Sleepiness should be reinvestigated through the lens of clinical neurophysiology: a mixed expertal and big-data Natural Language Processing approach.

Vincent P. Martin[1,2,3], Christophe Gauld[4,5], Jacques Taillard[3], Laure Peter-Derex[6,7], Régis Lopez[8,9], Jean-Arthur Micoulaud-Franchi[3,10*]

[1] Deep Digital Phenotyping Research Unit, Department of Precision Health, Luxembourg Institute of Health, L-1445 Strassen, Luxembourg

[2] Univ. Bordeaux, CNRS, Bordeaux INP, LaBRI, UMR 5800, F-33400 Talence, France

[3] Univ. Bordeaux, CNRS, SANPSY, UMR 6033, F-33000 Bordeaux, France

[4] Service Psychopathologie du Développement de l'Enfant et de l'Adolescent, Hospices Civils de Lyon & Université de Lyon 1, France

[5] Institut des Sciences Cognitives Marc Jeannerod, UMR 5229 CNRS & Université Claude Bernard Lyon 1

[6] Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR 5292, Lyon, France

[7] Centre for Sleep Medicine and Respiratory Diseases, Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon 1 University, Lyon, France

[8] National Reference Centre for Orphan Diseases, Narcolepsy-Rare hypersomnias, Sleep Unit, Department of Neurology, CHU de Montpellier, University of Montpellier, Montpellier, France

[9] Institute for Neurosciences of Montpellier (INM), University of Montpellier, Inserm, Montpellier, France

[10] University Sleep Clinic, University Hospital of Bordeaux, Place Amélie Raba-Leon, 33 076 Bordeaux, France.

Short title: Sleepiness should be studied using clinical neurophysiology

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*Corresponding author:

Jean-Arthur Micoulaud-Franchi

University Sleep Clinic, University Hospital of Bordeaux, Place Amélie Raba-Leon, 33 076 Bordeaux, France.

Phone: 00 33 622 364 019

Mail: jarthur.micoulaud@gmail.com

Abstract

Historically, the field of sleep medicine has revolved around electrophysiological tools. However, the use of these tools as a neurophysiological method of investigation seems to be underrepresented today, from both international recommendations and sleep centers, in contrast to behavioral and psychometric tools. The aim of this article is to combine a data-driven approach and neurophysiological and sleep medicine expertise to confirm or refute the hypothesis that neurophysiology has declined in favor of behavioral or self-reported dimensions in sleep medicine for the investigation of sleepiness, despite the use of electrophysiological tools. Using Natural Language Processing methods, we analyzed the abstracts of the 18,370 articles indexed by PubMed containing the terms 'sleepiness' or 'sleepy' in the title, abstract, or keywords. For this purpose, we examined these abstracts using two methods: a lexical network, enabling the identification of concepts (neurophysiological or clinical) related to sleepiness in these articles and their interconnections; furthermore, we analyzed the temporal evolution of these concepts to extract historical trends. These results confirm the hypothesis that neurophysiology has declined in favor of behavioral or self-reported dimensions in sleep medicine for the investigation of sleepiness. In order to bring sleepiness measurements closer to brain functioning and to reintroduce neurophysiology into sleep medicine, we discuss two strategies: the first is reanalyzing electrophysiological signals collected during the standard sleep electrophysiological test; the second takes advantage of the current trend towards dimensional models of sleepiness to situate clinical neurophysiology at the heart of the redefinition of sleepiness.

Keywords: natural language processing; neurophysiology; sleep medicine; sleepiness; text mining.

Introduction

Sleepiness is an introspective (i.e. subjective experience), physiological and behavioral state [6,12] presented by most individuals over a 24 h period [49,61]. However, when it occurs with a high frequency or during inappropriate situations, it can be qualified as excessive [49] and can be associated with other symptoms such as excessive quantity of sleep or sleep inertia, a syndrome called hypersomnolence. Hypersomnolence has numerous consequences on personal health since it is related to sleep, psychiatric, metabolic, cardiovascular and neurological disorders, with increased risks of morbidity and mortality [32,60]. Hypersomnolence also has a strong impact on public health due to the social and economic burden it imposes on society [7,39], with a specific social and political attention on road accident risks [8].

Although sleepiness and hypersomnolence have played a central role since the first nosological classifications of sleep disorders [21,22,57], systematic investigations of the definition of these symptoms are lacking, in contrast to work on fatigue [61] or more recently vigilance [59]. The problem of defining these constructs is important and plays a role in the variability of estimates of the prevalence of hypersomnolence, which can range from 1.5% to over 40% [31,49,68].

To refine the concepts of somnolence and hypersomnolence, we have previously proposed two complementary approaches [45]. On the one hand, a "*top-down* approach," based on expert knowledge of clinical and research issues in sleep medicine [42]. Such an approach distinguishes three sub-dimensions of hypersomnolence (namely excessive daytime sleepiness, excessive sleep quantity, and wake-up perturbations), themselves split into sub-dimensions (respectively: continuous drowsiness related to an insufficient level of arousal, excessive sleep propensity characterized by the occurrence of voluntary or involuntary sleep episodes and automatic behaviors for excessive daytime sleepiness; difficulties in interrupting sleep, confusion upon awakening and sleep inertia for wake-up perturbations).

However, a possible limitation of such an approach is that hypersomnolence is conceived through expert knowledge, which may be biased precisely because of this expertise. We have recently proposed a complementary approach to the delimitation of somnolence and hypersomnolence, which we have termed "*bottom-up*" [44]. This approach seeks to bring out possible sub-dimensions of somnolence and hypersomnolence by identifying and studying the tools designed to measure them [53]. We identified and classified all the tools for measuring sleepiness and hypersomnolence cited in the scientific literature, with the minimum of preconceptions about the dimensions they measure. Based on a systematic analysis of measurement tools, we hypothesized that this approach would enable us to highlight the different dimensions of somnolence and hypersomnolence in a way that is not based on expert knowledge, but on an historical approach to the successive evolution and adjustments of this complex, multidimensional concept.

For this approach, we used an *umbrella review* [24] of tools for measuring sleepiness in adults [44]. This work, carried out in line with PRISMA [50] recommendations, initially enabled us to select 36 review articles on the assessment of hypersomnolence published since 1982, within which 99 distinct hypersomnolence measurement tools were identified. Through an aggregative and inductive process, these tools were classified into 8 categories: Questionnaires (n = 54, 54.5%); Measures derived from electroencephalography (EEG) (n = 7, 7.1%); Polysomnography-derived measures (PSG) (n = 10, 10.1%); Performance-based measures (n = 12, 12.1%), Activity-based measures (n = 7, 7.1%); Eye-related measures (n = 3, 3.0%); Autonomic system measures (n = 4, 4.0%), Other measures (n = 2, 2.0%) [44]. EEG and PSG derived measures and some eye-related and autonomic system measures are considered as electrophysiological measurement tools.

In addition, for each tool, we looked for the publication date of the earliest literature article to our knowledge mentioning the use of this tool in an experimental context related to somnolence or hypersomnolence. Finally, this work enabled us to construct a graphical and interactive representation of these measurement tools[1], according to their first publication date, the category in which they were classified, and the number of mentions of each tool in the included journal articles [44]. This representation helped us to identify chronological elements reflecting the history of the development and adoption of sleepiness and hypersomnolence measurement tools from the 1960s to the present day [44].

Interestingly, this historical analysis has enabled us to identify the use of electrophysiological tools by the clinical neurophysiology community for the investigation of the nervous system functioning in relation to sleepiness as early as the 1960s, e.g. the Event Related Potential (ERP) in 1964 [27] or Quantified Electroencephalography [14]. Since the nervous system operates via electrical signals (action potentials and synaptic potentials), classical as well as

[1] Available online: https://chart-studio.plotly.com/~vincent.martin/7/#/

modern neurophysiological methods are primarily focused on quantifying electrical activity, commonly known as electrophysiology [43]. Nevertheless, it is worth noting that electrophysiology can be employed to assess behavior rather than exclusively examining the physiological activity within the nervous system. This appears to be the case as the field of sleep medicine evolved in relation to sleepiness: electrophysiological signals seems to be now interpreted by the sleep medicine community more to assess behaviors related to performance altered by sleepiness rather than as measures of neurophysiological processes related to brain functioning *per se* [12] (see Figure 1). Indeed, electrophysiological signals have been measured in soporific tasks, which became classical investigations in sleep medicine, such as real and simulated driving performances [11,28] or the Maintenance of Wakefulness Test (MWT) [47] principally to assess sleep onset behavior, in order to evaluate the capacity to remain awake and vigilant. Moreover, since the 1980s, the interest of the sleep community in psychometric tools has dominated innovation in the field of sleepiness measurement tools (almost half of the 99 measurement tools we identified are self-reported sleepiness questionnaires) [44]. In brief, while the interpretation of electrophysiological signals in a neurophysiological framework was a foundation for the investigation of sleepiness, interest in this approach seems to have reduced in sleep medicine.

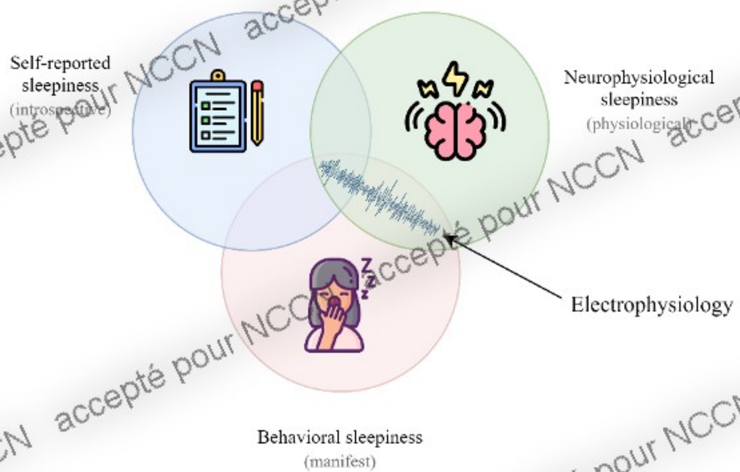

Figure 1 – Classical model of sleepiness at the cross road of self-reported, behavioral and neurophysiological dimensions. Inspired by [6].

The aim of this article is to combine a data-driven approach and neurophysiological and sleep medicine expertise to confirm or refute the hypothesis that neurophysiology has declined in favor of behavioral or self-reported dimensions in sleep medicine for the investigation of sleepiness, despite the use of electrophysiological tools. More specifically, we aim to combine Natural Language Processing techniques and bibliometrics in an historical perspective to analyze all published literature on the subject.

Methods

Our method consists of three steps. All methodological details are given in **Supplementary Materials: Method section**. The method is described in **Figure 2**.

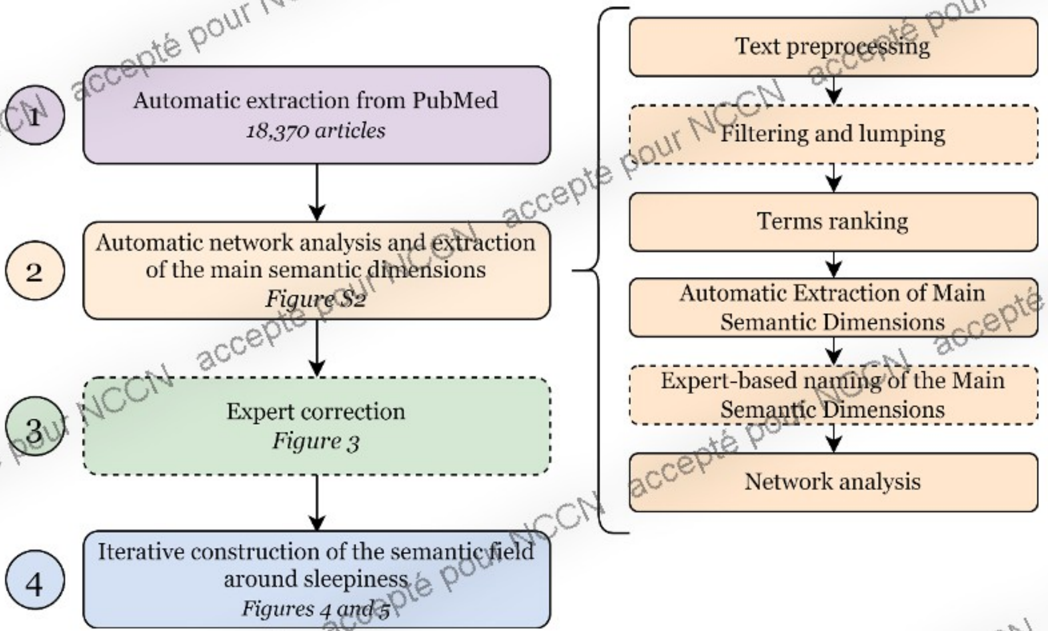

Figure 2: Overview of our mixed analysis method. Dashed boxes rely on expert knowledge. All the other boxes represent fully automated operations.

Corpus extraction and bibliometrics

Automatic extraction of biomedical database

We first performed an extraction of the biomedical database PubMed, including the titles, keywords, and abstracts of associated English terms for sleepiness published between January 1, 1600, and December 31, 2022. The MEDLINE search equation was the following: "sleepiness"[All Fields] OR "sleepy"[All Fields]. The search equation was intentionally as broad as possible, and no restriction was made on the volume of texts: the entire PubMed corpus using the terms of interest was extracted using the R package *pubmedR* (v.0.0.3). Due to a core limitation of this package (which cannot extract more than 10,000 items), we performed three sub-extractions of less than 10k items each and aggregated them before proceeding with the analysis.

Bibliometrics

In order to reflect qualitatively on the data contained in the extracted corpus, we identified the publication year of these articles, their type (abstract, journal article, …) and where they were published using the *biblioAnalysis* function of the *bibliometrix* package (v.4.1.2).

Automatic network analysis and extraction of the main semantic dimensions

In this data extraction and visualization step, the results come from a back-and-forth between the data extracted automatically using NLP algorithms and our expertise in neurophysiology and sleep medicine, enabling us to make informed choices about the parameters of the algorithms.

Text preprocessing

In a second step, we applied methods of Natural Language Processing to extract quantitative information from the qualitative corpus. After having extracted the abstracts of all these items (*bibliometrix* package, v.4.1.2), we used a text segmentation algorithm (*unnest_tokens* function of the R package tidytext, v.0.4.1) to slice all the abstracts into lowercase words.

Filtering and lumping

Then, since our goal is to study the semantic content of the corpus related to sleepiness and neurophysiology, we deleted stop-words (R package *stringr* v. 1.5.0) and specific terms related to the methodology that we identified in the extracted corpus and that are not related to sleepiness.

We then employed a lumping strategy, i.e., we manually searched for all the words and *ngrams* of different sizes (i.e. groups of two, three or four consecutive words) in the filtered corpus that corresponded to the same notion, and automatically lumped them into a unique token (R package *stringr* v. 1.5.0). The detail of this procedure is available in **Supplementary Materials: Method section** of this document. We applied this procedure iteratively both for term clusters emerging from the lexical graph and for neurophysiology-related terms previously identified expertly. The tokens that were automatically extracted from the abstracts are all in lowercase; the lumped tokens (n=41 distinct tokens) are thus reported beginning with an uppercase letter to distinguish them.

[Could you please insert here a box with the following definitions?

Ngram: Any combination of *n* words

Token: In this article, we designate by *token* any word or ngram

Lumped token: Tokens designating the same concept (i.e. "MSLT", "Multiple Sleep Latency Test" or "MSL" have been replaced by the same *lumped token* (in this example, "MSLT").]

Terms ranking

We then sorted all tokens by frequency of occurrence, from most frequent to least frequent. In doing so, we identified the top 10 most frequent tokens, as well as the ranking of tokens associated with neurophysiology.

Automatic Extraction of Main Semantic Dimensions

To further explore and identify the major semantic dimensions underlying the tokens included in the semantic network, we conducted an automatic topic modeling analysis [46,54]. For this purpose, we employed Latent Dirichlet Allocation [9], which revealed the underlying semantic dimensions of our corpus [56]. Both the number of topics and the attribution of each token to a topic are data-driven, resulting from the automatic topic modeling analysis.

Expert-based naming of the Main Semantic Dimensions

Then, on the basis of this analysis and our expertise in neurophysiology and sleep medicine, we have named each of these categories and linked them to the major subfields of sleep medicine related to sleepiness.

Network analysis

We then arranged the aforementioned tokens into an undirected lexical network to visualize and analyze the underlying structure of the links between these terms. We used a Gaussian Graphical Model [18], wherein we computed partial correlations among all nodes included in the network (using package *Hmisc*, v5.1) to measure the strength of their associations. To ensure statistical relevance, we kept only the edges corresponding to statistically significant correlations (Spearman test, $p < .05$).

The resulting graph was then visualized using the software *Gephi*. As in the previous literature, we selected the top 75 most frequent tokens to construct the lexical network ensuring optimal readability of the resulting network [62]. The code and data from the previous steps and the Gephi file are available in **Supplementary Data**.

Expert correction

To complement the previous automatic approach and to fuel the discussion, and to maintain the balance between automatic data analysis and expert approaches that guide our method, a certified sleep specialist (RL) expertly corrected the attribution of each token into a semantic dimension to make it correspond to clinical knowledge. For example, the token "KSS" (Karolinska Sleepiness Scale) or "SSS" (Stanford Sleepiness Scale) were first attributed to the *Sleep disorders* dimension and have been manually corrected so that they belong to the *Subjective sleepiness* dimension. The original automatic attribution of each token to their dimension is available in **Supplementary Material: Table S2**; the expertly-corrected version is available in **Table 2**. We then plotted a second version of the graphical representation of the lexical network based on this corrected categorization.

Iterative construction of the semantic field around sleepiness.

In order to gain a more nuanced understanding of the temporal dynamics in the construction of the field around sleepiness, we examined the temporal evolution of various keywords related to neurophysiology (determined expertly in the previous step of the method) and the dominant terms in the lexical network. We conducted this analysis cumulatively: for a given year n, we used all articles published before n, providing an overview of the existing knowledge domain up to year n.

In order to measure the popularity of tokens over the years, we established two metrics. The first one is the ratio of previously published articles mentioning each token. The higher this metric, the larger the proportion of articles published before the year n that have the targeted token in their title or abstract. The second metric is the rank of these tokens among the published articles: the lower the rank, the more significant the relative weight of the token compared to other tokens.

Results

Corpus extraction and bibliometrics

The literature search identified 18,370 articles for which "sleepiness" or "sleepy" were included in the title, abstract, keywords or MeSH terms, published between 1903 and 2022. These items were predominantly journal articles (n=14,006, 76.2%), comparative studies (n=1,110, 6.0%), clinical trials (n=1,099, 6.0%), case reports (n=809, 4.4%) and English abstracts (n=599, 3.3%). Since the majority of these items are journal articles, we refer to these items as *articles* in the following. Most of these articles were published between 2013 and 2022 (n=9185, 50%), with a quarter published between 2018 and 2022.

These articles were published in 2960 different journals; the 20 most represented ones are reported in Table 1 (covering 37.2% of 18,370 articles). For each journal, we reported its name and the number and proportion of research items of the corpus published in this journal. This list allows us to position the findings derived from this corpus within the field of medicine, as the most represented journals are all within this domain.

Journal	**Nb of articles**
SLEEP	937 (5.1%)
Sleep Medicine	791 (4.3%)
Journal of Clinical Sleep Medicine	525 (2.9%)
Sleep and Breathing	516 (2.8%)
Journal of Sleep Research	525 (2.9%)
CHEST	220 (1.2%)

Chronobiology international	218 (1.2%)
Plos One	214 (1.2%)
Sleep Medicine Reviews	160 (0.9%)
Nature and Science of Sleep	138 (0.8%)
Neurology	131 (0.7%)
American Journal of Respiratory and Critical Care Medicine	118 (0.6%)
The Laryngoscope	113 (0.6%)
Sleep Science	106 (0.6%)
European archives of oto-rhino-laryngology	98 (0.5%)
International Journal of environmental research and public health	98 (0.5%)
Frontiers in Neurology	97 (0.5%)
ECK Surgery	97 (0.5%)
Scientific Reports	97 (0.5%)

Table 1 - Most represented journals among the articles ever published containing the term 'sleepiness' or 'sleepy' in their title, abstract, keywords or MeSH terms, and indexed in PubMed.

Network analysis and extraction of the main semantic dimensions

Text preprocessing and filtering

The raw extracted corpus contained 4,173,784 words of which there were 55,466 distinct words before filtering and lumping. The filtering procedure on 1,186 stop-words and 37 methodology-related words filtered out almost half of 4,173,784 words (1,841,946 filtered words, 44.1%). The resulting filtered corpus contains 54,792 distinct words (2,331,838 in total).

Lumping

During the lumping phase, a total of 159,007 tokens (e.g., “Epworth scale”) were aggregated into 41 distinct lumped tokens (e.g., "ESS"). The resulting corpus after aggregation with the trigrams contains 1,760,301 distinct tokens and a total of 2,245,641 terms (see **Supplementary Material: Method section** for more information).

We applied this procedure both for terms related to clinical dimensions (grouping rules available in the code provided in an online git repository[2]) and for terms related to neurophysiology. For the latter, the lumped tokens were obtained according to the expert-based following rules:

- PSG (n=6970): psg (n=2306), polysomnograph* (n=4664)

- EEG (n=2,106): Electro encephalograph* (n=2), electroencephalograph* (n=304), EEG (n=1,800)
- MRI (n=566): Magnetic resonance imaging (212), MRI (n=267), fmri (n=87)
- Nervous system (n=425): Nervous system* (n=425)
- ERP (n=326): Event-related potential (n=0), Evoked potential (n=45), Event potential (n=58), ERP (n=74), P300 (n=149)
- Neurophysiology (n=147): Neurophysio* (n=147)
- Neuroimaging (n=90): Functional imaging (n=6), Neuroimaging (n=84)
- Psychophysiology (n=75): Psychophysio*(n=75)
- Myography (n=46): *myograph* (n=46)
- Neuromodulation (n=15): Neuro modulation (n=1), Neuromodulation (n=14)
- Neurostimulation (n=15): Neuro stimulation (n=0), Neurostimulation (n=14)
- Signal Processing (n=6): Signal processing (n=6)
- MEG (n=3): Magneto encephalograph* (n=0), meg (n=2), magnetoencephalograph* (n=1)

Terms ranking

The ten most frequent terms were:

- OSAS (Obstructive Sleep Apnea Syndrome): n=35,692,

[2] https://github.com/vincentpmartin/lexical.network.pubmed

- EDS (Excessive Daytime Sleepiness): n=22,660,
- ESS (Epworth Sleepiness Scale): n=19,237,
- CPAP (Continuous Positive Airway Pressure): n=11,755,
- AHI (Apnea–Hypopnea Index): n=7,983,
- Sleep Quality: n=7,353,
- PSG (Polysomnography): n=6,970,
- Insomnia: n=6,302,
- QoL (Quality of Life), n=5,633,
- PD (Parkinson Disease), n=5,618.

Among the terms related to neurophysiology, 6 are in the top 100 most represented tokens: PSG (4th), EEG (21st), MRI (36th), Nervous system (39th), ERP (42nd), Neurophysiology (57th). Three other terms are in the top 1,000 (Neuroimaging: 112th, Psychophysiology: 144th, Myography: 350th), while the remaining terms are highly underrepresented (Neuromodulation: 2062nd, Neurostimulation: 2302nd, Signal Processing: 8195th, MEG: 24488th). As a result, when selecting the top 75 most represented tokens for graph construction, only the tokens ‘PSG’,‘EEG’, ‘MRI’, ‘Nervous system’, ‘ERP’, and ‘Neurophysiology’ will be included.

Automatic Extraction of Main Semantic Dimensions

The metrics which decided the number of topics as returned by the *ldatuning* package are reported in **Supplementary Materials: Figure S1**. Based on these metrics, we chose to cluster the tokens into 4 groups. The automatic attribution of each term into one of these four clusters are reported in **Supplementary Materials: Table S1.**

Network analysis

The uncorrected lexical network of the filtered, lumped, and automatically grouped tokens into semantic topics is depicted in **Supplementary Materials: Figure S2**.

Expert correction

Some allocation of tokens to their topic by the automatic algorithm raises questions and does not correspond to the knowledge of the field. For example, the token 'CPAP' which is assigned by the algorithm to the dimension 'Sleep disorders' instead of 'OSAS' (even though it is an

OSAS treatment), or the PSG which is assigned to the category 'OSAS' instead of 'Objective sleepiness'. An expertly corrected version of the topic allocated to each token is available in **Table 2**. Moreover, since OSAS is included in sleep disorders, we lumped these two categories into a unique ‘Sleep disorders’ one (the corrected lexical network before lumping is depicted in **Supplementary Materials: Figure S3)**. Furthermore, for readability purposes and since they do not convey information, we manually filtered out highly frequent terms that did not carry specific meaning: ‘index sleepiness scale,’ ‘quality index sleepiness,’ ‘sleep index sleepiness,’ ‘sleepiness sleepiness scale,’ ‘sleepiness scale score,’ and ‘mild moderate severe.’ The final lexical network with tokens grouped into the expertly-corrected topics is depicted in **Figure 3**. For readability purposes, we have retained in **Figure 3** only the edges representing partial correlations greater in absolute value than 0.086.

Dim	Terms	Semantic dimension
N°1	ESS; Sleep Quality; QoL; PD; PSQI; SF36; BDI; Neuropsy; FSS; VAS; HAD; activities daily living; FOSQ; SSS; KSS; sleep habits questionnaire	Subjective sleepiness (self-reported sleepiness) and quality of life
N°2	Insomnia; ISI; RLS; Narcolepsy; Hypersomnia; ADHD; children; parasomnia; difficulty falling asleep; circadian rhythm sleep; prevalence sleep disorders; sleep disorders common; classification of sleep disorders; sleep disorder characterized; PD; UPDRS; traumatic brain injury; sleep wake disturbances; night time sleep; Sleep Behavior	Sleep disturbances, sleep disorders and comorbidities
N°3	EDS; Sleep duration; REM; MSLT; TST; PVT; Arousal; EEG; Hypersomnia; MWT; Sleep Behavior; MRI; Nervous system; slow wave sleep; ERP; sleep	Objective sleepiness (neurophysiological or behavioral sleepiness)

	wake cycle; sleep time sleep; Neurophysiology; PSG; motor vehicle accidents; heart rate variability;	
N°4	OSAS; SDB; CPAP; AHI; BMI; RDI; ODI; patients moderate severe; sleep breathing disorders; patients mild moderate; stop bang questionnaire; patients obstructive syndrome; upper airway resistance; lowest oxygen saturation; upper airway obstruction	OSAS

Table 2 – Expert-based attribution of tokens to semantic dimensions.

ESS: Epworth Sleepiness Scale; QoL: Quality of Life; PD: Parkinson Disease; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; SF36: Medical Outcome Short Form 36; BDI: Beck Depression Index; FSS: Fatigue Severity Scale; VAS: Visual Analogue Scale; HAD: Hopsital Anxiety and Depression scale; FOSQ: Functionnal Ouctomes of Sleep Questionnaire; SSS: Stanford Sleepiness Scale; KSS: Karolinksa Sleepiness Scale; RLS: Restless Legs Syndrome; Attention-Deficit/Hyperactivity Disorder; PD: Parkinson Disease; UPDRS: Unified Parkinson's disease rating scale;EDS: Excessive Daytime Sleepiness; Sleep duration; Rapid Eye Movements sleep; MSLT: Multiple Sleep Latency Test; TST: Total Sleep Time; PVT: Psychomotor Vigilance Test; EEG: Electroencephalography; MWT: Maintenance of Wakefulness Test; MRI Magnetic Resonance Imaging; ERP: Event-Related Potentials; PSG: Polysomnography; OSAS: Obstructive Sleep Apnea Syndrome; SBD: Sleep Disordered Breathing; CPAP: Continuous Positive Airway Pressure; AHI: Apnea-Hypopnea Index; BMI: Body Mass Index; RDI: Respiratory Disturbance Index; ODI: Oxygen Desaturation Index.

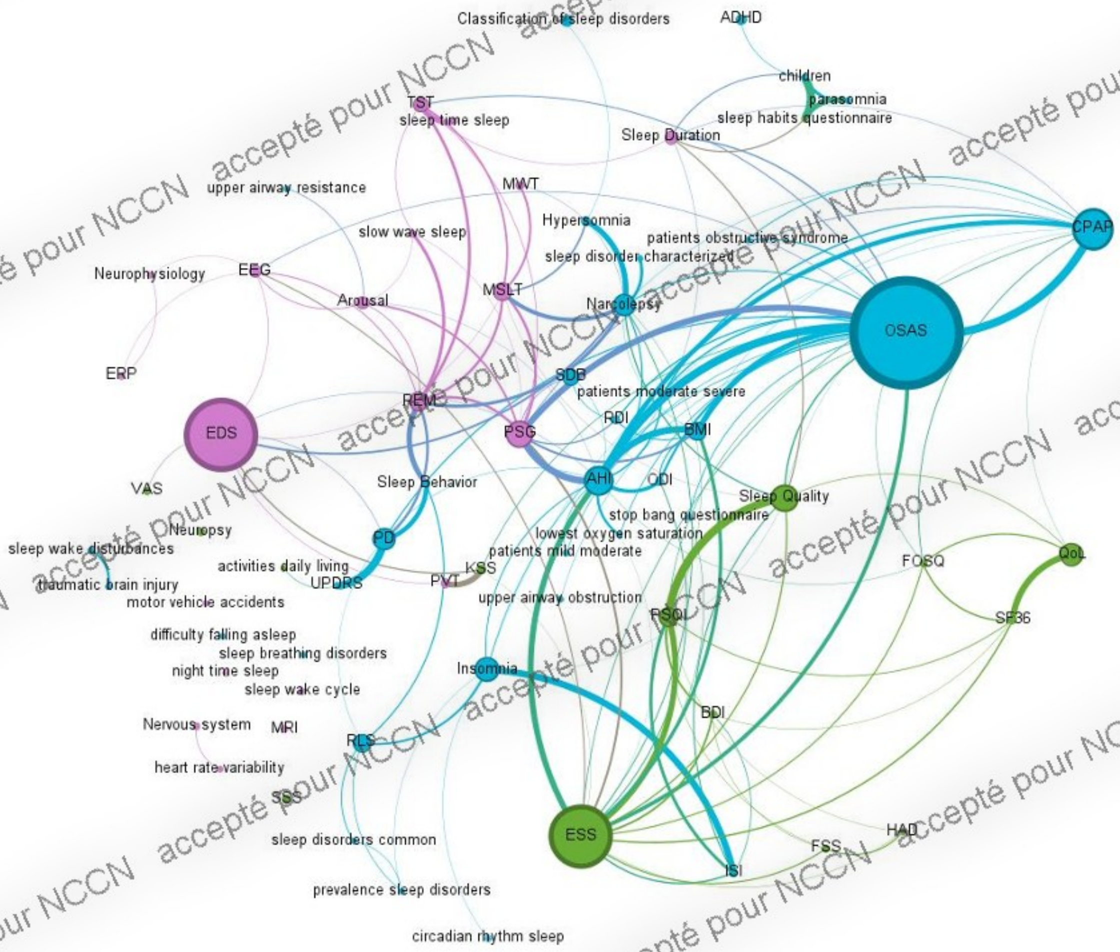

Figure 3 – Sleepiness lexical network and its expertly corrected semantic dimensions. Each circle represents a token from the lexical analysis. The diameter of each circle is proportional to its frequency of occurrence in the corpus, and the color of each circle indicates the topic it belongs to (Green: Subjective sleepiness, Purple: objective sleepiness, Blue: Sleep disorders). The thickness of the links between the circles is proportional to the absolute value of significant partial correlations between them. For example, the term 'OSAS' is the most prevalent, and its appearance is highly correlated with the appearance of the term 'PSG', and less correlated with the term 'FOSQ'.

The complete graph contains 935 edges representing significant correlations. With a third quartile at 0.068, three quarters of these edges (702 edges) represent partial correlations below this value. In contrast, 1% of the edges are associated with partial correlations greater than 0.34 (1st percentile), and 4 edges are associated with the same maximum correlation of r=0.4: these are the edges between 'Sleep Quality' and 'PSQI', 'OSAS' and 'AHI', 'sleep habits' and 'children', and 'OSAS' and 'CPAP'.

From a global perspective, it appears that subjective measurements of sleepiness (in green) interact very little with objective measures based on electrophysiological tools (in purple). In the middle between these two zones, the sleep disorders (in blue) are equally linked to one area and the other. Moreover, this network analysis also reflects a classical but nevertheless central association of clinical sleep medicine: the association between REM, Slow Wave Sleep, arousal, MSLT, MWT, EEG and total sleep time, corresponding to the PSG field; the association between REM, sleep behavior, and Parkinson, corresponding to the Rapid eye movement sleep behavior disorder (RBD) field; and the association between narcolepsy, MSLT, PSG and REM, corresponding to the central disorders of hypersomnolence field.

Iterative construction of the semantic field around sleepiness.

The cumulative number of articles based on publication years is represented in **Supplementary Materials: Figure S4**.

As mentioned in the methodology, we tracked the temporal evolution of both predominant terms related to neurophysiology and the predominant terms from the lexical network obtained in the previous section. To ensure the highest level of accuracy without compromising the readability of the figures, we selected the following terms for which we also reported the year of appearance in the titles and abstracts of articles containing the term "sleepiness" or "sleepy":

- Related to neurophysiology: PSG (1978), EEG (first appearance in 1971), ERP (1986), Nervous system (1977), MRI (1986), Heart Rate Variability (1997), Neurophysiology (1987), Psychophysiology (1977)
- Dominant terms of the lexical network: OSAS (1972), EDS (1972), ESS (1991), CPAP (1986), AHI (1978), Sleep Quality (1982), Insomnia (1975), QoL (1985), PD (1972)

The ratio of articles containing each token in the articles published before year *n* and their corresponding ranks are respectively shown in **Figures 4 and 5**.

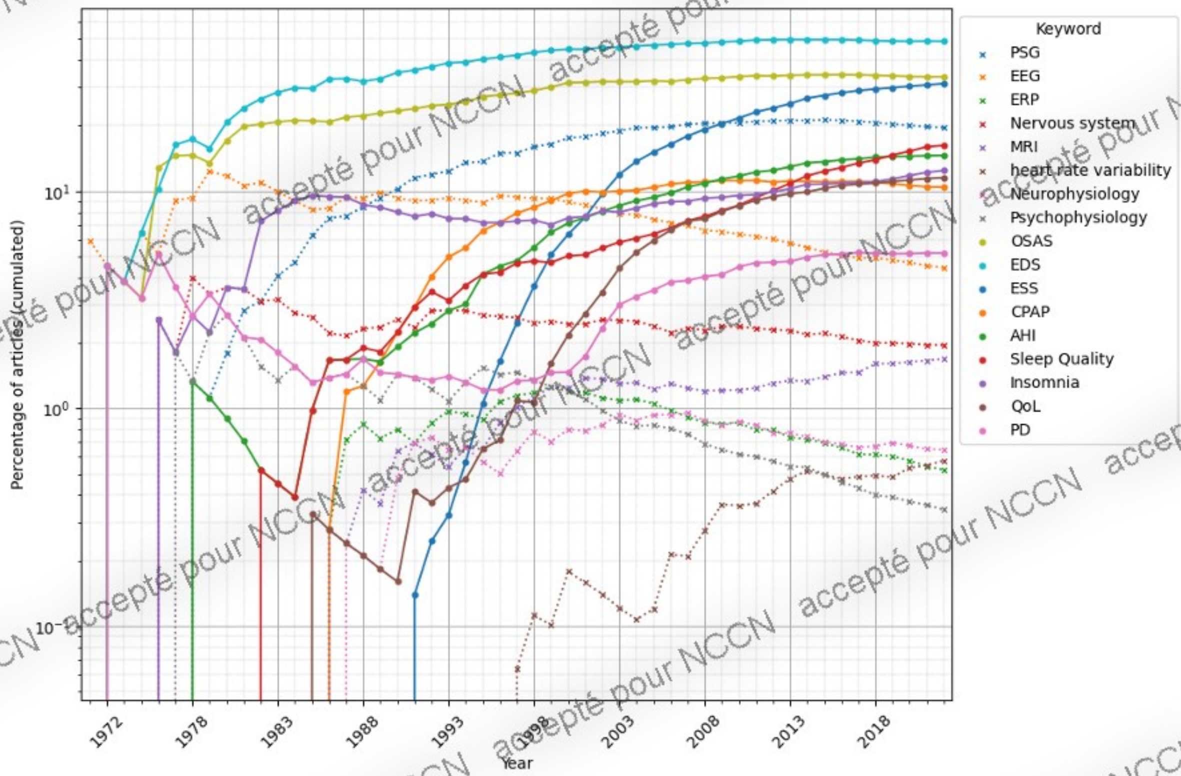

Figure 4 - Proportion of articles containing the word 'sleepiness' or 'sleepy' published before the year n containing each token (cumulative). For instance, in all articles published before 2013 (i.e., the entirety of the available literature at that time), 14% of the articles contained a token related to EDS. Terms related to neurophysiology are represented using dashed lines; the dominant terms of the network are represented using solid lines.

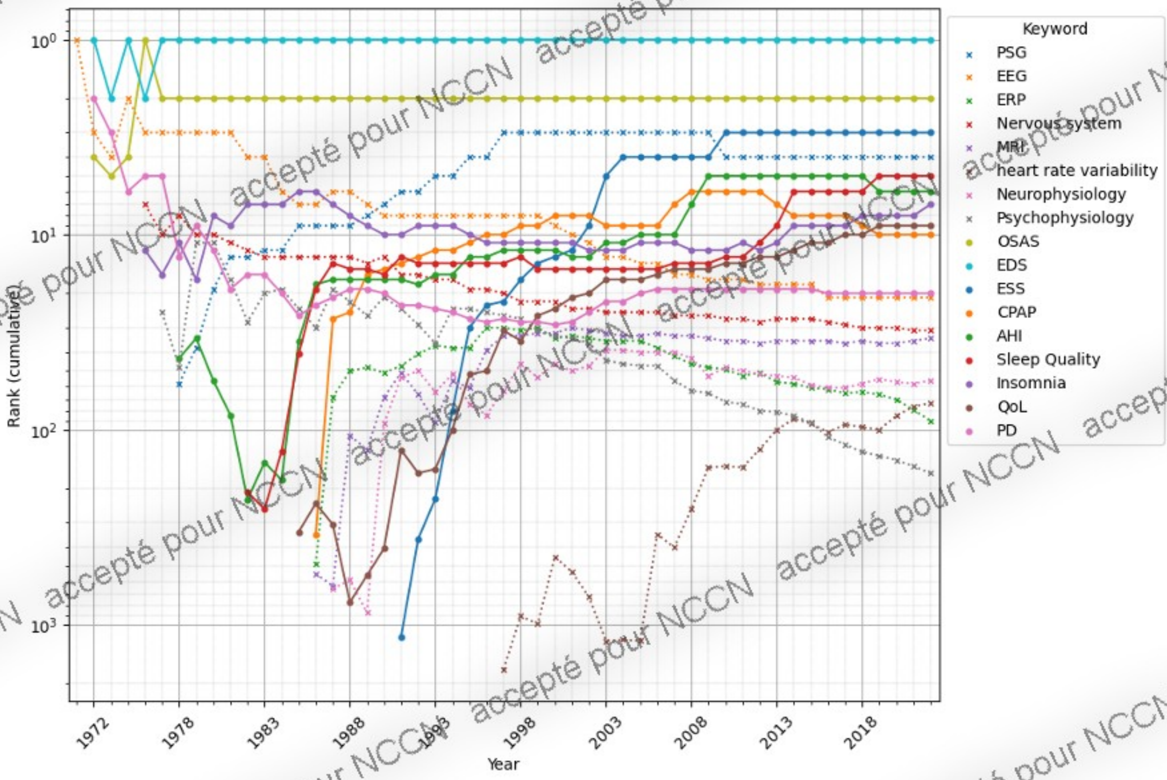

Figure 5 - Ranking of keywords contained in the abstracts and titles of articles containing the term 'sleepy' or 'sleepiness' (cumulative). For instance, in all articles published before 2008, PSG was the third most frequent token (appearing at least once per article), OSAS was the second most represented, and EDS was the third most represented. The vacant ranking positions in the figure are occupied by terms that are not among those we are focusing on. Terms related to neurophysiology are represented using small crosses; the dominant terms of the network are represented using small filled circles.

Overall, these figures reveal a decline in terms related to neurophysiology since the 2000s, with nearly all tokens related to neurophysiology decreasing or stagnating since that time. This is evident in the case of the flagship term, 'EEG': consistently in the top 10 tokens until 2001, its prominence has been on the decline since 1994 and now ranks 11th. It appears that 'EEG' has been surpassed by 'PSG' by the late 1980s, particularly due to the widespread implementation of the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) in sleep clinics. There are two exceptions to this trend: 'MRI,' which shows a slight increase, and 'heart rate variability (HRV),' which has steadily increased since its introduction into the corpus in 1997. We attribute this increase to the ease of HRV measurement, allowing for applications such as driving safety [67] or wearable devices [4].

In contrast, terms related to clinical aspects, introduced gradually throughout the 20th century, either show growth or remain constant, occupying the top positions. This is evident in the case of the token 'EDS,' which has consistently held the top position since 1977 (oscillating between 13% and 14% since 1993, but consistently ranking 1st since 1977). However, this result is not surprising given the corpus was selected from PubMed based on the presence of the term 'sleepiness'; excessive daytime sleepiness is a major symptom in sleep medicine [21,22]. Even more interestingly, OSAS has consistently maintained a strong presence in the literature. It has held the 2nd position since 1977 and has remained around 12 to 13% since 1998. The central role of OSAS in the field of sleep medicine related to sleepiness is thus historically established.

From a global perspective, these figures support the hypothesis of the construction of sleep medicine around clinical practice fields, right from its early years.

Discussion

In this article, we have proposed an expert-guided automated analysis of various topics surrounding sleepiness in all the literature ever published (and referenced in PubMed) containing the words 'sleepiness' or 'sleepy' (i.e., 18,390 articles). We have presented two types of analyses: one based on a lexical network, allowing us to explore the link between concepts related to sleepiness in all this literature; the other allowing us to explore the temporal dynamics of these concepts during the development of sleep medicine. The results of these analyses confirm the acceleration in the number of publications around sleepiness.

Firstly, our lexical network analysis has uncovered that the interest of the sleep community related to sleepiness is predominantly centered around subjective, i.e. self-reported questionnaires [3,33] (in green in Figure 3) and objective measures based on electrophysiological tools (in purple in Figure 3), i.e. sleep latency based on PSG [12,47], with very little interactions between them. An exception is the KSS, which is linked to the PVT: this comes from the methodology of developing the KSS, which was specifically designed to correlate with the Karolinska Drowsiness Test, a neurophysiological measure of falling asleep [2]. Nevertheless, it is to be noted that recent works focused on the alignment between subjective and objective sleepiness measurements [48,64].
Furthermore, sleepiness serves as a crucial marker for various sleep disorders [15,21], (colored in blue in Figure 3), bridging the two domains of self-reported questionnaires and

electrophysiological sleepiness measurements. Among these sleep disorders, Obstructive Sleep Apnea Syndrome (OSAS) in particular has engaged researchers and clinicians from the inception of sleep medicine [38], explaining its importance in our lexical network. This network analysis also reflects other classical associations of clinical sleep medicine in particular around RBD and central disorders of hypersomnolence.

Secondly, our temporal dynamic analysis has confirmed that neurophysiological approaches to sleepiness (e.g. based on EEG and ERP) are declining, in contrast to other specific sleepiness tools used by the sleep community. Despite a possible limitation due to the historical evolution of the vocabulary employed to describe sleepiness, these results confirm the hypothesis that neurophysiology has declined in favor of behavioral or self-reported dimensions in sleep medicine for the investigation of sleepiness, as we have already supposed in our previous umbrella review [44]. Interestingly, these results based on the study of previous publications seem to align with the current sleep clinical practice. Indeed, absent from the recommendations of the American Academy of Sleep Medicine or the diagnostic criteria for sleep disorders [21,37,51], neurophysiological investigation of sleepiness based on electrophysiological tools investigating brain functioning (and brain dysfunction) is not clearly used in today's sleep medicine structures.

However, our study should not underestimate the significant existing work in the study of sleep physiology and the mechanisms involved in sleepiness. Starting from the 1970's, numerous research initiatives capitalized on the polysomnographical investigation of sleep (combination of multiple electrophysiological signals including EEG) and the standardization of sleep stage scoring [55] to investigate the relationship between (neuro)physiology and sleepiness and to formulate underlying mechanisms. This was exemplified first through the search for a definition of OSAS [38]. Indeed, the pioneer clinical neurophysiology works of Gastaut et al. [19,20] and Guilleminault et al. [25,26] changed the paradigm from a ventilatory-centered approach of the Pickwick syndrome to a more complex brain-related sleep disturbance approach of OSAS causing sleepiness. Then, during the 1980's, this neurophysiological-centered approach was then applied to the study of narcolepsy, an emblematic disorder in the field of sleepiness. In this way, pioneering works explored the genetic link to narcolepsy [34] and the role of orexin in narcolepsy [40]. Moreover, the link between sleepiness and circadian rhythms [13] and homeostatic pressure [1,66], have provided experimental evidence to the Borbélys' model of interplay between homeostatic processes and circadian rhythm that was theorized as early as 1982 [10]. Nevertheless, current measures of sleepiness and investigations of OSAS in clinical settings are not aligned with these seminal neurophysiological works and mechanistic models. While the field of sleep medicine has been structured around electrophysiological and clinical measures and the search for reliable criteria for sleep disorders diagnosis, we have identified two avenues for reintroducing neurophysiology into sleep medicine in order to bring sleepiness measurements closer to brain functioning.

A first effort involves retaining the currently implemented normative electrophysiological tests (i.e., MSLT and MWT), based on PSG, for which healthcare professionals are trained and logistical processes are established across sleep centers worldwide. However, the focus could shift from the sole measurement of sleep onset latency which can be considered as a behavioral measure of falling asleep. Interestingly, in the context of sleepiness, PSG can be interpreted as a "boundary object" [63] between clinical sleep medicine and clinical neurophysiology, creating different measures used by different communities for collaborative clinical and research work. For instance, as early as 1986, Roth had worked on establishing the Polygraphic Score of Sleepiness [58], a linear combination of time spent in different sleep stages during PSG. This score showed significant differences between healthy subjects and patients with narcolepsy, idiopathic hypersomnia, and sleep apnea. Recent efforts have continued along these lines, particularly in the context of MSLT. Lopez et al. [41] proposed new metrics extracted from the same signal used to estimate sleep onset latency, such as total time in REM sleep and mean REM latency. These metrics demonstrated superior performance in identifying hypocretin deficiency in patients with hypersomnolence and narcolepsy. Similarly, novel sleep stages quantification methods like the VIGALL algorithm [30], the microstate analysis during MWT [5,16], or the study of stage transitions [17,35] represent metrics closely related to neurophysiology that can be extracted from electrophysiological signals already measured in sleep clinics, in order to investigate brain mechanisms related to sleepiness.

A second effort is the reintegration of clinical neurophysiology into sleep medicine towards a virtuous circle of vocabulary precision and stratification in regards to neurophysiological phenomena **(Figure 6)**. On one hand, the interpretation of electrophysiological signals in a neurophysiological framework must integrate with clinical "practical constraints" [65] such as clinical manifestations and symptoms (semiology and the different types of sleepiness complaints), diagnosis (sleep disorders and the different related sleepiness profiles), and prognosis of sleep disorders (e.g. behavioral harmful consequences such as sleepiness at the wheel leading to risk of accidents) [42,52]. On the other hand, clinical neurophysiology in sleep medicine must integrate with neurophysiological "realistic constraints"[65], aligning with mechanisms of sleepiness (related to brain dysfunction) that electrophysiological signals can help to identify [12]. This dual constraint – neurophysiology on clinical practice and vice versa – fosters the development of a virtuous circle, in which various subtypes of sleepiness could be specified in order to contribute to a more precise medical definition and characterization of sleepiness contributing to better evaluate and treat it [42,45]. To summarize, clinical neurophysiology would establish a fresh framework for studying and defining sleepiness and its associated phenomena. This would break sleep medicine free from its historical crystallization and its inability to extract from "path dependence"[29], which is the process where past events constrain later events, even challenging the sleep stages themselves [36], which have formed the bedrock of the physiology of sleep and sleepiness since the 1960s [23,55]. The reinvestment in neurophysiology thus offers an avenue to construct a semiological ontology of sleep medicine, intertwining medical vocabulary, clinical manifestations, and electrophysiological measures with brain mechanisms as offered by the clinical neurophysiology approach in medicine.

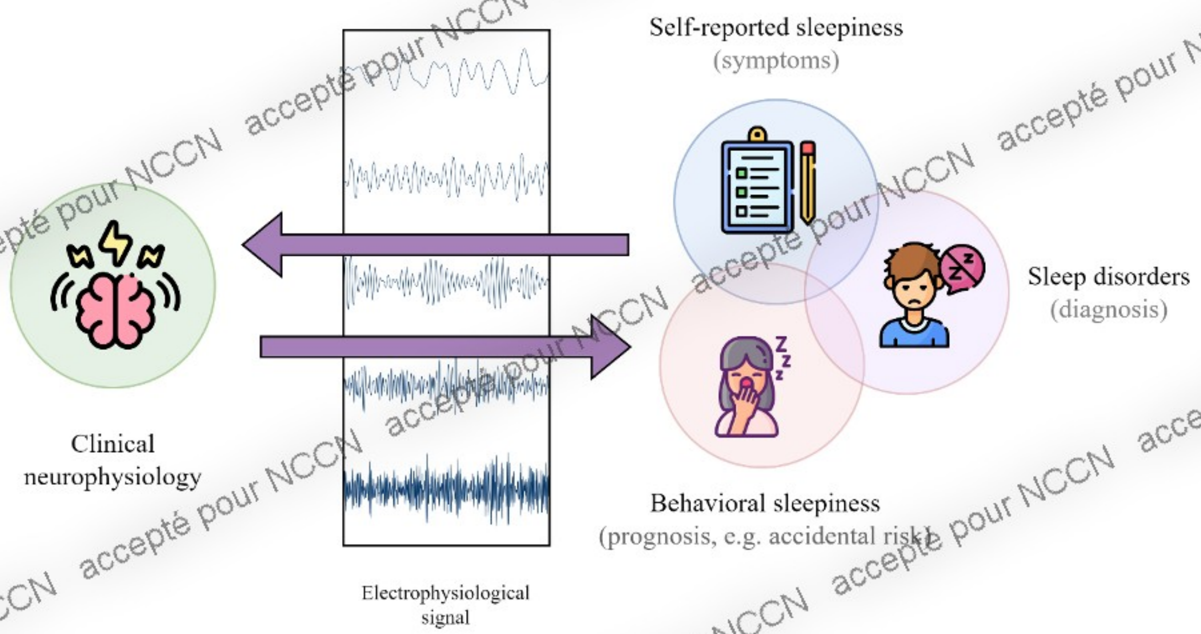

Figure 6 – Proposal of a double-constrained model to reinvest sleepiness through the lens of clinical neurophysiology. From left to right: clinical neurophysiology in sleep medicine must integrate with realistic neurophysiological constraints, aligning with mechanisms of sleepiness that electrophysiological signals can help to identify. From right to left: clinical neurophysiology

must integrate with clinical practical constraints such as clinical manifestations and symptoms, diagnosis, and prognosis of sleep disorders.

To conclude, keeping in mind the importance of refining the current models of the underlying mechanisms of sleep and sleepiness, the intersection of clinical neurophysiology with sleep medicine is brimming with potential. This underscores the significance of this special issue, which aims to disseminate the challenges of sleep medicine to the neurophysiology community. Following this introductory article on sleepiness, this issue delves into the current research status, clinical challenges, and prospects brought forth by the reintroduction of clinical neurophysiology in the study of sleepiness through vigilance [REF of this special issue], the wake-sleep transition [REF of this special issue], awakening [REF of this special issue], and sleep itself [REF of this special issue].

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Data availability and code for replication

The code we designed to obtain all the results, tables and figures in this manuscript are available online: https://github.com/vincentpmartin/lexical.network.pubmed

Conflicts of interest

The authors declare no conflicts of interest in connection with this study.

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