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RESEARCH ARTICLE

Lack of structural brain alterations associated with insomnia: findings from the ENIGMA-Sleep Working Group

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Summary

Existing neuroimaging studies have reported divergent structural alterations in insomnia disorder (ID). In the present study, we performed a large-scale coordinated meta-analysis by pooling structural brain measures from 1085 subjects (mean [SD] age 50.5 [13.9] years, 50.2% female, 17.4% with insomnia) across three

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international Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)-Sleep cohorts. Two sites recruited patients with ID/controls: Freiburg (University of Freiburg Medical Center, Freiburg, Germany) 42/43 and KUMS (Kermanshah University of Medical Sciences, Kermanshah, Iran) 42/49, while the Study of Health in Pomerania (SHIP-Trend, University Medicine Greifswald, Greifswald, Germany) recruited population-based individuals with/without insomnia symptoms 75/662. The influence of insomnia on magnetic resonance imaging-based brain morphometry using an insomnia brain score was then assessed. Within each cohort, we used an ordinary least-squares linear regression to investigate the link between the individual regional cortical and subcortical volumes and the presence of insomnia symptoms. Then, we performed a fixed-effects meta-analysis across cohorts based on the first-level results. For the insomnia brain score, weighted logistic ridge regression was performed on one sample (Freiburg), which separated patients with ID from controls to train a model based on the segmentation measurements. Afterward, the insomnia brain scores were validated using the other two samples. The model was used to predict the log-odds of the subjects with insomnia given individual insomnia-related brain atrophy. After adjusting for multiple comparisons, we did not detect any significant associations between insomnia symptoms and cortical or subcortical volumes, nor could we identify a global insomnia-related brain atrophy pattern. Thus, we observed inconsistent brain morphology differences between individuals with and without insomnia across three independent cohorts. Further large-scale cross-sectional/longitudinal studies using both structural and functional neuroimaging are warranted to decipher the neurobiology of insomnia.

KEYWORDS
brain volume, Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)-sleep, insomnia, meta-analysis

1 | INTRODUCTION

Insomnia is characterised by dissatisfaction regarding sleep quality or quantity, not attributable to sleep-disrupting external conditions. In particular, insomnia is defined by difficulties in falling asleep, difficulties maintaining sleep, early-morning awakenings with an inability to return to sleep, as well as subjective daily dysfunction (Morin et al., 2015; Sateia, 2014). Chronic insomnia disorder (ID) is the most common sleep disorder and is defined by insomnia symptoms occurring at least three times per week over a period of 3 months (Sateia, 2014), and is more prevalent in older individuals and in women (Morin et al., 2015; Riemann et al., 2022). Chronic ID is a persistent medical condition that is linked to adverse long-term physical and mental outcomes, including low quality of life, poor educational or work performance, memory impairment, higher risk of motor vehicle accidents, cardiovascular and metabolic diseases, anxiety, perinatal depression, major depressive disorder (MDD), bipolar disorder, post-traumatic stress disorder, and neurodegenerative disorders (Ahmadi et al., 2022; de Almondes et al., 2016; Emamian et al., 2019; Garbarino et al., 2017; Grandner et al., 2012; Riemann et al., 2022). Insomnia, rather than sleep duration, is an independent risk factor for suicide in patients with MDD across all age ranges (Simmons et al., 2020). The worldwide prevalence of insomnia symptoms is approximately 30%–35% and for ID is ~10% (Morin et al., 2015). Recently, the rate of insomnia has drastically increased during the coronavirus disease 2019 (COVID-19) pandemic in the general population across different countries. For example, an international, multicentre study ($n = 22{,}330$) of adults across 13 countries demonstrated that the rates of insomnia symptoms (36.7%), ID (17.4%), and anxiety (25.6%) were remarkable during the first wave of the COVID-19 pandemic; around twice the levels measured during non-pandemic periods (Morin et al., 2021). The annual economic cost of insomnia has been estimated at CAN$6.6 billion in Canada in 2007–2008 and US$45.2 billion in Australia in 2016–2017, mainly due to insomnia-related work absences, reduced productivity of affected individuals, and treatment of insomnia (Daley et al., 2009; Hillman et al., 2018). Despite the high prevalence, as well as the resulting socioeconomic and medical burden, the underlying pathophysiological mechanisms of insomnia are still poorly understood.

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Recently, various neuroimaging studies have been conducted to identify underlying neurobiological mechanisms of insomnia. Several structural magnetic resonance imaging (MRI) studies have reported grey matter alterations in ID in widespread cortical regions, including the orbitofrontal cortex, temporal cortex, precuneus, dorsomedial prefrontal cortex, and anterior cingulate cortex (Altena et al., 2010; Winkelman et al., 2013), as well as in subcortical regions, including the hippocampus, amygdala, thalamus, caudate, putamen, and nucleus accumbens (Emamian et al., 2021; Joo et al., 2013; Koo et al., 2017). However, their results are divergent and often conflicting. Interestingly, even in a coordinate-based meta-analysis (CBMA) using the activation likelihood estimation method, no consistent structural and functional regional alteration was identified across 19 neuroimaging studies (Tahmasian et al., 2018). The observed inconsistencies may be due to heterogeneity in clinical populations, small samples, diversity in image acquisition protocols and experimental designs, and flexible statistical approaches used in individual studies. However, one major limitation of the CBMA approach is relying on stereotaxic coordinates reported in existing publications that used different analytical protocols, which makes it susceptible to publication bias as well as methodological variation across these existing publications. Due to these issues, the important question is whether the lack of consistent findings in prior CBMA is due to the limited sample available for the meta-analysis or if there is no regional convergence of brain abnormalities in insomnia.

The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)-Sleep consortium (https://enigma.ini.usc.edu/ongoing/enigma-sleep) aims to increase the number of subjects analysed with sleep disturbances and harmonise the methods for preprocessing and analysis. The consortium uses unified protocols and combines data across various countries to better understand the neurobiology of sleep disorders at the international level (Tahmasian et al., 2021). Thus, to overcome the limitations of individual structural MRI studies and even CBMAs, we performed a coordinated meta-analysis of structural MRI in 1085 subjects with and without insomnia symptoms. Specifically, we analysed data from three cohorts participating in the ENIGMA-Sleep Group to measure cortical and subcortical brain differences between subjects with and without insomnia symptoms. Furthermore, to investigate the effect of insomnia on brain structure, we measured an insomnia brain score, which (similar to the brain age score) quantifies subtle but widespread deviations in regional brain structures (Frenzel et al., 2019; Weihs et al., 2021).

2 | METHODS

2.1 | Study populations

We included data from three cohorts within the ENIGMA-Sleep Group (Tahmasian et al., 2021). In particular, we analysed two case–control samples collected by the Kermanshah University of Medical Sciences (KUMS, Iran) and the University of Freiburg Medical Center (Freiburg, Germany), as well as a general population sample from the Study of Health in Pomerania (SHIP-Trend, Germany) (Volzke et al., 2011; Volzke et al., 2022). Cohort details are provided below and in Table 1.

The KUMS sample: the KUMS data are from a case–control sample including 55 patients with chronic ID and 49 healthy subjects. The patients with chronic ID were recruited from the Sleep Disorders Research Center, KUMS. All patients met the diagnostic criteria of chronic ID according to the third edition of the *International Classification of Sleep Disorders* (ICSD-3) criteria (Sateia, 2014) and psychiatric interview and overnight polysomnography (PSG) (to exclude other sleep disorders) before brain MRI acquisition. Healthy subjects were recruited through local advertisement and were defined as those with no present or past neurological or psychiatric illness, and all controls had a Pittsburgh Sleep Quality Index (PSQI) total score of < 5. The exclusion criteria included taking any neuropsychiatric medications, pregnancy, any other medical, neurological, psychiatric, or other sleep disorders, as well as contraindications to MRI. The study was approved by the Ethics Committee of KUMS, and written informed consent was obtained from all participants. The details of these data are described elsewhere (Emamian et al., 2021).

The Freiburg sample: the Freiburg sample is a case–control sample including 42 patients fulfilling the criteria for chronic ID (originally recruited as patients with primary insomnia) and 43 healthy participants. The patients with ID were recruited through the Sleep Disorders Clinic of the University of Freiburg Medical Center. Healthy controls were recruited through local advertisements. For screening purposes, all participants underwent a semi-standardised psychiatric and sleep-related interview. All participants were required to be free of any psychoactive medication for at least 2 weeks before and during study participation. The Institutional Review Board of the University of Freiburg Medical Center approved the original study protocols. Details of the data collection are described elsewhere (Regen et al., 2016; Spiegelhalder et al., 2013).

The SHIP-Trend sample: the SHIP-Trend is a general population cohort comprising 4420 individuals randomly drawn from local registries in Western Pomerania in Germany, who were assessed between 2008 and 2012 (Volzke et al., 2011; Volzke et al., 2022). After excluding all subjects who refused participation in the whole-body MRI or who fulfilled an exclusion criterion (e.g., the presence of a cardiac pacemaker), MRI scans were performed on a sub-sample of 2159 individuals. Of these, 1264 subjects underwent an in-depth sleep assessment including various questionnaires such as the Insomnia Severity Scale (ISI) (Morin et al., 2011), assessing the severity of various night- and day-time components of insomnia, and the PSQI (Buysse et al., 1989), assessing subjective sleep quality, as well as overnight PSG, during which the Apnea–Hypopnea Index (AHI) was assessed according to American Academy of Sleep Medicine (AASM) 2007 criteria (Iber, 2007; Ruehland et al., 2009). To account for the population-based nature of the SHIP-Trend, more stringent selection criteria were used to exclude subjects due to missing variables, the presence of gross structural abnormalities in the brain or

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TABLE 1 Baseline characteristics of the three cohorts

	KUMS (patients with ID/ healthy controls)	Freiburg (patients with ID/ healthy controls)	SHIP-Trend (general population; with/ without insomnia)
N	42/49	42/43	75/662
Age, years, mean (SD)	43.5 (10.8)/ 39.9 (12.4)	41.9 (14.0)/ 39.0 (8.9)	54.2 (10.9)/ 52.6 (13.7)
Gender, female, *n* (%)	27 (64.3)/ 27 (55.1)	26 (61.9)/ 25 (58.1)	52 (69.3)/ 301 (45.5)
ICV, cm^3, mean (SD)	1549.6 (182.8)/ 1581.9 (142.3)	1187.6 (244.0)/ 1132.0 (180.4)	1533.6 (147.0)/ 1594.8 (167.8)
ISI score, mean (SD)		14.9 (3.6)/ 2.1 (2.3)	17.2 (2.3)/ 5.9 (3.9)
PSQI score, mean (SD)			11.9 (3.1)/ 5.4 (3.3)
AHI, events/h, mean (SD)			7.5 (9.2)/ 8.9 (13.4)
Sleep medication, yes, *n* (%)			25 (33.3)/ 26 (3.9)

Abbreviations: AHI, Apnea–Hypopnea Index; Freiburg, University of Freiburg Medical Center; ICV, intracranial volume; ISI, Insomnia Severity Index; KUMS, Kermanshah University of Medical Sciences; PSQI, Pittsburgh Sleep Quality Index; SHIP, Study of Health in Pomerania.

the presence of multiple sclerosis, Parkinson's disease, epilepsy, or stroke.

2.2 | Insomnia definitions

In the KUMS sample, chronic ID was defined according to ICSD-3 criteria 2, while in the Freiburg cohort, the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) criteria were used (American Psychiatric Association, 2013). In the SHIP-Trend sample, the presence of insomnia symptoms was defined based on an ISI score of ≥15 (Gerber et al., 2016; Morin et al., 2011).

2.3 | The MRI acquisition and image processing

In both the SHIP-Trend and KUMS samples, a 1.5-T Siemens Magnetom Avanto scanner was used to obtain the three-dimensional brain MRI scans. Cortical reconstruction and volumetric segmentation were performed using FreeSurfer 7.2, using the Desikan-Killiany atlas for the cortical volumes (68 regions of interest) and the Automatic Segmentation (ASEG) atlas for subcortical volumes (34 regions of interest) (Desikan et al., 2006). In the Freiburg sample, a 3-T MRI (Magnetom TIMTrio, Siemens) was used, and the segmentation was performed with FreeSurfer 5.1 using a similar protocol. At this stage, FreeSurfer also assessed the intracranial brain volume. Due to the skewed distribution of the ventricle volumes (i.e., left/right lateral ventricle, left/right inferior lateral ventricle, third ventricle and fourth ventricle), a log transformation was performed on the corresponding regional measures. To correct for potential segmentation failures, outliers (i.e., values lying above 75th percentile + 3 × interquartile range [IQR] or below the 25th percentile − 3 × IQR) were removed and later imputed using the 'miss Forest' R-package (Stekhoven & Bühlmann, 2012).

2.4 | Statistical analyses

All statistical analyses were performed with R Version 4.2.

2.4.1 | Meta-analysis across three sites

Within each cohort, we used ordinary least squares regression with robust standard errors to investigate the relationship of the individual cortical and subcortical brain regions (outcome) to the presence of insomnia (exposure) (Long & Ervin, 2000). All models were adjusted for age, sex, age × sex, and intracranial volume (ICV). To account for the non-linear dependency between the various outcomes and age, restricted cubic splines with four knots were used using the 'rms' package (https://cran.r-project.org/web/packages/rms/). Additionally, as the SHIP-Trend sample is not a case–control sample, the models were also adjusted for the AHI, as well as for the self-reported intake of sleep medication. To pool the effects from the different cohorts, a fixed-effects meta-analysis was performed using the 'meta' package (Balduzzi et al., 2019). Effects were considered statistically significant at $p < 0.05$ using false discovery rate (FDR) correction for multiple testing (Benjamini & Hochberg, 1995).

2.4.2 | Insomnia brain score

The insomnia brain score was based on the cortical and subcortical volumes from the Freiburg sample. This cohort was used as it contains clinical patients with ID and has a similar population as the SHIP-Trend validation sample. This reduces the ethnic/genetic bias, that might be present if the KUMS sample were to be used. As applied previously (Frenzel et al., 2019), using the 'glmnet' R package (Friedman et al., 2010), logistic ridge regression was used to train a binary classifier, which optimally separated subjects with insomnia from subjects without, given the subject's cortical and subcortical volumes. The optimal shrinkage parameter, λ*, was defined as the λ with the smallest mean classification error estimated using a five-fold cross-validation with 40 repetitions. All features were standardised to a zero mean and unit variance, and age, sex, and ICV were also added to the logistic models as covariates of no interest to account for potential imbalances between the case and control group. The resulting model was then used to predict the insomnia brain score in the KUMS and the SHIP-Trend cohorts after standardising all features

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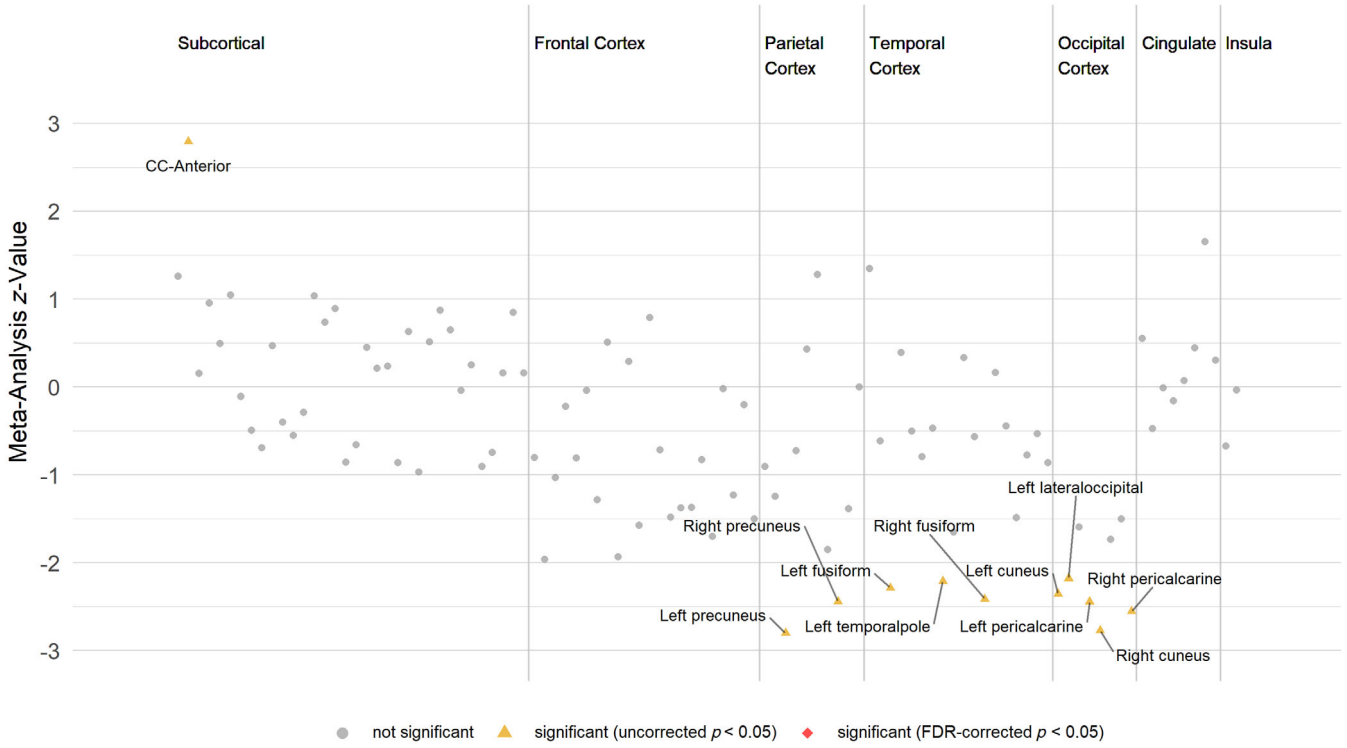

FIGURE 1 Morphometry of subcortical or cortical brain regions across all cohorts. *Z*-values from the fixed-effect meta-analysis aggregating the results from the Kermanshah University of Medical Sciences (KUMS), University of Freiburg Medical Center (Freiburg) and Study of Health in Pomerania (SHIP)-Trend cohorts. The 10 areas were nominally significant, while no region was significant after correcting for multiple testing (via the false discovery rate [FDR])

based on the mean and standard deviation assessed in the Freiburg sample. The insomnia brain score was computed to represent the log-odds of having insomnia in new individuals whose data were not used to train the model. Put differently, a higher insomnia score represents a higher similarity of the subject's brain to the brain of someone with ID, as defined in the Freiburg sample. To validate the score, the relationship between the score (outcome) and the presence of ID (exposure) was investigated in KUMS and SHIP-Trend using the same covariates as in the meta-analysis. To further understand potential underlying mechanisms, using the SHIP-Trend only, we additionally investigated the associations between the score and the continuous ISI score, as well as with the PSQI and its sub-scores.

3 | RESULTS

3.1 | Baseline characteristics of the sample population

In the KUMS sample, after excluding obstructive sleep apnea ($N = 1$) and with missing covariate data ($N = 14$), 91 subjects remained. For the Freiburg sample, 85 subjects were considered. For the SHIP-Trend sample, 737 subjects were considered after excluding subjects due to missing variables ($N = 3659$), structural abnormalities ($N = 14$), the presence of neurological disorders ($N = 3$) and reported strokes ($N = 7$). The baseline characteristics of the included sample are given in Table 1.

Regarding the segmentation outliers, in the KUMS sample, two outliers were identified. The (locally) optimal imputation was reached after four iterations with an estimated normalised root mean square error (NRMSE) of 0.00023 (Supplementary Figure S1 in Appendix S1). Similarly, in the Freiburg sample, two outliers were identified with a NRMSE of 0.14 reached after four iterations (Supplementary Figure S2 in Appendix S1). Finally, in the SHIP-Trend sample, 17 outliers were identified with a NRMSE of 0.0014 reached after three iterations (Supplementary Figure S3 in Appendix S1).

3.2 | Insomnia and morphometric brain measurements

After correcting for multiple testing ($p < 0.05$, FDR corrected), there was no significant association of insomnia with morphometry of subcortical or cortical brain regions in either the individual samples or on the meta-analysis level (Figure 1). Results of the subcortical volume analyses can be found in Supplementary Table S1 and Figure S4 in Appendix S1, while the results of the cortical grey matter volume analyses can be found in Supplementary Table S2 and Figure S5 in Appendix S1.

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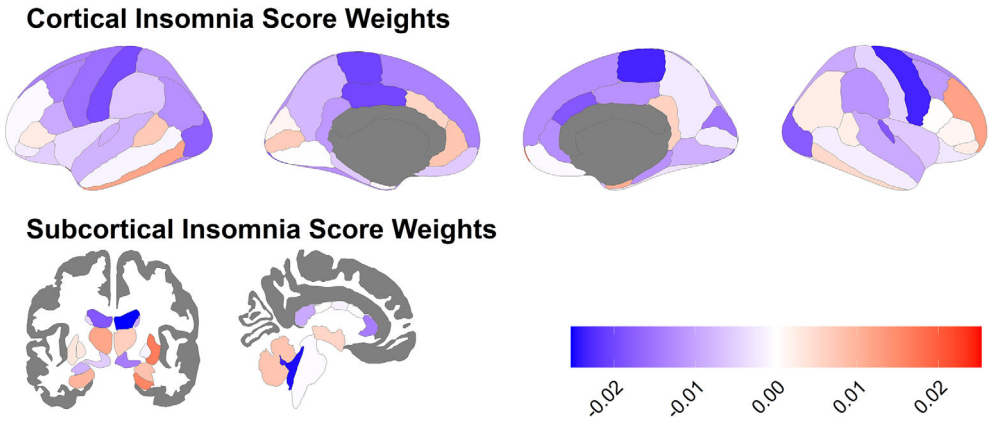

FIGURE 2 Weights assessed in the Freiburg cohort of the individual brain regions of the insomnia score using cortical and subcortical regions

3.3 | Insomnia-related brain atrophy patterns

The optimal shrinkage parameter was estimated at $\lambda = 3.88$, with a mean classification error of 43.6% (Supplementary Figure S6 in Appendix S1). A list of the resulting weights of the individual regions can be found in Supplementary Table S3 in Appendix S1 and Figure 2. However, no association was identified between the insomnia brain score and the presence of insomnia symptoms in the independent KUMS (estimate −0.012, 95% confidence interval [CI] −0.067 to 0.044; $p = 0.68$) or SHIP-Trend cohorts (estimate 0.016, 95% CI −0.020 to 0.052; $p = 0.37$). Similarly, no effect could be observed concerning the SHIP-Trend ISI sum score (estimate 0.0015, 95% CI −0.00075 to 0.0038; $p = 0.19$). Regarding the PSQI, on the other hand, a significant positive association was detected between the insomnia brain score and the PSQI sum score (estimate 0.0040, 95% CI 0.00062 to 0.0073; $p = 0.020$), as well as with the first component of the PSQI (estimate 0.020, 95% CI 0.0043 to 0.035; $p = 0.012$) assessing subjective sleep quality.

4 | DISCUSSION

To assess the potential structural brain abnormality in subjects with insomnia and to overcome several of the limitations of individual neuroimaging studies of insomnia (e.g., small sample sizes, inconsistent analysis methods), we performed a fixed-effect meta-analysis across three cohorts with a harmonised analytical protocol. We did not detect any significant association between insomnia symptoms and cortical or subcortical volumes. Afterward, we calculated the insomnia brain score in one sample, and we tested the model in the other two samples to predict individual insomnia-related brain atrophy. Again, while identifying some signals regarding subjective sleep quality, we did not observe a robust insomnia brain atrophy pattern across the three cohorts.

The results of the present study support previous neuroimaging meta-analysis, in which no consistent regional brain abnormality in ID was observed (Tahmasian et al., 2018). Thus, the present and previous neuroimaging meta-analyses did not reveal a strong link between brain regions and insomnia, and the previous reports of structural alterations associated with insomnia may not be replicable due to their small samples (usually <100 participants) or other variabilities in the included participants (e.g., recruiting a particular ID subtype). While the insomnia brain score reduces the issues caused by multiple testing, it is dependent on a global signal being present in the data. As no clear signal was identified in the meta-analysis, it is not surprising that the insomnia brain score did not demonstrate any robust results across the three sites. To our knowledge, this preliminary study is the first neuroimaging collaborative work in the field of insomnia to provide better insights into structural alterations in insomnia. Even so, we only had three samples, including two small samples with patients with ID and controls ($N \sim 90$) and one larger population-based sample ($N = 737$), in which only 11% of subjects had insomnia symptoms. Thus, we clearly need more data to address the question of whether the observed absence of significant findings in the present study is due to the limited available samples and statistical power or depends on the imaging modality chosen and the type of structural analysis, such as cortical thickness and surface area analysis.

Another potential reason for the observed weak structural findings in insomnia might be the clinical heterogeneity of insomnia. Insomnia is considered a heterogeneous disorder, which has different subtypes with noticeable inconsistencies in terms of pathophysiology, the clinical presentation of sleep-related and non-sleep-related symptoms, as well as treatment response (Benjamins et al., 2017). Blanken et al. (2019) performed data-driven subtyping of subjects with insomnia using high-dimensional multivariate phenotypic data of subjects with insomnia symptoms and found five ID subtypes, including 'highly distressed', 'moderately distressed but reward sensitive', 'moderately distressed and reward insensitive', 'slightly distressed with high reactivity', and 'slightly distressed with low reactivity'. Similarly, other studies identified discrepancies between insomnia subtypes in terms of demographics, daily symptoms, and PSG findings (Bjorøy et al., 2020; Kao et al., 2021). For example, Bjorøy et al. (2020) divided insomnia into seven subtypes and observed that subjects with a combination of sleep onset insomnia, sleep maintenance insomnia, and early morning awakening insomnia have a higher rate of anxiety, depression, alcohol consumption, and use more hypnotics than participants with other insomnia subtypes. A data-driven classification of objective PSG sleep duration and electroencephalography-based

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spectral power revealed three insomnia subtypes including 'short-sleep delta-deficient', 'normal-sleep delta-deficient', and 'normal neurophysiological sleep' (Kao et al., 2021). Another study based on event-related potential measures demonstrated that patients with psychophysiological insomnia could not inhibit information processing during sleep onset, while patients with paradoxical insomnia had higher attentional processing for inhibition (Turcotte et al., 2011). A previous structural brain analysis demonstrated distinct alterations between two subtypes of ID including paradoxical and psychophysiological insomnia (Emamian et al., 2021). In particular, there was a shape abnormality in the caudate, putamen, and nucleus accumbens in paradoxical insomnia, but shrinkage in the thalamus, amygdala, and hippocampus was observed in psychophysiological insomnia (Emamian et al., 2021). Using a machine-learning-based classification via a support vector machine algorithm, a preliminary study has observed that multimodal (structural and functional) brain data can distinguish paradoxical insomnia from psychophysiological insomnia (Afshani et al., 2022). These findings suggest a distinct role of cortical and subcortical brain regions in the pathophysiology of paradoxical and psychophysiological subtypes. Interestingly, Miller et al. (2018) applied cognitive-behavioural therapy for insomnia (CBT-I) protocols to manage different insomnia subtypes derived from PSG. The authors found that acceptability and tolerability to CBT-I differ between ID subtypes, i.e., patients with ID with normal sleep duration responded better to CBT-I than those with short sleep duration (Miller et al., 2018). However, the literature on this issue is not consistent. For example, another study found that CBT-I is equally effective in both insomnia groups with objective (based on PSG) short and normal sleep duration (Crönlein et al., 2020).

These findings together suggest that ID may not be a unified diagnostic entity but rather comprises various subtypes with their own particular multivariate profile of personality characteristics, sleep microstructure, cognitions, mood, and neuroimaging biomarkers (Benjamins et al., 2017; Blanken et al., 2019). Using sub-clinical criteria such as the ISI, which are unable to assess the complexity of ID, thereby ignoring the heterogeneity and subtypes of insomnia, as well as not considering the length of the illness, which was unfortunately not available, might have led to the failure to identify and replicate structural findings across our different cohorts.

5 | CONCLUSION

In the present study, we detected no structural brain differences between subjects with and without insomnia across three independent cohorts of ENIGMA-Sleep, neither in the meta-analysis nor in insomnia-related multivariate brain morphometry. Evidently, more cross-sectional samples are needed to address the question of whether the observed lack of structural findings in the present study is due to the limited available samples or other factors. Furthermore, upcoming collaborative works should assess the potential functional disruptions across intrinsic brain networks to elucidate the neural correlates of insomnia and its subtypes at the functional level. A recent study highlighted that thousands of subjects are needed to identify reproducible brain-wide association (Marek et al., 2022). Besides cross-sectional studies, longitudinal and interventional studies using both structural and functional neuroimaging data may aid in detecting the long-term effects of insomnia on the brain and evaluate the effect of insomnia treatments, such as CBT-I, on the brain activity/connectivity of patients with ID. The core aim of this initiative is to invite sleep clinicians/scientists across different countries to join us, as we have no choice but to work together to decipher the neurobiological mechanisms of insomnia (Tahmasian et al., 2021). We hope that the upcoming studies from the ENIGMA-Sleep consortium provide robust and replicable results using various datasets worldwide.

AUTHOR CONTRIBUTIONS

Antoine Weihs, Stefan Frenzel, Masoud Tahmasian, Kaustubh R. Patil, and Kai Spiegelhalder designed the study. Antoine Weihs and Stefan Frenzel performed the statistical analyses. Robin Bülow, Ralf Ewert, Habibolah Khazaie, Masoumeh Rostampour, Mortaza Afshani, Beate Stubbe, Henry Völzke, Hans J. Grabe, Kai Spiegelhalder, and Dieter Riemann collected data. Antoine Weihs and Masoud Tahmasian wrote the first draft of the manuscript. Hanwen Bi, Julian E. Schiel, Felix Hoffstaedter, Neda Jahanshad, Dieter Riemann, Sophia I. Thomopoulos, Paul M. Thompson, Sofie L. Valk, Mojtaba Zarei, Simon B. Eickhoff, Hans J. Grabe, Kaustubh R. Patil, and Kai Spiegelhalder revised the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests directly related to this work. Hans J. Grabe has received travel grants and speakers' honoraria from Fresenius Medical Care, Neuraxpharm, Servier, and Janssen Cilag and research funding from Fresenius Medical Care. Ralf Ewert

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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