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The neurophysiologic landscape of the sleep onset: a systematic review

Nazanin Biabani[1], Adam Birdseye[1,2], Sean Higgins[1,2], Alessio Delogu[3], Jan Rosenzweig[4], Zoran Cvetkovic[4], Alexander Nesbitt[1,2,5], Panagis Drakatos[1,2,6], Joerg Steier[2,6], Veena Kumari[1,7], David O'Regan[1,2,6], Ivana Rosenzweig[1,2]

[1]Sleep and Brain Plasticity Centre, Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, UK; [2]Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]James Black Centre, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, UK; [4]Department of Engineering, King's College London, London, UK; [5]Department of Neurology, Guy's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, UK; [6]School of Basic and Medical Biosciences, Faculty of Life Science and Medicine, King's College London, London, UK; [7]Centre for Cognitive Neuroscience (CCN), College of Health, Medicine and Life Sciences, Brunel University London, London, UK

Contributions: (I) Conception and design: N Biabani, I Rosenzweig; (II) Administrative support: All authors; (III) Provision of study materials or patients: N Biabani, I Rosenzweig; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: N Biabani, J Rosenzweig; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Ivana Rosenzweig, MD, PhD. Sleep and Brain Plasticity Centre, Department of Neuroimaging, Box 089, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London, SE5 8AF, UK. Email: ivana.1.rosenzweig@kcl.ac.uk.

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.

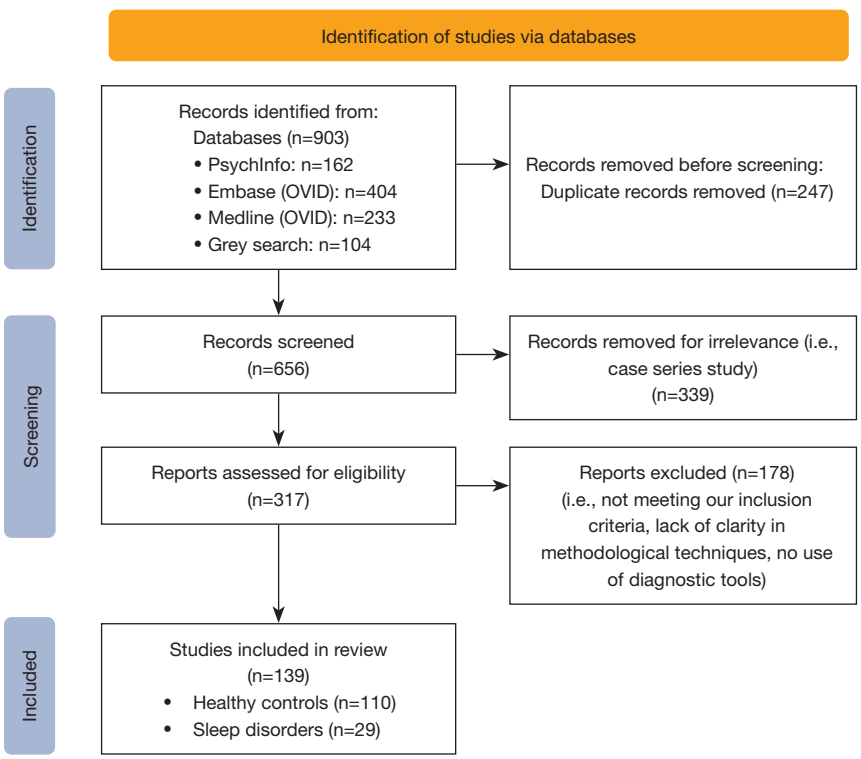

Figure 1 PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

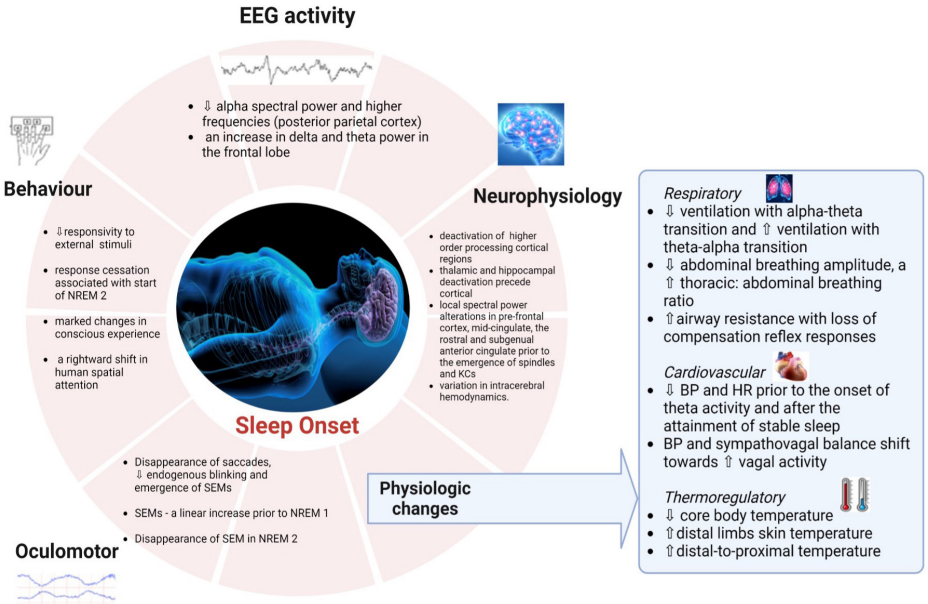

Figure 2 Schematic presentation of physiologic processes during the sleep-onset. EEG, electroencephalographic; BP, blood pressure; HR, heart rate; KC, K-complex; NREM, non-rapid eye movement; SEM, slow eye movement; SO, sleep onset; RT, reaction time.

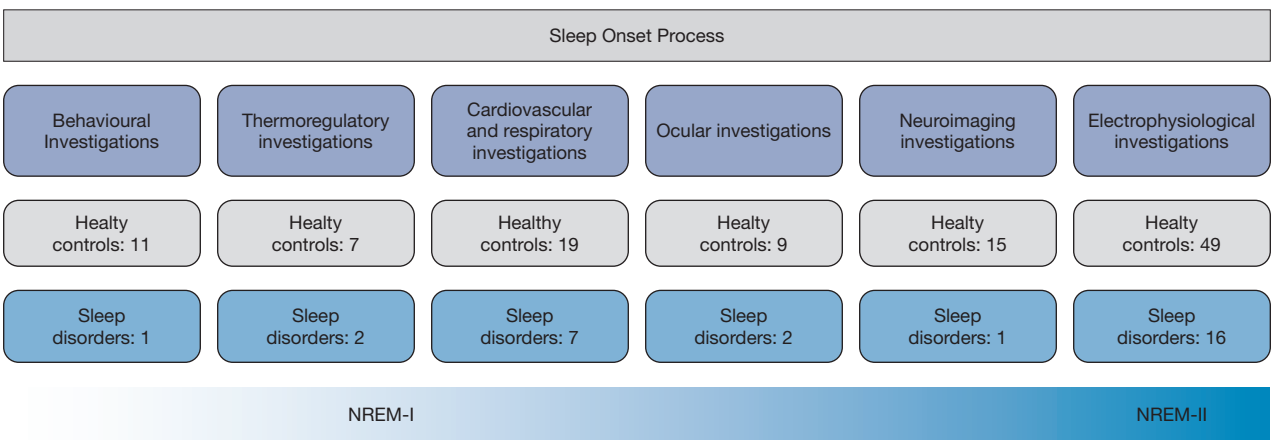

Figure 3 The number of studies identified for Sleep Onset Processes in healthy controls and individuals with sleep disorders. NREM, non-rapid eye movement sleep.

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

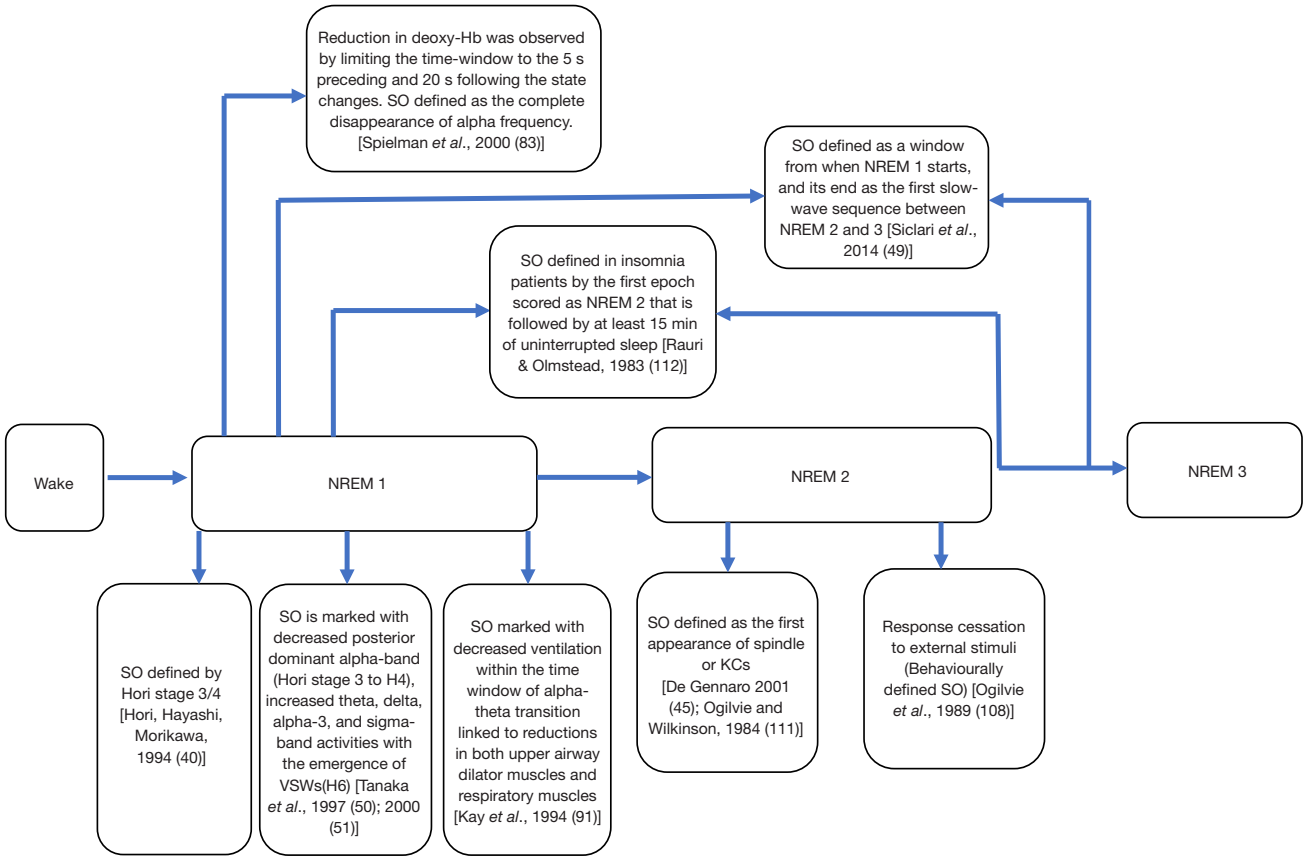

Figure 4 Example of diverse sleep-onset definitions across representative studies (40,45,49,50,51,83,91,108,111,112). KC, K-complex; NREM, non-rapid eye movement sleep; SO, sleep onset; VSW, vertex sharp wave.

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.

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Supplementary

Table S1 The sleep-onset process

Method of study	Main findings	Evaluation
Electroencephalogram (EEG)		
Spectral power		
Delta <4 Hz	• Earlier synchronisation and generalized increase, predominated over frontomedial regions [De Gennaro *et al.*, 2001a (44); 2001b (45); Hori, 1985 (46); Marzano *et al.*, 2013 (47); Ogilvie *et al.*, 1991 (52); Park *et al.*, 2015 (48); Siclari *et al.*, 2014 (49); Tanaka *et al.*, 1997 (50); Tanaka *et al.*, 2000 (51)] • Global increase of the post compared with pre-SO ratio following SD [Gorgoni *et al.*, 2019 (118)] • Generalised reduction of delta power and its ratio to beta in both pre-SO and post-SO intervals compared with young adults [Gorgoni *et al.*, 2021 (119)] • The incidence of frontal-intermittent-rhythmic delta activity at SO in older adults with no association with impaired cognitive performance [Kawai *et al.*, 2016 (120)]	Strengths: • Non-invasive • High temporal resolution • Effectively summarises immense amount of information obtained by EEG techniques and allows for identification of important spatio-temporal organisations of primary EEG frequencies with moment by moment precision • Comparisons can be made between a resting brain and when presented with a task or stimulus, to examine activity in the brain • Allows for the diagnosis of sleep pathologies • Spectra are estimated using several time samples (i.e., features estimated from signal power spectra robust to noise) Limitations: • Low spatial resolution • Labour-intensive • The presence of various EEG oscillatory activities cannot provide a definitive account as other biomarkers such as hormone secretion, metabolic activation, and variability in heart rate and sympathetic nervous system activation could also play a part • Fails to capture micro-oscillations • vulnerability to estimation bias when the data length is short • Removes all temporal dynamics of SOP
Theta 5–7 Hz	• Global increase with an occipital peak replacing the prevalence of alpha oscillations [Hori, 1985 (46); Marzano *et al.*, 2013 (47); Park *et al.*, 2015 (48); Siclari *et al.*, 2014 (49); Tanaka *et al.*, 1997 (50); Wright *et al.*, 1995 (38)] • Global increase of the post compared with pre-SO ratio following SD [Gorgoni *et al.*, 2019 (118)]	
Alpha 8–12 Hz	• Gradual pre-SO decrease of the occipital alpha, followed by a post-SO increase of frontocentral dominance of alpha [De Gennaro *et al.*, 2001a (44); Hasan and Broughton, 1994 (59); Hori, 1985 (46); Marzano *et al.*, 2013 (47); Park *et al.*, 2015 (48); Tanaka *et al.*, 1997 (50)] • Increased alpha power at SO [Ogilvie *et al.*, 1991 (52)] • Increased post compared with pre-SO ratio with frontocentral dominance following SD [Gorgoni *et al.*, 2019 (118)]	
Sigma 12–15 Hz	• Post-SO increase with a centro-parietal predominance [De Gennaro *et al.*, 2001a (44), 2001; Hori, 1985 (46); Marzano *et al.*, 2013 (47); Siclari *et al.*, 2014 (49); Tanaka *et al.*, 1997 (50)] • Absence of quantitative differences following SD [Gorgoni *et al.*, 2019 (118)]	
Beta 16–24 Hz Gamma 25–40 Hz	• Widespread decrease of the beta and gamma activity [De Gennaro *et al.*, 2001a (44), 2001b (45); Marzano *et al.*, 2013 (47); Park *et al.*, 2015 (48); Siclari *et al.*, 2014 (49)] • A generalised reduction of delta/beta ratio pre and post SO in older adults compared to younger adults [Gorgoni *et al.*, 2021 (119)] • No significant change in beta activity [Hori, 1985 (46)] • Significant decreases in beta power at pre-SO, with this trend sharply (and significantly) reversed at SO [Ogilvie *et al.*, 1991 (52)] • Absence of quantitative differences in the beta bands following SD [Gorgoni *et al.*, 2019 (118)]	
Oscillatory activity		
Delta <4 Hz	Global increase and frontalization of slow-wave activity (SWA) [Marzano *et al.*, 2013 (47)]	
Theta 5–7 Hz	• Maximum delta/theta (1.5–7 Hz) events ratio immediately following SO while the event frequency decreases from NREM-I onwards, further into NREM-II [Marzano *et al.*, 2013 (47); Achermann *et al.*, 2019 (58)] • Post-SO frontocentral increase in the oscillatory peak following SO [Gorgoni *et al.*, 2019 (118)]	
Alpha 8–12 Hz	• Transition from a posterior to an anterior predominance [Marzano *et al.*, 2013 (47); Achermann *et al.*, 2019 (58)] • Post-SO increase in the oscillatory peak following SD [Gorgoni *et al.*, 2019 (118)]	
Sigma 12–15 Hz	• Global and progressive increase following SO with a central maximum [Marzano *et al.*, 2013 (47); Achermann *et al.*, 2019 (58)] • Decreased global frequency with an antero- posterior gradient [Marzano *et al.*, 2013 (47); Achermann *et al.*, 2019 (58)] • Decreased sigma oscillatory events following SD [Achermann *et al.*, 2019 (58)]	
Beta 16–24 Hz Gamma 25–40 Hz	• Gradual reduction in the beta power with a maximum in temporo-frontal areas [Marzano *et al.*, 2013 (47)] • Post-SO centro-parietal increase in the beta frequency peak following SD [Gorgoni *et al.*, 2019 (118)] • Post-SO decline in the beta oscillatory peak in the lateral frontal regions and right occipital area [Marzano *et al.*, 2013 (47)] • Gamma activity not assessed	
Cortical source		Strengths: • Captures the microstructure of Sleep Onset Process (SOP), and its temporal dynamics detecting fluctuations in arousal and stage shifting • Allows for principled characterization of SOP, and diagnosis of SOP pathologies • EEG changes to be very systematic with a precise ordinal relationship between the Hori nine stages and reaction time Limitations: • Labour intensive • Time-consuming • Subjective • Does not account for phenomena such as K-complex associated arousals or mid temporal theta of drowsiness • Cannot be used for people in whom alpha levels are supressed • Can cause frequency bias during automated analyses, especially if an adequate number of samples (epochs) is not averaged. • May not provide an effective tool for the identification of various sleep pathologies • But can only be used for the sleep onset changes
Delta <4 Hz	• Progressive increase of the delta activity post-SO, most salient in the PFC and postcentral gyrus [Park *et al.*, 2015 (48); Fernandez Guerrero and Achermann, 2019 (53)] • Greater involvement of the frontal cortex following SD [Fernandez Guerrero and Achermann, 2019 (53)]	
Theta 5–7 Hz	• Progressive increase of the theta activity in the posterior region until it reaches a plateau, with greater involvement of the precuneus and cuneus [Fernandez Guerrero and Achermann, 2019 (53); Park *et al.*, 2015 (48)]	
Alpha 8–12 Hz	• Progressive increase of the alpha activity during the SOP, with highest values in the precuneus [Fernandez Guerrero and Achermann, 2019 (53); Park *et al.*, 2015 (48)]	
Sigma 12–15 Hz	• Progressive increase of the sigma activity post-SO, with the most salient involvement of the parietal lobe and a secondary contribution of the postcentral gyrus, the cuneus, and the lingual gyrus [Fernandez Guerrero and Achermann, 2019 (53)] • Earlier sigma peak but reduced activity involving fewer brain regions involved following SD [Fernandez Guerrero and Achermann, 2019 (53)]	
Beta 16–24 Hz Gamma 25–40 Hz	• Progressive reduction of the beta activity, with greater involvement of the parietal and occipital lobes [Fernandez Guerrero and Achermann, 2019 (53); Park *et al.*, 2015 (48)] • Faster decrease of the beta activity following SD [Fernandez Guerrero and Achermann, 2019 (53)]	
EEG event		
Delta <4 Hz	• Early SO slow-waves marked with large amplitudes, steep slopes, with frontomedial prevalence, and originating from the sensorimotor and the posteromedial parietal cortex [Siclari *et al.*, 2014 (49)] • Late SO slow-wave marked with smaller amplitudes and slopes, involving circumscribed parts of the cortex, with more evenly distributed origins [Siclari *et al.*, 2014 (49)]	
Theta 5–7 Hz	Not assessed	
Alpha 8–12 Hz	Not assessed	
Sigma 12–15 Hz	Early SO spindles are sparse, fast and predominantly local followed by a progressively slower, more diffuse and numerous patterns, involving more regions [Siclari *et al.*, 2014 (49)] Slow frontal spindles originate from anterior cingulate cortex and medial/lateral prefrontal cortex and fast centroparietal spindles from the precuneus and posterior cingulate cortex [Siclari *et al.*, 2014 (49)]	
Beta 16–24 Hz Gamma 25–40 Hz	Not assessed	
Cortical connectivity		
Delta <4 Hz	• Increased cortical coherence within ipsilateral frontal and central regions and also between contralateral frontal and central homologues during SO [Morikawa *et al.*, 1997 (56); Tanaka *et al.*, 1999 (121); 2000 (51)] • Increased coherence at the delta band during pre-SO compared with SO [De Gennaro *et al.*, 2004 (54)] • Progressive decrease of antero-posterior synchrony followed by a post-SO transition to an anterior-to-posterior propagation [De Gennaro *et al.*, 2004 (54), 2005 (55)] • Pre-SO dominated by the occipital-to-frontal information flow at delta band with SO being dominated by the frontal-to-parieto-occipital information flow at all bands [De Gennaro *et al.*, 2004 (54)] • Higher local interconnectedness during SOP [Ferri *et al.*, 2008 (62)] and lower long-range functional connectedness during more stable sleep [Vecchio *et al.*, 2017 (61)] • Higher level of connectivity from MPFC to the bilateral HPC and LPFC but decreased connection from DPFC and ipsilateral HPC [Fernandez Guerrero and Achermann, 2018 (57)] • Anterior-posterior decoupling of the DMN but enhanced connectivity between the PCC and both anterior and posterior cortical regions [Fernandez Guerrero and Achermann, 2018 (57)]	
Theta 5–7 Hz	• Increased ipsilateral and inter- hemispheric frontal and central coherence [Morikawa *et al.*, 1997 (56); Tanaka *et al.*, 2000 (51)] • Increased coherence at the theta band during pre-SO compared with SO [De Gennaro *et al.*, 2004 (54)] • Reduction in antero-posterior synchrony [Morikawa *et al.*, 1997 (56)], with a post-SO shift to an anterior-to-posterior propagation [De Gennaro *et al.*, 2004 (54)] • Pre-SO dominated by the occipital-to-frontal information flow at theta bands with SO being dominated by frontal-to-parieto-occipital information flow at all bands [De Gennaro *et al.*, 2004 (54)] • Following SO, theta activity modulates bidirectional information flow between the PCC and the bilateral IPL and the HPC, and from the bilateral HPC to the MCC [Fernandez Guerrero and Achermann, 2018 (57)]	
Alpha 8–12 Hz	• Decreased antero-posterior coherence and inter-hemispheric frontal coherence, and increased posterior coherence [Wright *et al.*, 1995 (38); Morikawa *et al.*, 2002 (60)] • Pre-SO dominated by the occipital-to-frontal information flow at alpha bands during pre-SO with SO being dominated by the frontal-to-parieto-occipital information flow at all bands [De Gennaro *et al.*, 2004 (54)] • Increased coherence in the upper alpha sub-band (11–12 Hz) with the beginning of sleep NREM-II along the antero-posterior gradient [De Gennaro *et al.*, 2004 (54); Morikawa *et al.*, 2002 (60); Tanaka *et al.*, 1997 (50)] • Increased connectivity from the PCC to most brain regions [Fernandez Guerrero and Achermann, 2018 (57)]	
Sigma 12–15 Hz	• Widespread coherence at the beginning of sleep, with a steeper increase in posterior regions [Morikawa *et al.*, 2002 (60)] • The frontal-to-parieto-occipital information flow at all bands during the SO [De Gennaro *et al.*, 2004 (54)] • Increased local and global interconnectivity in the frontal regions [Ferri *et al.*, 2008 (62); Vecchio *et al.*, 2017 (61)] • Increased connectivity after SO, with a stronger connectivity between the MCC and PCC with other regions [Fernandez Guerrero and Achermann, 2018 (57)] • Increased impact of MCC on the left IPL and a decreased impact on the right DPFC following SD [Fernandez Guerrero and Achermann, 2018 (57)]	
Beta 16–24 Hz Gama 25–40 Hz	• Increased beta propagation from frontal to parieto-occipital regions-inversion of the direction of information flow [De Gennaro *et al.*, 2004 (54)] • Gamma activity not assessed	
Sub-division of EEG frequency bands	• 82% and 78% of the occurrences of SO within a two-minute error for the NREM-I and spindle criteria respectively [Agnew and Webb, 1972 (100)] • The beginning of SO marked with increased delta and theta power and decreased alpha-1 power in the occipital lobe, and increased theta power in the parietal lobe followed by widespread decrease in alpha-1 and alpha-2 powers and greater increases of theta power in the occipitoparietal lobe. More stable sleep led to decreased, beta-2 and beta-3, powers decreased mainly in the frontal lobe and some regions of the parieto-temporo-limbic area [Park *et al.*, 2015 (48)] • Ordinal relationship between RT and the nine Hori stages: mean RT increased as each of stages H1 through H9 was entered corresponding to their subjective reports [Hori, Hayashi, Morikawa, 1994 (40)] • Increased delta and theta activities from the VSWs [the Hori stages 6 and 7) in the anterior-central regions [Tanaka *et al.*, 1998 (122)] • Increased alpha-3 sub-band activities from the Hori stage 9 in the anterior-central regions [Tanaka *et al.*, 1998 (122)] • Increased sigma activities from the Hori stage 8 in the central parietal regions [Tanaka *et al.*, 1998 (122)] • Decreased posterior dominant alpha-band with the disappearance of alpha-wave (H3 to H4); and increased theta, delta, alpha-3, and sigma-band activities with the emergence of VSWs (H6) [Tanaka *et al.*, 1997 (50); 2000 (51)] • Decreased alpha-2 coherence decreased from H3 during the SOP [Tanaka *et al.*, 1997 (50); 2000 (51)] • Rise of delta, theta, and alpha-3 coherence from H7, with these increases being associated with the onset of VSWs [Tanaka *et al.*, 1997 (50); 2000 (51)] • Increased average time of the alpha-wave train, intermittent (>50%) and the EEG flattening stage on Night 1[Tamaki *et al.*, 2005 (123)] • Increased stage changes on Night 1 [Tamaki *et al.*, 2005 (123)] • Increased stage changes between the alpha-wave intermittent stage (<50%) and the theta wave stage on Night 3 [Tamaki *et al.*, 2005 (123)]	

Table S1 *(continued)*

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Table S1 *(continued)*

Method of study	Main findings	Evaluation
Event-related potentials		Strengths: • The ease of recording, consistency with which the components occur, and their stimulus modality independence make them ideal candidates for use in the study of sleep-related pathology • Allows for the identification of complex changes in information processing as sleep begins • High temporal resolution Limitations: • SO duration can be very short, lasting only a few minutes in some subjects. Because of the short duration of the sleep onset period, there may not be sufficient time to present enough trials to allow the ERP to emerge from the large-amplitude background EEG. • Poor signal-to-noise ratio during the critical stage 1 • The ERPs are usually obtained by signal averaging; important moment-by-moment changes are lost • Low spatial resolution • Fails to capture micro-oscillations • Can be potentially arousing, disturbing sleep
Auditory-related evoked potentials		
P1	• P1 became increasingly augmented during SO [Ogilvie *et al.*, 1991 (52); de Lugt *et al.*, 1996 (124)]	
N1	• With increased RT, N1 becomes smaller in amplitude reaching baseline when subjects fail to respond [Colrain *et al.*, 2000 (125); Cote *et al.*, 2002 (126); de Lugt *et al.*, 1996 (124); Harsh *et al.*, 1994 (127); Nielsen-Bohlman *et al.*, 1991 (128); Ogilvie *et al.*, 1991 (52); Winter *et al.*, 1995 (129); Yasuda *et al.*, 2011 (130)] • At a rapid rate of stimulus presentation [every 600 ms), N1 became increasingly attenuated at SO [de Lugt *et al.*, 1996 (124)]	
P2	• With increased RT, the amplitude of P2 increases reaching its maximum when subjects fail to respond following SO [Cote *et al.*, 2002 (126); Harsh *et al.*, 1994 (127); Ogilvie *et al.*, 1991 (52); Winter *et al.*, 1995 (129); Yasuda *et al.*, 2011 (130)] • During NREM-II sleep, the P2 amplitude more than doubled in size [Ogilvie *et al.*, 1991 (52)] • At a rapid rate of stimulus presentation [every 600 ms) P2 became increasingly augmented at SO [de Lugt *et al.*, 1996 (124)] • SD had no effect on P2 amplitude [Peszka and Harsh, 2002 (131)]	
N2/N350	• It starts to appear during NREM-I-theta early in SO [Colrain *et al.*, 2000 (125); Harsh *et al.*, 1994 (127); Ogilvie *et al.*, 1991 (52)] • It is related to VSWs associated SO [Colrain *et al.*, 2000 (132); Harsh *et al.*, 1994 (127); Peszka and Harsh, 2002 (131); Yasuda *et al.*, 2011 (130)] and a KC associated SO with reduced amplitude [Colrain *et al.*, 2000 (125); Yasuda et al, 2011 (130)] • The absence of N2 at a rapid rate of stimulus presentation [every 600 ms) at SO [de Lugt *et al.*, 1996 (124)] • N350 amplitude increased with SO following increased tone intensity and SD [Peszka and Harsh, 2002 (131)] • Larger N350 at SO for deviant than for standard stimuli [Nielsen-Bohlman *et al.*, 1991 (128); Winter *et al.*, 1995 (129)]	
P3/P300	• A decline in the amplitude of P300 is observed in NREM-I-theta [Bastuji *et al.*, 1995 (133); Cote *et al.*, 2002 (126); Harsh *et al.*, 1994 (127); Ogilvie *et al.*, 1991 (52)] apparent at parietal sites rather than its frontal dispersion [Bastuji *et al.*, 1995 (133); Harsh *et al.*, 1994 (127)] • No P300 is observed in NREM-II or following undetected targets [Bastuji *et al.*, 1995 (133); Cote and Campbell, 1999 (134); Cote *et al.*, 2002 (126); Harsh *et al.*, 1994 (127); Ogilvie *et al.*, 1991 (52)] but only in responsive trials [Strauss *et al.*, 2022 (114)] • The long 400–450 ms latency of P300 with distinct posterior scalp distribution that is unique to SO but not being affected by the same experimental manipulations [Cote and Campbell, 1999 (134); Cote *et al.*, 2002 (126); Hull and Harsh, 2001 (135)]	
N550	• N550 emerges in NREM-II sleep [Colrain *et al.*, 2000 (125)] • Increased N550 amplitude with SO following increased tone intensity and SD with its appearance related to VSWs [Peszka and Harsh, 2002 (131)] • Evident frontally in late SO [Harsh *et al.*, 1994 (127)] • Well-defined in response to targets in attended condition during NREM-II [Harsh *et al.*, 1994 (127)]	
P900	• Increased P900 amplitude with SO [Peszka and Harsh, 2002 (131)] • P900 related to the appearance of KCs with its amplitude larger with increased tone intensity and SD [Peszka and Harsh, 2002 (131)] • Well-defined in response to targets in attended condition during NREM-II [Harsh *et al.*, 1994 (127)]	
Respiratory-related evoked potentials		
P1	• P1 is reduced in NREM-I [Webster and Colrain, 1998 (136)]	
N1	• Decrease in amplitude from wake to NREM-I [Webster and Colrain, 1998 (136)] • The respiratory stimulus elicited a N1 that decreased in amplitude at theta trials [Gora *et al.*, 1999 (137)] • NREM-II N1 further decreased relative to NREM-I theta [Gora *et al.*, 1999 (137)]	
P2	• Decrease in amplitude from wake to NREM-I [Webster and Colrain,1998 (136)] • Smaller P2 amplitude in wakefulness than during NREM-II [Gora *et al.*, 1999 (137)]	
N2	• N350 occurs following respiratory occlusions during the transition to NREM-I-theta and may be related to VSW at SO [Gora *et al.*, 2001 (138)] • Dominant in NREM-II sleep [Webster and Colrain, 2000 (139)]	
P3	• A P300/P450 is automatically elicited by the occlusion of breathing [Webster and Colrain, 2000 (139)] • A dramatic difference between the NREM-I-alpha and -theta in the amplitude of P300 [Gora *et al.*, 1999 (137)] • A parieto-occipital maximum of P300 with little dispersion to frontal regions [Gora *et al.*, 1999 (137)] • A more posterior parieto-occipital distribution with decreased amplitude of this late positive wave during NREM-II [Gora *et al.*, 1999 (137)]	
N550	• N550 did not appear until NREM-II sleep associated with SO [Webster and Colrain, 2000 (139)]	
P900	• Not assessed	
The mismatch negativity (MMN)	• The MMN was still observed in NREM-I, but was significantly reduced in amplitude [Nittono *et al.*, 2001 (140); Sabri *et al.*, 2000 (141)] and could no longer be recorded after NREM-I-theta at SO [Nittono *et al.*, 2001 (140)] • The MMN was followed by a central maximum positivity, the P3a, peaking at approximately 250 ms [Sabri *et al.*, 2000 (141)] • MMN could no longer be observed during NREM-II associated with SO [Sabri *et al.*, 2000 (141)] • P240 and N360 (N2) emerged for high deviant tone [Nittono *et al.*, 2001 (140)]	
Intracerebral EEG recordings		
Stereo-EEG (SEEG) recordings	• The thalamic [Magnin *et al.*, 2010 (74); Sarasso *et al.*, 2014 (142)] and hippocampal deactivation at SO precede that of the cortex by several minutes in contrast to the synchronous reactivation of both structures during wakefulness [Sarasso *et al.*, 2014 (142)] • Heterogeneity in the delays between the thalamus and cortex deactivation from one subject to another [Magnin *et al.*, 2010 (74)] • The occurrence of hippocampal spindles several minutes SO preceded neocortical events, with increasing delays along the cortical antero-posterior axis [Sarasso *et al.*, 2014 (142)] • The calcarine cortex is dominated by the theta oscillations at SO [Marzano *et al.*, 2013 (47)] • An increase in REM-like 1.5–3.0 Hz parahippocampal activity during wake–sleep transition, peaking following on average 30 s of SO, and reaching 82% of REM sleep value [Bódizs *et al.*, 2005 (106)] • The increase in 1.5–3.0 Hz parahippocampal activity followed alpha dropout, but did not relate to short-term fluctuations in alpha waves or sleep spindles [Bódizs *et al.*, 2005 (106)] • Non-REM sleep-specific slow (<1.25 Hz) activity showed a continuous increase during wake–sleep transition in both temporal scalp and parahippocampal recordings [Bódizs *et al.*, 2005 (106)]	Strengths: • Allows for directly measuring the local EEG activity in deep and subcortical cerebral structures Limitations: • Invasive • Limited longevity resulting from high degree of invasiveness • Tendency of progressive worsening of recorded signal quality
Neuroimaging methods		
Magnetoencephalography (MEG)	• Significant decrease of alpha spectral power and higher frequencies in posterior parietal cortex with the active inhibition in the frontal lobe leading to an increase in delta and theta power during SOP [Ioannides *et al.*, 2017 (75)] • Changes identified in NREM-I become more widespread during NREM-II associated with SO in addition to focal increases in alpha and low sigma band power in frontal midline cortical structures [Ioannides *et al.*, 2017 (75)] • Local spectral power alterations in pre-frontal cortex, mid-cingulate, the rostral and subgenual anterior cingulate just prior to the emergence of spindles and KCs [Ioannides *et al.*, 2017 (75)] • Using a 5-second epoch classification, stable non-responsiveness is only manifest few minutes after the emergence of the first spindles [Strauss *et al.*, 2022 (114)] • The global P300 was only present in responsive trials, regardless of vigilance states [Strauss *et al.*, 2022 (114)]	Strengths: • Non-invasive • High temporal resolution enabling the examination of rhythmic, oscillatory neural activity in different frequency bands • Well suited to examine the subtle dynamics of cortical processes as they unfold spontaneously in resting state • Better spatial resolution compared with EEG • Measures resting-state and task-based functional connectivity Limitations: • Expensive • Does not provide structural information • Neuromagnetic signals are weak and difficult to measure
Functional magnetic resonance imaging (fMRI)	• Significantly higher intra-hemispheric thalamic FC in idiopathic generalised epilepsy [IGE) patients than controls following SO [Bagshaw *et al.*, 2017 (77)] • Increased FC in thalamic regions that were predominantly functionally connected to somatomotor and occipital neocortices in healthy controls during SO [Bagshaw *et al.*, 2017 (77)] • FC alterations pertaining to the disorder always involving somatomotor and occipital regions at SO [Bagshaw *et al.*, 2017 (77)] • Altered thalamocortical functional connectivity. Both intra- and inter-hemispheric thalamic connectivity measured from functionally defined thalamic subdivisions became more consolidated with progression into sleep with the largest increases observed during NREM-II in in sensorimotor cortices [Hale *et al.*, 2016 (76)]	Strengths: • Non-invasive; • High spatial resolution • Whole brain coverage including sub-cortical regions providing • both structural and functional information • Measures resting-state and task-based functional connectivity • Highly reproducible and reliable; • Easy to acquire in clinical settings Limitations: • Discomfort of scanning environment • Loud acoustic noise • Susceptible to motion artifacts • Moderately expensive • Merely reflect changes of de-oxyhemoglobin concentrations providing indirect measure of neural activity
Positron emission tomography (PET)	• Reduced activity in the dorsolateral prefrontal and lateral orbital areas corresponded with decreased activity in the dorsomedial nucleus of the thalamus [Braun *et al.*, 1997 (78)] • Deactivation of sensory nuclei of the in the absence of reduction in post-rolandic sensory cortices activity level [Braun *et al.*, 1997 (78)]	Strengths: • Both anatomical and functional information can be obtained • high spatial resolution • Less sensitive to motion artifacts Limitations: • Expensive • Invasive (request inject radioactive tracer) • Low temporal resolution
Functional near-infrared spectroscopy	• Decreased in oxy-Hb and increase in deoxy-Hb [Hoshi *et al.*, 1994 (79); Näsi *et al.*, 2011 (80); Shiotsuk *et al.*, 1998 (81); Zhang and Khatami , 2015 (82)] coupled with decreased peripheral arterial oxygen saturation (SpO_2) and HR [Näsi *et al.*, 2011 (80)] • SO was associated with initial decrease of brain perfusion marked with decreased BV and oxy-Hb together with increased muscular BV and deoxy-Hb [Zhang and Khatami, 2015 (82)] • Decreased oxy-Hb and decreased deoxy-Hb during SO [Spielman *et al.*, 2000 (83)]	Strengths: • Non-invasive • Compatible with other modalities due to the absence of electro-optical interference • Safe and easy to set up • Provide changes in oxy- and deoxyhemoglobin concentrations • It allows for measurement of specific biochemical markers, cerebrovascular autonomic regulation and for localization response of approximately 1 s or less. Limitations: • Merely cerebral cortex instead of deep structure • Contaminated by the extracerebral hemodynamics
Transcranial doppler ultrasound	• Marked changes in CBF velocity during SO: increases with the transition from wakefulness to sleep (alpha–theta) and decreases with awakening from sleep [Klingelhöfer *et al.*, 1995 (143); Kotajima *et al.*, 2005 (144); Kuboyama *et al.*, 1997 (145)] • Lower CBF associated with stable non-REM sleep (SO) than wakefulness that reduces progressively as sleep stages become deeper [Hajak *et al.*, 1994 (146); Kotajima, *et al.*, 2005 (144); Kuboyama *et al.*, 1997 (145)] • A fall in mean flow velocity below the waking level during sleep NREM-II following SO [Hajak *et al.*, 1994 (146); Klingelhöfer *et al.*, 1995 (143)] • Higher flow patterns during sleep NREM-II following SO compared with CBF values after transition from SWS to sleep NREM-II [Hajak *et al.*, 1994 (146)]	• TDC- high temporal resolution • Non-invasive • Continuous long- term recording during an entire sleep period and simultaneous registration of associated variables
Xenon 133 inhalation	• Significantly decreased fast flow values with its most prominent change in the brainstem-cerebellar regions [Sakai *et al.*, 1980 (147)] • Higher hemispheric values during NREM-IIa compared with that of NREM-II following SWS [Sakai *et al.*, 1980 (147)]	
Physiological and behavioural measurements		
Cardiovascular and respiratory activities	• Ventilation decreases with the alpha–theta transition and increases with the theta–alpha transition [Burgess *et al.*, 1999 (95); Colrain *et al.*, 1987 (148); Shinar *et al.*, 2006 (96); Trinder *et al.*, 1992 (149)] with the magnitude of change associated with positive function of metabolic drive at time of the state change [Trinder *et al.*, 1992 (149)] • Rising airway resistance during SO [Kay *et al.*, 1994 (91)] with the compensation reflex responses being lost during SOP [Gora *et al.*, 1998 (150)] • Positive relationship between ventilation and level of arousal during periods of unstable ventilation in young healthy adults [Trinder *et al.*, 1997 (151)] • Greater amplification of state-related ventilatory fluctuations in individuals with higher peripheral chemoreceptor drive [Dunai *et al.*, 1999 (152)] • The arterial baroreflex has a marked influence on the heart beat interval (HBI) control at SO with a positive correlation between fluctuations of BP and those of subsequent HBI after SO [Hwang *et al.*, 2013 (153)] • Substantial falls in BP and HR before the initial onset of theta activity and again after the attainment of stable sleep following the cessation of spontaneous arousals [Burgress *et al.*, 1999 (95); Carrington *et al.*, 2005 (154); Shinar *et al.*, 2006 (96)] • Decreased BP and sympathovagal balance shift towards increased vagal activity, in close association with SO [Burgess *et al.*, 1997; 1999 (95); Carrington *et al.*, 2003 (98)] • No significant change in respiratory sinus arrhythmia (RSA), pre-ejection period (PEP), and T-wave amplitude (TWA) is detected with the attainment of stable NREM-II sleep during SO [Burgess *et al.*, 1999 (95)] • The fall of both BP and HR was retarded between the intervening phases of 3 (NREM I–II) and 4 (NREM II to the last microarousal prior to stable sleep) [Carrington *et al.*, 2005 (154)] • Both the rate and magnitude of the BP decline were negatively associated with the number of arousals during these intermittent phases [Carrington *et al.*, 2005 (154)] • Significant correlations between alpha level and changes in peripheral physiological variables in the vicinity of sustained alpha losses in high-alpha subjects [Perry & Goldwater, 1987 (94)] • A greater incidence of greater CO_2 tension in NREM-I and II on days 2 and 3 [Naifeh & Kamiya, 1981 (93)], in addition to lower abdominal breathing amplitude, and a higher thoracic:abdominal breathing ratio during SO [Naifeh & Kamiya, 1981 (93); Perry & Goldwater, 1987 (94)] • A significant decline in very low-frequency power before SO [Okamoto-Mizuno *et al.*, 2008 (155); Shinar *et al.*, 2006 (96)]; normalized LF [LF/(LF + HF)], and body temperature prior to SO both in the time course of the SO and in the consecutive phases [Okamoto-Mizuno *et al.*, 2008 (155); Shinar *et al.*, 2006 (96)]; decreased LF power and the absence of significant change in HF (based on HRV-power spectrum) [Shinar *et al.*, 2006 (96)] reflecting a shift towards parasympathetic predominance • Significantly higher normalised spectral power in LF bands following SO in participants with long SOL compared with participants with short SOL [Nano *et al.*, 2020 (156)] • Significantly lower normalised spectral power in HF band in individuals with long SOL, compared with individuals with short SOL, over three time periods (first 10 min intending to sleep, 10 mins prior to SO and 10 min after SO) [Nano *et al.*, 2020 (156)] • At alpha-theta transitions, phasic activity of diaphragm, intercostal, and genioglossus (GG) muscles fell and rose again, and phasic and tonic activities of tensor palatini (TP) fell and remained at low levels during theta stage [Worsnop *et al.*, 1998 (92)] • Approximately 50% of GG inspiratory units (phasic and tonic) ceased activity at SO, with the rest of the active inspiratory units showing a reduction in the proportion of each breath [Wilkinson *et al.*, 2008 (157)] • Tonic and expiratory units unaffected by SO, maintaining their discharge pattern over the alpha-theta transition [Wilkinson *et al.*, 2008 (157)] • A greater active proportion of expiratory modulated motor units in TP at SO [Nicholas *et al.*, 2012 (158)] • The expiratory units, along with inspiratory units, tended to become silent over SO suggesting that both expiratory and inspiratory drive components are reduced at SO in TP [Nicholas *et al.*, 2012 (158)] • No systematic reduction in the GG reflex to negative pressure at sleep onset [Shea *et al.*, 1999 (159)]	Strengths: • Great adjunct to other neuroimaging or electrophysiological measurements • East to implement • High temporal resolution for physiological measurements • Behavioural measures allow for information regarding overt cognitive processing to be obtained. Limitations: • Great interindividual variability • Less accurate temporal correspondence between behavioural and electrophysiological measures underestimating SO • Needs systematic investigations as it is variable with time and in association with other factors
Oculomotor activities	• A temporal coherence regarding the occurrence, the cycle time and the phase be-tween SEMs and a respiratory-like rhythm (autorhythmicity) [Rittweger, & Pöpel, 1998 (160)] • A disappearance of saccades, a reduction of endogenous blinking, and an appearance slow eye movements (SEMs) during SO [Pizza *et al.*, 2011 (99)] • SEM activity shows a linear increase before the beginning of sleep NREM-I [Agnew & Webb, 1972 (100); Hori *et al.*, 1982 (101); Ogilvie *et al.*, 1988 (102); De Gennaro *et al.*, 2000 (103)], declining progressively during the first minutes of NREM-II [Hiroshige *et al.*, 1999 (104); Pizza *et al.*, 2011 (99)] • Disappearance of SEM with the beginning of behaviourally defined SO [Ogilvie *et al.*, 1988 (102)] • Sleep spindles could trigger the reduction and the disappearance of SEMs in the late part of the SOP [De Gennaro *et al.*, 2000 (103)] • The split half of the distributions with respect to NREM-II onset indicated a positive correlation of delta power with the increase of SEM activity before SO, and of beta power with the decreased SEMs after SO [De Gennaro *et al.*, 2000 (103)] • Using Hori's scoring rules maximal SEM velocity was observed during sustained alpha suppression and delta-theta predominance at SOP [Porte, 2004 (105)] • During H7 and H8, characterised by VSW bursts and incipient spindles and KCs, SEM was maximal in amplitude during SOP [Porte, 2004 (105)] • Using nightcap, changes in spectral power of theta and alpha frequency bands correlated well with eyelid behaviour during SOP [Cantero *et al.*, 2002 (161)] • Changes in eyelid movement density predicted better than did changes in theta and alpha spectral power [Cantero *et al.*, 2002 (161)] • While hypnagogic dreams contained all the classic features of REM dreams, the relatively low frequencies of features such as self-representation and narrative plot (20% and 10%, respectively) highlight a dramatic difference between hypnagogic and REM dreams [Rowley *et al.*, 1998 (162)] • Although, there is no fixed order of appearance of dream features during SO, a preferred order is implied by their relative frequencies, with sensorimotor experience preceding the development of narrative plot [Rowley *et al.*, 1998 (162)]	
Thermoregulation	• A significant decline in core body temperature during SO [Zulley *et al.*, 1981 (87); Gillberg and Akerstedt, 1982 (163); Barrett *et al.*, 1993 (84); Murphy and Campbell, 1997 (86); Van Den Heuvel *et al.*, 1998 (88)] • In synchronized subjects, SO occurred, on the average, 1.34 h prior to the minimum of temperature. The desynchronized subjects had a broad bimodal distribution of SO (peaks 6.3 and 1.3 h before the minimum) [Zulley *et al.*, 1981 (87)] • Significant correlations between the interval from maximum rate of decline to SO and the amount of slow-wave sleep (SWS) during disentrainment [Murphy and Campbell, 1997 (86)] • Significantly decreased rectal core temperature (Tc) over time only in the Habitual Sleep condition [Van Den Heuvel *et al.*, 1998 (88)] • The greater decline in Habitual Sleep Tc was associated with significantly increased pe-ripheral hand and foot skin temperatures before SO [Van Den Heuvel *et al.*, 1998 (88)] • Higher subjective sleepiness measures in the Habitual Sleep Onset condition from 150 min prior until SO [Van Den Heuvel *et al.*, 1998 (88)] • The distal-to-proximal skin temperature gradient was the best predictor variable for SOL [Kräuchi *et al.*, 2000 (89)] • Increased wrist skin temperatures (using wrist-worn accelerometer) on average by 0.6° (of Celcius) in 10 min prior to the SO and could be tracked robustly along a slope of time [Partonen *et al.*, 2022 (90)]	
Behavioural measurements	• Decreased responsivity to external sensory stimuli coupled with sharp increases in EEG synchronisation as EEG stages passed from W through NREM I to II at SO demonstrated in (I) auditory reaction times [Birrell, 1983 (110); Ogilvie and Wilkinson, 1984 (111); Ogilvie *et al.*, 1989 (108); 1991 (52); Scott *et al.*, 2018 (164)]; (II) reaction times to vibratory stimuli [Scott *et al.*, 2021 (165)] with responses to stimuli typically ceasing between late-NREM-I sleep and NREM-II during SO; (III) duration of time intervals between consecutive self-generated motor responses in a finger tapping task with a greater proportion of slow-wave sleep (SWS) observed during transition from wakefulness to sleep in motor-generated tasks compared with the RTT [Casagrande *et al.*, 1995 (166), 1997 (113)]; (IV) combined simultaneously-recorded physiological measurements of behavioural, with EEG and respiratory data [Ogilvie and Wilkinson, 1984 (111); Ogilvie *et al.*, 1989 (108)]; ERP [Ogilvie *et al.*, 1991 (52)] characterising the SOP with markers of the reduction of alpha power, the increase of theta and delta power and the reduction of muscle activity in a sustained breathing paradigm [Prerau *et al.*, 2014 (167)]; (V) clock monitored microswitch release [Viens *et al.*, 1988 (109)] • Shorter SOL for the left hemisphere, considering both behavioural (cessation of the FTT for more than 2.5 s) and EEG SOL [Casagrande & Bertini, 2008 (168)] • Strong association of alpha level [as sleep Stage Wake (w) *vs.* NREM-I sleep] with behavioural level, and a strong association of alpha loss events with key closure events in alpha abundant (high-alpha) subjects [Perry & Goldwater, 1987 (94)] • Reduced alertness indexed by EEG or behavioural markers at SO in healthy controls is linked with a remarkable asymmetric increase in error rates to mislocate left-sided auditory stimuli to the right [Bareham *et al.*, 2014 (107)]	

BP, blood pressure; BV, blood volume; CBF, cerebral blood flow; DMN, default mode network; deoxy-Hb, deoxygenated haemoglobin; DPFC, dorsolateral prefrontal cortex; FC, functional connectivity; IPL, IPL, inferior parietal lobule; HF, high frequency; HR, heart rate; HRV, heart rate variability; HPC, hippocampus; KC, K-complex; LF, low frequency; LPFC, lateral prefrontal cortex; MCC, medial cingulate cortex; MMN, mismatch negativity; MPFC, medial prefrontal cortex; oxy-Hb, oxygenated haemoglobin; PCC, posterior cingulate cortex; PFC, prefrontal cortex; RT, reaction time; SD, sleep deprivation; SO, sleep-onset; SOP, sleep-onset period; SOL, sleep-onset latency; VSW, vertex sharp wave.

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Table S2 The sleep onset process in patients with sleep disorders

Method of study	Type of disorder	Main findings
Electroencephalogram (EEG)		
Standard sleep staging Sub-division of standard sleep stages	Narcolepsy without cataplexy (N-C) Narcolepsy with cataplexy (N+C) Idiopathic Hypersomnia (IH) Behaviourally induced inadequate sleep syndrome (BIISS) Periodic limb movement disorder (PLMD)	• SOREM periods in the IHL, BIISS and PLMD groups arose from NREM-II sleep, 75% of those in N+C arose from NREM-I and in N–C only 52% arose from NREM-I [Drakatos *et al.*, 2013 (169)] • Within the N-C group, those with SOREM periods arising from NREM-I had a shorter MSL [Drakatos *et al.*, 2013 (169)] • Significantly longer SusSL (three sleep NREM-I epochs or any other sleep stage epoch, than SL(the time elapsed to the occurrence of a single epoch of sleep NREM-I) in IH patients compared with N-C and N+C patients [Pizza *et al.*, 2011 (73)] • IH fluctuated through a wake-NREM-I before the onset of sustained sleep, while N+C and N-C shift abruptly into a sustained sleep [Pizza *et al.*, 2011 (73)] • Patients with insomnia, were best able to estimate their SL by the first epoch scored as NREM-II that is followed by at least 15 min of uninterrupted sleep [Rauri & Olmstead, 1983 (112)]
	Sleep onset insomnia (SOI)	• Patients with SOI had more 4-second epochs scored as awake, and took longer to achieve 30 continuous 4-second epochs of NREM sleep after the first epoch of NREM-I [Moul *et al.*, 2007 (63)] • A slower rate of accumulating sleep was detected only with the 4-s scoring during SOP [Moul *et al.*, 2007 (63)] • Momentary state-switching instabilities in SIO [Moul *et al.*, 2007 (63)]
Quantitative EEG		
Spectral power	Narcolepsy without cataplexy (N-C) Narcolepsy with Cataplexy (N+C)	• Significantly higher mean delta and theta amplitude across the SOP for narcoleptic REM naps and narcoleptic NREM-II naps compared with the SOP of normal NREM-II naps or normal NREM-I naps [Alloway *et al.*, 1999 (170)] • Significantly lower mean alpha amplitude for narcoleptic REM naps and narcoleptic NREM-II naps compared with normal naps containing just NREM-I [Alloway, *et al.*, 1999 (170)] • Significantly lower mean sigma amplitude for narcoleptic REM naps compared to normal NREM-I naps, and tended to be lower for narcoleptic REM naps compared to normal NREM-II naps [Alloway, *et al.*, 1999 (170)] • Mean beta amplitude did not differ between the narcoleptic and normal SOP [Alloway, *et al.*, 1999 (170)]
	Sleep-onset insomnia (SOI) Sleep maintenance insomnia (SMI) Restless Legs syndrome (RLS)	• Reduced alpha power for patients with insomnia [Lamarche and Ogilvie, 1997 (171); Freedman, 1986 (64)], combined with a failure to reduce alpha power and beta-1 power during the SOP [Staner *et al.*, 2003 (68)] • All frequencies below the beta range, have slower rise rates and reach lower levels in the insomnia group during SOP [Freedman, 1986 (64); Merica *et al.*, 1998 (65); Merica & Gaillard, 1992 (66); Perlis *et al.*, 2001 (67); Staner *et al.*, 2003 (68)] with increased beta power maximally during NREM-I [Perlis *et al.*, 2001 (67)] • Increased delta band (0.5–4 Hz) power and decreased beta band (15–30 Hz) power during the SOP [Alloway *et al.*, 1999 (170); Freedman, 1986 (64); Lamarche and Ogilvie, 1997 (171); Merica and Gaillard, 1992 (66)] • Significantly lower beta-2 frequency band (18–29.75 Hz) power in SOI than in SMI preceding SO [Cervena *et al.*, 2014 (69)] • Significantly higher alpha power for SMI group compared with good sleepers (GS) before SO [Cervena *et al.*, 2014 (69)] • In SOI group, delta power increased slower after sleep onset; beta2 and 3 (18–29.75 and 30–39.75 Hz) power decrease less abruptly before SO; beta1 (15–17.75 Hz) power increased through the whole SOP [Cervena *et al.*, 2014 (69)] • Less alpha during the first part of SOP, the absence of the dramatic drop in alpha across the SOP, less delta in the last quartile of the chronological analysis of the SOP were observed in individuals with psychophysiological insomnia [Lamarche & Ogilvie *et al.*, 1997 (171)] • Lower relative beta power in psychiatric insomnia cohort and higher relative beta power values in psychophysiological cohort during wakefulness [Lamarche & Ogilvie *et al.*, 1997 (171)] • Significantly higher frontal beta power and current density, and beta and gamma frontoparietal temporal coupling during waking and NREM-I in patients with SOI [Corsi-Cabrera *et al.*, 2012 (70)] • Increased alpha and beta bands and/or beta/delta ratio in RLS versus normal controls, during both early-SOP and late-SOP which were, however, smaller than the increases found in patients with insomnia [Ferri *et al.*, 2014 (71)]
Dynamic detrended fluctuation analysis	Narcolepsy without cataplexy (N-C) Narcolepsy with Cataplexy (N+C)	• Electrophysiological brain activity was changing rapidly across the SOP with a significantly larger SOP in individuals with narcolepsy [Kim *et al.*, 2009 (72)]
Event-related potentials		
Auditory-related evoked potentials	Sleep-onset insomnia (SOI) sleep maintenance insomnia (SMI)	• P2 amplitude was significantly smaller for poor sleepers compared with GS, following standard stimuli at all fronto-central sites, at SO. Groups did not differ in N1, N350, or P300 amplitudes in wake, NREM-I, or NREM-II [Kertesz, & Cote, 2011 (172)]
Cerebral blood flow		
Xenon133 inhalation	Narcolepsy Obstructive Sleep Apnea	• Increased CBF values in narcolepsy patients but decreased CBF values in patients with sleep apnea [Meyer *et al.*, 1987 (173)]
Physiologic measurements		
Cardiovascular and respiratory activities	Sleep-onset insomnia (SOI) sleep maintenance insomnia (SMI)	• A higher initial HR (an index primarily modulated by parasympathetic activity at rest) in baseline in SOI group, but no differences observed compared with healthy controls in pre- and post-SO [Freedman & Sattler, 1982 (174); De Zambotti *et al.*, 2011 (175)] • A significantly higher low-frequency percentage of HRV in pre-NREM- I with a reduction in HR 160s beginning prior to NREM- I onset amongst GS with HR of those with insomnia only to decline after NREM-I onset [Tsai *et al.*, 2019 (176)] • Both the insomnia cohort and healthy control had their HRs dropped to a level comparable to their HRs at 220 s and 80 s prior to NREM-II onset respectively [Tsai *et al.*, 2019 (176)] • Increased pre-ejection period (PEP) (related inversely to sympathetic β-adrenergic activity) after SO in controls, but remained unchanged in those with insomnia. PEP was also significantly lower in insomniacs than in GS in both conditions [De Zambotti *et al.*, 2011 (175)]
	Obstructive Sleep Apnea (OSA) Various Sleep Disorders (VSD)	• Diaphragm tone and end-expiratory lung volume frequently decreased following SO, with greater falls at transitions accompanied by respiratory events [Stadler *et al.*, 2010 (177)] • Small but consistent decrements in the activity of both the TP and GG muscles in healthy controls but large, significantly greater decrements in TP EMG in OSA patients at SO [Mezzanotte *et al.*, 1996 (178)] • Significant decrement in UA dilator muscle activity following SO [Fogel *et al.*, 2005 (179); Mezzanotte *et al.*, 1996 (178); Stadler *et al.*, 2010 (177)] • Greater fall in GG EMG in the OSA patients followed by subsequent muscle recruitment following alpha to theta transition (in whom upper airways dilator increases) [Fogel *et al.*, 2005 (179)] • Significant decrease in low-frequency power 2 mins prior to SO and no significant change in high-frequency power in all groups (controls, OSA, VSD) [Shinar *et al.*, 2006 (96)] • Higher sympathovagal balance in OSAS and VSD patients before and after SO [Shinar *et al.*, 2006 (96)]
Ocular activities	Obstructive Sleep Apnea (SOA)	• Mean slow eye movement (SEM) latency significantly correlated with SL at the MSLT [Fabbri *et al.*, 2010 (180)] • Both SEMs latency and SLs were significantly shorter in OSA than normal MSLT patients [Fabbri *et al.*, 2009 (181)]
Thermoregulation	Sleep-onset insomnia (SOI) sleep maintenance insomnia (SMI)	• The temperature rhythm markers of the insomnia group's rhythms were approximately 2.5 h later than those of the GS. Their usual bedtime fell within the "wake maintenance zone" of their delayed temperature rhythm [Morris *et al.*, 1990 (182)] • Positive correlation between the amount of wakefulness within the first hour after initial SO and maximum rate of decline relative to SO in individuals with SMI [Campbell and Broughton 1994 (85)]
Behavioural measurements	Sleep-onset insomnia (SOI) Sleep maintenance insomnia (SMI)	• Significant differences between the three different measures of SOL. Estimates of SOL provided by the subjects were significantly longer than those recorded by the switch activated clock which were significantly longer than their partners estimates [Franklin, 1981 (183)]

GG, genioglossus; GS, good sleepers; HR, heart rate; HRV, heart rate variability; SO, MSLT, multiple sleep latency test; SL, sleep latency; sleep-onset; SOP, sleep-onset period; SOL, sleep-onset latency; SusSL, sustained sleep latency; TP, tensor platini.

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Table S3 Methodological evaluation of studies using the EPHPP Quality Assessment Tool for Quantitative Studies

Author and year	Population studied	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Global rating
Agnew and Webb, 1972 (100)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Sakai *et al.*, 1980 (147)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Franklin, 1981 (183)	Insomniacs	Strong	Weak	Weak	Moderate	Weak	NA	Moderate
Naifeh and Kamiya *et al.*, 1981 (93)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Zulley *et al.*, 1981 (87)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Freedman and Sattler, 1982 (174)	Primary Insomnia	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Gillberg and Akerstedt, 1982 (163)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Hori *et al.*, 1982 (101)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Birrell., 1983 (110)	Healthy Controls	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
Rauri and Olmstead , 1983 (112)	Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong		Strong
Ogilvie and Wilkinson, 1984 (111)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Strong
Hori *et al.*, 1985 (46)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	N/A	Moderate
Freedman, 1986 (64)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Colrain *et al.*, 1987 (148)	Healthy Controls	Moderate	Weak	Strong	Moderate	Strong	NA	Moderate
Meyer *et al.*, 1987 (173)	Narcolepsy Obstructive Sleep Apnea Healthy Controls	Strong	Moderate	Moderate	Moderate	Moderate		Strong
Perry and Goldwater., 1987 (94)	Healthy Controls	Weak	Weak	Moderate	Moderate	Strong	Strong	Moderate
Ogilvie *et al.*, 1988 (102)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Viens *et al.*, 1988 (109)	Healthy Controls	Weak	Weak	Moderate	Moderate	Moderate	NA	Weak
Ogilvie *et al.*, 1989 (108)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Morris *et al.*, 1990 (182)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Nielsen-Bohlman *et al.*, 1991 (128)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Ogilvie *et al.*, 1991 (52)	Healthy Controls	Moderate	Weak	Strong	Moderate	Strong	NA	Moderate
Merica and Gaillard *et al.*, 1992 (66)	Insomniacs Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Trinder *et al.*, 1992 (149)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Barrett *et al.*, 1993 (84)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Campbell and Broughton, 1994 (85)	Secondary Insomnia	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Hajak *et al.*, 1994 (146)	Healthy Controls	Strong	Weak	Moderate	Moderate	Strong	Moderate	Moderate
Harsh *et al.*, 1994 (126)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Hasan &Broughton, 1994 (59)	Healthy Controls	Moderate	Weak	Moderate	Moderate	Strong	NA	Moderate
Hori *et al.*, 1994 (40)	Healthy Controls	Healthy Controls	Weak	Strong	Moderate	Moderate	NA	Moderate
Hoshi *et al.*, 1994 (79)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Kay *et al.*, 1994 (91)	Healthy Controls	Weak	Moderate	Strong	Moderate	Strong	NA	Moderate
Bastuji *et al.*, 1995 (133)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Casagrande *et al.*, 1995 (165)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Klingelhöfer *et al.*, 1995 (143)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Winter *et al.*, 1995 (129)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Wright *et al.*, 1995 (38)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	Strong	Moderate
De Lugt *et al.*,1996 (124)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Mezzanotte *et al.*, 1996 (178)	Obstructive Sleep Apnea Healthy Controls	Strong	Moderate	Strong	Moderate	Moderate	NA	Strong
Braun *et al.*, 1997 (78)	Healthy Controls	Strong	Weak	Moderate	Moderate	Strong	NA	Moderate
Burgess *et al.*, 1997 (97)	Healthy Controls	Moderate	Moderate	Strong	Moderate	Moderate	NA	Strong
Casagrande *et al.*, 1997 (113)	Healthy Controls	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
Kuboyama *et al.*, 1997 (145)	Healthy Controls	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
Lamarche and Ogilvie *et al.*, 1997 (171)	Psychophysiological Insomniacs Psychiatric Insomniacs Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Morikawa *et al.*, 1997 (56)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Murphy and Campbell 1997 (86)	Healthy Controls	Strong	Moderate	Moderate	Moderate	Strong	NA	Strong
Tanaka *et al.*, 1997 (50)	Healthy Controls	Strong	weak	Strong	Moderate	Strong	NA	Moderate
Trinder *et al.*, 1997 (151)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Gora *et al.*, 1998 (150)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Merica *et al.*, 1998 (65)	Insomniacs Healthy Control	Strong	Moderate	Moderate	Moderate	Strong	NA	Strong
Rittweger and Pöpel, 1998 (160)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Rowley *et al.*, 1998 (162)	Healthy Controls	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
Shiotsuka *et al.*, 1998 (81)	Healthy Controls	Moderate	Weak	Moderate	Moderate	Strong	NA	Moderate
Tanaka *et al.*, 1998 (122)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Van Den Heuvel *et al.*, 1998 (88)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Webster and Colrain, 1998 (136)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Worsnop *et al.*, 1998 (92)	Healthy Controls	Strong	Weak	Moderate	Moderate	Strong	Strong	Moderate
Alloway *et al.*, 1999 (170)	Narcolepsy Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Burgess *et al.*, 1999 (95)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Cote and Campbell,1999 (134)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Dunai *et al.*, 1999 (152)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Gora *et al.*, 1999 (137)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Hiroshige *et al.*,1999 (104)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Shea *et al.*, 1999 (159)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Tanaka *et al.*, 1999 (121)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Colrain *et al.*, 2000a (125)	Healthy Controls	Moderate	Weak	Moderate	Moderate	Strong	NA	Moderate
Colrain *et al.*, 2000b (132)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
De Gennaro *et al.*, 2000 (103)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Kräuchi *et al.*, 2000 (89)	Healthy Controls	Strong	Weak	Moderate	Moderate	Strong	NA	Moderate
Sabri *et al.*, 2000 (141)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Spielman *et al.*, 2000 (83)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Tanaka *et al.*, 2000 (51)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Webster and Colrain, 2000 (139)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
De Gennaro *et al.*, 2001a (44)	Healthy Controls	strong	Weak	Strong	Moderate	Strong	N/A	Moderate
De Gennaro *et al.*, 2001b (45)	Healthy Controls	strong	Weak	Strong	Moderate	Strong	N/A	Moderate
Gora *et al.*, 2001 (138)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Hull and Harsh, 2001 (135)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Nittono *et al.*, 2001 (140)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Perlis *et al.*, 2001 (67)	Primary Insomnia Insomnia secondary to major depression Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong

Table S3 *(continued)*

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Table S3 *(continued)*

Author and year	Population studied	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Global rating
Cantero *et al.*, 2002 (161)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Cote *et al.*, 2002 (126)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Morikawa *et al.*, 2002 (60)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Peszka and Harsh 2002 (131)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Carrington *et al.*, 2003 (98)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Staner *et al.*, 2003 (68)	Primary Insomniacs Depressive Insomniacs Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
De Gennaro *et al.*, 2004 (54)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Porte *et al.*, 2004 (105)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Bódizs *et al.*, 2005 (106)	Individuals with epilepsy	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
Carrington *et al.*, 2005 (154)	Healthy Controls	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
De Gennaro *et al.*, 2005 (55)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Fogel *et al.*, 2005 (179)	Obstructive Sleep Apnea Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	Strong	Strong
Kotajima *et al.*, 2005 (144)	Healthy Controls	Moderate	Weak	Strong	Moderate	Moderate	Strong	Moderate
Tamaki *et al.*, 2005 (123)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Shinar *et al.*, 2006 (96)	Obstructive Sleep Apnea Various Sleep Disorders Healthy Controls	Strong	Moderate	Moderate	Moderate	Strong	NA	Strong
Moul *et al.*, 2007 (63)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Casagrande and Bertini 2008 (168)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Ferri *et al.*, 2008 (62)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Okamoto-Mizuno, 2008 (155)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Wilkinson *et al.*, 2008 (157)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Fabbri *et al.*, 2009 (181)	Obstructive Sleep Apnea Healthy Controls	Strong	Moderate	Strong	Moderate	Moderate	NA	Strong
Kim *et al.*, 2009 (72)	Narcolepsy Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Fabbri *et al.*, 2010 (180)	Obstructive Sleep Apnea	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Magnin *et al.*, 2010 (74)	Individuals with refractory temporal lobe epilepsy	Moderate	Weak	Moderate	Moderate	Strong	NA	Moderate
Stadler *et al.*, 2010 (177)	Obstructive Sleep Apnea Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	Strong	Strong
Yasuda *et al.*, 2010 (130)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
De Zambotti *et al.*, 2011 (175)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Kertesz and Cote, 2011 (172)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	Moderate	Strong
Näsi *et al.*, 2011 (80)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Pizza *et al.*, 2011 (99)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Pizza *et al.*, 2011 (73)	Narcolepsy Idiopathic Hypersomnia	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Corsi-Cabrera *et al.*, 2012 (70)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Strong	Strong	NA	Strong
Nicholas *et al.*, 2012 (158)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Drakatos *et al.*, 2013 (169)	Narcolepsy Idiopathic Hypersomnia Behaviourally Induced Inadequate Sleep Syndrome Periodic Limb Movement Disorder	Strong	Moderate	Strong	Moderate	Moderate	NA	Strong
Hwang *et al.*, 2013 (153)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Marzano *et al.*, 2013 (47)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Bareham *et al.*, 2014 (107)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Cervena *et al.*, 2014 (69)	Primary Insomnia Secondary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Ferri *et al.*, 2014 (71)	Restless Legs Syndrome Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Prerau *et al.*, 2014 (167)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Sarasso *et al.*, 2014 (142)	Individuals with suspected diagnosis of drug-resistant extra-temporal focal epilepsy	Moderate	Weak	Moderate	Moderate	Strong	NA	Moderate
Siclari *et al.*, 2014 (49)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Park *et al.*, 2015 (48)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Zhang and Khatami, 2015 (82)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	Strong	Moderate
Hale *et al.*, 2016 (76)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
Kawai *et al.*, 2016 (120)	Healthy Controls	Moderate	Weak	Moderate	Moderate	Strong	NA	Moderate
Bagshaw *et al.*, 2017 (77)	Healthy Controls and individuals with idiopathic generalised epilepsy (IGE)	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Ioannides *et al.*, 2017 (75)	Healthy Controls	Moderate	Weak	Strong	Moderate	Strong	NA	Moderate
Vecchio *et al.*, 2017 (61)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Fernandez Guerrero and Achermann., 2018 (57)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Scott *et al.*, 2018 (164)	Healthy Controls	Strong	Weak	Strong	Moderate	Weak	NA	Weak
Achermann *et al.*, 2019 (58)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	NA	Moderate
Fernandez Guerrero and Achermann., 2019 (53)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Gorgoni *et al.*, 2019 (118)	Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Tsai *et al.*, 2019 (176)	Primary Insomnia Healthy Controls	Strong	Moderate	Strong	Moderate	Strong	NA	Strong
Nano *et al.*, 2020 (156)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	NA	Moderate
Gorgoni *et al.*, 2021 (119)	Healthy Controls	Strong	Weak	Strong	Moderate	Moderate	Strong	Moderate
Scott *et al.*, 2021 (165)	Healthy Controls	Strong	Weak	Strong	Moderate	Weak	Strong	Weak
Partonen *et al.*, 2022 (90)	Healthy Controls	Strong	Weak	Moderate	Moderate	Moderate	NA	Moderate
Strauss *et al.*, 2022 (114)	Healthy Controls	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate

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