreased initial drop in alpha power (68,69), and with lower overall delta activity (66,68), possibly indicative of higher cortical arousal. In keeping, higher beta and gamma frontoparietal temporal coupling during waking and NREM 1 was reported in patients with sleep onset insomnia (70). Conversely, in patients with restless legs syndrome, the increased EEG alpha and beta bands were demonstrated, prior and after the sleep onset, albeit smaller than the increases detected in patients with insomnia (71).

Rapid changes across the neurophysiologic landscape of the sleep onset have been shown for patients with narcolepsy (72,73). This was in opposition to findings in patients with idiopathic hypersomnia (73). A number of SOP studies also used event-related potentials (ERP) to investigate the neurophysiology of SO (*Figure 3*).

Notably, using simultaneous intracortical and intrathalamic recordings, it was shown that at the sleep onset the thalamic deactivation precedes that of the cortex by several minutes despite the synchronised reactivation of both structures upon awakening (74). Taken together, all neurophysiologic findings to date suggest that a descent into sleep is achieved through a dynamic set of events, characterized by the progressive involvement of distributed subcortical and cortical structures.

For further in-depth details of all pertinent findings of all multimodal investigations of the SOP in healthy, and in patients with sleep disorders, please refer to Tables S1,S2. Tables S1,S2 similarly list all the strength and limitation of various methodologies that were used.

Neuroimaging findings

Several neuroimaging studies similarly explored spatiotemporal dynamic of SOP (75). Altered thalamocortical functional connectivity (76) has been demonstrated to occur at the sleep onset, with subsequent increased consolidation of both intra- and inter-hemispheric thalamic connectivity (76). Moreover, increased functional connectivity was observed predominantly in thalamic regions that were functionally connected to somatomotor and occipital neocortices (77).

In a recent study that implemented large-scale functional magnetic resonance imaging (fMRI) recordings (41) an attempt was made to project the traditional stages of wakefulness and NREM sleep onto a probabilistic map of transitions across global network states (41). These temporally-sensitive analyses revealed that, unlike NREM 2, NREM 1 stage does not correspond to any specific clusters of whole-brain network states, in part owing to its vaguely defined parameters associated with the highest inter-rater scoring discrepancies (41). Regulation of cerebral blood flow during SOP has also been investigated and a heterogenous pattern in higher order frontoparietal association regions and unimodal occipitotemporal sensory cortices demonstrated (78).

In keeping, functional near-infrared spectroscopy (fNIRS) investigations have demonstrated that at the sleep onset, decreased oxygenated hemoglobin (oxy-Hb), together with cerebral blood volume and with increased deoxygenated hemoglobin (deoxy-Hb), are accompanied by either a decrease or no change in total hemoglobin (t-Hb) (79-82). This transition is accompanied by decreased heart rate and peripheral arterial oxygen saturation (SpO_2) (80).

Nonetheless, in opposition to these findings, when investigations were done by limiting the time-window to the 5 s preceding, and 20 s, following the state change, reductions in both concentration of oxy-Hb and deoxy-Hb were reported to occur during the SOP (83). For further in-depth details of all pertinent findings of all multimodal investigations of the SOP in healthy, and in patients with sleep disorders, please refer to Tables S1,S2. Tables S1,S2 similarly list all the strength and limitation of various methodologies that were used.

Physiologic and behavioural investigations

Over the last several decades, several groups have tried to describe distinct spatiotemporal biomarkers of SOP (39). For instance, there have been attempts to develop a specific SO scoring system that subdivides standard scoring stages W, NREM 1 and NREM 2 into nine EEG-based sequential stages (40).

Thermoregulation

Several studies focused on the sleep onset investigating thermoregulatory changes (*Figure 1*) (84-86), with temperature decline shown to occur, on average, over 60 min prior to the sleep onset (86,87). Interestingly, in patients with sleep maintenance insomnia, a significant positive correlation was reported between the amount of wakefulness within the first hour after initial sleep onset and maximum rate of decline relative to SO, possibly suggesting that the process of sleep initiation may be accomplished at this phase of the temperature cycle (85).

A significant increase in peripheral skin temperature was also shown to contribute to the concomitant decline in core body temperature that precedes sleep initiation (88). Furthermore, selective vasodilation of distal skin regions was reported to be a more powerful predictor of SO, with distal-to-proximal skin temperature gradient demonstrating a stronger correlation with sleep propensity, compared to core body temperature or its rate of change (89). Consistently, the wrist skin temperature was shown to increase on average by 0.6° (Celsius) in 10 min prior to the sleep onset (90).

Respiration

Similarly, several studies demonstrated that the sleep onset is associated with the rise in upper airway resistance (91), a fall in phasic activity of diaphragm, intercostal, and genioglossus muscles, with a subsequent increase (92). Furthermore, a shift from abdominal to a relatively greater thoracic expansion has been shown concomitant with NREM 1 stage (93,94).

Cardiovascular

At the sleep onset, an average fall in heart rate and blood pressure is observed (95,96) with no significant change in respiratory sinus arrhythmia, pre-ejection period, and T-wave amplitude, otherwise detected with the attainment of stable NREM 2 sleep (95). It has been suggested that increased vagal activity is primarily a function of sleep, whilst sympathetic activity likely reflects a circadian influence (95,97,98).

Oculomotor activity

At the sleep onset, significant oculomotor variations

occur, including a disappearance of saccades, a reduction of endogenous blinking, and an appearance of slow eye movements (99). A linear increase in slow eye movement activity has been shown before the beginning of NREM 1 stage (100-103), with a progressive decline during the first minutes of NREM 2 (99-104). Slow eye movement was reported to disappear at the onset of behavioural sleep (101,102).

Using Hori scoring system (40), slow eye movement velocity was shown to be maximal during sustained alpha suppression and delta-theta prominence (105). It has been also suggested that spectral power in the sigma band is the best predictor of slow eye movement variations (103). Positive correlation of delta power with the increase of slow eye movement activity before SO, and association of beta power with the decrease of slow eye movements, were all similarly noted (103). However, adding to the confusion of various findings, the similarity between NREM 1 and REM sleep EEG activity has also been noted historically, with REM sleep called emergent NREM 1 sleep (106). Although phasic REM bursts are usually absent during NREM 1 sleep, there are slow eye movements occurring occasionally prior to the appearance of sleep spindles (106).

Behavioural observations

More recently, marked changes in conscious experience, along with a rightward shift in human spatial attention, all occurring just prior and at the sleep onset have been demonstrated (107). Further respiratory pattern shifts, and performance lapses in reaction time tasks, have also been associated with the sleep onset and NREM 1 sleep. Overall, decreased response rates in reaction time tasks, intermittent response failure in self-generated motor tasks (108,109), respiratory (52) and subjective indices of arousal, have all been shown to be more pronounced between stages of wake and NREM 1, than between NREM 1 and NREM 2 stages (108). In addition, significant changes in amplitude were related to decreased responsivity in behavioural tasks for all late ERP components except P2 (52).

In summary, performance on behavioural tasks show gradually deteriorate with increasing sleepiness. The close agreement of the EEG NREM 2 and the behavioural criteria marked a decline in behavioural responding during the transition from NREM 1 to NREM 2 (110) with the associated cessation of behavioural response by NREM 2 (111). Arguably, the combination of behavioural, physiological and EEG measurements might be taken as suggestive of NREM 2 sleep stage as a cut of point for a true sleep onset, with NREM 1 presenting a diverse landscape of sleep-wake oscillations (108). For further in-depth details of all pertinent findings of all multimodal investigations of the SOP in healthy, and in patients with sleep disorders, please refer to Tables S1,S2. Tables S1,S2 similarly list all the strength and limitation of various methodologies that were used.

Discussion

The phenomenological aspects of neurophysiologic basis of wakeful consciousness, NREM and REM sleep are increasingly investigated, and understood. Conversely, the transition between wakefulness and sleep, the sleep onset process characterized by an abrupt change in consciousness, remains poorly understood (*Figure 2*). Moreover, SOP biomarkers are shown to widely differ across patient groups with sleep disorders.

Over the last several decades sleep-wake transitions have been investigated by with variety of electrophysiological and functional neuroimaging methods. In spite of the major scientific efforts, it is still a matter of debate whether NREM 1 sleep presents a true sleep state, or if it should be considered as a fluctuating metastate between wakefulness and sleep (106). Neurophysiologic investigations demonstrate a continuous transition between wakefulness and NREM 2 sleep, and the EEG features of NREM sleep evolve gradually during this transitional period (106).

Moreover, our findings demonstrate wide variability across studies, not only in wake-sleep state definitions used (*Figure 4*), but also in methodologic approaches, including time referencing, sleep latency definitions, and time interval stipulations. This diverse and unregulated approach to the SOP investigations may lead to omission, or misinterpretation, of the important granularity of the spatiotemporal physiologic SOP biomarkers in health, and in illness.

Furthermore, the arbitrary adoption of epoch lengths during sleep scoring may also contribute to polymorphic reports. For instance, it has been shown that adopting 20-s epoch scoring of the SOP provides a more accurate estimate of the sleep onset, while a 60-s epoch scoring of response cessation may be more indicative of the beginning of a prolonged period of sleep. Arguably, thus, interchangeable use of scoring criteria can also significantly affect the objective sleep latencies scores (113). Similarly, it has been shown that in studies using a five-second epoch Hori classification (40), stable non-responsiveness (i.e., sleep) was only evident a few minutes following the emergence of the first spindles (114). Similar discrepancies are evident

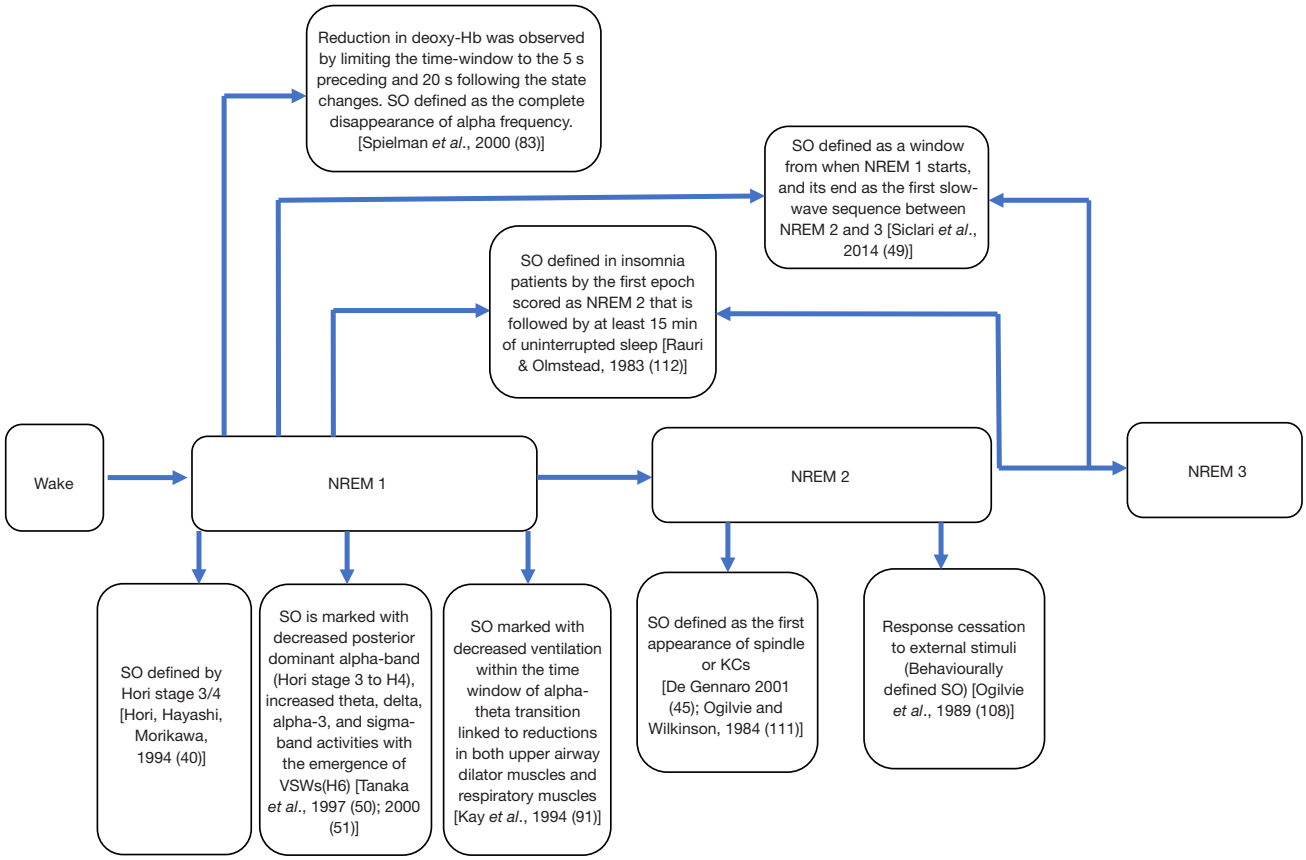

Figure 4 Example of diverse sleep-onset definitions across representative studies (40,45,49,50,51,83,91,108,111,112). KC, K-complex; NREM, non-rapid eye movement sleep; SO, sleep onset; VSW, vertex sharp wave.

in body of neuroimaging investigations and may similarly explain diverse physiologic manifestation reported to occur at the sleep onset (79-82).

Conclusions

In conclusion, our findings demonstrate current limited understanding of the sleep onset, and they highlight widely diverse historical definitions used for its definition. This, along with past technological limitations, has so far hampered an authoritative exploration of the spatiotemporal neurophysiologic and behavioural progression across the landscape of wake-sleep transition.

Thus, there is a recognised need for an international consensus on what constitutes a true sleep onset. A more standardised criteria for the SOP, along the most recent technological developments [e.g., silent MR imaging protocols (115); neurostimulation (116)] promise a new era in sleep research (12,25,117), where we may be for the first time able to explore the wake-sleep borderland as a potential therapeutic target for number of sleep disorders. A more comprehensive insight into the complex process of SO and its associated abnormalities in case of sleep disorders may contribute to understanding of individuals' condition, influencing their clinical outcome which will inevitably lead to more effective treatment strategies and more meaningful clinical care in the future.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Parrino L, Vaudano AE. The resilient brain and the guardians of sleep: New perspectives on old assumptions. Sleep Med Rev 2018;39:98-107.
2. Bak P, Tang C, Wiesenfeld K. Self-organized criticality: An explanation of the 1/f noise. Phys Rev Lett 1987;59:381-4.
3. Tagliazucchi E, Balenzuela P, Fraiman D, et al. Criticality in large-scale brain FMRI dynamics unveiled by a novel point process analysis. Front Physiol 2012;3:15.
4. Priesemann V, Valderrama M, Wibral M, et al. Neuronal avalanches differ from wakefulness to deep sleep--evidence from intracranial depth recordings in humans. PLoS Comput Biol 2013;9:e1002985.
5. Shao K, Ramirez Villegas JF, Logothetis NK, et al. A model of Ponto-Geniculo-Occipital waves supports bidirectional control of cortical plasticity across sleep-stages. bioRxiv 2021:2021.03.16.432817.
6. Ramirez-Villegas JF, Besserve M, Murayama Y, et al. Coupling of hippocampal theta and ripples with pontogeniculooccipital waves. Nature 2021;589:96-102.
7. Karashima A, Nakamura K, Watanabe M, et al. Synchronization between hippocampal theta waves and PGO waves during REM sleep. Psychiatry Clin Neurosci 2001;55:189-90.
8. Melani F, Zelmann R, Mari F, et al. Continuous High Frequency Activity: a peculiar SEEG pattern related to specific brain regions. Clin Neurophysiol 2013;124:1507-16.
9. Ruby P, Eskinazi M, Bouet R, et al. Dynamics of hippocampus and orbitofrontal cortex activity during arousing reactions from sleep: An intracranial electroencephalographic study. Hum Brain Mapp 2021;42:5188-203.
10. Lecci S, Fernandez LM, Weber FD, et al. Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep. Sci Adv 2017;3:e1602026.
11. Moruzzi G. The sleep-waking cycle. Ergeb Physiol 1972;64:1-165.
12. Halász P, Terzano M, Parrino L, et al. The nature of arousal in sleep. J Sleep Res 2004;13:1-23.
13. Lüthi A. Sleep: The Very Long Posited (VLPO) Synaptic Pathways of Arousal. Curr Biol 2019;29:R1310-2.
14. Staresina BP, Bergmann TO, Bonnefond M, et al. Hierarchical nesting of slow oscillations, spindles and

ripples in the human hippocampus during sleep. Nat Neurosci 2015;18:1679-86.
15. Tsunematsu T, Patel AA, Onken A, et al. State-dependent brainstem ensemble dynamics and their interactions with hippocampus across sleep states. Elife 2020;9:e52244.
16. Simor P, van der Wijk G, Nobili L, et al. The microstructure of REM sleep: Why phasic and tonic? Sleep Med Rev 2020;52:101305.
17. Logothetis NK, Eschenko O, Murayama Y, et al. Hippocampal-cortical interaction during periods of subcortical silence. Nature 2012;491:547-53.
18. Lüthi A. Sleep Spindles: Where They Come From, What They Do. Neuroscientist 2014;20:243-56.
19. Osorio-Forero A, Cardis R, Vantomme G, et al. Noradrenergic circuit control of non-REM sleep substates. Curr Biol 2021;31:5009-5023.e7.
20. Buzsáki G. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. Hippocampus 2015;25:1073-188.
21. Datta S. Activation of phasic pontine-wave generator: A mechanism for sleep-dependent memory processing. Sleep and Biological Rhythms 2006;4:16-26.
22. Caporro M, Haneef Z, Yeh HJ, et al. Functional MRI of sleep spindles and K-complexes. Clin Neurophysiol 2012;123:303-9.
23. Gnoni V, Drakatos P, Higgins S, et al. Cyclic alternating pattern in obstructive sleep apnea: A preliminary study. J Sleep Res 2021;30:e13350.
24. Karimi Abadchi J, Nazari-Ahangarkolaee M, Gattas S, et al. Spatiotemporal patterns of neocortical activity around hippocampal sharp-wave ripples. Elife 2020;9:e51972.
25. Terzano MG, Parrino L. Origin and Significance of the Cyclic Alternating Pattern (CAP). REVIEW ARTICLE. Sleep Med Rev 2000;4:101-23.
26. Fatima Y, Bucks RS, Mamun AA, et al. Sleep trajectories and mediators of poor sleep: findings from the longitudinal analysis of 41,094 participants of the UK Biobank cohort. Sleep Med 2020;76:120-7.
27. Javaheripour N, Shahdipour N, Noori K, et al. Functional brain alterations in acute sleep deprivation: An activation likelihood estimation meta-analysis. Sleep Med Rev 2019;46:64-73.
28. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 2014;81:12-34.
29. Siegel JM. Sleep in animals: a state of adaptive inactivity. In: Kryger MH, Roth T, Dement WC. editors. Principles and practice of sleep medicine. Amsterdam: Elsevier, 2011;5:126-38.
30. Ferrara M, De Gennaro L. Going local: insights from EEG and stereo-EEG studies of the human sleep-wake cycle. Curr Top Med Chem 2011;11:2423-37.
31. Vyazovskiy VV, Olcese U, Hanlon EC, et al. Local sleep in awake rats. Nature 2011;472:443-7.
32. D'Ambrosio S, Castelnovo A, Guglielmi O, et al. Sleepiness as a Local Phenomenon. Front Neurosci 2019;13:1086.
33. Ogilvie RD. The process of falling asleep. Sleep Med Rev 2001;5:247-70.
34. Iber C, Ancoli-Israel S, Chesson AL, et al. The new sleep scoring manual–the evidence behind the rules. J Clin Sleep Med 2007;3:107.
35. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, DC: Public Health Service, US Government Printing Office, 1968.
36. Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519-24.
37. Webb W. The natural onset of sleep. Sleep 1978:19-23.
38. Wright KP Jr, Badia P, Wauquier A. Topographical and temporal patterns of brain activity during the transition from wakefulness to sleep. Sleep 1995;18:880-9.
39. Broughton RJ. Polysomnography: Principles and applications in sleep and arousal disorders. In: Niedermeyer E, da Silva FHL. editors. Electroencepharography: Basic Principles, Clinical Applications and Related Field. Philadepphia, PA: Lippincott Williams & Wilkins, 1999:858-95.
40. Hori T, Hayashi M, Morikawa T. Topographical EEG changes and the hypnagogic experience. In: Ogilvie RD, Harsh JR. editors. Sleep onset: Normal and abnormal processes. Washington DC: American Psychological Association, 1994:237-53.
41. Lee YJ, Lee JY, Cho JH, et al. Interrater reliability of sleep stage scoring: a meta-analysis. J Clin Sleep Med 2022;18:193-202.
42. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992;49:624-9.
43. Thomas H, Ciliska D, Dobbins M. Quality assessment tool for quantitative studies. Toronto: Effective Public Health Practice Project McMaster University. 2003.
44. De Gennaro L, Ferrara M, Bertini M. The boundary between wakefulness and sleep: quantitative

electroencephalographic changes during the sleep onset period. Neuroscience 2001;107:1-11.
45. De Gennaro L, Ferrara M, Curcio G, et al. Antero-posterior EEG changes during the wakefulness-sleep transition. Clin Neurophysiol 2001;112:1901-11.
46. Hori T. Spatiotemporal changes of EEG activity during waking-sleeping transition period. Int J Neurosci 1985;27:101-14.
47. Marzano C, Moroni F, Gorgoni M, et al. How we fall asleep: regional and temporal differences in electroencephalographic synchronization at sleep onset. Sleep Med 2013;14:1112-22.
48. Park DH, Ha JH, Ryu SH, et al. Three-Dimensional Electroencephalographic Changes on Low-Resolution Brain Electromagnetic Tomography (LORETA) During the Sleep Onset Period. Clin EEG Neurosci 2015;46:340-6.
49. Siclari F, Bernardi G, Riedner BA, et al. Two distinct synchronization processes in the transition to sleep: a high-density electroencephalographic study. Sleep 2014;37:1621-37.
50. Tanaka H, Hayashi M, Hori T. Topographical characteristics and principal component structure of the hypnagogic EEG. Sleep 1997;20:523-34.
51. Tanaka H, Hayashi M, Hori T. Topographical characteristics of slow wave activities during the transition from wakefulness to sleep. Clin Neurophysiol 2000;111:417-27.
52. Ogilvie RD, Simons IA, Kuderian RH, et al. Behavioral, event-related potential, and EEG/FFT changes at sleep onset. Psychophysiology 1991;28:54-64.
53. Fernandez Guerrero A, Achermann P. Brain dynamics during the sleep onset transition: An EEG source localization study. Neurobiol Sleep Circadian Rhythms 2019;6:24-34.
54. De Gennaro L, Vecchio F, Ferrara M, et al. Changes in fronto-posterior functional coupling at sleep onset in humans. J Sleep Res 2004;13:209-17.
55. De Gennaro L, Vecchio F, Ferrara M, et al. Antero-posterior functional coupling at sleep onset: changes as a function of increased sleep pressure. Brain Res Bull 2005;65:133-40.
56. Morikawa T, Hayashi M, Hori T. Auto power and coherence analysis of delta-theta band EEG during the waking-sleeping transition period. Electroencephalogr Clin Neurophysiol 1997;103:633-41.
57. Fernandez Guerrero A, Achermann P. Intracortical Causal Information Flow of Oscillatory Activity (Effective Connectivity) at the Sleep Onset Transition. Front Neurosci 2018;12:912.
58. Achermann P, Rusterholz T, Stucky B, et al. Oscillatory patterns in the electroencephalogram at sleep onset. Sleep 2019;42:zsz096.
59. Hasan J, Broughton R. Quantitative topographic EEG mapping during drowsiness and sleep onset. 1994.
60. Morikawa T, Hayashi M, Hori T. Spatiotemporal variations of alpha and sigma band EEG in the waking-sleeping transition period. Percept Mot Skills 2002;95:131-54.
61. Vecchio F, Miraglia F, Gorgoni M, et al. Cortical connectivity modulation during sleep onset: A study via graph theory on EEG data. Hum Brain Mapp 2017;38:5456-64.
62. Ferri R, Rundo F, Bruni O, et al. The functional connectivity of different EEG bands moves towards small-world network organization during sleep. Clin Neurophysiol 2008;119:2026-36.
63. Moul DE, Germain A, Cashmere JD, et al. Examining initial sleep onset in primary insomnia: a case-control study using 4-second epochs. J Clin Sleep Med 2007;3:479-88.
64. Freedman RR. EEG power spectra in sleep-onset insomnia. Electroencephalogr Clin Neurophysiol 1986;63:408-13.
65. Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. Eur J Neurosci 1998;10:1826-34.
66. Merica H, Gaillard JM. The EEG of the sleep onset period in insomnia: a discriminant analysis. Physiol Behav 1992;52:199-204.
67. Perlis ML, Kehr EL, Smith MT, et al. Temporal and stagewise distribution of high frequency EEG activity in patients with primary and secondary insomnia and in good sleeper controls. J Sleep Res 2001;10:93-104.
68. Staner L, Cornette F, Maurice D, et al. Sleep microstructure around sleep onset differentiates major depressive insomnia from primary insomnia. J Sleep Res 2003;12:319-30.
69. Cervena K, Espa F, Perogamvros L, et al. Spectral analysis of the sleep onset period in primary insomnia. Clin Neurophysiol 2014;125:979-87.
70. Corsi-Cabrera M, Figueredo-Rodríguez P, del Río-Portilla Y, et al. Enhanced frontoparietal synchronized activation during the wake-sleep transition in patients with primary insomnia. Sleep 2012;35:501-11.
71. Ferri R, Cosentino FI, Manconi M, et al. Increased electroencephalographic high frequencies during the sleep

onset period in patients with restless legs syndrome. Sleep 2014;37:1375-81.
72. Kim JW, Shin HB, Robinson PA. Quantitative study of the sleep onset period via detrended fluctuation analysis: normal vs. narcoleptic subjects. Clin Neurophysiol 2009;120:1245-51.
73. Pizza F, Vandi S, Detto S, et al. Different sleep onset criteria at the multiple sleep latency test (MSLT): an additional marker to differentiate central nervous system (CNS) hypersomnias. J Sleep Res 2011;20:250-6.
74. Magnin M, Rey M, Bastuji H, et al. Thalamic deactivation at sleep onset precedes that of the cerebral cortex in humans. Proc Natl Acad Sci U S A 2010;107:3829-33.
75. Ioannides AA, Liu L, Poghosyan V, et al. Using MEG to Understand the Progression of Light Sleep and the Emergence and Functional Roles of Spindles and K-Complexes. Front Hum Neurosci 2017;11:313.
76. Hale JR, White TP, Mayhew SD, et al. Altered thalamocortical and intra-thalamic functional connectivity during light sleep compared with wake. Neuroimage 2016;125:657-67.
77. Bagshaw AP, Hale JR, Campos BM, et al. Sleep onset uncovers thalamic abnormalities in patients with idiopathic generalised epilepsy. Neuroimage Clin 2017;16:52-7.
78. Braun AR, Balkin TJ, Wesenten NJ, et al. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain 1997;120:1173-97.
79. Hoshi Y, Mizukami S, Tamura M. Dynamic features of hemodynamic and metabolic changes in the human brain during all-night sleep as revealed by near-infrared spectroscopy. Brain Res 1994;652:257-62.
80. Näsi T, Virtanen J, Noponen T, et al. Spontaneous hemodynamic oscillations during human sleep and sleep stage transitions characterized with near-infrared spectroscopy. PLoS One 2011;6:e25415.
81. Shiotsuka S, Atsumi Y, Ogata S, et al. Cerebral blood volume in the sleep measured by near-infrared spectroscopy. Psychiatry Clin Neurosci 1998;52:172-3.
82. Zhang Z, Khatami R. A Biphasic Change of Regional Blood Volume in the Frontal Cortex during Non-Rapid Eye Movement Sleep: A Near-Infrared Spectroscopy Study. Sleep 2015;38:1211-7.
83. Spielman AJ, Zhang G, Yang CM, et al. Intracerebral hemodynamics probed by near infrared spectroscopy in the transition between wakefulness and sleep. Brain Res 2000;866:313-25.
84. Barrett J, Lack L, Morris M. The sleep-evoked decrease of body temperature. Sleep 1993;16:93-9.
85. Campbell SS, Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow? Chronobiol Int 1994;11:126-31.
86. Murphy PJ, Campbell SS. Nighttime drop in body temperature: a physiological trigger for sleep onset? Sleep 1997;20:505-11.
87. Zulley J, Wever R, Aschoff J. The dependence of onset and duration of sleep on th circadian rhythm of rectal temperature. Pflugers Arch 1981;391:314-8.
88. van den Heuvel CJ, Noone JT, Lushington K, et al. Changes in sleepiness and body temperature precede nocturnal sleep onset: evidence from a polysomnographic study in young men. J Sleep Res 1998;7:159-66.
89. Kräuchi K, Cajochen C, Werth E, et al. Functional link between distal vasodilation and sleep-onset latency? Am J Physiol Regul Integr Comp Physiol 2000;278:R741-8.
90. Partonen T, Haukka J, Kuula L, et al. Assessment of time window for sleep onset on the basis of continuous wrist temperature measurement. Biological Rhythm Research 2022;53:897-907.
91. Kay A, Trinder J, Bowes G, et al. Changes in airway resistance during sleep onset. J Appl Physiol (1985) 1994;76:1600-7.
92. Worsnop C, Kay A, Pierce R, et al. Activity of respiratory pump and upper airway muscles during sleep onset. J Appl Physiol (1985) 1998;85:908-20.
93. Naifeh KH, Kamiya J. The nature of respiratory changes associated with sleep onset. Sleep 1981;4:49-59.
94. Perry TJ, Goldwater BC. A passive behavioral measure of sleep onset in high-alpha and low-alpha subjects. Psychophysiology 1987;24:657-65.
95. Burgess HJ, Trinder J, Kim Y. Cardiac autonomic nervous system activity during presleep wakefulness and stage 2 NREM sleep. J Sleep Res 1999;8:113-22.
96. Shinar Z, Akselrod S, Dagan Y, et al. Autonomic changes during wake-sleep transition: a heart rate variability based approach. Auton Neurosci 2006;130:17-27.
97. Burgess HJ, Trinder J, Kim Y, et al. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol 1997;273:H1761-8.
98. Carrington M, Walsh M, Stambas T, et al. The influence of sleep onset on the diurnal variation in cardiac activity and cardiac control. J Sleep Res 2003;12:213-21.
99. Pizza F, Fabbri M, Magosso E, et al. Slow eye movements distribution during nocturnal sleep. Clin Neurophysiol 2011;122:1556-61.
100. Agnew H, Webb W. Measurement of sleep onset by EEG criteria. American Journal of EEG Technology

1972;12:127-34.
101. Hori T. Electrodermal and electro-oculographic activity in a hypnagogic state. Psychophysiology 1982;19:668-72.
102. Ogilvie RD, McDonagh DM, Stone SN, et al. Eye movements and the detection of sleep onset. Psychophysiology 1988;25:81-91.
103. De Gennaro L, Ferrara M, Ferlazzo F, et al. Slow eye movements and EEG power spectra during wake-sleep transition. Clin Neurophysiol 2000;111:2107-15.
104. Hiroshige Y. Linear automatic detection of eye movements during the transition between wake and sleep. Psychiatry Clin Neurosci 1999;53:179-81.
105. Porte HS. Slow horizontal eye movement at human sleep onset. J Sleep Res 2004;13:239-49.
106. Bódizs R, Sverteczki M, Lázár AS, et al. Human parahippocampal activity: non-REM and REM elements in wake-sleep transition. Brain Res Bull 2005;65:169-76.
107. Bareham CA, Manly T, Pustovaya OV, et al. Losing the left side of the world: rightward shift in human spatial attention with sleep onset. Sci Rep 2014;4:5092.
108. Ogilvie RD, Wilkinson RT, Allison S. The detection of sleep onset: behavioral, physiological, and subjective convergence. Sleep 1989;12:458-74.
109. Viens M, De Koninck J, Van den Bergen H, et al. A refined switch-activated time monitor for the measurement of sleep-onset latency. Behav Res Ther 1988;26:271-3.
110. Birrell PC. Behavioral, subjective, and electroencephalographic indices of sleep onset latency and sleep duration. J Behav Assess 1983;5:179-90.
111. Ogilvie RD, Wilkinson RT. The detection of sleep onset: behavioral and physiological convergence. Psychophysiology 1984;21:510-20.
112. Hauri P, Olmstead E. What is the moment of sleep onset for insomniacs? Sleep 1983;6:10-5.
113. Casagrande M, De Gennaro L, Violani C, et al. A finger-tapping task and a reaction time task as behavioral measures of the transition from wakefulness to sleep: which task interferes less with the sleep onset process. Sleep 1997;20:301-12.
114. Strauss M, Sitt JD, Naccache L, et al. Predicting the loss of responsiveness when falling asleep in humans. Neuroimage 2022;251:119003.
115. Damestani NL, O'Daly O, Solana AB, et al. Revealing the mechanisms behind novel auditory stimuli discrimination: An evaluation of silent functional MRI using looping star. Hum Brain Mapp 2021;42:2833-50.
116. Grossman N, Bono D, Dedic N, et al. Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. Cell 2017;169:1029-1041.e16.
117. Halasz Pa, Bodizs Rba. Dynamic structure of NREM sleep. Berlin: Springer, 2013.

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