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CLINICAL REVIEW

EEG spectral analysis in insomnia disorder: A systematic review and meta-analysis

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SUMMARY

Insomnia disorder (ID) has become the second-most common mental disorder. Despite burgeoning evidence for increased high-frequency electroencephalography (EEG) activity and cortical hyperarousal in ID, the detailed spectral features of this disorder during wakefulness and different sleep stages remain unclear. Therefore, we adopted a meta-analytic approach to systematically assess existing evidence on EEG spectral features in ID. Hedges's *g* was calculated by 148 effect sizes from 24 studies involving 977 participants. Our results demonstrate that, throughout wakefulness and sleep, patients with ID exhibited increased beta band power, although such increases sometimes extended into neighboring frequency bands. Patients with ID also exhibited increased theta and gamma power during wakefulness, as well as increased alpha and sigma power during rapid eye movement (REM) sleep. In addition, ID was associated with decreased delta power and increased theta, alpha, and sigma power during NREM sleep. The EEG measures of absolute and relative power have similar sensitivity in detecting spectral features of ID during wakefulness and REM sleep; however, relative power appeared to be a more sensitive biomarker during NREM sleep. Our study is the first statistics-based review to quantify EEG power spectra across stages of sleep and wakefulness in patients with ID.

Introduction

Insomnia disorder (ID) is defined as a persistent difficulty with initiating and/or maintaining sleep, and/or waking up earlier than desired [1]. ID has become the second-most common mental disorder: approximately one-third of adults in general population experience at least one symptom of insomnia, with about 10% meeting the diagnostic criteria for ID [1,2]. Insomnia exerts a negative impact on daytime cognitive functions such as alertness, memory, attention, and executive function [3,4]. In addition, insomnia is a risk factor for other disorders, including cardiovascular disease [5], dementia [6], and various mental disorders [7]. Given the detrimental effects of insomnia on daytime functioning and health, studies designed to uncover the pathophysiological mechanisms underlying ID remain imperative.

The necessity of quantitative EEG measures in ID

Unlike other sleep disorders, clinical diagnoses of ID are currently based strictly on subjective reporting during clinical

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List of abbreviations

CI	confidence intervals
DSM	diagnostic and statistical manual of mental disorders
EEG	electroencephalography
HC	healthy control
ICD	international classification of diseases
ICSD	international classification of sleep disorders
ID	insomnia disorder
NM	not mentioned
NREM	non-rapid eye movement
OI	objective insomnia
PSG	polysomnography
REM	rapid eye movement
SI	subjective insomnia
SMI	sleep maintenance insomnia
SOI	sleep onset insomnia
W	wakefulness

interviews or on responses to self-report questionnaires. Subjective reports are often inconsistent with objective measures derived from actigraphy or polysomnography (PSG). This discrepancy has even led to the proposal of an insomnia subtype with various amounts of so-called "paradoxical insomnia", which is characterized by experiencing sleep as wakefulness [8]. Therefore, some researchers have recommended using a combination of subjective and objective measures in the clinical diagnosis and assessment of ID [9,10].

Although PSG has been considered as the "gold standard" for the objective assessment of sleep disorder, it is not considered necessary for a clinical diagnosis of ID, and has been recommended for research purposes only. Several factors may explain why traditional PSG measures are not widely accepted as objective indicators of insomnia. First, variations in sleep macrostructure may reflect large individual differences among patients with insomnia. Such individual differences may be related to genetic influences, stress reactivity, and personality traits [11,12]. Future studies may wish to evaluate whether PSG features are more consistent within newly discovered insomnia subtypes based on these characteristics [13]. Second, sleep staging derived from visual scoring of PSG or electroencephalography (EEG) data provides only a relatively crude measure of sleep quality. This method classifies sequential epochs (30 s) into four sleep stages, with a temporal resolution lower than that of quantitative EEG measures. Third, traditional PSG parameters exhibit lower night-to-night stability than quantitative EEG measures [14].

Previous research has employed many detailed methods to quantify differences between patients with ID and controls in EEG data during wakefulness and sleep [15–17]. The most common quantitative method employed in sleep studies is spectral analysis, which decomposes a time series of EEG data into power (squared amplitude) in frequency bins (μV^2/bin) [18]. The power can be expressed either as absolute or as relative to the summed power in all bins. When compared with traditional parameters of PSG macrostructure, spectral analysis provides a more continuous measure of each frequency bin, which may yield a more sensitive biomarker for distinguishing between patients with ID and those with healthy sleep patterns.

Current studies of EEG power spectra in ID

Over the last few decades, a substantial body of research has focused on the spectral analysis of sleep microstructure in patients with insomnia [9,10,19,20]. Some researchers have proposed that spectral analysis may represent an objective method for examining the pathophysiological mechanisms underlying insomnia [9,10]. Previous studies have compared EEG spectral features during rest-state wakefulness, sleep-onset, non-rapid eye movement (NREM) sleep between patients with insomnia and good sleepers. Most such studies have reported that ID is associated with significantly increased EEG activity in high-frequency bands (beta/gamma) during these periods [21–26], which may reflect cortical hyperarousal [19,27]. However, several other studies have yielded contradictory results [28–33]. For example, Wu and colleagues failed to observe significant differences in waking or NREM spectral power between the insomnia and healthy control (HC) groups [29]. Therefore, it remains unclear whether chronic insomnia is associated with consistent increases in the activity of high-frequency bands, and whether such increases occur specifically in the beta and/or gamma bands or spread to broader frequency bands.

Some narrative reviews have also summarized the results of EEG spectral analysis in patients with ID. A 2001 literature review of seven spectral studies by Perlis and colleagues concluded that beta EEG activity at/around sleep onset and during NREM sleep is increased in patients with ID [19]. Other reviews have reported similar conclusions [9,10,20]. However, these narrative reviews have some limitations. First, narrative reviews tend to compare the number of statistically significant and non-significant studies. This "vote-counting" process may result in misleading conclusions [34]. Second, narrative reviews do not include a quality assessment for each included study, which is indispensable for literature reviews. Third, several studies with larger sample sizes have been published since 2013. Including these studies will provide a more convincing result.

Meta-analysis has a clear set of rules: to search for relevant studies, to include and exclude studies from the analysis as appropriate, and to statistically synthesize data across the included studies. However, to date, no meta-analytic study has examined the impact of insomnia on EEG power spectra. Therefore, the present study aimed to provide an objective and statistics-based assessment of EEG power spectra in patients with ID using meta-analytic methods.

The present study

As previously mentioned, there are no objective measures to aid in the clinical diagnosis of ID. In the present study, we adopted a meta-analytic approach to systematically assess existing evidence related to the impact of ID on EEG spectral features, which may aid in the development of more objective measures. We expected to confirm and better delineate the conclusions regarding enhanced high-frequency power offered in previous narrative reviews. Importantly, previous reviews have failed to address methodological aspects of EEG spectral features, such as whether absolute or relative spectra are more appropriate. We therefore compared the sensitivity of absolute and relative power in detecting spectral features characterizing ID. Moreover, while resting-state EEG is now more commonly performed in patients with psychosomatic disorders [35,36], the extent to which spectral deviations in insomnia are similar during resting-state wakefulness and sleep states remains to be determined. We hypothesized that patients

with ID would exhibit continuously increased EEG activity in a broad range of high-frequency bands during both wakefulness and sleep.

Methods

Data sources and search strategy

We conducted this meta-analysis and systematic review in accordance with the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (http://prisma-statement.org/) (Supplementary Materials, Appendix 1). Published articles were identified via searches of the PubMed, Web of Science, EBSCO, ScienceDirect, PsycInfo, PsycArticle, Wiley, Springer, and Google Scholar databases. We searched for potentially relevant studies published between January 1st, 1980, and December 31st, 2019. The combinations of the following search terms were used in our research: For insomnia, we used terms including "insomnia", "sleep disorder", "sleep disturbance", and "poor sleep"; for spectral analysis, we used terms including "quantitative EEG", "quantitative electroencephalogram", "qEEG", "spectral", and "power"; for EEG activity, we used terms including "electroencephalography", "electroencephalogram", "EEG", and "PSG". PubMed, Web of Science, and EBSCO search engines were first employed using combinations of the above keywords (Supplementary Materials, appendix 2). In addition, we manually screened the reference lists of previous reviews and all retrieved articles to ensure that no relevant studies were omitted.

Study selection

The inclusion criteria for the studies identified from the literature search were as follows: 1) published in a peer-reviewed journal and written in English or Chinese; 2) case–control design; 3) the sampled population was diagnosed using structured or semi-structured clinical interview in accordance with international classification of diseases (ICD), international classification of sleep disorders (ICSD), or diagnostic and statistical, manual of mental disorders (DSM); 4) outcomes included at least one between-group comparison of the spectral power of six common frequency bands (delta, theta, alpha, sigma, beta, gamma); 5) the statistical information reported by the studies would allow for the calculation of effect size. We contacted corresponding authors to request further information when reported results were insufficient for calculating an effect size.

Following the initial inclusion criteria, studies were excluded from our analysis under the following conditions: 1) focus on comorbid medical, psychiatric, or sleep disorders other than insomnia; 2) focus on children, adolescents, or older adults with insomnia (age <18 or >65 y); 3) lack of a corresponding control group; 4) re-analysis of a subset of the original sample of another included study.

Quality assessment

The quality of the studies included in the current meta-analysis was assessed by two independent raters (W. Zhao and X. Chen) using the Joanna Briggs Institute (JBI) critical appraisal checklist for case control studies [37]. We extended the checklist with an additional item (item 11) addressing the clear reporting of EEG acquisition conditions (Supplementary Materials, Appendix 3) [38]. These items can be roughly classified into six categories: sample selection (items one–three), exposure measurement (items four, five, and nine), confounding factors (items six and seven), outcome assessment (item eight), statistical analysis (item 10), and EEG acquisition (item 11). Given that we primarily extracted means and standard deviations from the included studies, items related to sample selection, exposure measurement, and EEG acquisition were considered highly valuable. Therefore, the quality criterion for inclusion was set to at least five "yes" responses in total, consisting of at least one "yes" response for items one–three, at least two "yes" responses for items four–eight, and one "yes" response for item 11. In the case of a discrepancy between the two raters, a consensus was reached after discussion with another author (X. Lei). Cohen's Kappa was used to calculate interrater reliability.

Data extraction

Two of the authors (W. Zhao and X. Lei) determined whether the studies should be included based on the inclusion and exclusion criteria. The characteristics of the included studies were manually extracted by the first author (W. Zhao). See Table 1 for detailed information regarding these studies.

Data related to between-group comparisons of EEG frequency bands during resting-state wakefulness, NREM, or REM sleep were extracted and coded for synthesis and analysis. The current meta-analysis was interested in the six common EEG bands: delta, theta, alpha, sigma, beta, and gamma [39,40]. Because of the inconsistent and controversial subdivision in frequency bands across these included studies, we extracted outcomes simply based on semantic categories of rhythm name (i.e., delta, theta, alpha, sigma, beta, gamma). For example, if one study reported a delta range of 0.5–3.75 Hz, while another study reported a delta range of 0.5–3.5 Hz or 0.1–4 Hz, we synthesized the data even though it reduced the precision of the range of the frequency band. See Table 1 for more information related to the specific frequency ranges for each study.

Data synthesis and analysis

All analyses were conducted using Comprehensive Meta-Analysis (CMA version 3.0) software (https://www.meta-analysis.com/). Effect sizes and 95% confidence intervals (CIs) were calculated for between-group comparisons of EEG activity in each frequency band during wakefulness or sleep. Effect sizes were determined based on Hedges's *g*, which is a measure of standardized mean difference similar to Cohen's *d*. However, Hedges's *g* is associated with lower levels of bias than Cohen's *d* even at smaller sample sizes [41]. Hedges's *g* was calculated as the quotient of the spectral difference between the mean of the ID group against the mean of HC group, divided by the pooled weight standard deviation incorporating Bessel's correction:

$$g = \frac{\mu_{ID} - \mu_{HC}}{SD_{pooled}}$$

where μ_{ID} and μ_{HC} denote the mean values of the ID and HC groups, respectively. SD_{pooled} denotes the pooled weighted standard deviation, which was computed as follows:

$$SD_{pooled} = \sqrt{\frac{(n_{ID}-1)SD_{ID}^2 + (n_{HC}-1)SD_{HC}^2}{n_{ID}+n_{HC}-2}}$$

where n_{ID} and n_{HC} refer to the numbers of participants in the ID and HC groups, respectively. SD_{ID} and SD_{HC} refer to the standard deviation of the ID and HC groups, respectively. Effect sizes of 0.2, 0.5, and 0.8 are interpreted as small, medium and large, respectively [42]. If the included studies lacked the above statistics, Hedges's *g*

Table 1
Study characteristics of included studies in the meta-analysis.

Author (y) Location	N and gender (ID/HC)	Mean age (y) (ID/HC)	Insomnia diagnosis	Insomnia disorder and its subtypes	Insomnia duration (y)	Hypnotic medication status	Analyzed EEG channel	EEG frequency bands	Measures	Targeted period
Jacobs et al., 1993 [57] USA	12(7F)/14(9F)	ID: 37.8 ± 9.1 HC: 36.9 ± 7.4	clinical interview (DSM III-R)	sleep onset insomnia	11 ± 5.9	medication free	standard electrode placements as described by Rechtschaffen and Kales (1968)	δ (0.5–3.75 Hz); θ (4–7.75 Hz); α (8–12.75 Hz); β (13–31 Hz)	relative power	W
Regestein et al., 1993 [52] USA	20(15F)/20(12F)	ID: 37 ± 11 HC: 31 ± 11	sleep questionnaires and clinical interview	primary insomnia	0.5–32 (Mean 13.6)	NM	O1; O2; linked earlobe electrodes	α (8–12 Hz); non-α	absolute power	W
Merica et al., 1998 [58] Switzerland	20(12F)/19(10F)	ID: 30.2 ± 10.9 HC: 25.3 ± 4	clinical interview	psychophysiological & idiopathic insomnia	NM	ten day drug-free (13 no drugs; seven moderate doses of benzodiazepine)	F4-Cz	δ (0.5–3.75 Hz); θ (3.75–6.75 Hz); α (6.75–12.5 Hz); σ (12.5–14.75 Hz); β (14.75–30 Hz)	absolute power	NREM/REM
Perlis et al., 2001a & 2001b [21,22] USA	9(6F)/9(6F)	ID: 36.5 ± 10.8 HC: 38.1 ± 11.2	Sleep questionnaires and clinical interview	primary insomnia	≥0.5	medication free within 4 wk of laboratory study	(C3/A2+C4/A1)/2	δ (0.5–2.5 Hz); θ (2.5–7.5Hz); α (7.5–12 Hz); σ (12–14 Hz); β1 (14–20 Hz); β2 (20–35 Hz); γ (35–45 Hz)	relative power	W/NREM/ REM
Krystal et al., 2002 [45] USA	30(19F)/20(12F)	ID (SI): 56.1 ± 11.7 ID (OI): 54.3 ± 9.9 HC: 53.5 ± 10.4	clinical interview	persistent primary insomnia (subjective insomnia & objective insomnia)	SI:12.6 ± 7.8; OI:16.3 ± 14.4	NM	C3-A2	δ (0.5–3.5 Hz); θ (4–8 Hz); α (8.5–12 Hz); σ (12.5–16 Hz); β (16.5–30 Hz); γ (30.5–60 Hz)	relative power	NREM/REM
Bastien et al., 2003 [28] Canada	15(7F)/16(7F)	ID: 63.4 ± 5.4 HC: 63.1 ± 6.32	clinical interview (DSM-IV)	insomnia suffers	24.6 ± 19.4	3 mo washout period	C3-A2	δ (0–3.9 Hz); θ (3.9–7.02 Hz); α (7.02–11.7 Hz); σ (11.7–14.04 Hz); β1(14.04–21.84 Hz); β2 (21.84–30.03 Hz)	absolute power	NREM
Buysse et al., 2008 [44] USA	48(29F)/25(15F)	ID: 30.8 ± 7.2 HC: 30.6 ± 7.4	clinical interview (DSM-IV)	primary insomnia	NM	medications free	bilateral central EEG leads referenced to A1+A2	δ (0.5–4 Hz); θ (4–8 Hz); α (8–12 Hz); σ (12–16 Hz); β (16–32 Hz); γ (32–50 Hz)	absolute power	NREM
Corsi-Cabrera et al., 2012 [53] Mexico	10(4F)/10(5F)	ID: 25.9 ± 4.3 HC: 25.6 ± 4.6	sleep questionnaires and clinical interview	primary insomnia	0.52 ± 0.34	medication free	Fp1, F7, F3and Fz	β (17–30 Hz); γ (31–45 Hz)	absolute power	W/NREM
Israel et al., 2012 [14] USA	54(30F)/22(19F)	ID: 34.6 ± 9.7 HC: 26.5 ± 7.3	clinical interview (DSM-IV)	primary insomnia	NM	medication free	C3 and C4 referenced to linked mastoids (A1-A2)	δ (0.5–4 Hz); θ (4–8 Hz); α (8–12 Hz); σ (12–16 Hz); β (16–32 Hz)	relative power	NREM
Spiegelhalder et al., 2012 [24] Germany	25(16F)/29(18F)	ID: 47.8 ± 7.2 HC: 46.5 ± 5.0	clinical interview (DSM-IV-TR)	primary insomnia	12.9 ± 10.3	2 wk washout period	C3-A2	δ1 (0.1–1 Hz); δ2 (1–3.5 Hz); θ (3.5–8 Hz); α (8–12 Hz); σ (12–16 Hz); β1 (16–24 Hz); β2 (24–32 Hz); γ (32–48 Hz)	absolute power	NREM/REM

Wu et al., 2013 [29] USA	50(25F)/32(19F)	ID: 36.3 ± 8.9 HC: 32.7 ± 9.3	clinical interview (DSM-IV)	primary insomnia	<1 y: 3 1–5 yrs: 18 >5 yrs: 29	medication free	C3/C4-A1+A2	δ (0.5–4 Hz); θ (4–8 Hz); α (8–12 Hz); σ (12–16 Hz); β1 (16–20 Hz); β2 (20–32 Hz)	absolute power	W/NREM
Cervena et al., 2014 [30] Switzerland	20(7F)/10(5F)	ID (SOI): 34.2 ± 10.4 ID (SMI): 41.6 ± 9.3 HC: 41.4 ± 13.1	clinical interview (DSM-IV)	primary insomnia (sleep onset & maintenance insomnia)	SOI:10.7 ± 6.0 SMI:10.7 ± 9.3	3 wk washout period	C3-A2	δ (1–3.75 Hz); θ (4–7.75 Hz); α (8–11.75 Hz); σ (12–14.75 Hz); β1 (15–17.75 Hz); β2 (18–29.75 Hz); β3 (30–39.75 Hz)	absolute power	W
Chen et al., 2014 [31] USA	17(17F)/17(17F)	ID: 27.16 ± 6.67 HC: 27.56 ± 6.83	clinical interview (DSM-IV-TR & ICSD-2)	female insomniacs	NM	medication free	Fp1, Fp2, F7, F8, F3, F4, Fz, C3, C4, P3, P4, Pz T3, T4, T5, T6, O1, O2 (re-referenced to average)	δ (0.5–4 Hz); θ (4–8 Hz); α (8–14 Hz); β1 (14–20 Hz); β2 (20–35 Hz); γ (35–40 Hz)	relative power	W
Ferri et al., 2014 [54] Italy	11(6F)/14(7F)	ID: 58.9 ± 13.4 HC: 50.3 ± 15.83	clinical interview (DSM-IV-TR)	primary insomnia	NM	3 wk washout period	C3/A2 or C4/A1	δ (0.5–3.75 Hz); θ (4.0–7.75Hz); α (8–11.5 Hz); σ (11.75–14.75Hz); β (15–32 Hz)	absolute power & relative power	W
Neu et al., 2015 [55] Belgium	15(10F)/22(16F)	ID: 40.87 ± 10.9 HC: 38.45 ± 14.2	clinical interview (DSM-IV)	primary insomnia	NM	3 wk washout period	FP2-A1; C4-A1; O2-A1	δ (0.8–3.9 Hz); θ (4–7.4 Hz); α (7.5–12.4 Hz); σ (12.5–17.9 Hz); β (18–25 Hz)	relative power	NREM
Perrier et al., 2015 [56] France	14(9F)/10(6F)	ID: 47 ± 17 HC: 46 ± 15	clinical interview (DSM-IV)	primary insomnia	≥0.5	medication free	FP1, FP2, C3, C4, O1, O2, T3, T4 (referenced to linked mastoid A1 and A2)	δ (1.5–4 Hz); θ (4–7.5 Hz); α (7.5–12.5 Hz); σ (12.5–14 Hz); β (14–30 Hz)	relative power	NREM
Colombo et al., 2016 [25] Netherland	51(42F)/43(32F)	ID: 50.0 ± 13.4 HC: 46.1 ± 14.9	sleep questionnaires and clinical interview (DSM-V)	insomnia disorder	21.98 ± 15.16	2 mo washout period	256 channels (183 electrodes, re-referenced to the common average)	upper-α (11–12.7Hz); broad β (16.3–40Hz)	relative power	W
de Zambotti et al., 2016 [59] USA	22F/18F	ID: 50.4 ± 3.2 HC: 48.5 ± 2.3	clinical interview (DSM-IV)	menopausal insomnia	NM	medication free	C4-A2	δ (0.3-≤ 4 Hz); θ (4-≤ 8 Hz); α (8-≤ 12 Hz); σ (12-≤ 15 Hz); β1 (15-≤ 23 Hz); β2 (23-≤ 30 Hz)	absolute power	NREM
Riedner et al., 2016 [26] USA	8(6F)/8(6F)	ID: 41.5 ± 4.7 HC: 41.6 ± 4.8	clinical interview (DSM-IV)	chronic insomnia	8.8 ± 2.4	medication free for the duration of the study	256 channels (170 electrodes, re-referenced to the common average)	δ (1–4 Hz); θ (4–8 Hz); α (8–12 Hz); σ (12–15 Hz); β (15–25 Hz); γ (25–40 Hz)	absolute power	W/NREM
Kang et al., 2018 [32] USA	19(14F)/23(15F)	ID: 37.6 ± 14.9 HC: 33.5 ± 14.2	sleep questionnaires and clinical interview (DSM-IV)	primary insomnia	≥0.5	medication free	C3-A2	SWA (0.5–1 Hz); δ (1–4 Hz); θ (4–8 Hz); α (8–12 Hz); σ (12–15 Hz); β (15–20 Hz)	relative power	NREM

(*continued on next page*)

Table 1 (*continued*)

Author (y) Location	N and gender (ID/HC)	Mean age (y) (ID/HC)	Insomnia diagnosis	Insomnia disorder and its subtypes	Insomnia duration (y)	Hypnotic medication status	Analyzed EEG channel	EEG frequency bands	Measures	Targeted period
Kwan et al., 2018 [60] South Korea	15(15F)/15(13F)	ID: 22.67 ± 2.09 HC: 22.07 ± 2.15	sleep questionnaires and clinical interview (DSM-V)	comorbid-free insomnia	NM	1 mo washout period	FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2	θ (4–8 Hz); α (8–12 Hz); σ (12–15 Hz) β1 (15–25 Hz); β2 (25–30 Hz); γ (30–40 Hz)	absolute power	W
Frase et al., 2019 [61] Germany	19(13F)/19(13F)	ID: 43.8 ± 15.1 HC: 53.7 ± 6.9	sleep questionnaires and clinical interview (ICD-10)	insomnia disorder	NM	2 wk medication free prior to and during the study	C3-A2	δ (0.1–3.5 Hz); θ (3.5–8 Hz); α (8–12 Hz); σ (12–16 Hz); β (16–24 Hz); γ (24–50 Hz)	absolute power	W/NREM
Rezaei et al., 2019 [62] Iran	11(9F)/11(5F)	ID: 44 ± 13.27 HC: 41.64 ± 15.89	clinical interviews (ICSD-2)	Psychophysiological Insomnia	NM	NM	C3-A2	α (8–12 Hz)	absolute power	W/NREM/ REM
Kay et al., 2019 [33] USA	17(11F)/19(9F)	ID: 40 ± 7 HC: 36 ± 9	clinical interview (DSM-IV)	primary insomnia	NM	NM	C4/A1-A2	δ (0.5–4 Hz); θ (4–8 Hz); α (8–12 Hz); β1 (12–16 Hz); β2 (16–20 Hz); β3 (20–32 Hz);	relative power	NREM

Note: DSM, diagnostic and statistical manual of mental disorders; HC, healthy control; ICD, international Classification of diseases; ICSD, international classification of sleep disorders; ID, insomnia disorder; NM, not mentioned; NREM, non-rapid eye movement; OI, objective insomnia; REM, rapid eye movement; SI, subjective insomnia; SMI, sleep maintenance insomnia; SOI, sleep onset insomnia; W, wakefulness.

was determined using exact t or p values and the corresponding sample sizes. Similar to previous studies, if the reported outcomes were significant but no exact p values were provided, one-tailed p values were assumed to be 0.025. If outcomes were reported as $p < 0.05/0.01$, two-tailed p values were assumed to be 0.05/0.01. If reported results were not significant but no statistical values were provided to compute the exact p values, we conservatively assumed a one-tailed p value of 0.50 [43].

When EEG frequency bands were divided into several sub-bands, we computed the combined mean values and standard deviation. For example, Perlis and colleagues divided the beta band into beta-1 and beta-2 [22]. In this case, the combined mean was computed as $\overline{X}_{combined} = 1/2\,(\overline{X}_{beta1} + \overline{X}_{beta2})$, and the combined root mean square of the standard deviation was computed as

$$SD_{rms} = \sqrt{\left(\overline{SD}^2_{beta1} + \overline{SD}^2_{beta2}\right) \Big/ 2}$$

When reported results were broken down into subgroups (e.g., female and male insomnia [44]), or insomnia subtypes (e.g., subjective and objective insomnia [45]), a combined mean value was calculated as the weighted mean (by sample size) across subgroups, as follows:

$$\overline{X}_{combined} = \frac{n_{11}\overline{X}_{11} + n_{12}\overline{X}_{12}}{n_{11} + n_{12}}$$

In such cases, the combined standard deviation was also calculated as

$$SD_{combined} = \sqrt{\frac{(n_{11}-1)SD^2_{11} + (n_{12}-1)SD^2_{12} + \frac{n_{11}n_{12}}{n_{11}+n_{12}}(\overline{X}_{11} - \overline{X}_{12})^2}{n_{11} + n_{12} + 1}}$$

where $\overline{X}_{11}, \overline{X}_{12}$ refer to the mean value of subgroups one and two, SD_{11} and SD_{12} refer to the standard deviations, and n_{11} and n_{12} refer to the sample sizes [46].

We also performed two moderator analyses. We first used this analysis to compare the summary effects in two types of EEG power measures: absolute and relative power. In the current meta-analysis, the term "overall" represents the inclusion of both absolute and relative power findings. We then performed another moderator analysis to evaluate the effect of medication status on EEG power spectra in studies with hypnotic medication and medication free.

Model selection

Most meta-analyses are based on fixed- or random-effects models. Under the fixed-effects model, the within-study variance (sampling or estimation error) is the only source of uncertainty, and all factors that could influence the effect size are the same in all studies. The random-effects model, however, contains an additional source of uncertainty: between-studies variance. The selection of a model should be based on the expectation of whether the studies share a common effect size [47]. The included studies were inconsistent with regard to insomnia subtypes, medication status, analyzed EEG channel, and subdivision of EEG frequency bands, rendering it *a priori* unlikely that all studies share a common (true) effect size. Therefore, the random-effects model was utilized for the present meta-analysis.

Heterogeneity

The heterogeneity in the dispersion of effect sizes across studies was estimated using Q and I^2. Q is computed as the weighted sum of

the squared deviations of each study's effect size from the mean value. A significant Q-value ($p < 0.05$) indicates heterogeneity in the dispersion of effect sizes. I^2 indicates the ratio of true heterogeneity to total variance in the observed effects, ranging from 0% to 100%. I^2 values of 25%, 50%, and 75% reflect low, moderate, and high heterogeneity, respectively [48]. Significant heterogeneity alerts that the combined effect sizes are not robust and stable. In addition, the effect of model choice can also be assessed via heterogeneity analysis. The random-effects model is more balanced in study weights and more appropriate than the fixed-effects model if the heterogeneity of the included studies' effect sizes is larger than the low threshold of 25%. If heterogeneity in I^2 is larger than 25%, the random-effects model is preferred.

Publication bias

As previously noted [49], studies with statistically significant results are more likely to be published than those whose results are not statistically significant. Even though a meta-analysis will yield a mathematically based synthesis of the included studies, if these studies are a biased sample of all relevant studies, then the mean effect computed by the meta-analysis will reflect this bias. This issue is generally known as publication bias. In the current study, publication bias was evaluated via visual inspection of the funnel plots, Egger's regression test, and Duval and Tweedie's trim- and fill-method [50,51]. The funnel plot displays the relationship between sample size and effect size. In the funnel plot, a symmetrical distribution of effect sizes clustered around the mean effect size indicates the absence of publication bias. However, the interpretation of a funnel plot is largely subjective, and the visual impression can be further confirmed by using Egger's regression test. In this test, Egger's intercept and a 95% CI should be calculated. Intercepts that do not significantly differ from zero ($p > 0.05$) indicate the absence of publication bias. Moreover, the evidence of publication bias observed in the funnel plot can also be confirmed by Duval and Tweedie's trim- and-fill method. In this method, an iterative procedure is used to trim and fill the distribution of the studies' effect sizes from the positive side of the funnel plot. This procedure yields a numeric estimate of the missing negative effect sizes and the adjusted effect size to remove this bias. In order to gauge the likely impact of publication bias on all summary effects, we assessed such bias for all outcomes (148 effect sizes) and in all frequency bands during wakefulness, NREM sleep, and REM sleep.

Results

After removing duplicate records and then initially screening titles and abstracts, 45 full-text articles were selected based on the inclusion and exclusion criteria. Finally, a total of 24 studies (25 citations) met the full inclusion criteria. Among these studies, 13 investigated EEG power during wakefulness, 17 during NREM sleep, and five during REM sleep (see Fig. 1).

Characteristics of the included studies

Table 1 shows the characteristics of the included studies. As both studies by Perlis et al. shared the same original sample [21,22], we regarded them as one study. However, we included both in our analysis since they reported power spectra during different states (i.e., during wakefulness and REM sleep [21] and NREM sleep [22]). The 24 studies involved recruited a total of 977 participants (645 female, 66.02%), including 532 patients with ID (351 female, 65.98%) and 445 good sleepers (294 female, 66.07%). From these studies, we retrieved 148 effect sizes at six frequency bands during wakefulness or sleep. The first study was published in 1993 and the latest in 2019, with three studies published before 2000 (12.5%), four studies published between 2000 and 2010 (16.67%), and 17 studies published after 2011 (70.83%). Of the 24 studies, 12 were conducted in the USA (50%), two in Switzerland, two in Germany, and one each in other countries (Mexico, Italy, Belgium, France, Netherland, South Korea, Iran, and Canada).

In all studies, criteria for insomnia diagnosis (DSM/ICD/ICSD) were ascertained via structured or semi-structured clinical interviews and/or sleep questionnaires. The most common insomnia subtype was primary insomnia [14,21,22,24,29,30,32,33,44,45,52–56]. Other subtypes, subgroups, or labels included the following: sleep-onset insomnia [57], psychophysiological & idiopathic insomnia [58], female insomnia [31], menopausal insomnia [59], comorbid-free insomnia [60], chronic insomnia [26], insomnia disorder [25,61], and insomnia sufferers [28]. Eleven studies failed to report insomnia duration in patient groups [14,31,33,44,54,55,58–62], and the remaining studies, with one exception [53], reported that patients with ID had experienced insomnia for more than six months. Hypnotic medication status was not mentioned in four studies [33,45,52,62]. In the remaining studies, patients were either medication-free or had undergone a washout period of at least 10 d prior to the study.

Most of the included studies conducted PSG recording in a sleep laboratory, although ambulatory PSG was performed at home in four studies [32,45,56,57]. Ten studies conducted at least two nights of PSG recording, with the first night serving as an adaption period to control for the first-night effect [14,21,22,28–30,32,33,44,58,61]. However, in eight studies, only one night of PSG was performed [24,26,45,53,55,56,59,62]. Of the 13 studies investigating waking EEG power, eight (61.5%) assessed resting-state EEG data during eyes-closed conditions [29–31,52,54,57,61,62], three during wakefulness after sleep onset [21,26,53], one during eyes-open conditions [60], and one during both eyes-open and eyes-closed conditions [25]. Fourteen studies (58.33%) used the central EEG leads referenced to A1/A2 for power spectral analysis [14,21,22,24,28–30,32,33,44,45,54,59,61,62], and one study failed to clearly report the electrode montage used [57]. The remaining studies analyzed a mixed number of EEG leads ranging from one to 256. Studies exhibited considerable variability in how frequency bands were subdivided. Thirteen studies reported absolute EEG power [24,26,28–30,44,52,53,58–62], 10 studies reported relative EEG power [14,21,22,25,31–33,45,55–57], and one study reported both absolute and relative EEG power [54].

Quality assessment

We used the JBI critical appraisal checklist to evaluate the quality of the included studies. Table S1 shows the risk-of-bias assessment for the included studies. Almost all studies were judged to have a low risk of bias in most domains. Three studies measured insomnia symptoms (exposure, item 5) in a different way for cases and controls [26,30,52], while one study failed to clearly report how the groups differed [58]. All patients reported having an insomnia duration (exposure period, item 9) for greater than six months, except in 11 studies where the duration of illness was unclear. Average interrater agreement (k) was 0.85.

Power spectral analysis during wakefulness

To obtain an overall impression of EEG activity during wakefulness, we first performed meta-analyses of the aggregated data across six frequency bands (i.e., data obtained during resting-state wakefulness with eyes-open and eye-closed conditions, and waking epochs after sleep onset). As shown in Table 2, patients with ID exhibited significant and robust increases in the

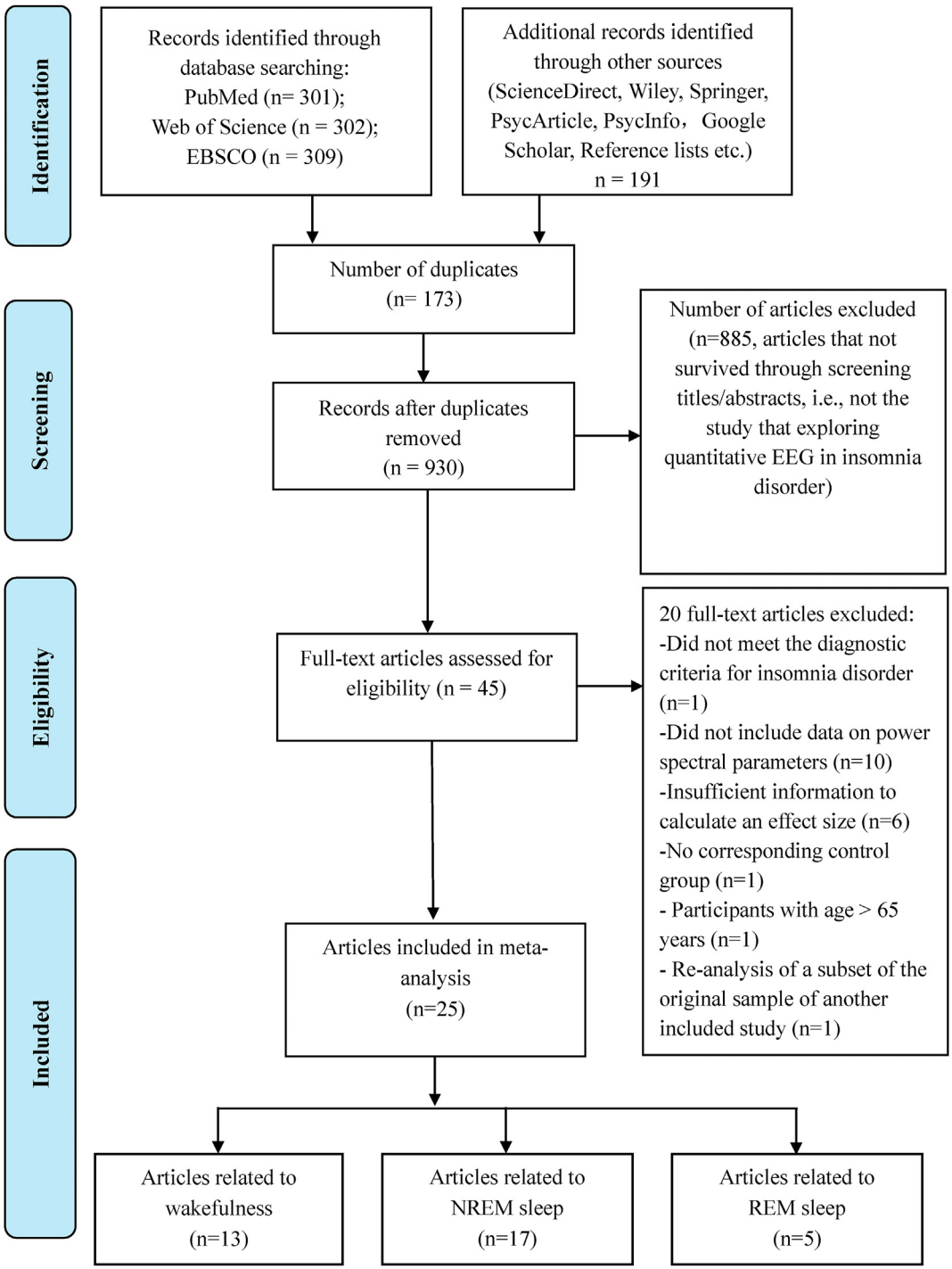

Fig. 1. PRISMA flow chart of the study selection process.

overall theta power only ($g = 0.317$, $p = 0.025$) when compared with HCs. Q-tests revealed the differences between absolute and relative power were not statistical significant across six bands ($Q_\delta = 0.519$, $p = 0.471$; $Q_\theta = 1.985$, $p = 0.159$; $Q_\alpha = 1.131$, $p = 0.288$; $Q_\sigma = 0.000$, $p = 1.000$; $Q_\beta = 0.143$, $p = 0.705$; $Q_\gamma = 3.442$, $p = 0.064$). However, separate analyses for absolute and relative power revealed significant and robust increases in absolute theta power ($g = 0.495$, $p = 0.009$), relative beta power ($g = 0.420$, $p = 0.023$), and absolute gamma power ($g = 0.691$, $p = 0.012$). Although we also found significant increases in overall alpha power ($g = 0.399$, $p = 0.004$), overall beta power ($g = 0.373$, $p = 0.007$), and absolute alpha power ($g = 0.523$, $p = 0.021$), these measures exhibited moderate and high heterogeneity in the dispersion of effect sizes [overall alpha power ($Q = 43.859$, $p = 0.000$, $I^2 = 77.199$), overall beta power ($Q = 20.308$, $p = 0.041$, $I^2 = 45.834$), and absolute alpha power ($Q = 16.902$, $p = 0.01$, $I^2 = 64.501$)]. Fig. 2 includes the forest plots with the respective effect size estimates (g) and 95% CIs for individual studies, illustrating EEG measures of absolute power, relative power and overall (Fig. 2, red and grey diamonds).

Table 2
Effect sizes, heterogeneity and publication bias on EEG frequency bands during wakefulness, NREM or REM sleep.

Target period and frequency	Measures	Number of comparisons	Total number of subjects (ID)	Total number of subjects (HC)	Hedge's g (95% CI)	Heterogeneity (Q)	Heterogeneity (I^2)	Egger's test (t)	Studies Trimmed	Adjusted values (95% CI)
Wake_δ	absolute power	5	108	83	−0.142 (−0.426, 0.143)	2.367	0	_	_	_
	relative power	3	40	45	−0.525 (−1.530, 0.480)	10.461**	80.882	_	_	_
	overall	8	137	114	−0.170 (−0.444, 0.104)	13.732	49.025	1.554	2	−0.354 (−0.661, −0.047)
Wake_θ	absolute power	5	108	83	0.495 (0.123, 0.866)**	5.937	32.629	_	_	_
	relative power	3	40	45	0.095 (−0.320, 0.510)	0.485	0	_	_	_
	overall	8	137	114	0.317 (0.040, 0.594)*	8.251	15.165	1.359	1	0.296 (0.025, 0.567)
Wake_α	absolute power	7	139	114	0.523 (0.080, 0.966)*	16.902*	64.501	_	_	_
	relative power	4	91	88	0.055 (−0.685, 0.795)	16.086**	81.350	_	_	_
	overall	11	219	188	0.399 (0.019, 0.779)*	43.859***	77.199	2.588*	0	_
Wake_σ	absolute power	4	97	69	−0.421 (−1.278, 0.436)	18.805***	84.047	1.218	1	−0.654 (−1.520, 0.212)
Wake_β	absolute power	7	133	108	0.315 (−0.089, 0.720)	13.656*	56.063	_	_	_
	relative power	5	100	97	0.420 (0.057, 0.784)*	5.930	32.548	_	_	_
	overall	12	222	191	0.373 (0.103, 0.644)**	20.308*	45.834	0.454	0	_
Wake_γ	absolute power	3	42	42	0.691 (0.149, 1.234)*	3.045	34.319	_	_	_
	relative power	2	26	26	−0.024 (−0.550, 0.502)	0.014	0	_	_	_
	overall	5	68	68	0.323 (−0.055, 0.701)	7.649	47.703	0.807	1	0.236 (−0.254, 0.726)
NREM_δ	absolute power	8	206	165	−0.097 (−0.386, 0.192)	13.167	46.835	_	_	_
	relative power	6	142	102	−0.388 (−0.656, −0.119)**	5.338	6.333	_	_	_
	overall	14	348	267	−0.253 (−0.450, −0.056)*	21.812	40.400	0.389	0	_
NREM_θ	absolute power	8	206	165	0.051 (−0.306, 0.408)	19.716**	64.496	_	_	_
	relative power	6	143	114	0.441 (0.103, 0.780)*	8.609	41.922	_	_	_
	overall	14	349	279	0.256 (0.011, 0.502)*	32.939**	60.534	1.220	4	0.030 (−0.243, 0.302)
NREM_α	absolute power	9	217	176	0.078 (−0.246, 0.402)	19.732*	59.457	_	_	_
	relative power	7	157	124	0.542 (0.213, 0.871)**	10.531	43.025	_	_	_
	overall	16	374	300	0.307 (0.076, 0.538)**	37.720**	60.233	1.320	4	0.112 (−0.151, 0.376)
NREM_σ	absolute power	8	206	165	0.169 (−0.073, 0.411)	9.407	25.584	_	_	_
	relative power	6	140	105	0.533 (0.166, 0.900)**	9.363	46.601	_	_	_
	overall	14	346	270	0.280 (0.078, 0.481)**	22.413*	41.997	0.622	0	_
NREM_β	absolute power	9	206	165	0.477 (0.232, 0.722)***	11.209	28.627	_	_	_
	relative power	7	167	134	0.477 (0.236, 0.719)***	5.869	0	_	_	_
	overall	16	373	299	0.477 (0.305, 0.649)***	17.089	12.222	1.813	1	0.451 (0.271, 0.631)
NREM_γ	absolute power	4	100	71	0.687 (0.121, 1.252)*	9.368*	67.976	_	_	_
	relative power	2	39	29	0.360 (−0.354, 1.073)	1.874	46.630	_	_	_
	overall	6	139	100	0.561 (0.118, 1.004)*	12.193*	58.992	1.947	2	0.313 (−0.160, 0.787)
REM_δ	absolute power	2	45	48	−0.039 (−0.940, 0.862)	4.815*	79.231	_	_	_
	relative power	1	30	20	0.000 (−0.557, 0.557)	0.000	0.000	_	_	_
	overall	3	75	68	−0.011 (−0.484, 0.463)	4.818	58.488	4.622	0	_
REM_θ	absolute power	2	45	48	−0.387 (−1.799, 1.026)	11.055**	90.955	_	_	_
	relative power	1	30	20	0.000 (−0.557, 0.557)	0	0	_	_	_
	overall	3	75	68	−0.052 (−0.570, 0.466)	11.524**	82.644	35.823*	0	_
REM_α	absolute power	3	56	59	0.651 (0.121, 1.182)*	3.850	48.049	_	_	_
	relative power	1	30	20	0.000 (−0.557, 0.557)	0	0	_	_	_
	overall	4	86	79	0.342 (−0.042, 0.726)	7.067	57.55	1.094	0	_
REM_σ	absolute power	2	45	48	0.780 (0.177, 1.383)*	2.023	50.565	_	_	_
	relative power	1	30	20	0.000 (−0.557, 0.557)	0	0	_	_	_
	overall	3	75	68	0.359 (−0.050, 0.768)	6.451*	68.998	1.178	0	_
REM_β	absolute power	2	45	48	0.722 (−0.006, 1.449)	2.942	66.012	_	_	_
	relative power	2	39	29	0.321 (−0.458, 1.101)	2.202	54.593	_	_	_
	overall	4	84	77	0.535 (0.004, 1.067)*	7.093	57.704	1.035	2	0.195 (−0.352, 0.741)
REM_γ	absolute power	1	25	29	0.388 (−0.144, 0.920)	0	0	_	_	_
	relative power	2	39	29	0.116 (−0.356, 0.589)	0.598	0	_	_	_
	overall	3	64	58	0.236 (−0.117, 0.589)	1.158	0	0.330	0	_

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

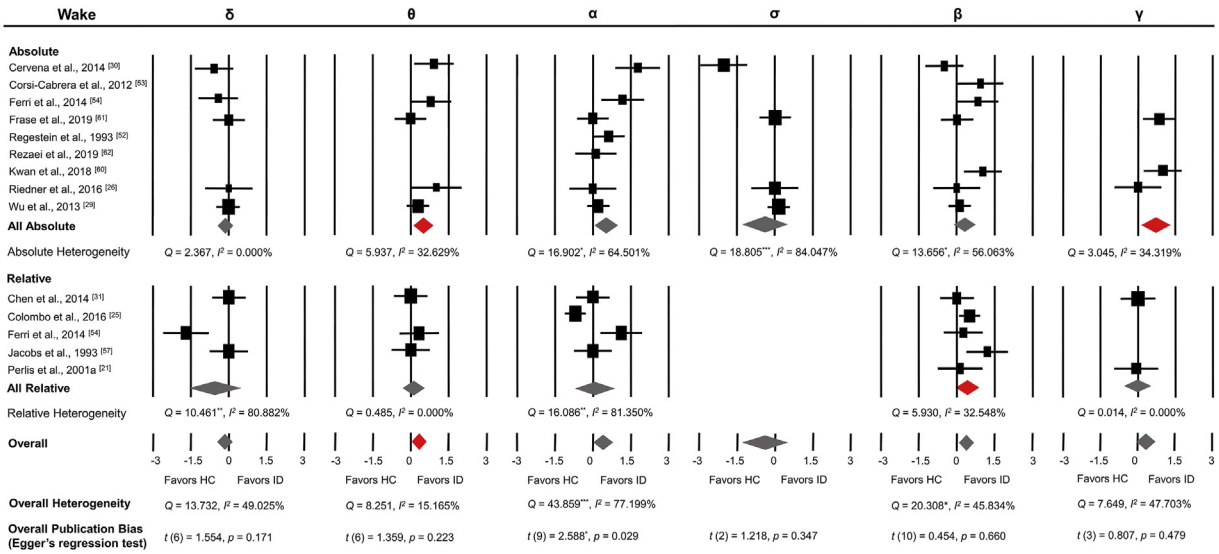

Fig. 2. Forest plots showing individual studies, each electroencephalography (EEG) power measure, and overall effect size estimates during wakefulness. Below each forest plot, we presented the heterogeneity and publication bias results. The positions of the squares on the *x*-axis indicate the effect size for each study; the bars indicate the 95% confidence intervals of the effect sizes; the red diamonds indicate the significant and robust results favoring insomnia disorder (ID); the grey diamonds indicate non-significant or non-robust results. HC, healthy control; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Power spectral analysis during NREM sleep

As shown in Table 2, compared with HCs, patients with ID exhibited significant decrease in overall delta power ($g = -0.253$, $p = 0.012$) and significant increase in overall beta power ($g = 0.477$, $p = 0.000$). *Q*-tests revealed the difference between absolute and relative power were not statistically significant in all bands ($Q_\delta = 2.079$, $p = 0.149$; $Q_\theta = 2.419$, $p = 0.120$; $Q_\sigma = 2.627$, $p = 0.105$; $Q_\beta = 0.000$, $p = 0.999$; $Q_\gamma = 0.495$, $p = 0.482$), except in alpha band ($Q_\alpha = 3.875$, $p = 0.049$). Separate analyses for absolute EEG power revealed that patients with ID exhibited significant and robust increase in absolute beta power ($g = 0.477$, $p = 0.000$). Separate analyses for relative EEG power revealed that patients with ID exhibited significant decrease in relative delta power ($g = -0.388$, $p = 0.005$) and significant increases in relative theta power ($g = 0.441$, $p = 0.011$), relative alpha power ($g = 0.542$, $p = 0.001$), relative sigma power ($g = 0.533$, $p = 0.004$), and relative beta power ($g = 0.477$, $p = 0.000$) than HCs. Although we also found significant increases in overall theta power ($g = 0.256$, p = 0.041), overall alpha power ($g = 0.307$, p = 0.009), overall sigma power ($g = 0.280$, p = 0.007), overall gamma power ($g = 0.561$, p = 0.013), and absolute gamma power ($g = 0.687$, $p = 0.017$), these measures exhibited moderate and high heterogeneity in the dispersion of effect sizes [overall theta power ($Q = 32.939$, $p = 0.002$, $I^2 = 60.534$), overall alpha power ($Q = 37.720$, $p = 0.001$, $I^2 = 60.233$), overall sigma power ($Q = 22.413$, $p = 0.049$, $I^2 = 41.997$), overall gamma power ($Q = 12.193$, $p = 0.032$, $I^2 = 58.992$), and absolute gamma power ($Q = 9.368$, $p = 0.025$, $I^2 = 67.976$)]. Fig. 3 includes forest plots with the respective effect size estimates (*g*) and 95% CIs for individual studies, reporting EEG measures of absolute power, relative power and overall (Fig. 3, red, blue, and grey diamonds).

Power spectral analysis during REM sleep

To our knowledge, only a limited number of studies have investigated whether EEG power spectra during REM sleep differ between patients with ID and HCs. When compared with HCs, patients with ID exhibited significant increases in overall beta power ($g = 0.535$, $p = 0.048$) (Table 2). *Q*-tests revealed that the differences between absolute and relative power were not statistical significant across six bands ($Q_\delta = 0.005$, $p = 0.943$; $Q_\theta = 0.249$, $p = 0.618$; $Q_\alpha = 2.758$, $p = 0.097$; $Q_\sigma = 3.467$, $p = 0.063$; $Q_\beta = 0.542$, $p = 0.462$; $Q_\gamma = 0.560$, $p = 0.454$). Separate analyses for absolute and relative EEG power revealed significant increases in absolute alpha power ($g = 0.651$, $p = 0.016$) and absolute sigma power ($g = 0.780$, $p = 0.011$) only. Heterogeneity analyses (Table 2) revealed that effect size estimates of absolute alpha, absolute sigma, and overall beta exhibited no significant heterogeneity. Fig. 4 includes forest plots with the respective effect size estimates (*g*) and 95% CIs for individual studies, showing effect sizes based on absolute power, relative power, and overall (Fig. 4, red and grey diamonds).

The medication-related case–control difference in EEG spectral power during wakefulness and sleep

In the current meta-analysis, four studies failed to report hypnotic medication status [33,45,52,62], nine studies recruited insomnia patients with no current sleep medication and/or antidepressant use [14,29,31,32,44,53,56,57,59], and the remaining studies required patients with ID to keep medication free for at least 10 d prior to EEG recording. Thus, we cannot exclude the possible effect of hypnotic medication on our findings.

To investigate the effect of medication status on EEG power spectra, we performed the subgroup analysis in studies with hypnotic medication or medication free. We primarily performed the subgroup analyses across the significant and robust results in EEG bands during wakefulness, NREM sleep, and REM sleep (see Table S2). *Q*-tests revealed the significant effect of medication status on beta activity during NREM sleep only ($Q_\beta = 8.828$, p = 0.003). However, further separate analyses revealed that both studies with hypnotic medication (M) and medication free (MF) exhibited significant case–control differences in beta power during NREM sleep ($g_M = 0.788$, p = 0.000; $g_{MF} = 0.263$, p = 0.016). Although we found no statistical significant effect of medication status on theta activity during wakefulness, separate analyses for studies with hypnotic

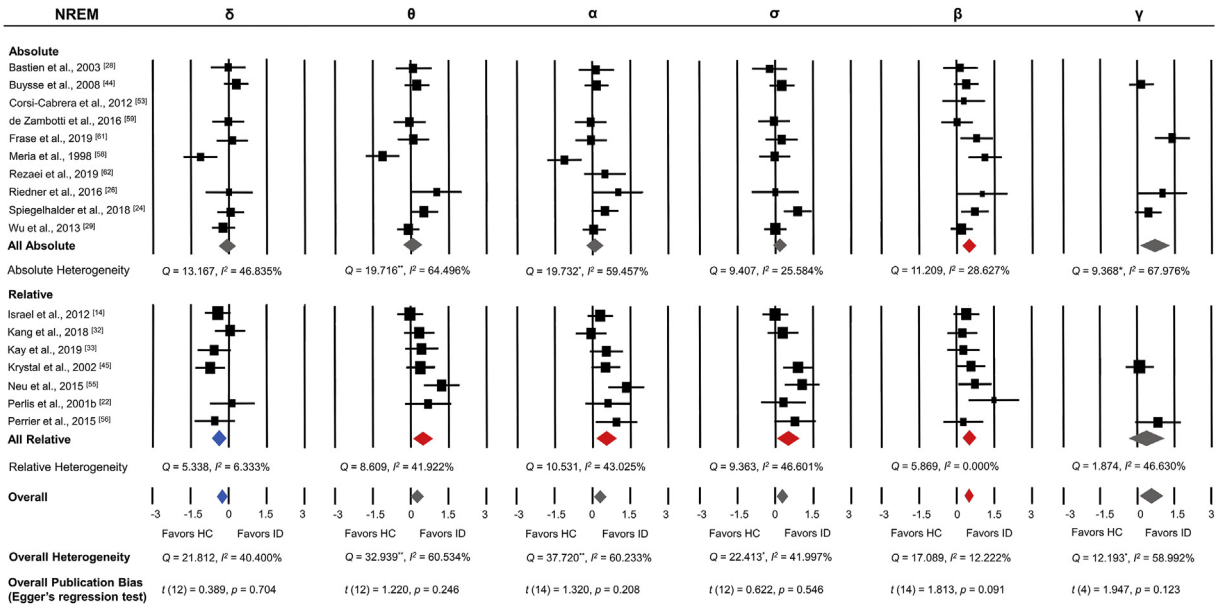

Fig. 3. Forest plots showing individual studies, each electroencephalography (EEG) power measure, and overall effect size estimates during non-rapid eye movement (NREM) sleep. As in Fig. 2 illustrated, but the blue diamonds indicate the significant and robust results favoring healthy control (HC). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

medication revealed significant case−control differences in waking theta power (g_M = 0.541, p = 0.008), but not for studies with medication free (g_M = 0.160, p = 0.341).

Publication bias analysis

To assess the possible effect of publication bias, we visually inspected the funnel plots, following which we performed Egger's regression test, and Duval and Tweedie's trim-and-fill method. We first assessed publication bias across all retrieved effect sizes. We then assessed such bias separately for each frequency band during wakefulness, NREM sleep, and REM sleep. As shown in Fig. S1, the funnel plot is asymmetrical, suggesting the existence of publication bias when all effect sizes are combined. Egger's test confirmed this result ($t_{146} = 2.374$, $p = 0.019$). Duval and Tweedie's trim-and-fill method revealed that the adjusted value ($g = 0.077$, CI: −0.014 to 0.167) for the 27 missing effect sizes to the left of the mean was lower than the observed value ($g = 0.237$, CI: 0.153 to 0.320). Although we observed obvious publication bias when all effect sizes were combined, separate analyses revealed no significant evidence of publication bias for each frequency band during different periods, except for waking alpha ($t_9 = 2.588$, $p = 0.029$) and REM theta ($t_1 = 35.823$, $p = 0.018$) (see Fig. S2 and Table 2).

Discussion

In the current study, we performed a systematic review and meta-analysis to assess the differences in EEG spectral power between patients with ID and HCs during wakefulness, NREM sleep, and REM sleep. During wakefulness, patients with ID exhibited significant and robust increases in absolute and overall theta power, relative beta power, and absolute gamma power. During NREM sleep, patients with ID exhibited significant and robust alterations in EEG power across all frequency bands except for gamma. In these patients, NREM sleep was associated with decreases in relative and overall delta power, and increases in absolute and overall beta power, relative power of theta, alpha, sigma and beta bands. During REM sleep, patients with ID exhibited significant increases in absolute alpha power, absolute sigma power, and overall beta power. In general, these findings demonstrate that ID is associated with increases in beta activity during both wakefulness and sleep, indicating that elevated beta activity may be a reliable and objective biomarker of cortical hyperarousal. Absolute and relative power had similar sensitivity in distinguishing patients with ID from HCs based on EEG data during wakefulness and REM sleep. However, during NREM sleep, group differences were more homogeneous for relative power than for absolute power. Importantly, our study is the first meta-analysis to quantify EEG power spectra across wakefulness, NREM sleep and REM sleep in patients with ID, and the results strongly support the notion that insomnia manifest as round-the-clock hyperarousal (i.e., “24-h”).

Insomnia-related alterations in waking EEG spectral features

Although existing narrative reviews of EEG in insomnia have discussed spectral features at/around sleep onset and during sleep [9,19], few studies have focused on resting-state EEG data obtained during wakefulness. In the present study, we estimated the overall effect across six frequency bands and the effect sizes of case−control differences for absolute and relative power in both separate and integrated analyses. Our meta-analysis indicated that given the significant heterogeneity (absolute and overall alpha power, overall beta power) and obvious publication bias (overall alpha) in some outcomes, increases in absolute and overall theta power, relative beta power and absolute gamma power may be the more sensitive and robust insomnia-related spectral features during wakefulness.

Previous studies have reported inconsistent results regarding alpha activity during wakefulness. While some studies reported increased alpha activity [30,52,54], others failed to reach the same conclusion [25,26,31,57,61,62]. Thus, we observed significant and moderate-to-high heterogeneity in the dispersion of effect sizes for both absolute and overall alpha power. These mixed results indicate that alpha power may be a marker of heterogeneity associated with

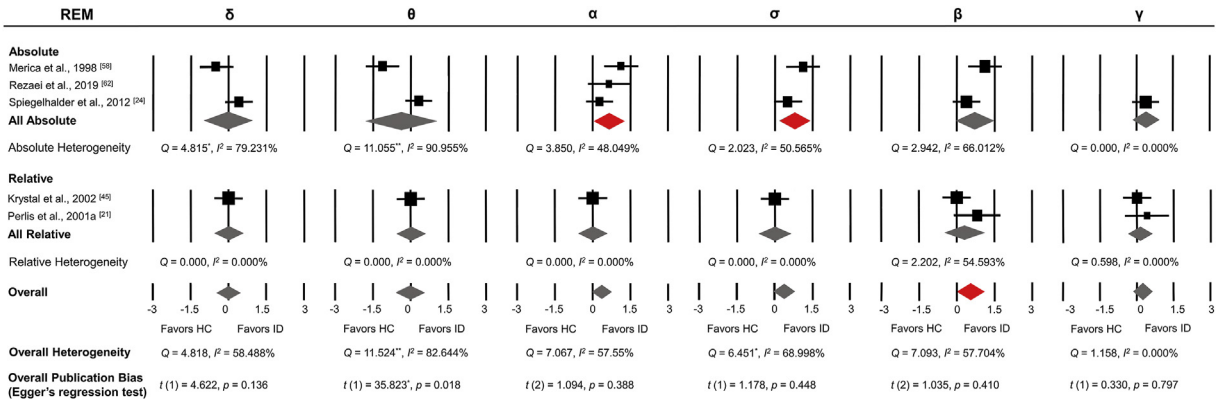

Fig. 4. Forest plots showing individual studies, each electroencephalography (EEG) power measure, and overall effect size estimates during rapid eye movement (REM) sleep. The illustrations of this figure are the same as that of Fig. 2. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ID or depend on unrecognized contextual determinants. In contrast, stable and robust group differences between patients with ID and HCs were observed for waking absolute and overall theta power. Few insomnia studies have focused on waking theta power. Increased theta power during wakefulness is associated with sleepiness and decreased cognitive performance [63–65]. Increased theta activity in patients with ID may mark sleepiness and fatigue due to disturbed nocturnal sleep or the use of hypnotic medication. Notably, despite their sleepiness, patients with ID do not fall asleep easily even when napping opportunities are provided during the day. The difficulty falling asleep that continues during the day may be related to increases in relative beta and absolute gamma power, which are considered as indicators of cortical hyperarousal. According to previous observations [66], when compared with normal sleepers, the hyperarousal brain states in patients with ID may associate with weaker suppression of metabolic activation in large parts of the brain after the beta increase. Previous reviews have noted that increased activity in high-frequency bands exists at/around sleep onset and during sleep [19,27]. The current meta-analysis extends this finding to resting-state wakefulness during the daytime. Some researchers have proposed that alterations in EEG power during wakefulness and NREM sleep are associated with one another [29]. Considering the time-consuming and complex analysis of EEG data during sleep, waking EEG activity may represent a promising and more feasible indicator to aid in the clinical diagnosis of ID and in the assessment of treatment effects.

Our meta-analysis revealed individuals with ID exhibit increased EEG power in absolute and overall theta power, relative beta power, and absolute gamma power during resting-state wakefulness, supporting the co-existence of sleepiness and cortical hyperarousal during the waking resting-state. These results may aid in developing more objective and reliable indicators of hyperarousal for ID.

Altered EEG spectral features across frequency bands during NREM sleep

Numerous studies have demonstrated that ID is characterized by increased high–frequency activity, primarily in the beta and/or gamma range [21–23,44,60]. Although some studies have also reported abnormal activity in other frequency bands, no studies to date have evaluated whether such spectral alterations are consistent across studies. Our meta-analysis revealed that the more sensitive and robust spectral features of patients with ID may be a decrease in relative and overall delta power (small-to-moderate effects), and significant increases in relative theta, alpha, sigma and beta power, and increases in absolute and overall beta power (small-to-large effects) relative to healthy sleeping controls subjects. No obvious publication bias was found in above outcomes. *Q*-tests revealed that the results of studies that assessed relative alpha power during NREM sleep were more homogenous than those that assessed absolute alpha power. Moreover, the use of relative power yielded robust group differences of small-to-medium effects for the delta, theta, alpha, sigma, and beta bands, while the use of absolute power yielded a moderate effect size for the beta band only.

As previously mentioned, increased beta activity during NREM sleep is considered to reflect cortical hyperarousal. Much less attention has been paid to frequency bands below beta, for which we may provide some hypothetical interpretations. First, cortical hyperarousal may not only be indexed by beta activity, but also by activity in higher and lower frequency bands. Second, lower delta activity may indicate decreased hyperpolarization of thalamocortical neurons during NREM sleep in patients with ID. However, we should consider a possible confounder, as people with insomnia experience less N3 (dominated by delta activity) [67], decreased delta activity during NREM sleep may also be related to the ratio of N3 and N2 during the NREM period analyzed. Future studies may further elucidate this question when more studies report spectral features separately for sleep stages of N3 and N2 during NREM sleep.

In summary, our meta-analysis indicated that individuals with ID exhibit alterations in almost all frequency bands during NREM sleep, potentially reflecting extended cortical hyperarousal. Such changes may co-exist with either decreased thalamocortical hyperpolarization during N3 or a shorter duration of N3 relative to N2 during the NREM period.

Increased high–frequency activity during REM sleep

Previous studies investigating EEG spectral features in ID during sleep focused mostly on NREM sleep. Recent studies have highlighted the importance of restless REM sleep [68–71]. Indeed, our meta-analysis included a much smaller number of studies regarding EEG spectral features during REM sleep that can distinguish patients with ID from HCs. Our findings indicated that people with ID exhibit increased absolute alpha and sigma power, and overall beta power during REM sleep. No obvious heterogeneity or publication bias was observed for the above outcomes. These results suggest that the significant increases in beta band power observed in patients with ID during wakefulness and NREM

sleep extend into REM sleep as well as neighboring frequencies. Since REM sleep is associated with enhanced emotional memory and regulation [72], altered EEG activity during REM sleep in patients with ID may be critical to understanding their characteristic difficulties with overnight regulation of emotional distress and hyperarousal [70,71,73].

Comparisons of absolute and relative power

To investigate whether absolute and relative spectral power differ in their sensitivity for distinguishing between patients with ID and HCs, we performed *Q*-tests and separate analyses in all individual frequency bands and in all states of wakefulness and sleep. For NREM sleep, relative alpha discriminated cases from controls significantly better than absolute alpha. Except for gamma band, relative power outperformed absolute power for all other frequency bands during NREM sleep. Mixed results were obtained for the comparisons of sensitivity in absolute and relative power during both wakefulness and REM sleep.

Although absolute power is the most frequently used measure in insomnia EEG research, relative power controls for individual differences that result in large variations in absolute power, including neurophysiological, anatomical, and physical properties of the brain and surrounding tissues [18]. Consequently, we believe that these two measures were similar when detecting spectral features during wakefulness and REM sleep. However, relative power may be more sensitive and reliable for distinguishing patients with ID from HCs during NREM sleep. Nonetheless, it remains to be determined whether this presents an artifact induced by the dominance of slow−wave activity in a 1/f-distributed spectral power.

Comparisons of studies with hypnotic medication and medication free

Previous studies have indicated that benzodiazepine users exhibited significantly increased sigma activity, and decreased delta and theta activity over the night than did good sleepers [28,74,75]. However, our meta-analysis revealed the significant effect of medication status on theta activity during wakefulness only. Therefore, we can conclude that the above results yielded in our meta-analysis are reliable and robust, except for increased theta activity during wakefulness, which may relate to the use of hypnotic medication.

Limitations

This meta-analysis has several limitations. First, due to the inconsistent subdivisions of EEG spectral bands across the included studies, the analysis was performed simply based on semantic categories of bands. Although this approach may have limited precision with respect to the borders of the significant case−control differences, our results do provide an overall indication. Moreover, case−control differences seem to involve broad bands rather than narrow spectral ranges. Future EEG spectral analyses should divide the frequency bands according to some common guidelines [40] or, preferably, present results across all individual frequency bins [25]. Second, only a small number of studies reported data of EEG power during REM sleep, any inference based on the results during REM sleep should be cautious. Third, heterogeneity among patients with ID may have influenced the reliability of our results. Indeed, previous studies have demonstrated the existence of different ID subtypes [13], which may affect EEG spectral characteristics [30,45], along with age, gender, and time of night [76]. Fourth, whereas we intended to assess the influence of EEG electrode montage on case−control differences in EEG power spectra, nearly three-fifths (14/24) of the included studies used central electrodes, while the rest used a variable number of electrodes ranging from one to 256. This made it difficult to quantify systematic differences. Finally, due to the limited number of studies, we were unable to perform analysis within the N2 and N3 stages of NREM sleep, or within specific sleep cycles.

Conclusion

In conclusion, our meta-analysis demonstrated that patients with ID exhibit significant and robust increases in beta band power during wakefulness and sleep that extend to neighboring frequency bands, suggesting a phenomenon of continuous cortical hyperarousal (i.e., “round-the-clock”). In addition, EEG data obtained during resting-state wakefulness revealed co-existing increases in theta activity, which have been found to associate with daytime sleepiness as well as the use of hypnotic medication. Patients with ID also appear to exhibit significant and robust decreases in delta power during NREM sleep. Thus, we hypothesize that ID may result from the abnormal activity of wake-promoting and sleep-promoting neural structures during daytime and sleep. With respect to methodology, our results indicate that relative power may be a more stable and sensitive measure for detecting NREM EEG deviations in patients with ID. The current meta-analysis is the first statistics-based review to explore EEG spectral characteristics in ID. Future studies should employ more measures for reporting the results of spectral analyses, with a special focus on potential differences in EEG spectral features among different insomnia subtypes.

Practice points

1. Insomnia disorder is a “round-the-clock” hyperarousal disorder indexed by increased beta band power, which extends to neighboring frequency bands.
2. The simultaneous occurrence of sleeping and waking EEG activity during daytime and sleep may help to explain subjective complaints in insomnia.
3. Relative power may be a more stable and sensitive biomarker for detecting NREM EEG deviations in patients with insomnia disorder.

Research agenda

1. Future EEG spectral analyses should divide the frequency bands according to some common guidelines or, preferably, present results across all individual frequency bins.
2. Future studies should evaluate whether EEG spectral features are more consistent across different insomnia disorder subtypes, different NREM stages or within specific sleep cycles.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2021.101457.

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