SLEEP, BRAIN AND NEUROPSYCHIATRIC DISORDERS

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SLEEP, BRAIN AND NEUROPSYCHIATRIC DISORDERS

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Prevalence and Related Factors of Insomnia Among Chinese Medical Staff in the Middle and Late Stage of COVID-19

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Background: The outbreak of novel coronavirus disease (COVID-19) has brought serious psychological pressure to people, especially medical health staff. At present, there are few studies on insomnia and related factors of medical health staff in the middle and late stage of the epidemic of COVID-19. Therefore, the purpose of this study was to investigate the prevalence of insomnia and its related risk factors among medical workers in China in the middle and later stage of COVID-19 epidemic, as well as the relationship between insomnia and psychological resilience.

Methods: From February 14 to March 29, 2020, a cross-sectional survey was conducted among 606 medical staff in China through Ranxing Technology's "SurveyStar" network platform. All subjects were assessed with the Insomnia Severity Index (ISI) and simplified Chinese version of Connor-Davidson Resilience scale (CD-RISC-10).

Results: In the middle and later stages of the COVID-19 outbreak, the incidence of insomnia among medical staff was 32.0%. Compared with non-insomnia group, the insomnia group had younger age, lower education level, longer daily working hours and less psychological resilience. In addition, the prevalence of insomnia was higher in medical staff with a history of somatic diseases. The severity of insomnia of Chinese medical staff was associated with age, education level, daily working hours, psychological resilience and somatic diseases.

Conclusions: Our study shows that nearly 1/3 of Chinese medical workers suffer from insomnia nearly a month after the COVID-19 outbreak. Compared with the general population, medical staff who are working with COVID are more prone to insomnia. Risk factors for insomnia include younger age, lower education level, longer working hours per day, and physical illness. The tenacious dimension of psychological resilience is a protective factor for insomnia.

Keywords: insomnia, COVID-19, prevalence, resilience, medical health staff

INTRODUCTION

Insomnia is a major mental problem for medical staff, especially during disease outbreaks. Previous studies have shown that during the SARS epidemic, the percentage of insomnia among Chinese health care workers ranged from 37.1% (1) to 52.3% (2–4), which was 5–7 times (6–12.2%) higher than the public population (2, 4, 5). In December 2019, the novel coronavirus disease (COVID-19) first appeared in Wuhan, Hubei, China (6), and then spread to other cities and even abroad (7). Because of its high infectivity and fatality rate, it brings tremendous psychological pressure to medical staff, which leads to an increase in the incidence of insomnia and seriously affects the mental health of medical staff (8, 9). In addition, insomnia is a major risk factor that increases depression, anxiety and suicide (10, 11).

A variety of common factors, such as age (4, 8, 9, 12, 13), women (4, 9, 12, 13), low education level (4, 9, 13), low income level (4), isolation environment (9), and marital status (4, 12, 13) has been shown to be associated with personal insomnia. Moreover, another risk factor for insomnia among medical staff includes job position, such as nurse (9). Other studies have shown that long-term working hours and steady-state overload are important factors for increased insomnia among medical health workers (1, 8, 9, 14–16). Taken together, insomnia is caused by different risk factors, and insomnia is still a major health problem for medical workers. Most previous studies have focused on the relationship between insomnia and the sociodemographic variables, and only a few studies have investigated the relationship between insomnia and psychological resilience (17–21). Psychological resilience is the ability to adapt to stress and adversity. Li et al. (18) and Cheng et al. (21) found that people with low resilience directly lead to poor sleep quality. Similarly, Brand et al. (22) reported that compared with the high resilience group, the low resilience group has lower sleep efficiency, more awakenings, and lighter sleep. A recent study also found a significant positive correlation between the resilience and the quality of sleep in pregnant woman (17). However, most of those studies were conducted among non-medical staff. Therefore, whether psychological resilience is a protective factor for sleep quality of medical staff is still unknown and deserves further study.

To our best knowledge, no study has reported the relationship between psychological resilience and insomnia of medical staff among Chinese Han population. Therefore, this study aimed to determine the prevalence and related factors of insomnia in Chinese medical staff through a cross-sectional design, including demographic data, daily working hours, somatic diseases, and psychological resilience.

METHODS

Subjects and Settings

A cross-sectional study was conducted from February 14 to March 29 2020. All questionnaires were distributed in the form of posters through the "SurveyStar" network platform (Ranxing Technology), which was forwarded through Wechat and other channels. The recruited medical staff logged in by scanning the QR code and filled in the questionnaire. Finally, a total of 606 valid data were collected.

The research protocol was approved by the Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences.

Measurements

A structured self-assessment questionnaire was conducted in this survey. Demographic data of all subjects were collected, including sex, age, height, weight, marital status, education level, occupation (doctors, nurses, or medical technicians), daily working hours, history of SARS epidemic in 2003, annual family income, history of somatic diseases, COVID-19 infection of relatives and friends, economic losses caused by COVID-19. The Chinese version of the Insomnia Severity Index (ISI) (23) was used to assess the severity of insomnia of all subjects. ISI is a self-report scale composed of 7 items. Each item is evaluated on a five-point Likert scale (from 0 = not at all to 4 = extremely), and the usual recall interval is the "last 2 weeks." The total score ranges from 0 to 28, and the higher the score, the greater the severity of insomnia. According to a previous study (24) a total score of 0–7 indicated no insomnia, 8–14 indicated sub-threshold insomnia, 15–21 indicated moderate insomnia, and 22–28 indicated severe insomnia. In this survey, a total score of ISI $\geq$ 8 indicated insomnia (9, 25).

Psychological resilience was measured by the simplified Chinese version of the 10- item Connor-Davidson Resilience Scale (CD-RISC-10). CD-RISC-10 is an important tool for assessing an individual's ability to cope with stress and rebound from difficult events or experiences (26), and has been widely used all over the world and in different populations (27). CD-RISC-10 is a five-point Likert (from 0 = never, 1 = rarely, 2= sometimes, 3 = often, and 4 = always) and a self-rating scale. The usual recall interval is "the past month." The total score ranges from 0 to 40, and a high total score indicates greater resilience (28). This scale includes two factors. One is strength, which mainly indicates the ability to deal with difficult problems, or the ability to achieve goals, and physical and mental resilience, which is composed of five items. The other is hardiness, which mainly refers to the ability to adapt to change in the face of setbacks or adversity, consisting of five items (29). The total score of these two factors ranges from 0 to 20 points.

Statistical Analyses

The demographic and mental health variables of insomnia and non-insomnia groups were compared using independent samples *t*-tests for continuous variables and chi-square for categorical variables. The prevalence of insomnia was described by percentage and analyzed by chi-square test. Binary logistic regression analysis was performed to assess which factors were significantly associated with insomnia. The correlation between insomnia and demographic and mental health variables was conducted by Pearson or Spearman correlation coefficients. Bonferroni correction was performed for each test to adjust for multiple tests. Then stepwise multiple regression analysis was applied to explore the significant predictive variables related to insomnia. IBM SPSS 22.0 was performed for all statistical

analysis. All *p*-values were two tailed and the significance level was <0.05.

RESULTS

Demographic and Mental Health Characteristics

The demographic and mental health characteristics of all subjects are shown in **Table 1**. There were 114 males (18.8%) and 492 females (81.2%). The average age of all subjects was 35.77 years old, ranging from 20 to 65 years old. The average body mass index (BMI) was 22.76 kg/m^2, ranging from 12.36 to 47.27 kg/m^2. 152 subjects (25.08%) were single and 454 (74.91%) were married. There were 80 (13.2%) subjects with a college degree or below, 380 (62.7%) with a bachelor degree, 92 (15.2%) with a master degree, and 54 (8.9%) with a doctoral degree. Among the jobs, there were 205 doctors (33.8%), 334 nurses (55.1%), and 67 medical technicians (11.1%). Eighty-four subjects (46.9%) worked <8 h a day, 268 subjects (44.2%) worked for 10 h or less, and 54 subjected (8.9%) worked for more than 10 h a day. In addition, the annual household income of 106 subjects (17.5%) was 30,000–80,000 yuan, 402 (66.3%) were 80,000–300,000 yuan, and 98 (16.2%) were 300,000–1,000,000 yuan. In 2003, 262 subjects (43.2%) experienced the SARS epidemic. 137 subjects (22.6%) had a history of somatic disease. The average CD-RISC-10 score of all subjects was 27.05. The average strength factor score was 13.66, and the average hardiness factor score was 13.39.

TABLE 1 | Demographic and mental health characteristics of medical staff with or without insomnia.

	Total	Non-insomnia group	Insomnia group	t/χ^2	*p*-Value
	606	**(*n* = 412, 68.0%)**	**(*n* = 194, 32.0%)**		
Sex				0.11	0.739
Male, *n* (%)	114 (18.8)	79/114 (69.30)	35/114 (30.70)		
Female, *n* (%)	492 (81.2)	333/492 (67.68)	159/492 (32.32)		
Age, years, M (SD)	35.77 (8.13)	38.45 (8.08)	34.33 (8.07)	3.01	0.003
BMI, M (SD)	22.76 (3.81)	22.56 (3.44)	23.18 (4.47)	−1.85	0.065
Marital status				5.19	0.023
Single, *n* (%)	152 (25.08)	92/152 (60.5)	60/152 (39.5)		
Married, *n* (%)	454 (74.91)	320/454 (70.5)	134/454 (29.5)		
Education				9.59	0.022
College degree and below, *n* (%)	80 (13.2)	45/80 (56.2)	35/80 (43.8)		
Bachelor degree, *n* (%)	380 (62.7)	256/380 (67.4)	124/380 (32.6)		
Master degree, *n* (%)	92 (15.2)	69/92 (75.0)	23/92 (25.0)		
Doctoral degree, *n* (%)	54 (8.9)	42/54 (77.8)	12/54 (22.2)		
Job position				12.56	0.002
Doctors	205 (33.8)	153 (74.6)	52 (25.4)		
Nurses	334 (55.1)	207 (62.0)	127 (38.0)		
Medical technicians	67 (11.1)	52 (77.6)	15 (22.4)		
Working hours/day (h)				12.09	0.002
≦8	284 (46.9)	208 (73.2)	76 (26.8)		
8–10	268 (44.2)	177 (66.0)	91 (34.0)		
>10	54 (8.9)	27 (50.0)	27 (50.0)		
History of SARS epidemic in 2003				1.92	0.166
No	344 (56.8)	226 (65.7)	118 (34.3)		
Yes	262 (43.2)	186 (71.0)	76 (29.0)		
Annual household incomes (Yuan)				7.03	0.03
30,000–80,000	106 (17.5)	61 (57.5)	45 (42.5)		
80,000–300,000	402 (66.3)	279 (69.4)	123 (30.6)		
300,000–≥1,000,000	98 (16.2)	72 (73.5)	26 (26.5)		
History somatic disease				**8.67**	**0.003**
No	469 (77.4)	333 (71.0)	136 (29.0)		
yes	137 (22.6)	79 (57.7)	58 (42.3)		
CD-RISC-10					
Total score, M (SD)	27.05 (8.71)	28.67 (8.65)	23.60 (7.80)	6.94	<0.001
Strength factor, M (SD)	13.66 (4.51)	14.45 (4.47)	11.97 (4.13)	6.51	<0.001
Hardiness factor, M (SD)	13.39 (4.35)	14.22 (4.33)	11.63 (3.84)	7.12	<0.001

Prevalence of Insomnia and Comparison of Demographic and Mental Health Variables Between Insomnia and Non-insomnia Participants

As shown in **Table 1**, the prevalence of insomnia among medical staff was 32.0% (194/606). The average age of the insomnia group was significantly younger than that of the non-insomnia group ($p = 0.003$). The prevalence of insomnia in single subjects was significantly higher than that in married subjects ($p = 0.023$). The prevalence of insomnia in college degree and below was significantly higher 43.8% (35/80) than that bachelor degree 32.6% (124/380), master degree 25.0% (23/92) and doctoral degree 22.2% (12/54) ($p = 0.022$, Bonferroni corrected $p < 0.05$). The prevalence of insomnia among nurses was significantly higher than that in doctors and medical technicians ($p = 0.002$, Bonferroni corrected $p < 0.01$). The incidence of insomnia in the group working more than 10 h a day was significantly higher than that in the 8–10 h group and the 8 h group ($p = 0.002$, Bonferroni corrected $p < 0.01$). The rate of insomnia in medical staff with somatic disease was significantly higher than that in non-somatic disease group ($p = 0.003$).

The total score, strength factor and hardiness factor scores of CD-RISC-10 in insomnia group were significantly lower than those in non-insomnia group (all $p < 0.001$). There was no significant difference in BMI, history of SARS epidemic in 2003 (all $p > 0.05$). The lowest annual household incomes group had significantly highest rate of insomnia ($p = 0.03$) (**Table 1**). In addition, after controlling for gender as a covariate, these differences remained significant (all $p < 0.05$).

Correlation of Insomnia and Demographic and Mental Health Measures

The average ISI total score in all medical staff was 6.27 ± 6.13. Pearson correlation analysis showed that ISI was correlated with age ($r = -0.134, p < 0.001$), marital status ($r = -0.086, p < 0.05$), education level ($r = -0.143$, $p < 0.001$), daily working hours ($r = 0.1$, $p < 0.01$), physical illness ($r = 0.095$, $p < 0.05$), strength factor ($r = -0.304, p < 0.001$), and hardiness factor ($r = -0.327$, $p < 0.001$). Further, except for marital status, all these associates remained significant ($p < 0.05$) after the Bonferroni correction. **Table 2** shows the association between ISI and demographic data or mental health variables.

Factors Associated With Insomnia

Multiple stepwise regression was performed to identify demographic and mental health variables that were associated with ISI. There were five variables that statistically predicted ISI [$F_{(5,600)} = 20.05$, $p < 0.001$, $r^2 = 0.136$], including hardiness factor, daily working hours, education level, physical illness, and age. The coefficients of these variables are shown in **Table 3**.

DISCUSSION

To our best knowledge, this is the first study to investigate the percentage of insomnia and its related risk factors among medical staff under the long-term influence of COVID-19 pandemic in China, as well as the relationship between insomnia and psychological resilience. The main findings of this survey included: (1) the percentage of insomnia in medical staff was 32.0%; (2) medical staff working with COVID were more prone to insomnia than the general population; (3) the risk factors of insomnia in medical staff were younger age, lower education level, longer working hours per day, and physical illness; (4) hardiness factor of psychological resilience was the protective factor for insomnia of medical staff.

Our cross-sectional study indicated that during the COVID-19 epidemic in China, the percentage of medical staff who suffered from insomnia was 32.0%, which was lower than the previous studies of 34.0% (30), 36.1% (9), 38.4% (31), but was relatively higher than the 30.5% prevalence of non-medical personnel under the COVID-19 epidemic (31). The difference in the incidence of insomnia was most likely to be related to the following reasons. First, contrary to previous studies, the duration of our investigation was longer, from February 14 to March 29, 2020. At the beginning of the COVID-19 outbreak, medical staff lacked awareness of the disease and lacked protective equipment, which increased their anxiety, fear, and insomnia. With the spread of the COVID-19, medical staff has had a better understanding of the disease, treatment for the disease has been improved, and anxiety, fear and insomnia have been alleviated. Second, more medical staff have been sent to Wuhan, reducing the pressure on medical staff. Third, the government and various units have taken a series of timely and effective psychosocial interventions and support measures (6). Taken together, these studies have shown that with the progression of the COVID-19 epidemic, the prevalence of insomnia gradually decreases, but is still higher in medical staff than that of the Chinese public during the COVID-19 epidemic.

Furthermore, our study found that the ISI total score was negatively correlated with age in Chinese medical staff, which is consistent with previous studies showing that medical staff in the insomnia group were between 18 and 25 years old (9). As pointed out by Huang and Zhao (8), during COVID-19 outbreak, younger participants are more likely to suffer from anxiety and depressive than older people. The possible reason is that young medical have relatively lack of clinical experience in the face of inadequate working environment, including long waiting lists of patients, heavy workload, insufficient resources, and daily working overload, which can easily lead to anxiety, depression, insomnia and other problems. But gender was not related to the insomnia during COVID-19 outbreak, which was consistent with previous studies (8, 9).

In addition, we found that marital status was associated with insomnia, which is in line with a previous study (9) reporting that the insomnia rate of single medical staff was higher than that of married subjects (38.1 vs. 34.43%). However, other studies showed that married participants have a higher rate of insomnia than single participants (12, 13, 32). The possible reason for these inconsistent results is that the participants come from different places. The subjects recruited in this study and Zhang et al. (9) study were hospital staff from all over the country, including front-line medical staff. But the subjects of Li et al. (32) all came from Ningbo city. In another study, the subjects were from the

TABLE 2 | Association between ISI and demographic data and mental health variables.

Variables	ISI	Sex	Age	Marital	Education	Job position	Working duration	Annual incomes	Somatic disease	Resilience	Strength	Hardiness
ISI	1											
Sex	0.052	1										
Age	−0.134***	−0.172***	1									
Marital	−0.086*	−0.074	0.480***	1								
Education degree	−0.143***	−0.193**	0.275***	0.158***	1							
Job position	0.069	0.322**	−0.220***	−0.119**	−0.381***	1						
Working duration	0.100**	−0.081*	0.115**	0.031	0.131**	−0.185***	1					
Annual incomes	−0.070	−0.011	0.295***	0.249***	0.376***	−0.117***	0.115**	1				
Somatic disease	0.095*	−0.002	0.217***	0.103**	0.035	−0.049	0.092*	0.094*	1			
Resilience	−0.321***	−0.064	0.218***	0.045	0.176***	−0.053	0.011	0.176***	0.022	1		
Strength	−0.304***	−0.050	0.210***	0.037	0.167***	−0.049	0.006	0.178***	0.020	0.983***	1	
Hardiness	−0.327***	−0.076	0.217***	0.051	0.179***	−0.055	0.16	0.168***	0.024	0.982***	0.932***	1

**Indicates that there was a significant corelation. *P < 0.05; **p < 0.01; ***p < 0.001.*

TABLE 3 | Predictors generated by multivariate logistic regression with ISI total score as dependent variables.

	Coefficients		Standardized coefficients	*T*	*p*-Value	95.0% confidence interval for B	
	B	Std. Error	Beta			Lower bound	Upper bound
(Constant)	13.479	1.290		10.450	0.000	10.946	16.012
Hardiness factor	−0.420	0.055	−0.298	−7.636	0.000	−0.529	−0.312
Working hours/day	1.097	0.365	0.115	3.004	0.003	0.380	1.815
Education	−0.679	0.315	−0.086	−2.154	0.032	−1.297	−0.060
Somatic disease	1.652	0.569	0.113	2.904	0.004	0.535	2.769
Age	−0.063	0.031	−0.083	−2.022	0.044	−0.123	−0.002

general population (13). Therefore, it is necessary to further investigate the differences in the incidence of insomnia among medical staff with different marital status. In addition, we found that medical staff with lower education level were at a higher risk of insomnia, which was consistent with several previous studies (9, 13) showing that low education level was associated with a high risk of insomnia in the general population and medical staff in China. The main reason is that it is more difficult for medical staff with low education level to grasp the information related to disease outbreaks, and their working ability is relatively poor. During the COVID-19 outbreak, they had a stronger fear of the disease, which may affect their sleep quality (9). It is worth noting that our study further indicated that medical staff who had longer working hours per day reported more serious symptoms of insomnia. This was in line with previous studies showing that medical staff who worked longer than usual reported more severe insomnia (30, 33). A potential explanation is that during the COVID-19 epidemic, both frontline and non-frontline medical staff spent a lot of time participating in the antiepidemic work, irregular shifts, excessive workload and longer working hours made them more stressed than usual (16, 32). These stresses constituted a source of unbalanced load, leading to burnout syndrome (BS) (34) and may significantly impair sleep (15, 31). As expected, insomnia was significantly associated with somatic diseases in medical staff, and with the increase in comorbid somatic diseases in the entire sample, the prevalence of insomnia became higher. Consistent with other studies, patients with chronic physical diseases have an increased risk of insomnia (31, 35). Whether medical staff or non-medical staff, organic diseases are independent risk factors for insomnia (9). One possible explanation is that physical complaints, such as headache and cardiovascular disease are more likely to enhance autonomic hyperarousal. Second, during the COVID-19 epidemic, medical staff with physical diseases may worry about infection, resulting in more serious symptoms of anxiety and insomnia. Moreover, negative thoughts about threatening symptoms may lead to persistent insomnia (36).

Another important finding of this study was that all the dimensions and total score of psychological resilience were significantly negatively correlated with the ISI total score. Our study also showed that non-insomnia medical staff had better psychological resilience and stronger strength and hardiness. This was in accordance with other studies showing that participants with low resilience directly lead to poor sleep quality

(17, 20), such as lower sleep efficiency, more awakening times, and lighter sleep than those with higher resilience (22).

However, in this study, multiple stepwise regression found that only the hardiness subscale of the psychological resilience was the significant protective factor for insomnia in medical workers. Hardiness reflects a person's ability to rebound from adversity, emotional control, decision-making, and problem-solving. Previous study reported that hardiness was a protective factor for negative health outcomes among the five factors of resilience (hardiness, optimism, persistence, support, and spirituality) (37). These findings indicate that psychological resilience is a protective factor for insomnia in medical staff.

Our research had several limitations. First, this survey adopted a cross-sectional design, based on the WeChat program and self-administered questionnaire. Second, the duration of the survey is comparatively short, which cannot effectively verify whether there is dynamic balance overload as COVID-19 progresses. Third, only ISI was used to assess the severity of insomnia. It is possible that many other sleep problems had not been assessed. Fourth, we did not compare the difference in insomnia between frontline and non-frontline medical workers. It is not obvious whether the data on insomnia in medical staff working with COVID is different from the insomnia in medical workers dealing with routine diseases. Fifth, the pre-epidemic status was not collected, which may lead to biased results. In addition, the most important limitation is the source of recruitment. This sample could be not representative because the older medical staff could not use social networks. This is evident because of low mean age of participants (35 years).

In conclusion, this study revealed that during the COVID-19 outbreak, the prevalence of insomnia among medical staff was higher than that of the Chinese public. The related risk factors included younger age, lower education level, physical disease, and longer working hours per day. In addition, the hardiness of psychological resilience was a protective factor for insomnia of medical staff. Therefore, when carrying on the psychological intervention to the medical staff, we need to consider different social and psychological factors. The most important intervention is to improve the psychological adaptability of medical staff.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ: conceptualization, methodology, writing—reviewing, editing, and supervision. DLiu: formal analysis, writing—original draft, and funding acquisition. SL, LZ, DLi, DoH, HD, HG, DaH, YL, and ZM: investigation, resources, and data curation. WL, QM, and MX: conceptualization, writing—review, and editing. All authors contributed to the article and approved the submitted version.

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Commonalities and Differences in NREM Parasomnias and Sleep-Related Epilepsy: Is There a Continuum Between the Two Conditions?

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Introduction: Differential diagnosis between disorders of arousal (DoA) and sleep-related hypermotor epilepsy (SHE) often represents a clinical challenge. The two conditions may be indistinguishable from a semiological point of view and the scalp video-polysomnography is often uninformative. Both disorders are associated with variable hypermotor manifestations ranging from major events to fragments of a hierarchical continuum of increasing intensity, complexity, and duration. Given their semiological overlap we decided to explore the sleep texture of DoA and SHE seeking for similarities and differences.

Methods: We analyzed sleep macrostructure and CAP (cyclic alternating pattern) parameters in a cohort of 35 adult DoA patients, 40 SHE patients and 24 healthy sleepers, all recorded and scored in the same sleep laboratory. Nocturnal behavioral manifestations included minor motor events, paroxysmal arousals and major attacks in SHE, and simple, rising, or complex arousal movements in DoA.

Results: Compared to healthy controls, DoA and SHE showed similar amounts of sleep efficiency, light sleep, deep sleep, REM sleep, CAP subtypes. Both groups also showed slow wave sleep fragmentation and an increased representation of stage N3 in the second part of the night. The only discriminating elements between the two conditions regarded sleep length (more reduced in DoA) and sleep instability (more elevated in SHE). In DoA recordings, all motor episodes arose from NREM sleep: 37% during light NREM stages and 63% during stage N3 (simple arousal movements: 94%). In SHE recordings, 57% of major attacks occurred during stage N3.

Conclusions: So far, emphasis has been placed on the differentiation of sleep-related epilepsy and NREM arousal disorders. However, the impressive analogies between DoA and SHE suggest the existence of an underestimated continuum across the conditions, linked by increased levels of sleep instability, higher amounts of slow wave sleep and NREM/REM sleep imbalance. Sleep texture is extremely similar in the two conditions, although CAP metrics disclose quantitative differences. In particular, SHE patients

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show a higher arousal instability compared to DoA subjects. Given their clinical and epidemiological overlap, a common genetic background is also hypothesized. In such a perspective, we suggest that the consolidated dichotomy DoA vs. SHE should be reappraised.

Keywords: disorders of arousal, parasomnia, sleep-related hypermotor epilepsy, SHE, cyclic alternating pattern, CAP, sleep microstructure

INTRODUCTION

Disorders of arousal (DoA) encompass heterogeneous motor behaviors (parasomnias) during non-REM sleep, e.g., sleepwalking, sleep terror, and confusional arousals, arising as a result of incomplete awakening (1).

DoA can be triggered by sleep deprivation, sleep disorders, medication, or psychosocial stressors and are accompanied by variable degrees of autonomic activation. Misperception, mental confusion, partial unresponsiveness to external stimuli, and retrograde amnesia are commonly reported during DoA episodes (2). Given its association with complex hypermotor behaviors and abnormal arousal reactions during sleep, the differential diagnosis between DoA and sleep-related hypermotor epilepsy (SHE) is often a challenging issue for clinicians. Both sleep disorders can either persist from childhood or appear *de novo* and may require different treatment strategies. DoA include a spectrum of disorders encompassing different motor manifestations with increasing semiological complexity which have been classified (3) as simple arousal movements (SAM), rising arousal movements (RAM) and complex arousal movements (CAM) and may occur in the same patient and in the same night. SHE itself is part of a spectrum ranging from minor motor events (MME), paroxysmal arousals (PA) and major attacks (4–8), often coexisting in the same patient and sometimes in the same night.

The clinical and polysomnographic differentiation between SHE, parasomnias and physiologic movements during sleep has always raised semiological difficulties and according to some authors a clearcut distinction cannot be carried out without video-polysomnographic analysis (v-PSG) (9). In contrast, Vignatelli et al. (10) describe major disagreement among sleep experts and trainees in distinguishing between PA and non-epileptic arousals. Other studies underlined the discriminatory informations provided by the sleep stage at onset, while ictal EEG features appear less useful (11).

DoA are traditionally considered as manifestations of fragmentary arousals occurring mostly during slow-wave sleep (SWS) (12): the mind is asleep, but the motor system is awake. Rhythmic movements within DoA are generally rare and may be seen either as part of exploratory movements in abortive sleepwalking or as part of complex DoA. In contrast, behaviors in SHE often display rhythmic components, including body rocking and rolling, bipedal cycling, and kicking. The differential diagnosis between DoA and SHE also relies on frequency and distribution pattern of the events: DoA episodes occur sporadically and less stereotyped in the first part of the night (dominated by deep NREM sleep) and are boosted by stage changes; SHE events are more frequent and highly stereotyped, prevail during light NREM stages, and may be preceded by abrupt arousal (8).

As behavioral events peculiar to DoA and SHE may occur in the same patient during the same night, differential diagnosis may become complicated, especially when only minor/mild events are available in the v-PSG recording. While major attacks in SHE are typically stereotyped and triggered by paroxysmal discharges, minor motor events may widely vary and appear similar to physiological movements during sleep. Furthermore, the association between minor motor events and epileptiform discharges is weak: it has been suggested that the former could reflect the activation of some innate motor patterns, not necessarily linked to paroxysmal events (7). In DoA patients, the awake EEG is normal, while PSG recordings often document the abrupt appearance of high-amplitude rhythmic slow waves before the episodes, followed by the persistence of either partial or complete sleep activity in the post-arousal recordings (1).

Brain activity during sleep is physiologically controlled by two driving forces: the sleep-promoting system and the arousal-promoting system, the latter connecting the sleeper with the surrounding world and crucial to restore wakefulness (13). This interplay is mirrored by the dynamic texture of sleep, which, within certain ranges, warrants flexible and adaptive strategies. Within NREM sleep stages, phasic EEG events are lumped in periodic clusters which define a cyclic alternating pattern (CAP). Recognized as the EEG biomarker of sleep instability, CAP is composed of a phase A of greater arousal (k-complexes, delta burst, polyphasic bursts, arousals) and a phase B of lesser arousal (baseline interval between consecutive A phases). While sleep stages and cycles are the expression of sleep macrostructure, CAP oscillations organized in sequences constitute sleep microstructure, which occurs either spontaneously or evoked by external stimuli and yields to consistent autonomic reactions (14). As the A phases of CAP encompass different transient events, they are classified as subtypes A1, A2, and A3, based on reciprocal proportion of high-voltage slow waves (EEG synchrony) and low-amplitude fast rhythms (EEG desynchrony). In the physiological architecture of sleep, subtypes A1 parallel the homeostatic process, while subtypes A2 and A3 are closely linked to the ultradian cyclicity. During the descending slope of sleep cycles CAP sequences preserve sleep against perturbations, boosting SWS, whereas during the ascending slope of the sleep cycle, microstructural fluctuations lighten sleep, and prepare the onset of REM periods. Therefore, CAP sequences can provoke both "arousal promoting" and "sleep promoting" reactions,

depending on the background homeostatic pressure, and on the ongoing sleep stages (15, 16).

Previous studies showed a significant increase of CAP both in SHE (14) and in DoA patients (17) compared to healthy controls. Moreover, clinical events in both SHE and DoA are often triggered by an arousal event (phase A of CAP) indicating that SHE and DoA share common sleep features which can explain why it can become extremely difficult to distinguish the two conditions and why the same patient can present both seizures and parasomnias.

So far, particular emphasis has been placed on the differentiation of SHE and NREM arousal disorders (18). However, the two conditions share an impressive amount of common features. In particular, periodism, the attacks coinciding with the typical CAP recurrence (19), modulates both nocturnal epileptic (20) and parasomnic episodes (17, 21). In such a perspective, we suggest that the consolidated dichotomy DoA vs. SHE should be reappraised. To explore boundaries, gaps and overlaps in the two conditions, standard PSG measures, CAP parameters, and video findings of adult subjects with DoA were analyzed and compared with the data of age-balanced SHE patients and healthy controls recorded and scored in the same sleep laboratory.

MATERIALS AND METHODS

Subjects

We reviewed the database of the Sleep Disorders Center at Parma University Hospital selecting patients with diagnosis of DoA who underwent nocturnal video-PSG in the time period between 2007 and 2019. A total of 234 patients were scrutinized, 199 patients were excluded for variable reasons including: coexistence of sleep disorders others than DoA, concomitant psychiatric or neurological conditions, incomplete follow-up or unavailability of video-PSG recording. We included all consecutive adult patients ($\geq$ 18 years old) with at least 2 neurological visits and an overnight lab-setted v-PSG who received a diagnosis of DoA according to the ICSD criteria (International classification of Sleep Disorders, III Edition, American Academy of Sleep Medicine, 2014). A randomly selected group of patients with a clinical history of paroxysmal arousal, nocturnal wandering or hyperkinetic seizures, composed the SHE group (14), based on the diagnostic criteria established in 2016 (8). Eligible healthy controls were paid volunteers free of psychiatric, neurologic, and/or medical disorders, recruited through advertisement at the university hospital.

Exclusion criteria for all the subjects (patients and controls) were the following: (1) concomitant neurological, psychiatric or any other sleep disorders; (2) intake of medications known to influence sleep.

For each DoA patient we collected complete demographical and clinical data from medical recording and then anonymously abstracted them using a standardized data extraction spreadsheet. Specifically we recorded informations relative to age at onset, episodes frequency (divided in low: 1–2 per month; moderate: 1 per week; high: > 1 per week), previous personal medical history, family history for sleep disorders, with specific attention to NREM-parasomnia. Daytime sleepiness was assessed by means of the Epworth Sleepiness Scale (ESS): a score > 10 was considered clinically relevant. All enrolled patients carried out at least one lab-set full-night v-PSG recording.

The clinical, demographic and v-PSG features regarding SHE patients and healthy sleepers were collected from the Sleep Disorders Center at Parma University Hospital database. The major findings of epileptic patients and normal controls were published in a previous report (14). The study was regularly approved by the Local Ethics Committee with protocol number 9/2019/OSS*/AOUPR.

PSG Evaluation

PSG recording was based on the international 10:20 system with 19 EEG channels on the scalp (Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6, FZ, CZ, PZ) referenced on mastoid, EOG for both eyes, EMG of the mentalis and limb muscles, ECG and synchronized audio-visual recording. A standard calibration of 50 mV/ mm with a time constant of 0.1 s and a high frequency filter in the 30 Hz range were applied. For all subjects bedtime was fixed at 10.30 pm. A resting wakefulness EEG of at least 20 min of duration was evaluated by a neurologist with expertise in epilepsy and sleep disorders. The detection of an apnea–hypopnea index >5/h and/or periodic limb movement (PLM) index >15/h of sleep represented exclusion criteria. Specifically "apneas" were defined as complete cessation of airflow for > 10 s, "hypopneas" were characterized by at least 30% drop in airflow from baseline value for at least 10 s and accompanied by either 3% reduction in SatO2% with respect to pre-event baseline and/or by an EEG arousal; "respiratory effort related arousal" were defined as sequences of breaths lasting at least 10 s and associated with increased respiratory efforts leading to arousal from sleep, not fulfilling diagnostic criteria for apnea nor hypopnea, in line with American Academy of Sleep Medicine (AASM) scoring rules (22).

Sleep Macrostructure

PSG scoring was carried out according to AASM rules (22). We measured sleep efficiency (SE), total sleep time (TST), stage 1 (N1) sleep time, stage 2 (N2) sleep time, stage 3 (N3) sleep time, REM sleep time.

Sleep Microstructure

CAP was performed following standardized guidelines (23) using Embla REM-logic software. For CAP analysis the following variables were evaluated: CAP rate (CAP time/total non-REM time × 100), CAP rate in NREM stages; CAP subtypes A1, subtypes A2, and subtypes A3.

Classification of Nocturnal Motor Episodes

When DoA patients presented motor episodes during the recording night we described the clinical semiology and the sleep stage distribution. According to Loddo et al. (3), behavioral patterns of DoA patients were classified as: simple arousal movements (SAMs), rising arousal movements (RAMs) and complex arousal movements (CAMs). More specifically, SAMs referred to simple head movements comprehensive of head

flexion/extension (SAM-A), with or without limb (SAM-B), or trunk minor motor activation (SAM-C). SAMs are far the commonest nocturnal motor manifestation in adults with DoA. RAMs are characterized by more complex in-bed motor patterns (trunk flexion or sitting) sometimes associated with speaking. Finally CAMs represent the most elaborate DoA motor pattern: patients with CAMs may leave their bed, manipulate objects, scream, or walk in the room.

Nocturnal epileptic seizures were classified as minor motor events, paroxysmal arousals and major events. Specifically minor motor events were represented by brief, simple and stereotyped movements involving either head, trunk or limbs; paroxysmal arousals were associated with sudden arousal and stereotyped motor activation with variable association of autonomic reactions and/or vocalization, lasting from 5 to 10 s and finally major events were the most complex episodes, consisting in complex stereotyped hypermotor patterns (including tonic–dystonic or hyperkinetic seizures and epileptic nocturnal wandering) with frequent autonomic activation, lasting on average 20–30 s (6). Only epileptic motor events supported by v-PSG evidence were taken into consideration.

STATISTICAL ANALYSIS

Statistical analysis was performed using the open-source software Jamovi (24). All quantitative data were expressed as mean and standard deviation (SD). Qualitative data were reported as absolute frequency and percentage. A one-way ANOVA test assessed the differences among the mean values in the 3 groups (healthy controls, DoA, SHE). Normality of the data and homogeneity of variances were tested by the Shapiro-Wilk test and Levene's test, respectively. Categorical data were analyzed by the Pearson's chi-square test. Statistical significance was set at $p < 0.05$. Tukey *post-hoc* test was used to explore differences between groups after ANOVA. Effect size were also reported for ANOVA (Cohen's f and partial eta-squared) (25) and for Chi-square (Cramer's V) to measure the strength of the relationship between variables.

RESULTS

Subjects

Due to strict inclusion criteria the final sample included 35 DoA subjects (12 female and 23 male, with a mean age of 28 ± 5 years). The SHE group included 40 subjects (20 male and 20 female; mean age: 31 ± 10 years). The control population encompassed 24 subjects (12 male and 12 female; mean age: 28 ± 7 years). The three groups showed similar age distribution (**Table 1**).

DoA Group

A family history for sleep disorders was documented in 6 cases (17%), disease onset during childhood was reported by 22 patients (63%), while the other 13 subjects (37%) developed NREM sleep parasomnia after the age of 18. Five patients (14%) presented high frequency of DoA episodes (>1 per week), 15 patients (43%) reported usually one episode per week and the remaining 15 patients (43%) had a mean of one or two episodes per month. Five patients (14%) suffered from concomitant psychiatric diseases including depression, anxiety and panic attacks. Daytime sleepiness (measured by ESS, cut-off >10) was found in 9 patients (23%).

SHE Group

In most patients with SHE, nocturnal motor events were already present at childhood. One patient suffered from mild perinatal hypoxia, two presented febrile convulsion during childhood and one had minor head trauma. No patient reported a family history of epilepsy, but 10 patients described parasomnias in first-degree relatives. Diurnal seizures were never reported and no patient showed coexisting neurologic, psychiatric or medical disorders known to affect sleep architecture. All SHE patients complained of excessive daytime sleepiness (ESS: 16 ± 4). Wakefulness EEG showed focal epileptiform abnormalities only in a minority of cases (5/40, 12.5%). Semiology of nocturnal episodes included paroxysmal arousals, focal tonic-dystonic seizure, hyperkinetic seizure, or prolonged motor behavior including epileptic nocturnal wandering. Brain MRI was unremarkable in all SHE patients. According to 2017 ILAE classification (26) all included subjects were classified as affected by focal epilepsy of unknown etiology.

Sleep Macrostructure

The standard sleep measures in the three groups are detailed in **Table 1.** One-way ANOVA highlighted significant differences between groups with respect to TST, N3 and REM representation. Tukey *post-hoc* test revealed that, compared to healthy controls, TST was reduced significantly in DoA (−76 min, $p = 0.0001$) but not significantly in SHE (−28 min, $p = 0.166$). TST was also significantly lower in DoA compared to SHE (−48 min, $p = 0.002$). Overall, SE was not modified ($p = 0.065$) but both DoA (88%) and SHE (85%) presented values < 90%.

The three groups showed similar amounts of light sleep (N1 + N2). Overall stage N3 was significantly different between the three groups ($p = 0.011$), being enhanced in DOA (+6%, $p = 0.054$) and in SHE (+8%, $p = 0.010$) with respect to healthy sleepers but no difference was found between the two clinical conditions ($p = 0.792$). Compared to healthy sleepers, REM sleep was reduced ($p < 001$) in DoA (−8%, $p = 0.0001$) and in SHE (−6%, $p = 0.0001$) with similar values in both conditions ($p = 0.269$).

In the 9 DoA patients complaining of excessive daytime sleepiness compared to the remaining 26 DoA subjects with an ESS ≤ 10, higher percentages of N3 (33 ± 9 vs. 24 ± 7; p = 0.004) and lower amounts of REM sleep (13% ± 5 vs. 18% ± 5; p = 0.014) were found.

Sleep Microstructure

Tables 1, **2** showed the mean microstructural data in the three groups. Overall one-way ANOVA described significant differences between the three groups with respect to CAP rate, CAP rate in N2 and CAP rate in N3.

In details, compared to healthy controls, CAP rate values were higher ($p < 0.001$) in DoA (+ 19%) and even more elevated in SHE (+ 40%), with significant differences between the two

TABLE 1 | Sleep macro and microstructure features in the three groups.

Features	*N*	Group	Values (Mean +/– SD)	*P*-value	*post-hoc*	Effect size
Age (year)	24 35 40	HC DoA SHE	28 +/– 7 28 +/– 5 31 +/– 10	$p = 0.187$	HC vs. DoA: $p = 0.950$ HC vs. SHE: $p = 0.327$ DoA vs. SHE: $p = 0.227$	Overall effect size Cohen's $f = 0.193$ HC vs. DoA: $f = 0.000$ HC vs. SHE: $f = 0.153$ DoA vs. SHE: $f = 0.171$ $F_{(2,\ 96)} = 1.7063$ Partial eta-square = 0.034
Sex (F/M)	24 35 40	HC DoA SHE	12/12 12/23 20/20	$p = 0.323$	HC vs. DoA: $p = 0.228$ HC vs. SHE: $p = 1.000$ DoA vs. SHE: $p = 0.168$	Phi, Cramer's V = 0.151 Cohen's w = 0.151
TST (min)	24 35 40	HC DoA SHE	466 +/ 24 389.92 +/– 56.97 438 +/– 74	**$p < 0.001$**	HC vs. DoA: $p = 0.000$ HC vs. SHE: $p = 0.166$ DoA vs. SHE: $p = 0.0020$	Overall effect size Cohen's $f = 0.539$ HC vs. DoA: $f = 0.518$ HC vs. SHE: $f = 0.196$ DoA vs. SHE: $f = 0.374$ $F_{(2, 96)} = 12.728$ Partial eta-square = 0.210
SE (%)	24 35 40	HC DoA SHE	93 +/– 5 87.59 +/– 11.59 85 +/– 17	$p = 0.065$	HC vs. DoA: $p = 0.269$ HC vs. SHE: $p = 0.051$ DoA vs. SHE: $p = 0.667$	Overall effect size Cohen's $f = 0.255$ HC vs. DoA: $f = 0.168$ HC vs. SHE: $f = 0.255$ DoA vs. SHE: $f = 0.092$ $F_{(2, 96)} = 2.817$ Partial eta-square = 0.055
N1 + N2 (%)	24 35 40	HC DoA SHE	55 +/– 14 55.03 +/– 8.6 53 +/– 12	$p = 0.693$	HC vs. DoA: $p = 0.939$ HC vs. SHE: $p = 0.779$ DoA vs. SHE: $p = 0.726$	Overall effect size Cohen's $f = 0.084$ HC vs. DoA: $f = 0.001$ HC vs. SHE: $f = 0.066$ DoA vs. SHE: $f = 0.075$ $F_{(2, 96)} = 0.368$ Partial eta-square = 0.007
N3 (%)	24 35 40	HC DoA SHE	20 +/– 13 26.44 +/– 8.55 28 +/– 10	**$p = 0.011$**	HC vs. DoA: $p = 0.054$ HC vs. SHE: $p = 0.010$ DoA vs. SHE: $p = 0.792$	Overall effect size Cohen's $f = 0.299$ HC vs. DoA: f=0.229 HC vs. SHE: f=0.292 DoA vs. SHE: f=0.063 $F_{(2, 96)} = 4.705$ Partial eta-square = 0.089
REM (%)	24 35 40	HC DoA SHE	25 +/– 5 17.02 +/– 5.2 19 +/– 6	**$p < 0.001$**	HC vs. DoA: $p = 0.000$ HC vs. SHE: $p = 0.000$ DoA vs. SHE: $p = 0.269$	Overall effect size Cohen's $f = 0.570$ HC vs. DoA: $f = 0.559$ HC vs. SHE: $f = 0.431$ DoA vs. SHE: $f = 0.159$ $F_{(2, 96)} = 15.648$ Partial eta-square = 0.246
CAP rate (%)	24 35 40	HC DoA SHE	32 +/– 5 50.86 +/– 10.24 72 +/– 11	**$p < 0.001$**	HC vs. DoA: $p = 0.000$ HC vs. SHE: $p = 0.000$ DoA vs. SHE: $p = 0.000$	Overall effect size Cohen's $f = 1.733$ HC vs. DoA: $f = 0.782$ HC vs. SHE: $f = 1.703$ DoA vs. SHE: $f = 1.004$ $F_{(2, 96)} = 134.7$ Partial eta-square = 0.737

(Continued)

TABLE 1 | Continued

Features	N	Group	Values (Mean +/– SD)	P-value	post-hoc	Effect size
CAP A1 (%)	24 35 40	HC DoA SHE	63 +/– 12 59.87 +/– 14.90 56 +/– 17	$p = 0.193$	HC vs. DoA: $p = 0.722$ HC vs. SHE: $p = 0.180$ DoA vs. SHE: $p = 0.516$	Overall effect size Cohen's $f = 0.189$ HC vs. DoA: $f = 0.080$ HC vs. SHE: $f = 0.184$ DoA vs. SHE: $f = 0.115$ $F_{(2, 96)} = 1.6702$ Partial eta-square = 0.034
CAP A2 (%)	24 35 40	HC DoA SHE	21 +/– 8 17.9 +/– 10.35 22 +/– 9	$p = 0.154$	HC vs. DoA: $p = 0.421$ HC vs. SHE: $p = 0.909$ DoA vs. SHE: $p = 0.142$	Overall effect size Cohen's $f = 0.199$ HC vs. DoA: $f = 0.128$ HC vs SHE: $f = 0.043$ DoA vs SHE: $f = 0.194$ $F_{(2, 96)} = 1.9086$ Partial eta-square = 0.038
CAP A3 (%)	24 35 40	HC DoA SHE	16 +/– 6 22.25 +/. 13.25 22 +/– 10	$p = 0.052$	HC vs. DoA: $p = 0.071$ HC vs. SHE: $p = 0.076$ DoA vs. SHE: $p = 0.994$	Overall effect size Cohen's $f = 0.257$ HC vs. DoA: $f = 0.233$ HC vs. SHE: $f = 0.229$ DoA vs. SHE: $f = 0.011$ $F_{(2, 96)} = 3.0576$ Partial eta-square = 0.060

DoA, disorder of arousal; SHE, sleep-related hypermotor epilepsy; HC, healthy controls; TST, total sleep time; SE, sleep efficiency. Significant results are marked in bold.
Continuous variables: p-value from one-way Anova with Tukey HSD post-hoc test.
Categorical data: p-value from Pearson's Chi-square test with likelihood-ratio test.
Effect size: according to Jacob Cohen f values of 0.10, 0.25, and 0.40 represent small, medium, and large effect sizes, respectively; partial eta squared is a measure of the proportion of the total variance in a dependent variable that is associated with the membership to different groups. Values of eta-squared of 0.01, 0.06, and 0.14 represent small, medium, and large effect sizes, respectively.

TABLE 2 | CAP rate during stage N2 and N3 of NREM sleep in the three groups.

Features	Group	Values (Mean +/– SD)	P-value	post-hoc	Effect size
CAP rate SWS (%)	HC DoA SHE	30 +/– 8 65,9 +/– 17,3 76 +/–24	**$p < 0.001$**	HC vs. DoA: $p = 0.000$ HC vs. SHE: $p = 0.000$ DoA vs. SHE: $p = 0.0792$	Overall effect size Cohen's $f = 10,607$ HC vs. DoA: $f = 0.7624$ HC vs. SHE: $f = 1.0440$ DoA vs. SHE: $f = 0.2427$ $F_{(2, 90)} = 45.618$ eta squared = 0.503
CAP rate N2 (%)	HC DoA SHE	34 +/– 6 50,1 +/– 14,7 55 +/– 14	**$p < 0.001$**	HC vs. DoA: $p = 0.000$ HC vs. SHE: $p = 0.000$ DoA vs. SHE: $p = 0.2588$	Overall effect size Cohen's $f = 0.6993$ HC vs. DoA: $f = 0.4951$ HC vs. SHE: $f = 0.6902$ DoA vs. SHE: $f = 0.1705$ $F_{(2, 90)} = 21.045$ eta squared = 0.319

DoA, disorder of arousal; SHE, sleep-related hypermotor epilepsy; HC, healthy controls; SWS, slow wave sleep. Significant results are marked in bold P-values from one-way Anova with Tukey HSD post-hoc test. Effect size: according to Jacob Cohen f values of 0.10, 0.25, and 0.40 represent small, medium, and large effect sizes, respectively; partial eta squared is a measure of the proportion of the total variance in a dependent variable that is associated with the membership to different groups. Values of eta-squared of 0.01, 0.06, and 0.14 represent small, medium, and large effect sizes, respectively.

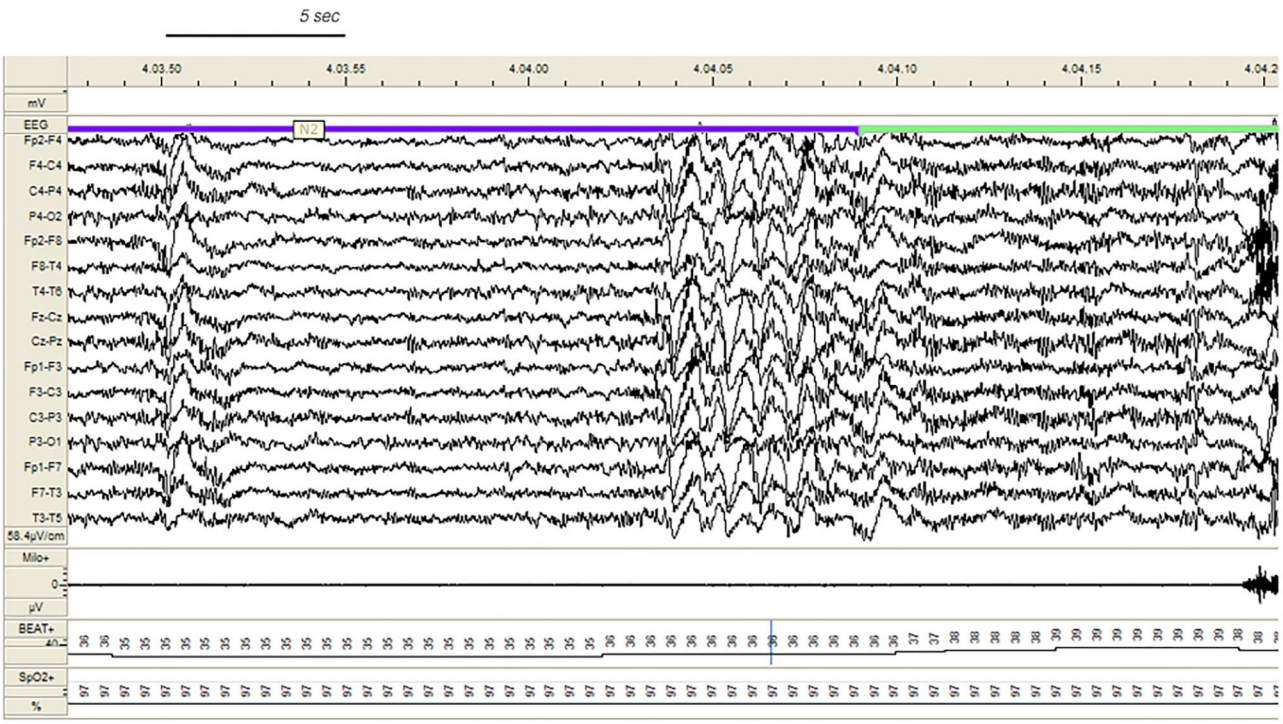

FIGURE 1 | Confusional arousal beginning during stage N2 in a DoA patient. A high amplitude EEG burst of spiky slow waves precedes the episode. Notice the coexistence of autonomic arousal (heart rate acceleration) and the absence of respiratory events; EEG sensitivity 58.4 mV/cm; Milo+, chin electromyography; BEAT, heart frequency; SpO2+, oxygen saturation.

conditions (p =0.0001). In the three groups, CAP subtypes maintained the physiological ranking A1 > A3 > A2, with a similar increased representation of phases A3 ($p = 0.052$) in DoA (+6%, p = 0.071) and SHE (+6%, $p = 0.076$), presenting trends toward significancy.

CAP rate values in stages N2 and N3 were significantly higher in both DoA and SHE compared to healthy sleepers ($p < 0.001$) (details in **Table 2**).

EEG Features

Epileptiform discharges during wakefulness occurred only in 5 SHE patients. During sleep, EEG abnormalities were identified in 28 of the 35 DoA patients (80%) and in all the SHE patients, the vast majority being represented by focal spikes. Comparing DoA patients with EEG abnormalities vs. DoA patients showing normal EEG no significant differences were detected with respect to sleep macrostructural and microstructural features: TST (p = 0,140), SE ($p = 0,367$), N1 + N2% ($p = 0,297$), N3% ($p = 0,728$), REM% ($p = 0,080$), CAP rate ($p = 0,911$), CAP subtype A1 (p = 0,677), A2 ($p = 1,000$), A3 ($p = 0,676$).

Classification of Nocturnal Motor Episodes

DoA Group

During v-PSG registration at least one DoA episode occurred in 27 patients (77%). All episodes were recorded during NREM sleep and in most cases arised from a phase A of CAP (**Figure 1**): 37 % occurred during light NREM sleep (stages N1 and N2) and 63% during N3. DoA episodes included episodes of confusional arousals, sleep terrors, sleep-walking, vocalizations (moaning or mumbling), laughing, simple movements (face or nose touching), eye opening, oro-masticatory movements. A total of 48 episodes were recorded: they were classified as simple arousal movements (SAM) (45 episodes), rising arousal movements (RAM) (2 episodes) or complex arousal movements (CAM) (1 episode). The SAM group included 9 SAM-A (20%), 23 SAM-B (51%) and 13 SAM-C (29%) patterns.

SHE Group

In the SHE group, 33 patients (83%) reported multiple nocturnal episodes every night, whereas self-reported or witnessed seizures recurred weekly in 7 patients. Approximately 60% of the total amount of NREM sleep seizures arose from N2, but most major events (57%) showed a preferential occurrence during SWS (**Figure 2**). Ninety percent of total NREM seizures occurred during a CAP sequence, and CAP-related seizures always occurred in association with a phase A.

DISCUSSION

Both DoA and SHE presented impressive overlaps of sleep macro- and microstructural parameters. Compared to healthy controls, the two sleep disorders showed similar amounts of sleep efficiency, light sleep (N1+N2), deep sleep (N3), REM sleep, CAP subtypes (A1, A2, A3). Both groups also showed SWS fragmentation and an increased representation of stage N3 in

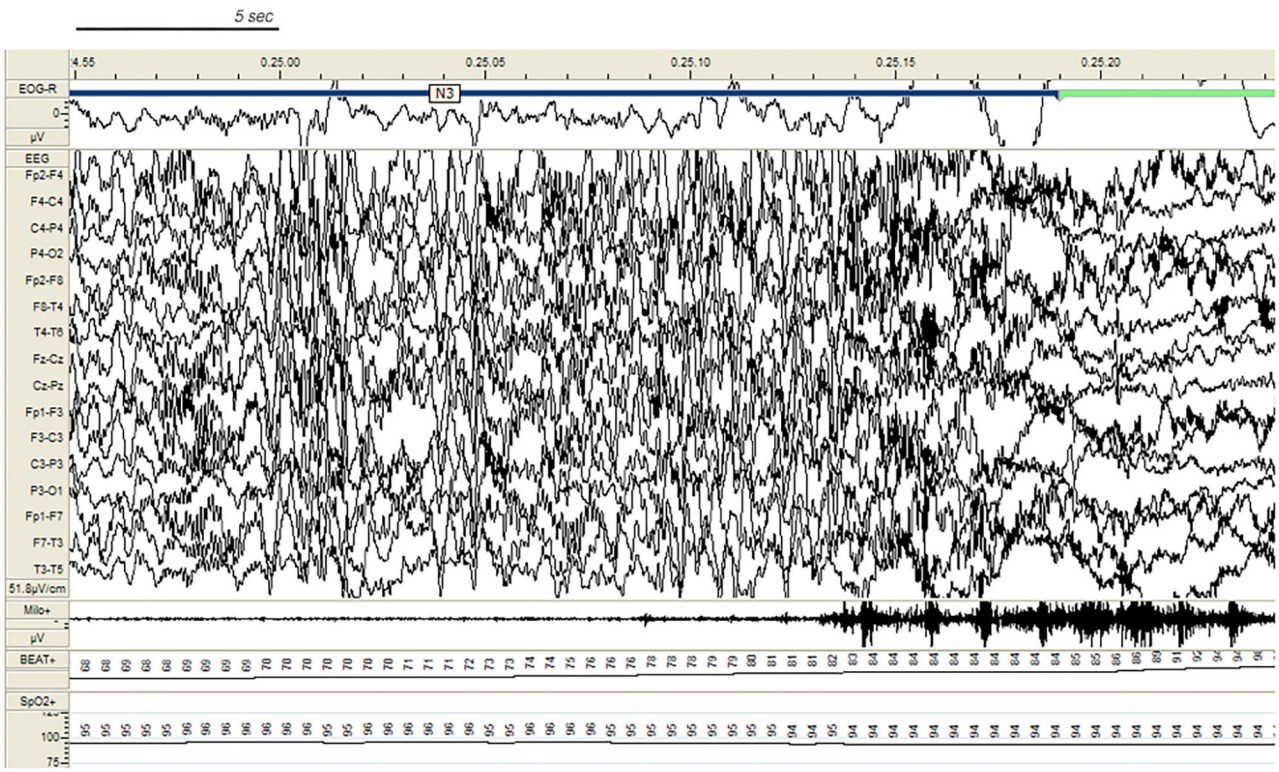

FIGURE 2 | Paroxysmal arousal in a patient with SHE beginning during stage N3. Bursts of generalized high amplitude epileptiform discharges can be appreciated. Autonomic activation coexists. EEG sensitivity 51.8 mV/cm; Milo+: chin electromyography; BEAT, heart frequency; SpO2+, oxygen saturation.

the second part of the night. The only discriminating elements between the two conditions regarded sleep length (TST more reduced in DoA) and sleep instability (CAP rate more elevated in SHE).

Sleep Texture

The PSG alterations of DoA and SHE seem to be peculiar to the conditions. Indeed other sleep disorders including insomnia, periodic limb movements, sleep disordered breathing may present reduced sleep efficiency and increased sleep instability, but a significant increase of stage N3 is a really uncommon finding. In our DoA sample, the excess of SWS probably accounted for the lack of sleepiness in most patients (77%). On the contrary, in the SHE group, the protective action of N3 on daytime vigilance was counteracted by an excessive amount of CAP rate, a magnitude already described in severe obstructive sleep apnea (27–29), which is often accompanied by daytime sleepiness. The supplement of unstable sleep in the SHE group is fueled by a number of disturbing factors including ictal and interictal EEG paroxysms acting as noise equivalents on the neural circuitry (**Figure 3**). In a study on SHE patients (30) treated with antiepileptic agents, CAP rate dropped from 71% (no medication) to 59% (medication), remaining widely above the expected physiological value of 33% (healthy controls). Effective treatment reduced the total amount of sleep seizures of approximately 25%, but the persistence of EEG discharges fanned arousal oscillations during NREM sleep, producing an increase of reactive A phases and therefore boosting high CAP rate values. It is interesting to notice that medication in SHE patients was associated with an additional growth of stage N3 (+3%), which was impressively high (28%) even without medication.

Trait vs. State Features

DoA and SHE share a number of specific EEG trait-markers and state-markers embedded within their sleep texture. Whether the elevated percentages of N3 are an intrinsic feature (trait) of both SHE and DoA or the compensatory by-product of a non-consolidated SWS due to motor events and/or EEG paroxysms occurring in NREM sleep (state) remains an open question. Probably, both assumptions stem from a common root. In DoA patients, impairment of sleep intensity and depth (31, 32) determines vulnerable and discontinuous slow waves during stage N3 (33). DoA sleep recordings are also characterized by an excessive fragmentation of SWS independent of concomitant parasomniac behaviors (34). Moreover, patients with DoA suffer from more frequent and longer arousals and awakenings from N3 than controls (35). Factors interfering with the build-up and maintenance of SWS, such as an excess and/or an abnormal distribution of CAP could also play a role in the pathophysiology of the disease. Accordingly, both SHE and DoA recordings were characterized by high amounts of SWS in the second half of the night: probably the result of an adaptive intra-night homeostatic

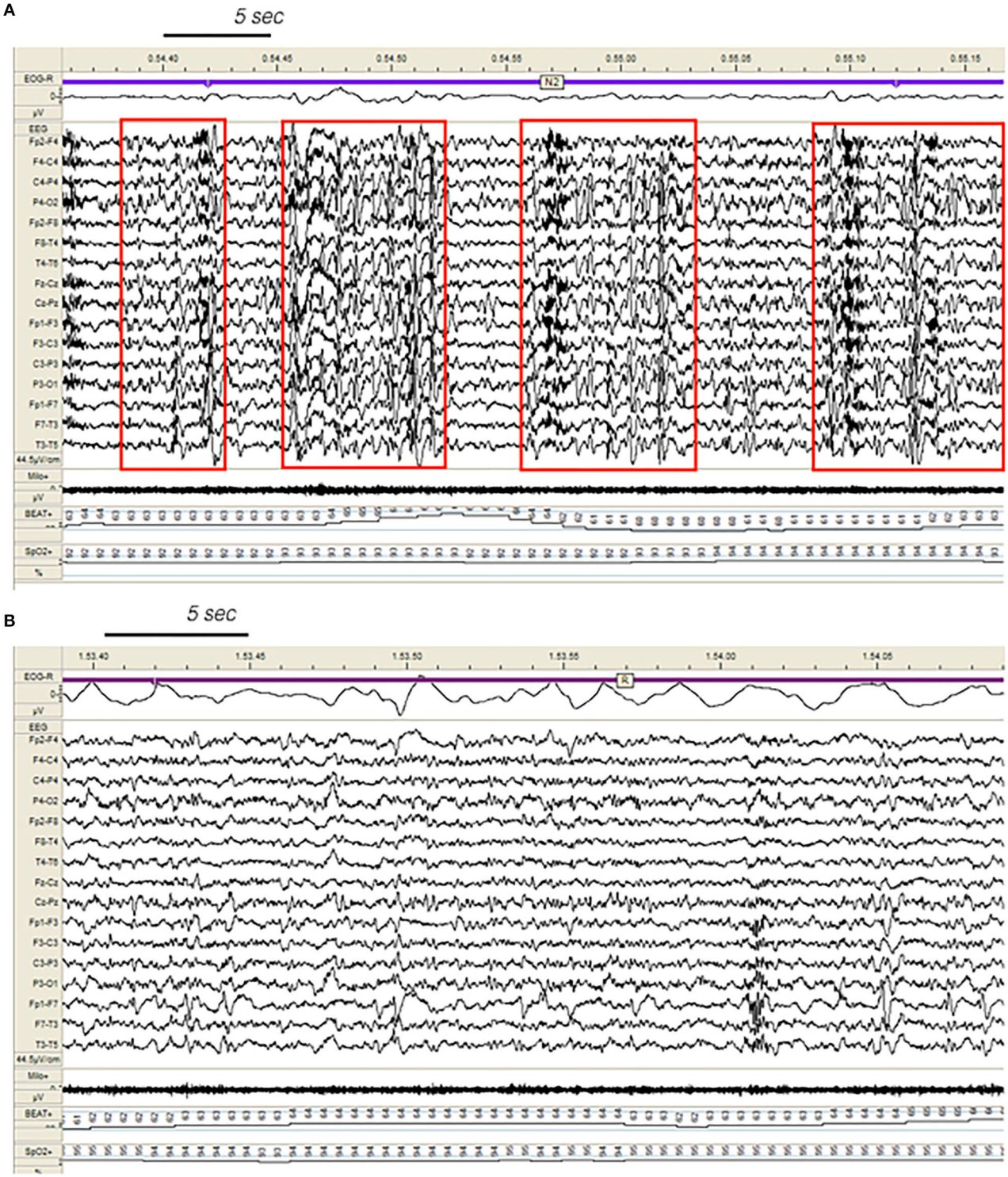

FIGURE 3 | Dynamics of epileptiform discharges during NREM and REM sleep in a patient with SHE. **(A)** Bursts of generalized epileptiform discharges enhancing cyclic alternating pattern (CAP) fluctuations during stage N2 in a patient with SHE. Red boxes highlight CAP cycles. Transient heart rate fluctuations consistent with sleep instability. **(B)** REM sleep constrains epileptic phenomena and may provide information on the localization of seizure onset zone (left focal fronto-temporal spikes and sharp-waves). EEG sensitivity 44.5 mV/cm; Milo+, chin electromyography; BEAT, heart frequency; SpO2+, oxygen saturation.

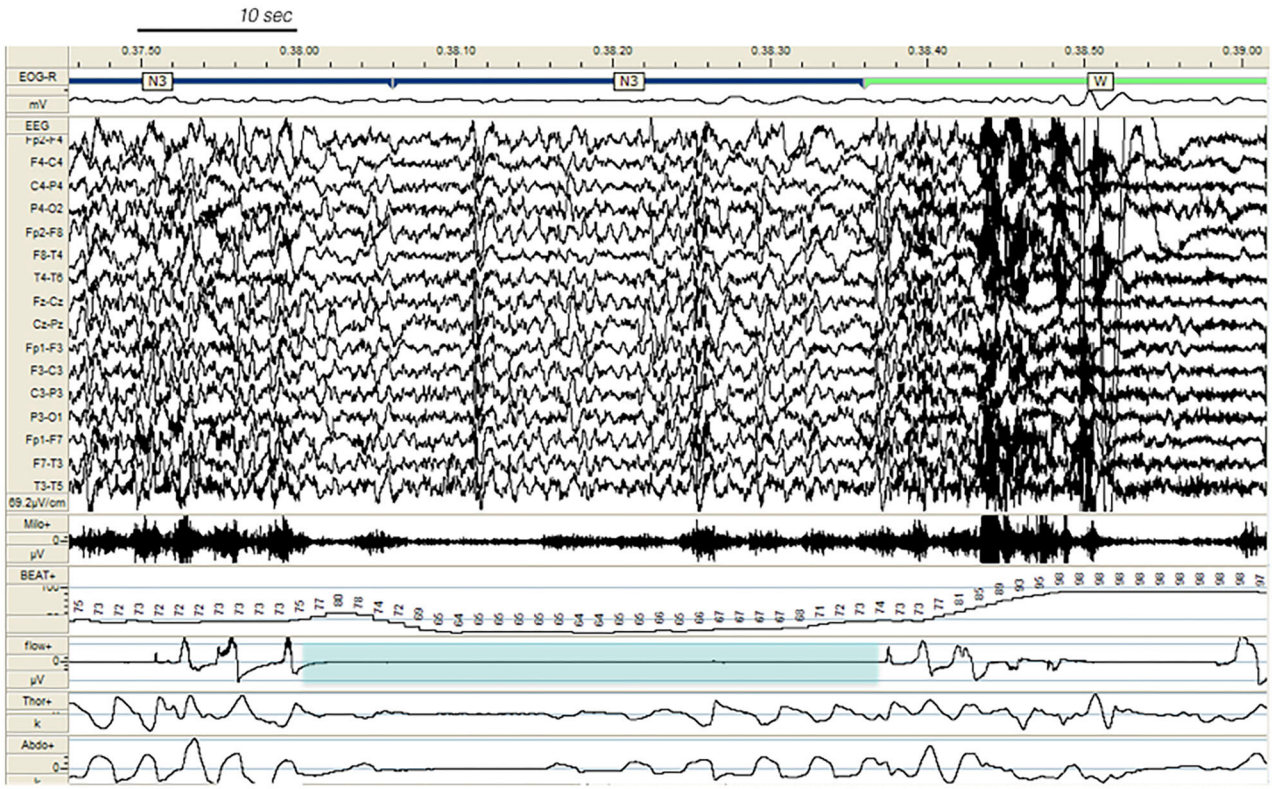

FIGURE 4 | Paroxysmal arousal in a patient with SHE and untreated obstructive sleep apnea (not included in the study), beginning during stage N3 and triggered by a respiratory event (blue shadow). Bursts of generalized epileptiform discharges, slightly prevailing over the left hemisphere, which can be appreciated throughout the recording, are increased in amplitude during arousals. EEG sensitivity 69.2 mV/cm; Milo +, chin electromyography; BEAT, heart frequency; flow+, airflow thermistor; Thor+, plethysn1ography thoracic band; Abdo+, plethysmography abdominal band.

recovery of stage N3 due to disturbed and inadequate SWS consolidation occurring in the initial sleep cycles.

Triggers

In our study, 80% of DoA subjects and all SHE patients presented EEG abnormalities during sleep, a perturbing factor which can trigger a phase A of CAP and subsequent arousal instability. In addition, a number of sleep disorders can also promote the unstable NREM sleep background on which DoA and SHE events occur. The triggering role of sleep deprivation (2, 36), medications; (37, 38), and sleep disordered breathing (38), (see **Figure 4**), including upper airway resistance syndrome (21) should be systematically searched for and treated in the presence of parasomnias or sleep-related epileptic episodes. Some authors (12, 39) have considered hypersynchronous slow delta activity (HSDA), i.e., bursts of high amplitude slow delta with fronto-central gradient occurring during NREM sleep, as the typical triggering EEG pattern of DoA (**Figure 1**). However, HSDA presents a clear overlap with CAP subtype A1 (21) and the unstable background may lead to stage N3 vulnerability which promotes the occurrence of motor episodes. According to our results both DoA and SHE patients presented significantly higher levels of SWS instability with respect to healthy sleepers (CAP in N3 being, respectively, +36 and + 46%). Similar results were described in a cohort of adult DoA patients and designated as "SWS fragmentation index" (34). In this dynamic landscape, subtypes A3 (21), which are the longest A phases of CAP (40) and are increased in sleepwalkers (21), probably play a weakening effect on N3 consolidation and are involved in the typical sleep-state dissociation when SWS and arousals coexist.

NREM/REM Imbalance

Our SHE and DoA recordings were characterized by a significant reduction of REM sleep suggesting an imbalanced control of REM-on and REM-off forces. REM and NREM sleep are mutually linked and regulated by a reciprocal interaction (41). REM sleep also attenuated the spreading of EEG paroxysms, acting as a protective stage towards propagation of epileptiform discharges (42) (**Figure 3**).

Neurophysiological and neuroimaging studies in subjects with DoA have provided evidence of abnormal brain functioning not only during SWS but also during REM sleep (43). Quantitative EEG analysis carried out in sleepwalkers during non-sleepwalking nights shows that the absolute power of delta waves is significantly lower in sleepwalkers compared

to controls during the first NREM-REM cycle ($p = 0.03$) and a very important trend ($p = 0.059$) is noted for the second sleep cycle (21). REM sleep is frequently curtailed also in adults (44) and children (45) suffering from sleep-related epilepsy. When antiepileptic medication attenuates the occurrence of major episodes in SHE patients, sleep cycles recover a physiological architecture and a normal REM-latency due to a more solid sleep structure especially in the first part of the night (30). In contrast, the A3 phases, which are also physiologically involved in the ultradian process of sleep (46) and show increased amounts in both untreated SHE (14) and DoA (21, 34), are unaffected by antiepileptic therapy (30).

Clinical Manifestations: The Role of Sleep Staging and Arousal Instability

In line with previous reports, the commonest motor manifestation in our DoA group was represented by SAM (94%). A v-PSG assessment of 334 DoA episodes documented that 84% were SAM, 10% were RAM and 5% were CAM (47). In SHE patients, the majority of NREM seizures arose from stage N2, but most major attacks showed a preferential occurrence during SWS (57%). The different distribution of motor episodes across the night and within the NREM stages is a widely accepted issue (6, 35, 48). According to a recent study, the occurrence of at least one minor event during stage N3 is highly suggestive for DoA, while the occurrence of at least one major event outside stage N3 is highly suggestive for SHE (47). However, in the same study, the number of major events in stage N3 per subject coincided in both DoA and SHE patients (47), suggesting that sleep staging is not a major element for the differential diagnosis (8).

Probably, a different modulation of NREM stages on major and minor motor events in DoA and SHE patients is a more plausible statement. A close relation between MME and arousal fluctuations is also a consolidated issue (20). Therefore, besides classifying pathologies (DoA and SHE) according to the stage-distribution of nocturnal episodes, perhaps a greater attention on the unstable balance between arousal-promoting and sleep-promoting forces may provide additional informations regardless of the ongoing sleep stage.

Central Pattern Generators (CPG)

As the great majority of nocturnal episodes were simple arousal movements (94% in the DoA group) or minor motor events (75% in the SHE group), the recorded behaviors probably expressed the fragments of a hierarchical continuum characterized by increasing intensity, complexity, and duration of the nocturnal episodes. The motor patterns which are already written in the brain codes need a window of arousal to become visibly apparent (40). Encoded CPG seem to be involved in the genesis of involuntary movements during sleep (49). The CPG system is composed of spinal and brainstem networks regulated by a supraspinal circuitry and produces coordinated and stereotyped locomotor movements such as walking or swimming, important for survival (50). The repetitive arousals of CAP activate these cortico-subcortical-spinal pathways, facilitating or releasing sleep-related behaviors such as NREM parasomnia or seizures. Regardless of the sleep disturbance, the arousal-induced activation of the CPG system generates stereotyped motor manifestations that often cause difficulties in the differential diagnosis between NREM parasomnias and SHE (**Figure 5**). It must be recalled that even highly stereotyped minor motor events can occur in the absence of an epileptiform discharge (7). In other words, CAP can be a common denominator of an arousal-related motor dishinibition whether or not epileptic in origin (51). The behavioral outcome relies on a number of factors including the local cerebral regions and activated networks.

NREM vs. REM Parasomnias

These findings corroborate the impressive overlap between DoA and SHE in terms of semiology, EEG features, sleep patterns, cerebral regions and common triggers. Even if we are dealing with two distinct conditions, the blurred boundaries between them support the possibility of a continuum between DoA and SHE. The imbalance between arousal and sleep forces may entail variable motor manifestations determined by multiple factors, i.e., genetic predisposition, involvement and thresholds of specific brain areas and neural circuits, CPG, paroxysmal discharges, and activation of epileptic networks. However, the numerous commonalities suggest that DoA and SHE share basic NREM sleep-related pathogenetic mechanisms. Accordingly, the high amounts of CAP rate found in both DoA and SHE patients are opposed to the reduced levels of CAP rate in REM sleep parasomnias (52).

Arousal Models Commonalities for DoA and SHE

So far three fascinating pathophysiological hypothesis focusing on arousal system functioning have been formulated to explain commonalities between SHE and DoA, respectively, named the "liberation," "dissociation," and "pathological" arousal models (53). The first focuses on functional de-inactivation of frontal lobe by subcortical nuclei (CPG) due to variable external or internal stimuli (54); the second recognizes the simultaneous mixed sleep and awake state existence as a major determinant for clinical manifestations (55, 56); the third harmonizes the previous models, assuming the existence of a gain-of-function of frontal cortical acetilcholine receptors in both SHE and DoA, explaining their semiological differences according to underlying facilitatory circumstances (53).

Limitations and Unanswered Questions

Despite these consistent clues, a number of questions need to be addressed. Is the strong convergence between DoA and SHE basically due to our clinical difficulty to distinguish single sleep disorders? Are we using adequate tools to investigate behavioral manifestations during sleep? Are we dealing with a two-faced entity, which can offer one of the two sides of

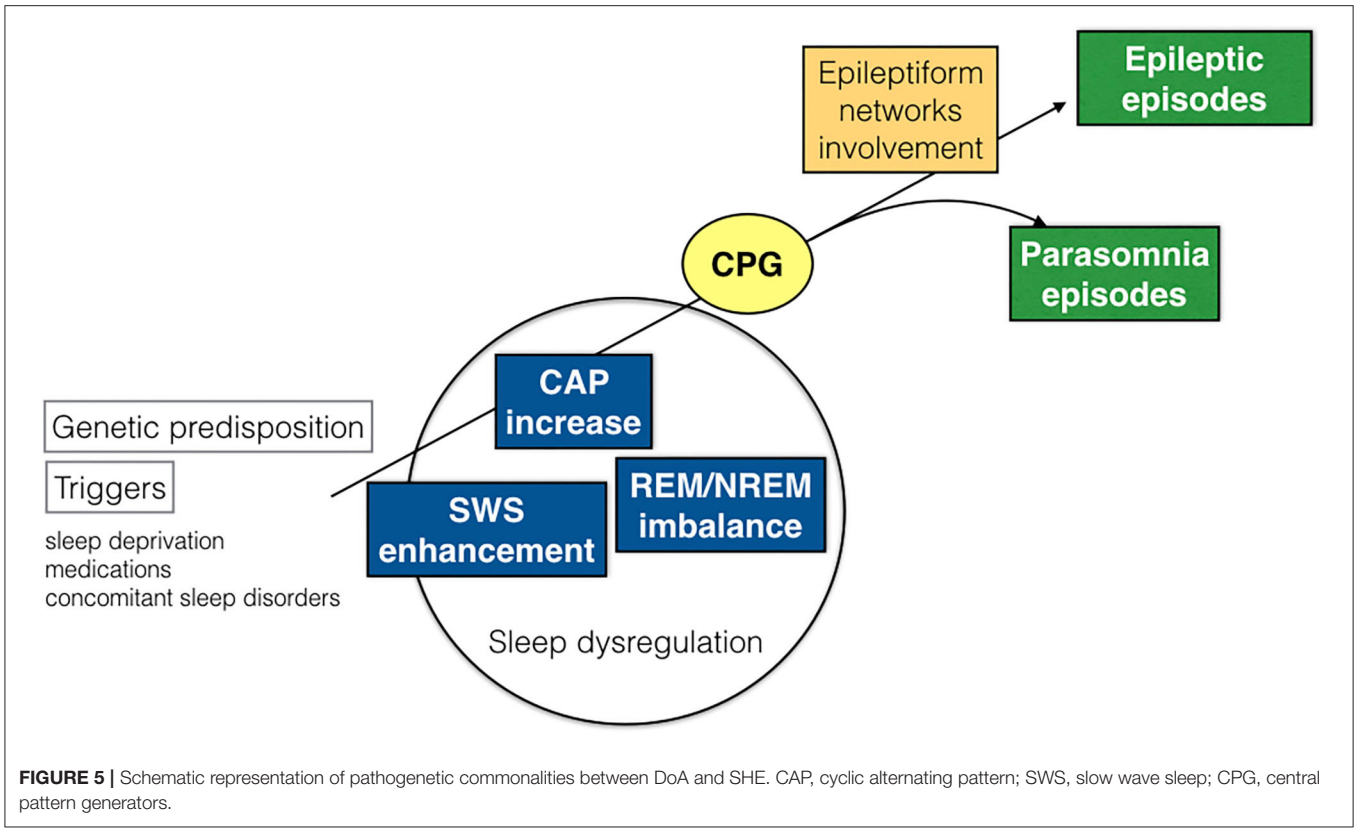

FIGURE 5 | Schematic representation of pathogenetic commonalities between DoA and SHE. CAP, cyclic alternating pattern; SWS, slow wave sleep; CPG, central pattern generators.

the coin even in the same patient and in the same night? Does it really matter to establish that a nocturnal motor event occurs in stage N2 or stage N3 if the common background is an unstable NREM sleep? Why are antiepileptic drugs often effective in the treatment of DoA episodes? Challenging issues, which represent intrinsic weaknesses of the study but encourage further investigations on the distinctive features and common nature of DoA and SHE. Another limitation of our investigation could be attributed to its retrospective nature, to the relatively small sample and to partial exploitation of published data (14). However, the entire framework–recruitment and recording–was carried out in a homogeneous setting (Sleep Disorders Center at Parma University Hospital) and scoring was completed by the same sleep team. Finally our SHE cohort included 10/40 patients with a positive family history for NREM sleep parasomnia in their first-degree members. Even if none of the included SHE patients presented nocturnal DoA-like manifestations nor other known sleep disorders, previous studies demonstrated (6, 57) that epileptic and parasomnic events frequently coexist and their semiological differentiation, especially when minor motor episodes prevail, is often a challenging issue (10) which requires accurate evaluation (3).

Conclusions and Perspectives

SHE is considered a rare disease, with a crude prevalence among adults around 1.8/100.000 (58), while the prevalence rate of sleepwalking is estimated 5% in children and 1.5% in adults (59). As a possible explanation of these diverging data, SHE represents the tip of the iceberg acting in the same pathophysiological continuum of DoA, with potential underestimation due to the numerous diagnostic issues described in the present study. A common genetic background shared by DoA and SHE is also hypothesized. Familial aggregation of patients with diagnosed SHE and the higher frequency of arousal parasomnias in SHE probands and their relatives compared with a control population (18, 57, 60) support an intriguing affinity. The involvement of cholinergic pathways has been suggested in abnormal arousal reaction (57, 61). In particular, acetilcholine is one the major neurotransmitters of the ascending reticular activating system and nicotinic acetylcholine receptors are widely distributed in the brain and modulate arousal oscillations at cortical and subcortical levels (53, 62). Given the clinical and electrophysiological commonalities between SHE and DoA and their frequent overlap in the same patients and families, further research on the cholinergic system and other neurotransmitters involved in the modulation of arousal and sleep is a mandatory challenge (63).

Recently, a provocative paper highlighted the impressive parallelism between DoA and SHE based on the arousal system's hyperfunction and NREM sleep dissociation states (64). A brilliant conclusion on the dual nature of DoA and SHE is also available in The Philosophy of Sleep written almost 200 years ago. The author describes "the case of a watchmaker's apprentice who had an attack of sleep-walking every fortnight. In this state,

though insensible to all external impressions, he would perform his work with his usual accuracy, and was always astonished, on awaking, at the progress he had made. The paroxysm began with a sense of heat in the epigastrium extending to the head, followed by confusion of ideas and complete insensibility, the eyes remaining open with a fixed and vacant stare. This case, which undoubtedly originated in some diseased state of the brain, terminated in epilepsy" (65).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, under request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico dell'area Vasta Emilia Nord (AVEN). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GB, NB, IT, NA and RC collected the data. GP made statical analysis. CM and LP drafted the manuscript. All authors contributed to the design of the study protocol, critically reviewed the manuscript, and approved its submitted version.

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Chronotype, Sleep, and Depressive Symptoms Among Chinese College Students: A Cross-Sectional Study

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Objective: To describe the prevalence of chronotype and depressive symptoms among Chinese college students and to examine the association between chronotype and depressive symptoms.

Methods: From April to May 2019, a cross-sectional survey was conducted among 1,179 Chinese college students from 2 universities in Anhui and Jiangxi provinces. A total of 1,135 valid questionnaires were collected, the valid response rate was 98.6%. The questionnaire investigated age, gender, major, height, weight, only child status, living place, self-reported family economy, and self-reported study burden. The chronotype was assessed by the Morning and Evening Questionnaire (MEQ). Depressive symptoms and sleep quality were evaluated by the Patient Health Questionnaire 9 (PHQ-9) and the Pittsburgh Sleep Quality Index (PSQI), respectively. A Chi-square test was used to examine the proportion of depressive symptoms among Chinese college students with different demographic characteristics. The generalized linear model was used to analyze the relationships between chronotype and depressive symptoms.

Results: The proportion of morning types (M-types), neutral types (N-types), and evening types (E-types) of college students were 18.4, 71.1, and 10.5%, respectively. The proportion of mild depression, moderate depression, and moderate to severe depression of participants were 32.4, 6.0, and 4.2%, respectively. Compared to the M-types, after controlled for age, gender, major, sleep quality, self-reported study burden, father's education level, and self-reported family economy, depressive symptoms were positively correlated with E-types ($OR = 2.36$, 95% CI: 1.49–3.73).

Conclusions: There was a significant association between chronotype and depressive symptoms among Chinese college students. Further longitudinal studies were needed to clarify the causal relationship between chronotype and depressive symptoms.

Keywords: chronotype, depressive symptoms, sleep quality, circadian rhythms, college students

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INTRODUCTION

Chronotype was a unique personal biological clock system that was determined by daytime activities and bedtime preferences. The cyclic factor that determines this preference was called a circadian preference, which largely depends on an individual's endogenous component (1). Circadian preference was a continuum but was usually divided into three chronotypes: morning types (M-types), neutral types (N-types), and evening types (E-types) (2). At the onset of adolescence, a sharp shift toward E-types starts, reaching its peak at the end of youth, followed by a steady shift toward M-types as the aging process occurs (3, 4). In a large student sample, the proportion of E-types was 24% and was higher than M-types (16%) (5).

Chronotype affects the psychological health of individuals. Studies have shown that E-types have been associated with increased risk for depressive symptoms (6), and people who stay up late were acknowledged to be more likely to experience depressive symptoms (7). Other studies have shown that E-types have been related to many adverse health outcomes, including mental and physical health problems (8, 9). Besides, E-types can be highly impulsive and use more fatal suicide methods than M-types (10). Thus, the inclination to be an M-types was generally recognized as a protective factor. In contrast, the propensity to be an E-types was a risk factor for triggering personality features associated with a mental disorder (1).

The risk of depressive symptoms sharply rises as a transition from childhood to adolescence. Meanwhile, college students undergo significant changes during campus life due to free of parent-imposed constraints in China. Thus, their lifestyle behaviors can be unhealthy, such as late sleeping, extended screen time, and lack of physical activity (11). In addition to lifestyle changes, many college students also deal with novel challenges arising from adolescent physiological changes, such as a biologically driven delayed sleep phase, which may lead to adverse health outcomes (12). There was evidence suggests that college students were at high risk of depressive symptoms, despite being socially advantaged. Studies have shown that the overall prevalence of depressive symptoms among college students was 52.6% (13). Furthermore, epidemiology studies have indicated that college students with higher levels of depressive symptoms tend to encounter an increased risk of adverse events such as poor academic performance (14), higher levels of substance use (15), and higher levels of suicide (16).

Previous studies have demonstrated that adolescents with E-types have an increased risk of depressive symptoms (17, 18). Two studies conducted among college students indicated that E-types were more likely than M-types to report depressive symptoms (19, 20). However, studies conducted in patients found inconsistent results, which failed to find an association between E-types and depressive symptoms (21, 22). Given the higher prevalence of late bedtimes and the higher risk of depressive symptoms among college students, we conducted an epidemiological investigation of the association between chronotype and depressive symptoms among Chinese college students to provide evidence for further prevention and control of depression in college students.

METHODS

Participants

A total of 1,179 college students were recruited from a medical university and a comprehensive normal university located in Hefei, Anhui Province, and Shangrao, Jiangxi Province, using stratified cluster sampling between April to May 2019. Firstly, two cities were selected by convenient sampling. Then, two universities were based on stratified cluster sampling. Lastly, faculties and classes were selected randomly from the selected universities. Teachers and professional investigators distributed a quick response code to the students for scanning by using their cell phones to complete the electronic questionnaires. A total of 1,135 valid respondents were analyzed, and the response rate was 98.6%.

The current study was approved by the Ethics Committee of Anhui Medical University. Written informed consent was obtained from all of the participants.

Sociodemographic Data

A self-administered questionnaire, including information on sociodemographic indicators, height, weight, chronotype, depressive symptoms, and sleep quality was administered during a 10–20 min session in the classroom. The following sociodemographic characteristics were obtained: age, gender, only child status, living place (urban, rural area), self-reported family economy (low, high), and self-reported study burden (low, high).

Chronotype

Chronotype was assessed by the Morning and Evening Questionnaire (MEQ). The MEQ was the validity and high-reliability tool used to describe chronotype of sleep or phase preferences and was the most widely used tool for identifying chronotype (23). This study used MEQ-5 to assessed the chronotype of college students. The total score ranges from 4 to 25 points. According to the score, chronotype can be divided into three types: E-types (4–11 points), N-types (12–17 points), and M-types (18–25 points) (24). Cronbach's α in this study was 0.68.

Depressive Symptoms

Depressive symptoms were evaluated by the Patient Health Questionnaire 9 (PHQ-9). The PHQ-9 scale contains nine items, which cover the experience of pleasure, feeling down, sleep disruption, energy levels, appetite, feeling a failure, trouble concentrating, speaking slowly or being fidgety, and having negative thoughts around suicide or self-harm over the previous 2 weeks (25). The total score ranges from 0 to 27 points. According to the score, depressive symptoms can be divided into four types: no depression (4–11 points), mild depression (5–9 points), moderate depression (10–14 points), moderate to severe depression (15–27 points) (26). Cronbach's α in this study was 0.81.

Sleep Quality

Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI). Nineteen individual items generate seven component scores: subjective quality of sleep, sleep latency, sleep duration,

sleep efficiency, sleep disorders, medication use, and daytime dysfunction (27). The sum of these seven components' scores yields one global score, the PSQI scores, ranging from 0 to 21. According to the score, sleep quality can be divided into two types: sleep quality good (0–7 points) and sleep quality poor (8–21 points) (27). Cronbach's α in this study was 0.71.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (Statistical Package for the Social Sciences). The Chi-square test was performed to compare the incidence of depressive symptoms among different sociodemographic variables, chronotype, and sleep quality. The generalized linear model was used to analyze the relationships between chronotype and depressive symptoms. Odds ratios (*OR*s) and 95% confidence intervals (95% *CI*s) were calculated for the explanatory factors and adjusted for confounding factors, including age, gender, major, sleep quality, self-reported study burden, father's education level, and self-reported family economy. Statistical significance was set at $P < 0.05$.

RESULTS

Characteristics of Participants

Table 1 displays the characteristics and group differences of 1,135 college students aged between 15 and 26 years old (mean ± SD: 18.8 : 1.2 years), 432 were males (38.1%), and 703 were females (61.9%). Of the 1,135 participants, the proportion of mild depression, moderate depression, moderate to severe depression of college students were 32.4, 6.0, and 4.2%, respectively. However, there were no sex-based differences in depressive symptoms ($P = 0.581$). Depressive symptoms revealed no statistically significant differences by living place ($P = 0.441$), only child status ($P = 0.921$), and mother's education level ($P = 0.312$). College students were from study burden high, a family with a low self-reported family economic status or father's education level low showed higher rates of depressive symptoms. The difference was statistically significant ($P < 0.05$). Moreover, compared to other majors, the school of sports' college students showed higher rates of depressive symptoms ($P = 0.002$).

The Distribution Characteristics of Chronotype and Depressive Symptoms

The proportion of M-types, N-types, and E-types were 18.4, 71.1, and 10.5%, respectively. The proportion of depressive symptoms in E-types was 56.3% and was higher than M-types (34.4%) and N-types (42.8%). Compared to the M-types and N-types, there were fewer cases of no depression and mild depression in the E-types (**Table 2**). Compared to the M-types, there were more cases of moderate depression and moderate to severe depression in the E-types (**Table 2**). The difference was statistically significant ($P < 0.05$).

Associations of Chronotype, Sleep Quality, and Depressive Symptoms

The proportion of poor sleep quality in M-types, N-types, and E-types were 9.6, 13.3, and 20.2%, respectively. In the M-types and E-types, college students with moderate depression and moderate to severe depression were more likely to have poor sleep quality than those with no depression and mild depression (**Table 3**). In the N-types, college students with mild depression, moderate depression, and moderate to severe depression were more likely to have poor sleep quality than those with no depression (**Table 3**). The difference was statistically significant ($P < 0.05$).

Generalized Linear Model Analysis of Chronotype and Depressive Symptoms

The generalized linear model analysis indicated that depressive symptoms of college students were statistically positively correlated with N-types ($OR = 1.38$, 95%CI: 1.01–1.88) and E-types ($OR = 2.48$, 95%CI: 1.60–3.85) (**Table 4**). After controlled for age, gender, major, sleep quality, self-reported study burden, father's education level, and self-reported family economy, depressive symptoms of college students were positively correlated with E-types ($OR = 2.36$, 95%CI: 1.49–3.73) (**Table 4**). The association was statistically significant ($P < 0.05$).

DISCUSSION

To our knowledge, this was the first study conducted to examine the association between chronotype and depressive symptoms among Chinese college students. We found that E-types were positively correlated with depressive symptoms of college students. Furthermore, we also found that sleep problems play a significant role in the association between E-types and depressive symptoms. Compared to the general population, there appeared a high frequency of individuals at risk of depressive symptoms in the sample (42.6%), including mild depression (32.4%), moderate depression (6.0%), and moderate to severe depression (4.2%). However, the mean prevalence of depressive symptoms of college students was 30.6%, based on previous studies (28). Furthermore, in the present study, the proportion of depressive symptoms in E-types was 56.3% and was higher than M-types (34.4%) and N-types (42.8%). However, other research found most depressed individuals to be N-types (29).

There was a rapid transformation toward E-types in modern society due to increased technological preferences, with a substantial effect on chronotype (30). Meanwhile, with increased age and adolescence development, college students showed significant eveningness chronotype due to adolescent physiological changes such as a biologically driven delayed sleep phase (31). In the present study, the proportion of M-types (18.4%) was higher than E-types (10.5%). However, in another study of college students, the proportion of E-types (28.6%) was higher than M-types (12.7%) (32). Furthermore, in the present study, the proportion of poor sleep quality in E-types was 20.2% and was higher than M-types (9.6%) and N-types (13.3%).

TABLE 1 | Characteristics of depressive symptoms in college students (%).

Variable	n	PHQ-9				χ^2-value
		No depression	Mild depression	Moderate depression	Moderate to severe depression	
Gender						1.96
Male	432	245 (56.7)	136 (31.5)	30 (6.9)	21 (4.9)	
Female	703	406 (57.8)	232 (33.0)	38 (5.4)	27 (3.8)	
Major						26.10[b]
School of public health	232	150 (64.7)	66 (28.4)	12 (5.2)	4 (1.7)	
School of nursing	334	201 (60.2)	112 (33.5)	14 (4.2)	7 (2.1)	
School of chemistry and environmental sciences	265	141 (53.2)	92 (34.8)	16 (6.0)	16 (6.0)	
School of sports	304	159 (52.3)	98 (32.2)	26 (8.6)	21 (6.9)	
Self-reported study burden						16.40[a]
Low	21	11 (52.4)	8 (38.1)	0 (0.0)	2 (9.5)	
Medium	695	420 (60.4)	209 (30.1)	46 (6.6)	20 (2.9)	
High	419	220 (52.5)	151 (36.0)	22 (5.3)	26 (6.2)	
Living place						5.04
Rural	633	347 (54.8)	222 (35.1)	39 (6.2)	25 (3.9)	
Urban	502	304 (60.5)	146 (29.1)	29 (5.8)	23 (4.6)	
Only child status						0.49
Yes	268	158 (59.0)	84 (31.3)	16 (6.0)	10 (3.7)	
No	867	493 (56.9)	284 (32.8)	52 (6.0)	38 (4.3)	
Father's education level						19.70[b]
Primary school and below	257	130 (50.6)	88 (34.2)	18 (7.0)	21 (8.2)	
Middle school	539	306 (56.8)	182 (33.8)	32 (5.9)	19 (3.5)	
Senior high school and above	339	215 (63.4)	98 (28.9)	18 (5.3)	8 (2.4)	
Mother's education level						7.09
Primary school and below	497	270 (54.3)	171 (34.4)	31 (6.3)	25 (5.0)	
Middle school	396	227 (57.3)	132 (33.3)	22 (5.6)	15 (3.8)	
Senior high school and above	242	154 (63.6)	65 (26.9)	15 (6.2)	8 (3.3)	
Self-reported family economy						14.08[a]
Low	272	139 (51.1)	98 (36.0)	15 (5.5)	20 (7.4)	
Medium	800	470 (58.8)	255 (31.9)	49 (6.1)	26 (3.2)	
High	63	42 (66.7)	15 (23.8)	4 (6.3)	2 (3.2)	

[a] *P-value* < 0.05.
[b] *P-value* < 0.001.

The current results were consistent with previously reported associations between chronotype and sleep quality (33).

Adolescence and young adulthood were associated with an E-types orientation, which could be due to social factors and developmental maturation processes (34). Also, circadian rhythm might be affected by college students' lifestyle, potential addictions, and general habits. Nowadays, an emerging body of evidence has shown the impact of caffeinated beverages in disrupting an individual's preferred sleep timing or chronotype (35–37). However, college students who were extreme E-types may voluntarily shorten their hours of sleep in response to exams, review lessons, or engage in entertainment and social contact purposes. Notably, additional caffeinated intake was acquired to maintain focus. Previous studies have also found that light exposure was considered an essential zeitgeber in circadian systems (38), affecting melatonin secretion and extending the entrainment phase, thereby developing E-types (39). As for college students, they will spend more time staying indoors (such as classrooms and dorms) than outdoors and generally experience a zeitgeber reduction because they were exposed to less light during the daytime. Furthermore, studies had also shown that using a mobile phone for playing, surfing, and texting in bed before sleep was associated with a relative eveningness chronotype (40).

At the same time, the risk of depressive symptoms of college students increases sharply (41). Previous studies have also shown that circadian rhythm and sleep disruptions may have a significant role in the vulnerability to mood disorders and the precipitation of disorder symptoms (42). Yet little research has examined the effect these changes can have on college students' mental health and the role that chronotype plays in this process. The current study revealed E-types were positively correlated

TABLE 2 | Distribution characteristics of chronotype and depressive symptoms.

Depressive symptoms	n	Chronotype			χ^2-value
		M-types	N-types	E-types	
PHQ-9					19.47[a]
No depression	651	137 (21.0)	462 (71.0)	52 (8.0)	
Mild depression	368	54 (14.7)	268 (72.8)	46 (12.5)	
Moderate depression	68	9 (13.2)	48 (70.6)	11 (16.2)	
Moderate to severe depression	48	9 (18.8)	29 (60.4)	10 (20.8)	

[a] *P-value < 0.05.*

TABLE 3 | Associations of chronotype, sleep quality and depressive symptoms in college students.

Chronotype	Sleep quality	n	PHQ-9				χ^2-value
			No depression	Mild depression	Moderate depression	Moderate to severe depression	
M-types	Good	189	131 (69.3)	49 (25.9)	7 (3.7)	2 (1.1)	54.32[b]
	Poor	20	6 (30.0)	5 (25.0)	2 (10.0)	7 (35.0)	
N-types	Good	700	444 (63.4)	217 (31.0)	29 (4.1)	10 (1.4)	140.76[b]
	Poor	107	18 (16.8)	51 (47.7)	19 (17.8)	19 (17.8)	
E-types	Good	95	49 (51.6)	39 (41.1)	4 (4.2)	3 (3.2)	35.73[b]
	Poor	24	3 (12.5)	7 (29.2)	7 (29.2)	7 (29.2)	

[b] *P-value < 0.001.*

TABLE 4 | Generalized linear model analysis of chronotype and depressive symptoms.

Chronotype	PHQ-9	
	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)
M-types	1.00	1.00
N-types	1.38 (1.01–1.88)[a]	1.33 (0.96–1.84)
E-types	2.48 (1.60–3.85)[b]	2.36 (1.49–3.73)[a]

Adjusted for age, gender, major, sleep quality, self-reported study burden, father's education level, and self-reported family economy.
[a] *P < 0.05.*
[b] *P < 0.001 compared with the referent.*

with depressive symptoms of college students. Similarly, a Croatia study has shown that E-types have been associated with depressive symptoms of college students (43). In a Dutch college student study, E-types can predict more depressive symptoms ($\beta = -0.082$, $P = 0.028$) (44). Furthermore, E-types individuals were more likely to report a past diagnosis of a depressive disorder and an earlier onset of depressive symptoms among college students (45). Hence, E-types appears to be an independent risk factor for depressive symptoms among college students, though more studies were warranted to confirm this observation.

Moreover, studies have shown that lifestyle-related risk factors can contribute to depressive symptoms, such as screen time, unhealthy diets, sedentary lifestyles, stressful events, physical activity, and sleep problems (46). Sleep problems have been proposed to play a mediating role in the association between E-types and depressive symptoms (47). Studies have shown that E-types were associated with shorter sleep duration, poorer sleep quality, and insufficient sleep (48). Compared to the M-types and N-types, there were more poor sleep quality cases in the E-types in the present study. College students with moderate depression and moderate to severe depression were more likely to have poor sleep quality than those with no depression. In general, E-types were more likely to suffer from sleep problems. Depressive symptoms and sleep problems tend to interact with each other in many cases. Thus, sleep problems can play a significant role in the depressive symptoms experienced by E-types.

People who were E-types were more likely to have depressive symptoms. The main mechanism underlying chronotype and mood problems seems to involve variations in biological clock genes (*CLOCK*, *PER1,* and *PER2*) (43). Biological clock genes play an essential role in the critical period of adolescent brain development. Their abnormal expression may change the temporal structure of teenage brain maturation and development, which may lead to dysrhythmia and abnormality of biological rhythm, thus weakening the synchronization between internal and external rhythms, leading to the occurrence of depressive symptoms (49). Furthermore, the underlying mechanisms linking E-types and depressive symptoms have also been explored. E-types have been associated with a lower behavioral activation system, which in turn leads to lower reward responsiveness and lower positive affect, and consequently depressive symptoms (50).

The strengths of the present study include the large sample that has been included in the study, which may make our findings convincing. In addition, we used the generalized linear model to better estimate the associations between chronotype and depressive symptoms. Despite the above strengths, our study has several limitations. First, the cross-sectional survey limits the power with which the causal relationships can be determined. Further longitudinal studies were needed to clarify the causal relationships of chronotype and depressive symptoms. Second, self-reported questionnaires might not allow drawing solid consequences. Third, self-reported depressive symptoms may differ from clinically diagnosed criteria for depressive symptoms. Finally, the relationship between chronotype and depressive symptoms were known findings internationally. However, this was the first time explored by Chinese college students.

CONCLUSION

This study showed a significant correlation between eveningness chronotype and depressive symptoms among Chinese college students. Moreover, college students with depressive symptoms were more likely to have poor sleep quality than those without. Therefore, depressive symptoms prevention efforts that examine both eveningness chronotype and sleep quality were vital for early detection of depression among college students.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Anhui Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XW and FT conceived and designed the experiments. ST and YY performed the experiments. TL, YX, and LZ analyzed the data. HX contributed reagents, materials, and analysis tools. TL wrote the paper. TL contributed to study design. All authors who contributed to the manuscript gave their approval for its submission to Frontier in neurology. The work presented here has not been published previously and is not being considered for publication elsewhere. The author(s) read and approved the final manuscript.

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CASE REPORT
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Exploding Head Syndrome Accompanied by Repeating Panic Attacks: A Case Report

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To the best of our knowledge, we report here for the first time a case of exploding head syndrome (EHS) that caused repeating panic attacks. A 62-year-old woman experienced a sudden sensation of a loud noise just before going to sleep. The frequency of these episodes rapidly increased to multiple times per night, and she soon began to fear sleep, which led to the occurrence of nighttime panic attacks. She was diagnosed with EHS at our sleep clinic, and clonazepam was prescribed accompanied by reassurance about the benign nature of this syndrome. The intensity of the loud noise gradually reduced, and her fear of sleep and panic attacks disappeared at around the same time. In this report, we argue the importance of gaining further knowledge about EHS, including that about complicating psychiatric symptoms and that about its treatment.

Keywords: exploding head syndrome, sleep disorder, parasomnia, panic attack, clonazepam, case report

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INTRODUCTION

Exploding head syndrome (EHS) is a parasomnia characterized by episodes in which loud noises or explosions are perceived when going to sleep or awakening (1). Although only a small number of cases of EHS leading to psychiatric complications have been reported (2), episodes of EHS often cause fear and distress in affected patients (1). Here, we present a case of EHS as a suggested cause of repeating panic attacks. To the best of our knowledge, this is the first time a case of EHS leading to panic attacks has been reported. Additionally, we briefly discuss the importance of gaining further knowledge about this syndrome and its treatment.

CASE DESCRIPTION

A 62-year-old woman was admitted to the clinic at Nihon University Itabashi Hospital Sleep Medicine Center to investigate a 14-month history of a sudden sensation of a loud noise inside her head (**Figure 1**). She described the noise as the sound of a guitar string and honking bus horn, and only experienced it when going to sleep. The noise sensation was not accompanied by pain. Initially, she experienced these episodes less than once per month; however, the frequency rapidly increased to more than once a night, but the cause of this increase was unknown. She developed a fear that the loud noise would occur again when going to bed, which caused difficulty falling asleep. Subsequently, she began to experience frequent nighttime panic attacks accompanied by shortness of breath as a main symptom. She finally decided to call an ambulance and visited

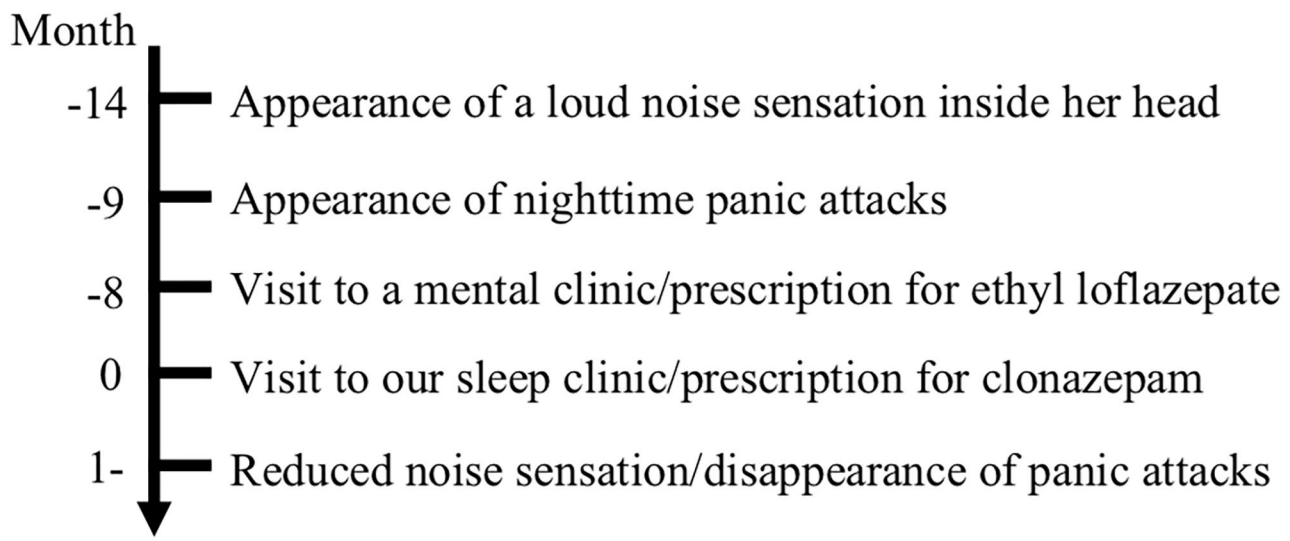

FIGURE 1 | Case history timeline.

the emergency room repeatedly. She was referred to a mental clinic, where she was diagnosed as having panic attacks based on the International Classification of Diseases, 10th revision, and prescribed ethyl loflazepate for 3 months, but this did not stop the loud noise sensation. She then visited our sleep clinic, where she described having a clear recollection of the episodes and an intense fear that she must have a serious brain disease. She had no medical or psychiatric history except for ureteral stones, no family history of psychiatric disorders, no psychosocial history, and no psychiatric symptoms except for panic attacks and a fear of sleep. She had no complaints of headaches or nightmares, no abnormal findings in a physical examination, including neurological, cardiovascular, and respiratory examinations, and no abnormal findings in laboratory examinations, including a blood test, C-reactive protein and liver function, and renal and thyroid functions. Moreover, no abnormal findings were observed in T1-weighted, T2-weighted, fluid-attenuated inversion recovery, or diffusion-weighted magnetic resonance images obtained using a 1.5 T scanner. She did show symptoms of insomnia, especially poor subjective sleep quality, based on the Japanese version of the Athens Insomnia Scale (3), with a score of 10 points [range: 0–24 points, a cutoff score $\geq$8 indicates insomnia (4)]. Polysomnography (PSG) showed no evidence of sleep disorders, and electroencephalography recorded during PSG showed no epileptiform activity, while she experienced a horn noise when going to sleep. Subsequently, she was diagnosed with EHS, and patient education was provided with reassurance about the benign nature of the syndrome. In addition, clonazepam 0.25 mg was prescribed to help reduce her loud noise sensations and alleviate her panic attacks. She was adequately given information about the treatment she received, and she shared their perspective on the treatment. She adhered to her medication without fail, and no adverse effect was observed. The intensity of the noise sensations gradually decreased, and her panic attacks and fear of sleep disappeared at around the same time. After 6 months of treatment with no change of clonazepam dose, the frequency of episodes decreased to once a week. We obtained informed written consent from the patient authorizing publication of clinical case.

DISCUSSION

Here, we described a patient with EHS who was repeatedly admitted to the emergency room because of panic attacks and anticipatory anxiety for the sensation of a loud noise. In this case, it took more than 1 year for the patient to be admitted to our sleep clinic and receive a diagnosis of EHS. Although EHS has a benign prognosis (5, 6), the phenomenon is often frightening to those who believe that it is caused by a problem in the brain (7). Since the symptoms of EHS are often relieved only by patient education and reassurance about the benign nature of the syndrome (7–9), early detection is beneficial for affected patient. EHS is not well-known among most clinicians, even though it has been reported to have a high lifetime prevalence of 30–40% (10). Therefore, knowledge about this syndrome, including that about complicating psychiatric symptoms, and its treatment should be shared widely between clinicians.

In this case, we prescribed a small amount of clonazepam, a benzodiazepine, because it is useful for preventing panic attacks, probably because of its serotonergic properties (11), as well as its GABAergic properties. In addition to preventing panic attacks, clonazepam may have decreased the frequency of EHS episodes and the intensity of the loud noise. EHS has been reported to be ameliorated by clomipramine (8), amitriptyline (12), and duloxetine (2), all of which have serotonergic properties, similar to clonazepam. The common characteristics of these agents may suggest that the symptoms of EHS can be suppressed via the serotonin system. However, since EHS can be relieved only

through patient education and reassurance (7–9), the clinical effects of clonazepam on EHS should be confirmed in further case-control studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YK, AK, MU, and MS contributed to the conception and design of the study. AK, KS, YG, and MS acquired the data. YK and AK wrote the first draft of the manuscript. YK and MS wrote sections of the manuscript. All authors contributed to revising the manuscript and read and approved the final version to be submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.613420/full#supplementary-material

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Non-pharmacological Treatment for Elderly Individuals With Insomnia: A Systematic Review and Network Meta-Analysis

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Background: Insomnia causes a huge socioeconomic burden among the elderly, and is not simply a health problem. This study aimed to determine the comparative advantage of the effectiveness and acceptability of non-pharmacological interventions available for elderly individuals with insomnia.

Methods: Comprehensive searches in 13 medical databases were performed to find relevant randomized controlled trials (RCTs) up to August 2019. Two independent reviewers performed study selection, data extraction, and quality assessment of included RCTs using the Cochrane Collaboration's risk of bias. A network meta-analysis within the frequentist model was performed by combining direct and indirect evidence from all available RCTs. The primary outcomes were effectiveness as measured by the Pittsburgh Sleep Quality Index (PSQI) total score and acceptability by the incidence of all-cause drop-out.

Results: Twenty-eight RCTs involving 2,391 participants were included. Compared to wait-list, acupuncture (standardized mean difference −4.37, 95% confidence interval −8.53 to −0.12), acupuncture combined with benzodiazepines (−5.20, −9.82 to −0.57), behavioral therapy (−10.44, −17.31 to −3.58), benzodiazepines (−4.28, −8.45 to −0.11), benzodiazepines combined with cognitive behavioral therapy (CBT) (−7.18, −12.17 to −2.19), and CBT (−4.93, −8.63 to −1.22) showed significant superiority in their effectiveness. No significant comparative superiority or inferiority was found in terms of acceptability.

Conclusions: In terms of effectiveness as indicated by the PSQI total score, compared to wait-list, superior benefits were observed for acupuncture, acupuncture combined with benzodiazepines, behavioral treatment, benzodiazepines, benzodiazepines combined with CBT, and CBT. Importantly, combined treatments, including benzodiazepines combined with CBT or with acupuncture, were generally superior to

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other monotherapies. In terms of acceptability, there was not enough data to draw conclusions. However, most RCTs included had methodological problems related to the lack of blinding procedure, suggesting a risk of effect size overestimation.

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Keywords: aged, systematic review, network meta-analysis, elderly, insomnia

INTRODUCTION

Insomnia is a common mental health problem that can be defined as "*a complaint of trouble initiating or maintaining sleep which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep*," according to the American Academy of Sleep Medicine (1). The American Insomnia Survey, an epidemiological survey, showed that insomnia in the general population reached 22.1% based on the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)-IV-TR (2). The prevalence of insomnia increases with age, and its prevalence in the elderly is known to be around 20–55% (1, 3, 4). Chronic insomnia constitutes a vicious cycle that makes the disease more susceptible to fixation. Risk factors for insomnia include poor mental health, poor sleep, and obesity (5). Several non-pharmacological approaches and pharmacotherapy can be applied to treat insomnia. According to international guidelines, cognitive-behavioral therapy for insomnia (CBT-I) is considered a standard treatment (1, 6, 7). If CBT-I alone is not effective, pharmacotherapy or other behavioral interventions may be considered (8). However, the administration of drugs—especially benzodiazepine hypnotics—should be carefully performed considering the benefits and risks (1, 6, 7).

In the elderly, insomnia has important characteristics that are quite different from insomnia in the general population. There are several reasons why insomnia issues are important to the elderly. First, in elderly people, the vulnerability to insomnia increases with aging-related changes (9), and some medications that the elderly are regularly taking can cause insomnia. Second, there is growing evidence that insomnia is associated with cognitive impairments (10), dementia (11), depression (12), cardio-cerebral vascular events (13, 14), other health conditions (15), and even mortality (16), which are often associated with the elderly. Therefore, insomnia in the elderly is not only a health-related problem but also carries a socioeconomic burden. Third, among current available existing treatments for insomnia, pharmacotherapies are sometimes associated with serious adverse reactions in the elderly. Although benzodiazepines and other sedative-hypnotic drugs can be used to treat problems related to anxiety or insomnia, their use is not recommended or limited because they are associated with serious side effects such as increased risks of falls and hip fractures among the elderly (17–19). Furthermore, CBT-I is an effective treatment for the improvement of insomnia in the elderly (20); however, there is still a need for some treatment options that can complement or be alternated with this treatment because it is labor-intensive and usually takes generally 6 to 8 weeks. Therefore, it is important to find an effective, simple, and safe treatment method for insomnia in the elderly. This is particularly true for non-pharmacological methods. Moreover, although several non-pharmacological interventions, including CBT-I, have been discussed in the treatment of insomnia, understanding their comparative effectiveness and acceptability allows for optimal medical choice.

Although evidence-based clinical guidelines specifically addressing sleep disturbances in the elderly are lacking, the most recent evidence-based recommendation in 2009, developed by international experts on sleep disorders, include pharmacotherapies including benzodiazepines, non-benzodiazepines, and melatonin receptor agonists, as well as non-pharmacological treatments including CBT-I (21). Moreover, these guidelines also suggested non-pharmacological treatments, including complementary and integrative medicine (CIM) modalities such as acupuncture/acupressure, Tai Chi, and weight training (21). For the efficient distribution of medical resources and optimal medical choices, it is important to prioritize among the various approaches. In this regard, network meta-analysis (NMA) is a useful tool for developing clinical practice guidelines (CPGs) because it enables direct and indirect quantitative comparisons of different interventions and, above all, helps to prioritize these interventions (22). In other words,

Abbreviations: AE, adverse event; AIS, Athens Insomnia Scale; AMED, the Allied and Complementary Medicine Database; AUC, area under the curve; BBTI, brief behavioral treatment for insomnia; BT, behavioral treatment; CBT, cognitive behavioral therapy; CBT-I, cognitive-behavioral therapy for insomnia; CCMD, the Chinese Classification of Mental Disorders; CENTRAL, the Cochrane Central Register of Controlled Trials; CI, confidence interval; CIM, complementary and integrative medicine; CINAHL, the Cumulative Index to Nursing and Allied Health Literature; CNKI, China National Knowledge Infrastructure; CPG, clinical practice guideline; *DSM*, the *Diagnostic and Statistical Manual of Mental Disorders*; GDS, the Geriatric Depression Scale; GRADE, the Grading of Recommendations Assessment, Development and Evaluation; HAMA, the Hamilton Anxiety Rating Scale; HAMD, the Hamilton Depression Rating Scale; ICD, the International Statistical Classification of Diseases and Related Health Problems; ICSD, the International Classification of Sleep Disorders; IRB, the Institutional Review Board; ISI, the Insomnia Severity Index; KCI, Korea Citation Index; KISS, Koreanstudies Information Service System; KMbase, Korean Medical Database; LSEQ, the Leeds Sleep Evaluation Questionnaire; MD, mean difference; MoCA, Montreal cognitive assessment; NMA, network meta-analysis; OASIS, Oriental Medicine Advanced Searching Integrated System; OR, odds ratio; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSQI, the Pittsburgh Sleep Quality Index; RCT, randomized controlled trial; RISS, Research Information Service System; SF-36, the 36-Item Short Form Survey; SMD, standardized mean difference; SOL, sleep onset latency; SSRI, selective serotonin reuptake inhibitor; SUCRA, surface under the cumulative ranking probabilities; TER, total effective rate; TESS, the Treatment Emergent Symptom Scale; TST, total sleep time; WASO, wake time after sleep onset.

NMA allows both direct and indirect comparisons to compare the effectiveness, safety, and acceptability of three or more treatment options. This has led to NMA to be adopted as a new methodology by many international CPGs (23, 24).

The aim of this review was to compare individual non-pharmacological interventions in the treatment of insomnia in the elderly in terms of effectiveness, acceptability, and safety. We applied a systematic review and NMA methodology to generate a clinically useful evidence-based hierarchy of non-pharmacological interventions for insomnia in the elderly, according to their effectiveness, acceptability, and safety, using both NMA and classical pair-wise meta-analysis.

METHODS

The protocol of this NMA was registered in PROSPERO (registration number CRD42019145518). This review was reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting of systematic review incorporating NMA of health care interventions (**Supplementary Table 1**) (25).

Search Strategy

Comprehensive searches were conducted in the following 13 electronic medical databases from their inception dates to August 5, 2019: six English-language databases [MEDLINE via PubMed, EMBASE via Elsevier, the Cochrane Central Register of Controlled Trials (CENTRAL), the Allied and Complementary Medicine Database (AMED) via EBSCO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, and PsycARTICLES via ProQuest], five Korean-language databases [Oriental Medicine Advanced Searching Integrated System (OASIS), Koreanstudies Information Service System (KISS), Research Information Service System (RISS), Korean Medical Database (KMbase), and Korea Citation Index (KCI)], and two Chinese-language databases [China National Knowledge Infrastructure (CNKI) and Wanfang Data]. Manual searches of the reference lists of the relevant systematic reviews and included studies were also conducted to identify further eligible studies. Not only the literature published in journals, but also gray literature, such as theses and conference proceedings, were allowed. No restriction on language was imposed. The search strategies for each database are presented in **Supplementary Tables 2–14**.

Eligible Criteria

Types of Studies

Only randomized controlled trials (RCTs) were included. Studies using inappropriate random sequence generation methods such as allocation by odd or even date of birth or admission day were excluded. To minimize sources of potential heterogeneity, we excluded cluster-randomized trials and cross-over trials.

Types of Participants

Studies on elderly people with a minimum age of 60 years, with the diagnosis of insomnia, using standardized diagnostic tools such as *DSM* (26), the International Statistical Classification of Diseases and Related Health Problems (ICD) (27), the International Classification of Sleep Disorders (ICSD) (28), and the Chinese Classification of Mental Disorders (CCMD) (29), were included. If the study did not present the participants' age criteria or age ranges and presented only the average age, they were excluded because their minimum age was not identified. There was no restriction on the severity of insomnia, sex, ethnicity, or race of patients. Studies were excluded if the patients have drug allergies or other serious medical conditions such as cancer, liver disease, or kidney disease.

Types of Interventions and Comparators

Studies comparing any two of the following non-pharmacological interventions proposed in the most recent international guideline for elderly individuals with insomnia (21) were included irrespective of the form (e.g., group or individual) and duration of treatment: cognitive behavioral therapy (CBT), behavioral treatment (BT) including multi-component behavioral treatments for insomnia, sleep hygiene only (including sleep education), sleep restriction only, stimulus control only, relaxation therapy (including meditation), exercise (including walking and weight training), Tai Chi (including qigong), and acupuncture (including acupressure). Placebo, no treatment, or active controls, including conventional medication, were allowed as control interventions. The inclusion for conventional medication was as follow according to the Cochrane NMA review protocol of pharmacological treatments for insomnia (30): antidepressants (amitriptyline, doxepin, mirtazapine, and trazodone), benzodiazepines (brotizolam, clonazepam, diazepam, estazolam, flunitrazepam, flurazepam, haloxazolam, loprazolam, lorazepam, lormetazepam, midazolam, nimetazepam, nitrazepam, quazepam, rilmazafone, temazepam, and triazolam), benzodiazepine-like agents (eszopiclone, zaleplon, zolpidem, and zopiclone), melatoninergic drugs (melatonin and ramelteon), and orexin receptor antagonists (suvorexant). For the combined treatment study, up to two combinations of defined interventions for the intervention group and control group (e.g., CBT-I plus walking, relaxation plus benzodiazepines) were allowed. In multi-arm trials, study groups assessing interventions other than those mentioned above were not eligible.

Types of Outcome Measures

Primary outcomes

(1) Sleep quality measured by validated assessment tools, such as the Pittsburgh Sleep Quality Index (PSQI) (31), the Insomnia Severity Index (ISI) (32), or the Leeds Sleep Evaluation Questionnaire (LSEQ) (33).

(2) Acceptability measured by drop-outs for any reason (as an indirect indicator of participants' adherence).

Secondary outcomes

(1) Drop-outs because of any adverse event (AE).

(2) Data from polysomnography including sleep onset latency (SOL), wake time after sleep onset (WASO), and total sleep time (TST).

(3) AEs measured by the Treatment Emergent Symptom Scale (TESS) (34) or the incidence of AEs.

Timing of Outcome Assessment

For the outcomes of sleep quality and polysomnography data, we considered the outcomes at 6-week post-treatment. If there was no 6-week post-treatment evaluation, the results at the closest time point were considered. However, the results of 6–8 weeks were given priority. That is, the 8-week post-treatment evaluation result was preferred over the 4-week post-treatment evaluation result.

Study Selection and Data Extraction

Two researchers (C-YK, BL) independently conducted study selection and data extraction processes. Any disagreement about study selection and data extraction was resolved through discussion. The titles and abstracts of all searched studies were reviewed for relevance, and then the full texts of the eligible studies were evaluated for final inclusion. The data were extracted using a standardized data collection form (Excel 2007, Microsoft, Redmond, WA, USA). The extracted items included the first author's name; year of publication; country; sample size and the number of drop-outs; details about the participants, treatment intervention, control intervention, and comparisons; duration of the intervention; outcome measures; and AEs associated with interventions. If the data were insufficient or ambiguous, the corresponding authors of the included studies were contacted by e-mail to request additional information.

Risk of Bias Assessment

Two researchers (C-YK, BL) independently assessed the methodological quality of the included RCTs, using the Cochrane risk of bias assessment tool (35), which includes the following items: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each item was assessed as being of "low risk," "high risk," or "unclear risk" of bias. Moreover, the Jadad scale was used to supplement the methodological quality assessment (36). This scale is used to evaluate the appropriateness of the randomization, blinding, and the descriptions of withdrawals and dropouts, with a total score ranging from 0 (very poor) to 5 (rigorous) (36). Any discrepancies were resolved through their discussion. The potential baseline imbalance can cause a bias in the estimated effects of intervention in RCTs (35), which in turn can affect the similarity hypothesis in NMA. Therefore, in cases of other sources of bias, we assessed them as "low risk" when the statistical similarity on participant's mean age, insomnia period, insomnia severity, and so on at baseline between the groups, as described. The risk of bias figures were created using Review Manager Version 5.3 software (Cochrane, London, UK).

Data Analysis

Pair-Wise Meta-Analysis (Conventional Meta-Analysis)

Pair-wise meta-analysis was performed on the primary and secondary outcomes for studies using the same types of intervention, comparison, and outcome measure. To perform the pair-wise meta-analysis, Review Manager Version 5.3 software (Cochrane, London, UK) was used. Continuous outcomes and dichotomous outcomes were pooled as the standardized mean difference (SMD) and odds ratio (OR), with 95% confidence intervals (CIs). By using both the chi-squared test and the I-squared statistic (I^2), heterogeneity of effect measures between the studies was assessed. The value of $I^2 \geq 50\%$ was considered to be substantial, and the value of $I^2 \geq 75\%$ to be considerable heterogeneity (37). When the heterogeneity was considerable ($I^2 \geq 75\%$), a random-effects model was used; otherwise, a fixed-effects model was used. Also, when there were fewer than five studies included in the meta-analysis, only a fixed-effects model was used (38, 39).

Network Meta-Analysis

The NMA within the frequentist model was performed by combining direct and indirect evidence from all available RCTs. Stata software version 16.0 (StataCorp, Texas, USA) was used to perform the analysis. For NMA in Stata software, a multivariate meta-analysis package was installed and utilized. Performing NMA using the Stata software in this review generally followed the methodology described by Shim and Yoon (40). The data entered into Stata were converted into analysis data through network setup. If the number of occurrences was zero ($d = 0$), this was corrected using the augmented method and then included in the analysis. That is, a default value of 0.5 was assigned to the intervention group and the control group instead of 0. This increased the sample size per treatment by 1 (40). The reference group was set up as a wait-list group. For the assessment of consistency, inconsistency and consistency models were tested by using the design by treatment interaction model (i.e., global approach) and node-splitting test identifying the statistical difference between direct and indirect comparisons for each treatment (i.e., local approach), respectively. The effect sizes and 95% CIs between each intervention were presented as network forest and intervalplot. In addition, network rank and surface under the cumulative ranking probabilities (SUCRA) were used to confirm comparative advantages between the treatments. In SUCRA, a cumulative probability graph is drawn, and the area under the curve (AUC) is calculated for each treatment, allowing for ranking comparison. Finally, raw data of effect size by treatment was described through the network league table.

Additional Analysis

If sufficient studies were available, we performed subgroup analyses for the primary outcomes according to the disease period (>3 months, which means chronic insomnia) to investigate sources of potential inconsistency or heterogeneity. If sufficient studies were available, we performed sensitivity analyses for the primary outcomes to identify the robustness of meta-analysis results by only including studies with low risks of bias, having a low risk of bias in all domains. Moreover, the robustness of meta-analysis results was also confirmed by removing outliers.

Publication Bias

In NMA, there is no validated statistical test method other than visual confirmation using a funnel plot for the detection of publication bias. In addition, conventional funnel plots used in the pair-wise meta-analysis cannot assess publication bias in NMA. Therefore, in this review, we tried to identify the asymmetry of the network funnel plot for the primary outcomes to detect the possibility of publication bias.

Quality of Evidence

We assessed the quality of evidence regarding the effect estimates derived from NMA for the primary outcome measures using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (41). For direct comparisons, we assessed the risk of bias, indirectness, imprecision, inconsistency, and publication bias. For indirect comparisons, the lowest ratings of the two direct comparisons forming the most dominant first-order loop and intransitivity were considered. The higher rating of the direct or indirect estimates was applied to the quality of evidence for NMA and categorized as high, moderate, low, or very low.

RESULTS

Characteristics of Included Studies

A total of 31,149 citations and three citations were identified through the database search and manual search, respectively. After screening of title and abstract and careful review of full-text, 28 RCTs (42–69) with 2,391 participants in 64 arms were included in this review (**Figure 1**). The following 17 kinds of interventions were used: (1) acupuncture, (2) acupuncture combined with benzodiazepines, (3) acupuncture combined with CBT, (4) acupuncture combined with relaxation, (5) acupuncture combined with sleep education, (6) attention control, (7) benzodiazepines, (8) benzodiazepines combined with CBT, (9) benzodiazepines combined with exercise, (10) BT, (11) CBT, (12) sleep education, (13) selective serotonin reuptake inhibitor (SSRI), (14) melatonin, (15) qigong, (16) relaxation, and (17) wait-list.

The mean sample size of included RCTs was 85.39, and the range of participants' ages ranged from 63 to 85. Five studies (17.86%) were conducted in America (42, 45, 47, 55, 58), while 22 (78.57%) were conducted in China (43, 44, 46, 48–54, 57, 59–69), and the remaining one (3.57%) in Iran (56). Twenty studies (71.43%) described the mean disease duration, ranging from 3 months to 18 years (42, 45, 48, 49, 51–55, 57–59, 61–66, 68, 69). Nineteen studies (67.86%) described the participants' baseline PSQI total scores, ranging from 9 to 17 points (47–49, 51–57, 59, 60, 62–65, 67–69). Converting 1 month and 30 days to 4 weeks, the average treatment duration in the included studies was 6 weeks, except for one study with an unclear treatment duration (50). One study (3.57%) was a four-arm study (65), six studies (21.43%) were three-arm studies (46, 48, 52, 54, 63, 64), and the remaining 21 studies (75%) were two-arm studies (42–45, 47, 49–51, 53, 55–62, 66–69). As outcomes of insomnia severity, PSQI was used the most (n = 20, 71.43%) (46–49, 51–57, 59–64, 67–69), followed by total effective rate (TER) ($n = 14$, 50.00%) (43, 50, 52, 54, 57, 59–61, 63, 64, 66–69), sleep diary ($n = 6$, 21.43%) (42, 45, 47, 55, 58, 66), polysomnography data ($n = 4$, 14.29%) (42, 44, 47, 50), the Athens Insomnia Scale (AIS) ($n = 3$, 10.71%) (46, 49, 63), ISI ($n = 2$, 7.14%) (55, 59), and actigraphy data ($n = 2$, 7.14%) (55, 58). In addition, outcomes of mental health such as the Hamilton Depression Rating Scale (HAMD), the Hamilton Anxiety Rating Scale (HAMA), the Geriatric Depression Scale (GDS) were used in nine studies (32.14%) (42, 47, 48, 51, 53, 55, 57, 66, 69). Two studies (7.14%) used outcomes related to quality of life such as the 36-Item Short Form Survey (SF-36) (47, 69). No study reported AE by TESS, while there were 10 studies reporting the incidence of AE during study (43, 45, 47, 48, 51, 52, 63–65, 69). The baseline characteristics of each study are presented in **Table 1**. Excluded studies and reasons are presented in **Supplementary Tables 15–26**.

Risk of Bias of Included Studies

Regarding the Jadad scale, the average score was 2.39 and only 12 studies had scores of 3 or higher. Regarding the risk of bias tool, most of the included studies used random sequence generation methods with low risk of bias (44, 45, 47–49, 51–55, 58, 59, 64–69), such as random number tables or simple randomization, while some studies without a description of randomization method was rated to have an unclear risk of bias on this domain (42, 43, 46, 50, 56, 57, 60–63). Except for three studies that used sealed opaque envelopes for allocation concealment (55, 59, 69), the rest of the studies did not describe allocation concealment. Only Alessi et al. (55) performed blinding on both participants and personnel, and outcome assessors. Among the remaining studies, 24 studies did not describe the blinding of participants and personnel, and the risk of performance bias was rated as high due to the nature of the intervention (42–52, 54, 56–60, 62–68). Two studies described that double-blinding was not performed (53, 69). Xue et al. (61) described that they performed double-blinding but did not describe the method, therefore, the risk of bias for the domain was assessed as unclear. Lin et al. (48) and Alessi et al. (55) described that they performed the blinding of outcome assessors. In 18 studies, there were no drop-out cases (42–44, 46, 49–52, 54, 57, 59–63, 65–67). Some drop-out cases existed in the remaining studies; however, the numbers of drop-out cases were considered to not affect the study results (45, 47, 48, 56, 64, 68, 69), and/or appropriate statistical analysis (i.e., intent-to-treat analysis) was applied (53, 55, 58). One study that did not report some of outcome data in the control group (44), two studies that did not preset the raw PSQI data collected (43, 62), one study that did not present the PSQI total score (61), and one study that did not present the raw ISI data collected (66) were assessed as having a high risk of bias in the selective reporting domain. Regarding other biases, according to our protocol, 25 studies described statistical homogeneity between groups in the baseline were evaluated as having a low risk of bias (42–50, 52–57, 59, 61–69) (**Supplementary Figures 1**, **2**). Only seven studies (47, 53, 55, 56, 58, 65, 67) described approval from the Institutional Review Board (IRB), and 19 studies (47, 48, 50–53, 55–65, 68, 69) described that they had received participants' consent before the trial.

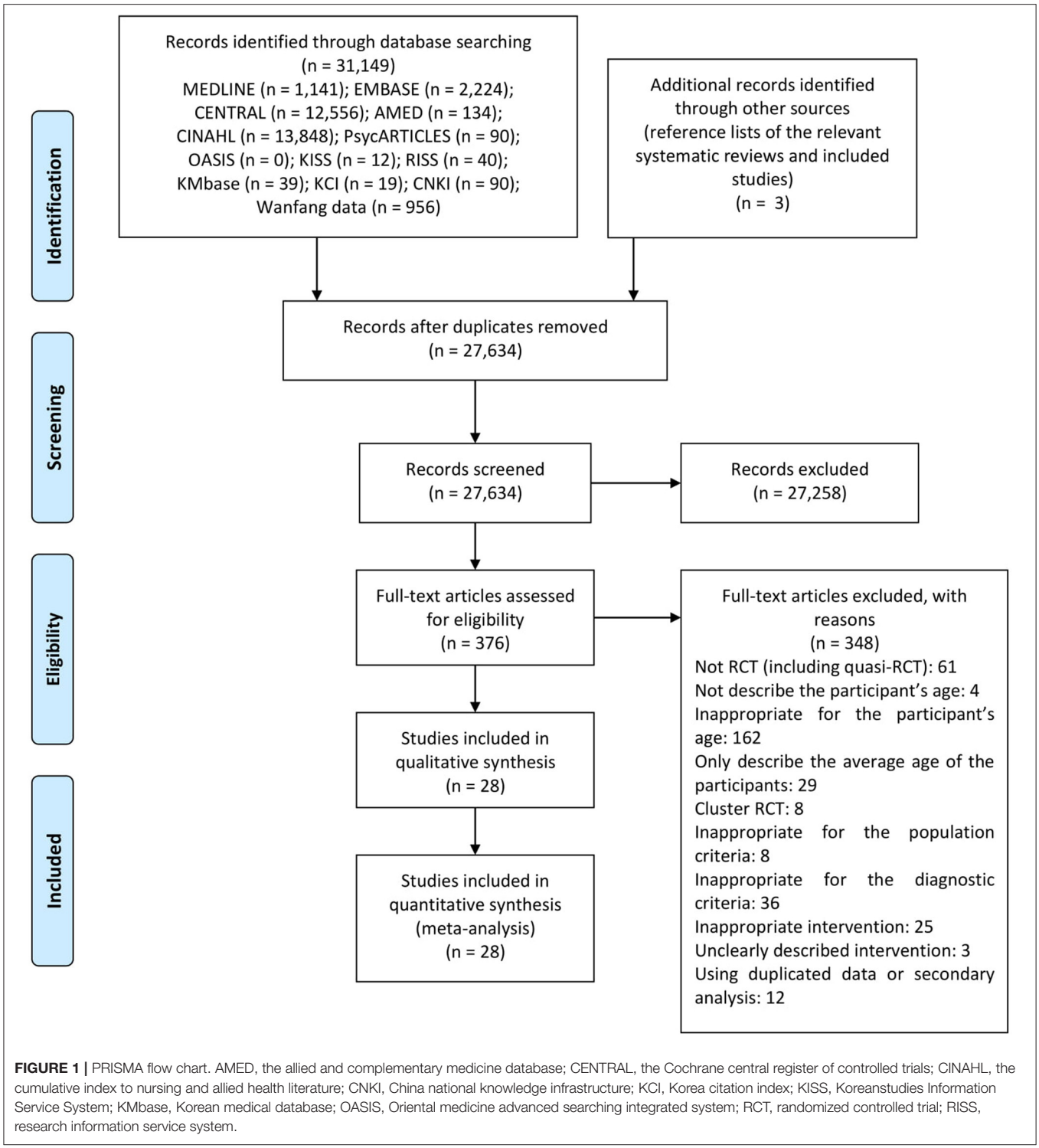

FIGURE 1 | PRISMA flow chart. AMED, the allied and complementary medicine database; CENTRAL, the Cochrane central register of controlled trials; CINAHL, the cumulative index to nursing and allied health literature; CNKI, China national knowledge infrastructure; KCI, Korea citation index; KISS, Koreanstudies Information Service System; KMbase, Korean medical database; OASIS, Oriental medicine advanced searching integrated system; RCT, randomized controlled trial; RISS, research information service system.

Comparative Effectiveness

PSQI Total Score (Primary Outcome)

NMA

Through NMA for PSQI total score, we estimated the relative effect of the 13 interventions (**Figure 2**). The consistency model could be accepted (p-value of testing for inconsistency = 0.1901, of node-splitting test = 0.104 to 0.988). Based on the mean rank and SUCRA, the priorities in terms of effectiveness measured by PSQI total score were as follow: (1) BT, (2) benzodiazepines combined with CBT-I, (3) acupuncture combined with benzodiazepines, (4) benzodiazepines combined with exercise, (5) qigong, (6) CBT-I, (7) melatonin, (8) sleep

TABLE 1 | Characteristics of included randomized controlled trials.

Study ID (Country)	Sample size (include→ analyzed)	Mean age (range) (yr)	Diagnostic criteria (and severity)	Duration (range)	(A) Treatment intervention	(B) Control intervention	Duration of treatment/ F/U	Outcomes	Jadad score* (Q1–5)
Morin et al. (42) (America)	24 (12:12)→ 24 (12:12)	67.1 ± 5.3 (NR)	ICSD-I	13 ± 14.1 yr (NR)	CBT-I	Wait-list	8 wk/3, 12 mon	1. Sleep diary 2. Polysomnography 3. Self-made questionnaire (sleep-related distress, severity, interference, etc.) 4. BDI 5. STAI 6. POMS	1 (1/0/0/0/0)
Song et al. (43) (China)	96 (48:48)→ 96 (48:48)	(A) 65 (60–78) (B) 67 (63–80)	CCMD-2-R	(A)5–54 mon (NR) (B) 6–52 mon (NR)	ACU, relaxation	Paroxetine 10–20 mg qd	10 wk/NA	1. TER	1 (1/0/0/0/0)
Yang et al. (44) (China)	82 (40:42)→ 82 (40:42)	71.4 ± 6.27 (NR)	CCMD-3	NR	Zolpidem 10 mg qd, CBT-I	Zolpidem 10 mg qd	3 mon/NA	1. Self-made questionnaire (sleep hygiene evaluation) 2. Polysomnography	2 (1/1/0/0/0)
McCrae et al. (45) (America)	24 (unclear)→ 20 (11:9)	77.2 ± 8.0 (NR)	ICSD-II, DSM-4 (Average number of insomnia nights/wk was 4.7 (SD: 1.5).)	10.6 ± 17.0 yr (1.5–62.0)	Multicomponent behavioral treatment	Sleep hygiene education	4 wk/NA	1. Sleep diary	3 (1/1/0/0/1)
Weng and Liao (46) (China)	78 (26:26:26)→ 78 (26:26:26)	70.71 (NR)	CCMD-3	NR	(A1) EA (A2) EA, estazolam 1 mg qd	Estazolam 1 mg qd	4 wk/NA	1. PSQI 2. AIS	1 (1/0/0/0/0)
Buysse et al. (47) (America)	82 (42:40)→ 79 (39:40)	(A) 72.5 ± 6.6 (NR) (B) 70.8 ± 7.8 (NR)	DSM-IV-TR, ICSD-2 (PSQI (A) 10.44 ± 0.48 (B) 10.38 ± 0.47)	NR	BBTI	Information control	4 wk/6 mon	1. HAMD 2. HAMA 3. PSQI 4. Epworth Sleepiness Scale 5. SF-36 6. Sleep diary 7. Actigraphy 8. Polysomnography	3 (1/1/0/0/1)
Lin et al. (48) (China)	150 (50:50:50)→ 133 (46:43:44)	(A1) 67.88 ± 4.38 (NR) (A2) 67.75 ± 4.80 (NR) (B) 66.21 ± 7.68 (NR)	ICSD-R (PSQI > 7 (A1) 17.78 ± 2.26 (A2) 17.81 ± 2.21 (B) 17.66 ± 2.42)	(A1) 4.67 ± 3.14 yr (NR) (A2) 4.92 ± 2.43 yr (NR) (B) 4.93 ± 2.62 yr (NR)	(A1) ACU (A2) ACU, biofeedback relaxation	Biofeedback relaxation	8 wk/6 mon	1. PSQI 2. HAMA 3. HAMD	3 (1/1/0/0/1)
Zhu et al. (49) (China)	220 (111:109)→ 220 (111:109)	(A) 71.03 ± 8.38 (60–79) (B) 71.54 ± 6.34 (60–79)	CCMD-3 (PSQI 9.77 ± 1.82 (A) 9.73 ± 1.71)	1.2 ± 0.59 yr (0.5–2) (B) 1.2 ± 0.66 yr (0.5–2)	1. Aerobic exercise 2. Estazolam 0.5–1.5 mg qd	Estazolam 0.5–1.5 mg qd	8 wk/NA	1. PSQI 2. AIS 3. Cardiopulmonary exercise testing 4. TER	3 (1/1/0/0/1)

(Continued)

TABLE 1 | Continued

Study ID (Country)	Sample size (include→ analyzed)	Mean age (range) (yr)	Diagnostic criteria (and severity)	Duration (range)	(A) Treatment intervention	(B) Control intervention	Duration of treatment/ F/U	Outcomes	Jadad score* (Q1–5)
Liu (50) (China)	67 (34:33)→ 67 (34:33)	(A) 83 ± 2.5 (80–88) (B) 85 ± 3.4 (82–90)	CCMD-3	NR	Acupressure, sleep education	Sleep education	NR	1. TER 2. Polysomnography	2 (1/0/0/0/1)
Ren and Li (51) (China)	64 (32:32)→ 64 (32:32)	69.8 ± 7.8 (65–79)	ICSD-II (PSQI ≥ 8 (A) 14.38 ± 2.24 (B) 13.56 ± 2.50)	21.3 ± 6.7 mon (NR)	ACU	Melatonin capsule (melatonin 3 mg qd)	4wk/NA	1. PSQI 2. GDS	3 (1/1/0/0/1)
Wang et al. (52) (China)	98 (33:35:30)→ 98 (33:35:30)	(A1) 73 ± 6 (65–84) (A2) 73 ± 6 (65–81) (B) 73 ± 6 (65–87)	CCMD-3 (PSQI (A1) 15.73 ± 3.79 (A2) 15.86 ± 3.75 (B) 15.67 ± 3.67)	(A1) 15.0 ± 7.1 mon (4–26) (A2) 15.0 ± 6.9 mon (3–26) (B) 15.1 ± 7.3 mon (6–28)	(A1) ACU (A2) ACU, estazolam 1 mg qd, oryzanol 20 mg tid	Estazolam 1 mg qd, oryzanol 20 mg tid	4 wk/4 wk	1. PSQI 2. Clinical effective rate	2 (1/1/0/0/0)
Zhang et al. (53) (China)	64 (32:32)→ 64 (32:32)	(A) 78.57 ± 2.94 (NR) (B) 77.63 ± 3.01 (NR)	DSM-IV (PSQI (A) 11.50 ± 3.28 (B) 11.27 ± 3.62)	6 mon	MBSR	Wait-list	8 wk NA	1. PSQI 2. SAS 3. GDS	3 (1/1/0/0/1)
Xu et al. (54) (China)	81 (27:27:27)→ 81 (27:27:27)	68.15 ± 7.25 (60–72)	CCMD-3 (PSQI (A1) 14.02 ± 3.58 (A2) 14.21 ± 3.84 (B) 14.05 ± 3.28)	6.51 ± 2.18 yr (3 mon−10 yr)	(A1) CBT (A2) CBT, oxazepam 15 mg 1T qd	Oxazepam 15 mg 1T qd	4 wk/NA	1. TER 2. PSQI 3. Serum levels of IL-1 (ng/L), IL-6 (ng/L), TNF-α (ug/ml), and cortisol (ug/L)	2 (1/1/0/0/0)
Alessi et al. (55) (America)	159 (106:53)→ 159 (106:53)	(A) 72.2 ± 7.7 (NR) (B) 72.1 ± 7.9 (NR)	ICSD-2 (PSQI (A) 9.4 ± 3.5 (B) 8.3 ± 3.2)	3 mon	CBT-I	Sleep education	6 wk/6, 12 mon	1. Sleep diary 2. Sleep efficiency (Actigraphy) 3. PSQI 4. ISI 5. PHQ-9 6. 12-item Short-Form Study	5 (1/1/1/1/1)
Reza (56) (Iran)	44 (22:22)→ 39 (19:20)	(A) 69.21 ± 5.96 (NR) (B) 66.70 ± 5.89 (NR)	DSM-IV (PSQI>5 (A) 12.95 ± 2.73 (B) 12.7 ± 2.96)	NR	CBT	Wait-list	4 wk/3mon	1. PSQI	2 (1/0/0/0/1)
Duan (57) (China)	78 (39:39)→ 78 (39:39)	(A) 72.19 ± 13.58 (NR) (B) 73.74 ± 13.26 (NR)	ICSD (PSQI (A) 14.26 ± 2.32 (B) 13.98 ± 2.53)	(A) 21.5 ± 6.7 mon (NR) (B) 21.7 ± 6.3 mon (NR)	ACU	Melatonin capsule (melatonin 2.05 mg) qd	4 wk/NA	1. PSQI 2. GDS 3. TER	2 (1/0/0/0/1)
Chan et al. (58) (America)	62 (32:30)→ 62 (32:30)	(A) 67.97 ± 5.97 (NR) (B) 71.03 ± 9.06 (NR)	ICSD-II	(A) 9.51 ± 12.37 yr (NR) (B) 18.55 ± 16.95 yr (NR)	BBTI	Attention control	4 wk/3 mon	1. Sleep diary 2. Actigraphy	3 (1/1/0/0/1)

(Continued)

TABLE 1 | Continued

Study ID (Country)	Sample size (include→ analyzed)	Mean age (range) (yr)	Diagnostic criteria (and severity)	Duration (range)	(A) Treatment intervention	(B) Control intervention	Duration of treatment/ F/U	Outcomes	Jadad score* (Q1–5)
Liang (59) (China)	70 (35:35)→ 70 (35:35)	(A) 68 ± 6 (61–64) (B) 67 ± 7 (60–75)	CCMD-3 (PSQI (A) 13.97 ± 3.05 (B) 14.02 ± 2.64)	(A) 5.37 ± 2.66 yr (0.5–11) (B) 5.44 ± 3.12 yr (1–12)	Ear acupuncture	Estazolam 1 mg 1T qod	30 d/NA	1. TER 2. PSQI 3. ISI	2 (1/1/0/0/0)
Lin et al. (60) (China)	90 (46:44)→ 90 (46:44)	NR	ICD-10, DSM-IV, CCMD-3 (15 ≥ PSQI ≥ 7 (A) 12.30 ± 1.35 (B) 12.63 ± 1.44)	NR	Ear acupressure	Estazolam 1 mg 1T qd	4 wk/NA	1. PSQI 2. TER	2 (1/0/0/0/1)
Xue et al. (61) (China)	80 (40:40)→ 80 (40:40)	(A) 69.1 ± 2.15 (60–78) (B) 69.02 ± 2.14 (61–79)	Criteria from Chinese Medical Association Neurology Branch Sleep Disorders Group	(A) 1.86 ± 0.35 yr (7 mon−3 yr) (B) 1.87 ± 0.34 yr (6 mon−3 yr)	ACU	Estazolam 1–2 mg qd	2 mon/NA	1. TER 2. PSQI (total score was not presented) 3. Transcranial doppler (systolic flow velocity of the vertebral artery and basilar artery)	3 (1/0/1/0/1)
Zhang (62) (China)	160 (80:80)→ 160 (80:80)	66.3 ± 4.2 (65–82) (B) 68.5 ± 3.2 (65–80)	Chinese Guideline of Adult Insomnia Diagnosis and Treatment 2012 Edition ≥ PSQI ≥ 21 18.3 ± 3.1 (B) 19.1 ± 3.4)	(A) 23 ± 3.8 mon (6 mon−10 yr) (B) 26 ± 4.2 mon (6 mon−13 yr)	CBT-I, estazolam 2 mg qd	Estazolam 2 mg qd	8 wk/6 mon	1. PSQI (the score was not presented) 2. Drug reduction rate	2 (1/0/0/0/1)
Chen et al. (63) (China)	90 (30:30:30)→ 90 (30:30:30)	(A) 63.4 ± 2.4 (61–68) (B1) 64.4 ± 2.5 (60–69) (B2) 64.6 ± 2.7 (60–70)	CCMD-3 (PSQI (A) 14.2 ± 0.72 (B1) 14.1 ± 0.73 (B2) 13.9 ± 0.80)	(A) 2.7 ± 1.5 yr (6 mon−7 yr) (B1) 3.0 ± 1.5 yr (1–8) (B2) 2.5 ± 1.5 yr (2–7)	(A) ACU	(B1) Alprazolam 0.4 mg 1T qd (B2) HM, ACU	1 mon/NA	1. TER 2. PSQI 3. AIS	2 (1/0/0/0/1)
Mo (64) (China)	90 (30:30:30)→ 83 (27:27:29)	(A1) 69.78 ± 7.21 (NR) (A2) 71.07 ± 6.57 (NR) (B) 70.21 ± 6.39 (NR)	CCMD-3 (PSQI > 7 PSQI (A1) 14.30 ± 1.41 (A2) 13.52 ± 1.67 (B) 13.55 ± 1.53)	(A1) 10.48 ± 9.37 mon (NR) (A2) 10.37 ± 11.90 mon (NR) (B) 10.59 ± 9.42 mon (NR)	(A1) ACU (method A) (A2) ACU (method B)	Estazolam 1 mg qd	4 wk/1 mon	1. TER 2. PSQI 3. FS-14 4. Recurrence rate	3 (1/1/0/0/1)
Yuan et al. (65) (China)	120 (30:30:30:30)→ 120 (30:30:30:30)	(A) 67.4 ± 6.00 (NR) (B1) 65.5 ± 5.12 (NR) (B2) 66.3 ± 4.23 (NR) (B3) 65.5 ± 5.12 (NR)	CCMD-3 (PSQI (A) 13.21 ± 2.01 (B1) 14.62 ± 1.85 (B2) 14.62 ± 1.85 (B3) 14.1 ± 3.60)	(A) 13.4 ± 3.28 mon (NR) (B1) 13.2 ± 10.25 mon (NR) (B2) 12.7 ± 9.65 mon (NR) (B3) 14.2 ± 5.03 mon (NR)	(A) ACU	(B1) Estazolam 1 mg 1T qd (B2) HM (B3) HM, ACU	4 wk/NA	1. TER 2. PSQI 3. TCM symptom score	2 (1/1/0/0/0)
Xu et al. (65) (China)	86 (43:43)→ 86 (43:43)	(A) 73.4 ± 11.6 (NR) (B) 74.5 ± 12.1 (NR)	ICSD-3 (self-rating scale (not specified)>40)	(A) 6.8 ± 1.1 yr (NR) (B) 7.1 ± 1.3 yr (NR)	CBT, ACU	CBT	8 wk/NA	1. TER (ISI score) 2. Sleep diary 3. SAS 4. SDS	2 (1/1/0/0/0)

(Continued)

TABLE 1 | Continued

Study ID (Country)	Sample size (include→ analyzed)	Mean age (range) (yr)	Diagnostic criteria (and severity)	Duration (range)	(A) Treatment intervention	(B) Control intervention	Duration of treatment/ F/U	Outcomes	Jadad score* (Q1–5)
Liu (67) (China)	78 (39:39)→ 78 (39:39)	(A) 75.20 ± 4.38 (66–83) (B) 75.18 ± 4.32 (69–82)	CCMD (PSQI (A) 15.10 ± 2.23 (B) 15.15 ± 2.20)	NR	Estazolam 1 mg 1T qd, oryzanol 10 mg 2T tid, ACU	Estazolam 1 mg 1T qd, oryzanol 1 0 mg 2T tid	4 wk/NA	1. PSQI 2. TER (clinical symptom)	2 (1/1/0/0/0)
Yu and Gao (68) (China)	60 (30:30)→ 56 (28:28)	(A) 71.3 ± 5.7 (60–80) (B) 72.3 ± 4.8 (63–79)	CCMD-3 (PSQI ≥ 7 (A) 14.82 ± 2.07 (B) 14.29 ± 2.67)	(A) 4.43 ± 2.50 yr (0.5–10) (B) 4. 99 ± 2.44 yr (1–11)	ACU	Estazolam 1–2 mg 1T qd	4 wk/NA	1. PSQI 2. TER (PSQI score) 3. MoCA	3 (1/1/0/0/1)
Wei (69) (China)	74 (37:37)→ 61 (32:29)	(A) 66.76 ± 3.58 (NR) (B) 66.24 ± 4.30 (NR)	DSM-5 (PSQI (A) 13.38 ± 3.22 (B) 12.76 ± 3.86)	(A) 29.21 ± 40.57 mon (NR) (B) 30.95 ± 42.25 mon (NR)	Qigong	CBT	8 wk/NA	1. TER (clinical symptom) 2. PSQI 3. SF-36 4. SAS 5. SDS	3 (1/1/0/0/1)

ACU, acupuncture; AIS, Athens insomnia scale; BBTI, brief behavioral treatment for insomnia; BDI, Beck depression inventory; CBT-I, cognitive behavioral therapies for insomnia; CCMD, Chinese classification of mental disorders; DSM, diagnostic and statistical manual of mental disorders; EA, electro-acupuncture; FS-14, fatigue scale-14; GDS, geriatric depression scale; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton depression rating scale; HM, herbal medicine; ICSD, international classification of sleep disorders; IL, interleukin; ISI, insomnia severity index; MBSR, mindfulness-based stress reduction; MoCA, Montreal cognitive assessment; NA, not applicable; NR, not reported; PHQ-9, patient health questionnaire-9; POMS, profile of mood states; PSQI, Pittsburgh sleep quality index; SAS, self-rating anxiety scale; SDS, self-rating depression scale; SF-36, 36-item short form survey; STAI, state-trait anxiety inventory; TCM, traditional Chinese medicine; TER, total effective rate; TNF, tumor necrosis factor.

Among the included studies, Mo (64) with three-arm, compared two different kinds acupuncture to benzodiazepines (i.e., estazolam). Therefore, we divided Mo (64) into Mo (2018a) and Mo (2018b) in the data analysis to compare the two acupuncture methods and benzodiazepines, respectively. That is, Mo (2018a) included the whole value of the first acupuncture group and half value of the control group, and Mo (2018b) included the whole value of the second acupuncture group and half value of the control group. Chen et al. (63), a three-arm RCT, included herbal medicine combined with acupuncture group, that did not meet our intervention criteria. Moreover, Yuan et al. (65), a four-arm RCT, included herbal medicine combined with acupuncture group and herbal medicine group. Therefore, those groups including herbal medicine were excluded from our analysis.

**The five questions (Q1–5) for the Jadad score were as follows: (1) Was the study described as randomized? (2) Was the appropriate randomization method applied? (3) Was the study described as double-blind? (4) Was the appropriate blinding method applied? (5) Was there a description of withdrawals and dropouts?*

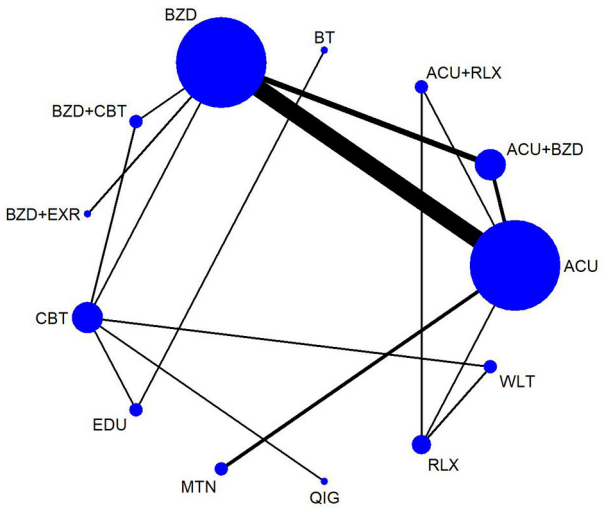

FIGURE 2 | Network map for PSQI total score. ACU, acupuncture; BT, behavioral treatment; BZD, benzodiazepines; CBT, cognitive behavioral therapy; EDU, sleep education; EXR, exercise; MTN, melatonin; QIG, qigong; RLX, relaxation.

education, (9) acupuncture, (10) acupuncture combined with relaxation, (11) benzodiazepines, (12) relaxation, and (13) wait-list. According to the netleague table presenting the comparative effectiveness of treatments (in favor of bolding marks), **acupuncture** (SMD −4.37, 95% CI −8.53 to −0.12), **acupuncture combined with benzodiazepines** (SMD −5.20, 95% CI −9.82 to −0.57), **BT** (SMD −10.44, 95% CI −17.31 to −3.58), **benzodiazepines** (SMD −4.28, 95% CI −8.45 to −0.11), **benzodiazepines combined with CBT** (SMD −7.18, 95% CI −12.17 to −2.19), and **CBT** (SMD −4.93, 95% CI −8.63 to −1.22) were all statistically significantly superior to wait-list. Moreover, sleep education and relaxation were both statistically significantly inferior to **BT** (SMD 6.13, 95% CI 1.98 to 10.28; SMD 8.00, 95% CI 0.87 to 15.13). Compared to wait-list, acupuncture combined with relaxation (SMD −4.18, 95% CI −9.08 to 0.72), benzodiazepines combined with exercise (SMD −5.41, 95% CI −11.21 to 0.38), melatonin (SMD −4.38, 95% CI −9.42 to 0.67), and qigong (SMD −5.46, 95% CI −10.94 to 0.02) showed superior benefits, with borderline significances. However, sleep education (SMD −4.31, 95% CI −9.78 to 1.15), or relaxation (SMD −2.44, 95% CI −5.98 to 1.09) did not show significant or near-significant differences with the wait-list (**Table 2**, **Figure 3**, **Supplementary Figures 3–9**, **Supplementary Table 27**).

Pair-wise meta-analysis

As results of pair-wise meta-analysis, statistically significant differences existed between the following comparisons (in favor of bolding marks): (1) acupuncture vs. **acupuncture combined with relaxation** (SMD 0.56, 95% CI 0.14 to 0.99), (2) **acupuncture** vs. relaxation (SMD −0.50, 95% CI −0.92 to −0.08), (3) **acupuncture combined with benzodiazepines** vs. benzodiazepines (SMD −1.24, 95% CI −1.56 to −0.91; I^2 = 95%), (4) **acupuncture combined with relaxation** vs. relaxation (SMD −1.00, 95% CI −1.44 to −0.55), (5) **BT** vs. sleep education (SMD −6.13, 95% CI −7.20 to −5.05), (6) benzodiazepines vs. **benzodiazepines combined with CBT** (SMD 2.51, 95% CI 1.78 to 3.23), (7) benzodiazepines vs. **benzodiazepines combined with exercise** (SMD 1.14, 95% CI 0.85 to 1.42), (8) **benzodiazepines** vs. CBT (SMD −2.77, 95% CI −3.53 to −2.01), (9) **benzodiazepines combined with CBT** vs. CBT (SMD −2.89, 95% CI −3.67 to −2.11), (10) **CBT** vs. sleep education (SMD −0.61, 95% CI −0.95 to −0.28), (11) CBT vs. **qigong** (SMD 0.53, 95% CI 0.02 to 1.04), (12) **CBT** vs. wait-list (SMD −6.55, 95% CI −8.20 to −4.89), and (13) **relaxation** vs. wait-list (SMD −1.04, 95% CI −1.56 to −0.52) (**Supplementary Table 31**).

Sensitivity analysis

According to network funnel plots (**Supplementary Figure 26**) and pair-wise meta-analysis of PSQI total scores, Weng and Liao (46) was the major outlier. After removing this outlier, in NMA, the consistency model could be accepted (p-value of testing for inconsistency = 0.4359, of node-splitting test = 0.172 to 0.987). According to the results of the netleague table, except for the significant difference (SMD −4.37, 95% CI −8.53 to−0.21) in the acupuncture vs. wait-list being changed to borderline significance (SMD −4.27, 95% CI −8.57 to 0.04), no change was found in the remaining significant differences, compared to before removal of the outlier (**Supplementary Figure 10**, **Supplementary Table 28**). Moreover, in the pair-wise meta-analysis, significant differences between acupuncture combined with benzodiazepines and benzodiazepines were maintained (SMD −1.47, 95% CI −1.87 to −1.07; I^2 = 97%) (**Supplementary Table 32**).

Polysomnography Data (Secondary Outcome)

Pair-wise meta-analysis

Only four studies reported each sleep index from polysomnography data, and the network was disconnected by three components (**Supplementary Figure 11**). Therefore, NMA for polysomnography data was not appropriate, and only pair-wise meta-analysis was performed. As results, statistically significant differences existed between the following comparisons (the favored treatment is bolded): (1) benzodiazepines vs. **benzodiazepines combined with CBT** (SMD −3.51, 95% CI −4.22 to −2.81), (2) **CBT** vs. wait-list (SMD 0.79, 95% CI 0.20 to 1.38), (3) **acupuncture combined with sleep education** vs. sleep education (SMD 6.84, 95% CI 5.56 to 8.13) in sleep efficiency (%); (4) **BT** vs. sleep education (SMD −0.85, 95% CI −1.31 to −0.38) in WASO (min); (5) benzodiazepines vs. **benzodiazepines combined with CBT** (SMD 2.02, 95% CI 1.49 to 2.56), (6) **acupuncture combined with sleep education** vs. sleep education (SMD −2.11, 95% CI−2.72 to −1.51) in number of awakenings (n); (7) benzodiazepines vs. **benzodiazepines combined with CBT** (SMD −1.05, 95% CI −1.51 to −0.59), (8) **acupuncture combined with sleep education** vs. sleep education (SMD 2.38, 95% CI 1.74 to 3.01) in sleep maintenance rate (%); (9) BT vs. **sleep education** (SMD 0.75, 95% CI 0.29 to 1.21) in SOL (min); (10) BT vs. **sleep education** (SMD −0.90, 95% CI −1.36 to −0.43) in TST (min); (11) **CBT** vs. wait-list (SMD −0.99, 95% CI −1.59 to −0.39), (12) benzodiazepines vs.

TABLE 2 | Head-to-head comparisons for effectiveness and acceptability of the non-pharmacological interventions.

WLT	**−4.37 (−8.53, −0.21)**	**−5.20 (−9.82, −0.57)**	–	–	**−4.18 (−9.08, 0.72)**	–	**−10.44 (−17.31, −3.58)**	**−4.28 (−8.45, −0.11)**	**−7.18 (−12.17, −2.19)**	**−5.41 (−11.21, 0.38)**	**−4.93 (−8.63, −1.22)**	**−4.31 (−9.78, 1.15)**	**−4.38 (−9.42, 0.67)**	**−5.46 (−10.94, 0.02)**	**−2.44 (−5.98, 1.09)**	–
1.06 (0.11, 10.66)	**ACU**	−0.82 (−3.10, 1.45)	–	–	0.19 (−3.72, 4.11)	–	**−6.07 (−12.91, 0.77)**	0.09 (−1.23, 1.42)	−2.81 (−6.91, 1.30)	−1.04 (−5.27, 3.19)	−0.55 (−4.22, 3.11)	0.06 (−5.38, 5.50)	−0.01 (−2.86, 2.85)	−1.09 (−6.54, 4.37)	1.93 (−1.60, 5.46)	–
1.08 (0.05, 23.85)	1.02 (0.12, 8.68)	**ACU+BZD**	–	–	1.02 (−3.48, 5.51)	–	−5.25 (−12.34, 1.85)	0.92 (−1.25, 3.09)	−1.99 (−6.47, 2.50)	−0.22 (−4.79, 4.35)	0.27 (−3.84, 4.38)	0.88 (−4.87, 6.63)	0.82 (−2.83, 4.47)	−0.26 (−6.03, 5.50)	2.75 (−1.38, 6.89)	–
0.71 (0.01, 50.32)	0.67 (0.01, 69.85)	0.66 (<0.01, 104.67)	**ACU+CBT**	–	–	–	–	–	–	–	–	–	–	–	–	–
0.37 (<0.01, 121.71)	0.35 (<0.01, 153.31)	0.34 (<0.01, 209.01)	0.52 (<0.01, 477.22)	**ACU+EDU**	–	–	–	–	–	–	–	–	–	–	–	–
2.31 (0.18, 29.02)	2.18 (0.52, 9.18)	2.14 (0.16, 28.07)	3.26 (0.03, 388.24)	6.30 (0.01, 3,087.11)	**ACU+RLX**	–	−6.26 (−13.87, 1.34)	−0.10 (−4.18, 3.98)	−3.00 (−8.47, 2.46)	−1.24 (−6.96, 4.49)	−0.75 (−5.70, 4.20)	−0.14 (−6.51, 6.24)	−0.20 (−5.04, 4.64)	−1.28 (−7.67, 5.11)	1.73 (−2.18, 5.65)	–
0.03 (<0.01, 6.40)	0.03 (<0.01, 8.25)	0.03 (<0.01, 11.52)	0.04 (<0.01, 26.97)	0.08 (<0.01, 13.74)	0.01 (<0.01, 4.22)	**ATC**	–	–	–	–	–	–	–	–	–	–
0.05 (<0.01, 9.02)	0.05 (<0.01, 11.73)	0.05 (<0.01, 16.51)	0.07 (<0.01, 39.03)	0.14 (<0.01, 19.22)	0.02 (<0.01, 6.02)	1.64 (0.46, 5.88)	**BT**	**6.16 (−0.61, 12.94)**	3.26 (−3.74, 10.26)	5.03 (−2.85, 12.91)	**5.52 (−0.27, 11.30)**	**6.13 (1.98, 10.28)**	6.06 (−1.35, 13.48)	4.98 (−2.07, 12.04)	**8.00 (0.87, 15.13)**	–
1.03 (0.10, 10.99)	0.97 (0.39, 2.40)	0.95 (0.12, 7.69)	1.45 (0.01, 152.62)	2.80 (0.01, 1,249.05)	0.44 (0.08, 2.40)	34.04 (0.12, 9,929.17)	20.71 (0.08, 5,225.40)	**BZD**	−2.90 (−6.84, 1.04)	−1.14 (−5.15, 2.88)	−0.65 (−4.19, 2.89)	−0.04 (−5.39, 5.32)	−0.10 (−3.25, 3.05)	−1.18 (−6.55, 4.19)	1.83 (−1.82, 5.49)	–
0.94 (0.05, 18.00)	0.89 (0.08, 9.38)	0.87 (0.04, 18.13)	1.33 (0.01, 180.82)	2.57 (<0.01, 1,395.30)	0.41 (0.03, 6.21)	31.16 (0.09, 11,252.12)	18.96 (0.06, 5,953.63)	0.92 (0.10, 8.40)	**BZD+CBT**	1.77 (−3.86, 7.39)	2.25 (−1.70, 6.20)	2.87 (−2.77, 8.50)	2.80 (−2.20,7.80)	1.72 (−3.93, 7.37)	**4.74 (−0.23, 9.70)**	–
1.05 (0.01, 102.95)	0.99 (0.02, 55.70)	0.97 (0.01, 82.99)	1.48 (<0.01, 653.30)	2.85 (<0.01, 4,040.03)	0.45 (0.01, 32.58)	34.66 (0.03, 34,491.43)	21.09 (0.02, 18,635.54)	1.02 (0.02, 51.77)	1.11 (0.01, 101.21)	**BZD+EXR**	0.49 (−4.87, 5.84)	1.10 (−5.60, 7.80)	1.04 (−4.07,6.14)	−0.04 (−6.75, 6.66)	2.97 (−2.46, 8.40)	–
0.71 (0.14, 3.58)	0.67 (0.06, 7.85)	0.66 (0.03, 15.95)	1.00 (0.02, 51.54)	1.93 (0.01, 509.11)	0.31 (0.02, 4.58)	23.48 (0.14, 3,874.82)	14.29 (0.10, 2,005.45)	0.69 (0.06, 8.22)	0.75 (0.04, 14.17)	0.68 (0.01, 70.49)	**CBT**	0.61 (−3.41, 4.64)	0.55 (−4.09,5.19)	−0.53 (−4.57, 3.51)	2.48 (−1.69, 6.65)	–
0.36 (0.01, 25.07)	0.34 (<0.01, 34.83)	0.33 (<0.01, 52.23)	0.50 (<0.01, 131.73)	0.97 (0.02, 50.36)	0.15 (<0.01, 18.24)	11.80 (0.45, 305.91)	7.18 (0.36, 143.50)	0.35 (<0.01, 36.20)	0.38 (<0.01, 51.21)	0.34 (<0.01, 149.73)	0.50 (0.01, 25.67)	**EDU**	−0.06 (−6.21,6.08)	−1.14 (−6.85, 4.56)	1.87 (−3.92, 7.66)	–
1.06 (0.03, 39.75)	1.00 (0.06, 16.34)	0.98 (0.03, 33.17)	1.49 (0.01, 338.59)	2.89 (<0.01, 2,354.13)	0.46 (0.02, 10.62)	35.09 (0.06, 19,489.65)	21.35 (0.04, 10,413.06)	1.03 (0.05, 19.45)	1.13 (0.03, 43.55)	1.01 (0.01, 136.69)	1.49 (0.04, 61.90)	2.97 (0.01, 669.72)	**MTN**	−1.08 (−7.24, 5.08)	1.93 (−2.60, 6.47)	–

(Continued)

TABLE 2 | Continued

WLT	**−4.37 (−8.53, −0.21)**	**−5.20 (−9.82, −0.57)**	**–**	**–**	**−4.18 (−9.08, 0.72)**	**–**	**−10.44 (−17.31, −3.58)**	**−4.28 (−8.45, −0.11)**	**−7.18 (−12.17, −2.19)**	**−5.41 (−11.21, 0.38)**	**−4.93 (−8.63, −1.22)**	**−4.31 (−9.78, 1.15)**	**−4.38 (−9.42, 0.67)**	**−5.46 (−10.94, 0.02)**	**−2.44 (−5.98, 1.09)**	**–**
1.25 (0.16, 9.53)	1.18 (0.08, 18.48)	1.16 (0.04, 35.35)	1.77 (0.03, 109.60)	3.41 (0.01, 1,026.76)	0.54 (0.03, 10.55)	41.45 (0.22, 7,907.93)	25.22 (0.15, 4,111.71)	1.22 (0.08, 19.32)	1.33 (0.06, 31.97)	1.20 (0.01, 145.87)	1.77 (0.52, 6.01)	3.51 (0.06, 216.35)	1.18 (0.02, 59.55)	**QIG**	3.01 (−2.79, 8.82)	**–**
1.75 (0.21, 14.74)	1.65 (0.46, 5.94)	1.62 (0.14, 19.33)	2.46 (0.02, 247.43)	4.76 (0.01, 2,047.50)	0.76 (0.16, 3.51)	57.81 (0.21, 16,233.03)	35.18 (0.14, 8,534.35)	1.70 (0.37, 7.85)	1.86 (0.14, 24.71)	1.67 (0.02, 113.09)	2.46 (0.23, 26.86)	4.90 (0.05, 488.86)	1.65 (0.08, 35.63)	1.39 (0.10, 20.45)	**RLX**	**–**
2.31 (0.02, 249.75)	2.18 (0.03, 144.57)	2.14 (0.02, 236.73)	3.26 (0.01, 1,597.30)	6.30 (<0.01, 9,718.97)	1.00 (0.02, 51.42)	76.50 (0.07, 8,3336.72)	46.55 (0.05, 45,096.91)	2.25 (0.03, 163.24)	2.45 (0.02, 295.34)	2.21 (0.01, 739.13)	3.26 (0.03, 387.50)	6.49 (0.01, 3161.95)	2.18 (0.01, 336.63)	1.85 (0.01, 256.16)	1.32 (0.02, 90.86)	**SSRI**

ACU, acupuncture; ATC, attention control; BT, behavioral treatment; BZD, benzodiazepines; CBT, cognitive behavioral therapy; EDU, sleep education; EXR, exercise; MTN, melatonin; PSQI, the Pittsburgh Sleep Quality Index; QIG, qigong; RLX, relaxation; SSRI, selective serotonin reuptake inhibitor; WLT, wait-list.

The table shows the acceptability as drop-outs for any reasons (lower left portion) and effectiveness as PSQI total score (upper right portion). Interventions are reported in order of alphabet. In case of acceptability, if the number of occurrences is zero, this is corrected by the augmented method to include in the analysis. That is, a default value of 0.5 is assigned to the intervention group and the control group instead of 0, which increase the sample size per treatment by 1. Effects are presented as odds ratio for drop-outs for any reasons and standardized mean difference for PSQI total score. The results bolding and underlined meant it had statistical significance, while only bolding results meant it had borderline significance. Comparisons between treatments should be read from left to right. The cell where the row of one treatment and the column of the other treatment meet shows the estimated effect size. In the case of effectiveness, if the mean difference is <0, it means that the effectiveness of the column treatment is better. In the case of acceptability, if the odds ratio is <1, it means that the acceptance of row treatment is better.

benzodiazepines combined with CBT (SMD 1.65, 95% CI 1.15 to 2.15), and (13) **acupuncture combined with sleep education** vs. sleep education (SMD −2.25, 95% CI −2.87 to −1.63) in awake duration (min) (**Supplementary Table 33**).

Comparative Acceptability

Drop-Outs for Any Reasons (Primary Outcome)

NMA

A total of 17 interventions were analyzed for the NMA for drop-outs for any reason (**Figure 4**). The consistency model could be accepted (p-value of testing for inconsistency = 0.9993, of node-splitting test = 0.786 to 1.000). According to the netleague table presenting the comparative acceptability of treatments, there was no statistically significant head-to-head comparison. In most comparisons, the 95% CI was very wide, which is thought to be due to the very small number of events (**Table 2**, **Supplementary Figures 12–18**, **Supplementary Table 29**).

Pair-wise meta-analysis

In most studies, there were no drop-out cases. No significant differences were found between the groups in the pair-wise meta-analysis (**Supplementary Table 34**).

Drop-Outs for AEs (Secondary Outcome)

NMA

A total of 15 interventions were analyzed for the NMA for drop-outs for AEs. The consistency model could be accepted (p-value of testing for inconsistency = 1.0000, of node-splitting test = 0.980 to 1.000). According to the netleague table presenting the comparative acceptability of treatments, there was no statistically significant head-to-head comparison. In most comparisons, the 95% CI was very wide, which is thought to be due to the very small number of events (**Supplementary Figures 19–25**, **Supplementary Table 30**).

Pair-wise meta-analysis

In most studies, there were no drop-out cases. No significant differences were found between the groups in the pair-wise meta-analysis (**Supplementary Table 35**).

Safety

Incidence of AEs (Secondary Outcome)

For the incidence of AEs, quantitative synthesis was judged to be inadequate because the number of AEs and the number of patients experiencing AE were mixed. There were 10 studies (43, 45, 47, 48, 51, 52, 63–65, 69) that reported the incidences of AEs. Among them, five (45, 47, 48, 51, 69) reported no AEs, while one (52) only reported some dry mouth occurred in estazolam group, without noting the exact number of episodes. In Song et al. (43), there were 18 cases of dry mouth, 16 cases of constipation, five cases of nausea, four cases of excessive sweating, and three cases of dizziness or mild headache occurred in paroxetine groups (n = 48), while there were no AEs in the acupuncture combined with relaxation group (n = 48). In Chen et al. (63), there was one case of narcolepsy, one case of dizziness, one case of fatigue, and one case of dry mouth in the alprazolam group (n = 30), while there were no AEs in the acupuncture group (n = 30). In Mo (64),

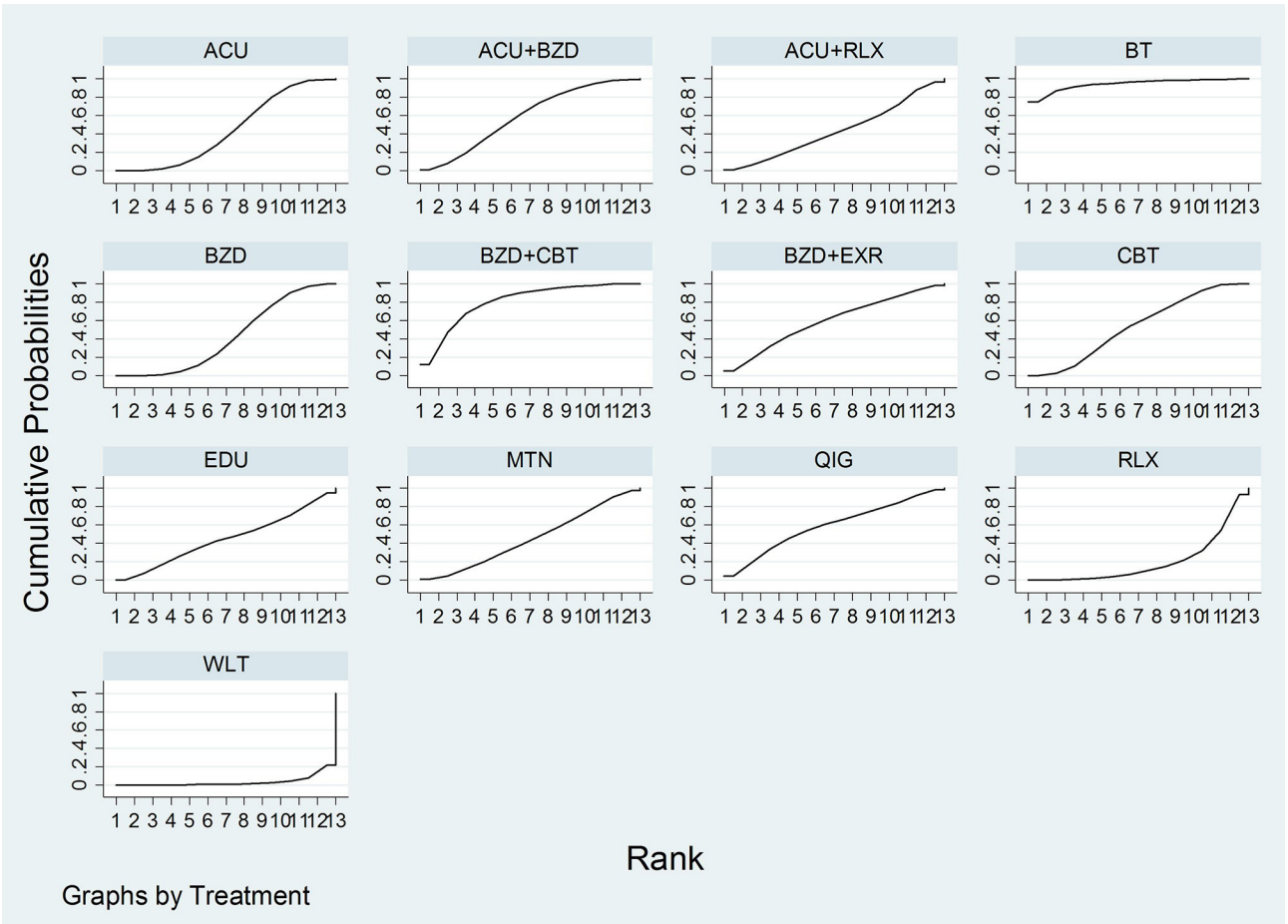

FIGURE 3 | SUCRA for PSQI total score. ACU, acupuncture; BT, behavioral treatment; BZD, benzodiazepines; CBT, cognitive behavioral therapy; EDU, sleep education; EXR, exercise; MTN, melatonin; QIG, qigong; RLX, relaxation.

there was one case of ecchymoma in each of the two acupuncture groups (both, $n = 27$), while there were two cases of dry mouth, two cases of fatigue, two cases of day sleepiness, and one case of both dry mouth and fatigue occurred in the estazolam group ($n = 29$). In Yuan et al. (65), there was one case of mild dizziness and one case of stomach discomfort in the acupuncture group ($n = 30$), while there were two cases of mild dizziness and one case of fatigue in the estazolam group ($n = 30$).

Publication Bias

To assess publication bias, network funnel plots without reference intervention of primary outcomes were made as follows. In the PSQI total score, there was a pronounced outlier on the left side (**Supplementary Figure 26**), and sensitivity analysis was performed excluding this outlier, Weng and Liao (46). As a result, the removal of this outlier did not significantly affect the results of the study. In the drop-outs for any reason analysis, no cue of obvious asymmetry was observed; therefore, the probability of publication bias was considered to be low (**Supplementary Figure 27**).

Quality of Evidence

The GRADE levels of NMA for the PSQI total score were mostly moderate to low (**Supplementary Table 36**). The GRADE levels of NMA for drop-outs for any reason were generally low (**Supplementary Table 37**). The main reasons for downgrading were the risk of bias and imprecision of the meta-analyzed results.

DISCUSSION

This systematic review with NMA conducted a comprehensive search to assess the comparative effectiveness and acceptability of non-pharmacological interventions on insomnia in the elderly. As a result, a total of 28 RCTs were included in this review.

Summary of Evidence

In terms of methodological quality, randomizations were performed properly in most of the included studies. However, the absence of blinded participants and personnel in most included studies could have led to overestimation of the effect sizes, although this can be considered as an inevitable limitation given the basic characteristics of non-pharmacological interventions.

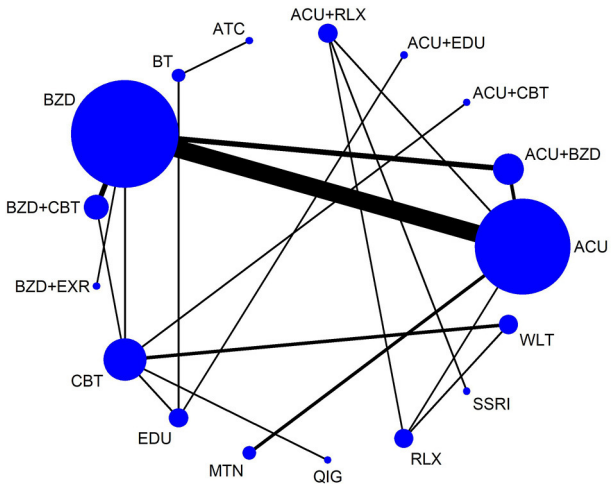

FIGURE 4 | Network map for drop-outs for any reason. ACU, acupuncture; ATC, attention control; BT, behavioral treatment; BZD, benzodiazepines; CBT, cognitive behavioral therapy; EDU, sleep education; EXR, exercise; MTN, melatonin; QIG, qigong; RLX, relaxation; SSRI, selective serotonin reuptake inhibitor; WLT, wait-list.

In addition, the lack of assessor blinding in most studies suggests a risk of expectation bias and should be addressed in further trials. Proper randomization and verification of statistical similarity between groups at baseline (other bias) in the included studies support the similarity assumptions in NMA. In general, the overall quality of the RCTs included in this review was low to moderate, leading to low quality of evidence for NMA findings. High-quality studies were rare, and there was some risk of overestimation associated with a lack of blinding.

(1) In terms of comparative effectiveness for the PSQI total score, it was found that the following interventions were more effective than wait-list: acupuncture, acupuncture combined with benzodiazepines, BT, benzodiazepines, benzodiazepines combined with CBT, and CBT with statistical significance, and acupuncture combined with relaxation, benzodiazepines combined with exercise, melatonin, and qigong with borderline significance. Some interventions showed significantly better effectiveness than CBT or benzodiazepines based on pair-wise meta-analysis: benzodiazepines ($p < 0.00001$), benzodiazepines combined with CBT ($p = 0.005$) and qigong ($p = 0.04$) compared to CBT, and acupuncture combined with benzodiazepines ($p < 0.00001$), benzodiazepines combined with CBT ($p = 0.005$), and benzodiazepines combined with exercise ($p < 0.00001$) compared to benzodiazepines. Interestingly, in general, combined treatments tended to be more effective than monotherapy. In other words, benzodiazepines combined with CBT and acupuncture combined with benzodiazepines showed overall superior effectiveness in the results of NMA as well as of pair-wise meta-analysis. For the polysomnography data, similar to the results of the PSQI total score, the combined treatment showed overall superiority for some outcomes of sleep architecture. (2) In terms of comparative acceptability, NMAs with 17 interventions and 15 interventions were performed for drop-outs for any reason and any AEs. In both cases, however, the number of events occurred was very small, which did not produce meaningful results, including statistical significance in either NMA or pair-wise meta-analysis. (3) In terms of comparative safety, heterogeneity of the reported safety profiles made quantitative synthesis impossible. Although there have been few reported cases of AE, the incidence of AEs during pharmacological treatments, including estazolam, paroxetine, and alprazolam, tended to be higher than that of acupuncture. Gastrointestinal AEs such as dry mouth, constipation, and nausea were most common in the pharmacological treatment groups.

Subgroup analysis based on disease duration was planned, and the disease durations were longer than at least 3 months in all included studies that specified participants' baseline disease duration. Therefore, subgroup analysis, according to the disease duration, could not be performed. Moreover, sensitivity analyses based on the methodological quality of included RCTs were planned; however, only one study (55) was rated to be a high-quality RCT, having a low risk of bias in all domains. Given the nature of non-pharmacological interventions, even though high risks of blinding of participants and personnel domains were allowed, none of the studies rated the risks of bias in the remaining domains low. Therefore, sensitivity analyses, according to the methodological quality, could not be performed. According to the result of the network funnel plot of PSQI total score, significant asymmetry was found, and sensitivity analysis was performed to remove the outliers (46). In the sensitivity analysis to remove outliers, except for the significant difference in the acupuncture vs. wait-list being changed to borderline significance in NMA, no change was found in the remaining significant differences, compared to before removal of the outlier.

The prescription of benzodiazepines is increasing today, and the important thing is that this tendency is more pronounced in primary care than in psychiatrists (33, 70). However, the American Geriatrics Society does not recommend the use of benzodiazepines or non-benzodiazepine hypnotics in the elderly (18), as this vulnerable group may experience greater harms including fatal side effects such as falls and hip fractures (17–19). However, further evidence-based strategies still need to be established for discontinuing benzodiazepines in the elderly and some alternatives to complement these drugs (71). In this sense, to overcome the limitations of pharmacotherapies, especially of benzodiazepine in the elderly, a recent systematic review also analyzed the efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medications in elderly individuals with insomnia (72). The authors analyzed 24 clinical studies, including 21 RCTs, and concluded that limited evidence suggests suvorexant, doxepin, and possibly ramelteon may be effective and safe pharmacological alternatives for treating elderly individuals with insomnia (72). As the authors excluded non-pharmacological interventions at the study selection process, the findings of the study could be complementary to the results of this review.

In summary, this review found some comparatively effective strategies, especially combined non-pharmacological treatments, for insomnia in the elderly, while it did not find any significant comparative advantage in terms of acceptability. In the safety

profile, there was limited evidence that acupuncture is overall safe. However, due to the methodological limitations of the included studies, the inability to conduct sensitivity analysis on high-quality RCTs is a limitation of the reliability of the results. In particular, strict allocation concealment and assessor blinding seem to be a major issue for further researches in this area to enhance their methodological quality.

Clinical Interpretation

The most interesting finding of this review was that combined treatments were effective strategies for treating elderly individuals with insomnia in terms of overall effectiveness. In other words, combined treatments such as acupuncture combined with benzodiazepines and benzodiazepines combined with CBT-I showed excellent effectiveness in improving insomnia in the elderly. Based on the meanrank and SUCRA, the priorities of combined treatments, including benzodiazepines combined with CBT-I, acupuncture combined with benzodiazepines, and benzodiazepines combined with exercise, were generally confirmed. Moreover, pair-wise meta-analyses of PSQI total score and polysomnography data also confirmed the superiority of combined treatments for sleep quality and sleep architecture, respectively.

The other notable result was the comparative effectiveness of CIM approaches on elderly individuals with insomnia. Especially in the case of acupuncture, it was an efficient adjuvant strategy for benzodiazepines to improve their effectiveness. None of the included studies used acupuncture combined with CBT-I. However, some previously published studies suggest that CBT-I, known as the first-line treatment for insomnia, and acupuncture may have different therapeutic characteristics. These studies have found that acupuncture showed weaker effects of improving insomnia itself compared to CBT-I, but showed an excellent effect in improving accompanying conditions, especially pain and pain-related insomnia (73–76). Although acupuncture may still need more solid evidence to be recommended for routine treatment of elderly individuals with insomnia (77), the treatment seems to be useful as an adjuvant strategy to complement conventional treatments. Given that benzodiazepines should be used very carefully in the elderly (18), these drugs in combination with acupuncture may increase the effectiveness. This interaction could possibly reduce the dose of benzodiazepines. Also, given the high prevalence of pain in the elderly (78), acupuncture may have the potential to improve both pain-related insomnia and pain condition in this population.

Another interesting finding is that BT was ranked the most effective in the SUCRA of PSQI total score. According to the results of NMA, BT was significantly superior to wait-list as well as sleep education and relaxation in improving PSQI total score and tended to be superior to benzodiazepines and CBT with borderline significance. This finding was based on the results of a 4-week RCT comparing multicomponent behavioral treatment and sleep education (47). Two other studies (45, 58) also used multicomponent behavioral treatments, but they were not included in this analysis because they did not report the PSQI total score. Buysse et al. (47) described the BT, brief behavioral treatment for insomnia (BBTI), which focuses on behavioral elements of insomnia treatment rather than cognitive components compared to CBT-I. They also explain that because CBT-I is limited by the number of specialty-trained clinicians and by its duration or cost of treatment, a simpler and more acceptable BBTI can be more efficient and effective. Although the PSQI total score was not reported, McCrae et al. (45) also found that the BT group showed significant improvements compared to the sleep education group in sleep diary-measured SOL ($p < 0.01$) and sleep efficiency ($p < 0.01$), after 4 weeks of treatment. Moreover, Chan et al. (58), which used BBTI for 4 weeks, found that the BT group showed significant improvements compared to the attention control group in sleep diary-measured sleep variability outcomes including sleep efficiency ($p < 0.01$) and TST ($p = 0.03$), and actigraphy-measured sleep variability outcomes including SOL ($p = 0.01$) and sleep efficiency ($p = 0.03$). Although there is still little evidence to conclude, BT, which removes cognitive components from CBT-I and emphasizes behavioral elements, is worth comparing to CBT-I, which is considered as the first-line treatment of elderly individuals with insomnia. In particular, in older people with cognitive impairments such as dementia, BT with less cognitive components may be more effective, but this is still a hypothesized effect. It is expected that further studies will be conducted to compare the effectiveness and acceptability of BT and CBT-I according to the characteristics of patients with insomnia. Regarding cognitive impairments, although not included in the outcomes of interest, one of the included studies reported changes in cognitive function using the Montreal Cognitive Assessment (MoCA) (68). In this study (68), acupuncture for 4 weeks was associated with significantly improved total MoCA scores as well as spatiotemporal/executive ability, attention, and delayed memory compared to estazolam (all $p < 0.05$). However, since only one study reported changes in cognitive function, the reliability of the findings was low.

Lastly, the difference between BT and sleep education in the pair-wise meta-analysis of polysomnography data should be pointed out. The results are based on one RCT (47) with 4 weeks of treatment and 3 months of follow-up. After treatment duration (at the fourth week), compared with the sleep education group, the BT group showed better results in WASO and sleep efficiency, but showed significantly inferior results in SOL and TST. Buysse et al. (47) interpreted these results as being influenced by the initial sleep restriction. In other words, due to the initial strict sleep restriction, the TST temporarily decreased while sleep efficiency increased. As this sleep restriction was relaxed, the SOL and TST of the BT group were improved at the 6-month follow-up.

Based on the effectiveness, acceptability, and safety data found in this review, when treating elderly individuals with insomnia in clinical practice, it may be helpful to combine two or more treatments, and individual treatment strategies can be established based on the patient's preferences and accompanying symptoms. For example, acupuncture may be an important treatment component for patients with insomnia and pain or with poor cognitive status. CBT-I may be difficult to apply to these individuals. Moreover, BT without the cognitive component may also be an alternative in elderly individuals with insomnia who suffer from such cognitive difficulties. However, since the treatment may reduce TST in a short period of 4 weeks or fewer,

it is necessary to consider other strategies or provide sufficient explanations before treatment in cases where compliance is a concern. Although not found in our review, adherence to treatments in elderly patients may be related to factors such as disease-related knowledge, health literacy, cognitive function (79), and frailty syndrome (80). Therefore, compliance with non-pharmacological treatment, pharmacological treatment, or combined treatment strategies in elderly patients with insomnia require further investigation.

Strengths and Limitations

NMA is a valuable meta-analysis method that allows the selection of the most efficient options among several treatment options. Although non-pharmacological treatments are very important for elderly individuals with insomnia owing to the limited availability of pharmacotherapy in comparison to adults with insomnia (18), to the best of our knowledge, no attempt has been made to analyze the comparative effectiveness of the different non-pharmacological treatments available, until recently. This review has the advantage of using NMA methodology to derive the comparative advantage of several non-pharmacological treatments in terms of effectiveness, acceptability, and safety in elderly individuals with insomnia based on current evidence. The results can help clinicians, patients, and policymakers to make informed decisions as to the optimal non-pharmacological treatments for the treatment of insomnia in the elderly.

However, several limitations should be pointed out. First, the number of RCTs included is small compared to the interventions covered in this review. This leads to the limitation that most of the results, especially in pair-wise meta-analysis results, are based on one or two RCTs. This may indicate a lack of relevant trials on this issue. Indeed, the issues of "older adults" and "non-pharmacological treatments" seem to have received less attention in research compared with "pharmacological treatments" (81–83). Elderly individuals with insomnia, however, carry huge medical and social burdens (10–16). It is therefore urgent to support clinical trials of non-pharmacological treatments for elderly individuals with insomnia at the social and/or national levels. Second, unlike the protocol in this study, SMD, rather than the mean difference (MD), was used for continuous outcomes. This is because the consistency model between some comparisons was not established in the inconsistency test of the PSQI global score. Instead, SMD was used. Here, a consistency model was established between all comparisons. In addition, in the meta-analysis, SMD has a generalizability advantage over MD, so it may be a better unit for this review (31). Third, the various methods of acupuncture were not considered in the analysis of this review. This review found that acupuncture may be a promising adjuvant for elderly individuals with insomnia. However, different methods of acupuncture can also have different effects on insomnia. For example, a recent NMA with Bayesian analysis analyzed 52 RCTs and concluded that scale acupuncture is most effective for treating primary insomnia (84). Therefore, in future studies, expert consensus about the most effective acupuncture methods for treating elderly individuals with insomnia in clinical settings should be derived, and acupuncture trials based on the standardized acupuncture methods should be conducted. Fourth, only nine RCTs (42, 47, 48, 52, 55, 56, 58, 62, 64) conducted follow-up and only five (42, 47, 48, 55, 62) of them reported long-term follow-up data over 6 months. Like in the case of Buysse et al. (47), the sleep improvement effect of BT may need to be observed in the long-term. Moreover, CBT-I, which corrects dysfunctional beliefs about sleep itself, may have different effects in the long-term than other non-pharmacological interventions, considering its mechanism (e.g., prevent relapse of insomnia) (85, 86). On the other hand, recent research indicated that the cognitive effects of CBT-I are not significantly associated with improvements in insomnia symptoms (87). Therefore, these issues need to be further clarified through long-term follow-up trials to determine which factors, including cognitive elements of CBT-I, affect long-term insomnia symptoms. Fifth, in terms of acceptability and safety, there were not enough cases reported in the original RCT included in this review to conclude. This may suggest that non-pharmacological treatments were generally acceptable and safe; however, it also may indicate potentially poor reporting in drop-out and safety profiles among original RCTs. Given the importance of these outcomes, especially in older people, future studies should report more stringent drop-out and AEs occurrences. Sixth, the overall quality of the RCTs included in this review was low to moderate, particularly at risk of some overestimation due to lack of blinding procedures. Due to the nature of non-pharmacological interventions, the lack of blinding of participants and personnel seems inevitable. However, the rigorous implementation of assessor blinding can be an important quality assurance procedure that addresses the problem of overestimation. Future studies should address efforts to minimize the risk of overestimation, with particular emphasis on assessor blinding. Seventh, in this review, pharmacological treatments, including benzodiazepines, were considered in assessing the relative effectiveness of non-pharmacological treatments of interest. Since this review aimed to investigate the comparative effectiveness of some non-pharmacological treatments or combination treatment strategies for elderly insomnia, the findings should not be interpreted to indicate the effectiveness and safety profile of pharmacological treatment alone. Finally, cost-effectiveness is an important area of health care, especially CBT-I, which has barriers to use due to the shortage of trained practitioners and its duration and/or cost of treatment (86). The results of this review have shown promising results for a CIM modality, acupuncture. Given that the cost-effectiveness of this treatment has been demonstrated in various clinical conditions (88–90), the cost-effectiveness of interventions, including acupuncture for elderly individuals with insomnia, should be further investigated.

CONCLUSIONS

In terms of effectiveness in PSQI total score, compared to wait-list, acupuncture, acupuncture combined with benzodiazepines, BT, benzodiazepines, benzodiazepines combined with CBT, and CBT showed superior benefits. Importantly, combined treatments, including benzodiazepines combined with CBT or with acupuncture, were generally superior to other monotherapies. In terms of acceptability,

there was not enough data to conclude. In terms of safety, there was limited evidence that acupuncture is overall safe than pharmacological interventions. However, most of the RCTs included had methodological problems, especially related to the lack of blinding procedure, suggesting the risk of overestimation of their effect size. Therefore, future studies should address efforts to minimize the risk of overestimation, with particular emphasis on the assessor blinding procedure.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The study was conceptualized by C-YK. C-YK and BL searched and selected the trials, and extracted, analyzed, and interpreted the data. C-YK drafted the manuscript. MC, T-HK, B-HJ, SC, and JK helped with the study design and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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frontiers in Neurology

ORIGINAL RESEARCH
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Accuracy of Actigraphy Compared to Concomitant Ambulatory Polysomnography in Narcolepsy and Other Sleep Disorders

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Actigraphy provides longitudinal sleep data over multiple nights. It is a less expensive and less cumbersome method for measuring sleep than polysomnography. Studies assessing accuracy of actigraphy compared to ambulatory polysomnography in different sleep-disordered patients are rare. We aimed to compare the concordance between these methods in clinical setting. We included 290 clinical measurements of 281 sleep laboratory patients (mean age 37.9 years, 182 female). Concomitant ambulatory polysomnography and actigraphy were analyzed to determine the agreement in patients with obstructive sleep apnea, narcolepsy, periodic leg movement disorder, hypersomnia, other rarer sleep disorders, or no organic sleep disorder. Bland-Altman plots showed excellent accuracy, but poor precision in single night results between the two methods in the measurement of sleep time, sleep efficiency, and sleep latency. On average, actigraphy tended to overestimate sleep time by a negligible amount, −0.13 min, 95% confidence interval [−5.9, 5.6] min in the whole sample. Overestimation was largest, −12.8 [−25.1, −0.9] min, in patients with obstructive sleep apnea. By contrast, in patients with narcolepsy, actigraphy tended to underestimate sleep time by 24.3 [12.4, 36.1] min. As for sleep efficiency, actigraphy underestimated it by 0.18 [−0.99, 1.35] % and sleep latency by 11.0 [8.5, 13.6] min compared to polysomnography. We conclude that, in measuring sleep time, actigraphy is reasonably reliable and helpful to be used for a week or two to exclude insufficient sleep in patients with the suspicion of narcolepsy. However, the effectiveness of actigraphy in determining sleep seems to decrease in subjects with low sleep efficiencies.

Keywords: actimetry, sleep quantity, diagnostics, central disorders of hypersomnolence, insufficient sleep

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INTRODUCTION

Polysomnography (PSG) in a sleep laboratory has remained the gold standard in measuring the quality of sleep for decades. Technological advancements have refined the method throughout the years, but also produced alternative methods for sleep measurement that could have many advantages over PSG in terms of price and ease of usability in the habitual sleep environment (1).

One of the advantages of actigraphy (ACG) is that it provides longitudinal sleep data over multiple nights. ACG is less expensive, less cumbersome, and easier to use than PSG. ACG is clearly more accurate in estimating sleep time than sleep logs (2). It is probably the most widespread tool for assessing circadian rhythm sleep-wake disorders (2). In addition, its use in measuring different properties of sleep has increased. In a recent clinical practice guideline, American Academy of Sleep Medicine (AASM) introduced several recommendations about the use of ACG in the assessment of patients suspected with central disorders of hypersomnolence, insufficient sleep syndrome, sleep-disordered breathing, or insomnia disorders (3). These recommendations include the use of ACG integrated with home sleep apnea test devices to estimate total sleep time during recording in patients suspected of sleep apnea, and to monitor total sleep time prior to multiple sleep latency test (MSLT) in patients suspected of narcolepsy (3).

However, compared to PSG, ACG has been reported to be less reliable in recognizing short periods of wake and to overestimate measured sleep times (4). Based on previous studies, the validity of ACG somewhat decreases with the decline of sleep efficiency (2, 5, 6). An essential problem with the field is that ACG algorithms of different manufacturers lack shared technical solutions and terms, precluding direct comparisons (7). Quantitative criteria for the assessment of other aspects of sleep than circadian rhythm by ACG were missing for a long time (8–10).

The recent review by AASM set the clinical significance thresholds for the maximum allowable mean difference and the maximum allowable 95% confidence interval (CI) in sleep time between ACG vs. PSG to 40 min among patients with central disorders of hypersomnolence (2). Of note, the task force identified only one study about the concordance of ACG and PSG prior to MSLT among subjects with the suspicion of narcolepsy or hypersomnia (11), and the threshold was set to the same as in those diseases with more available ACG data, like insomnia and insufficient sleep syndrome. In addition, the threshold in sleep efficiency was set to 5% and in sleep latency to 30 min, but these limits were given only for insomnia patients (2).

Only a limited number of actigraphic studies with small number of subjects has been conducted with patients with central disorders of hypersomnolence. Over a decade ago, a study examined the concordance of ACG and PSG prior to MSLT among subjects with suspicion of narcolepsy or hypersomnia (11). Recently, effects of different sensitivity settings of actigraphy regarding its congruence with PSG among idiopathic hypersomnia patients were studied (12). In young operated patients with craniopharyngioma, in higher risk for narcolepsy, PSG, and ACG were also compared recently (13). Actigraphy in sleep apnea patients has been studied by several groups (8, 14–16).

According to ICSD-3, narcolepsy is divided to narcolepsy type 1 (NT1) or narcolepsy type 2 (NT2). NT1 is caused by a selective destruction of hypothalamic hypocretin-producing neurons, while the etiology of NT2 is unknown and usually not hypocretin-related. Patients with NT2 do not have cataplexy, but the other symptoms—excessive daytime sleepiness, disturbed sleep, and parasomnias—are shared in NT1 and NT2.

We aimed to compare the concordance of ACG and ambulatory PSG in subjects having excessive daytime sleepiness (EDS) or other sleep-related symptoms with or without organic sleep disorders to see if ACG is reliable in all diagnostic groups, with a special interest in narcolepsy.

Abbreviations: AASM, American Academy of Sleep Medicine; ACG, actigraphy; AHI, apnea-hypopnea index; AST, actual sleep time (in actigraphy); CCC, Lin's concordance correlation coefficient; CI, confidence interval; DSPS, delayed sleep phase syndrome; EDS, excessive daytime sleepiness; EEG, electroencephalography; ICSD-3, International Classification of Sleep Disorders, third edition; LoA, limit of agreement; MSLT, multiple sleep latency test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; PSG, polysomnography; RLS, restless legs syndrome; SE, sleep efficiency; SL, sleep latency; ST, sleep time; TST, total sleep time (in polysomnography).

METHODS

The Helsinki and Uusimaa Ethics Committee approved this study (7/2016). As the study was conducted based on documents completed during normally scheduled patient visits, no written informed consent was required.

Subjects

Initially, study material consisted of all consecutive concomitant ambulatory PSG and ACG recordings conducted at our sleep laboratory in routine clinical practice in the university hospital during 4.5 years, in total 314 recordings. Some of the PSGs failed and, consequently, we included 290 technically reliable enough sleep studies in the study material. Altogether, the data was gathered from 281 individual subjects with the remaining nine recordings being repeated measurements. Actigraphy recordings did not have any technical problems. Subjects were referred for suspicion of sleep-related breathing or movement disorders, central disorders of hypersomnolence, or parasomnias. The subjects were independent in activities of daily living and did not require the assistance of an aide.

Measurements

An Actiwatch (Cambridge Neurotechnology Ltd, Cambridgeshire, UK) or a MotionWare (CamNtech Ltd, Cambridge, UK) system were used as the ACG devices in this study. Of note, MotionWare system is the successor to Actiwatch made by the same manufacturer. Thus, all the parameters used in this study are identical, and comparable analysis settings were used. During the preceding afternoon, the subjects were carefully guided and prepared at the sleep laboratory for the ambulatory PSG and concomitant ACG and then sent home to sleep in their own beds for the night. The subjects would then return to the laboratory the next morning to return the equipment. In several cases, especially when a central disorder of hypersomnolence was suspected, the subjects were given the ACG device already a fortnight beforehand to be worn at all times so that their circadian rhythms and sleep time could also be evaluated over multiple nights. If there was no such suspicion, ACG was only studied one night, concomitantly with PSG.

The raw data from the ACG devices was processed using an analysis program provided by the manufacturer. The epoch length was 1 min. The definitions of the used ACG parameters were described in detail previously (17). As in PSG, sleep latency (SL) is the difference between bedtime and sleep start, and sleep efficiency (SE) is the percentage of time spent asleep between bedtime and get up time. Actual sleep time (AST) in ACG and total sleep time (TST) in PSG are analogous, both defined as the amount of sleep between sleep start and sleep end.

An Embla Titanium (Embla, Denver, CO, USA) ambulatory PSG system was used for the PSG measurements. Ambulatory PSG comprised six electroencephalography (EEG) derivations, two electro-oculography channels, submental muscle tonus, airflow by nasal pressure transducer, thoracoabdominal respiratory movements, pulse oximeter, body position, electrocardiogram, and electromyography from tibialis anterior muscles. PSG recordings were set to start about an hour before the subject intended to go to bed and to end well after their estimated get up time in the morning. At home, the subject wrote down the exact time for lights off and lights on and also marked them by pressing a button on the ACG device. Afterwards, the identical analyzed time for both PSG and ACG was the time from lights off to lights on. When central disorders of hypersomnolence were suspected and the subject had the MSLT the following day, they had to get up at least 1.5 h before the start of the test, while most of the subjects were able to sleep as long as they wanted. The PSG data was scored manually by medical specialists with experience in sleep scoring according to international criteria (18, 19).

Diagnostic Groups

Once the clinical examinations of a subject were complete and a diagnosis was set, the subject was categorized based on the diagnosed organic sleep disorder (if any). Narcolepsy was diagnosed according to ICSD-3 criteria (20). Those patients, who were diagnosed before 2014, were reclassified to NT1 or NT2 according to ICSD-3. Hypersomnia group comprised of idiopathic hypersomnia and other hypersomnia syndromes (ICD-10 code G47.1), and this diagnosis was set strictly according to ICSD-3 criteria (20). Obstructive sleep apnea (OSA) was diagnosed if the apnea-hypopnea index (AHI) had a value higher than 5 per hour. In addition, six patients with narcolepsy also had mild OSA, three had moderate OSA, and one had severe OSA as a co-morbidity, but as it did not affect the results, they were classified to the narcolepsy group. The slight difference in defining AHI according to older and newer hypopnea criteria did not affect the results (18, 19).

Periodic limb movement disorder (PLMD) was diagnosed if the periodic limb movement index during sleep was higher than 15 per hour. Of note, the diagnosis of PLMD cannot be set in the context of any other sleep disorder (20) and our subjects were categorized to this group only if they did not have OSA, narcolepsy, or hypersomnia. To be precise, some subjects in this group had restless legs syndrome (RLS) symptoms while awake together with periodic leg movements while sleeping and their clinical diagnosis was RLS, whereas subjects without RLS symptoms had PLMD (20). We combined these subgroups in the study and focused on PSG findings.

The "Others" group included six patients with NREM parasomnias, three with REM sleep behavior disorder, and two with irregular sleep-wake rhythm disorder. Subjects in the "No sleep disorder" group experienced various degrees of tiredness and/or sleepiness, but no sleep apnea, PLMD, narcolepsy, or hypersomnia were found in the sleep studies. Almost all of them slept objectively too little, and probably also the rest had need for longer sleep than they got. Some had mild depressive symptoms or stress, but no clinical diagnosis of depression or anxiety disorder.

Statistical Analyses

The statistical analysis of the data was carried out with IBM SPSS® Statistics 24.0 (IBM, Armonk, NY, USA), and Stata/SE 16.1 for Mac (StataCorp, College Station, TX, USA). The normality of variables were tested by inspecting the skewness and kurtosis from histograms and Shapiro-Wilk tests. To evaluate agreement between the two methods, Bland-Altman plots were drawn (21, 22). Due to non-parametric distribution of the majority of mean differences, quintile method and logarithmic transformation as proposed by Bland and Altman were used to determine additional limits of agreement (23, 24). To account for the proportional bias, Bland-Altman plots were adjusted for trend and regression lines as well as Passing-Bablok diagrams are shown (25). Mean differences were also plotted against PSG measures since the PSG is considered a golden standard in these measures. Lin's concordance correlation coefficients (CCC) with 95% CI using z transformation were calculated to investigate association (26).

RESULTS

The study material comprised actigraphy and PSG recordings done to 281 subjects. Their ages varied between 16 and 90 years (mean 37.9 y) and 62.8% were female. In addition to first-time recordings, PSG was done twice to nine subjects. In six of those cases, the reason was a necessary repetition of an MSLT. In the three remaining cases, the repetition was done to clarify a finding after some minor technical problems. When analyzed separately, the results in the group of repeated recordings were consistent with the other results, and as our aim was to analyze concordance between the methods in different recordings, not subjects, we decided to include those repeated recordings, as well. Altogether, 290 recordings were included in this study. The distribution of diagnosed sleep disorders, which are described in detail in the methods section, is summarized in **Table 1**.

Mean differences between the ACG and PSG measures followed non-parametric distributions (Shapiro-Wilk $P < 0.05$) in the whole sample and in other subgroups than narcolepsy, NT1, NT2, and hypersomnia. Histograms demonstrated high kurtosis around zero with multiple outliers, which is seen also in Passing-Bablok plot (**Figure 1**). An extreme outlier e.g., demonstrated a subject with history of Parkinson's disease, restless legs, disturbed nocturnal sleep with only 80 min of total sleep in PSG and 386 min in ACG. Outliers were kept in the

TABLE 1 | Diagnostic groups and subgroups.

Diagnostic groups and *subgroups*	*N*	Female	Male	Mean age (SD), years
OSA	102	48	54	48.1 (14.2)
Narcolepsy	42	24	18	25.7 (9.1)
NT1	*37*	*24*	*13*	*25.7 (9.5)*
NT2	*5*	*0*	*5*	*26.1 (5.1)*
PLMD	28	24	4	39.4 (11.9)
Others (parasomnia)	11	4	7	31.8 (12.0)
Hypersomnia	6	4	2	35.3 (19.3)
No organic sleep disorder	101	78	23	33.0 (11.2)
All subjects	290	182	108	37.9 (14.8)

Number, gender distribution, and age on average (standard deviation) in all diagnostic groups and narcolepsy subgroups (in italics). OSA, obstructive sleep apnea; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PLMD, periodic limb movement disorder.

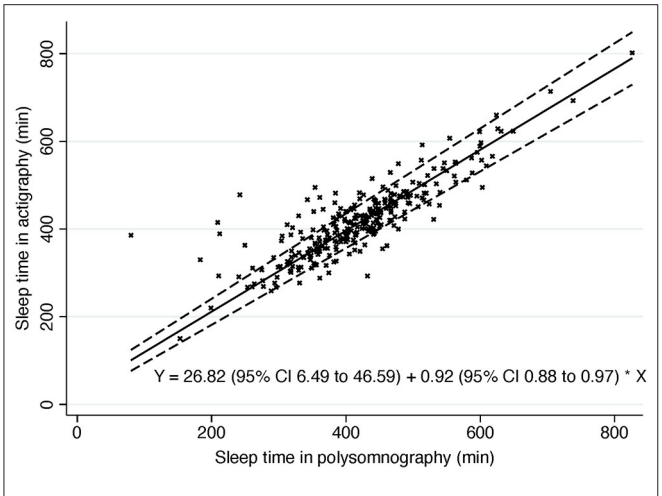

FIGURE 1 | Passing-Bablok of sleep time. Dashed line, 95% confidence interval. Solid line, Passing-Bablok regression line. Y, Passing-Bablok fit.

sample, and non-parametric methods were used as suggested by Bland and Altman (23). Logarithmic transformation did not change the distribution of mean differences.

Sleep Time

A priori, we set the clinical significance threshold for mean difference in sleep time to ± 40 min based on the AASM guidelines (2, 3). The mean difference in the whole sample was only −0.13 min (95% CI −5.9 to 5.6) indicating very low bias and high accuracy (**Table 2**). The mean differences were also in the reference area in all the subgroups. Of all the individual measurements, 70.7% were in this AASM reference area.

The Passing-Bablok regression of sleep time showed some but rather low proportional bias in sleep time measures in ACG compared to PSG (slope estimate 0.92; 95% CI 0.88, 0.97) (**Figure 1**). In other words, there is a trend for actigraphy to overestimate sleep time especially when sleep time is short in PSG with few extreme outliers (**Figure 2**).

TABLE 2 | Concordance of sleep time between actigraphy and ambulatory polysomnography.

Diagnostic groups and *subgroups*	N	Mean difference [95% CI], min	Inside AASM limits, %	LoA, min	CCC [95% CI]
OSA	102	−12.8 [−25.1, −0.5]	61.8	−135.75, 110.14	0.732 [0.633, 0.808]
Narcolepsy	42	24.3 [12.4, 36.1]	69.0	−50.26, 98.78	0.673 [0.490, 0.800]
NT1	*37*	*27.3 [14.1, 40.4]*	*64.9*	*−50.19, 104.73*	*0.655 [0.453, 0.823]*
NT2	*5*	*2.0 [−7.4, 11.4]*	*100*	*−12.86, 16.86*	*0.983 [0.849, 0.998]*
PLMD	28	−0.55 [−20.8, 19.7]	71.4	−102.68, 101.57	0.823 [0.658, 912]
Others (parasomnia)	11	23.5 [−7.3, 39.7]	81.8	−23.56, 70.60	0.962 [0.877, 0.988]
Hypersomnia	6	−0.75 [15.4, 16.9]	100	−29.33, 30.83	0.990 [0.933, 0.999]
No organic sleep disorder	101	0.019 [−7.1, 7.1]	77.2	−70.26, 70.30	0.923 [0.889, 0.946]
All subjects	290	−0.13 [−5.9, 5.6]	70.7	−97.49, 97.23	0.845 [0.810, 0.875]

Mean differences and their 95% confidence intervals in sleep time between ACG and PSG, the proportion of the differences being inside the clinical significant thresholds of AASM, calculatory limits of agreement, and Lin's concordance correlation coefficients and their 95% confidence intervals ($P < 0.05$ in all) across all diagnostic groups and narcolepsy subgroups (in italics). CI, confidence interval; AASM, American Academy of Sleep Medicine; LoA, limits of agreement; CCC, Lin's concordance correlation coefficient; OSA, obstructive sleep apnea; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PLMD, periodic leg movement disorder.

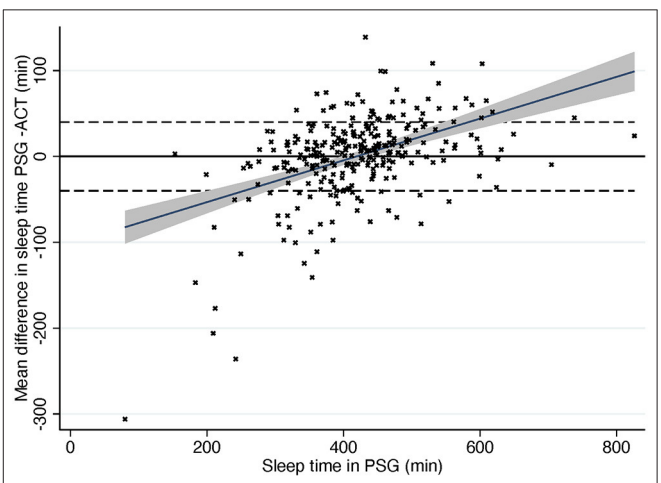

FIGURE 2 | Difference in sleep time compared to total sleep time in PSG. Dashed line, ± 40 min according to AASM criteria. Gray area, 95% confidence interval for regression line. Solid line, mean difference. PSG, polysomnography; ACG, actigraphy.

While being very accurate, Bland-Altman plot showed rather wide (−97.49, 97.23) limits of agreement (LoA). Non-parametric distribution and outliers increase limits of agreement that are based on the standard deviation of the bias. In the subgroups

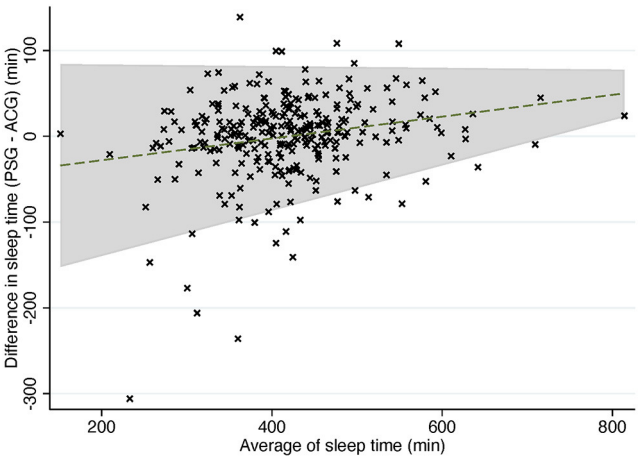

FIGURE 3 | Trend Bland-Altman plot: difference in sleep time compared to average of sleep time in PSG and ACG. Dashed line, mean difference. Gray area, 95% confidence interval for regression line. PSG, polysomnography; ACG, actigraphy.

where mean differences followed normal distribution (NT1, NT2, narcolepsy, and hypersomnia) LoA were clearly narrower. After removing 5% of the extreme mean differences from both ends—quintile method for non-parametric distributions as suggested by Bland and Altman (23)—LoA in the whole sample were −64.49 (95% CI −70.8, −58.1) and 52.24 (95% CI 46.0, 58.5).

In trend Bland-Altman plot, the mean difference was −53.26 + 0.13*average, and LoA ± 2.46*(56.49–0.06*average) (**Figure 3**).

As for concordance correlation, CCC showed high concordance in groups "no organic sleep disorder" and "others (parasomnia)" and also in smaller hypersomnia and NT2 subgroups but poor to moderate in other analyses (**Table 2**). In total sample, CCC was 0.8454 (95% CI 0.810 to 0.875) which can be considered as moderate.

Sleep Efficiency

Table 3 depicts the difference of average sleep efficiencies measured by PSG and ACG, i.e., SE in PSG—SE in ACG. Overall, ACG tended to underestimate SE by a very small amount, 0.18, 95% CI [−0.99, 1.35] % in the whole sample. The underestimation was larger, 6.24 [3.42, 9.05] %, in the NT1 subgroup than in the NT2 subgroup. The underestimation was also clear in the others group with mainly patients with parasomnias. By contrast, in patients with OSA, ACG tended to overestimate SE.

AASM set the clinical the clinical significance thresholds for the maximum allowable 95% CI in sleep efficiency between ACG and PSG to 5% (2). In total, only 55.5% of the measurements were inside these limits. All the CCCs were poor, except in the NT2 group.

Sleep Latency

As is seen in **Table 4**, ACG seems to underestimate sleep latency in general, overall on average 11.0, 95% CI [8.5, 13.6] min. The underestimation was the largest, 16.8 [11.1, 22.4] min, in the OSA group. The underestimation was also clear among subjects with no organic sleep disorders. The sole exception to this underestimation by ACG was the narcolepsy group in which the actigraphic SL estimates were very close—on average only 0.049 min longer—to SL in PSG.

AASM set the clinical significance thresholds for the maximum allowable 95% CI in sleep latency between ACG and PSG to 30 min (2). In total, 89.9% of the recordings were inside these limits. All the CCCs were poor.

Men and women as a group did not differ statistically significantly in any of the above-mentioned sleep parameters. Expectedly, older subjects had shorter sleep time, lower sleep efficiency, and longer sleep latency, both in PSG and in ACG. The differences in Bland-Altman analyses or CCC were negligible (data not shown).

DISCUSSION

For our knowledge, this is the first study comparing ACG and PSG at home. Most people sleep better in familiar environment than in the sleep laboratory (27). As ACG is worn during daily life, including nights at home, this method gives a more exact view of how actigraphy typically performs in different sleep disorders, compared to validation studies with in-lab PSG.

Our results with sleep time were concurrent with previous findings. In previous studies looking at subjects with the suspicion of narcolepsy or hypersomnia, ACG underestimated sleep time by 15.1 min (13) or 15.6 min (11), while our result was 24.3 min for narcolepsy and 0.75 min for hypersomnia group. Further, the slight overestimation of TST by ACG in the OSA group is in line with the recent meta-analysis where ACG was found to overestimate the TST of patients with OSA by 14.5 min (2), while our result was 12.8 min. In our study, accuracy was similar in younger or older subjects, but also opposite results have been shown (28).

The findings in this study suggest that ACG is a reliable tool for estimating TST for many but not all patients with sleep disorders. On average, ACG excelled well in estimating TST with an extremely small bias, only 7.8 s and 95% CI of < 6 min. Our mean results fit very well in the clinical significance thresholds for the maximum allowable 95% CI of the mean difference between ACG vs. PSG, set in the recent guidelines by AASM (2). Nevertheless, the large variety of the results is of specific concern. While mean differences between the methods are minor, the results are imprecise in the whole sample. The threshold for maximum allowable 95% CI in the difference in sleep time is too strict for 30% of the measurement pairs in our study. Especially, periodic leg movements and even mild sleep maintenance insomnia seemed to affect the accuracy of sleep time in our subjects.

As is seen in **Figure 4**, actigraphy is accurate when sleep efficiency is high but much less so when sleep efficiency decreases. When a subject has low sleep efficiency, they usually lie immobile but awake, and ACG interprets it as sleep, thus

TABLE 3 | Concordance of sleep efficiency between actigraphy and ambulatory polysomnography.

Diagnostic groups and *subgroups*	*N*	Mean difference [95% CI], %	Inside AASM limits, %	LoA, %	CCC [95% CI]
OSA	102	−2.22 [−4.68, 0.24]	51.0	−26.80, 22.36	0.332 [0.173, 0.475]
Narcolepsy	42	5.63 [3.11, 8.15]	42.9	−10.23, 21.49	0.346 [0.116, 0.540]
NT1	*37*	*6.24 [3.42, 9.05]*	*35.1*	−10.31, 22.78	*0.327 [0.085, 0.532]*
NT2	*5*	*1.14 [−0.33, 2.61]*	*100*	−1.17, 3.45	*0.931 [0.591,0.990]*
PLMD	28	0.51 [−3.71, 4.72]	53.6	−20.79, 21.81	0.429 [0.124, 0.659]
Others (parasomnia)	11	4.16 [1.89, 6.46]	63.6	−2.57, 10.88	0.644 [0.299, 0.840]
Hypersomnia	6	−0.20 [−3.85, 3.45]	83.3	−7.01, 6.61	0.134 [−0.680, 0.800]†
No organic sleep disorder	101	−0.17 [1.66, 1.32]	63.4	−14.97, 14.62	0.665 [0.547, 0.757]
All subjects	290	0.18 [−0.99, 1.35]	55.5	−19.68, 20.03	0.464 [0.375, 0.544]

Mean differences and their 95% confidence intervals in sleep efficiency between ACG and PSG, the proportion of the differences being inside the clinical significant thresholds of AASM, calculatory limits of agreement, and Lin's concordance correlation coefficients and their 95% confidence intervals ($P < 0.05$ in all others except the one marked with †) across all diagnostic groups and narcolepsy subgroups (in italics). CI, confidence interval; AASM, American Academy of Sleep Medicine; LoA, limits of agreement; CCC, Lin's concordance correlation coefficient; OSA, obstructive sleep apnea; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PLMD, periodic leg movement disorder.

TABLE 4 | Concordance of sleep latency between actigraphy and ambulatory polysomnography.

Diagnostic groups and *subgroups*	*N*	Mean difference [95% CI], min	Inside AASM limits, %	LoA, min	CCC [95% CI]
OSA	102	16.8 [11.1, 22.4]	84.3	−39,28, 72.82	0.237 [0.121, 0.346]
Narcolepsy	41	−0.049 [−4.1, 4.0]	97.6	−25.34, 25.24	0.352 [0.069, 0.583]
NT1	*36*	*–0.2 [–4.8, 4.4]*	*97.2*	−26.74, 26.36	0.361 [0.060, 0.603]
NT2	*5*	*0.98 [–8.5, 10.4]*	*100*	−13.96, 15.92	−0.401 [−0.901, 0.556]†
PLMD	27	8.4 [−1.1, 17.9]	92.6	−38.73, 55.47	0.120 [−0.171, 0.392]
Others (parasomnia)	11	3.2 [−2.6, 9.0]	100	−13.75, 20.20	0.541 [0.039, 0.825]
Hypersomnia	6	3.4 [−4.0, 10.8]	100	−10.38, 17.21	0.835 [−0.474, 0.956]
No organic sleep disorder	100	11.8 [8.7, 14.9]	90.0	−18.97, 42.53	0.787 [0.709, 0.846]
All subjects	287	11.0 [8.5, 13.6]	89.9	−32.22, 54.30	0.520 [0.446, 0.588]

Mean differences and their 95% confidence intervals in sleep latency between ACG and PSG, the proportion of the differences being inside the clinical significant thresholds of AASM, calculatory limits of agreement, and Lin's concordance correlation coefficients and their 95% confidence intervals ($P < 0.05$ in all others except the one marked with †) across all diagnostic groups and narcolepsy subgroups (in italics). CI, confidence interval; AASM, American Academy of Sleep Medicine; LoA, limits of agreement; CCC, Lin's concordance correlation coefficient; OSA, obstructive sleep apnea; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PLMD, periodic leg movement disorder.

overestimating sleep time heavily. **Figure 4** shows also the opposite situation: subjects with normal or good sleep efficiency where ACG underestimated sleep time. Most of these subjects had narcolepsy, especially NT1, or parasomnia. It is a logical finding when the operating principle of actigraphy is taken into consideration. Patients with narcolepsy and/or parasomnia may present abnormal motor behavior in REM and NREM sleep and periodic limb movements (17, 29). ACG would interpret these movements as patients being awake although they would in fact still be asleep.

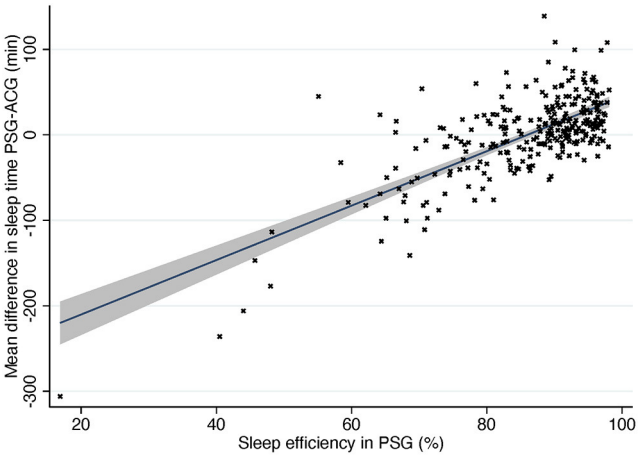

FIGURE 4 | Difference in sleep time compared to sleep efficiency in PSG. Solid line, mean difference. Gray area, 95% confidence interval for regression line. PSG, polysomnography; ACG, actigraphy.

As for sleep efficiency and sleep latency, there were clear differences between subjects with no sleep disorder and patients having narcolepsy or OSA. Our findings were concurrent with those in previous studies. ACG tends to underestimate sleep latency, probably since subjects usually lie immobile for a while before falling asleep (4). Surprisingly, the narcolepsy subgroup was an exception and was found to have ACG SL measurements that were very concordant with PSG equivalents. This is probably because patients with narcolepsy tend to fall asleep abnormally fast instead of lying immobile but awake. In some cases with narcolepsy, ACG showed even longer sleep latencies than PSG, which may be due to the combination of sleep onset REM and REM without atonia (17, 29). Narcolepsy differs from other sleep disorders in many ways, and the direction of misestimation of sleep time and sleep latency by ACG seems to be one of the differences, at least every now and then.

Periodic leg movements as a disorder or together with another sleep disorder seemed to deteriorate the agreement in all sleep parameters. Since periodic limb movements during sleep are often unrecognized by the patient, it is important to bear in mind this possibility, especially if there are discrepancies in the findings. More research is needed to clarify the effects of sleep-related movement disorders to the reliability of ACG.

To summarize our core findings, ACG shows excellent accuracy i.e., negligible bias or mean difference in sleep time and sleep efficiency, and low bias also in sleep latency. However, the precision of actigraphy in a single night measurement is rather poor as demonstrated by e.g., wide limits of agreement and only moderate number of measurement pairs fitting inside the AASM reference area (24). Still, precision increases with replication and since actigraphy is always done across 7–14 nights, regression toward mean and replication increase precision remarkably.

Insufficient sleep—either behaviorally induced or secondary to some problems with sleep—is a very common cause of EDS and, consequently, the background reason for many patient visits to sleep laboratories. Before conducting more complicated diagnostic tests, such as PSG or MSLT for narcolepsy diagnosis, ACG seems to be a practical tool to show that the cause of EDS could be the lack of adequate amount of sleep related to individual need instead of any specific sleep disorder. ACG is far from being perfect, but there is no better method to assess sleep time across several nights. Actigraphic data is more reliable than data derived from sleep logs (2, 30).

What is more, an actigraphy recording, lasting for 2 weeks or longer, is superior to most other methods in showing delayed sleep phase syndrome (DSPS) or other circadian rhythm sleep-wake disorders. DSPS is common in adolescents and young adults—the same age group where narcolepsy often starts. Actigraphy cannot distinguish between behavioral and genetic DSPS, but it shows the current sleep and wake times. DSPS with very late bedtimes often leads to difficulties in staying awake during the morning hours, and even REM sleep can occur in MSLT sessions if the patient usually sleeps until noon.

To avoid false positive diagnoses of narcolepsy, the use of ACG for at least a week should precede every diagnosis of narcolepsy based on MSLT results (3, 17, 20, 31). This is of the utmost importance for the diagnosis of NT2, where cataplexy and hypocretin deficiency are not found, and the differential diagnosis for insufficient sleep syndrome and DSPS is thus much more difficult than in NT1. Naturally, for a narcolepsy diagnosis, essential symptoms need to be present and all other possible causes excluded (20).

In our clinic, we always use ACG for a fortnight before MSLT so that the last night of ACG recording is the PSG night (ambulatory or in-lab) and we compare the concomitant findings. Consequently, we know if the PSG night was typical for the patient and if the results from the preceding 13 nights of ACG recording were accurate. This procedure substantially increases the reliability of ACG in everyday clinical practice.

Additionally to the help in diagnostics, ACG can be used to assess treatment responses, as the method is known to be highly sensitive in a within-subject design [see Sadeh and Acebo (32)]. There are several illustrative examples of the use of ACG to demonstrate drug-induced changes in PLMD or narcolepsy or CPAP-induced changes in OSA (33–36).

Limitations

Some limitations of the study need to be acknowledged. Although we had an extensive subject base, which included patients having the most common clinical sleep disorders, we lacked patients with insomnia as their primary diagnosis. Additionally, the number of NT2 and hypersomnia patients were very small, as these diagnoses are rare, when strict diagnostic criteria are used. In comparing concordance of PSG and ACG, we were especially interested in whole-night measures used in clinical practice and we did not do an epoch-by-epoch comparison of the raw data, which would have enabled us to investigate the sensitivity and specificity of ACG in more detail.

Conclusions

Actigraphy can be a practical tool for measuring some aspects of sleep in situations where PSG is not available for multiple nights or when a full examination is unnecessary to start with. In addition to its established use in circadian rhythm studies, actigraphy is reasonably good at estimating TST. Thus, it is useful in the diagnostic examinations of narcolepsy to see if the subject slept sufficiently during the nights preceding an MSLT for the test to be reliable. However, extreme care should be taken in interpreting the reported values, if the subject has other sleep problems than central disorders of hypersomnolence, as then these values might be misestimated.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Helsinki and Uusimaa Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the manuscript. AA and TJ contributed to study design, data collection, statistical analyses, interpreting the results, and writing the manuscript. TS and MP contributed to statistical analyses, interpreting the results, and writing the manuscript.

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Alterations of Subcortical Brain Structures in Paradoxical and Psychophysiological Insomnia Disorder

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Insomnia disorder (ID) is a common illness associated with mood and cognitive impairments. Subtyping ID is an ongoing debate in sleep medicine, but the underlying mechanisms of each subtype is poorly understood. Growing evidence suggests that subcortical brain structures play the key roles in pathophysiology of ID and its subtypes. Here, we aimed to investigate structural alteration of subcortical regions in patients with two common ID subtypes i.e., paradoxical and psychophysiological insomnia. Fifty-five patients and 49 healthy controls were recruited for this study and T1-weighted images and subjective and objective sleep parameters (i.e., Pittsburgh Sleep Quality Index and polysomnography) were collected from participants. Subcortical structures including the hippocampus, amygdala, caudate, putamen, globus pallidus, nucleus accumbens, and thalamus were automatically segmented in FSL. Volume and shape (using surface vertices) of each structure were compared between the groups, controlled for covariates, and corrected for multiple comparisons. In addition, correlations of sleep parameters and surface vertices or volumes were calculated. The caudate's volume was smaller in patients than controls. Compared with controls, we found regional shrinkage in the caudate, nucleus accumbens, posterior putamen, hippocampus, thalamus, and amygdala in paradoxical insomnia and shrinkage in the amygdala, caudate, hippocampus, and putamen in psychophysiological insomnia. Interestingly, comparing two patients groups, shape alteration in the caudate, putamen, and nucleus accumbens in paradoxical insomnia and shrinkage in the thalamus, amygdala, and hippocampus in psychophysiological insomnia were observed. Both subjective and objective sleep parameters were associated with these regional shape alterations in patients. Our results support the differential role of subcortical brain structures in pathophysiology of paradoxical and psychophysiological insomnia.

Keywords: insomnia disorder, paradoxical insomnia, psychophysiological insomnia, shape analysis, gray matter volume, subcortical brain structures

INTRODUCTION

Insomnia disorder (ID) is characterized by problems in initiating or maintaining sleep, or early morning awakening. The daytime consequences are fatigue, mood disturbance, and cognitive impairment (1, 2). Definition of chronic ID, based on the third edition of International Classification of Sleep Disorders (ICSD-3) criteria (3, 4), requires insomnia symptoms to occur for at least three times per week and lasts for more than 3 months. Rising prevalence of ID (3.9–22.1%) is probably due to genetic and psychosocial factors including aging population, high level of stress, and increasing rate of depression and anxiety in the modern societies (1). In addition to a significant economic burden (5), ID is associated with elevated body-mass index (BMI), higher rate of cardiovascular diseases, increased amount of motor vehicle accidents, and various psychiatric comorbidities such as depression (6–11). Despite all the severe medical and mental consequences of ID, its pathophysiology is poorly understood.

Several neuroimaging studies revealed widespread structural and functional cortical changes (12–14) including gray matter atrophy in the orbitofrontal cortex, dorsolateral prefrontal, pericentral cortices, temporal cortex, and precuneus, but increased gray matter volume in the anterior cingulate cortex (ACC). For review see (13, 14). The role of subcortical brain regions in pathophysiology of ID was previously examined, although the results were inconsistent and difficult to replicate. For review see (13, 14). A surface-based shape analysis of 27 patients with ID revealed that poor sleep quality and higher arousal are associated with subcortical atrophy including the hippocampus, amygdala, basal ganglia, and thalamus that was linked with impaired cognitive functions (15). Gong et al. also found regional atrophy in the amygdala, which was related to the severity of insomnia and anxiety in ID patients (16). Moreover, the critical role of amygdala toward negative sleep-related stimuli (17), the role of hippocampus on sleep-related maladaptive rumination (18, 19), and the role of caudate on hyperarousal state of patients (20) have been observed in ID previously. These studies collectively point to an important role of subcortical brain regions in pathophysiology of ID. Recently, we performed a neuroimaging meta-analysis on 19 ID studies, but failed to identify convergent regional abnormality (21). This indicates that ID heterogeneity is not only due to the variant neuroimaging data acquisition and analysis methods, but also related to clinical variability of the patients e.g., including different ID subtypes (22, 23). Thus, there is a clear need for more detailed investigations of the brain structures on the well-characterized subtypes of ID.

The second version of ICSD introduced several ID subtypes such as paradoxical insomnia and psychophysiological insomnia (24). Paradoxical insomnia is characterized by subjective sleep loss and daily insomnia symptoms, but normal objective sleep profile [e.g., using polysomnography (PSG)], indicating a discrepancy between subjective and objective sleep patterns (25). On the other hand, psychophysiological insomnia is characterized by the "learned sleep-preventing association," which indicates that pre-sleep condition appears to be classically conditioned to the bedroom environment and prevents sleep (26). Hence, paradoxical insomnia is defined by misperception of sleep, while psychophysiological insomnia is characterized by fear of sleep and bedroom environment. The ICSD-3 highlights that physiological abnormalities in sleep tracing are present in various subtypes, but they are often subtle and could not be detected by available routine sleep recording methods and hence, subtyping ID should be ignored in clinical practice (3). However, several studies support subtyping ID, using various neurophysiological, cognitive and psychological methods (22, 25, 27, 28). Recently, Blanken et al. applied a data-driven approach on a multidimensional set of biologically based traits in a large-scale population and identified five new ID subtypes (29). This study further suggests that ID should be considered as a heterogenic disorder (22) and subtyping may resolve inconsistencies to identify differential etiologies of ID (29).

In the present study, we explored possible structural alterations in the subcortical gray matter structure (i.e., the caudate, putamen, pallidum, nucleus accumbens, thalamus, amygdala, and hippocampus) using volume and shape analyses based on surface vertices. Our main question was whether there is any structural difference between two main ID subtypes and whether these changes are associated with insomnia symptoms. It was assumed that there are more structural alterations in the areas responsible for sleep perception and regulation of sleep-wake patterns in patients with paradoxical insomnia, while there are more changes in the regions responsible for sleep-related anxiety and hyperarousal in patients with psychophysiological insomnia.

METHODS

Subjects

We recruited 116 participants in the study. Chronic ID patients were recruited from Sleep Disorders Research Center, Kermanshah University of Medical Sciences. All patients were interviewed by a sleep specialist (H.K.) and met diagnostic criteria of ID according to ICSD and psychiatric interview, overnight PSG, and Pittsburgh Sleep Quality Index (PSQI) before brain MRI acquisition. Healthy subjects were recruited through local advertisement and were defined as those with no neurological or psychiatric illness at present or past and total PSQI score < 5. Our exclusion criteria included taking any neuropsychiatric medications, pregnancy, any other medical, neurological, or psychiatric conditions, as well as contraindications to MR imaging. The study was approved by Ethics Committee of Kermanshah University of Medical Sciences and written informed consent was obtained from all participants. Two patients with comorbid periodic leg movement, five patients with mild/moderate obstructive sleep apnea, one patient with hydrocephaly, two patients with brain mass, and two subjects with too much movements in the scanner (which caused distortion in the images) were excluded from the study. Finally, analyses were performed on 55 chronic ID patients (including 29 individuals with paradoxical insomnia and 26 patients with psychophysiological insomnia), as well as 49 healthy subjects.

Insomnia Assessments

The patients were asked to avoid taking coffee, tea, heavy diet, and smoking during the day of the experiment. Our imaging assessment was carried out when the patients stopped taking any hypnotic medication for at least a week before imaging assessment. We excluded any patient, who was addicted to hypnotic medications such as benzodiazepines. The subjects arrived to the sleep center at 9 pm and completed the demographic and PSQI questionnaires. PSG measurements using SOMNOscreen^{TM} plus model (Somnomedics, Germany) were performed at least 7 h based on the usual sleeping habits of subjects. Sleeping room was standardized for any noise and visual stimulus based on the international protocols (30). Diagnosis of ID subtypes was mainly based on ICSD-2 (24). All patients met diagnostic criteria for chronic ID based on ICSD-3 as well (3, 4), which are largely congruent with ICSD-2. They include a subjective report of sleep initiation or maintenance problems, adequate opportunity to sleep, as well as daytime consequences. In addition, insomnia symptoms were presented for at least three times per week and lasts for more than 3 months in our chronic ID groups. The insomnia symptoms were not associated with substance abuse and other psychiatric or sleep disorders. Paradoxical insomnia was diagnosed by the complaints of short sleep duration and poor sleep quality despite near-normal objective sleep patterns in PSG i.e., the misperception index ≥ 0.9 (31). Detailed criteria for paradoxical insomnia diagnosis include (i) subjective insomnia symptoms, but total sleep time (TST) $>$ 6 h and 30 min and sleep efficiency (SE) $>$ 85% using overnight PSG; (ii) discrepancy between objective (PSG) and subjective (self-report) sleep measures (i.e., a difference of 60 min or more for TST, or a difference of at least 15% for SE) (32). Psychophysiological insomnia were defined based on psychiatric interview, subjective insomnia symptoms, as well TST $<$6 h and 30 min and SE $<$85% (24), indicating that subjective and objective sleep assessment parameters are congruent in patients with psychophysiological insomnia. There is no difference on sleep quality, assessed by PSQI questionnaires, between the patients groups ($p > 0.05$) (**Table 1**).

MRI Acquisition and Quality Control

MRI was performed using a whole-body 1.5T Siemens Magnetom Avanto scanner with an 8- channel head coil. Structural images were acquired with a high-resolution, T1-weighted MPRAGE (TR = 1,950 ms, TE = 3.1 ms, flip angle = 15°, FOV = 256 × 256 mm^2, matrix = 256 × 256 mm^2, voxel size = 1 × 1 × 1 mm^3, 176 sagittal slices). All images were visually checked by a radiologist to rule out any gross brain pathology. Quality control of data was carried out using the University of Southern California quality assurance pipeline (https://qc.loni.usc.edu/).

Segmentation of Subcortical Structures and Shape and Volume Analyses

The FIRST tool (part of FMRIB Software Library) was used to automatically segment seven subcortical brain structures including the caudate, putamen, pallidum, nucleus accumbens, thalamus, amygdala, and hippocampus in each hemisphere (33, 34). In brief, the FIRST is a probabilistic adaptation of the active appearance model. The method is informed by the shape and intensity variations of a structure from a training set for the purpose of automatically segmenting the structures. Surface of each structure is modeled by a deformable mesh, composed of a set of triangles and vertices. There are a fixed number of vertices with arbitrary positions for each structure. A multivariate Gaussian model of vertex location and intensity variation is used and is based on having point correspondence across subjects (same number and labeling of vertices across subjects). The necessary correspondence is imposed during the parameterization of the labeled images with a deformable model. The model is fit to new images by maximizing the posterior probability of shape given the observed intensities (33).

Between groups shape comparisons were carried out by comparing coordinates of each corresponding vertex, i.e., vertex-wise analysis, described in the FIRST tool (33, 34). We used the Randomize (part of FSL), which is a non-parametric permutation testing (10,000 permutations in our study) and allows modeling and inference using standard general linear model (GLM) design (35). We also compared the mean volume of subcortical regions

TABLE 1 | Demographics and clinical characteristics of all participants.

Variables	Paradoxical insomnia ($n = 29$)	Psychophysiological insomnia ($n = 26$)	Controls ($n = 49$)	*P*-value (Paradoxical vs. Controls)	*P*-value (Psychophysiological vs. Controls)	*P*-value (Psychophysiological vs. Paradoxical)
Age (years)	43.76 ± 10.78	47.15 ± 12.08	38.92 ± 12.1	0.079	0.006	0.27
Gender (Male: Female)	10:19	13:13	20:29	0.51	0.51	0.25
Sleep quality (total PSQI score)	15.93 ± 2.72	15.88 ± 3.10	2.96 ± 1.59	0.00	0.00	0.95
Disease duration (years)	6.69 ± 6.75	9.3 ± 9.35	-	-	-	0.23
Total sleep time (min)	420.21 ± 37.28	299.81 ± 101.83	-	-	-	0.00
Sleep efficiency (%)	87.58 ± 7.4	63.1 ± 21.32	-	-	-	0.00

Data are presented as mean ± SD.
PSQI, Pittsburgh sleep quality index.

between groups using GLM design in the FIRST. For both shape and volume analyses, we controlled for age, gender, and total brain volume as covariates of no-interest. For shape analysis, we used threshold-free cluster enhancement (TFCE) correction (36) to avoid arbitrary thresholds selection. Correction for multiple comparisons was applied using false discovery rate (FDR) correction (37). In patients, association between vertices and total PSQI/sleep efficiency was assessed using Spearman's rho two-tailed tests, with correction for covariates of no-interest (i.e., age, gender, and total brain volume) and multiple comparisons using FDR correction. Finally, for volume comparison, we used Least Significant Difference adjustment for multiple comparisons.

RESULTS

Clinical Findings

Demographic data are presented in **Table 1**. No statistical differences were found for age ($p = 0.079$) or gender ($p = 0.51$) between healthy controls and paradoxical insomnia patients, while there were significant differences in age ($p = 0.006$), but not in gender ($p = 0.51$) between healthy controls and psychophysiological insomnia patients. The paradoxical and psychophysiological insomnia groups had no significant differences regarding age ($p = 0.27$) and gender ($p = 0.25$). In addition, paradoxical ($p = 0.000$) and psychophysiological ($p = 0.000$) insomnia patients had higher PSQI scores (poor sleep quality) than healthy controls, without any significant difference between two ID groups ($p = 0.95$). As expected, TST ($p = 0.000$) and SE ($p = 0.000$) were significantly better in paradoxical vs. psychophysiological insomnia patients. No statistical differences were found for duration of disease ($p = 0.23$) between two ID subtypes. Regarding total brain volume, healthy control subjects (1569.4 ± 22.5 cm^3) had significantly larger brains than paradoxical (1447.3 ± 30.8 cm^3) or psychophysiological insomnia groups (1485.7 ± 33.0 cm^3) with p-values of 0.001 and 0.04, respectively. There was no significant difference between total brain volume of paradoxical and psychophysiological insomnia patients ($p = 0.3$).

Volumetric Findings of Subcortical Structures

Mean volume of the left caudate was significantly smaller in the patient with paradoxical insomnia compared to psychophysiological insomnia, as well as to the control group. In addition, volume of bilateral caudate was different between paradoxical insomnia and psychophysiological insomnia (**Table 2**).

Vertex-Wise Shape Analysis Findings

Comparing paradoxical insomnia with healthy subjects, we found alterations in the anterior dorsal caudate, tail of left hippocampus, dorsal anterior thalamus, superior part of right amygdala, and anterolateral part of left putamen ($p < 0.05$, FDR corrected) (**Figure 1A**). Comparing psychophysiological insomnia with control individuals, we observed shrinkage in the anterior amygdala, dorsal part of right caudate, head and body of hippocampus (left tail > right tail), lateral part of putamen (right tail > left tail) ($p < 0.05$, FDR correction) (**Figure 1B**). Moreover, comparing two ID groups showed that bilateral hippocampus (head, ventral aspect of the body and dorsal aspect of the tail), dorsal thalamus, and anterior amygdala were shrunk in psychophysiological insomnia compared to paradoxical insomnia. In contrast, the caudate, putamen and nucleus accumbens (mainly the right side) showed relative shrinkage in paradoxical insomnia than psychophysiological insomnia ($p < 0.05$, FDR correction) (**Figure 1C**).

TABLE 2 | Volume of subcortical structures (mm^3). Data are presented as mean ± SD.

Structure	Healthy controls	Paradoxical insomnia	Psychophysiological insomnia
Left accumbens	832 ± 134	791 ± 119	794 ± 166
Left amygdala	1845 ± 288	1616 ± 335	1805 ± 268
Left caudate[*$]	4804 ± 535	4654 ± 655	4627 ± 390
Left hippocampus	5074 ± 438	4760 ± 518	5129 ± 553
Left pallidum	1840 ± 198	1758 ± 180	1845 ± 220
Left putamen	5259 ± 547	4967 ± 516	5157 ± 494
Left thalamus	8086 ± 706	7462 ± 757	8006 ± 706
Right accumbens	679 ± 127	633 ± 131	650 ± 103
Right amygdala	1805 ± 312	1725 ± 295	1705 ± 300
Right caudate[#]	4937 ± 565	4758 ± 559	4685 ± 406
Right hippocampus	5160 ± 434	4959 ± 455	5307 ± 422
Right pallidum	1827 ± 193	1736 ± 189	1831 ± 152
Right putamen	5226 ± 553	4958 ± 526	5085 ± 510
Right thalamus	7809 ± 681	7265 ± 739	7823 ± 643

[*] *Comparing control with paradoxical insomnia ($F = 6.273$, $P = 0.014$).*
[$] *Comparing paradoxical with psychophysiological insomnia ($F = 4.666$, $P = 0.035$).*
[#] *Comparing paradoxical with psychophysiological insomnia ($F = 7.592$, $P = 0.008$).*

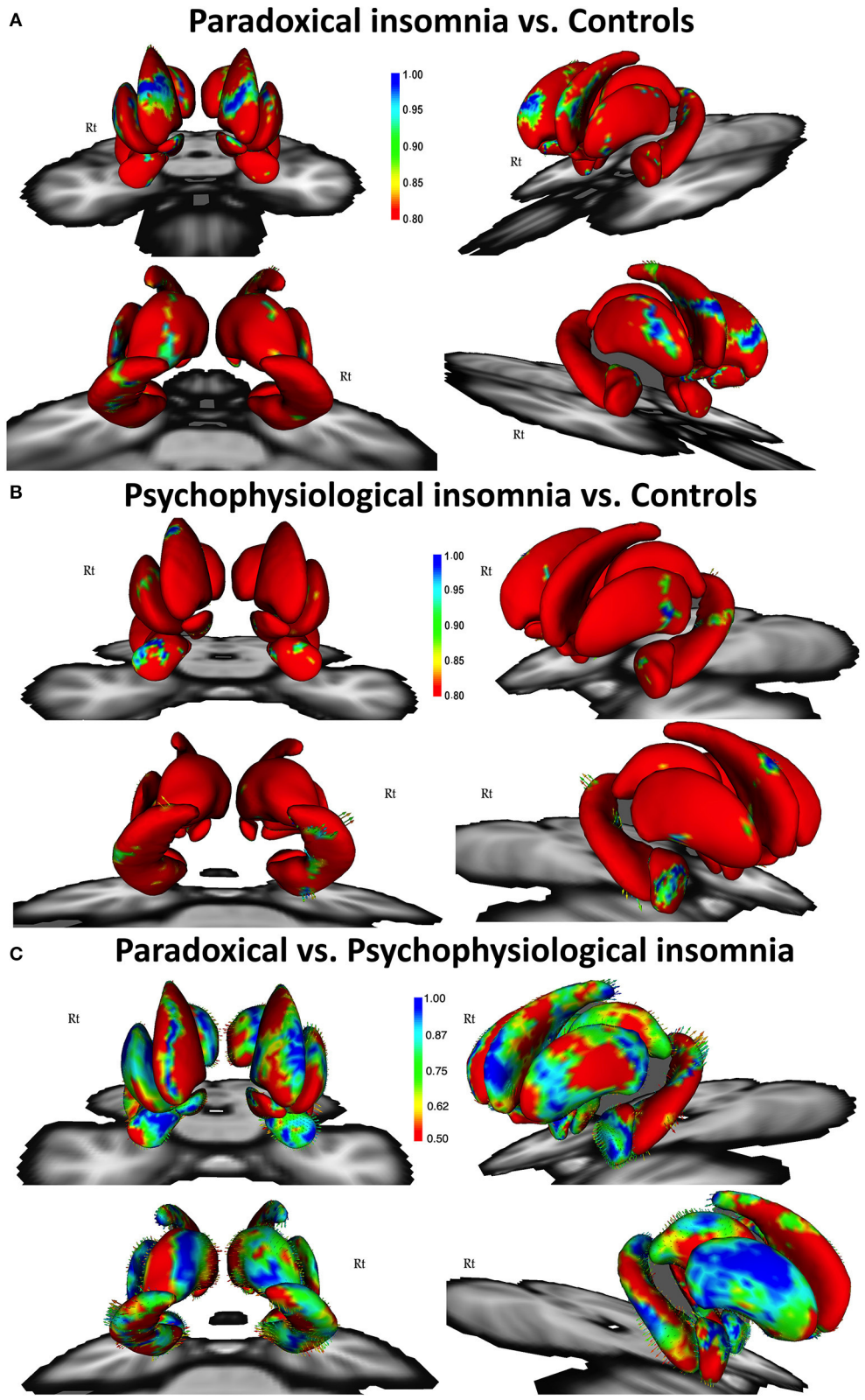

FIGURE 1 | Vertex-wise surface analysis comparing patients with paradoxical insomnia vs. control group **(A)**, patients with psychophysiological insomnia vs. control group **(B)**, patients with paradoxical insomnia vs. psychophysiological insomnia **(C)** including covariates of no-interest (i.e., age, gender, and total brain volume). Color bar shows false discovery rate (FDR) corrected *p*-values.

Association Between Shape Abnormalities and Sleep Parameters

Patients with paradoxical insomnia, showed positive correlations between PSQI and shape changes in the putamen, nucleus accumbens, head and body of hippocampus (right tail > left tail), and anterior and posterior extremes of the caudate, but negative correlation with body of right caudate (**Figure 2A**). SE negatively correlated with dorsal and ventral part of the caudate, but positively correlated with head and tail of the caudate (right > left), nucleus accumbens, and posterior putamen (**Figure 2B**).

In patients with psychophysiological insomnia, PSQI scores were negatively correlated with the anterior amygdala, head and tail of caudate, head and body of hippocampus, and posterior dorsal thalamus, but positively correlated with the lateral part of putamen (**Figure 2C**). In addition, SE was positively correlated with shape changes in the anterior amygdala, right dorsal putamen and caudate, as well as inferior part of the hippocampus and posterior dorsal left thalamus, but negatively correlated with lateral part of the putamen (**Figure 2D**).

DISCUSSION

ID is clinically a heterogeneous disorder and current ID literature indicates remarkable inconsistencies in terms of clinical features and treatment response (22, 29), which suggests that a bottom-up classification of ID should be reconsidered in sleep medicine (22, 25). Recently, a data-driven approach using multivariate profiles of affect, personality, and life history of 2,224 participants with ID and 2,098 controls was performed (29). Their result identified five new 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 (29). Previously, Turcotte et al. using event-related potentials measures demonstrated that psychophysiological insomnia had inability to inhibit information processing during sleep onset, but paradoxical insomnia showed enhanced attentional processing, which results in a higher need for inhibition (38). The present study suggests structural difference, not only between ID and healthy subjects, but also between paradoxical and psychophysiological insomnia, indicating importance of previously suggested subtypes in ICSD-2 for ID. In particular, we demonstrated that subcortical brain areas of patients with two ID subtypes undergo different structural alterations, and these changes are associated with both subjective and objective sleep-related measures.

Given the fact that the caudate nucleus showed atrophy and shrinkage in paradoxical insomnia (and not in psychophysiological insomnia), our shape and volumetric findings indicate a critical role of caudate in subjective-objective sleep discrepancy in paradoxical insomnia (25, 27, 39). A typical patient with paradoxical insomnia often feels that s/he has not

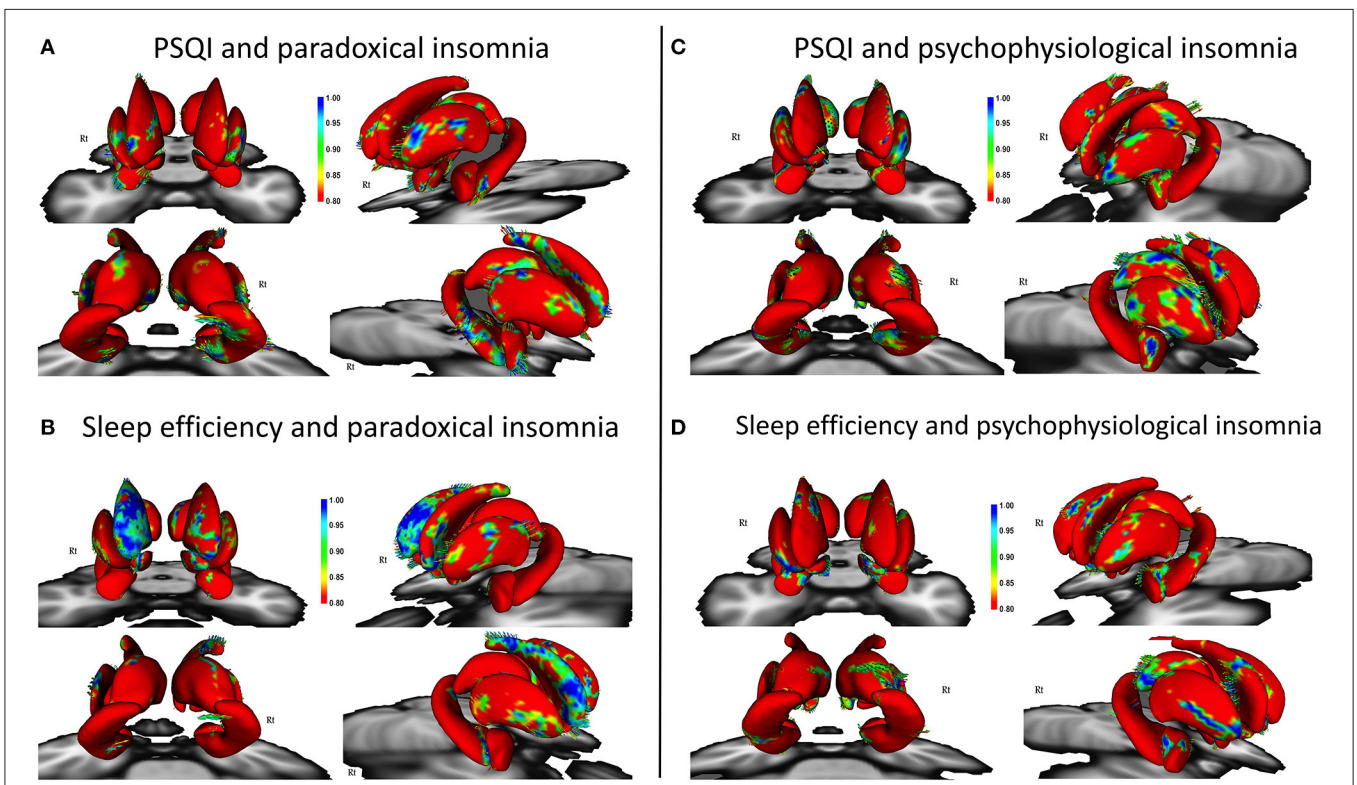

FIGURE 2 | Correlation of Pittsburgh Sleep Quality Index (PSQI) and sleep efficiency with surface changes in patients with paradoxical insomnia **(A,B)**; Correlation of PSQI and sleep efficiency with surface changes in patients with psychophysiological insomnia **(C,D)** including covariates of no-interest (i.e., age, gender, and total brain volume). Color bar shows false discovery rate (FDR) corrected *p*-values.

slept enough, but polysomnographic data shows normal sleep duration. Our notion is in support of a crucial function of the caudate in pathophysiology of ID (20), particularly those with paradoxical insomnia who have sleep-state misperception (39). There is considerable evidence that the striatum (including caudate and putamen) plays an important role in sleep behavior. The caudate receives input from the orbitofrontal and parietal cortices, and the putamen receives input from the somatosensory, primary motor, and premotor cortices (40). Structural alterations in the cortically connected area such as the orbitofrontal cortex to the caudate has been reported previously in ID (13). The basal ganglia are recognized for disparate functions not only regulating movements, cognitive, affective and somatosensory functions, but also regulating sleep-wake patterns (40, 41). Indeed, dorsal striatum augments wakefulness and nucleus accumbens regulates sleep-wake pattern by promoting sleep (41). Sleep disturbances contribute to the striatal dopamine levels too. Adenosine and dopamine receptors in the ventral striatum promote wakefulness by motivational behavior, but locomotor and arousal systems are inhibited during sleep (41). Stoffers et al. demonstrated an impaired recruitment of the head of left caudate nucleus during executive functioning, which was associated with hyperarousal severity in ID patients (20). This may be predispose and perpetuate hyperarousal and insomnia. However, cognitive behavioral therapy for insomnia (CBT-I) did not normalize the observed hypoactivation of the caudate during the executive task performance (20). Literature is lacking for the specific role of the putamen in ID, but shrinkage in the putamen in obstructive sleep apnea and rapid eye movement (REM) sleep behavior disorder, and also increased synaptic dopamine in putamen in restless legs syndrome have been reported earlier (42–44). These findings collectively point out to the critical role of the striatum including the caudate and putamen in pathophysiology of ID, particularly paradoxical insomnia.

On the other hand, patients with psychophysiological insomnia revealed that poor subjective sleep quality (i.e., higher total PSQI score) was associated with regional shrinkage of thalamus, amygdala, hippocampus, putamen and caudate. In addition, low sleep efficiency was linked with shrinkage in the thalamus, amygdala, hippocampus, caudate, and dorsal putamen, as well as hypertrophy in the right posterior thalamus. Comparing two patients groups showed that although various subcortical regions undergo structural changes in psychophysiological insomnia, it is mainly associated with shrinkage in thalamus, amygdala, and hippocampus. This is in line with the hyperarousal model of insomnia and emotional memory impairment in ID (14, 45). This model suggests that ID is characterized by increased arousal at the physiological, endocrine, cognitive or emotional levels and increased amygdala activity (17). Importantly, poor subjective and objective sleep quality is linked with enlargement of lateral putamen, which might be a compensatory mechanism to dysfunction of the limbic circuits. Similar to our findings, Koo et al. found an association between subcortical atrophic shape abnormalities in the thalamus, amygdala, hippocampus, and basal ganglia in a group of ID patients and such patterns was associated with cognitive decline in those patients (15).

The amygdala plays a key role in processing negative emotional arousal and fear-inducing stimuli and therefore is involved in the hyperarousal model of ID (14, 45). Gong et al. also reported atrophy in the left superficial and right basolateral nucleus of amygdala, the association of insomnia severity with shape of the right centromedial nucleus, and the link between anxiety and shape of the basolateral nucleus of amygdala (16). Beside structural changes, functional imaging studies demonstrated that the amygdala response to insomnia-related stimuli is more robust in ID than healthy controls with lower habituation (17). Furthermore, decreased functional connectivity between amygdala and insula, striatum, and thalamus, as well as increased functional connectivity of amygdala with premotor and sensorimotor cortex in ID have been reported (46). Impaired connectivity and dysfunction of the amygdala due to emotional processing is a shared phenomenon in major depressive disorder (MDD) and ID (9, 17, 46). It has been demonstrated that amygdala volume is larger in MDD patients with insomnia symptoms compared to MDD patients without insomnia, regardless of the depression subtype (e.g., melancholic or psychotic) (9, 47).

Similar to the current study, hippocampal atrophy was previously reported in patients with ID (13). It has been revealed that distinct connectivity patterns of anterior and posterior hippocampus involve in memory processing and encoding success (48, 49). A multimodal parcellations and behavioral decoding of hippocampal sub-regions demonstrated a head–body and tail partition, subdivided along the anterior–posterior and medial–lateral axis and behavioral analyses suggested an emotion–cognition gradient along the anterior–posterior axis (50). According to our results, major hippocampal abnormality was observed within the head and body of the hippocampus. Previously, Joo et al. found that patients with ID had bilateral atrophy in the body and tail of hippocampus (i.e., CA2 and DG), which was associated with impaired cognitive functions, as well as in the head of hippocampus (i.e., CA1), which is associated with poor sleep quality (51). Some studies identified disruption of hippocampal functional connectivity within the default mode network (DMN) in ID (52). In particular, enhanced functional connectivity between the retrosplenial cortex/hippocampus and different hubs of the DMN is reported in ID previously (52). CBT-I normalized DMN hyperactivity and improved symptoms and quality of life of patients with psychophysiological insomnia (53). A meta-analysis found that patients with ID consistently have poor daily performance in several cognitive functions including working memory, episodic memory, and problem solving, which may be related to hippocampal dysfunction in ID (54).

The figure of thalamus in sleep regulation is well-established as well (55, 56). The anterior and dorsomedial nuclei of thalamus are responsible for organization of wake-sleep pattern, and affect pineal melatonin production and secretion (57). Thalamic lesions cause severe and persistent insomnia in the animal models (57). Severe impairment in mitochondrial function, protein synthesis, and neuronal loss in mediodorsal thalamus has been observed in fatal familial insomnia (58). Few studies on ID demonstrated structural and functional abnormalities in the thalamus. For example, patients with ID

showed thalamic atrophy, as well as disruption of thalamus's functional connectivity with the ACC, orbitofrontal cortex, hippocampus, caudate, and putamen which were negatively correlated with PSQI score (59). Kim et al. observed cortical and thalamic hyperactivity in response to sleep-related tasks in psychophysiological insomnia (60). These studies indicate maladaptive role of amygdala, hippocampus, and thalamus in pathophysiology of ID, mainly in psychophysiological subtype.

LIMITATIONS

The results of this study should be interpreted with cautious, due to several potential limitations. Small sample size together with potential variability in shape analysis may over-estimate some structural alterations or miss some others. A stronger magnetic field e.g., 3T or 7T would increase signal to noise of the images and therefore increase the accuracy of subcortical segmentations. Moreover, in the current study, mean age of patients were higher than healthy subjects and it has been demonstrated that age has an important effect in gray matter structures in subjects with sleep disturbances (61, 62). Smaller total brain size could be argued to contribute in the group difference reported in this work. However, the effect of any total brain atrophy associated with normal aging would be diminished when age was taken as a covariate of no-interest, as applied in our analysis. In fact, total brain volume was lower in paradoxical than in psychophysiological insomnia patients. This argues that perhaps there is biological effect in paradoxical insomnia, which is associated with brain atrophy beyond what is normally seen in aging. Thus, although we included age as covariates of no-interest in all analyses, careful matching of the groups and controlling for the effects of comorbid anxiety and depression should be considered in the future studies. Combination of structural assessment with functional MRI and/or positron emission tomography (PET) using a multimodal approach could further enlighten the role of subcortical structures in pathophysiology of ID and its subtypes. Unfortunately, such tools were not available in our center at the time of study. Further longitudinal studies with high magnetic fields and molecular imaging techniques in a larger cohort are needed to endorse our findings.

CONCLUSION

The present work demonstrated structural alterations in the amygdala, hippocampus, corpus striatum, and thalamus in ID. Shape alterations were prominent in the caudate, putamen, and nucleus accumbens in paradoxical insomnia and were noticeable in the thalamus, amygdala, and hippocampus in psychophysiological insomnia. The volume of caudate was different between ID patients and controls, as well as between ID subtypes. The structural changes are associated with subjective and objective sleep symptoms and support different neurobiological mechanisms between paradoxical and psychophysiological insomnia. This study highlights the need for classification of ID and may have a great impact on clinical trials and developing better treatment for ID in future. Clearly, we need global sharing of multimodal imaging-genetic data using world-wide initiatives like ENIGMA-Sleep (http://enigma.ini.usc.edu/ongoing/enigma-sleep/) in sleep medicine (63).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kermanshah University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FE, MT, MK-A, SM, HK, and MZ contributed to design and conceptualization of the idea. FE, KN, and MR collected data. MM and MZ analyzed data. All authors drafted the manuscript and revised the manuscript for intellectual content.

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SYSTEMATIC REVIEW
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Individual Insomnia Symptom and Increased Hazard Risk of Cardiocerebral Vascular Diseases: A Meta-Analysis

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Objective: Previous studies suggested that insomnia was associated with an increased risk of cardiocerebral vascular diseases (CVDs) but not clear in different insomnia symptoms. We performed a meta-analysis to investigate the association of individual insomnia symptoms and risk of CVDs.

Methods: In this meta-analysis, we systematically searched published articles by using electronic databases including PubMed, Cochrane Library, MedLine, and Google Scholar. Studies were enrolled if they indicated clear insomnia symptoms, prospective, and evaluated the association of insomnia symptoms and CVD outcome in adults free of CVDs at baseline.

Results: There were seven prospective cohort studies with sample sizes ranging from 2,960 to 487,200 included in this meta-analysis. Mean follow-up duration was 10.6 years. Insomnia symptoms of having difficulty initiating or maintaining sleep (DIS or DMS), non-restorative sleep (NRS), and early morning awakening (EMA) were analyzed in this study. All studies were compared under a random-effects model. NRS, DIS, and DMS were, respectively, related to 16% [hazard ratio (HR) 1.16, 95% CI 1.07–1.24], 22% (HR 1.22, 95% CI 1.06–1.40), and 14% (HR 1.14, 95% CI 1.02–1.27) higher risk of first-ever CVD incidence during the follow-up. Based on our analysis, EMA was not a risk factor of CVDs (HR 1.06, 95% CI 0.99–1.13).

Conclusion: This study suggested that symptoms of DIS, DIM, or NRS were associated with a higher risk of CVD incidence in insomnia patients free of CVDs at baseline. But this association was not significant in insomnia patients complaining about EMA.

Keywords: insomnia, symptom, cardiovascular disease, stroke, meta-analysis

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INTRODUCTION

Insomnia, defined as a person feeling of having difficulty initiating (DIS) or maintaining sleep (DMS) or feeling of non-restorative sleep (NRS), is the most common sleep disorder throughout the world, with an average prevalence of 33% (1–3). As a disease with high prevalence, insomnia could cause a health burden of an annual expenditure of 92.5–107.5 billion dollars years ago (4), which is a critical issue that needs to be solved.

There were about 35.7% of Chinese residents who complained about poor sleep quality in the research of China Chronic Disease and Risk Factor Surveillance (5). Even worse, insomnia has been proven to be associated with several ill health conditions, including hypertension, depression, diabetes, as well as neurological disorders (6–8). In recent years, some prospective studies indicated that insomnia disorder was associated with increased risks of cardiocerebral vascular diseases (CVDs) (9–12). However, the relationship of individual insomnia symptoms and risk of CVDs is still controversial because the inclusion criteria of insomnia patients in the published studies were not consistent.

DIS and DMS were identified as risk factors of CVDs, while early morning awakening (EMA) was associated with an increased risk in the study of Zheng et al. but insignificant in a Swedish cohort (13, 14).

Therefore, the aim of this study was to systematically review related prospective cohort studies and conduct a meta-analysis of all the available studies in order to investigate the association between different insomnia symptoms and the risk of first-ever CVDs.

METHODS

Selection of Studies

We systematically searched published articles (through February 24, 2020) by using electronic databases including PubMed, Cochrane Library, MedLine, and Google Scholar. The keywords relating to insomnia as MeSH terms and text words ("Disorders of Initiating and Maintaining Sleep" or "Early Awakening" or "Insomnia" or "Insomnia Disorder" or "sleep complaints" or "sleep disturbance" or "Sleeplessness" or "poor sleep quality") were used in combination with keywords relating to CVD ("myocardial infarction" or "myocardial ischemia" or "coronary artery disease" or "coronary heart disease" or "Cerebrovascular Accidents" or "stroke" or "cardiovascular disease" or "cardiocerebral vascular disease"). We limited our search to prospective cohort studies, supplemented by manually reviewing the reference of all retrieved papers. There was no language restriction of the studies. The inclusion criteria for the eligible articles were as follows: (1) the study should be prospective cohort or longitudinal cohort with follow-up; (2) patients with age >18 years, free of CVDs at baseline; (3) report specific insomnia symptoms and clear methods of sleep disorder assessment; (4) primary or secondary outcome should be the association of sleep disorder and CVDs; (5) the quantitative estimates of the univariate or multivariate adjusted hazard ratio (HR) and 95% confidence intervals (CIs) for CVD outcomes associated with insomnia symptoms should be provided. Relative risks (RRs) were considered equivalent to HR in the prospective cohort study; (6) the follow-up duration of each study should be longer than 2 years. Any study that did not meet the inclusion criteria was excluded. The articles were initially included or excluded based on title, abstract, and finally based on the complete article, decided by two independent interviewers.

Data Extraction

The following data were extracted from the final included studies as the baseline characteristics: first author's name, year of publication, country, number of subjects at baseline, male gender proportion, mean age at baseline, insomnia symptoms of subjects, methods of insomnia disorder assessment, study outcome, follow-up duration, variables adjusted for confounding factors at the univariate or multivariate model. We also extracted HR and 95% CIs for CVD outcomes associated with insomnia symptoms for the statistical analysis.

Statistical Analysis

The HR we used for analysis was from the most complete adjustment for confounders in the original study (adjusted confounders were shown in **Table 1**). All analyses used random-effects models, with heterogeneity assessed using the I^2 statistic. Heterogeneity across studies was considered substantial if $I^2 > 50\%$. In order to identify the source of heterogeneity, we performed sensitivity analyses by eliminating each included study step by step and a subgroup analysis according to gender. Publication bias was evaluated by means of the Egger's test. We performed the statistical analysis by STATA version 15 (StataCorp LLC, College Station, Texas, USA), and statistical significance was considered when a two-tailed $p < 0.05$.

RESULTS

Study Identification and Selection

Based on our search strategy, there were a total of 3,623 records identified through the databases. We excluded 3,556 articles by title and abstract and then reviewed the full text to further exclude 60 studies according to the inclusion criteria of our study (follow chart shown in **Figure 1**).

Finally, there were seven prospective cohort studies included in this meta-analysis (13–19). Of these, there were three studies that separately analyzed the association between CVD outcome and different insomnia symptoms according to males and females, which means that they analyzed two outcomes in the same study. Therefore, we entered each of them as a single paper for the statistical analysis; as a result, there were 10 studies enrolled in the final analysis.

The entered articles included studies from China, USA, Germany, Norway, and Sweden, with sample sizes ranging from 2,960 to 487,200. The mean follow-up duration of this cohort was 10.6 years. As for the assessment of insomnia symptoms, two of the studies used the dichotomous variable (yes or no) (13, 15) while others used three to four category choices [(14, 16–19); e.g., never, occasionally, often, almost every night], in which cases we used the most serious category as the presence of insomnia symptoms based on the same criteria of the original articles. We evaluated the quality of these cohort studies by Newcastle–Ottawa Scale (NOS) (details shown in **Table 1**).

TABLE 1 | Characteristics of enrolled cohort studies.

References	Country	Subjects (*n*)	Male (%)	Age (years)	Insomnia symptoms	Insomnia assessment	Outcomes	Follow-up (years)	Adjusted factors	Quality score
Zheng et al. (13)	China	4,87,200	40.90	51	DDF/DIMS/EMA	Self-reported insomnia symptoms for at least 3 d/wk. at baseline	IHD/acute MI/stroke	9.6	Age; education level; annual household income; marital status; alcohol consumption; smoking status; tea consumption; physical activity level; intake frequencies of red meat, fresh fruits and fresh vegetables; family history of heart attack and stroke; BMI; prevalent hypertension and diabetes mellitus at baseline; frequent use of sleep aid medications; frequency of snoring during sleep and depression or anxiety symptoms	5
Helbig et al. (15)	Germany	15,746	50.24	48.2	TFA/DSA	Self-report in a personal interview at baseline	Stroke	14	Age, educational level, physically active, alcohol consumption, current smoking activity, BMI, hypertension, diabetes, and dyslipidemia	5
Canivet et al. (14)	Sweden	13,617	43.10	45–69	DFA/Waking up during the night/waking up too early/Not feeling rested after sleeping	Instrument based on DSM-IV diagnostic criteria for insomnia	MI/stroke/ death due to IHD	13	Age	5
Laugsand et al. (16)	Norway	51,982	44.68	49.4	DIS/DMS/NRS	Self-administered questionnaire	AMI	11.4	Age, sex, marital status, education level, shift work, systolic blood pressure, total cholesterol, diabetes mellitus, BMI, physical activity, smoking, depression, and anxiety	5
Schwartz et al. (17)	USA	2,960	33.33	73	TFA/Trouble waking during night/Trouble waking too early/ Restless sleep	Four questions about insomniac complaints were asked at the baseline visit	MI	3	Age, gender, race, education level, number of prescription medications, self-rated health and depression	5

(Continued)

TABLE 1 | Continued

References	Country	Subjects (*n*)	Male (%)	Age (years)	Insomnia symptoms	Insomnia assessment	Outcomes	Follow-up (years)	Adjusted factors	Quality score
Meisinger et al. (18)	Germany	6,896	50.87	57.5	DIS/DMS	Two separate 3 category interview questions were asked	MI	10.1	Age, survey, BMI, education level, dyslipidemia, alcohol intake, parental history of MI, physical activity, regular smoking, hypertension, diabetes, and menopause status of women	5
Westerlund et al. (19)	Sweden	41,192	35.50	52.8	DFA/DMA/EMA/NRS	Sleep questionnaire included 13 items on sleep disturbances	MI/stroke//death from CVDs	13.2	Age, sex, education, employment status, smoking, alcohol, snoring, work schedule, depressive symptoms, self-rated health, physical activity, BMI, diabetes, lipid disturbance, and hypertension	5

EMA, early morning awakening, also referred as trouble waking too early; NRS, non-restorative sleep, also referred as restless sleep or not feeling rested after sleeping; DIS, difficult initiate sleep, also referred as trouble falling asleep; DMS, difficult maintain sleep, also referred as waking up during the night, trouble waking during night, difficult staying asleep; TFA, trouble falling asleep; DSA, difficult staying asleep; DIMS, difficult initiate and maintain sleep; IHD, ischemic heart disease; MI, myocardial infarction; CVDs, cardiovascular diseases; AMI, acute myocardial infarction; BMI, body mass index.

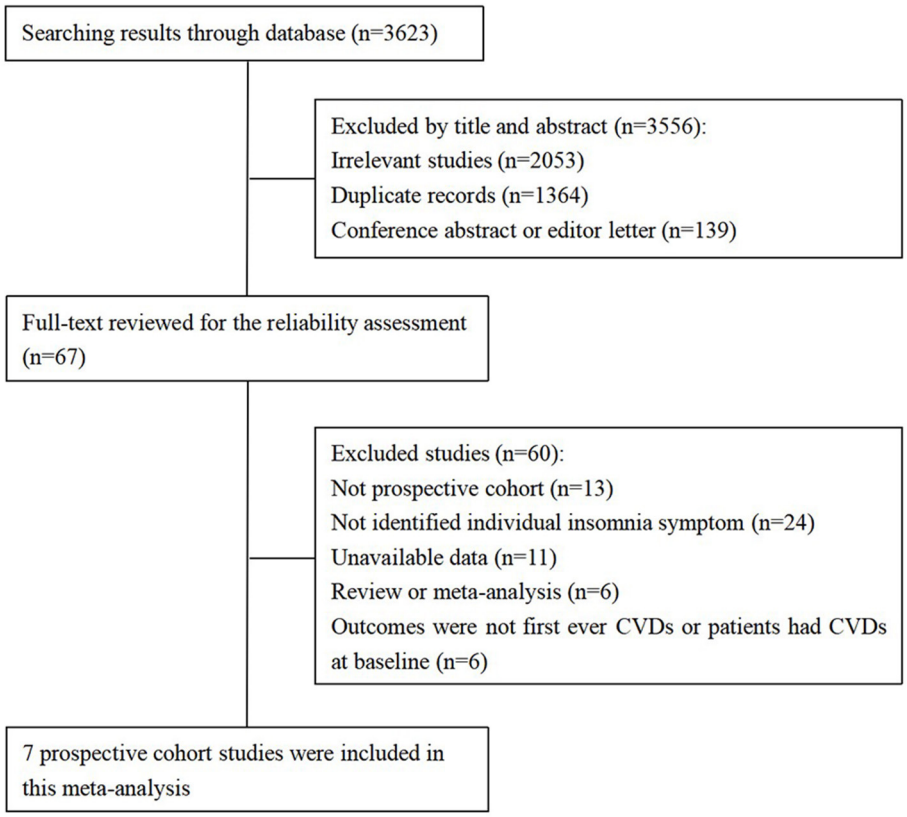

FIGURE 1 | The flowchart of studies selection.

Insomnia Symptoms and Cardiocerebral Vascular Outcomes

After pooling all 10 studies' comparisons under a random-effects model, which were divided by different insomnia symptoms, the meta-analysis showed patients with NRS was in 16% higher risk of CVDs compared to those without corresponding symptoms (HR 1.16, 95% CI 1.07–1.24). Subjects who complained DIS and DMS had 22 and 14% increased risk of suffering CVDs, respectively, with respect to those without these two complaints (DIS: HR 1.22, 95% CI 1.06–1.40; DMS: HR 1.14, 95% CI 1.02–1.27). The association of EMA symptom and CVD incidence risk was not significant in data analysis (**Figure 2**). Overall, different insomnia symptoms were significantly associated with a 13% higher risk of suffering CVDs compared to subjects without any insomnia complaint (HR 1.13, 95% CI 1.08–1.19). There was no significant heterogeneity across the study of EMA and NRS, but a borderline heterogeneity was shown across the study of DIS and DMS. The overall heterogeneity was also significant with $I^2 = 56.8\%$ ($p < 0.001$).

Sensitivity Analyses and Publication Bias

As we had mentioned above, studies of patients with DIS and DMS symptoms reported borderline significant heterogeneity. Actually, according to our search strategy, the study of Eaker et al. (20) was also included at the beginning, but in our primary data analysis, the heterogeneity was much higher in the DIS studies ($I^2 = 62.5\%$, $p = 0.04$; after being excluded, $I^2 = 51.3\%$, $p = 0.036$). Therefore, we did not include this study in our final analysis. In order to figure out other possible difference across the studies, we performed a subgroup study based on gender for the sensitivity analysis. Since not all included studies had separate HR and 95% CI for CVDs and insomnia symptoms according to male and female, we only use the available data. The subgroup analysis based on the available studies showed that females with DIS and DMS symptoms reported much higher heterogeneity compared to males (**Table 2**). Egger's test was used to assess the publication bias of this study, which showed no significant results ($p = 0.097$).

DISCUSSION

Insomnia is the most common sleep disturbance globally, which can cause both mental and physical illness. Previous studies have indicated insomnia disorder as a new risk factor of CVDs, other than the traditional atherosclerotic risk factors. However, insomnia patients may complain about different symptoms, including difficulty falling asleep, difficulty maintaining asleep, waking up too early in the morning, and feeling restless after one-night sleep. Patients might have all or just some of these symptoms. It is not clear if all these symptoms had the same

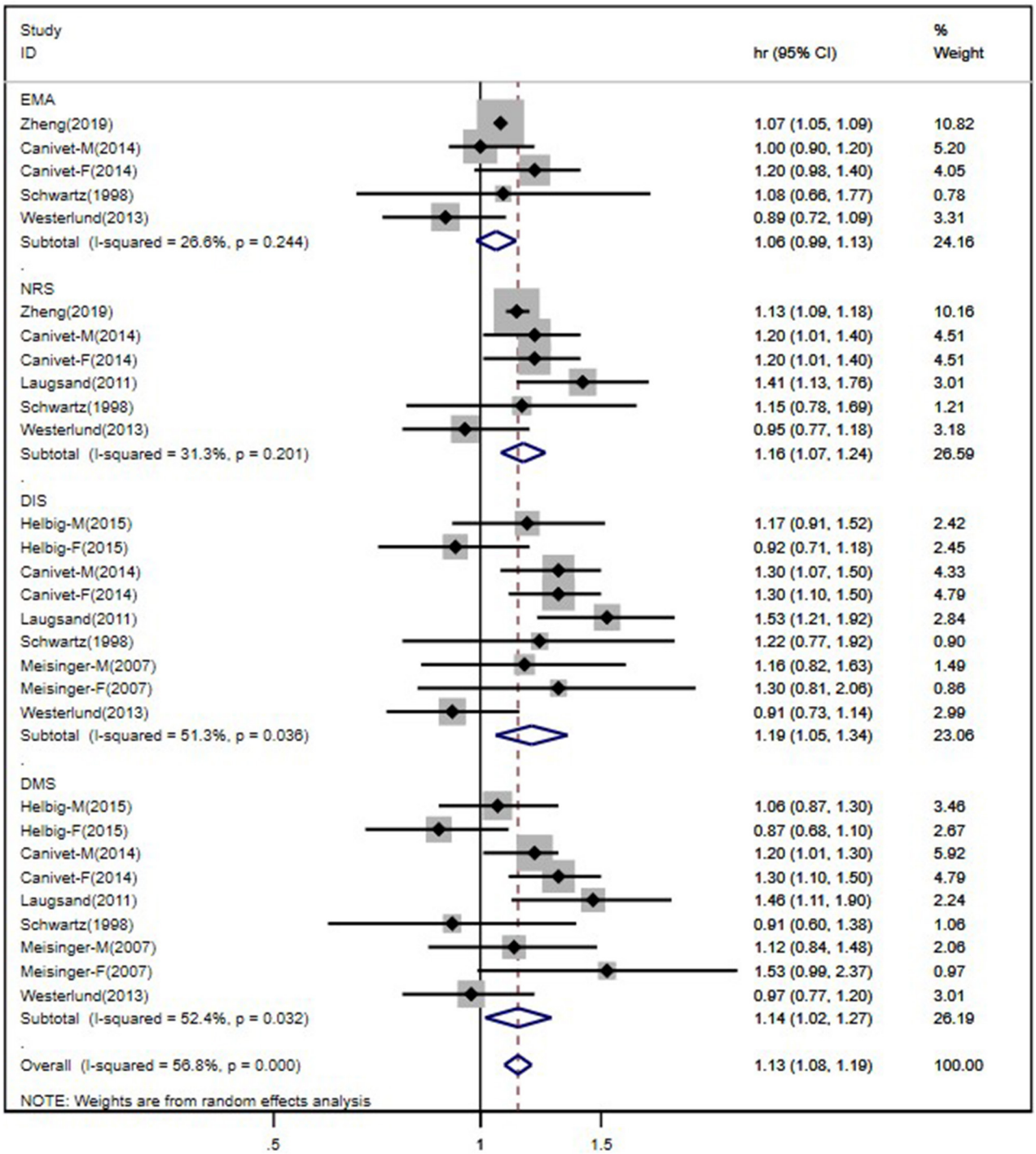

FIGURE 2 | Forest plot of studies evaluating the association of individual insomnia symptoms and risk of cardiocerebral vascular disease.

association with CVD incidence risk. As a result, this meta-analysis aimed to investigate the relationship between each insomnia symptom and the risk of first-ever CVDs.

Our meta-analysis showed an overall increased risk of CVDs in patients with insomnia symptoms, which was consistent with findings of previous studies. Patients with complaints of DIS (HR 1.22, 95% CI 1.06–1.40), DIM (HR 1.14, 95% CI 1.02–1.27), or NRS (HR 1.16, 95% CI 1.07–1.24) were in higher risk of CVDs individually in this study. Our data indicated that insomnia patients complaining of DIS had much

TABLE 2 | Subgroup analysis by genders.

	Studies (*n*)	HR (95%CI)	Weight (%)	Heterogeneity, *p*-value
EMA				
Male	2	1.05 (1.01–1.08)	33.72	$I^2 = 0.0\%$, $p = 0.517$
Female	2	1.08 (1.06–1.11)	66.28	$I^2 = 24.1\%$, $p = 0.251$
NRS				
Male	3	1.18 (1.11–1.25)	28.38	$I^2 = 0.0\%$, $p = 0.921$
Female	3	1.13 (1.09–1.17)	71.62	$I^2 = 33.0\%$, $p = 0.225$
DIS				
Male	4	1.25 (1.10–1.41)	49.38	$I^2 = 0.0\%$, $p = 0.884$
Female	4	1.27 (0.99–1.63)	50.62	$I^2 = 71.8\%$, $p = 0.014$
DMS				
Male	4	1.15 (1.05–1.27)	55.96	$I^2 = 0.0\%$, $p = 0.777$
Female	4	1.22 (0.95–1.58)	44.04	$I^2 = 70.3\%$, $p = 0.117$

EMA, early morning awakening, also referred as trouble waking too early; NRS, non-restorative sleep, also referred as restless sleep or not feeling rested after sleeping; DIS, difficult initiating sleep, also referred as trouble falling asleep; DMS, difficult maintaining sleep, also referred as waking up during the night, trouble waking during night, difficult staying asleep. Forest plot shown in ***Supplementary Figure 1****.*

higher risk of CVD than other insomnia symptoms, which was consistent with previous literature. Zheng et al. (13) combined DIS and DMS as one insomnia symptom (DIMS) in a prospective cohort study of 487,200 Chinese adults. The results showed that DIMS was associated with both ischemic heart disease and ischemic stroke but not hemorrhagic stroke (13). Moreover, DIS or NRS was found to be related to 55 or 32% increased risk of CVD mortality, respectively, among 23,447 US men (21). DIS and DMS were related to a higher risk of total strokes (fatal and non-fatal) at first, but this relationship became insignificant after adjusting for age and other risk factors of stroke in the population-based MONICA/KORA Augsburg Cohort Study (15). Our study did not detect a significantly increased risk of CVDs in insomnia patients with EMA symptom. EMA was related to a slight increase in CVD incidence in the study of China Kadoorie Biobank (HR 1.07, 95% CI 1.05–1.09) (13), while the relationship was remarkable neither in male nor female within a Swedish cohort, which consisted of 13,617 subjects ages 45–64 without CVDs at baseline (14).

The mechanisms of increased risk of CVDs in patients with insomnia symptoms are still unclear. The elevated sympathetic and hypothalamic–pituitary–adrenal axis activity is one of the possible mechanisms (22). DIS and DMS in insomnia patients could induce overall short sleep duration, which was proven to be associated with hypercortisolemia and increased catecholaminergic and autonomic activity, resulting in increased blood pressure and impaired glucose metabolism (23–26). High risk of genotype might be another contributing mechanism (27). Furthermore, an experimental study indicated that insomnia disorder could cause abnormal circulating levels of growth hormone, leptin, and ghrelin in younger adults, aggravating the risk of obesity in this population (28). All these factors can lead to an increased risk of CVD incidence.

LIMITATIONS

There were several limitations in the present meta-analysis. Firstly, the insomnia symptoms of enrolled studies were assessed by self-reported questionnaires or interviews. This may lead to a possible higher risk of selection bias due to the interviewers as well as recall and report bias caused by the participants. Some objective instrument (e.g., polysomnography) could be used in future investigations, but the medical expense is still an unsolved problem. Secondly, since we only included studies with clear insomnia symptoms instead of a general conception, this led to the limited number of entered articles compared to previous reviews. However, with the acceptable quality score and large scale of each cohort study and the result of different associations between individual insomnia symptom and CVD risk, our meta-analysis still provided a remarkable reference for future research. Additionally, we could not enter all the included studies in the sensitivity analysis because not all studies provided the separate HR and 95% CI according to male and female. But the primary results showed that there were much more higher heterogeneity across the female subgroup in all insomnia symptoms, especially for DIS and DMS, which showed borderline heterogeneity in the overall analysis. Therefore, female was accepted as the possible origin of heterogeneity and needs to be further investigated in a future study of CVD incidence risk in insomnia patients with different symptoms.

CONCLUSIONS

In conclusion, this meta-analysis indicated that symptoms of DIS, DIM, or NRS were associated with a higher risk of CVD incidence in insomnia patients free of CVDs at baseline. But this association was not significant in insomnia patients complaining of EMA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

LR and YW conceived and designed the study. TL and SH independently extracted data from the eligible studies and any argument was resolved either by discussion or by involving YW when necessary. SH performed the paper writing with the assistance of TL. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.654719/full#supplementary-material

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REM Sleep EEG Activity and Clinical Correlates in Adults With Autism

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We tested the hypothesis of an atypical scalp distribution of electroencephalography (EEG) activity during Rapid Eye Movement (REM) sleep in young autistic adults. EEG spectral activity and ratios along the anteroposterior axis and across hemispheres were compared in 16 neurotypical (NT) young adults and 17 individuals with autism spectrum disorder (ASD). EEG spectral power was lower in the ASD group over the bilateral central and right parietal (beta activity) as well as bilateral occipital (beta, theta, and total activity) recording sites. The NT group displayed a significant posterior polarity of intra-hemispheric EEG activity while EEG activity was more evenly or anteriorly distributed in ASD participants. No significant inter-hemispheric EEG lateralization was found. Correlations between EEG distribution and ASD symptoms using the Autism Diagnostic Interview-Revised (ADI-R) showed that a higher posterior ratio was associated with a better ADI-R score on communication skills, whereas a higher anterior ratio was related to more restricted interests and repetitive behaviors. EEG activity thus appears to be atypically distributed over the scalp surface in young adults with autism during REM sleep within cerebral hemispheres, and this correlates with some ASD symptoms. These suggests the existence in autism of a common substrate between some of the symptoms of ASD and an atypical organization and/or functioning of the thalamo-cortical loop during REM sleep.

Keywords: autism, ADI-R, REM sleep, qEEG, EEG distribution

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments of social communication and restrictive/repetitive behaviors (1). An atypical brain developmental curve during critical periods is thought to be involved in the physiopathology of ASD, including brain overgrowth in frontal and temporal areas during the early ages followed by a decline of cortical gray matter thickness during adolescence and young adulthood (2, 3).

Quantitative electroencephalography (QEEG) during wakefulness has been extensively used to characterize brain functioning and its relation to autistic symptoms in ASD children and adolescents (4). However, given the age-specific physiopathology of brain atypicalities in ASD, these results may not apply to adults. There are only two QEEG studies in adults with ASD, and even if comparable methods were used, results are inconsistent (5, 6). An eyes-closed QEEG study comparing ASD adults and control aged between 18 and 38 years found group differences in frontal, pre-frontal, parietal and occipital areas, and less relative alpha activity across all these regions (6). Conversely, using the same eyes-closed recording protocol, Mathewson et al. (5) found no

group differences between ASD and typically developing adults on alpha activity while in eyes-open procedure they observe more alpha activity in posterior areas in ASD individuals. These inconsistencies can be explained by the presence of psychiatric comorbidities (6), medications (5, 6), and a wide range of IQ (from 64 to 136) (5).

Resting-state QEEG during wakefulness is also sensitive to experimental settings, including environmental and sensorial inputs (4, 7). Because sensory integration problems are common in autistic individuals with an estimated rate of 90% (8), the experimental environment and sensorial input could influence EEG activity (9). These confounding factors can be controlled by recording the EEG during Rapid Eye Movement (REM) sleep because it is a time of decreased influence of peripheral sensorial input (10, 11) during which a spontaneous and endogenous activation of neural networks occur, making it an ideal condition to study the brain activity.

Sleep studies have shown decreased slow-wave sleep together with atypical non-REM sleep EEG patterns in children and adults on the autism spectrum compared to neurotypical participants, including a decreased density and/or deviant topographical distribution of sleep spindles (12–16), K-complexes (15), and EEG slow-waves (17–21). Studies on REM sleep have not disclosed REM sleep architecture atypicalities in autism but QEEG showed significantly lower spectral power for beta frequency over parietal and occipital recording sites compared to neurotypical controls (22, 23). Specifically in children on the autism spectrum, REM sleep theta spectral power was found to be lower compared to neurotypicals for the left parietal recording sites in one study (23) but not in another (24). In adults with ASD, QEEG analyses disclosed lower NREM sleep delta frequency power over parieto-occipital recording sites but not in the frontal areas as expected (19), suggesting an atypical recruitment of frontal areas. Taken together these results suggest an atypical developmental pattern of the thalamocortical network in children and adults on the autism spectrum.

In order to further test the functioning of the thalamocortical loop in ASD, the present study investigated the topography and distribution of EEG activity along the antero-posterior and transverse axes during REM sleep using a simple but innovative method using spectral power relative distribution. We expected that high-functioning ASD adults would show less beta activity on parietal and occipital electrodes compared to neurotypical adults. Based on previous results on EEG topography in adults with ASD (19, 22), we hypothesized that REM sleep EEG spectral power of high-functioning ASD adults would be anteriorly biased, i.e., higher in anterior than posterior recording sites. Because children with ASD showed an inter-hemispheric left asymmetry in the temporal area (25), we parsimoniously expected the same in adults. To assess the functional consequences of the expected EEG findings, we also explored whether atypical QEEG ratios were statistically associated with scores obtained by the same participants on ASD symptomatology.

TABLE 1 | Demographic, biometric, and clinical characteristics.

	NT	ASD	Student-t/X^2 p-values
Participants (n)	16	17	-
Sex (% male)	93.8	94.1	0.93
Age (years)	20.4 ± 4.6	21.6 ± 3.7	0.40
Manual dominance (L/A/R)	1/0/14	3/2/12	-
Cephalometry			
Circumference (cm)	37.5 ± 2.0	37.1 ± 1.6	0.39
Sagittal (cm)	35.5 ± 1.6	36.1 ± 2.2	0.38
Coronal (cm)	56.4 ± 1.9	57.6 ± 2.4	0.12
Intellectual quotient			
Full IQ	111.2 ± 11.6	103.6 ± 12.05	0.09
Performance IQ	109.2 ± 12.1	102.7 ± 14.0	0.19
Verbal IQ	111.0 ± 10.1	103.2 ± 16.2	0.14
ADI-R			
Social	-	20.4 ± 3.7	-
Communication	-	14.9 ± 4.6	-
Interest	-	7.1 ± 3.4	-

*Results are presented as mean ± standard deviation. IQ, intelligence quotient; L, left handed; A, Ambidextrous; R, right handed. *p <0.05; - = statistical test not performed.*

MATERIALS AND METHODS

Participants

Seventeen ASD participants and 15 neurotypical (NT) controls of similar chronologic age and full-scale IQ (FSIQ) participated in this study (**Table 1**). Individuals with ASD were recruited from the specialized autism clinic of a tertiary care hospital. The diagnosis was based on the Autism Diagnostic Interview-Revised (ADI-R) (26), conducted by a psychiatrist and confirmed by an explicit assessment of DSM-IV criteria (American Psychiatric Association, 1994) through direct observation with the Autism Diagnostic Observation Schedule (27) and/or full clinical investigation. Only participants with a full scale intelligence quotient of at least 80, as indicated by their results on the Wechsler Adult Intelligence Scale, 3rd Edition (28), were included. Exclusion criteria were a complaint or a diagnosis of a sleep disorder, a chronic or current illness, a recent history of night work, drug abuse or current use of psychoactive drugs, as documented by a home-made questionnaire, evidence of psychopathology, as recorded by an experienced clinical psychologist or psychiatrist. The NT group was recruited through public advertisements distributed to hospital employees, parents and friends of laboratory staff, as well as in francophone colleges and universities in the Montréal area. All participants received financial compensation for their involvement in this research. The guidelines of the Declaration of Helsinki were followed by obtaining informed consent to participate, and the research project was approved by the Ethical Review Board of Rivière-des-Prairies Hospital.

Polysomnography Recording

Participants were asked to keep a regular sleep-wake schedule for 14 days before coming to the laboratory, and to refrain from

napping during the day before the recording; none were regular nappers. Beverages containing caffeine and alcohol were not allowed after 12:00 noon.

Participants were recorded for two consecutive nights. Recordings were performed in sound attenuated, well shaded, temperature controlled bedrooms at the sleep laboratory of the Hôpital en santé mentale Rivière-des-Prairies. Participants had the possibility to go to bed and rise at their preferred time. All data reported in this paper come from the second night in the laboratory. The first night was used for adaptation to the recording equipment, the procedures, and the environment. During the first night, respiratory flow and effort were monitored using oronasal cannula and thoraco-abdominal strain gauges, respectively, and transcutaneous finger pulse oximetry was used to monitor arterial blood oxygen saturation. Bilateral anteror tibilais EMG was recorded to detect periodic movements in sleep. EEG was recorded with a 22-electrodes montage positioned according to the international 10–20 system with linked earlobes references (29, 30). A Grass Neurodata Model 15 Acquisition System was used for recording, and signals were digitized at a sampling rate of 256 Hz using Harmonie 5.0B software (Stellate, Montréal, Canada). Filter settings and amplification factors were 1/2 amplitude low frequency filter = 0.3 Hz, 1/2 amplitude high frequency filter = 100 Hz, gain x 1,000 = 20.

Sleep was scored according to standard methods, using 20-s epochs (31). Sleep latency was defined as the occurrence of the first 10 consecutive min of stage 1 sleep or the first epoch of any other sleep stage after lights off. REM sleep periods occur when rapid eye movements, muscular atony, and low amplitudes mixed frequencies were present for more than 50% of an epoch. Ten minutes of non-REM sleep was required between two different REM sleep periods. REM sleep latency was defined as the interval between sleep latency and the first REM sleep epoch. Sleep efficiency was computed as the percentage of sleep time between sleep latency and the final awakening. Polysomnographic recordings did not reveal any patients with an Apnea-Hypopnea Index of 10 or higher nor a Periodic Leg Movement Index of 10 or higher. No cases with epileptiform EEG, with or without corresponding behavioral manifestations, were encountered.

REM Sleep EEG Spectral Activity Data Acquisition

REM sleep EEG samples of 15 four-s segments were taken in similar proportions through the first four REM sleep periods, totaling 60 s of artifact-free EEG signal for each of the 16 electrodes used, i.e.,: Fp_1, Fp_2, F_3, F_4, F_7, F_8, C_3, C_4, T_7, T_8, P_3, P_4, P_7, P_8, O_1, and O_2. EEG samples were taken during ocular (EOG) quiescent periods. Particular attention was paid to discard EEG segments containing EMG artifacts. EEG samples were Fast-Fourier transformed with a resolution of 0.25 Hz and cosine window smoothing. Spectral analysis was performed on the total frequency and four frequency bands were extracted using a commercially available package (Harmonie 5.0B, Stellate, Montréal): Delta (0.75–3.75 Hz), Theta (4.0–7.75 Hz), Alpha (8.0–12.75 Hz), and Beta (13.0–19.75 Hz).

REM Sleep EEG Distribution Calculation of Intrahemispheric Ratios

Intrahemispheric antero-posterior EEG activity ratios between proximal recording sites (i.e., immediately neighboring electrodes) and between distal recording sites were computed with the following formula: [(posterior electrode – anterior electrode)/(posterior electrode + anterior electrode) * 100]. Positive values thus indicate a posterior bias, i.e., that spectral power is higher over the posterior recording site compared to the anterior recording site, relative to the total power expressed by the sum of the two; negative values consequently indicate an anterior bias distribution. This method was previously used by us in neurotypical adults on wake and REM sleep EEG (32).

REM Sleep EEG Distribution Calculation of Interhemispheric Ratios

Interhemispheric activity ratios between left and right homologous electrodes were computed with the following formula: [(right electrode – left electrode)/(right electrode + left electrode) * 100]. Positive values thus indicate a right bias and negative values indicate a left bias distribution.

Statistical Analysis

Demographic and Sleep Characteristics

Statistical analyses were performed with SPSS 25.0 (SPSS Science, Chicago, Illinois, USA). Statistical significance was set at $p < 0.05$. Student *t*-tests and Person Chi-squares were used to test group differences (ASD vs. NT) on demographics (age, sex, IQ) and sleep variables.

REM Sleep EEG Spectral Activity

One-way ANOVAs were used to test differences between ASD and NT groups on log-transformed absolute power values for each electrode for the four frequency bands (Delta, Theta, Alpha, and Beta), and total activity. Levene's test for homogeneity of variance were systematically applied. Effect sizes were calculated using Partial Eta Squares (η_p^2) and full data are provided in the **Supplementary Material**. To compensate for multiple tests performed, only results with large effect sizes were considered as statistically significant ($\eta_p^2 \geq 0.14$) (33).

REM Sleep EEG Intrahemispheric and Interhemispheric Ratios

Group comparisons (ASD vs. NT) on each frequency band for each electrode pairs were done using one-way ANOVAs. Levene's test for homogeneity of variance were also applied. Effect sized were determined with Partial Eta Squares As indicated by Lakens (33), only results with large effect size, i.e., $\eta_p^2 \geq 0.14$, are reported as statistically significant (33).

The Relationship Between REM Sleep Atypical EEG Activity Distribution and ASD Symptoms

The association between atypically-distributed QEEG ratio values and ADI-R subscales scores (social, communication, restricted interests) was assessed with Pearson correlation coefficients.

TABLE 2 | Sleep characteristics in 17 young autistic adults (ASD) and 16 neurotypical controls (NT).

	NT	ASD	Student-*t* *p*-values
Sleep Latency (min)	8.6 ±5.1	18.0 ±14.7	0.02*
TST (min)	459.4 ±49.5	436.1 ±89.9	0.38
Awakenings (number)	22.6 ±17.2	25.1 ±15.9	0.68
Awakenings (min)	24.7 ±29.8	23.5 ±19.2	0.89
Efficiency (%)	95.0 ±5.8	95.0 ±4.2	0.99
Stage 1 (%)	5.0 ±3.0	6.1 ±3.6	0.34
Stage 2 (%)	59.0 ±7.9	61.1 ±8.5	0.50
Stage 3 (%)	8.3 ±2.9	6.1 ±3.5	0.07
Stage 4 (%)	5.1 ±6.7	2.4 ±4.6	0.20
Stage 3+4 (%)	13.4 ±7.6	8.6 ±6.7	0.07
REM (%)	22.6 ±2.8	24.2 ±6.8	0.41
REM latency (min)	70.8 ±17.0	70.0 ±14.8	0.89
REM periods (number)	5.1 ±0.6	4.5 ±1.0	0.05
REM duration	117.4 ±22.0	121.3 ±48.2	0.78

Results are presented as (mean ± standard deviation).
*REM, Rapid eye movement; TST, total sleep time; min, minutes. *p <0.05.*

RESULTS

No significant between-group differences were found in demographic data (**Table 1**). We found significantly longer sleep latency and a trend for less REM sleep periods in the ASD group compared to the NT group (**Table 2**).

Topography of REM Sleep EEG Activity

REM sleep EEG beta and theta activity was significantly lower for the centro-posterior electrodes in the ASD group compared to the NT group (**Figure 1** and **Supplementary Table 1**). More specifically, groups differences appeared on bilateral central electrode [C3 beta ($F_{(1, 30)} = 6.40$, $p = 0.02$); C4 beta ($F_{(1, 30)} = 6.47$, $p = 0.02$)], right parietal area [P4 delta ($F_{(1, 30)} = 5.24$; $p = 0.03$); beta ($F_{(1, 30)} = 7.79$; $p = 0.009$); total ($F_{(1, 30)} = 5.50$; $p = 0.03$), P8 beta ($F_{(1, 30)} = 7.84$, $p = 0.01$)] and bilateral occipital electrodes [O1 beta ($F_{(1, 28)} = 12.64$, $p = 0.001$), theta ($F_{(1, 28)} = 7.25$, $p = 0.01$), delta ($F_{(1, 28)} = 5.20$, $p = 0.03$), total ($F_{(1, 28)} = 5.79$, $p = 0.02$); O2 beta ($F_{(1, 30)} = 9.60$, $p = 0.004$), theta ($F_{(1, 30)} = 7.25$, $p = 0.01$) delta ($F_{(1, 30)} = 6.10$, $p = 0.02$), and total ($F_{(1, 30)} = 6.16$, $p = 0.02$)].

REM Sleep Distribution of Intrahemispheric Proximal Ratios

The NT group generally showed higher ratios on posterior EEG distribution compared to ASD and the ASD group displayed smaller antero-posterior electrodes differences compared to the NT group. **Figure 2** highlight the significant positive (posteriorly biased) proximal ratio differences (see **Supplementary Table 2** for all results). Significantly different positive proximal ratios were found both frontal/pre-frontal area: F3-Fp1 [delta ($F_{(1, 30)} = 7.86$, $p = 0.009$), total ($F_{(1, 30)} = 5.94$, $p = 0.02$)] and F4-Fp2 [delta ($F_{(1, 30)} = 6.65$; $p = 0.015$)]. Left centro-frontal area showed posteriorly biased ratios on C3-F7 [delta ($F_{(1, 29)} = 8.21$, $p = 0.008$); beta ($F_{(1, 29)} = 4.98$, $p = 0.03$); total ($F_{(1, 29)} = 6.43$, $p = 0.017$)]. Parieto-temporal electrodes ratios were significantly positive for P4-T8 [delta ($F_{(1, 30)} = 5.35$, $p = 0.028$)], P7-T7 [delta ($F_{(1, 29)} = 4.52$, $p = 0.042$)], and P8-T8 [delta ($F_{(1, 30)} = 5.48$, $p = 0.026$)]. Right occipito-parietal ratio was significant for O2-P8 [delta ($F_{(1, 30)} = 10.14$, $p = 0.003$); total ($F_{(1, 30)} = 5.81$, $p = 0.022$)].

The only case where the ASD group showed a greater ratio than the NT group involved electrodes pairs for which the ASD group displayed a significant anterior polarity, i.e., we found significant negative ratios for the right centro-frontal electrodes C4-F4 [theta ($F_{(1, 30)} = 4.77$, $p = 0.037$)].

Intrahemispheric Ratios of EEG Activity Between Pairs of Distal Recording Sites

Results showed a higher posterior biased distribution of spectral activity in the group of NT participants compared to the ASD group. Differences between the distal posterior and the anterior electrodes were also lower in the ASD group when ratios had a posteriorly-biased distribution (**Figure 3** and **Supplementary Table 3**).

Group comparisons on intrahemispheric distal ratios showed significant posteriorly-bias differences of the NT group on occipito-temporal electrode pairs O1-T7 [delta ($F_{(1, 28)} = 10.38$, $p = 0.003$); theta ($F_{(1, 30)} = 6.70$, $p = 0.015$); beta ($F_{(1, 30)} = 5.19$, $p = 0.03$); total ($F_{(1, 28)} = 9.45$, $p = 0.005$)], O2-T8 [delta ($F_{(1, 30)} = 12.98$, $p = 0.001$); total ($F_{(1, 30)} = 6.87$, $p = 0.014$)], occipito-frontal O1-F7 [delta ($F_{(1, 28)} = 10.52$, $p = 0.003$); theta ($F_{(1, 28)} = 7.89$, $p = 0.009$); beta ($F_{(1, 28)} = 5.21$, $p = 0.03$); total ($F_{(1, 28)} = 9.57$, $p = 0.004$)], O2-F8 [delta ($F_{(1, 30)} = 13.29$, $p = 0.001$); theta ($F_{(1, 30)} = 6.93$, $p = 0.013$); total ($F_{(1, 30)} = 9.82$, $p = 0.004$)], O2-F4 [total ($F_{(1, 30)} = 4.76$, $p = 0.037$)] and occipito-pre-frontal electrode pairs O1-Fp1 [delta ($F_{(1, 28)} = 14.05$, $p = 0.001$); theta ($F_{(1, 28)} = 8.56$, $p = 0.007$); total ($F_{(1, 28)} = 11.87$, $p = 0.002$)], O2-Fp2 [delta ($F_{(1, 30)} = 22.78$, $p = 0.000$); theta ($F_{(1, 30)} = 9.35$, $p = 0.005$); total ($F_{(1, 30)} = 17.34$, $p = 0.000$)]. Parieto-frontal electrode pairs P4-F8 [delta ($F_{(1, 30)} = 11.11$, $p = 0.002$); total ($F_{(1, 30)} = 7.05$, $p = 0.013$)], P3-F7 [delta ($F_{(1, 29)} = 5.79$, $p = 0.023$)], and parieto-pre-frontal electrode pairs P4-Fp2 [delta ($F_{(1, 30)} = 29.18$, $p = 0.000$); theta ($F_{(1, 30)} = 5.84$, $p = 0.022$); total ($F_{(1, 30)} = 15.77$, $p = 0.000$)], P3-Fp1 [delta ($F_{(1, 30)} = 7.10$, $p = 0.012$)] were also significantly posteriorly biased, as well as centro-pre-frontal electrode pairs C3-Fp1 [delta ($F_{(1, 30)} = 10.6$, $p = 0.003$); alpha ($F_{(1, 30)} = 5.26$, $p = 0.029$); beta ($F_{(1, 30)} = 5.32$, $p = 0.028$); total ($F_{(1, 30)} = 8.81$, $p = 0.006$)], C4-Fp2 [delta ($F_{(1, 30)} = 9.86$, $p = 0.004$); alpha ($F_{(1, 30)} = 4.84$ $p = 0.036$); total ($F_{(1, 30)} = 7.72$, $p = 0.009$)].

Anterior ratios biased results were found on right occipito-frontal electrode pairs O2-F4 [delta ($F_{(1, 30)} = 5.64$, $p = 0.024$)], parieto-frontal P4-F4 [delta ($F_{(1, 30)} = 8.90$, $p = 0.006$); total ($F_{(1, 30)} = 5.52$, $p = 0.026$)] and the right parieto-pre-frontal electrode pair P8-Fp2 [delta ($F_{(1, 30)} = 6.44$, $p = 0.017$); total ($F_{(1, 30)} = 6.20$, $p = 0.019$)].

Interhemispheric Ratios of EEG Activity Between Homologous Pairs of Recording Sites

No significant group differences were found (**Supplementary Table 4**).

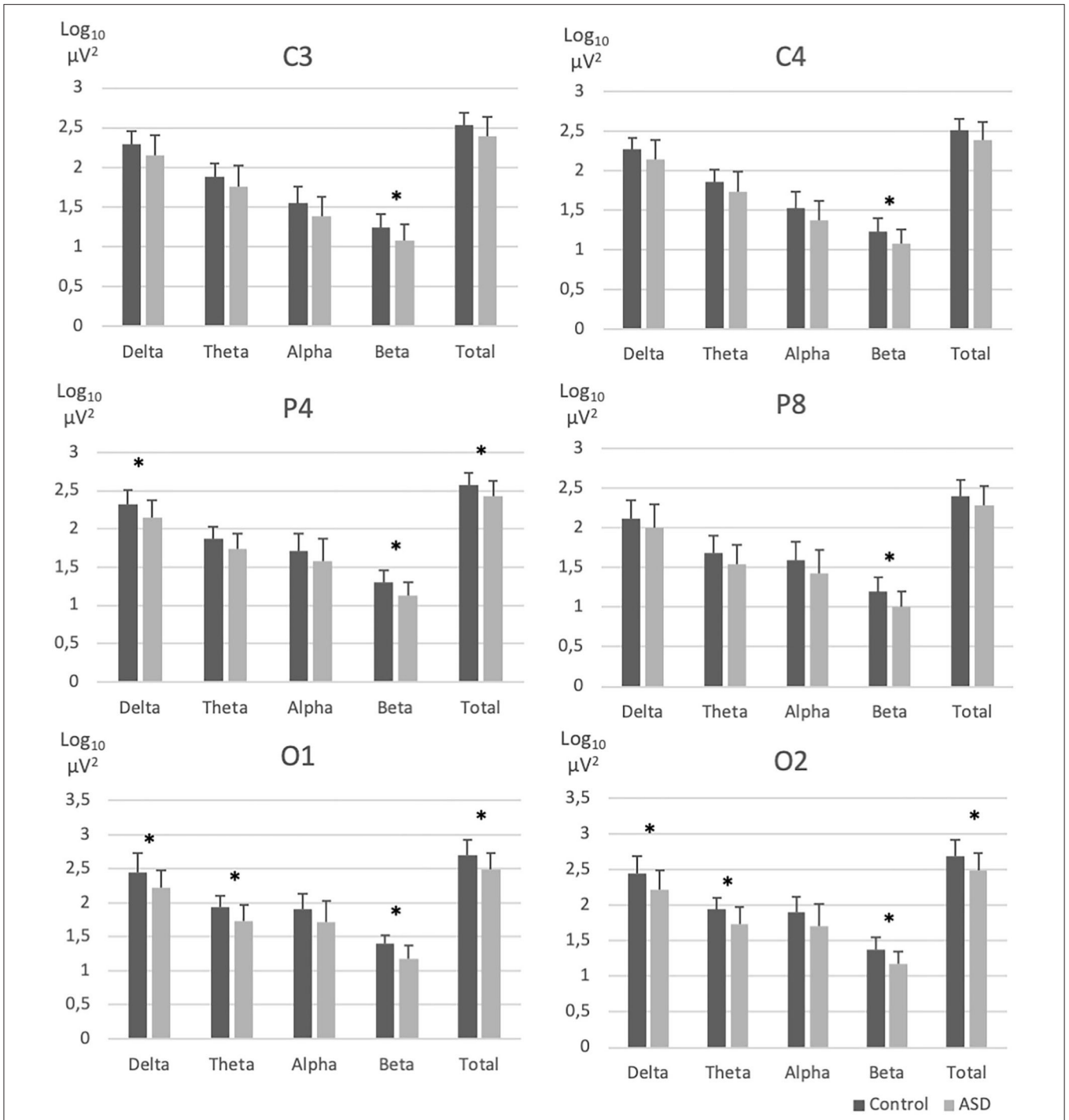

FIGURE 1 | EEG absolute spectral power across frequency bands in electrodes with significant group differences. ASD, Autism spectrum disorder; EEG, Electroencephalography; NT, Neurotypical. Error bars represent standard errors of the means. *$p < 0.05$.

The Relationship Between ADI-R Scores and Atypical QEEG Intrahemispheric Activity Ratios

According to the previous results, correlations were performed only on the four pairs of electrodes with a significant atypical distribution, namely C4-F4, O2-F4, P4-F4, and P8-Fp2. ADI-R communication scale scores were significantly negatively correlated with the activity ratio between C4-F4 and between P4-F4 recording sites in the alpha frequency range (**Figures 4A,B**). ADI-R social interaction scores were significantly negatively correlated with the activity ratio between

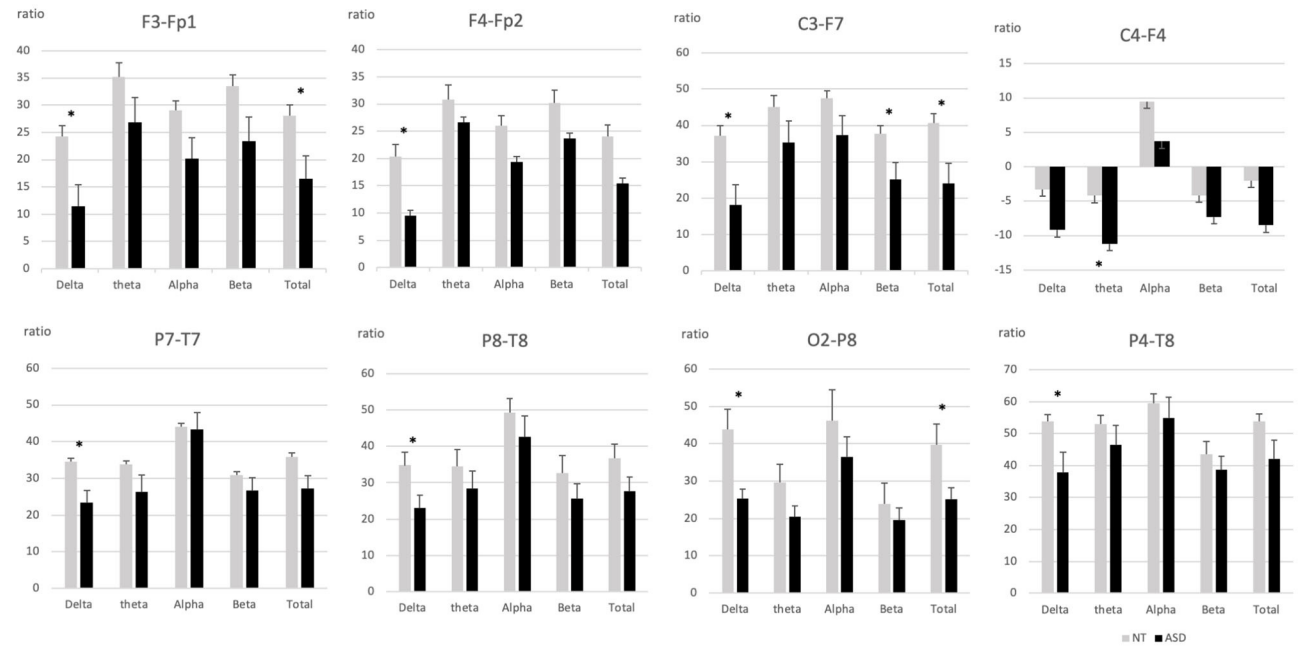

FIGURE 2 | Intrahemispheric proximal ratios across frequency bands in pairs if electrodes with significant group differences. ASD, Autism spectrum disorder; NT, Neurotypical. Error bars represent standard errors of the mean. *$p < 0.05$.

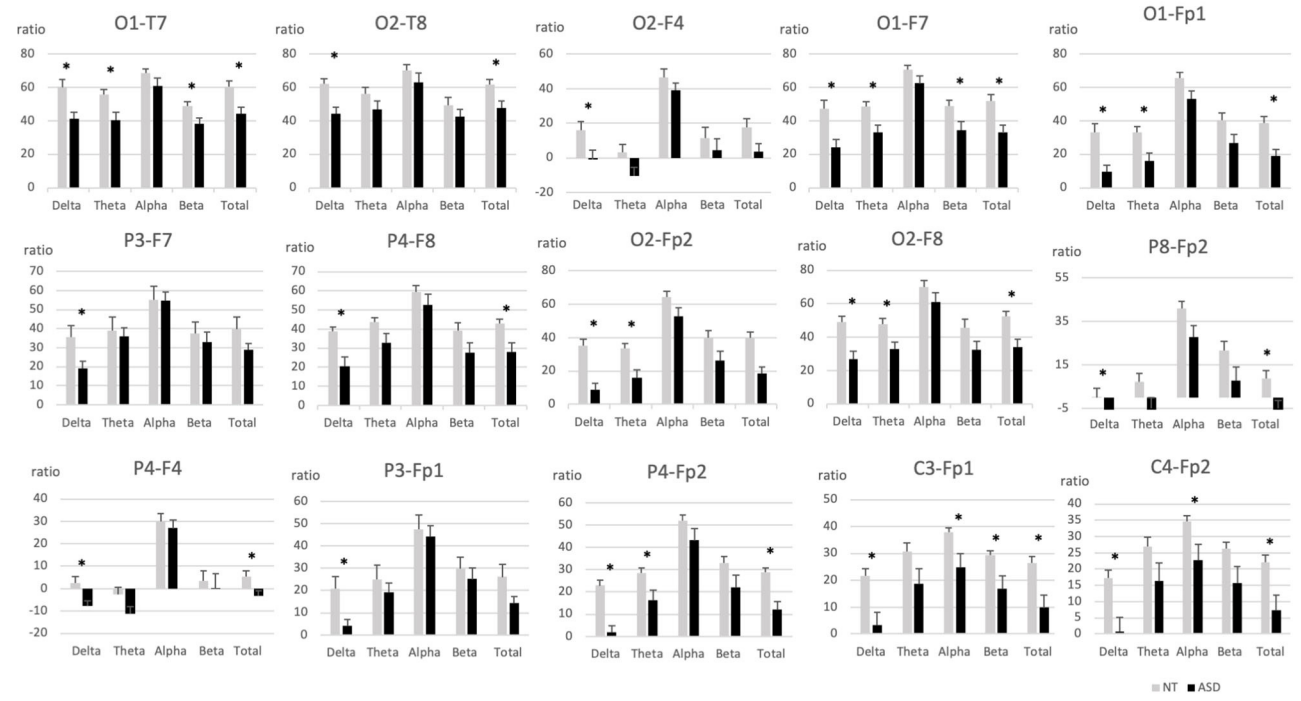

FIGURE 3 | Intrahemispheric distal ratios across frequency bands in pairs of electrodes with significant group differences. ASD, Autism spectrum disorder; EEG, Electroencephalography; NT, Neurotypical. Error bars represent standard errors of the mean. *$p < 0.05$.

C4-F4 recording sites in the alpha frequency range (**Figure 4C**). ADI-R interest scale scores were positively correlated with the activity ratio between O2-F4 and between P4-F4 recording sites in the theta frequency range (**Figures 4D,E**) and also positively between P8-Fp2 recording sites in the beta frequency range (**Figure 4F**).

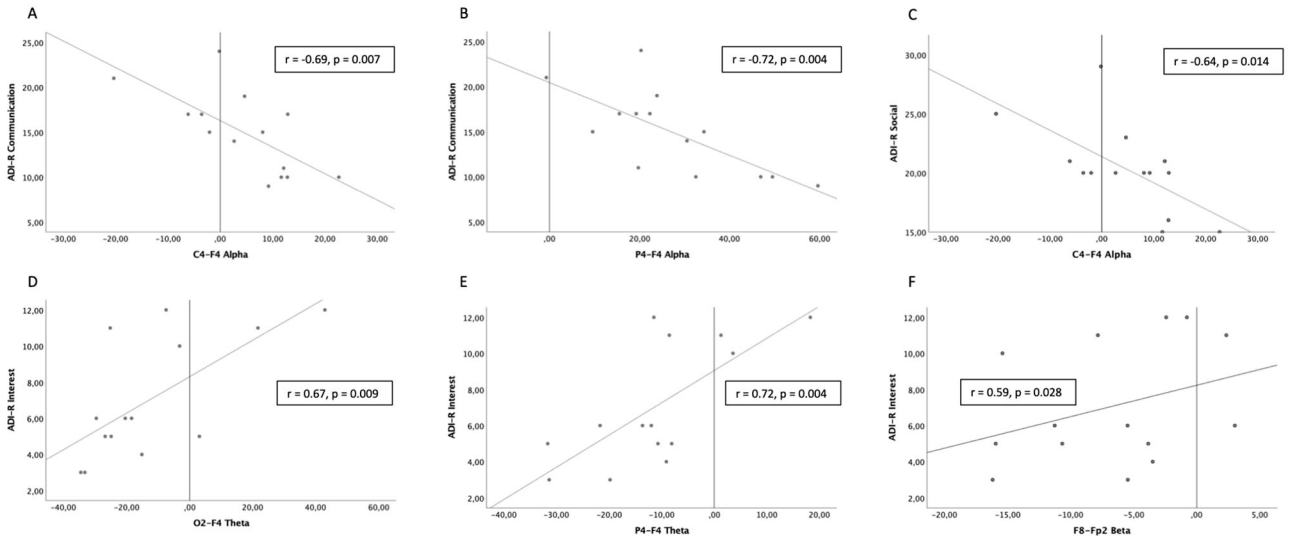

FIGURE 4 | Significant correlations between scores on the Autism Diagnostic Interview-Revised (ADI-R) and intrahemispheric ratios of EEG activity in Autism Spectrum Disorder (ASD) participants. **(A,B)** Communication scores with C4-F4 and P4-F4 activity ratios in the alpha frequency range. **(C)** Social interaction scores with C4-F4 activity ratios in the alpha frequency range. **(D,E)** Restricted interests and repetitive behaviors scores with O2-F4 and P4-F4 activity ratios in the theta frequency range. **(F)** Restricted interests and repetitive behaviors scores with P8-Fp2 activity ratios in the beta frequency range.

DISCUSSION

This study compared REM sleep EEG activity topography and distribution between ASD adults and a NT adult comparison group. The hypothesis of a lower EEG activity in the ASD group over occipital and parietal recoding sites compared to the NT group was supported, with the additional finding of a lower EEG activity over central recording sites. As expected, the intra-hemispheric EEG activity was found to be posteriorly biased in the NT group while it was more evenly or anteriorly distributed in ASD participants. We did not find, however, any interhemispheric group differences. Finally, the higher anteriorly-biased ratios over the right centro-frontal and parieto-frontal areas were associated with higher scores on the communication scale of the ADI-R, whereas the higher anteriorly-biased ratios of the right parieto-frontal and occipito-frontal areas were associated with lower scores on the restricted interests scale.

EEG Topography

Cerebral lateralization in ASD has been a topic of discussion since the mid 1970s (34). The first peer-reviewed journal article on EEG lateralization in autism is possibly that of Dawson et al. (35), with evoked potentials recorded during wake with three electrodes Cz (vertex), midway between C3 and T5 (left hemisphere), and mid-way between C4 and T6 (right hemisphere) and using a simple, imprecise formula (right minus left latencies and amplitudes of evoked responses to a verbal stimulus). The present findings confirm and extend previous results by Daoust et al. (22) in adults and adolescents, because both studies found decreased in REM sleep EEG total power in occipital recording sites of the ASD group. In the present study, additional differences were found over central recording sites. Because the study of Daoust et al. (22) included adolescents, the present findings on central recording sites could be related to developmental aspects. As a matter of fact, a recent retrospective cross-sectional structural MRI study showed an increasing intra-regional cortical thickness variability with age in autism, specifically in occipital, parietal and central areas (36). Longitudinal studies in carefully diagnosed persons with ASD and combining EEG with brain imaging are needed to better understand the effect of atypical cortical development patterns on EEG activity in ASD.

One functional meaning of the present results relates to mental activity during REM sleep, i.e., dreaming. Based on questionnaires, we have previously shown that recall of dream content for the past month was lower in ASD adults compared to controls (37),while others have reported that dream recall was associated with increased beta EEG activity over occipital recording sites (38). This is consonant with the fact that, in the present study, beta EEG activity over occipital recording sites was found to be lower in the ASD group. This is also in agreement with the fact that, on one hand, dream narratives collected following REM sleep awakenings in the laboratory were found to be shorter and that the content was impoverished in ASD adults, including fewer emotional elements while (37), on the other hand, emotions in dreams were reported to be positively correlated with a rightly-biased occipital EEG asymmetry (39).

Relationships Between REM Sleep and Waking EEG Activity

Studies investigated resting-state waking EEG in adults with ASD using an eyes-closed resting-state protocol, which could mimic the sleeping state, found mixed results. Mathewson et al. (5) focused on absolute alpha power frequency and found no group difference over the whole scalp. Murias et al. (6) found frequency-specific group contrasts on relative EEG activity, where anterior

and posterior sites generated less alpha activity, which was compensated with relatively more beta and theta activity, respectively. Because EEG oscillations in the theta range is thought to reflect local cortical processing whereas alpha activity would be rather associated with global cortical processing, their results support the existence of a local overconnectivity and large scale under-connectivity in ASD (40).

Conversely to eyes-closed resting-state, REM sleep represent the spontaneous activity of the brain without interference from external stimuli (10). Sleep studies suggested that different frequency bands during sleep could be associated with specific functional aspects of REM sleep; beta activity would reflect the activation of the neuronal network involved in the control of REM sleep (41) whereas theta activity during REM sleep would be associated with cognitive processing (42). Hence, lower beta and theta activity found in centro-parietal-occipital areas in the present study could represent, on one hand, the expression of an atypical network controlling REM sleep and, on the other hand, an impaired REM sleep-related cognitive processing in ASD individuals.

Lower EEG Power Differences Across the Scalp During REM Sleep in ASD

The distribution of REM sleep EEG activity was mostly posteriorly distributed in NT as well as in the ASD group. Interestingly, ASD individuals had less EEG activity differences between intrahemispheric anteroposterior recording sites compared to NT. This suggests atypicalities in thalamo-cortical and cortico-cortical functioning in ASD (10), which is supported by the recent findings of particularities in cortico-cortical and thalamo-cortical projections. Studies using structural magnetic resonance imaging (MRI) investigated cortical thickness found gray matter reductions in all cortical regions of adults with ASD (43–46). Moreover, also using structural MRI, Ecker et al. (47) showed that cortico-cortical connectivity was locally and globally reduced in ASD. These results suggest that lower cortical EEG activity and its atypical distribution between proximal recording sites in ASD could be explained by gray matter and cortico-cortical connectivity atypicalities.

Longitudinal studies using structural MRI in ASD showed an atypical white matter development from childhood to adulthood, including a significant decrease in the mean volume of white matter (46) as well as an absence of increasing fractional anisotropy with age (48). The latter study also reported that axial diffusivity was decreasing with age in ASD, but not in typically developing individuals. These suggest the presence in ASD of fewer/thinner axons, decreased myelination, and less coherence in the directions of myelination over development, which could influence EEG difference between distal electrodes (48–51).

Taken together, imaging studies support the idea of atypical development of neural circuits through adulthood that could influence REM sleep EEG production and distribution in adult ASD. Atypical gray and white matter development could affect the cortico-cortical and thalamo-cortical neurophysiological activity and lead to an atypical topography of EEG activity as shown here as well as in previous studies on REM sleep (22) and on non-REM sleep EEG (19).

Anteriorly-Biased EEG Power Distribution in ASD

Higher anteriorly-biased EEG distribution in ASD was found in right parieto-frontal/pre-frontal, occipito-pre-frontal, and centro-frontal areas. While this anteriorly-biased EEG distribution could be explained, at least partly, by a lower EEG spectral power in posterior electrodes the literature rather points toward atypical spectral power in anterior areas. On one hand, studies investigating resting-state networks using MRI, EEG, and magnetoencephalography have shown network atypicalities that included frontal areas, such as the default mode and the sensorimotor networks (52–54). Moreover, EEG overconnectivity was found in bilateral frontal and left parietal areas (53). On the other hand, EEG coherence activity during REM sleep in adults with autism (55) showed a different pattern, with a lower connectivity in the right frontal area while occipital areas were overconnected to other intrahemispheric regions compared to neurotypical controls. This posterior overconnectivity could reflect a greater influence of the white matter between occipital areas and other regions (56), whereas the lower spectral power in occipital areas could be a result of lower gray matter density (57).

Functional Imbalance of QEEG Distribution in Bilateral Parieto-Occipital and Right Frontal Areas During REM Sleep

Although we found significant differences in slow (Delta, Theta) and high (Beta) EEG frequency distribution, it may be early to interpret the functional specificity of each frequency band at this point but the results can be discussed at the level of functional intrahemispheric QEEG imbalance involving the bilateral parieto-occipital and the right frontal areas. REM sleep plays a key role in memory consolidation, emotional processing (58), and is the physiological support of dreaming (38) (and see EEG Topography, above). During REM sleep, the frontal area is active and has been associated with recent emotional processing and memory (59). Consequently, right frontal EEG activity could represent a greater load of emotional regulation/consolidation during REM sleep in ASD, or an atypical process of emotion regulation/consolidation. Both REM and NREM sleep are implicated in memory consolidation (60, 61) and frontal NREM sleep slow EEG activity is positively associated with the learning index of a sensory-motor procedural task in ASD (19). This support the activation of the frontal area in memory consolidation during sleep in individuals with ASD.

Parieto-occipital areas are supporting the production of visual oneiric content (62, 63). Oneiric content has been found to be less elaborate in ASD after controlling for confounding factors (37). Therefore, lower QEEG in the parieto-occipital areas could reflect the poor quality of visual oneiric content during REM sleep.

Relationship Between ASD Symptoms and REM Sleep Anteriorly-Biased QEEG Activity Distribution

Anteriorly-biased activity ratios on proximal as well as distal pairs of recording sites were associated with higher scores

on the ADI-R social and communication scales (i.e., low social and communication skills) while anteriorly-biased activity ratios on distal pairs of recording sites were associated with lower scores on the ADI-R interest scale (i.e., less restricted interests and repetitive behaviors) in the ASD group. All significant correlations involved EEG activity recorded over the right hemisphere. Interestingly, abilities that are crucial for adapted social interactions (i.e., attribute thoughts and feelings to self and others) and communication (i.e., pragmatic language) are reported to involve the right hemisphere (64–66). Moreover, the right frontostriatal loop has been identified as a potential neuronal substrate of restricted interests and repetitive behaviors in autism (67, 68). To our knowledge, no study has investigated the associations between the ADI-R scales and EEG distribution activity in ASD and the present results adds to the existing literature suggesting that an atypical right hemisphere functioning could contribute to ASD behavior as measured by the ADI-R.

Strength and Limitations

This research innovates by investigating cortical activity distribution across brain regions using a simple method. Considering sensorial challenge encountered by ASD individuals during the wake state, another strength of the present method is the use of REM sleep EEG to minimize interference from external inputs.

Recent imaging studies have shown increased intraregional cortical thickness variability in individuals with ASD (36, 54). In this context, the relatively small sample studied here could be seen as a limitation. However, the ASD participants were clinically characterized in the most stringent manner, including the absence of medication, intellectual disability, psychiatric or sleep disorder.

CONCLUSION

We found an atypical scalp distribution of EEG activity in ASD participants during REM sleep, with less activity in centro-posterior areas and lower EEG power differences across recording sites. Significant higher anterior EEG distribution was shown in ASD and this anterior bias was associated with ASD core symptoms, such as poor communication skills and less restricted interests. Our results provide new and independent evidence of the presence of a relation between EEG activity and the ASD phenotype. Concurrently, this highlights the importance of studying REM sleep EEG activity in subsequent studies that would like to establish a detailed portrait of clinicopathological associations with EEG activity in the ASD population.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because these data are confidential and need an authorization from the ethical review board of the Hôpital Rivière-des-Prairie to be shared. Requests to access the datasets should be directed to comite.ethique.recherche.cnmtl@ssss.gouv.qc.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical review board of Hôpital en santé mentale Rivière-des-Prairies. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KG contributed to the study design, data analysis and interpretation, manuscript redaction, and revisions. CB contributed to the study conception and design, data collection, data analysis, manuscript redaction, and revisions. LB contributed to study design, data interpretation, manuscript redaction, and revisions. RG contributed to study conception and design, data collection, data analysis, data interpretation, manuscript redaction, and revisions. All authors approved the final version for publication and are accountable for all aspect of the work.

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Agomelatine, A Potential Multi-Target Treatment Alternative for Insomnia, Depression, and Osteoporosis in Postmenopausal Women: A Hypothetical Model

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Insomnia, which is associated with menopausal depression, is a common symptom of menopause. Both symptoms have a common etiology, and can affect each other significantly. Pharmacological interventions, including hypnotics and antidepressants, and non-pharmacological therapies are generally administered in clinical practice for insomnia treatment. As another menopausal disorder, osteoporosis is described as a disease of low bone mineral density (BMD), affecting nearly 200 million women worldwide. Postmenopausal osteoporosis is common among middle-aged women. Since postmenopausal osteoporosis mainly results from low estrogen levels, menopausal hormone therapy (HT) is considered the first-line option for the prevention of osteoporosis during the menopausal period. However, almost no study has evaluated novel treatments for the combined prevention of insomnia, depression, and osteoporosis. Hence, it is necessary to develop new multi-target strategies for the treatment of these disorders to improve the quality of life during this vulnerable period. Melatonin is the major regulator of sleep, and it has been suggested to be safe and effective for bone loss therapy by MT-2 receptor activity. As a result, we hypothesize that agomelatine, an MT-1 and MT-2 receptor agonist and 5-HT_{2C} receptor antagonist, holds promise in the combined treatment of insomnia, depression, and osteoporosis in middle-aged women during menopause.

Keywords: menopause, insomnia, depression, osteoporosis, melatonin, agomelatine

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INTRODUCTION

Menopause, described as the termination of menstruation, indicates a significant transition regarding reproductive status in women. The menopausal transition (MET), starting 4–6 years before the discontinuation of menses (1), is associated with hormonal fluctuations and physiological and psychological symptoms, such as sleep disturbances, hot flashes (HF), and mood changes—the frequency, severity, and duration of which may vary among women (2). Among these symptoms, as a climacteric vasomotor symptom (VMS) (3), HF is a criterion for MET and has been reported to occur in about 80% of women (1). Hot flashes includes a sensation of heat, sweating, and chills (4). Globally, about 470 million women are in the postmenopausal phase; the number of which increases by 1.5 million each year, and it is expected to reach 1.2 billion by 2030.

Approximately 50–85% of these women will experience VMS associated with menopause (5). In several studies, the relationship between sleep disorders and VMS has been investigated. Findings of a previous study, conducted among 962 midlife women, revealed a marked relationship between sleep disorders and VMS. About 81.3% of these women had severe VMS and poor-quality sleep; and 43.8% of them met the criteria for chronic insomnia (6). Additionally, the severity of insomnia was reported to have a correlation with HF and night sweats, and these symptoms are associated with a large-scale possibility of a diagnosis of insomnia (28.5% in women with HF and 10.5% in women without HF) (6). In accordance with the "domino effect theory," HF disrupts sleep and leads to insomnia, which then increases vulnerability to depression. As a result, insomnia follows sleep disruption, and depression follows insomnia in a vicious cycle (6, 7). Additionally, Caruso et al. (2) reported that age-related irregularities in circadian rhythm may have a role as a mechanism preceding both sleep and mood disorders.

BIDIRECTIONAL RELATIONSHIP BETWEEN INSOMNIA AND MAJOR DEPRESSION IN MENOPAUSE

Clinical depression (including major depression) is known to be widespread with lifelong rates for women being 1.5–2 times higher than those for men. It is a complicated disorder, having several factors relevant to emotional, physical, and functional morbidity (8). Women may be at increased risk of depression during hormonal periods, such as MET, puberty, and pregnancy (9); and depressive symptoms are known to worsen throughout MET (1). Insomnia is described as a difficulty in initiating or sustaining sleep or the feeling that sleep is non-restorative, despite adequate opportunity for sleep (10). Insomnia is suggested to have a close relationship with depression and depressive disorders along the MET period (4). Insomnia symptoms are one of the most common complaints reported during the peri- and post-menopausal periods (11). Approximately 25–30% of the population have symptoms of insomnia, and this rate increases to 39–60% among women in the peri-menopausal period. Insomnia has been shown to increase the risk of developing depressive symptoms by 2–3 times during the peri-menopausal period of a woman's life (2), and more importantly, it often triggers depression (11). A 13-year mental health longitudinal study by the Study of Women's Health Across the Nation (SWAN) revealed that insomnia may have a contribution to the permanence and relapse of major depressive disorder (MDD) throughout menopause (8). Hence, it seems that women having sleep problems at MET may be at risk of depression in subsequent years. Disturbed sleep, a major criterion of depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is prevalent among women having clinical depression (8). Considering this relationship between insomnia and depression, women with menopausal insomnia seem likely to be at greater risk of depression due to the additional burden of poor sleep. Thus, the determination of safe and effective treatments for menopause-related insomnia disorders that also ameliorate comorbid depressive symptoms is advisable (11). All these results indicate that alleviating insomnia would improve not only insomnia symptoms but also depressive symptoms. Tal et al. (5) reported that treatment for sleep disturbance enhanced treatment of depression or alleviated depressive symptoms altogether.

INSOMNIA TREATMENT BY NON-HORMONAL PHARMACOLOGICAL OPTIONS

For the diagnosis and treatment of insomnia, cognitive behavioral therapy for insomnia (CBT-I) is proposed as the first-line treatment for chronic insomnia in adults of any age in the general population. However, pharmacological alternatives are recommended when CBT-I is not effective or available (7). These options include benzodiazepines, non-benzodiazepine hypnotics (Z-drugs), antidepressants, antipsychotics, and melatonin as non-hormonal pharmacological options (12). Additionally, menopausal hormone therapy (HT) is effective for sleep disorders in menopausal women (7). However, results based on several clinical studies investigating the effects of HT on insomnia in menopause are inconsistent (13), and numerous factors are involved in this treatment process, including the range of treatment protocols, dosages, and formulations (14). More importantly, a recent meta-analysis involving a search of 424 defined articles, from which 42 trials, showed that only menopausal women with VMS have an improvement in the quality of life with HT (15). Therefore, non-hormonal interventions, including antidepressants, seem likely to be better for use in this context for treating insomnia in this patient population. The use of antidepressants is not recommended in the treatment of menopause-related insomnia unless depression is present (12). Given that insomnia and depression have high comorbidity (16, 17) and shared etiology (18, 19), gold standard treatments for insomnia relevant to menopause should also ideally treat comorbid depressive symptoms in peri- and post-menopausal women at risk for depression (11). As mentioned before, since insomnia is the main criterion for depression according to DSM-5, insomnia treatment in menopausal women is also of great importance for the treatment of depression. Additionally, it would provide an alternative strategy for the indirect treatment of osteoporosis, which has a direct relationship with depression during menopause.

THE EFFECT OF DEPRESSION ON MENOPAUSE-INDUCED OSTEOPOROSIS

Osteoporosis is defined as a disease of low bone mineral density (BMD) or excessive bone loss, affecting 200 million women worldwide (20). Postmenopausal osteoporosis is prevalent in middle-aged women. Half the population of postmenopausal women have been suggested to suffer from an osteoporotic fracture in their lifetime, and those who have had a fracture are at high risk of subsequent fractures (21). More importantly, fractures resulting from osteoporosis are known to be more widespread than stroke, myocardial infarction, and breast cancer, combined. For women aged 50 years, the risk of a

fracture due to osteoporosis is 50% in their lifetime (22). As mentioned before, depression is a disease that affects women more than men (8) and is directly related to decreased BMD (20). The relationship between menopause-induced depression and osteoporosis reveals that depression is a risk factor for osteoporosis during the postmenopausal period. During this period, women with depression have lower BMD, and are more likely to have osteoporosis than non-depressed postmenopausal women (20).

AGOMELATINE

Agomelatine is an antidepressant that combines non-monoaminergic signaling with the classical monoaminergic mechanism. It was first introduced to the market in 2009 and was licensed for MDD treatment in adults (23). It acts as an agonist of melatonergic-1 (MT-1) and melatonergic-2 (MT-2) receptors, and as a neutral antagonist for serotonergic (5-HT_{2C}) receptors (24). Agomelatine is beneficial in MDD treatment and effective in the alleviation of sleep complaints (25). Agomelatine's monoaminergic and melatonergic mechanisms of action restore sleep and increase mood throughout the day. As a result, patients' quality of life is improved (25). Melatonergic and 5-HT_{2C} receptors are expressed in the suprachiasmatic nucleus, cerebral cortex, hippocampus, amygdala, and thalamus, which are involved in the pathophysiology of depression (26). MT-1 receptor expression has a daily rhythm regulated by daylight and the internal clock. Likewise, the expression of 5-HT_{2c} receptor mRNA has a circadian rhythm. Hence, agomelatine can be said to have a two-way effect. At night, the melatonin system dominates and favors sleep, whereas diurnal dominant 5-HT_{2c} blockade favors wakefulness (27). Interactivity between 5-HT_{2c} and MT receptors contributes to agomelatine's efficacy in depression by resynchronizing disrupted circadian rhythms (28). The binding affinities, half-life, and relative potencies of agomelatine and melatonin are presented in **Table 1** (29).

AGOMELATINE AND MELATONIN IN DEPRESSION, INSOMNIA, AND BONE ACTIVITY

A recent systematic review involved randomized double-blind controlled clinical trials on patients with mood disorders, including MDD. In these studies reviewed, melatonin was used as an augmentation strategy in MDD (30). Among these studies, Dolberg et al. (31) revealed that using 5–10 mg slow-release (SR) melatonin with 20 mg of fluoxetine had no effect on MDD. Similarly, Serfaty et al. (32), using 6 mg melatonin only, had no effect. A third study, however, revealed that buspirone (15 mg) combined with melatonin-SR (3 mg) elicited a more significant antidepressant effect than placebo or buspirone monotherapy (33). Consistent with these results, a systematic review and meta-analysis showed that melatonin had no therapeutic or prophylactic effect against depression or depressive symptoms (34). Therefore, melatonin may be thought to not have an antidepressant effect *per se* (35). Consequently, the antidepressant activity of melatonin has been suggested as controversial (35). According to expert opinion, the evidence supporting the clinical use of melatonin should be carefully reviewed (30). Regarding agomelatine, most reviews consensually support the idea that agomelatine has antidepressant efficacy (36–40). Moreover, according to a meta-analysis study, the antidepressant efficacy of agomelatine has been established by 20 trials with 7,460 participants that agomelatine was significantly more effective than placebo in MDD (41). Doses of 25–50 mg/day have been used in comparative experiments and placebo-controlled trials. The doses of agomelatine have been indicated to be within this range (42). However, almost no study has investigated the effects of agomelatine on MDD in menopausal women. Heun et al. (43) in comparing the effectiveness of agomelatine (25–50 mg/day p.o.) to that of placebo in an 8-week treatment schedule of elderly patients ($\geq$ 65 years old) with recurrent MDD, proposed agomelatine (25–50 mg/day) to be more effective and well tolerated in elderly patients with depression. Additionally, agomelatine has been shown to be well tolerated by patients with only minimum deviations from placebo, and it has a good safety profile in such patients, including elderly patients (43). Besides, 69.5% of the 151 patients who received agomelatine were elderly women in this study. To the best of our knowledge, however, no study compared the antidepressant activity of agomelatine and melatonin on menopausal period in the literature. Thus, apart from melatonin, the current results suggest that agomelatine may be addressed as a reasonable choice for the elderly population, including menopausal women because of its good tolerability, effectiveness on symptoms, and better adverse effect profile.

As mentioned earlier, there is a bidirectional relationship between insomnia and MDD in menopause. Insomnia has been suggested to increase the risk of experiencing depressive symptoms by 2–3 times during the peri-menopausal period (2), and it often causes depression (11). Melatonin has been suggested to relieve all subjective sleep symptoms of postmenopausal women with insomnia (7). Additionally, melatonin has a moderate hypnotic effect in insomnia treatment and does not cause morning hangover symptoms (44–46). In the last few decades, prolonged-release melatonin (PRM) (2 mg) for insomnia with reduced sleep quality in people over 55 years old has been accepted (47, 48). It is the only melatonin-containing drug that was accepted, and its prolonged-release mechanism mimics the internal melatonin secretion pattern by progressively releasing melatonin (7). PRM (2 mg) improved sleep efficiency,

TABLE 1 | Some properties of melatonin and agomelatine (29).

	Melatonin	Agomelatine
Binding affinity	MT_1: 0.085 nM	MT_1: 0.062 nM
	MT_2: 0.263 nM	MT_2: 0.268 nM
Half-life	45 min	1–2 h
Protein binding	70%	95%
Relative potency	MT_1:1	MT_1:1
	MT_2:1	MT_2:1

morning wakefulness, and quality of life, as well as sleep latency, among people aged 55–80 years—these benefits were sustained or augmented over 6 months (47). The majority of hypnotic-related safety issues do not arise with PRM (2 mg). Accordingly, PRM (2 mg) can be suggested as a useful therapeutic option for menopausal women and stands for a safer choice over benzodiazepine or Z-drugs (7).

Regarding the effects of agomelatine on insomnia, it is suggested to have benefits with initial insomnia. Additionally, it increases sleep duration and performance, and decreases daytime drowsiness. However, it does not affect the sleep architecture of patients with depression (49). In a randomized double-blind controlled study, agomelatine presented significantly better improvement than venlafaxine on insomnia in patients with depression (28). In another randomized double-blinded study, Quera-Salva et al. (50) showed that agomelatine more significantly reduced sleep latency than escitalopram. In randomized clinical trials comparing agomelatine to selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, agomelatine enhanced all parts of the sleep–wake cycle, especially during the initial stages of sleep and sleep quality, as well as daytime alertness (51). Agomelatine has also been found to be effective in alleviating circadian rhythm disturbances reported in patients with MDD (29). Melatonin treatment in menopause for insomnia has been suggested to reduce sleep disturbances during menopause. Although no study directly compares melatonin and agomelatine in the treatment of insomnia, agomelatine seems to hold promise for insomnia treatment in menopausal women.

Melatonin is known to have positive effects on bone health and is suggested to have likely therapeutic potential on postmenopausal osteoporosis (52). Li et al. (53) reviewed the role and importance of melatonin in bone metabolism. In relation to the effects of melatonin on osteoporosis, Sharan et al. (52) showed that melatonin reverses bone loss by greatly increasing bone formation in ovariectomized mice, which are the animal models of menopause-induced osteoporosis. According to the study findings, MT-2 is the receptor responsible for the effect of melatonin on osteoblasts, whereas inactivation of MT-1 does not affect bone mass. Conversely, agomelatine, as an MT-1 and MT-2 agonist, has not been studied in osteoporosis occurring among menopausal women. However, one recent study showed that agomelatine has ameliorative effects on bone fracture healing in rodents (54). Bone mass is known to be formed by either excessive osteoclastic bone resorption or reduced osteoblastic bone formation. The bone remodeling process starts by proliferation, differentiation, and activation of mononuclear precursors. Two crucial proteins have important roles in these processes: receptor activator of NF-κB ligand (RANKL) and its soluble decoy receptor osteoprotegerin (OPG). RANKL binds to its cellular receptor RANK and stimulates differentiation and activation in osteoclasts resorbing bone. Osteoprotegerin inhibits osteoclastogenesis by binding and inactivating RANKL (55). Zhou et al. (56) reported that RANKL was suppressed by melatonin. Compatible with these findings, in the same study, the OPG/RANKL ratio, which is an important determinant of bone mass and skeletal integrity (57), has been suggested to be elevated by melatonin in bone marrow mesenchymal stem cells. Additionally, NF-κB was inactivated via the MT-2 receptor, which is responsible for melatonin-regulated osteogenesis. Hence, considering all these results, agomelatine may possibly have such an effect via the MT-2 receptor on osteoporosis in menopausal women.

THE HYPOTHESIS

Guided by literature, we hypothesize that agomelatine may be a new alternative in the combined treatment of insomnia, depression, and osteoporosis in menopausal women, treating these three disorders concurrently in comorbid conditions.

EVALUATION OF THE HYPOTHESIS

Insomnia and depression are known to have a mutual relationship without clarity of the direction of effect on each other (58). This relationship also indicates that the association between depression and insomnia is not simply a cause-effect relationship, but instead a complex bidirectional one (59). Altogether, treatment of insomnia most likely may positively affect depressive symptoms in menopausal women due to their comorbidity. In a recent study supporting this situation, insomnia treatment was reported to significantly contribute to the reduction of depressive symptoms (11). Hypnotics and antidepressants are generally prescribed for the treatment of patients with comorbid of depression and sleep problems. However, hypnotics may lead to depression (59). Benzodiazepine hypnotics have many different side effects, including next-day hangover and rebound insomnia, and the next-day hangover is reported to be the most frequent complaint reported by patients using benzodiazepines. Benzodiazepines were suggested to significantly decrease sleep latency and increased total sleep duration (60). However, they are associated with significant adverse events on long-term use (60). Concerning SSRIs as a treatment for insomnia, a comprehensive review of the literature suggests that escitalopram is a safer alternative, as an SSRI, among the various antidepressants, especially with comorbid depression, for the treatment of insomnia in menopause (13).

However, SSRIs are suggested to probably increase fracture risk by decreasing BMD. Conversely, according to a US randomized placebo-controlled trial conducted that assessed the effect of escitalopram on bone turnover markers, escitalopram does not change it in short-term usage. Additionally, the trial confirmed that the result of the study could not be generalized for the long-term use of other SSRIs (61). Moreover, antidepressants in this group have many different side effects (62), and one of the most prominent of these side effects was reported to be on sleep (60). From this point of view, since agomelatine has a better side-effect profile, efficacy, and tolerability in the treatment of depression than SSRIs, as an antidepressant and sleep regulator, due to its ability to alleviate complaints about sleep disorders (60), it stands out as a new multi-target

alternative for insomnia, depression, and osteoporosis treatment with minimum adverse effects.

CONCLUSION

Regarding the domino effect observed in the vicious cycle involving insomnia and depression, the use of agomelatine, an antidepressant that has been proven effective in both disorders, to break this cycle would reduce both the treatment burden and global financial burden of drug consumption for patients with comorbidity insomnia and depression. Concurrently, the treatment is predicted to contribute to the improvement of osteoporosis, which seriously affects the quality of life of middle-aged women and causes bone tissue fractures in subsequent years. This bidirectional therapeutic effect provided by agomelatine is very important, since improvements in sleep in patients with depression are associated with a reduction in the recurrence rate of depressive symptoms (60). Therefore, the ameliorative effect to be achieved with agomelatine in patients with comorbid depression and insomnia would ensure that both disorders would be cured along with osteoporosis.

FUTURE PERSPECTIVE

If our hypothesis is correct, agomelatine would come into prominence as a multi-target agent due to its curative effect on insomnia, depression, and osteoporosis, which are commonly seen in menopausal women. However, some important points need to be stressed. First, the use of agomelatine would seem to be a rational choice for middle-aged women comorbid with depression and insomnia due to its bidirectional effects. Additionally, since agomelatine has a good therapeutic potential for depression, it may have an indirect preventive role against osteoporosis, given that depression itself is an important risk factor for osteoporosis. Based on a recent study, it can as well directly heal osteoporosis through MT-2 receptors (52). Concerning agomelatine's antidepressant and sleep constructive effect in menopausal women, only one pilot study has been conducted to date (63). Seemingly, agomelatine, as a novel therapeutic avenue for being a multi-target drug, would treat all three diseases concurrently in this specific patient population, since health issues (especially for insomnia and depression) in middle-aged women are likely linked together and coexist.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AY developed the hypothesis and wrote the manuscript. MRO contributed to the literature review and manuscript editing. HK is the coordinator of the paper, he critically revised the article for important intellectual content. All authors contributed to the article and approved the submitted version.

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A Novel Group Cognitive Behavioral Therapy Approach to Adult Non-rapid Eye Movement Parasomnias

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Background: Following the success of Cognitive Behavioral Therapy (CBT) for insomnia, there has been a growing recognition that similar treatment approaches might be equally beneficial for other major sleep disorders, including non-rapid eye movement (NREM) parasomnias. We have developed a novel, group-based, CBT-program for NREM parasomnias (CBT-NREMP), with the primary aim of reducing NREM parasomnia severity with relatively few treatment sessions.

Methods: We investigated the effectiveness of CBT-NREMP in 46 retrospectively-identified patients, who completed five outpatient therapy sessions. The outcomes pre- and post- CBT-NREMP treatment on clinical measures of insomnia (Insomnia Severity Index), NREM parasomnias (Paris Arousal Disorders Severity Scale) and anxiety and depression (Hospital Anxiety and Depression Scale), were retrospectively collected and analyzed. In order to investigate the temporal stability of CBT-NREMP, we also assessed a subgroup of 8 patients during the 3 to 6 months follow-up period.

Results: CBT-NREMP led to a reduction in clinical measures of NREM parasomnia, insomnia, and anxiety and depression severities [pre- vs. post-CBT-NREMP scores: P (Insomnia Severity Index) = 0.000054; P (Paris Arousal Disorders Severity Scale) = 0.00032; P (Hospital Anxiety and Depression Scale) = 0.037]. Improvements in clinical measures of NREM parasomnia and insomnia severities were similarly recorded for a subgroup of eight patients at follow-up, demonstrating that patients continued to improve post CBT-NREMP.

Conclusion: Our findings suggest that group CBT-NREMP intervention is a safe, effective and promising treatment for NREM parasomnia, especially when precipitating and perpetuating factors are behaviorally and psychologically driven. Future randomized controlled trials are now required to robustly confirm these findings.

Keywords: cognitive behavioral therapy, NREM parasomnia, parasomnia, treatment, therapy

INTRODUCTION

Non-Rapid Eye Movement (NREM) parasomnias, or arousal disorders, are common in adults, where they represent a constellation of different unwanted behaviors and experiences, arising from or associated with sleep, for example from sleep walking to sexsomnia (1). In addition to night-time symptoms, they can also result in next day excessive tiredness, as well as adversely affect mood, cognition, and quality of life (2). Genetic predisposition plays a role and it is most evident in sleepwalking (3). Arousal disorders can be an important cause of sleep-related injury (4, 5), and it is crucial that their severity can be reliably diagnosed and assessed. More recently, Arnulf et al. (5) developed the Paris Arousal Disorders Severity Scale (PADSS), which has been consistently demonstrated across different NREM parasomnia phenotypes to reliably monitor and measure the clinical symptoms and severity of arousal disorders.

The understanding of the exact neurobiology and the maladaptive arousal mechanisms that underlie phenotypes of NREM parasomnia remains in its infancy (3, 6–8). Management is commonly multifaceted with an emphasis on psychoeducation and ideally on non-pharmacological measures (3). Pharmacotherapy is nonetheless frequently used in the treatment of NREM parasomnias (9). However, it is not always effective or wanted by patients, often because of fear of side-effects and dependency (3). Treatment success rates vary between different NREM parasomnia phenotypes, and polypharmacy may be required (9). In some cases, certain treatments, such as antidepressants, can worsen or even precipitate parasomnia symptoms (10). As NREM parasomnias are often chronic conditions, pharmacological treatment may be required long-term, which is often undesirable, especially when the patient is a young adult. Even when pharmacotherapy is successful, NREM parasomnias can re-emerge following treatment cessation, particularly if priming and precipitating factors remain unaddressed (11).

Of note is that affective disorders, and especially anxiety disorder, may lead to an increased frequency of negative emotions in NREM parasomnia mentation, and that this in turn may further increase daytime anxiety (12). Moreover, it has been argued that the reported distress associated with parasomnia/nightmare experience may have a more significant impact on patients' quality of life, even more so than the frequency of parasomnic events [for an in-depth review of this topic please refer to (12)]. In keeping with this, to date, several psychotherapeutic approaches, for example: via Gestalt therapy (13) and imagery rehearsal therapy (14), have been shown to successfully target dysphoric parasomnias and to treat associated significant clinical distress.

In order to address the growing need for non-pharmacological therapies for NREM parasomnias (15), we have recently developed a novel, group-based, Cognitive Behavioral Therapy (CBT-NREMP) programme. The pathophysiological precipitants of NREM parasomnias suggest that CBT interventions, which address co-morbid insomnia, anxiety, stress and other relevant psychological difficulties, may be beneficial in its management (16). Our goal was therefore to primarily target factors which may trigger and maintain parasomnias over time, by incorporating and building-on core principles from the well-established and cost-effective model (17) Cognitive Behavioral Therapy for Insomnia (CBT-I) (18). The novel CBT for NREM parasomnia (CBT-NREMP; **Supplementary Material**) protocol includes a comprehensive programme that covers psychoeducation on the etiology of NREM parasomnias, sleep hygiene, sleep rescheduling to optimize homeostatic regulation, stimulus control to re-establish an association between the bed/bedroom and sleep, and specified body-based and cognitive relaxation techniques. By changing maladaptive sleep-related behaviors, thoughts and anxiety, CBT-NREMP treatment is specifically designed to target those priming and precipitating factors which cause parasomnias to persist over time. Moreover, it enables an individual to gain insight into their own thoughts as well as their emotional and behavioral processes regarding the self. The CBT programme is delivered in a safe group environment that additionally utilizes the spontaneity and creativity of the individual and the group. Here we report on the preliminary treatment outcomes of our novel CBT-NREMP programme.

MATERIALS AND METHODS

Design, Ethics, and Data Collection

All adult patients who had completed a whole programme (i.e., five sessions) of structured group CBT-NREMP between November 2018 and January 2020 were retrospectively identified, and their clinical findings, including demographics and the scores of several clinical questionnaires routinely used in our tertiary sleep disorder center, were collected from the center's clinical sleep database and analyzed. Altogether 46 patients were identified matching that criteria, and of those, a subgroup of eight patients were identified for whom 3 to 6 months follow up assessment findings were also available (**Figure 1**).

As per our clinical governance, framework the specified requirements to enroll in CBT-NREMP included a previously conducted video polysomnography (vPSG) investigation, and a confirmed diagnosis of NREM parasomnia by a qualified sleep physician, based on International Classification of Sleep Disorders third edition (ICSD-3) criteria (1). In addition to these inclusion criteria, all referred patients were screened by an experienced psychiatrist/psychologist, to confirm and assess their ability to participate in the group psychotherapy, as well as to ascertain the patient's ability to understand, speak and write English language, and to confirm their willingness and ability to give informed consent. The CBT-NREMP exclusion criteria included: co-morbid sleep disorders (apart from comorbid insomnia), current or past neurologic or psychiatric illness, traumatic brain injury, current alcohol and/or substance dependency disorders, developmental disorders and intellectual disability.

For the purposes of this study, the effectiveness of CBT-NREMP was evaluated by analyzing the outcomes of the three major clinical questionnaires from the clinical sleep database, including the Insomnia Severity Index (ISI) (19), Hospital Anxiety and Depression Scale (HADS) (20), and the Paris

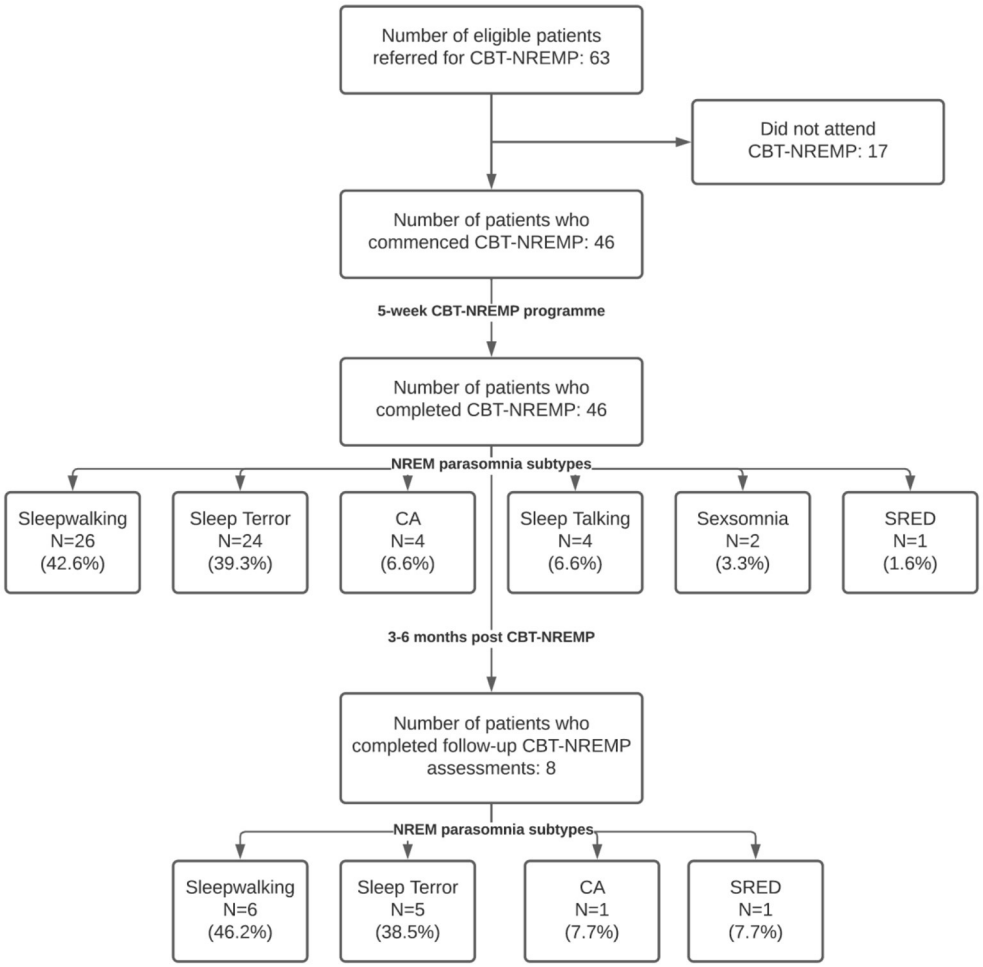

FIGURE 1 | Flow diagram of the studied cohort. *Nota Bene:* some patients had $n > 1$ subtype of NREM parasomnia recorded. Percentages indicate the prevalence of each NREM parasomnia subtype in our cohort. CBT-NREMP, cognitive behavioral therapy for non-REM parasomnia; CA, confusional arousal; SRED, sleep-related eating disorder; NREM, non-REM; n, number.

Arousal Disorders Severity Scale (PADSS) (5) at baseline, post-CBT-NREMP, and at follow-up (FU) 3 to 6 months later.

ISI is a self-rated scale, used to assess severity of insomnia in the clinical and research settings (21). The scale uses a seven-item self-report questionnaire that examines the nature, severity, and impact of insomnia. The evaluated dimensions include severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A five-point Likert scale is used to rate each item (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28 (21). Based on the total score the absence of insomnia (0–7); sub-threshold insomnia (8–14); moderate insomnia (15–21); or severe insomnia (22–28) can be identified (19). Similarly, HADS is also a self-rated scale, used to assess severity of depression and anxiety symptomatology (20). This 14-item scale includes seven items each for anxiety and depression subscales, where scoring for each item ranges from zero to three. A subscale score >8 denotes anxiety or depression. PADSS is a self-administered questionnaire designed to assess the severity of parasomnia (5). The scale has excellent psychometric properties, as well as valid and reliable subscales (22). It provides a means to assess the efficacy of new intervention treatments, as well as changes over longer periods of time. It consists of 17 items related to severity of parasomnia, with total score ranges from 0 to 50 (5); the scale has three parts, including an inventory of behaviors (PADSS-A), the frequency of episodes (PADSS-B), and the general consequences of the disorder (PADSS-C). The scale is self-completed and measured as follows: dangerous behaviors (17 items with three possible answers: never = 0, sometimes = 1, often = 2), frequency of episodes (equal to or more than two episodes per night = 6, one per night = 5, equal to or more than 1 episode per week = 4, equal to or more than 1 episode per month

= 3, equal to or more than 1 episode per year = 2, <1 episode per year = 1, never had any = 0), and consequences of the disorder (5 items with three response options: never = 0, sometimes = 1, often = 2). The best cutoff score for the overall PADSS (range 0–50) was found at 13/14 and had high sensitivity (83.6%) and specificity (87.8%) (5). It has been shown in the past that the complexity of behaviors emerging from N3 sleep as assessed by the vPSG correlate positively with the scores for the PADSS-total, PADSS-A, and PADSS-C (5, 22).

The study was granted ethical approval by the Hospital Clinic Research Ethics Committee (Project-No-12025, GSTT NHS, UK) to retrospectively ascertain anonymized data in full compliance with the EU General Data Protection Regulation and the Declaration of Helsinki.

CBT-NREMP Treatment

The structured group CBT programme consisted of five, weekly, 90 min CBT-NREMP sessions, with a maximum of eight participants per group. CBT-NREMP was conducted by an experienced sleep medicine psychiatrist or a trained psychologist according to a strict predetermined treatment protocol. Our protocol provided therapists with clear guidance on how to structure their therapy, as laid out in **Supplementary Methods**. The first sessions focused on building a therapeutic alliance and psychoeducation. The interventions sessions focused on both short- and long-term goals. Different cognitive and behavioral techniques (**Supplementary Material**) were applied to reach these goals. Homework was given in each session with the last session of therapy focusing on consolidation and relapse prevention. Experienced CBT-clinicians monitored adherence to the treatment principles in weekly group supervisions throughout the therapy period to ensure treatment fidelity. Clinical notes from the therapy sessions were regularly reviewed during supervisory sessions with focus on the initial phase of treatment, case formulation, treatment strategy and termination of therapy.

Statistical Analyses

Descriptive statistics were used to summarize the data as mean ± standard deviation (SD), and with median, 25th and 75th percentiles for continuous non-parametric variables. Due to non-normality of the data, as assessed by Kolmogorov-Smirnov test, the non-parametric Wilcoxon signed rank test (paired comparisons) with Holm-Bonferroni corrections was used (5, 23) to test difference in severity between the CBT-NREMP group's insomnia (i.e., ISI), parasomnia (i.e., PADSS) and depressive and anxiety symptomatology (i.e., HADS) pre- and post-CBT scores. In addition, *post hoc analyses* were done for differences across the three time points, at the baseline, immediately following the CBT-NREMP and at the 3 to 6 months follow up (i.e., pre-, post-, and FU) for eight participants for whom follow-up data were available. A value of $P < 0.05$ was considered to be statistically significant and Holm-Bonferroni corrections were performed for the *post-hoc* analyses. The analyses were done using a statistical package R, version 4.0.2 for all statistical analyses (24).

RESULTS

Forty-six patients, of whom 25 were male (54.3%), aged 19 to 73 years-old (mean ± SD: 35.8 ± 11.4 years) underwent a structured, comprehensive 5 weeks CBT-NREMP group intervention. Patients were asked to complete baseline ISI, HADS, and PADSS assessments prior to starting CBT-NREMP, and the same assessments were subsequently completed after the CBT-NREMP intervention (**Tables 1**, **2**).

At the baseline, patients' PADSS scores reflected the clinical severity of their untreated NREM parasomnia (mean PADSS score: 19.46 ± 6.32; **Table 1**). Patients scored moderately high on clinical measures of insomnia (ISI: 15.28 ± 4.36), with the baseline HADS outcome scores suggestive of subthreshold levels of anxiety and low mood (HADS-A: 8.14 ± 4.84 vs. HADS-D: 7.02 ± 4.05).

The CBT-NREMP intervention successfully reduced measures of clinical severity of NREM parasomnia (PADSS: $P_{Prevs Post} = 0.00032$; **Table 2**). Further significant improvements were noted in clinical measures of insomnia ($ISI_{Prevs Post}$: $P = 0.000054$; **Table 2**), which were reduced to clinical subthreshold values (**Table 1**), as well as in patients' self-reported severity of anxiety and depressive symptoms ($HADS_{Prevs Post}$: $P = 0.037$; **Table 2**).

Preliminary Findings on Sustainability of the CBT-NREMP Intervention

A subgroup of eight patients (17.4%) was followed after the CBT-NREMP intervention for up to 6 months (please also see **Supplementary Material**). By comparison to the socio-demographics of the larger group, the smaller subgroup consisted of younger (29.5 ± 8.1 years), predominantly female (six, 75%) patients, who at the outset reported higher clinical measures of severity of NREM parasomnia (PADSS scores: 24.75 ± 3.62; **Supplementary Table 1**) and anxiety (HADS-A: 11.25 ± 5.18; **Supplementary Table 1**).

Here, the CBT-NREMP intervention also significantly reduced the clinical measures of severity of NREM parasomnia and insomnia (**Supplementary Table 2**). These improvements were maintained, with further reduction in clinical measures of frequency and severity for NREM parasomnia and insomnia reported to continue for up to 6 months following the intervention (ISI: $P = 0.042$; PADSS: $P = 0.041$; **Supplementary Table 2**).

The CBT-NREMP intervention, however, did not lead to a statistically significant reduction in clinical measures of low mood and anxiety for this subgroup (HADS: $P = 0.22$). Nonetheless, the longitudinal reduction in the mean HADS scores was recorded across the assessment time-points (HADS *Pre*: 17.5 ± 8.64; *Post CBT-NREMP*: 14.88 ± 4.52; *FU 3 to 6* months:11.88 ± 7.02; **Supplementary Table 1**), with the most consistent improvement reported to occur during the follow-up period of up to 6 months after the intervention (HADS-A: $P = 0.057$; **Supplementary Table 2**). This may suggest a delayed nature of this response, or its secondary development as a consequence of primary improvements in sleep measures.

TABLE 1 | Outcomes of ISI, HADS, and PADSS assessments in 46 NREM parasomnia patients at baseline (Pre) and following the CBT-NREMP treatment (Post).

Assessment	Pre		Post	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
ISI	15.28 (4.36)	15 (12.25, 18)	12.09 (4.6)	12 (9.25, 15)
HADS	15.18 (6.55)	16 (11,19)	13.13 (5.98)	13 (8, 17.75)
HADS-A	8.14 (4.84)	7 (4.75, 12)	7.22 (4.24)	7 (4, 9.75)
HADS-D	7.02 (4.05)	6 (4,10)	5.91 (3.74)	6 (3,9)
PADSS	19.46 (6.32)	19 (16, 23.75)	17.53 (6.11)	17 (14,22)
PADSS-A	9.8 (4.67)	10 (6.25, 13.5)	8.41 (4.16)	8 (5,10)
PADSS-B	4.41 (1.11)	4 (4,5)	4.46 (1.21)	4 (4, 5.75)
PADSS-C	5.24 (1.78)	5 (4,7)	4.84 (2.01)	5 (3, 6.25)

ISI, Insomnia Severity Index; HADS, Hospital Anxiety and Depression Scale (total score); HADS-A, Hospital Anxiety and Depression Scale-Anxiety subset score; HAD-D, Hospital Anxiety and Depression Scale—Depression subset score; PADSS, Paris Arousal Disorders Severity Scale (total score); PADSS-A, Paris Arousal Disorders Scale-subset A score; PADSS-B, Paris Arousal Disorders Scale subset-B score; PADSS-C, Paris Arousal Disorders Scale subset-C score. Q1, 25% percentile. Q3, 75% percentile. SD, standard deviation.

TABLE 2 | Results of Wilcoxon signed rank tests comparing pre- and post-CBT-NREMP intervention scores for ISI, HADS, and PADSS assessments in 46 NREM parasomnia patients.

Assessment	Difference from Pre- to Post-CBT median (Q1, Q3)	Difference in median (95% CI)	Wilcoxon signed rank test	*P*-value
ISI	3 (0, 6.75)	3 (1, 6)	710.5	**0.000054**
HADS	1 (−1, 6)	3 (−0.84, 5.84)	514.5	**0.037**
HADS—A	1 (−1, 3)	0 (−1, 2.97)	512	0.089
HADS—D	1 (0, 2)	0 (−2, 3.5)	467.5	**0.034**
PADSS	1 (0, 3)	2 (−1.40, 6)	560	**0.00032**
PADSS—A	1 (−0.75, 2.75)	2 (0, 3.5)	600.5	**0.003**
PADSS—B	0 (0, 0)	0 (−1, 1)	71.5	0.826
PADSS—C	0 (−0.25, 1)	0 (−1, 2)	306.5	0.119

ISI, Insomnia Severity Index; HADS, Hospital Anxiety and Depression Scale; PADSS, Paris Arousal Disorders Severity Scale. Q1, 25% percentile. Q3, 75% percentile. CI, confidence interval. CBT, cognitive behavioral therapy. Statistically significant values are shown in bold.

DISCUSSION

The findings of our longitudinal study support the clinical utility for a novel CBT-NREMP intervention that targets distinct sleep, behavioral and emotional regulation factors. More specifically, we demonstrate that 5 weeks of a structured group CBT intervention in adult patients with NREM parasomnia can lead to a significant reduction in its severity. This is shown by a robust reduction in total PADSS and PADSS-A patients' scores (**Table 1**), both known to closely correlate with vPSG-ascertained severity (and complexity) of parasomnia behaviors that emerge from N3 sleep (5, 22).

In addition, we demonstrate that CBT-NREMP intervention can simultaneously lead to a clinically significant reduction in the patients' severity of insomnia, as evidenced by the reduction in the ISI scores. In our study, the ISI scores were robustly reduced from moderate to subthreshold values, with concomitant improvement in affective symptomatology (**Table 1**).

We also demonstrate that the effects of CBT-NREMP can be maintained, and that they continue to improve over a period of up to 6 months following the intervention (**Supplementary Table 2**). To the best of our knowledge, our study is the first to demonstrate the effectiveness, and arguably also the safety, of a structured CBT for adult NREM parasomnia.

Utilizing CBT in the treatment of sleep disorders holds substantial promise, and is clinically expanding (25). Where once medication-only treatments were favored, there has recently been a paradigm shift toward CBT-based interventions, which are viewed more favorably by patients (26), and treatment guidelines (27). CBT for insomnia (CBT-I) is already well-established as the gold-standard treatment, and principally operates by reducing perpetuating and precipitating factors associated with the condition (28). NREM parasomnias similarly manifest with priming (e.g., sleep loss, anxiety, stress, poor sleep hygiene), and precipitating factors (e.g., environmental noise) (16). Therefore, they should be amenable to a targeted CBT intervention, as our study amply demonstrates. Treating NREM parasomnias with CBT-NREMP, as opposed to medication, may have a number of potential advantages, including fewer known side-effects, and an explicit focus on treating the factors that may be responsible for perpetuating parasomnias in an effort to produce more durable effects.

Despite this, the body of literature on cognitive and behavioral interventions for NREM parasomnia is limited to case reports

or smaller case-series, which often target just one parasomnia phenotype (29). In the past, selective application of CBT-I, mindfulness-based stress reduction and CBT for stress have been shown to helpfully target all phenotypes of NREM parasomnias (9). In our experience, patients with NREM parasomnia commonly struggle to benefit from other CBT paradigms, where they often feel apart from the rest of the group. For example, it can be understandably challenging for a patient with sleepwalking to engage in, and accept, a therapy which solely focuses on insomnia. Indeed, the development of our targeted group CBT-NREMP arose in part from this unmet patient need.

Despite the striking and sustainable improvements reported by our patients, several notable limitations merit further mention. Firstly, CBT-NREMP was designed as an economical and inclusive group intervention, which could be potentially delivered in a variety of clinical settings and that reliably targets diverse physiologic phenotypes of arousal disorders. Whilst this was beyond the scope of our study, future studies should ideally examine whether taking a stepped-care approach would be more beneficial for different settings or NREM parasomnia phenotypes, possibly avoiding any potential selection bias. For example, any such multifaceted CBT-NREMP intervention could arguably start with group therapy sessions that address common therapeutic targets in parasomnia (e.g., safety, sleep hygiene), with subsequent individual interventions focusing on specific and more complex phenotypes, such as trauma-related presentations and sexomnia.

Secondly, whilst the findings of our study suggest that a robust short term (e.g., 3 to 6 months) maintenance of CBT-NREMP effects is possible, this effect was only shown in eight, as opposed for 46 original study patients, due to unforeseen and early study closure during the Covid-19 pandemic. This smaller subgroup had a widely differing sociodemographic in that the patients were notably younger, they reported higher baseline anxiety, and they were predominantly women. Hence, the CBT-NREMP sustainability should be confirmed in a larger patient cohort, and the specific CBT-NREMP effects and their sustainability ideally recorded over a significantly longer period of time.

Another potential limitation worth mentioning is that our assessment was based primarily on patients' subjective reports. The self-reported scores, recorded in PADSS, ISI and HADS questionnaires are, however, widely used, and all three have been robustly validated for clinical and research purposes (5, 21, 30). Nonetheless, the subjective nature of patients' reports may arguably render any truly objective interpretation of CBT-NREMP's effectiveness invalid. We challenge the clinical significance of this limitation, given that the major aim of any clinical treatment of NREM parasomnia is primarily offered to ensure patients' safety, and secondly, to address the patients' symptoms according to their own criteria (9).

Taken together, the findings of our study demonstrate that structured group CBT for adult NREM parasomnia is a safe, effective, and a highly promising treatment. Due to its unique design, CBT-NREMP intervention may be especially effective in those patients in whom precipitating and perpetuating factors are likely behaviorally and psychologically driven. However, in order to reliably build on our preliminary study, future randomized controlled trials are required. Ideally, any such trial should include prospective multimodal physiologic and neuroimaging investigation to decipher neuromechanisms which underlie and promote differential effects of CBT-NREMP's intervention. Following this approach, it is hoped that with time we will also gain further insight into the role that patients' gender and their emotional fragility may play. Going forward, it would be important to understand how they may impact objective CBT-NREMP outcomes, including the electroencephalographic arousal signatures and their behavioral correlates.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hospital Clinic Research Ethics Committee (Project-No-12025, GSTT NHS, UK) to retrospectively ascertain anonymized data in full compliance with the EU General Data Protection Regulation and the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DO'R, AN, and IR: conceptualization. DO'R, AN, NB, PD, HS, GL, JS, AB, ID, SH, and IR: methodology and study administration. All authors contributed to drafting and reviewing the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.679272/full#supplementary-material

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Cognitive Dysfunction in Insomnia Phenotypes: Further Evidence for Different Disorders

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Study Objectives: To determine cognitive profiles in individuals with short sleep duration insomnia (SSDI) and normal sleep duration insomnia (NSDI; also, paradoxical insomnia), compared to healthy sleepers.

Method: Polysomnographic (PSG) and neuropsychological data were analysed from 902 community-based Raine Study participants aged 22 ± 0.6 years of whom 124 met criteria for insomnia (53 with NSDI and 71 with or SSDI) and 246 were classified as healthy with normal sleep (i.e., without insomnia or other sleep disorders). Measurements of self- report (attention and memory) and laboratory-assessed (attention, episodic memory, working memory, learning, and psychomotor function) cognition and mood, and PSG-based sleep stages (% total sleep time; %TST) were compared between these 3 groups.

Results: In comparison to the healthy sleeper group, both insomnia groups had poorer self-reported attention, memory, mood, and sleep, and poorer laboratory-assessed attention (inconsistency). The NSDI group had less consistent working memory reaction time than healthy-sleepers or those with SSDI. The SSDI group had more inconsistency in executive function (shifting), and showed greater %TST in stage N1 and N3, and less REM sleep than either healthy-sleepers or those with NSDI.

Conclusions: Individuals with NSDI demonstrated greater working memory inconsistency, despite no laboratory assessed sleep problems, implicating early signs of pathophysiology other than disturbed sleep. Those with SSDI demonstrated different sleep architecture, poorer attention (inconsistency), and greater executive function (inconsistency) compared to healthy-sleepers and those with NSDI, implicating sleep disturbance in the disease process of this phenotype.

Keywords: insomnia, neuropsychology, phenotypes, paradoxical, short-sleep, cognition

INTRODUCTION

Insomnia is a highly prevalent sleep disorder (1), characterised by self-reported dissatisfaction with sleep quality or quantity, frequently expressed as difficulty initiating or maintaining sleep, or experiencing non-restorative sleep over many days, and accompanied by significant distress or daytime impairment (2). Risk factors for developing insomnia include female gender, older age, and chronic illness or pain (3). Comorbidities include other sleep disorders and psychiatric disorders, the latter being present in ∼40% (1), obesity and metabolic problems (4). Consequences include an increased risk of accidents, poorer work productivity, higher pain levels, and more emotional and mental health problems (5). Cognitive problems are often found using laboratory-based computerised neuropsychological tests in individuals with insomnia (6, 7).

In a recent systematic review and meta-analysis of insomnia and cognitive performance, Wardle-Pinkston et al. (6) reported small to medium differences in the cognitive domains of complex attention, working memory, episodic memory, and executive function between individuals with and without insomnia. An earlier meta-analysis by Fortier-Brochu et al. (8) also reported small to medium effects for episodic memory, working memory, and executive functions (problem solving), whilst finding no differences in attention. Further, an investigation by Ballesio et al. (9), focussing on executive functions, found small effects for reaction times, but not accuracy, in the subdomains of inhibition, flexibility, and working memory.

The findings of these three papers contrast with those from a meta-analysis by Fulda and Shulz (10) who reported no differences in working memory, episodic memory, or attention, but did find contrasting ability between those with and without insomnia in a different aspect of executive functioning (generativity). Taken together, these reviews indicate that insomnia is associated with small to moderate, but variable, effects on cognition within the domains of working memory, episodic memory, and executive function.

Such inconsistencies may result from three possibilities: (1) Treating insomnia as a homogenous disorder, when it is not; (2) Assessing cognition using measures that are not sensitive to subtle changes in cognition, and/or; (3) Using older samples where age and comorbidity may confound the results. The review by Wardle-Pinkston et al. proposed that results may be variable due to differences in lab-assessed (i.e., objective) sleep factors between individuals with insomnia and psychometric testing sensitivity (6). These concepts are expanded upon below.

Two different phenotypes of insomnia are consistently identified: insomnia with short sleep duration (SSDI) and insomnia with normal sleep duration (NSDI; also called paradoxical insomnia or sleep state misperception) (11). These two phenotypes have different daytime symptoms (12), nocturnal symptoms (13), self-reported cognitive problems (14, 15), and underlying biology (16), all of which may also be associated with dissimilar objective neurocognitive challenges.

Individuals with SSDI have a short sleep period, and can accurately self-report wakefulness in the presence of lab-assessed wakefulness (13). They experience daytime fatigue, and self-reported problems with attention and memory (13). Further, SSDI is associated with self-reported and lab-assessed cognitive difficulties, mood disruption, physiological hyperarousal, and a higher risk of hypertension, diabetes, and all-cause mortality (17). SSDI also appears to be a biological marker of genetic predisposition to chronic insomnia (17).

In contrast, people with NSDI report short sleep time whilst lab-assessments indicate normal sleep time, and report being awake when PSG indicates sleep (16), termed sleep state-misperception. NSDI is also associated with self-reported and objective cognitive difficulties, mood disruption, and cortical hyperarousal (17). The Default Mode Network (DMN), is associated with self-referential information processing and has been shown to remain active in patients with insomnia, when it would deactivate in a healthy sleeper (16, 18, 19). Problems with the DMN are thought to result in deficits in self-referential and goal-directed behaviours (i.e., executive functions) (20), and have been implicated in mood disorders (12) and the development of dementia (15). This process may underlie the paradoxical experience of feeling awake while biologically asleep in those with NSDI (21).

Further, some of the inconsistent findings across reviews may be due to using measures of cognition that are not sensitive to small and/or early changes. All reviews [bar Fulda and Shulz, (10)] report small to moderate effects across papers, and propose that cognitive test sensitivity may account for differences across studies. To-date, the studies examining cognition in OSA have utilised traditional measures of accuracy and mean reaction time. None has explored intra-individual variability, which may be a more sensitive measure of cognitive performance. A measure of intra-individual variability, inconsistency, refers to intra-individual, short-term fluctuations in performance across trials, within a task, and can be measured using the intra-individual standard deviation (ISD) of reaction time on a trial-by-trial basis. Intra-individual variability has been demonstrated to be more sensitive than accuracy and mean reaction time to subtle cognitive changes, that may be exhibited in mild or early onset of disease (22, 23).

Finally, being middle-aged or older is itself associated with subtle decline in cognition and is frequently associated with greater comorbidity and disease burden (24–27). Declines in cognition are demonstrated in psychometric assessments using measures of reaction time, accuracy (frequently show an accuracy/speed trade-off), and in studies incorporating inconsistency measures (27). Given that the majority of studies of cognition in insomnia have recruited participants of middle to older age [e.g., in Wardle-Pinkston et al. (6) the mean age of participants across studies was 44.9 years], ageing effects in cognition may have confounded findings.

The present research aimed to contrast the cognitive function of individuals with SSDI and NSDI using self-report and computerised assessments providing measures of accuracy, speed, and inconsistency of performance, examining the cognitive constructs of attention, learning, working memory, executive function, and psychomotor funtion, in a sample of young adults.

We asked:

1. Do individuals with SSDI or NSDI differ from age-matched healthy sleeper controls from the same sample and, if yes, on what aspects of cognition?
2. How are the cognitive profiles of individuals with SSDI and NSDI different?
3. How are mood, daytime function outcomes, and sleep profiles of individuals with SSDI and NSDI different?

With regard to sleep, we hypothesised that: The SSDI group would have poorer self report and lab-assessed sleep than the NSDI and healthy sleepers, and; The NSDI group would have poor self-report but not lab assessed sleep than the healthy sleepers. Second, with regard to cognition, we hypothesised that: The NSDI and SSDI groups would report similar problems for self-report cognition, mood, and daytime function, and these would be greater than those reported by healthy sleepers, and; The SSDI group would show more extensive lab-assessed cognitive difficulties than the NSDI group.

MATERIALS AND METHODS

Participants

The present analyses used data from the Raine Study, a multigenerational longitudinal epidemiological study established in 1989 (for more study details visit; rainestudy.org.au). Data from Generation 2 (Gen2) participants[1] who completed the sleep study, actigraphy, and cognitive testing at the Gen2-22-year follow-up were used ($n = 902$).

Individuals with either a diagnosis of insomnia (DSM-5) or who met the insomnia criterion on the insomnia symptom questionnaire (ISQ; $n = 156$) were separated into NSDI ($n = 63$) or SSDI ($n = 93$) based on the Research Diagnostic Criteria (RDC) for PSG (28). For NSDI the RDC requires that PSG shows scored total sleep time (TST) $\geq$6.5 h, sleep efficiency (SE; TST/Time in bed $\times$ 100) $\geq$85%. For SSDI, the RDC requires short-sleep duration, PSG-based TST$<$6.5 h.

While participants were categorised by sleep study, they were retained if their self-report sleep diary data validated short or normal sleep duration: normal-sleep duration ($n = 53$) or short-sleep duration ($n = 71$). This was to ascertain if this single night of sleep under PSG was typical of an individual's sleep.

A healthy sleeper sample was constructed from those participants from the Raine Study who were without insomnia or other sleep disorders, had SE $\geq$85%, and TST $\geq$6.5 h on PSG ($n = 324$). Participants were retained if they reported normal sleep duration (TST$>=$ 6.5 h) on their sleep diary ($n = 246$).

Participants who did not meet the insomnia selection criteria, healthy sleeper criteria, had a history of neurological, neurodevelopmental, significant psychiatric history, shift-work, or other sleep disorder/s (e.g., sleep apnoea with apnoea hypopnoea index$\geq$15 and/or restless legs syndrome) were excluded ($n = 532$) from analyses.

A flow chart of study group selection is shown in **Figure 1**.

[1]The Raine Study index participants, who were born into the study between 1990 and 1991.

MATERIALS

Sleep Study/PSG

Participants were administered full overnight Level 1 polysomnography (PSG) [Compumedics E-Series (Compumedics, Melbourne Australia)] and scored using Compumedics PSG 3 software at the Centre for Sleep Science, University of Western Australia. Equipment placement, sleep staging and event scoring was completed by experienced sleep technologists according to American Academy of Sleep Medicine criteria (29).

Cogstate Computerised Battery

This computerised battery (30) provided tasks of attention (Card Identification), executive functioning (Set Shifting), learning (Continuous Paired Associates), psychomotor function (Detection Test), and working memory (One-back Task). The tasks show good correlations to traditional neuropsychological assessments (30) even when measured in populations that exhibit subtle cognitive changes (31). The Cogstate records both accuracy (whether the trial was answered correctly) and speed (time to make a correct response) on a trial-by-trial basis, allowing calculation of accuracy, mean response time, and variability in response time (inconsistency) using intra-individual standard deviations, for each task assessed.

To date, a few small sample studies examining cognition in obstructive sleep apnoea have included cognitive inconsistency amongst their measures. All have found greater IIV (i.e., more inconsistency or less cognitive stability) in those with obstructive sleep apnoea compared to healthy controls (32). IIV has not been reported in insomnia.

Prospective and Retrospective Memory Questionnaire

A 16-item questionnaire (33) that provides a self-reported assessment of prospective and retrospective memory errors. The scale demonstrates good construct validity and internal reliability ($\alpha = 0.80$–89) (33). Scores were generated for prospective and retrospective subscales.

Attention-Related Cognitive Errors Scale

This 12-item questionnaire (34) provides a measure of everyday mistakes made when not paying sufficient attention to a task. The values are summed to give an overall score. ARCES scores are highly correlated with other scales assessing errors of sustained attention (35).

Pittsburgh Sleep Symptom Questionnaire-Insomnia/Insomnia Symptom Questionnaire

A 13-item self-report tool (36) designed and used to identify insomnia symptoms and provide a case definition of insomnia. The items are consistent with the RDC (28) for insomnia and compared with interview methods of diagnosing insomnia the ISQ has good internal reliability ($\alpha = 0.89$), moderate sensitivity (50–67%) and good specificity (91%) (36).

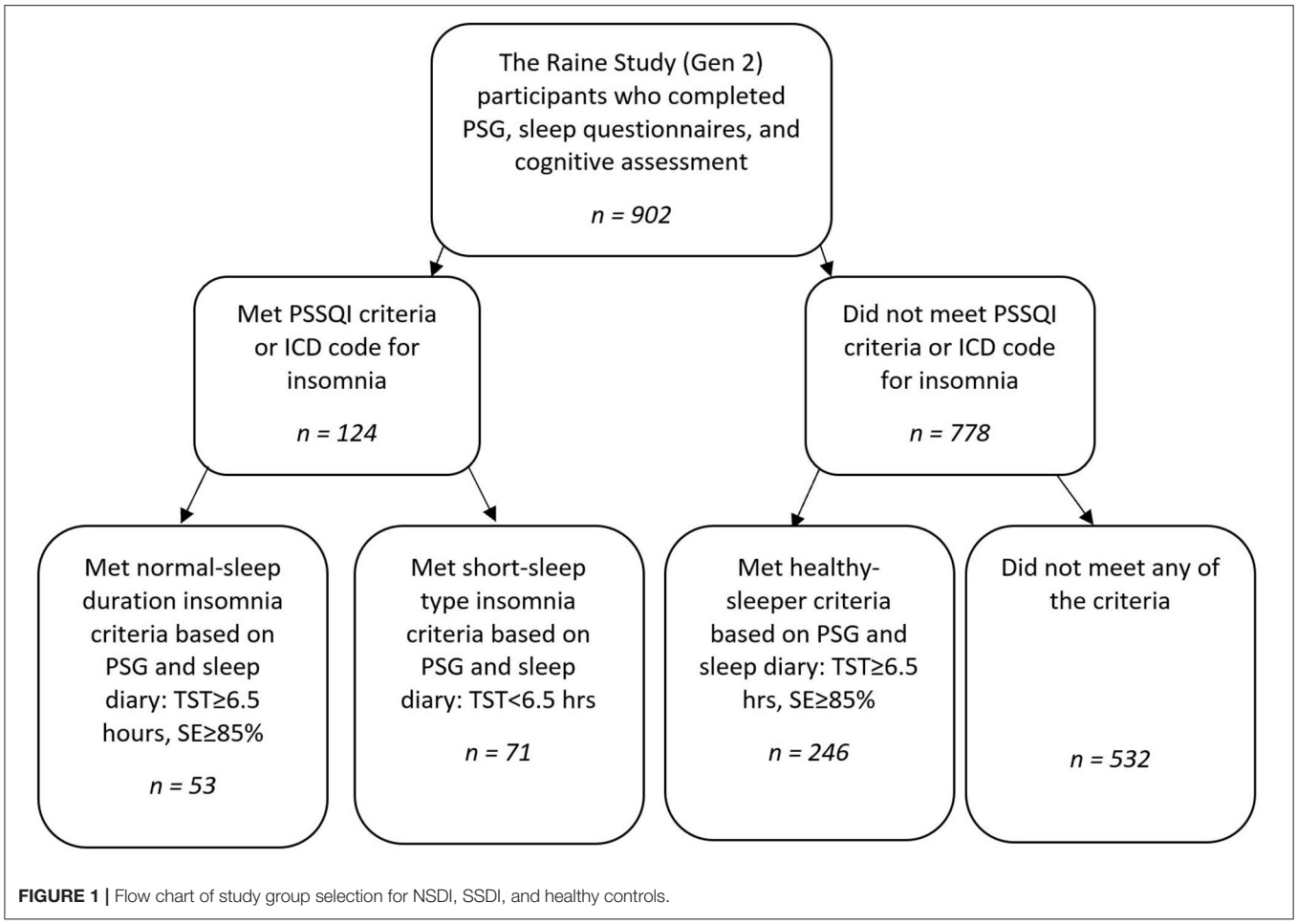

FIGURE 1 | Flow chart of study group selection for NSDI, SSDI, and healthy controls.

Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10)

This questionnaire (37) has 10-items designed to assess the impact of daytime sleepiness on daytime activity. The FOSQ-10 has good internal consistency ($\alpha = 0.87$) and demonstrates changes over time with successful treatment of sleep disorders (38). Scores are reported for general productivity, vigilance, social outcomes, activity level, and sexual desire.

Pittsburgh Sleep Quality Index

An 18-item questionnaire (39) that is designed to assess sleep habits, disturbances, and daytime impairments. This scale shows good internal consistency ($\alpha = 0.73$) and shows a strong correlation with other scales assessing daytime function (40).

Epworth Sleepiness Scale

This self-administered 8-item scale (41) assesses sleepiness in several every-day situations. The questionnaire has good internal consistency ($\alpha = 0.73$–0.90). Excessive sleepiness is a score of 10 or more.

Depression Anxiety and Stress Questionnaire-21 Item

This well-established 21-item questionnaire (42) assesses symptoms of depression, anxiety, and stress. It has demonstrated good internal reliability ($\alpha = 0.82$–0.97) (42) and is an appropriate mood measure for sleep disordered populations, as it does not contain sleep-related items (43). Scores were generated for depression, anxiety, and stress subscales.

Procedure

Neuropsychological testing and questionnaires were administered to all participants the night of or the morning after their sleep study at the Centre for Sleep Science. There was no adaptation night for this sleep study, hence we examined if this night was representative of an individual's habitual sleep against a weeklong sleep diary.

Analysis

Descriptive statistics for the SSDI, NSDI, and healthy-sleeper groups are presented in **Table 1**.

Residuals of the dependent variables were checked for and approximated normality as assessed through visual inspection of normality plots, p-p plots, and metrics of skew and kurtosis. Due

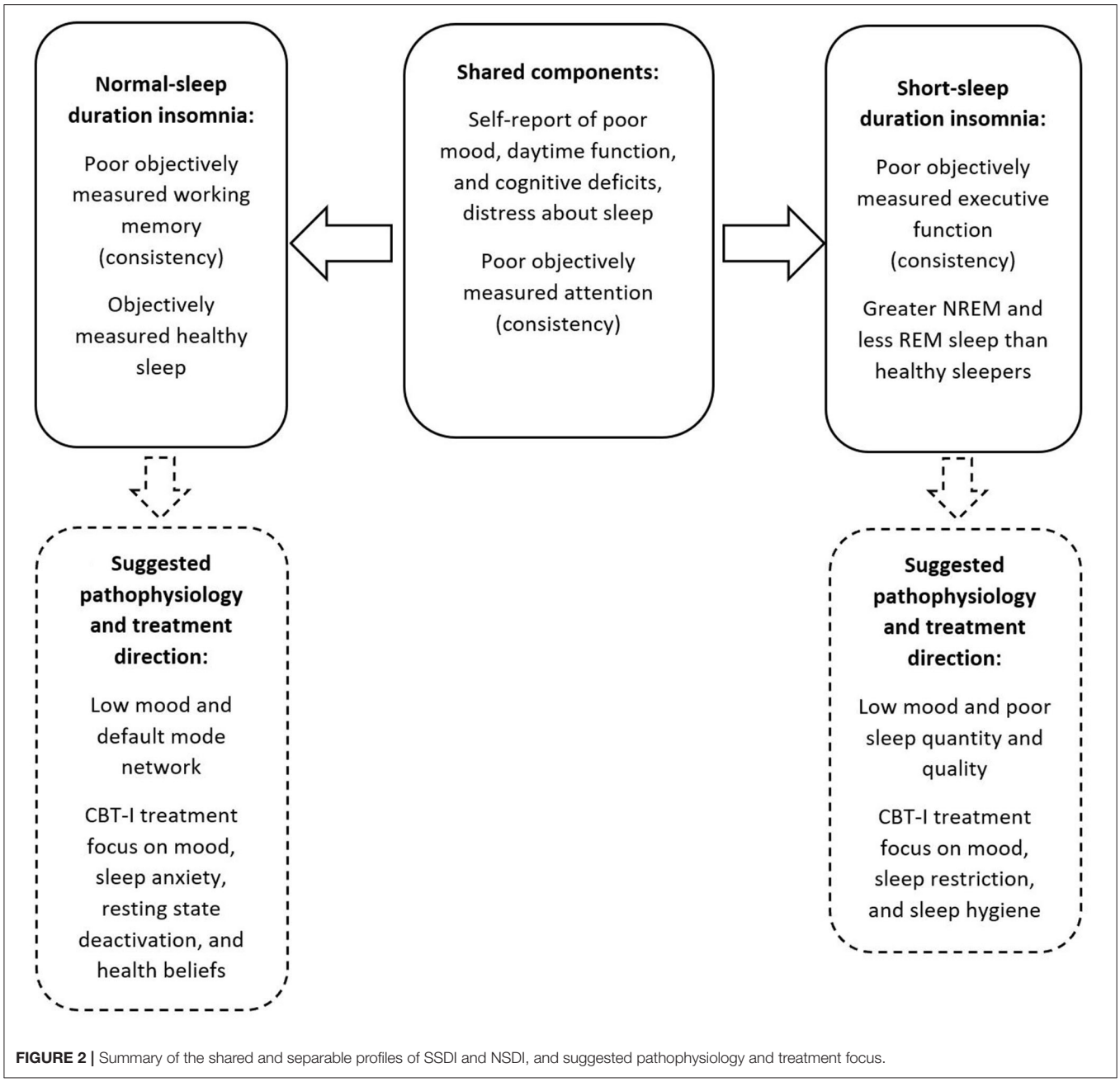

FIGURE 2 | Summary of the shared and separable profiles of SSDI and NSDI, and suggested pathophysiology and treatment focus.

to the differences in sample size, homogeneity of variance was assessed and was not violated. Independence of observations was met as all participants were counted in only one group (healthy, long-sleep duration, or short-sleep).

MANOVAs were conducted to compare the effect of group (normal-sleep duration insomnia, short-sleep type insomnia, and healthy sleepers) on lab-assessed sleep differences (PSG—-percentage N1, N2, N3, and REM), lab-based (Cogstate) and self-report cognition (retrospective and prospective memory subscales of the PRMQ and ARCES total score), self-reported mood (DASS-21- stress, anxiety and depression subscale scores), and self-reported daytime function (FOSQ—-general productivity, vigilance, social outcomes, activity level and sexual desire subscale scores). Lab-based (Cogstate) domains of cognition examined were attention, executive functioning, working memory, learning, and psychomotor function. For all domains, tests of accuracy, speed, and inconsistency of performance were assessed for group differences. Where tests of sphericity were violated an adjusted F value is reported. An alpha level of 0.05 was used, except where omnibus group interaction or main effect differences were found, then *post-hoc* Bonferroni-corrected tests were conducted (0.05 × number of tests).

TABLE 1 | Descriptive statistics and lab-assessed sleep detail (PSG staged sleep; Stage as % of total sleep time) for the healthy sleepers, those with NSDI, and SSDI.

	Healthy-sleep ($n = 246$)	NSDI ($n = 53$)	SSDI ($n = 71$)
Descriptive statistics			
- Gender male n (%)	130 (48.1%)	15 (31.9%)	32 (34.4%)
- Age M ± SD (yrs)	22.2 ± 0.6	22.1 ± 0.6	22.2 ± 0.6
- BMI	22.0 ± 4.8	21.5 ± 4.5	21.3 ± 5.1
- Smoker (%)	28 (10.3%)	11 (20.0%)	18 (17.3%)
- ESS (total)	5.5 ± 0.1	8.9 ± 3.7	7.3 ± 3.8
- PSQI (total)	3.8 ± 1.6	6.1 ± 2.2	8.1 ± 3.2
Lab-assessed sleep detail			
- TST (hrs)	7.1 ± 0.4	7.3 ± 0.4	5.7 ± 0.8
- SE (%)	99.6 ± 0.6	100.0 ± 0.0	43.0 ± 5.0
- N1 (%TST)	8.41 ± 4.28	7.25 ± 3.22^	10.14 ± 5.02*
- N2 (%TST)	46.73 ± 7.24	47.04 ± 7.35	44.94 ± 8.19
- N3 (%TST)	25.35 ± 5.04	25.45 ± 7.22^	29.24 ± 9.17*
- REM (%TST)	19.50 ± 5.89	20.26 ± 5.19^	15.68 ± 6.20*

*Effect sizes are reported in text for significant differences. TST, total sleep time; SE, sleep efficiency; ESS, Epworth sleepiness scale; PSQI, Pittsburgh sleep quality index; TST and SE values are taken from overnight sleep study; * indicates that the marked group showed a significant difference to the healthy sleepers group. ^ indicates a significant difference between the NSDI and SSDI groups.*

RESULTS

Overall, these data show that the cohort was relatively young (22-yrs), that lab-assessed sleep efficiency was poor in those with SSDI, and that both phenotypes reported high levels of sleepiness, and low levels of sleep quality (as per cut-offs on the PSQI).

Lab-Assessed Sleep Differences

Means for sleep study data are presented in **Table 1**.

Interactions were significant for group by sleep stage, Roy's Largest Root, $F_{(3, 427)} = 2267.69$, $p < 0.001$. Indicating that time spent in sleep stages varied by group.

Post-hoc comparisons indicated that participants with SSDI spent a larger percentage of TST in N1 compared to the healthy sleepers [$p < 0.001$; Cohen's $d = 0.39$ (95% CI, LL = 0.12, UL = 0.65)] and to those with NSDI [$p < 0.001$; Cohen's $d = 0.67$ (95% CI, LL = 0.31, UL = 1.02)]. Those with SSDI also spent a higher percentage of TST in N3 than those with healthy sleep [$p < 0.001$; Cohen's d = 0.63 (95% CI, LL = 0.36, UL = 0.89)] or with NSDI [$p < 0.001$; Cohen's $d = 0.45$ (95% CI, LL = 0.09, UL = 0.81)]. Finally, those with SSDI had lower %REM than healthy sleep [$p < 0.001$; Cohen's $d = 0.72$ (95% CI, LL = 0.46, UL = 0.99)] and NSDI [$p < 0.001$; Cohen's $d = 0.88$ (95% CI, LL = 0.52, UL = 1.23)].

In summary, participants with SSDI demonstrated a greater percentage of their total sleep time in NREM sleep and less time in REM sleep than the healthy sleepers or those with NSDI.

Lab-Assessed Cognition

Interactions were not significant for accuracy or reaction time, however, a significant group by cognitive test interaction was found for inconsistency, Roy's Largest Root, $F_{(8, 1212)} = 3.15$, $p = 0.002$, revealing a different pattern of cognitive performance for each group.

For attention (inconsistency) the healthy sleeper group showed more consistent response times than the NSDI [$p < 0.001$; Cohen's $d = 0.91$ (95% CI, LL = 0.61, UL = 1.20)] and the SSDI ($p = 0.006$; Cohen's $d = 0.44$ (95% CI, LL = 0.18, UL = 0.71) groups. For working memory (inconsistency), the healthy sleepers had more consistent response times than the NSDI [$p = 0.005$; Cohen's $d = 0.31$ (95% CI, LL = 0.01, UL = 0.61)] but not the SSDI group. For executive function, shifting (inconsistency) healthy sleepers were more consistent in their response times than the SSDI group [$p < 0.001$; Cohen's $d = 0.55$ (95% CI, LL = 0.29, UL = 0.82)], but not the NSDI. Means for all lab-assessed cognitive tests are presented in **Table 2**.

There were no group differences on psychomotor function or learning, nor any interactions with group.

Taken together, these results indicate that the healthy participant group experienced better lab-assessed cognition overall and that both insomnia groups demonstrated greater inconsistency; the NSDI group demonstrated poorer working memory than the healthy sleepers; and, the SSDI group demonstrated poorer executive function, shifting, than the healthy sleepers.

Self-Report Cognition

Interactions were significant for group by self-report cognitive test, Roy's largest root, $F_{(3, 423)} = 11.29$, $p < 0.001$.

Post-hoc comparisons indicated that all mean scores for all self-reported cognition assessments for the healthy sleeper group were significantly better than the NSDI ($p < 0.001$) and SSDI groups ($p < 0.001$), however the insomnia groups did not differ. Means are presented in **Table 3**.

These results indicate that people from both the SSDI and NSDI groups reported poorer attention, retrospective, and prospective memory than individuals with healthy sleep, and that the insomnia groups did not differ from one another.

TABLE 2 | Means and standard deviations for lab-assessed cognitive assessments (CogState) for the healthy sleepers, those with NSDI, and SSDI.

	Healthy-sleep ($n = 246$)	NSDI ($n = 53$)	SSDI ($n = 71$)
Attention (card identification: IDN)			
- Accuracy	1.35 ± 0.17	1.31 ± 0.27	1.38 ± 0.12
- Speed	2.63 ± 0.06	2.64 ± 0.08	2.65 ± 0.07
- Consistency	0.07 ± 0.02	0.09 ± 0.03*	0.08 ± 0.03*
Executive function (set-shifting: SETS)			
- Accuracy	1.11 ± 0.12	1.11 ± 0.12	1.09 ± 0.11
- Speed	2.72 ± 0.17	2.73 ± 0.17	2.73 ± 0.02
- Consistency	0.32 ± 0.07	0.34 ± 0.11	0.36 ± 0.08*
Learning (continuous-paired: CPAL)			
- Accuracy	1.22 ± 0.26	1.26 ± 0.23	1.23 ± 0.26
- Speed	3.22 ± 0.14	3.23 ± 0.13	3.21 ± 0.12
- Consistency	0.89 ± 0.23	0.87 ± 0.24	0.90 ± 0.22
Psychomotor function (detection test: DET)			
- Accuracy	1.41 ± 0.31	1.40 ± 0.28	1.43 ± 0.03
- Speed	2.45 ± 0.08	2.44 ± 0.09	2.45 ± 0.09
- Consistency	0.07 ± 0.04	0.08 ± 0.04	0.08 ± 0.04
Working memory (one-back task: ONB)			
- Accuracy	1.23 ± 0.26	1.25 ± 0.27	1.23 ± 0.25
- Speed	2.80 ± 0.09	2.81 ± 0.13	2.81 ± 0.09
- Consistency	0.12 ± 0.03	0.13 ± 0.04*	0.13 ± 0.03

*Effect sizes are reported in text for significant differences. Higher inconsistency scores indicate more inconsistent/poorer performance. Higher speed scores indicate slower/poorer performance. Higher accuracy scores indicate higher/better performance; * indicates that the marked group showed poorer performance than the healthy sleepers group.*

TABLE 3 | Means and standard deviations for the self-reported cognition assessments (PRMQ and ARCES) for the healthy sleepers, those with NSDI, and SSDI.

	Healthy-sleep ($n = 246$)	NSDI ($n = 53$)	Cohen's d, 95% CI (L,U)	SSDI ($n = 71$)	Cohen's d, 95% CI (L,U)
PRMQ total scale	33.74 ± 8.01	41.07 ± 9.70*	0.88 (0.58, 1.18)	40.04 ± 9.95*	0.74 (0.48, 1.01)
- Prospective memory subscale	18.10 ± 4.54	22.24 ± 5.16*	0.89 (0.59, 1.19)	21.64 ± 5.47*	0.74 (0.48, 1.01)
-Retrospective memory subscale	15.64 ± 4.03	18.82 ± 5.16*	0.75 (0.45, 1.28)	18.54 ± 5.14*	0.67 (0.41, 0.94)
ARCES	30.21 ± 6.27	36.64 ± 7.67*	0.98 (0.69, 1.28)	35.98 ± 7.32*	0.89 (0.62, 1.15)

** indicates that the marked group showed a significant difference to the healthy sleepers group. Self-report shows no difference in performance between SSDI and NSDI sleepers. Subscale scores, prospective and retrospective memory scores were used in the repeated measures ANOVA.*

Self-Reported Mood and Daytime Function

Interactions were significant for group by mood [Roy's Largest Root: $F_{(3,402)} = 5.868$, $p < 0.001$] and daytime function by group [Roy's Largest Root: $F_{(5,391)} = 26.596$, $p < 0.001$].

Post-hoc comparisons indicated that mean scores for all assessments of self-reported mood ($p < 0.001$) and functional sleep outcomes ($p < 0.001$, with the exception of the FOSQ vigilance subscale, $p = 0.003$) were significantly higher in both insomnia groups than in healthy sleepers, though the insomnia groups did not differ. Means are presented in **Table 4**.

These results suggest that both the NSDI and SSDI groups report poorer mood across higher depression, stress, and anxiety, and report that their poor sleep impacts on their ability to function day-to-day, with regards to productivity, vigilance, social outcomes, activity levels, and sexual desire, than healthy sleepers.

DISCUSSION

This paper aimed to characterise the two main insomnia phenotypes (SSDI and NSDI) with detailed lab and self-report cognitive and mood assessments, in a large sample of Gen2 participants from the Raine Study. The results demonstrate that those with SSDI and NSDI self-report problems with attention and memory, daytime function due to poor sleep. Further, those with SSDI and NSDI show greater inconsistency in performance on objective attention tasks. Those with SSDI show less consistent executive functioning and those with NSDI show less consistent working memory, than those with healthy sleep. Further, those with SSDI demonstrated sleep architecture that was different from NSDI and healthy sleepers, while those with NSDI showed relatively healthy lab-assessed sleep. These differences are summarised in **Figure 2**.

TABLE 4 | Means and standard deviations for self-reported mood and daytime function assessments (DASS-21 and FOSQ questionnaires) for the healthy sleepers, those with NSDI, and SSDI.

	Healthy-sleep ($n = 246$)	NSDI ($n = 53$)	Cohen's d, 95% CI (L,U)	SSDI ($n = 71$)	Cohen's d, 95% CI (L,U)
DASS-21 total scale	14.46 ± 13.45	42.41 ± 26.32	1.70 (1.40, 2.00)	40.03 ± 23.89	1.56 (1.30, 1.83)
- Depression subscale	4.24 ± 6.11	13.86 ± 10.57*	1.36 (1.06, 1.65)	13.33 ± 9.57*	1.29 (1.03, 1.56)
- Anxiety subscale	3.15 ± 4.03	10.23 ± 8.55*	1.38 (1.09, 1.68)	9.38 ± 7.87*	1.21 (0.95, 1.48)
- Stress subscale	6.40 ± 5.93	16.98 ± 10.40*	1.53 (1.23, 1.83)	17.50 ± 9.88*	1.59 (1.32, 1.85)
FOSQ total scale	18.00 ± 1.60	15.37 ± 2.63	1.44 (1.14, 1.74)	15.72 ± 2.41	1.26 (0.99, 1.52)
- General productivity subscale	3.45 ± 0.53	2.72 ± 0.78*	1.26 (0.96, 1.55)	2.88 ± 0.75*	0.97 (0.71, 1.24)
- Vigilance subscale	3.59 ± 0.43	3.20 ± 0.60*	0.84 (0.54, 1.14)	3.37 ± 0.60*	0.47 (0.20, 0.73)
- Social outcomes subscale	3.84 ± 0.02	3.46 ± 0.71*	1.28 (0.98, 1.57)	3.46 ± 0.10*	0.75 (0.72, 0.78)
- Activity level subscale	3.49 ± 0.44	2.84 ± 0.72*	1.30 (1.00, 1.60)	2.83 ± 0.61*	1.37 (1.10, 1.63)
- Sexual desire subscale	3.64 ± 0.57	3.11 ± 0.84*	0.85 (0.55, 1.15)	3.29 ± 0.83*	0.55 (0.28, 0.81)

** indicates that the marked group showed poorer performance than the healthy sleeper group. Self-report shows no difference in performance between SSDI and NSDI sleepers. Subscale scores, depression, anxiety and stress scores, were used in the repeated measures ANOVA for mood, and subscale scores for general productivity, vigilance, social outcomes, activity level, and sexual desire were used in the repeated measures ANOVA for daytime function.*

Self-Reported Mood, Function, and Sleep

In line with the literature (1, 6, 13), those with both SSDI and NSDI self-report problems with cognition (attention and memory), daytime function, mood, and sleep quality. As self-reported sleep quality, daytime function, and mood are core components of an insomnia diagnosis (2), this result is not surprising. Further, these findings suggest that SSDI and NSDI do not differ in terms of self-report measures of cognition, however they do differ on objective assessments.

Lab-Assessed Cognition and Sleep

Both phenotypes of insomnia exhibit inconsistency in attention. Whilst Wardle-Pinkston et al. (6) also reported attention problems in insomnia in their meta-analysis, Fulda and Schulz (10) and Fortier Brochu et al. (8) did not, but all three studies reported accuracy. This sample, using a younger sample than previous studies, found no evidence of problems with attention accuracy, but did find greater inconsistency in the speed of responding to attention trials in insomnia. Likewise, whilst past studies, also with older participants, have reported deficits in working memory and executive function accuracy (6, 8, 10), we found more subtle effects in inconsistency of responding in these domains. These differences were varied across the insomnia phenotypes: those with NSDI were less consistent in working memory despite relatively healthy sleep, while those with SSDI were less consistent in executive functioning, and had different sleep architecture (more N1 and N3, and less REM, as a percentage of total sleep time) than healthy sleepers and those with NSDI.

A high amount of N3 sleep, seen here in those with SSDI, has been noted to indicate rebound sleep. This is considered 'recovery sleep' as shown after sleep deprivation or chronic sleep restriction (44). This supports the diagnosis of SSDI, provided by PSG, diary, and self-report symptoms in this study, and supports the idea that the cognitive problems shown in SSDI are the result of chronic sleep loss. Conversely, those with NSDI showed subtle objective and self-reported cognitive deficits, despite no evidence of lab-based sleep loss.

That separable cognitive profiles and sleep profiles were demonstrated for the different phenotypes suggests future directions for providing a differential diagnosis. Currently, as in this paper, overnight sleep study or actigraphy are used to assess the mismatch between self-report and lab-assessed sleep and distinguish short- from normal normal-sleep duration insomnia (28). However, sleep studies, actigraphy, and full neuropsychological assessment can be expensive and time consuming, and are activities requiring a high degree of specialised training. The present paper suggests that cognitive tasks such as those used here, may provide further information to profile those with insomnia. When computerised, these tasks are relatively quick (7-min in healthy participants), and easy to administer. However, these results require replication by other groups and the ability of these differences to discriminate groups requires validation.

Working memory and executive functions are separable but related components of cognition. Working memory is a limited capacity cognitive system that can hold information ready for processing for a limited time (45). The executive function factor assessed here, shifting, is related to working memory, as it assists with shifting attentional control quickly (46). Other aspects of executive function [updating, generativity, fluid problem solving, and inhibition (46, 47)] were not assessed in the present paper, and as such we have an incomplete picture of executive function in these subtypes of insomnia. A complete examination of executive functions in insomnia phenotypes will provide greater understanding of how executive functions are impacted and deepen our understanding of different cognitive profiles in insomnia.

There were no psychomotor or learning problems for either phenotype uncovered in these analyses. These findings are in line with past studies of psychomotor function (6, 8, 10) and in contrast to past explorations of learning in insomnia (6). Learning, in the current sample, may not have been problematic

as Generation-2 from the Raine Study were young (Age, M = 22 years, at the time of assessment). Young age is protective for cognition. Wardle-Pinkston et al. (6) investigated age as a moderator in their analyses showing that older age was associated with larger effect sizes in the differences between healthy sleepers and individuals with insomnia. To explore the impact of age, future research could investigate phenotypic differences in the progression of cognitive deficits in longitudinal datasets, or compare cognitive function in older and younger samples. The Raine Study will make an excellent space to explore this concept as data continue to be collected on the same individuals, their parents (Generation 1), their grandparents, (Generation 0) and now the children of Generation 2 (i.e., Generation 3).

Where there were cognitive differences, for both phenotypes of insomnia these were in maintaining consistent response times throughout a testing trial, whilst accuracy and speed were not impacted (6, 8, 10). This finding, taken together with the small effects evidenced in meta-analyses and inconsistent findings across the field, identifies a need for sensitive measures of cognition that capture moment-to-moment performance stability, such as intra-individual variability (IIV) (48). Previous studies have not examined inconsistency, reporting only measures of accuracy and speed, meaning it is possible these consistency differences were present in earlier samples. The literature on IIV indicates it is a sensitive measure of early cognitive change and is predictive of later cognitive dysfunction and decline (49). Future follow-up assessments of the Raine Study participants will be able to track those showing early cognitive instability to see if clearer cognitive problems, in accuracy, speed, and/or a wider set of cognitive domains, develop.

Further, the present sample were relatively healthy, young individuals involved in research from before birth to their mid-twenties, possibly leading to selection bias. As comorbidity, including overweight and psychological diagnoses, can independently impact sleep, sleep disorders, and cognition (50), future studies may wish to investigate the interaction of comorbidity and/or other demographic features with cognition in those with insomnia.

Pathophysiology

Hyperarousal is a core pathophysiological feature of insomnia, in general, and is explained in two different models: a psychological model and a physiological model. The psychological model posits that worry and rumination about life stress, and about sleep itself, disrupt sleep, whereas, the physiological model posits that hyperarousal is due to a higher level of neuroendocrine and metabolic functioning, which disrupts sleep.

While it is possible that cognition and sleep, in both insomnia phenotypes, are impacted by psychological processes, as certainly belief impacts biological health in other areas, including stress (51) and treatment uptake (52, 53), such a model, with one road to pathology, does not explain the different cognitive and sleep profiles of these disorders, as evidenced here. There is some discussion in the literature of differing types of hyperarousal across the two phenotypes. Short sleep is associated with physiological hyperarousal while NSDI is associated with cortical hyperarousal (17). While physiological hyperarousal is a heightened stress state due to negative thoughts, cortical hyperarousal is increased activation of the reticular formation causing an increase in wakefulness. The result from the present paper provide further evidence of two different disorders that may have different underlying causes of hyperarousal.

Short-Sleep Duration Insomnia

Disrupted sleep appears to be a core feature of short-sleep duration insomnia, with less total time asleep, a higher % of NREM, and lower percent of REM sleep, when compared to those with healthy sleep and NSDI. This pattern of sleep architecture is similar to that seen in attention deficit hyperactivity disorder (ADHD) (54), another disorder of hyperarousal. This suggests potential for some shared pathophysiology, for example, problems in the dorsolateral pons, an area of the brain implicated in modulating arousal and sleep states (55, 56). This biological basis for poor sleep may then impact mood and thinking, and then move into a more cyclic relationship between these features.

Further, short sleep duration is associated with chronic insomnia (17). As chronicity in many other disorders is associated with poorer health and cognitive outcomes (24), it is surprising that the results of the present paper do not indicate more severe cognitive problems for those with SSDI. However, the sample was young and relatively healthy, and as cognitive problems were only witnessed in inconsistency (an indicator of early cognitive change), it is possible these individuals have not had sufficient exposure to insomnia, and/or that young age may provide a "buffer" for cognitive problems. For example, N3 declines with age, whereas in the present sample, there was greater quantity of N3 sleep, perhaps reflecting a homeostatic way of compensating for sleep loss that may not be present in an older sample. Examination of the impact of chronicity among these two phenotypes is an important future direction.

Normal-Sleep Duration Insomnia

By contrast, poor lab-assessed sleep is not a core feature of NSDI, despite less consistent response times to cognitive tasks in comparison to healthy sleepers. This suggests that something else is affecting cognition and mood than the sleep disruption seen in SSDI.

The DMN is a network of interacting brain regions that is active when a person is at rest (18) and is thought to be responsible for "off-line" cognitive functions. This network has been implicated in the paradoxical experience of feeling awake while lab-assessed assessments detect sleep, and has been purported to be responsible for cognitive problems in other neurological disorders, including schizophrenia (57), where there are also working memory deficits and problems with self-referential thoughts (58). As such, NSDI appears not to be a sleep disorder *per se*, rather a disorder of neural networks.

Impact on Diagnosis and Treatment

Different pathophysiology, as suggested by these results, directly impacts the most appropriate therapy and suggests a need for early differential diagnosis.

Cognitive behavioural therapy for insomnia (CBTi) is considered a first-line treatment for insomnia with results

superior to benzodiazepines (59). Among other aspects, CBTi includes core components to address unhelpful health beliefs, low mood, and unconsolidated sleep. These factors are important modifiable precipitating and maintaining features of insomnia. While CBTi demonstrates good results, not all patients receive benefits from this treatment (59). It is plausible that those who do not benefit are those for whom the underlying cause has not been addressed. For example, if short-sleep duration is due to biologically-based hyperarousal then CBTi may have limited ability to address such predisposing factors.

Further work to understand these potentially different disorders and their pathophysiology is crucial to inform therapy and provide more individualised treatments.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available as the data belong to the Raine Study. Requests to access this data can be made to this administering institution. Requests to access the datasets should be directed to https://rainestudy.org.au/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Ethics Committee, University of Western Australia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Excessive Daytime Sleepiness in Obstructive Sleep Apnea Patients Treated With Continuous Positive Airway Pressure: Data From the European Sleep Apnea Database

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Excessive daytime sleepiness (EDS) is a symptom of obstructive sleep apnea (OSA) that resolves under treatment with continuous positive airway pressure (CPAP). In some patients, sleepiness persists despite CPAP treatment. We retrospectively analyzed data on subjective residual EDS, assessed as an Epworth Sleepiness Scale score (ESS) >10, in patients from the European Sleep Apnea Database ($n = 4,853$, mean age ± SD 54.8 ± 11.8 years, 26.1% females), at baseline and at the first visit (median follow-up: 5 months, interquartile range 3–13). An ESS > 10 occurred in 56% of patients at baseline and in 28.2% of patients at follow-up. Residual EDS was analyzed in 2,190 patients (age: 55.1 ± 12.0 years, 26.1% females) with sleep monitoring data (median follow-up: 3 months, interquartile range 1–15). Sleep studies during CPAP use were obtained in 58% of these patients; EDS was reported by 47.2% of patients at baseline and by 30.3% at follow-up. Residual OSA, defined as an apnea–hypopnea index >10/h, and insufficient CPAP adherence, defined as nightly use <4 h, occurred with similar frequency in patients with and without EDS at follow-up. Prevalence of residual EDS was highest (40%) in patients with a first follow-up visit at 0–3 months, then it was 13–19% in patients with a first

follow-up visit after 4 months to 2 years. The change in ESS ($n = 2,190$) was weakly correlated with CPAP use ($R^2 = 0.023$, $p < 0.0001$). Logistic regression showed that an ESS score >10 at the first follow-up visit was associated directly with ESS at baseline and inversely with duration of follow-up, and CPAP use (R^2 of the model: 0.417). EDS showed heterogeneity in different European countries both at baseline and at the first follow-up visit, suggesting modulation by cultural and lifestyle factors. In conclusion, residual EDS in CPAP-treated OSA occurred in approximately one in four patients at follow-up; its prevalence was highest (40%) in the first 3 months of treatment and subsequently decreased. The finding of residual EDS in a significant percentage of optimally treated OSA patients suggests that wake-promoting agents may be useful, but their indication should be evaluated after at least 3 months of treatment.

Keywords: residual sleepiness, CPAP adherence, follow-up, Epworth Sleepiness Scale, sleep duration, sleep latency

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by complete or partial collapse of the upper airway during sleep, intermittent snoring, increasing inspiratory efforts, sleep fragmentation, and cyclic hypoxemia and hypercapnia (1). Excessive daytime sleepiness (EDS) is a major symptom of OSA, occurring in approximately a quarter to half of OSA patients (1, 2) and is associated with increased risk of accidents at work or while driving (3, 4). Continuous positive airway pressure (CPAP) is the most effective and commonly used treatment for OSA (5). CPAP application through a tightly fitted nasal or oronasal mask, at a sufficient pressure level titrated in each patient, prevents upper airway collapse and the pathophysiological consequences of OSA. CPAP treatment improves EDS either assessed subjectively by the Epworth Sleepiness Scale (ESS) or objectively by the Maintenance of Wakefulness Test (MWT) (5) and prevents sleepiness-related driving accidents (4).

The effect of CPAP treatment on EDS is multifactorial and conceptually linked to the improvement of sleep by alleviation of sleep disordered breathing. Despite a placebo effect (6, 7), all studies agree that therapeutic CPAP is more effective than subtherapeutic CPAP, not only on subjective but also on objective sleepiness measurements. The minimal important difference in ESS score associated with CPAP use has been estimated as a decrease in ESS score from baseline between two and three points (8, 9).

As expected, the CPAP-related improvement in EDS depends on adherence to treatment and differs according to the instrument used to assess sleepiness (10). In their seminal paper, Weaver and coworkers reported that CPAP treatment for 3 months resolved subjective EDS in 66% of adult patients classified as sleepy at baseline (ESS >10). The frequency of EDS resolution increased with CPAP use, but ∼20% of the patients remained subjectively sleepy despite an 8-h nightly use of CPAP (10).

The persistence of EDS in OSA patients treated with CPAP may be affected by sleep duration, use of drugs, or comorbid conditions such as depression. After correcting for such confounding factors, a 6% prevalence of persistent EDS was estimated in CPAP-treated OSA patients after 1 year of treatment (11). Variable prevalence rates of residual EDS, between 13 and 40%, have been reported (12–14). Length of follow-up in these studies varied from 3 to 24 months (12–14). Each of these studies was conducted in a single country, and the potential influence of cultural or specific national conditions on residual EDS was not considered.

The purpose of this study was to assess the current prevalence of persistent EDS in CPAP-treated OSA patients in the large European Sleep Apnea Database (ESADA) cohort and to explore predictors among a large number of factors, including regional influences. Data were collected after a median CPAP treatment duration of 5 months.

PATIENTS AND METHODS

The ESADA has prospectively collected data in over 30,000 unselected adult patients (age 18–80 years) with suspected OSA syndrome studied in several European Centres of Sleep Medicine. A full description of the ESADA Database is available elsewhere (15). Briefly, collected data at baseline include anthropometrics, comorbidities, and use of drugs according to Anatomical Therapeutic Chemical Classification System codes. Sleep data, collected by polygraphy or polysomnography, include apnea–hypopnea index (AHI), oxygen desaturation index 3%, mean and lowest oxygen saturation (SpO_2), and time spent at $SpO_2 <$ 90% (T90); data on sleep stages were available only in patients undergoing polysomnography and were not considered in this analysis. Exclusion criteria in the ESADA cohort are previous diagnosis of OSA syndrome, limited life expectancy, and current alcohol or drug abuse. All patients provided written informed consent for the anonymous use of their data. Each study site obtained approval of the study by the local ethical committee.

Figure 1 reports the flowchart for inclusion in the study. Patients who received no treatment, or were treated with bi-level ventilation, or had incomplete data were excluded. Data obtained in patients on CPAP treatment at the first follow-up visit were analyzed to assess the prevalence of residual EDS and

its predictive factors. Subjective EDS either at baseline or follow-up was defined as ESS score >10, an ESS score of 10 being the upper limit recorded in normal subjects (16). Sleep monitoring data at follow-up (residual AHI, mean hours of CPAP use) and their source (polysomnography, cardiorespiratory polygraphy, download of CPAP device) were recorded.

First, the prevalence of residual EDS was assessed on all patients with data at follow-up (n = 4,853). Then, a detailed analysis was performed in a subgroup (n = 2,190) with sleep monitoring data at follow-up (**Figure 1**). Sleep monitoring (PSG or PG) on CPAP was obtained in approximately 60% of this sample (**Table 1**). To account for possible causes of residual EDS on CPAP treatment, patients were stratified according to the occurrence of residual OSA, i.e., AHI $\leq$ 10 or >10/h, and the daily adherence to CPAP treatment, i.e., CPAP use <4 or $\geq$4 h. In addition, in each patient, the change in EDS status from baseline to follow-up was recorded, and four groups were defined and further analyzed: EDS at both baseline and follow-up; EDS at baseline and no EDS at follow-up; no EDS at baseline and EDS at follow-up, no EDS at either baseline or follow-up.

Statistical analysis: Patients without and with EDS at follow-up were compared by unpaired t-test for continuous variables and by χ^2 test for categorical variables. One-way analysis of variance or the Wilcoxon signed-rank test was used to compare baseline and follow-up data in the four groups defined according to the different combinations of EDS at baseline and follow-up. Significance was corrected for multiple comparisons. Logistic regression was used to analyze the factors associated with ESS > 10 at follow-up, based on results of this and previous studies (10–14, 17). The following variables were tested: age, sex, body mass index (BMI), ESS, AHI and comorbidities at baseline, subjective sleep latency at baseline, use of automatic or fixed CPAP, hours of CPAP use, subjective sleep duration at follow-up, and length of follow-up. Collinearity among variables was tested by Spearman rank correlation, and variables with Rho < 0.70 were retained for analysis. Statview 5.0.1 (SAS Institute) and IBM SPSS Statistics Version 22 were used for analysis. Statistical significance was at $p < 0.05$ for all tests.

RESULTS

The study sample included 4,852 OSA patients on CPAP treatment at a first follow-up visit. The median follow-up duration was 5 months [interquartile range (IQR): 3–13 months]. Compared with baseline ESS score (median and IQR): 10 (6–14), median ESS score on CPAP treatment was four-point lower [post-CPAP: 6 (3–10), $p < 0.0001$]. Subjective EDS was reported by 56% of patients at baseline and by 28.2% at the first follow-up visit.

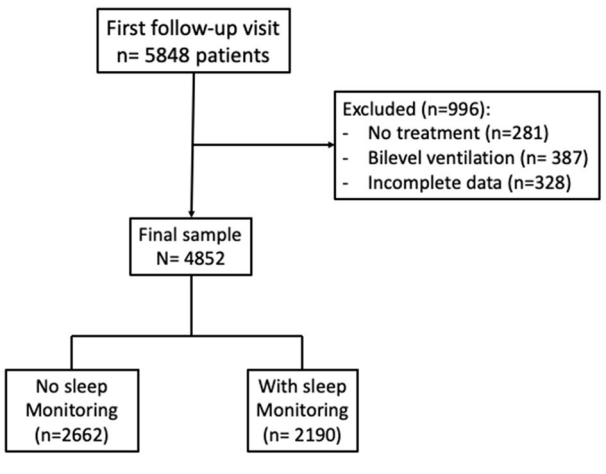

FIGURE 1 | Flow-chart of the study.

TABLE 1 | Source of sleep monitoring data at the first follow-up visit in patients without and with residual excessive subjective sleepiness (EDS).

	Total (n = 2,190)	EDS+ (n = 664)	EDS− N = 1,526
Polysomnography, *n* (%)	103 (4.7)	36 (5.4%)	67 (4.4%)
Cardiorespiratory poligraphy, *n* (%)	1,405 (54.2%)	523 (78.8%)	882 (62.6%)
Limited channel study, *n* (%)	4 (0.2%)	2 (0.3%)	2 (0.1%)
Data download, *n* (%)	678 (31.0%)	103 (15.5%)	575 (40.8%)

TABLE 2 | Differences at baseline between patients without and with excessive daytime sleepiness (EDS) at the first follow-up visit (n = 2,190).

Variables	No EDS at follow-up (n = 1526)	EDS at follow-up (n = 664)	p
Age (years)	55.7 ± 11.7	53.9 ± 12.4	**0.0015***
Females, *n* (%)	27.6%	23.4%	**0.03**
BMI (kg/m^2)	33.0 ± 6.6	34.2 ± 6.6	**<0.0001***
AHI (events/h)	34.0 [21.0–51.4]	38.0 [23.0–60.0]	**<0.0001**‡
ODI 3% (events/h)	31.0 [18.0–50.9]	38.1 [21.9–59.8]	**<0.0001**‡
Lowest SpO_2 (%)	77.1 ± 9.3	76.2 ± 10.0	**0.029***
Mean SpO_2 (%)	91.9 ± 3.3	91.4 ± 3.4	**0.0032***
Time spent at SpO_2 <90% (%)	3.9 [0.7–12.5]	5.3 [0.7–14.5]	0.159‡
ESS score	8 [5–11]	14 [12–17]	**<0.0001**‡
Subjective sleep duration (h)	6.9 ± 1.4	6.7 ± 1.4	**0.0017***
Subjective sleep latency (min)	10.0 [5.0–30.0]	5.0 [2.0–20.0]	**<0.0001**‡
Coronary artery disease (%)	8.6%	7.1%	0.25†
Systemic hypertension (%)	49.6%	53.2%	0.12†
Type 2 diabetes (%)	12.4%	14.5%	0.19†
COPD (%)	7.0%	8.1%	0.33†
Asthma (%)	3.6%	2.3%	0.16†
Insomnia (%)	2.1%	1.4%	0.24†
Psychiatric disease (%)	4.8%	3.8%	0.28†
Follow-up duration (months)	5 [1–19]	1[0–7]	**<0.0001**‡

**one-way ANOVA (means±SD); ‡Mann-Whitney U-test test (medians and interquartile ranges); † χ^2 test (percent).*
Significantly different variables are marked in bold.

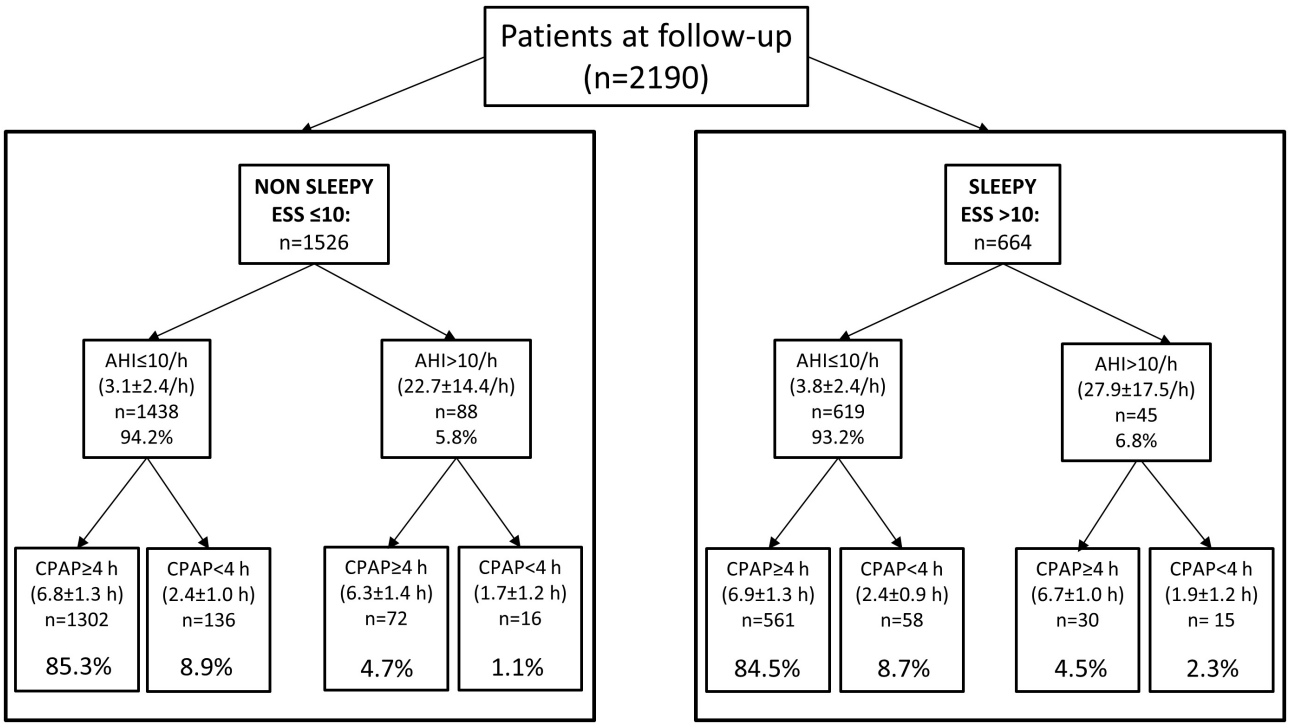

FIGURE 2 | Analysis of the sample (sleep monitoring data available in 2,190 patients) according to resolution of OSA and adherence to CPAP treatment in patients without and with EDS at follow-up. Mean ± SD for AHI and CPAP use are reported in each box. Percentage of patients with incomplete OSA resolution or poor CPAP adherence was similar in patients with and without persistent sleepiness at follow-up (percentages in lower boxes refer to the non-sleepy and sleepy samples, respectively).

Sleep monitoring data during CPAP were available in 2,190 patients. In these patients, the median follow-up duration was 3 months (IQR 1–15). The prevalence of EDS at baseline (47.2%) was slightly lower than that found in the entire sample (56%). ESS score after CPAP treatment was three-point lower than at baseline [baseline: 10 (6–14), post-CPAP: 7 (4–12), $p < 0.0001$], and the prevalence of EDS at follow-up was 30.3%.

Compared with patients without sleep monitoring data ($n = 2{,}662$), patients with sleep monitoring data during CPAP treatment were of similar age and sex and showed slightly higher BMI; they reported longer subjective sleep duration and shorter sleep latency, besides showing a lower AHI, mean and lowest SpO_2, and a similar percentage of time spent at SpO_2 < 90%. From a clinical point of view, however, the differences between groups were small (**Supplementary Table 1**). The group with sleep monitoring data showed a lower prevalence of type 2 diabetes, psychiatric disease, and drug treatment compared with the group without sleep monitoring data at follow-up (**Supplementary Table 1**).

Analysis of Patients With Sleep Monitoring Data at Follow-Up ($n = 2{,}190$)

Polysomnography or cardiorespiratory polygraphy was obtained in 60% of the sample (**Table 1**). In patients with EDS at follow-up, data on residual AHI were collected from CPAP devices in 15.5% of cases. Most patients (81.1%) were treated with automatic CPAP (**Supplementary Table 2**). Compared with non-sleepy patients at follow-up, patients with EDS at follow-up were more often males, younger and more obese, showed slightly more severe OSA, and were sleepier at baseline, whereas comorbidities were similar in the two groups (**Table 2**).

Patients were then stratified according to residual AHI (≤10 or >10/h) and adherence to CPAP treatment, i.e., CPAP use <4 or ≥4 h (detailed data are reported in **Figure 2**). The percentage of patients with incomplete resolution of OSA, i.e., AHI > 10/h, and poor CPAP adherence, i.e., <4 h/night, was 2.3% (15/664) in patients with EDS at follow-up compared with 1.1% (16/1,526) in patients without EDS at follow-up.

ESS scores were similar in sleepy patients at baseline, independent of the occurrence of EDS at follow-up (**Figure 3A**). A large decrease in ESS was found in sleepy patients at baseline in whom EDS resolved with CPAP treatment (Δ ESS $= -8.7 \pm 3.8$, $n = 403$). Very few ($n = 34$) of the non-sleepy patients at baseline ($n = 1{,}157$) reported EDS at follow-up (2.9%, Δ ESS $= 4.7 \pm 3.9$) (**Figure 3B**).

At baseline, patients with persistent EDS at follow-up were more obese than all the other groups and showed the highest prevalence of type 2 diabetes and the lowest prevalence of asthma; time to follow-up was also significantly shorter than in all the other groups (**Table 3**). Patients with EDS at follow-up showed the highest AHI and oxygen desaturation index 3%, and lowest SpO_2 variables at diagnosis compared with the other groups;

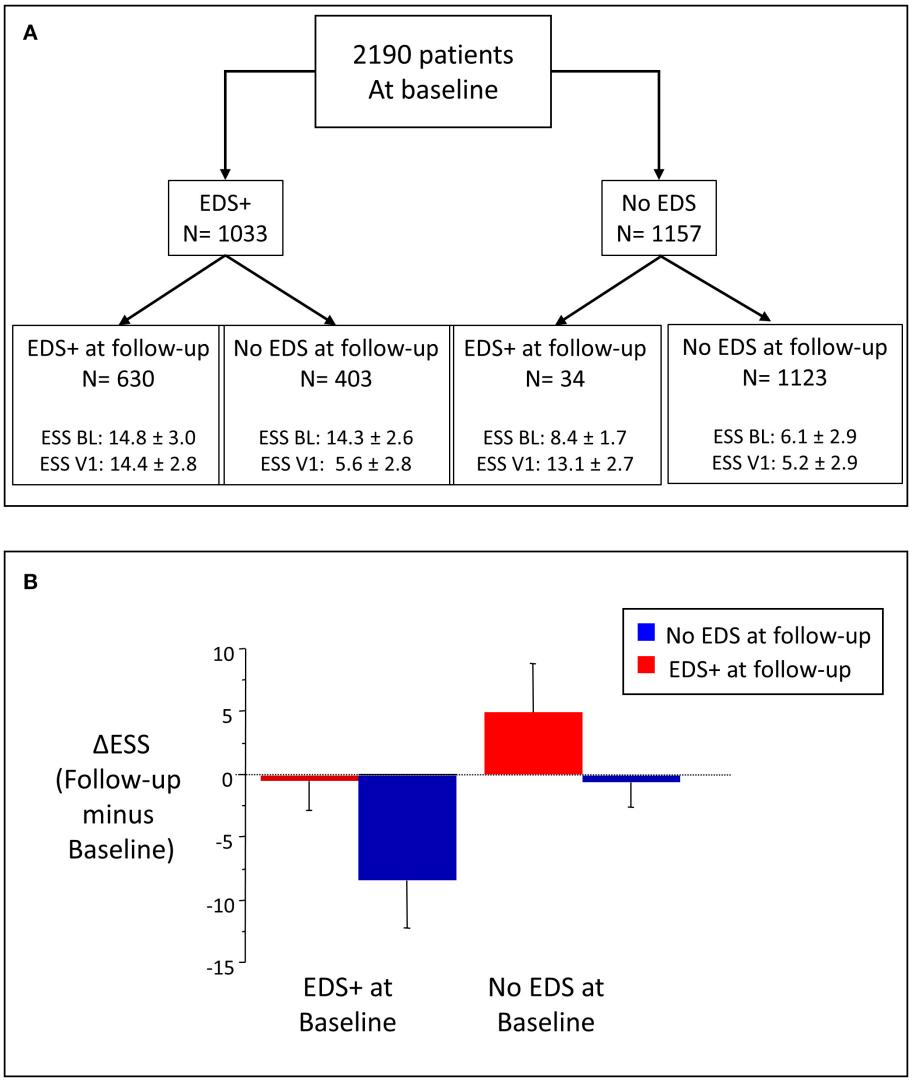

FIGURE 3 | (A) Stratification of patients in four groups, according to occurrence of EDS at baseline and follow-up. EDS+: EDS present; BL: Baseline; V1: first follow-up visit. **(B)** Change in EDS (Δ EDS) in the four groups; Δ EDS calculated as EDS at follow-up minus EDS at baseline.

their median subjective sleep latency at baseline was 5 min compared with values ≥10 min in the other groups. Subjective sleep latency remained low in patients with persistent EDS at follow-up (**Table 4**).

A weak relationship was found between hours of CPAP use and change in ESS ($R^2 = 0.023$, $p < 0.0001$, $n = 2{,}190$). In patients with EDS at follow-up, the slope of the relationship between the change in ESS (Δ ESS, follow-up minus baseline) and baseline ESS was less than half the slope found in patients with resolution of EDS after CPAP treatment (**Figure 4**). The prevalence of EDS at follow-up was highest in sleepy patients at baseline undergoing the follow-up visit in the first 3 months of treatment; subsequently, the prevalence of persistent EDS decreased slightly over time, from 21.9% at 3–6 months to 15.1% at more than 2 years (**Figure 5**, p for trend < 0.0001).

Logistic regression was used to analyze the predictors of ESS score >10 at follow-up ($n = 2190$, R^2 of the model: 0.417). The following variables were identified as correlates:

- ESS at baseline (0.139 [95% CI 0.015/0.263] $p = 0.028$)
- Hours of nightly CPAP use (−0.514 [95% CI −0.767/−0.261], $p < 0.0001$)
- Follow-up duration in months (−0.051 [95% CI −0.064/−0.039] $p < 0.0001$)
- Interaction ESS at baseline*hours of CPAP use/day (0.051 [0.031/0.071, $p < 0.0001$)

There was a trend for AHI at baseline (−0.006 [95% CI −0.013/0.001] $p = 0.088$), and average subjective sleep length at follow-up (−0.10 [95% CI −0.215/0.013], $p = 0.084$) to be inversely related with persistent EDS. Age, sex, BMI, subjective

TABLE 3 | Clinical data at baseline according to occurrence of excessive daytime sleepiness at baseline and at the first follow-up visit, $n = 2,190$.

Variables	EDS baseline/ EDS follow-up ($n = 630$)	EDS baseline/ No EDS follow-up ($n = 403$)	No EDS baseline/ EDS follow-up ($n = 34$)	No EDS baseline/ No EDS follow-up ($n = 1,123$)	*p*-value
Age (years)	53.6 ± 12.4	53.6 ± 11.8	59.2 ± 10.7[#]	56.4 ± 11.6	**<0.0001***
Females (%)	23.3	25.1	20.6	28.1	0.13[†]
BMI (kg/m^2)	34.4 ± 6.6	32.7 ± 6.4	30.8 ± 5.4	33.1 ± 6.7	**<0.0001***
ESS score at baseline	14.0 [12.0–17.0]	14.0 [12.0–16.0]	9.0 [7.0–10.0][§]	6.0 [4.0–9.0][§]	**<0.0001[‡]**
Coronary artery disease (%)	6.5	9.3	17.6	8.3	0.07[†]
Systemic hypertension (%)	53.1	50.8	55.9	49.2	0.42[†]
Type 2 diabetes (%)	14.9	9.3	5.9	13.6	**0.03[†]**
COPD (%)	8.1	5.5	8.8	7.5	0.44[†]
Asthma (%)	2.2	7.0	5.5	2.7	**0.002[†]**
Insomnia (%)	1.3	2.3	2.9	2.1	0.58[†]
Psychiatric disease (%)	3.8	7.5	2.9	3.8	**0.015[†]**
Follow-up duration (months)	1 [0–5]	16 [7–30][§]	14.5 [6.0–43.0][§]	2 [0–12][§]	**<0.0001[‡]**

**one-way ANOVA, means and SDs; [†] χ^2 test (percent); [‡]Kruskal-Wallis test (medians and interquartile ranges). [§]statistically different compared to the group with EDS at baseline and at first follow-up visit; [#]different from groups with EDS at baseline.*
Significantly different variables are marked in bold.

sleep latency, comorbidities, or use of fixed or automatic CPAP did not enter the model. In summary, EDS at follow-up was associated with high ESS at baseline, short nightly CPAP use, and short follow-up duration at first control visit. The highly significant interaction term indicates that a high degree of sleepiness at baseline reduced the effect of CPAP adherence on the outcome.

Finally, the geographic distribution of EDS was explored at baseline and follow-up in the entire sample ($n = 4,853$). This analysis was limited to countries with data on at least 50 patients (50–1,839) (**Figure 6**). Prevalence of EDS was highly variable, occurring in 39.8–84.8% of patients at baseline and in 3.6–45.6% of patients at follow-up. The highest prevalence rates of EDS were recorded in the samples from Sweden, United Kingdom, and Ireland at baseline and in the samples from Greece and Ireland at follow-up.

DISCUSSION

Approximately one in four patients treated with CPAP reported EDS at follow-up. The prevalence of residual EDS was highest when the follow-up visit occurred during the first 3 months of CPAP treatment. Incomplete resolution of OSA and/or poor adherence to CPAP were similar in patients with and without EDS at follow-up. The major predictive factors of residual EDS were baseline EDS, hours of CPAP use, and length of follow-up. At least part of the variability in EDS at follow-up might be related to geographical/cultural differences in patients' samples or subjective EDS reporting.

The analysis of CPAP-treated OSA patients from the ESADA cohort revealed a quite high prevalence of EDS at the first follow-up visit. The sample of treated OSA patients was large and representative of patients from several European countries. Importantly, sleep data at follow-up were collected during sleep studies on CPAP in 45% of the entire sample, and data downloaded from CPAP devices accounted only for 15.5% of patients with residual EDS in the sample with sleep monitoring data during CPAP treatment. Prevalence of EDS at follow-up was 28.2% in the entire sample, highlighting that EDS during OSA treatment is a clinically relevant, and often overlooked, problem. Residual EDS was more prevalent in patients assessed early during follow-up, then its frequency slowly decreased over time.

Compared with patients without EDS at follow-up, patients with persistent EDS were younger and more obese and showed slightly more severe OSA at baseline; they were sleepier at baseline and reported shorter sleep duration and sleep latency, in agreement with data reported in previous studies on EDS after treatment. In the study by Pepin and coworkers, patients with residual EDS were younger and sleepier at diagnosis, but the prevalence of EDS after 1 year of treatment was lower than in our study, being 12% in the overall sample, and only 6% after excluding patients with known causes of EDS, including restless leg syndrome and depression (11). In the study by Gasa and coworkers, persistent EDS during CPAP treatment was associated with baseline ESS score and was more prevalent in patients with moderate OSA; they also noted that a small number of non-sleepy patients at baseline became sleepy on CPAP treatment (5.6 vs. 2.9% in the current study) (12). As for the possible role of residual AHI or level of adherence to CPAP treatment, the prevalence of incomplete OSA resolution or poor CPAP adherence was similar in subjects with and without persistent EDS. Weaver et al. also reported no difference in the average use of CPAP between sleepy and non-sleepy OSA patients at 3-month follow-up (10). The prevalence of EDS decreased with increasing hours of CPAP use; however, ∼20% of patients using CPAP for >8 h/night reported residual EDS

TABLE 4 | Sleep monitoring data at baseline and at the first follow-up visit according to occurrence of excessive daytime sleepiness (EDS) at baseline and follow-up.

Variables		EDS baseline/ EDS follow-up (n = 630)	EDS baseline/ No EDS follow-up (n = 403)	No EDS baseline/ EDS follow-up (n = 34)	No EDS baseline/ No EDS follow-up (n = 1,123)	p-value
Nocturnal monitoring:	BL					–
PSG (n)		52	71	8	125	
PG (n)		578	332	26	998	
limited channel (n)		0	0	0	0	
Nocturnal monitoring:	FU					–
PSG (n)		31	25	5	42	
PG (n)		512	100	11	782	
limited channel (n)		2	1	0	1	
CPAP download (n)		85	277	18	298	
AHI (events/h)	BL	38.3 [23.0–60.4]	35.0 [18.2–53.9]	24.9§ [13.3–37.4]	33.1§ [21.3–51.0]	**<0.001‡**
	FU	3.9 [2.3–5.8]	2.1§ [0.9–4.4]	1.9 [1.0–4.8]	3.1§ [1.4–5.1]	**<0.0001‡**
ODI 3% (events/h)	BL	39.2 [22.5–60.7]	30.2§ [15.6–51.0]	17.9§ [12.8–36.6]	31.0§ [19.4–50.8]	**<0.0001‡**
	FU	4.2 [2.8–6.3]	2.9§ [0.9–7.0]	3.6 [1.3–17.3]	3.6§ [2.1–5.5]	**<0.0001‡**
Lowest SpO_2 (%)	BL	75.9 ± 10.0	76.1 ± 10.1	80.9 ± 8.4§	77.5 ± 8.9§	**0.0002***
	FU	86.0 ± 6.8	82.9 ± 15.2§	86.9 ± 6.0	86.3 ± 8.8	**0.003***
Mean SpO_2 (%)	BL	91.4 ± 3.4	91.9 ± 3.5§	92.4 ± 3.6§	91.9 ± 3.2§	**0.009***
	FU	93.8 ± 4.5	91.2 ± 16.1	95.5 ± 1.4	93.5 ± 8.4	**0.02***
Time spent at SpO_2 <90% (% of recorded time)	BL	5.4 [0.7–14.7]	5.3 [1.6–21.2]	3.0 [0.7–10.0]	3.6 [0.6–11.5]	**0.025‡**
	FU	0.2 [0.0–1.4]	0.1 [0.0–2.1]	0.0 [0.0–0.7]	0.1 [0.0–0.9]	0.081‡
Subjective sleep duration (h)	BL	6.7 ± 1.4	7.0 ± 1.4§	7.0 ± 1.2	6.9 ± 1.4§	**0.002***
	FU	6.7 ± 1.4	7.0 ± 1.2	6.8 ± 1.2	6.7 ± 1.3	**0.046***
Subjective sleep latency (min)	BL	5.0 [2.0–25.0]	10.0§ [5.0–30.0]	15.0 [5.0–16.3]	10.0§ [2.0–30.0]	**<0.0001‡**
	FU	5.0 [2.0–20.0]	10.0§ [7.0–20.0]	10.0 [2.0–15.0]	10.0§ [2.0–30.0]	**<0.0001‡**

*BL, Baseline, FU, first follow-up visit; PSG, Polysomnography; PG, Cardiorespiratory Polygraphy; *one-way ANOVA, means and SDs; ‡Kruskal-Wallis test (medians and interquartile ranges), §different from the group with EDS at baseline and first follow-up visit.*
Significantly different variables are marked in bold.

(10). In the study by Antic and coworkers, 40% of patients with moderate–severe OSA reported EDS after 3 months of CPAP treatment (14). Our analysis took into account the length of follow-up, and, similar to previous results (10, 14), we found a high prevalence of EDS when the follow-up visit was in the first 3 months of CPAP treatment. We cannot exclude a selection bias, i.e., patients with persistent EDS may have asked for an early visit because of problems associated with CPAP treatment. We also acknowledge that we did not longitudinally assess patients at different time points during follow-up, and the higher prevalence of EDS in the first 3 months needs confirmation in future studies.

Because the sample included patients with and without EDS at baseline, we analyzed the longitudinal changes in ESS according to initial and final EDS status. Of 2,190 patients, 47.2% were sleepy at baseline (n = 1,033), and 61% of them (n = 630) were sleepy at follow-up. These figures may reflect a selection bias, i.e., sleep monitoring data would more likely be obtained in symptomatic than asymptomatic patients at follow-up. Patients with persistent EDS showed a very short sleep latency compared with the other groups both at baseline and follow-up. Although sleep latency is expected to be short in sleepy patients, our data suggest that a very short sleep latency could help in the clinical identification of patients more likely to remain sleepy

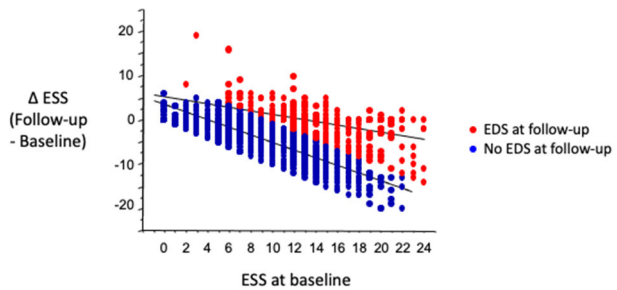

FIGURE 4 | In patients sleepy at baseline, slope of relationship between change in ESS (Δ ESS, EDS at follow-up minus EDS at baseline) and baseline ESS was much lower in patients with than in patients without EDS at follow-up. Equations describing regressions are in patients with EDS at follow-up (red dots): ΔESS = 5.35 – 0.41 • ESS at baseline; $R^2 = 0.29$, $p < 0.001$; in patients without EDS at follow-up (blue dots): ΔESS: 3.35–0.80 • ESS at baseline; $R^2 = 0.68$, $p < 0.001$.

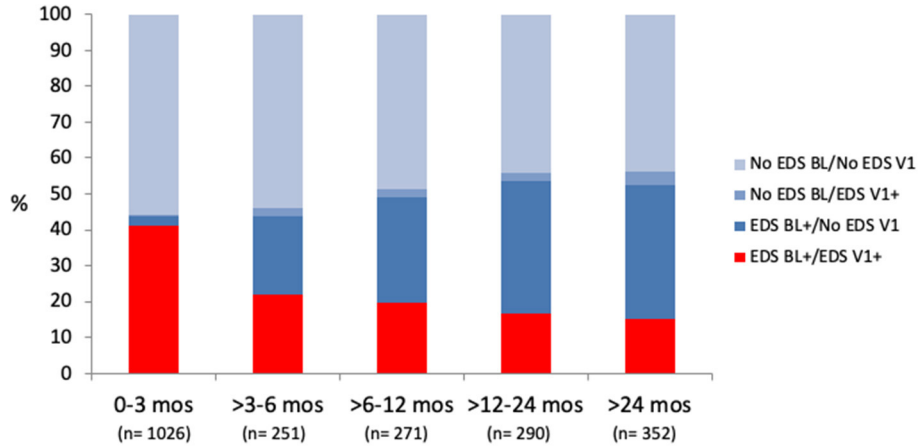

FIGURE 5 | Distribution of four groups, stratified based on occurrence of EDS at baseline (BL) and follow-up (V1), according to time of first follow-up visit. Persistent EDS at follow-up (in red) was more frequent in patients seen during first 3 months of CPAP treatment ($p < 0.0001$ by X^2, p for trend < 0.0001). No EDS BL/No EDS V1: ESS $\leq$ 10 at baseline and follow-up; No EDS BL/EDS V1+: ESS $\leq$ 10 at baseline and ESS $>$ 10 at follow-up; EDS BL + /No EDS V1: ESS $>$ 10 at baseline and ESS $\leq$ 10 at follow-up; EDS BL + /EDS V1+: ESS $>$ 10 at both baseline and follow-up.

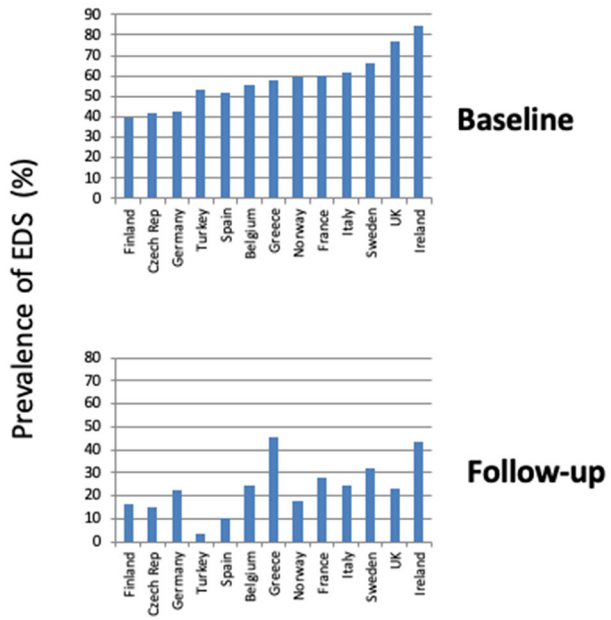

FIGURE 6 | Prevalence of EDS at baseline and first follow-up visit in different ESADA countries in entire sample. Only countries reporting data on at least 50 patients are shown.

on CPAP. However, short sleep latency did not enter the logistic model.

Incomplete resolution of EDS could reflect the individual susceptibility to hypoxic brain damage or sleep fragmentation. Convincing data on the pathogenesis of intermittent hypoxia-induced sleepiness and on the role of sleep fragmentation have been obtained in rodents. A loss of 40% of wake-promoting catecholaminergic neurons has been shown in rodents after chronic intermittent hypoxia exposure for 6 months (18). White matter damage (19) and possible vicious cycles of oxidative damage involving both neurons and microglia (20) have been reported after chronic intermittent hypoxia in mice. Similarly, neuronal damage was reported in wake active regions after 4 weeks of sleep fragmentation (21). In humans, the mechanisms preventing full recovery from EDS remain unknown, but imaging studies hold some promise, as abnormal findings in the frontal area (22) and white matter alterations (23) were found in patients with persistent EDS during CPAP treatment. In our study, ESS scores on CPAP decreased less in patients with persistent EDS than in patients without EDS at follow-up, for similar pretreatment ESS levels. This result agrees with the report by Gasa et al. (12) who found that some improvement in symptoms occurred with CPAP treatment in patients with persistent EDS at follow-up, albeit to a lesser extent than patients with no residual EDS.

A small group of patients not sleepy at baseline became sleepy on CPAP. These patients were older compared with the other groups. The low number of patients prevents any meaningful analysis, but this subgroup may show different clinical features compared with patients with persistent EDS, i.e., high prevalence of coronary artery disease or sleepiness due to adverse effects of CPAP.

The variable prevalence of EDS in different European countries both at baseline and follow-up may reflect the variability in several factors, including the local prevalence of obesity, cultural factors, and lifestyle habits, such as caffeine and alcohol consumption. This topic deserves further study.

As for factors associated with persistent sleepiness, EDS at follow-up tended to be negatively related to baseline AHI, in agreement with the results reported by Gasa et al. (12) who found that persistent EDS was associated with mild–moderate OSA rather than severe OSA. Obesity is a potential cause of daytime sleepiness, even in the absence of OSA (24). The role of obesity in the pathogenesis of EDS is supported by its improvement/resolution after weight loss, independently of

changes in AHI (25). However, BMI did not enter the logistic model in our study.

Other studies have searched for predictors of persistent EDS in CPAP-treated OSA patients (12, 26). Our data add the important information that prevalence of residual EDS in CPAP-treated patients, after an initial high value during the first 3 months of treatment, similar to previous studies (10, 14), slowly decreased during the first 2 years of treatment. This finding opens the way to pharmacological treatment of EDS. New drugs, i.e., solriamfetol and pitolisant, have been recently studied in OSA patients and appear effective without major adverse effects (27–29). The indications to drug treatment are still undefined, but according to our results, it seems advisable that their prescription should occur at least after 3 months of CPAP treatment.

Our study shows some important limitations. First, sleep monitoring data were available in only 45.1% of patients undergoing the first follow-up visit. The analyzed subgroup of 2,190 patients showed a higher prevalence of EDS at follow-up than the entire sample, suggesting a selection bias. On the other hand, such an enrichment with a high percentage of persistently sleepy OSA patients on CPAP may increase the robustness of the analysis of predictors for persistent EDS. Moreover, the patients with and without sleep data at follow-up were similar for anthropometrics and OSA severity at baseline. Second, the analysis did not take into account the type of sleep study at baseline or follow-up. The ESADA cohort includes patients studied at baseline with either polysomnography or cardiorespiratory polygraphy, and the impact of different diagnostic methods has been previously discussed (30). In our study, differences between polysomnography and cardiorespiratory polygraphy were not taken into account either at baseline or at follow-up, as this would have caused a fragmentation of the sample in multiple subgroups complicating statistical analysis and decreasing statistical power. On the other hand, data at follow-up were obtained by sleep studies in many patients, whereas other studies relied exclusively on data downloaded from CPAP machines (12). Third, the database does not include depression among the recorded comorbidities. Depression is recognized as a major risk factor for EDS in CPAP-treated patients (17). The use of drugs for depression was reported by a minority of patients (N05-Psycholeptic drugs by 2.6% and N06-Psychoanaleptics by 6.3% of the patients), and we cannot exclude that untreated mild depression might have affected the prevalence of EDS. Finally, the ESS provides a subjective assessment of EDS, and its reliability and repeatability have been critically discussed (31, 32). Objective tests to assess sleepiness would be hardly applicable in large samples, but differences in ESS scores pre- and posttreatment were quite large and above the clinically meaningful differences reported by other studies, making it likely that they reflect true changes in EDS before–after treatment. In a recent study assessing objective sleepiness in effectively CPAP-treated patients with persistent EDS, 19 of 29 subjects (65%) were sleepy or severely sleepy at the Multiple Sleep Latency Test (33). Moreover, in the APPLES Study, MWT data were obtained in addition to ESS after 6 months of CPAP treatment, with good agreement between the prevalence of subjective and objective EDS. ESS score >10 was reported by 22% of the sample, and prevalence of sleep latency < 17 min at MWT was 23% (13).

In conclusion, our data provide an estimate of the current prevalence of persistent EDS in CPAP-treated patients, around 40% in the first 3 months and between 10 and 20% after that. Occurrence of sleepiness at baseline, CPAP adherence, sleep duration at follow-up, and the timing of the follow-up visit predicted explained 40% of the variance in persistent EDS. Assessment of persistent EDS should be at least after 3 months of CPAP treatment, as EDS resolves over time in half of the patients reporting EDS at the start of CPAP treatment.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from the European Sleep Apnea Database (ESADA), the following licenses/restrictions apply: the dataset analyzed in this study is available upon reasonable request from the ESADA office. Requests to access these datasets should be directed to Ludger Grote, ESADA office, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, ludger.grote@lungall.gu.se.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of all ESADA Centers. The analysis presented is retrospective and was performed on the anonymized database. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB, JP, CB, OM, and FF: conceptualization. TS, HH, JV, OB, GT, IB, AP, JK, and SM: data collection. LG: funding acquisition. MB, FC, SB, and FF: data analysis and statistics. MB, FC, CB, OM, and FF: writing—original draft. JP, JV, TS, OB, GT, IB, WM, AP, JK, HH, SM, and LG: writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.690008/full#supplementary-material

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Trauma Immediately Preceding REM-Behavior Disorder: A Valuable Prognostic Marker?

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Background: The definition of rapid eye movement (REM) sleep behavior disorder (RBD) has varied over the years. Rapid eye movement sleep behavior disorder can be considered isolated or idiopathic or can occur in the context of other disorders, including trauma-associated sleep disorder (TSD) and overlap parasomnia. However, whether trauma in RBD carries any prognostic specificity is currently unknown.

Study Objectives: To test the hypothesis that RBD secondary to trauma is less likely to result in the development of neurodegeneration compared to idiopathic RBD (iRBD) without trauma in the general population.

Methods: A retrospective cohort study of 122 consecutive RBD patients (103 males) at two tertiary sleep clinics in Europe between 2005 and 2020 was studied. Patients were diagnosed as having iRBD by video polysomnography (vPSG) and had a semi-structured interview at presentation, including specifically eliciting any history of trauma. Patients with secondary RBD to recognized causes were excluded from the study. Patients with iRBD were categorized into three groups according to reported trauma history: (1) No history of trauma, (2) traumatic experience at least 12 months prior to RBD symptom onset, and (3) traumatic experience within 12 months of RBD symptom onset. Idiopathic RBD duration was defined as the interval between estimated onset of RBD symptoms and last hospital visit or death. Follow-up duration was defined as the interval between iRBD diagnosis and last hospital visit or death.

Results: In a follow-up period of up to 18 years, no patient who experienced trauma within 12 months preceding their iRBD diagnosis received a diagnosis of a neurodegenerative disorder ($n = 35$), whereas 38% of patients without trauma within the 12 months of symptom onset developed a neurodegenerative illness. These patients were also significantly more likely to have a family history of α-synucleinopathy or tauopathy.

Conclusions: The development of RBD within 12 months of experiencing a traumatic life event, indistinguishable clinically from iRBD, did not lead to phenoconversion to a

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neurodegenerative disorder even after 18 years (mean follow up 6 years). We suggest that a sub-type of RBD be established and classified as secondary RBD due to trauma. Additionally, we advocate that a thorough psychological and trauma history be undertaken in all patients presenting with dream enactment behaviors (DEB).

Keywords: RBD, trauma, REM-behavior disorder, dream enactment behaviors, DEB

DEFINITIONS

- RBD patients with no trauma history (Group 1)
- RBD patients with trauma that occurred >12 months before RBD diagnosis (Group 2)
- RBD patients with trauma that occurred <12 months before RBD diagnosis (Group 3).

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM parasomnia characterized by the loss of normal muscle atonia during REM sleep, in association with complex motor activity that usually represents dream enactment behaviors (DEB) (1, 2). The prevalence of RBD has been estimated to be between 0.5 and 2% in the general population (3, 4), with a higher incidence in men after the age of 50 years (5). Rapid eye movement sleep behavior disorder is categorized as either idiopathic/isolated, occurring in the absence of other diseases, or secondary. In secondary RBD, there are other underlying causes present, such as brain lesions, neurological diseases, or provoking antidepressant medications (2). Idiopathic, or isolated, RBD (iRBD) is increasingly but not uniformly considered an α-synucleinopathy (6, 7). However, not all iRBD patients develop a neurodegenerative disorder (7). Whether this is due to insufficient time for the full clinical characteristics of neurodegenerative disease to develop or a lack of α-synuclein/tau pathology in the brain of these patients or an undisclosed history of trauma is unknown at present.

By way of comparison, a recently described parasomnia, trauma-associated sleep disorder (TSD), has substantial symptomatic and clinical overlap with RBD (8, 9) and is thought to be induced by severe psychological trauma. Only a small number of TSD laboratory cases have been reported in the literature (10). As a result, and due to overlap with RBD, identifying TSD as a distinct parasomnia has remained controversial. Additionally, all TSD cases reported in the literature have been active or ex-military personnel, whereas cases from the general population remain to be described (10).

This study aimed to test the hypothesis that nocturnal dream enactment accompanied by REM sleep without atonia (RSWA) has different prognostic implications in iRBD in the context of trauma, in patients recruited from the general population. Given the overlap between RBD diagnostic criteria and reported TSD symptoms, as well as the association between RBD symptom onset in the context of a traumatic experience in a previously reported small number of iRBD patients (11), we hypothesized that patients from the general population with a history of trauma would be phenotypically dissimilar to patients with iRBD and no recent (<1 year) history of trauma. Twelve months from trauma to DEB was chosen as this was the longest time between trauma exposure and symptom onset reported in the case studies of TSD by Mysliwiec et al. (10). An additional control group of iRBD patients that reported traumatic event exposure prior to 12 months of RBD symptom onset was also included, to ascertain whether timing of trauma was relevant.

METHODS

This was a retrospective, cohort study of consecutive RBD patients referred to tertiary sleep referral centers in the United Kingdom and the Czech Republic between May 2005 and February 2020. Formal ethical approval was not deemed necessary by the local research committee since we utilized only anonymised, secondary data derived as part of standard clinical practice. All research was carried out in accordance with Helsinki criteria (World Medical Association, 2001) (12). In our practice, in Edinburgh, it is standard to take a mental health history and to ask about trauma and adverse adult and childhood experiences as part of the patient interview in any patient presenting with a parasomnia. Furthermore, this work was considered to be a service evaluation whereby the information was taken from routine practice and no new questionnaires/interview questions were introduced to gather this information. The dataset derived in the present manuscript was de-identified prior to it being captured and analyzed and all data are presented in aggregated form. This is standard procedure as laid out in the Caldicott principles.

Patient data were obtained using NHS electronic patient notes accessed through TrakCare (www.intersystems.com/TrakCare), a system used to record clinical data in secondary care (hospital) environments. All data were extracted between January 2019 and March 2020. The patient data obtained were collected between May 2005 and February 2020 by medical health care professionals.

Abbreviations: AD, Alzheimer's disease; AHI, apnoea hypopnea index; BMI, body mass index; DLB, dementia with Lewy bodies; EMG, electromyography; iRBD, idiopathic RBD; LPT, lateral pontine tegmentum; LDTN, laterodorsal tegmental nucleus; LC, locus coeruleus; MCRF, medullary magnocellular reticular formation; MSA, multiple systems atrophy; PD, Parkinson's disease; PPT; pedunculopontine; PPT, peduncupontine; PSG, polysomnography; PC, precoeruleus; PTSD, post-traumatic stress disorder; RBD, rapid eye movement sleep behavior disorder; RSWA, REM sleep without atonia; RN, red nucleus; SCN, spinal cord neuron; SC, subcoeruleus; SN, substantia nigra; TSD, trauma-associated sleep disorder; vlPAG; ventrolateral periaqueductal gray; vPSG, video polysomnography; WASO, wake time after sleep onset.

At patient presentation, a semi-structured interview was conducted, documenting clinical characteristics, sleep habits, dream content of any reported dreams and history of trauma. Patients were excluded from this study if neurodegenerative syndromes manifested prior to RBD symptom development or if patients were on antidepressant therapy, or had a diagnosis of narcolepsy, as these patients were considered to have secondary RBD according to the ICSD-3 Diagnostic Criteria defined as follows: *repeated episodes of sleep related vocalizations or complex motor behaviors, documented by polysomnography to occur during REM sleep, with REM sleep demonstrating RSWA, and is not better explained by another sleep disorder, mental disorder, medication, or substance use* (2). Patients were also excluded if they had a diagnosis of overlap parasomnia.

Trauma was defined using the ICD-10 trauma definition: …*a "delayed or protracted response to a stressful event or situation (of either brief or long duration) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone"* (13). For comparative purposes, the DSM-5 criteria (*"actual or threatened death, serious injury, or sexual violence"*) were also used (14). Trauma assessment was undertaken by a single medical professional in a blinded manner. Patients were categorized into three groups: (1) No history of trauma, (2) traumatic experience <12 months prior to RBD symptom onset, (3) traumatic experience >12 months prior to RBD symptom onset. No patient in the iRBD group had been diagnosed with post-traumatic stress disorder previously or on presentation. A family history of an alpha-synucleinopathy, dementia/tauopathy, or other neurodegenerative condition was also noted.

Rapid eye movement sleep behavior disorder duration was defined as the interval between self-reported/estimated onset of RBD symptoms and last follow-up visit or death. Follow-up duration was defined as the interval between RBD diagnosis and last follow-up visit or death. All RBD patients met full International Classification for Sleep Disorders-3 criteria (2). Patients with RSWA considered secondary to other etiologies, e.g., medication, were not included in this study.

Patients underwent overnight video polysomnography (vPSG) within 1–6 months of presentation. Video-PSGs were scored by registered sleep physiologists using AASM guidelines (15).

Patients were included in the study if any of the following instances of REM without atonia were present:

A) Excessive sustained Chin EMG activity of 2x Stage R atonia was observed for at least 50% of an epoch of REM.
B) 50% of 3-s mini epochs contained bursts of transient Chin or Leg EMG activity (0.1–5 s) at least four times greater than Stage R atonia.

The RSWA index (percentage of Stage R with atonia) was not calculated, as this optional reporting statistic was added into AASM Scoring Manual at version 2.6 (2020), after data collection for this study had taken place. The AASM Scoring Manual Version 2.6 has an extra rule regarding EMG tone in REM—Any Chin EMG >2 times Stage R atonia was observed (between 5 and 15 s), and uses 2x not 4x for transient muscle activity. The methods used in this study reflect the fact that version 2.4 was used for analysis of data.

TABLE 1 | Type of traumatic event and time at which it was experienced in relation to iRBD onset.

Trauma type (ICD-10 criteria)	Trauma greater than 12 months prior to symptom onset ($n = 14$)	Trauma within 12 months of RBD symptom onset ($n = 37$)
Physical or sexual abuse	21% ($n = 3$)	16% ($n = 6$)
Witness of the death of a loved one*	14% ($n = 2$)	16% ($n = 6$)
Operation*	7% ($n = 1$)	11% ($n = 4$)
War related	7% ($n = 1$)	3% ($n = 1$)
Road traffic accident	0% ($n = 0$)	3% ($n = 1$)
Near drowning	29% ($n = 4$)	0% ($n = 0$)
Assaulted	0% ($n = 0$)	3% ($n = 1$)
Severe personal, family or work-related stress*	14% ($n = 2$)	26% ($n = 9$)
Not disclosed	7% ($n = 1$)	26% ($n = 9$)

Traumatic event types experienced by patients.
**Events not classified in DSM V as trauma.*

Statistical analysis was undertaken using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to assess for normality. For discrete variables, the Chi-square test was used. For continuous variables, one-way ANOVA and the Kruskal-Wallis tests were used. Results are reported as number and percentage or mean ± standard deviation (sd). Kaplan-Meier analysis was used to assess risk of developing α-synucleinopathies, and the Mantel Cox test was used to compare the survival curves between groups. All tests were two-tailed where appropriate for subgroup comparisons, and significance was set at $p \leq 0.05$. As this was a finite population and as there are no previous studies differentiating these populations, power calculations were not considered necessary.

RESULTS

The RBD cohort overall comprised 103 men (84.4%) and 19 women (15.6%), with a mean age of estimated RBD onset of 53.7 ± 13.9 years (range: 19–76 years). The mean age at RBD diagnosis was 59.1 ± 12.1 years (range: 25–89 years) and the mean duration of RBD prior to presentation was 5.7 ± 4.4 years (range: 0.5–13 years). Thirty-seven patients (30.3%) reported trauma <12 months preceding RBD symptom onset, 14 patients (11.5%) reported trauma >12 months preceding RBD symptom onset, with all meeting the ICD-10 classification of trauma and 53% meeting the stricter standard DSM-V criteria for trauma (**Table 1**). The remaining 71 patients (58.2%) did not report any traumatic life events. Clinical characteristics across the groups are shown in **Table 2**. All four patients who had a medical

TABLE 2 | Differences in clinical characteristics across groups diagnosed with iRBD.

Clinical characteristics	No trauma ($n = 71$)	Trauma greater than 12 months prior to RBD symptom onset ($n = 14$)	Trauma within 12 months of RBD symptom onset ($n = 37$)	*P value*
Male:Female ratio ($n = 122$)	62:9	11:3	30:7	0.57
Estimated age at RBD onset (years) ($n = 56$)	56.21 ± 10.85	49.87 ± 7.18	54.61 ± 14.19	0.42
Age at RBD diagnosis (years) ($n = 114$)	60.92 ± 10.44	54.50 ± 9.36	57.53 ± 15.28	0.13
Duration of RBD (years) ($n = 115$)	5.62 ± 4.81	7.43 ± 4.16	5.09 ± 3.68	0.34
AHI (<5 normal, <15 Mild OSA), <30 Moderate OSA, ≥30 Severe OSA ($n = 103$)	20.99 ± 18.15	28.35 ± 37.21	12.42 ± 10.64	0.08
BMI ($n = 106$)	29.54 ± 5.51	31.17 ± 8.59	28.49 ± 5.71	0.40
Smoker ($n = 67$)	14:25 (56%)	3:6 (50%)	5:14 (36%)	0.77
Alcohol use disorder (DSM V) ($n = 116$)	4 (6%)	0 (0%)	1 (3%)	0.58
Constipation ($n = 84$)	5 (14%)	1 (7%)	1 (3%)	0.47
Self-report of anosmia or changes in sense of smell ($n = 84$)	6 (14%)	3 (21%)	4 (15%)	0.87
Family history of alpha-synucleinopathies ($n = 109$)	8 (14%)	3 (27%)	0 (0%)	0.05
Subsequent diagnosis of neurodegenerative disorder	26 (37%)	6 (43%)	0 (0%)	0.01

Differences in clinical characteristics between groups (Group 1, n = 71; Group 2, n = 14; Group 3, n = 37). Results are reported as mean ± standard deviation or number and percentage.

history of sleepwalking had onset in childhood and their NREM parasomnia did not recur in adulthood.

Incidents of violent nocturnal behaviors (e.g., kicking, punching, biting, and scratching) or occasions during which the bed partner was hurt did not differ significantly across the three groups (see **Figure 1A**). Likewise, there was no significant differences across groups in terms of dream themes (see **Figure 1B**; $p > 0.05$, data not shown). Both trauma groups reported dreams related to past experiences.

There were no significant differences in REM sleep latency or any additional PSG variables across trauma groups (**Table 3**). Measurement parameters of autonomic activity (time point and length of measurement) have not been specified by Mysliwiec et al. (8) and so could not be replicated in our study.

Self-report of anosmia or recent reduction in sense of smell was 15% across all groups at presentation, with no statistically significant difference across groups (**Table 2**).

In our cohort, 32 patients (26.2%) received a diagnosis, in each case verified by a specialist neurologist, of a neurodegenerative disease after a mean follow-up duration of 870 ± 1,109 days (range: 0.5–18 years) from symptom onset. Disorders that manifested during follow-up (which were not present at RBD diagnosis) were: Parkinson's disease ($n = 20$), Lewy Body dementia ($n = 7$), Progressive supranuclear palsy ($n = 1$), Alzheimer's disease ($n = 2$), and Motor neurone disease with frontotemporal dementia ($n = 2$). Of these patients, 26 (81.3%) had no trauma history (PD $n = 15$, DLB $n = 5$, PSP $n = 1$, AD $n = 2$, MND $n = 2$), and the remaining 6 (18.7%) patients experienced trauma longer than 12 months prior to RBD symptom onset (PD $n = 6$). No patients in Group 3 received a neurodegenerative disease diagnosis during follow-up (see **Figure 2**), whereas 36.6% of patients in Group 1 and 42.9% of patients in Group 2 went on to develop a neurodegenerative disorder. A significant difference was found in neurodegenerative disease development across groups ($p = 0.01$).

No patients in Group 3 had a family history of neurodegenerative disorders, whereas eight patients (14%) in Group 1 and three patients (27%) in Group 2 had a family history of α-synucleinopathies ($p = 0.05$); see **Table 2**.

DISCUSSION

This is the first study to our knowledge to report in detail on trauma associated with "iRBD" onset. Because all patients were phenotypically indistinguishable at presentation and fulfilled criteria for iRBD clinically, we argue that a history of trauma when clearly established as occurring within 12 months of dream-enactment behavior, mandates that it be classified as secondary RBD. Our results demonstrate a significant difference in the disease-free survival rate of patients who had experienced trauma

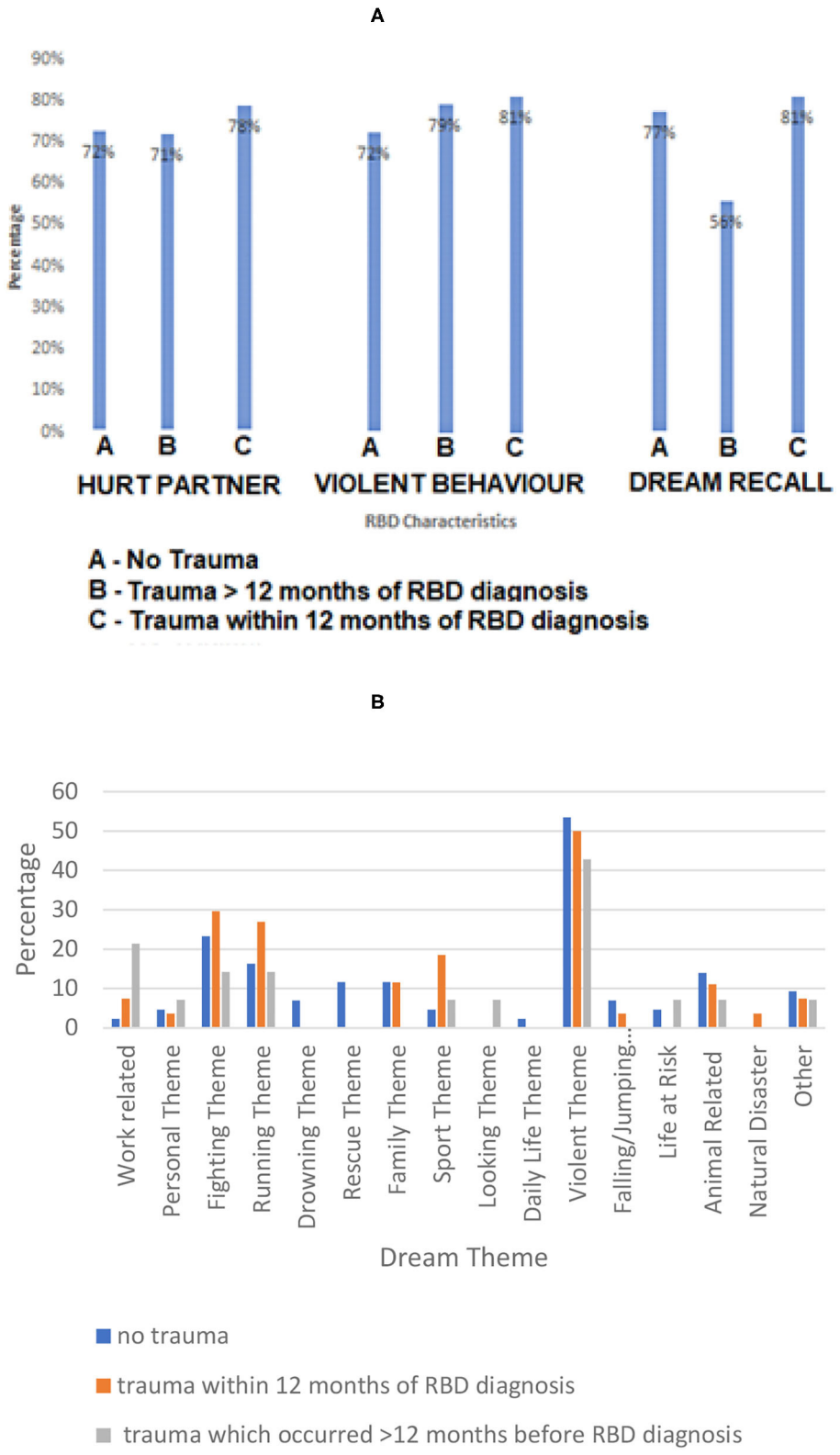

FIGURE 1 | RBD characteristics **(A)** and dream themes **(B)** across groups. **(A)** RBD characteristics for RBD patients with no trauma history (Group 1); trauma which occurred within 12 months of RBD diagnosis (Group 3); trauma which occurred >12 months before RBD diagnosis (Group 2). Percentage of patients is relative to trauma group for **(A,B)**. No significant difference between groups was found in the reported dream recall, incidence of violent nocturnal behavior or incidence in

(Continued)

FIGURE 1 | which a bed partner was hurt ($p > 0.05$, data not shown). **(B)** Differences in self-reported dream themes for RBD patients between groups (no trauma history; trauma which occurred prior to RBD diagnosis.). No significant difference was found in the percentage of dream themes between groups ($p > 0.05$, data not shown). Error bars are excluded as bars represent strict counts.

TABLE 3 | Differences in PSG variables across iRBD groups.

PSG variables	No trauma ($n = 71$)	Trauma greater than 12 months prior to RBD symptom onset ($n = 14$)	Trauma within 12 months of RBD symptom onset ($n = 37$)	*P*-value
REM sleep latency (min)	137 ± 78.72	117 ± 65.92	106 ± 68.92	0.45
Sleep latency (min)	45 ± 35.60	41 ± 32.29	44 ± 74.03	0.16
WASO (min)	120 ± 54.15	105 ± 42.27	102 ± 55.36	0.28
REM sleep (%)	15 ± 7.49	18 ± 9.50	19 ± 9.20	0.10
Stage N1 (%)	7 ± 10.29	5 ± 7.39	6 ± 8.28	0.67
Stage N2 (%)	60 ± 17.38	66 ± 16.33	56 ± 16.79	0.19
Stage N3 (%)	10 ± 11.76	5 ± 5.56	13 ± 12.20	0.05
Sleep efficiency (%)	64 ± 14.58	66 ± 16.43	68 ± 18.34	0.26

Differences in PSG variables across groups (no trauma history, n = 53; trauma which occurred >12 months prior to RBD diagnosis, n = 13; trauma which occurred within 12 months prior to RBD diagnosis, n = 30). Results are reported as mean ± standard deviation or number. PSG variables did not differ significantly across groups (p > 0.05).

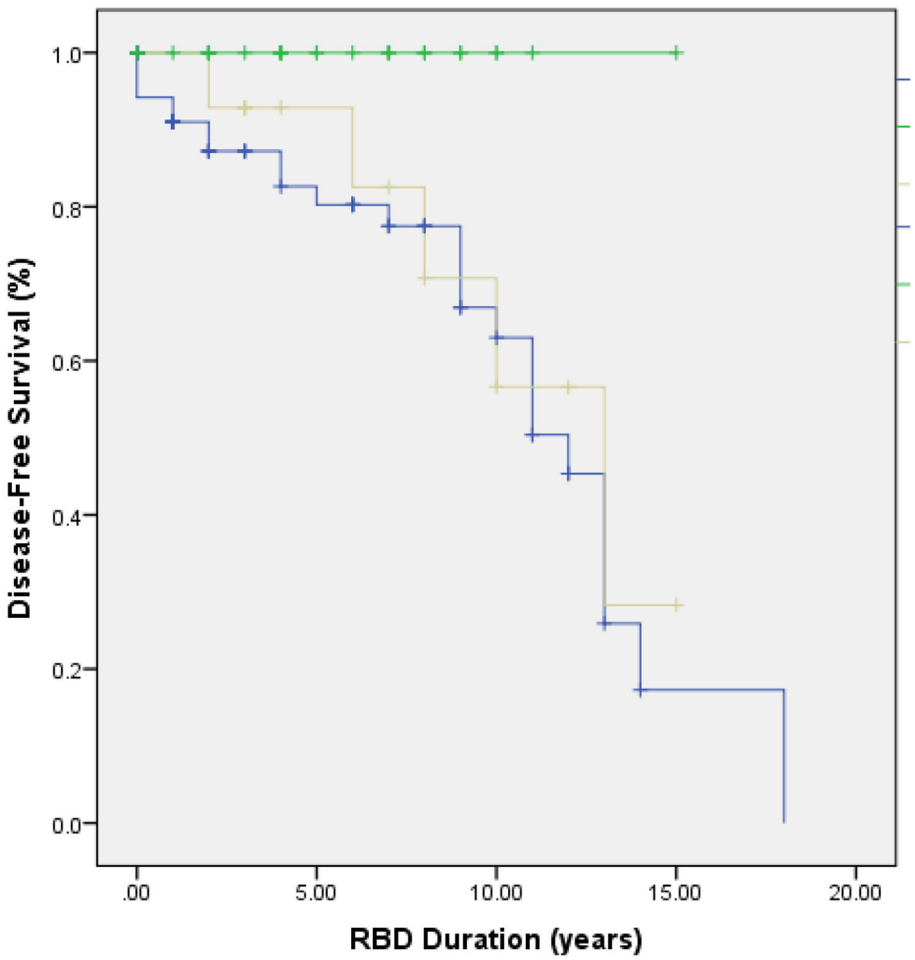

FIGURE 2 | Kaplan-Meier plot of neurodegenerative disease-free survival in Group 1 (blue line), Group 2 (yellow line), and Group 3 (green line). Disease-free survival in RBD patients differed significantly across groups ($p = 0.01$).

within 12 months of RBD onset as compared to those who had never experienced trauma, or who had experienced historical trauma, prior to RBD onset. At present, it is debatable whether the cohort presented in this study represents "non-military" TSD, as none had a formal diagnosis of PTSD despite reporting often very severe and impactful experiences.

Longitudinal studies have consistently demonstrated that many RBD patients go on to develop an α-synucleinopathy or (less commonly) tauopathy (16). Postuma et al. reported a conversion rate to a neurodegenerative syndrome of 6.3% per year after diagnosis (17) and found 73.5% patients converted after 12-year follow-up. Similar results were found in several other longitudinal studies of RBD cohorts summarized in a recent systematic review and meta-analysis (18). Currently, no reports of phenoconversion to neurodegenerative disease in TSD patients exist. In our cohort, no patients in Group 3 and 38% of patients in Groups 1 and 2 were diagnosed with a neurodegenerative disorder. As the follow-up period for most patients in our cohort was under 10 years, this result may be inconclusive; it is possible that more patients may go on to develop a neurodegenerative disease, if the estimates are correct (17, 19). Nevertheless, our observation has important implications for the understanding of the pathological mechanisms of RSWA and iRBD in the context of trauma and for phenotyping patients appropriately in clinic as well as discussing prognosis.

Our iRBD patient cohort was comprised predominantly of men, consistent with previous findings (17, 18). The reason for this sex difference is unclear. A plausible explanation may be referral bias, as clinical expression of RBD in males has been reported to be more violent and vigorous than in females (11), making males more prone to seek medical attention. Until this study, no female patients had been reported with trauma associated RBD (10).

Rapid eye movement sleep behavior disorder patients younger than 40 years often have secondary forms of RBD (1, 2). Trauma-associated sleep disorder patients reported in the literature are also considerably younger (8), which may be attributable to the demographics of the military. Thirteen percent of patients with recent trauma in our cohort were under 40 years of age, as compared to 3% with historical or no trauma.

In this study, no differences in sleep latency, sleep efficiency, or sleep architecture across groups were found, although both the recent trauma group and historical trauma group had decreased REM latency compared to the group without trauma. These findings, particularly in relation to REM, are interesting considering increased REM sleep latency has been found in fear conditioned rats and mice (20). Fear conditioned mice also have decreased REM epochs (21) and REM length (22). Alternatively, in the absence of aversive stimuli, animals display increased percentages of REM sleep, and duration during the sleep period (21). Fear conditioned animals have been proposed as models for trauma (20), suggesting that trauma affects REM sleep architecture, which may explain the decreased REM latency reported in TSD and the two groups with trauma in our study (8). Unfortunately, human studies are less conclusive: although REM latency may be affected by trauma, in our study, REM latency was decreased. While some PSG studies of traumatized individuals with and without PTSD report REM sleep abnormalities (23), others do not (24).

Invoking the studies on TSD when considering trauma, symptoms of autonomic hyperarousal are included them as part of the diagnostic criteria for TSD (10). Yet only one incident of hyperarousal is documented in TSD patients in the literature and measurement parameters are not specified (8). For this reason, autonomic activity measurements could not be determined in our study using any valid/validated criteria, and our patients should therefore be considered as having RBD secondary to trauma. During normal REM sleep, there is marked suppression of sympathetic activity (25) and in previous reports, RBD patients have been shown to lack autonomic reactivity such as tachypnea and tachycardia despite vigorous limb movements (1).

Our data concurs with findings from previous RBD studies in that dream content mainly involves defense against people or animals and escape from life-threatening situations (11, 26). We found no significant differences in dream themes across groups. Interestingly, patients with and without a trauma history reported dreams that replayed prior life experiences. This has not been reported previously for RBD patients (6, 11), however is consistent with reports in TSD (10). Although in both cases dreams are unpleasant, RBD dreams tend to have similar themes unrelated to past experiences, whereas TSD dreams involved accounts of previous, personal events (10). This type of personal trauma-associated nightmare has been extensively reported in patients with post-traumatic stress disorder (27), indicating that these nightmares are possibly a consequence of trauma.

Reports also suggest that TSD involves more extensive and vigorous movements than RBD (10). We found no differences in violent nocturnal behaviors or incidents in which bed partners were hurt between iRBD patients that experienced trauma and patients with no trauma history. Furthermore, none of the patients displayed disruptive nocturnal behavior during non-REM sleep. One potential explanation may be because patients with concomitant disorders of arousal are likely to attract a diagnosis of overlap disorder and were not included in the cohort analyzed.

We found lower percentages of anosmia or a reduction in sense of smell at diagnosis, and of constipation than reported by Postuma et al. (17), which may be related to our reliance on self-report without objective assessment. Constipation prevalence was 8% across groups, also significantly lower than in the 2019 multicenter study (17).

Functional neuroimaging in humans has found changes in volumetric and cerebral blood flow patterns in wakefulness and sleep, following traumatic event exposure (28). Structures affected include several brainstem nuclei implicated in REM sleep generation and the amygdala (28) which is critical for the processing of fear consolidation, emotional distress, and fear extinction, and is hyperactive in humans following a traumatic experience (29). Liu et al. found that fear conditioning in mice resulted in increased activity in the raphe nucleus and locus coeruleus via the amygdala, with increased twitching during REM sleep (30). This disruption of REM sleep is thought to occur via maintained inhibition of cholinergic activity (21). Animal

studies have also shown that projections from the amygdala may generate vocalizations via activation of the central gray matter (31). Thus, the possibility that the amygdala may contribute to RSWA may be a direction for future research. However, only a small number of laboratory studies on the effects of trauma on sleep disturbances exist, and current animal models do not effectively mirror human symptoms (21).

Some limitations of this study must be noted. Healthy controls with and without trauma are necessary to ensure there is no independent association between trauma and neurodegeneration. To the best of our knowledge, no studies have previously tested such a link. Secondly, a major limitation was that trauma was used as a biomarker. A temporal correlation between traumatic experience and RBD symptom onset does not indicate causation in all cases i.e., in some patients, RBD onset may have occurred regardless of traumatic experience. Thus, using an alternative measure, such as autonomic hyperarousal which occurs exclusively in TSD and not RBD would have been beneficial. This was not possible for this study as set thresholds for autonomic hyperarousal measures do not appear to exist. Thirdly, trauma reports relied on patient self-report and individuals may feel reluctant to recount their traumatic event due to resistance to re-experiencing emotion associated with the event (32). Therefore, the actual number of traumatized RBD patients may be higher than self-reported in this study. Not all participants were formally assessed by a psychiatrist as part of standard clinical care but all participants at our clinics are made aware that psychological, mood, and traumatic life experiences may have a bearing on their sleep and sleep quality so are more likely to disclose important information in this regard. Lastly, it is important to note that psychological trauma is very common in the community. In Scotland alone, a population-wide survey published in 2019 showed that 15% of people had suffered significant adverse childhood experiences, with 7% reporting sexual abuse in childhood (33).

In our cohort, 32 patients (26%) developed a neurodegenerative disorder during the follow-up period (range: 0.5–18 years from diagnosis), with a mean RBD duration of 5.7 ± 4.46 years. However, RBD can precede neurodegeneration by more than 20 years, and phenoconversion has been reported to be as high as 80% (19). More patients may be expected to phenoconvert to a neurodegenerative disorder in the future, and longitudinal follow-up of the patients is ongoing. Finally, this was a retrospective cohort study with some data subject to individual recall bias, although bed partners assisted in completing the sleep history wherever possible. Currently, we are prospectively documenting phenoconversion in our growing cohort of patients. Additionally, the validation of sensitive and specific biomarkers will allow us to ascertain better our clinical observations in the very near future (34).

Finally, scoring criteria that are forever being revised present another limitation to studies in this area, making comparisons to older studies more difficult. It is important to point out that the AASM Manual for Scoring Sleep for Associated Events added two new rules regarding RSWA in the latest version (version 2.6), after data collection and sleep scoring of this cohort was completed. The new additions change both the amplitude of EMG required to score phasic events, and importantly insert an optional reporting measure of RSWA %, which is a potential biomarker in predicting neurodegeneration.

In conclusion, we found that the development of RBD clinically with RSWA on polysomnography within 12 months of experiencing a traumatic life event has not led to phenoconversion to a neurodegenerative disorder to date. Patients presenting with the emergence of DEB in the context of recent trauma were also unlikely to have a family history of α-synucleinopathies or tauopathies. We suggest that a subtype of RBD classified as secondary RBD due to trauma be established. Lastly, this study also highlights the importance of a family history of neurodegeneration as a prognostic marker of earlier decline in iRBD, as has been previously noted (35, 36). Long-term follow-up of the cohort continues.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RR: concept, statistics, writing, and editing. SW and NH: data collection, statistics, and writing. IM: concept and editing. JE: editing. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Toward a Digital Future in Bipolar Disorder Assessment: A Systematic Review of Disruptions in the Rest-Activity Cycle as Measured by Actigraphy

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Background: Disruptions in rest and activity patterns are core features of bipolar disorder (BD). However, previous methods have been limited in fully characterizing the patterns. There is still a need to capture dysfunction in daily activity as well as rest patterns in order to more holistically understand the nature of 24-h rhythms in BD. Recent developments in the standardization, processing, and analyses of wearable digital actigraphy devices are advancing longitudinal investigation of rest-activity patterns in real time. The current systematic review aimed to summarize the literature on actigraphy measures of rest-activity patterns in BD to inform the future use of this technology.

Methods: A comprehensive systematic review using PRISMA guidelines was conducted through PubMed, MEDLINE, PsycINFO, and EMBASE databases, for papers published up to February 2021. Relevant articles utilizing actigraphy measures were extracted and summarized. These papers contributed to three research areas addressed, pertaining to the nature of rest-activity patterns in BD, and the effects of therapeutic interventions on these patterns.

Results: Seventy articles were included. BD was associated with longer sleep onset latency and duration, particularly during depressive episodes and with predictive value for worsening of future manic symptoms. Lower overall daily activity was also associated with BD, especially during depressive episodes, while more variable activity patterns within a day were seen in mania. A small number of studies linked these disruptions with differential patterns of brain functioning and cognitive impairments, as well as more adverse outcomes including increased suicide risk. The stabilizing effect of therapeutic options, including pharmacotherapies and chronotherapies, on activity patterns was supported.

Conclusion: The use of actigraphy provides valuable information about rest-activity patterns in BD. Although results suggest that variability in rhythms over time may be a specific feature of BD, definitive conclusions are limited by the small number of studies assessing longitudinal changes over days. Thus, there is an urgent need to extend this work to examine patterns of rhythmicity and regularity in BD. Actigraphy research holds great promise to identify a much-needed specific phenotypic marker for BD that will aid in the development of improved detection, treatment, and prevention options.

Keywords: bipolar disorder, actigraphy, digital technology, circadian rhythms, rest, sleep, treatment

INTRODUCTION

Bipolar disorder (BD) is a mood disorder characterized by episodes of depression and mania, interspersed with periods of relative stability termed euthymia (1). Based on the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-5; 2), BDI is diagnosed if an individual has experienced a manic episode, while BDII is diagnosed when elevated mood symptoms have only reached the level of hypomania. Individuals with BD often spend more time in depression. Course features such as the frequency of episodes, and clinical features such as the presence of psychotic symptoms and comorbidities, vary among individuals with the disorder. Given the clinical heterogeneity of BD, markers for early identification, differentiation from related mood disorders such as major depressive disorder (MDD), and discovery of novel treatment targets are vital. Notably, criteria for the hallmark manic and hypomanic episodes include increases in activity levels and decreases in sleep though individuals may feel rested. These features suggest the potential importance of the study of activity and rest patterns in elucidating the pathophysiology of BD and in improving detection and interventions.

Rest-Activity Patterns in Bipolar Disorder

Prior to the advent of actigraphy research in BD, in addition to sustained changes in emotional states, disturbed sleep and activity patterns were observed clinically to also be core features of acute episodes of BD. These patterns present differently depending on mood states and can be predictive of both onset and severity of illness (3). Daily rhythms are central to the presentation of both depression and mania, such that changes in both sleep and activity levels play a prominent role in the criteria for acute episodes of BD as outlined in the DSM-5 (2). Sleep problems present in depressive episodes in the form of insomnia or hypersomnia in the majority of cases (4), whereas hypo/manic episodes are often characterized by marked reductions in sleep accompanied by subjective reports of not feeling tired (5). Further, individuals with BD, even when euthymic, have been observed to show delayed onset of the sleep-wake phase and lower levels and later timing of melatonin secretion, an important hormone in circadian rhythm regulation (6–8). Successful chronotherapeutic interventions that modify rest-activity patterns in BD have been reported (9–11), suggesting that they constitute promising intervention targets.

Disruptions in rest-activity patterns have been previously linked to the onset of BD episodes, such that hypomania and mania has been reported following a night of sleep deprivation (12). Pinho et al. (13) found a significant relationship between disruptions in patterns of daily activity and sleep and the severity of depressive symptoms, such that the degree of disruption in patterns was associated with psychosocial dysfunction. The persistence of disruptions during euthymic periods, albeit at a lower magnitude, also suggests that this feature of BD can persist outside of syndromal mood episodes and might be a trait feature of the disorder. During euthymia, individuals with BD have shown reduced daytime activity (14, 15) and greater intra-daily variability of rest-activity patterns (15, 16) compared to healthy controls (HCs). Difficulty in falling and staying asleep (17–19) and early morning awakening persist during euthymic periods (20). Additional studies suggest that disturbed rhythms during euthymia may relate to vulnerability for future episodes and adverse outcomes as they have been associated with a greater severity of subsequent depressive and manic episodes over a 12-month period (21), a history of psychosis, and suicide attempts (22).

The Importance of Capturing Both Rest and Daily Activity

Biological processes that underlie circadian rhythms are implicated in the sleep-wake cycle. Quantifiable proxy markers for this cycle are rest and activity patterns, both of which, notably, can influence each other. Holistic examinations of disturbance across the 24-h cycle, not just during the rest period, (23–26), are therefore warranted. This comprehensive approach to rhythmicity is further reflected in the DSM-5 diagnostic criteria for episodes of BD which include increased energy or activity alongside decreased need for sleep in manic episodes, and psychomotor retardation and loss of energy alongside insomnia or hypersomnia in depressive episodes (2).

Traditional Methods for the Assessment of Rest-Activity Patterns

Sleep-specific measures and measures of the peripheral neurohormone, melatonin, have largely been employed in past studies of the sleep-wake cycle in persons with mood disorders. Polysomnography (PSG) and sleep diaries have traditionally provided objective and subjective information about sleep patterns, respectively. These methods support

clinical reports of disrupted sleep patterns in BD across mood states and in comparison to both HCs and those with MDD [characterized by periods of depression in the absence of hypo/mania] (27, 28). However, these methods provide only limited data about activity during wakefulness, and while sleep diaries may also include questions about activity, they are often limited in scope and rely on subjective responses. Nevertheless, correcting melatonin abnormalities has been suggested to be the mechanism underlying the therapeutic effect of mood-stabilizing pharmacotherapies. For example, lithium and sodium valproate have been shown to reduce melatonin suppression, thus increasing overall melatonin levels (6, 29), and potentially targeting mania vulnerability (30). Outside of pharmacological interventions, chronotherapies such as bright light therapy, which is known to influence melatonin secretion, have been shown to be clinically effective in depression by advancing the phase of the sleep-wake rhythm (10, 31).

The Future of Rest-Activity Pattern Assessment in Bipolar Disorder: Actigraphy

In order to better understand BD, digital technologies have been leveraged to noninvasively collect biometric parameters when individuals are in their everyday environments (32, 33). Temporal profiles of rest and activity, measured with digital actigraphy methods, hold promise for elucidating a novel phenotypic marker for BD (34, 35). Identification of a salient time-varying phenotypic marker for BD may also reveal pathophysiological mechanisms of BD, which ultimately could serve as the basis for novel detection, treatment, and prevention strategies. Prior methods used to characterize the time-varying patterns of BD, such as retrospective self-reports, are limited in their ability to provide accurate data at high levels of granularity (36). The high temporal resolution of actigraphy offers an alternative approach to capturing the time-varying characteristics of BD, and over time, may lead to advancements in early identification and treatment.

Thus, actigraphy assessment of the rest-activity cycle addresses the need for longitudinal and temporally sensitive objective assessments in individuals' natural environment. Wristwatch-like wearable actigraphy devices assess gross motor activity using measures of acceleration speed *via* accelerometers, providing low cost and non-invasive rest-activity assessments (37). It is important to note that actigraphy does not measure sleep directly, but rather uses movement as a proxy for estimating sleep, although terminology used in previous publications often include the use of the word "sleep." Parameters estimated from actigraphy data include the duration of rest or sleep periods, activity levels during rest or sleep periods, time in bed (TIB), total sleep time (TST), sleep onset latency, and daytime naps (38). **Table 1** describes common actigraphy parameters in more detail. Measurements are time-stamped and made continuously, often at high measurement frequencies, for example, every 1-min. This data collection format facilitates data visualization using readily available software packages. Actigraphy has a high rate of concordance with PSG and sleep diaries in healthy populations (39–41) and in individuals with BD. For instance, similar patterns of sleep and rest quality and duration have been reported across the three measures, showing high levels of inter-correlation (42) in BD (42–45), and the ability of actigraphy to sensitively distinguish between BD depressive, manic, and euthymic episodes (46).

Notably, while actigraphy is effective in estimating rest-activity patterns, it does not provide deeper measures of sleep such as brain activity (EEG), heart rhythm (ECG), or eye movements (EOG) that are provided by PSG (47). Therefore, actigraphy cannot characterize sleep physiology and sleep architecture. Actigraphy data also requires careful interpretation as, for example, time resting in bed could be mistaken for sleep time. For that reason, referring to the period encompassing sleep as "rest," or the "rest period," is considered most appropriate for actigraphy measures. Furthermore, it is important to distinguish circadian rhythmicity from 24-h activity patterns. Certain actigraphic measures, such as interdaily stability (IS), relative amplitude (RA), and intradaily variability (IV), are often used erroneously to characterize endogenous circadian function (48). Similarly, L_5 onset and M_{10} onset are also often used as markers for circadian phase timing, and changes to these variables are often erroneously concluded to be phase advances or delays. While these measures provide information about 24-h activity patterns, rhythm stability, and fragmentation (see **Table 1**), they must not be interpreted as markers of endogenous function. Therefore, actigraphic constructs are discussed here in the context of rest-activity patterns. But it should be noted that rest-activity patterns may serve only as a proxy measure for the sleep-wake cycle, which in turn, may serve as a proxy measure of overall circadian function. It is important to note that the sleep-wake cycle is one of a number of physiological, behavioral, and cognitive functions under partial control of the circadian system, and thus, a disruption in the rest-activity or sleep-wake cycle does not necessarily equate to underlying circadian rhythm dysfunction.

The Current Systematic Review

The current review aims to summarize actigraphy assessments in BD published to date, encompassing both rest and activity profiles. As a key goal is to review evidence supportive of the potential clinical significance, special focus is given to findings that help to elucidate (a) the ability of these patterns to distinguish BD from comparison groups, including HC and other clinical groups; (b) the relationship these patterns have with distinct mood states within BD and with other clinical, cognitive, and brain features of the disorder; and (c) the propensity for actigraphy to decipher the therapeutic effects of treatment interventions on mood measures in BD. We therefore address three research questions: (a) what are the rest-activity patterns associated with adult BD and how do they differ from those in HCs and other clinical comparison groups? (b) what relationship do these patterns have with other characteristics of BD, including mood, cognition, and neurobiology? (c) what effect do interventions, encompassing both pharmacological and non-pharmacological therapies, have on these patterns in BD?

Actigraphy measures have previously been employed in empirical studies of BD for at least 15 years, with a number

TABLE 1 | Overview of commonly used actigraphy parameters.

	Variable name	Description
Rest	TST	Total sleep time. The time between sleep onset and offset/final wake time, minus any periods of wakefulness in between (WASO).
	TIB	Time in bed. The duration spent in bed, calculated as the time between going to bed and arising, usually aided by pressing an "event marker" button on the actigraph, if available.
	WASO	Wake after sleep onset. The total number of nocturnal waking minutes.
	Sleep efficiency (SE)	Percentage of time asleep between sleep onset and offset/final wake time.
	Sleep onset latency (SOL)	The number of minutes between bedtime and sleep onset.
	Fragmentation index (FI)	The amount of movement or restlessness in a rest period.
	L_5 onset	Onset of the lowest 5 h of activity in a 24-h period. A proxy marker for sleep/rest onset.
	L_5 activity	Activity levels over the lowest 5 h of activity in a 24-h period, after L_5 onset. A proxy marker for sleep/rest activity.
Daytime activity	M_{10} onset	Onset of the most active 10 h in a 24-h period. A proxy marker for day/activity onset.
	M_{10} activity	Activity levels over the greatest 10 h of activity in a 24-h period, after M_{10} onset. A proxy marker for day/diurnal activity.
Rest-activity rhythms	Relative amplitude (RA)	Differentiation score of activity during the ten most active hours in a 24-h period (M_{10} activity) compared to activity during the five least active hours in a 24-h period (L_5 activity). Therefore, differentiation in activity during active and rest states. Scored between 0 and 1, with a lower RA representing lower differentiation.
	Intradaily variability (IV)	A variability marker of the difference in patterns within a day. Greater values represent greater rhythm fragmentation. Greater fragmentation indicates more transitions between rest and active states.
	Interdaily stability (IS)	A stability marker of the difference in patterns across days. Greater values represent greater stability of rhythm. Greater stability indicates more consistency of rest-activity patterns between days.

of systematic reviews measuring their ability to capture rest-activity disturbances in those with BD [e.g., (17, 49)]. However, the clinical utility and significance of this method has not yet been assessed, and thus the translation of this method to clinical practice has not yet been widely achieved. This is increasingly important given the recent shift toward digital and longitudinal methods that are adept at assessing temporally sensitive mood disorders. Therefore, the current review aims to show how actigraphy technology can pave the way for better capturing the temporally dynamic nature of BD, and ultimately aid in the discovery of mechanisms underlying BD and more nuanced targets for detection, treatment, and prevention.

METHODS

Data Sources

Studies were independently identified by authors PP and GdQC through manual searches of the electronic databases PubMed, MEDLINE, PsycINFO, and EMBASE. While a broad systematic method was used, following PRISMA guidelines (50), emphasis was placed on a thorough literature search of actigraphy studies in BD. To this end, the following terms were used in our primary search (further detailed in **Supplementary Table 1**): "actigraphy,", "actigraph," "actimetry," "accelerometry," "smart watch," or "health watch" (separated by OR) in combination (using AND) with the terms "BD" and "bipolar" (separated by OR). Only research-grade actigraphy devices were searched for (excluding commercially available devices such as FitBit or Apple Watch) in order to ensure data reliability and validity, based on clinical specificity issues (51). Eligible papers included studies of BD samples. No lower publication date limit was applied, and the search was continued until 19th February 2021. All selected articles were published in peer-reviewed journals in English.

Data Extraction

Information extracted from identified manuscripts were sorted into four categories: study details (author names, year of publication, and title); demographic and clinical details of subject samples [number of participants, age (mean and standard deviation), gender, diagnosis category, mood status (i.e., depressed, manic, and euthymic), and medication status]; actigraphy methodology (device name, body location, recording time or duration, and sampling/recording rate used); and main study outcomes (daily activity, rest/sleep, and 24-h patterns as outlined in **Table 1**). Data was independently and manually extracted by PP and GdQC by going through each article and Supplementary Material, if available. Any discrepancies were discussed, checked, and cleared by the authors.

In order to capture all relevant cross-sectional and longitudinal studies using actigraphy, BD subtypes BDI, BDII, and BD NOS or OS [(not) otherwise specified, i.e., with symptoms of BD that do not meet full diagnostic criteria] under both DSM (2) and International Classification of Diseases (52) diagnostic manuals were included. All pharmacological and non-pharmacological interventions employed in actigraphy studies of BD were included to address the third research question. Overall comparators included HCs, those with related psychiatric disorders [MDD, anxiety disorders, schizophrenia, borderline personality disorder (BPD)], insomnia, or general mental health service users. Actigraphic outcomes relating to patterns over 24-h, daytime activity, and markers of rest and nighttime period were used as outcomes.

Articles were excluded from the final list during the manual data extraction process if they aimed to validate methods (i.e.,

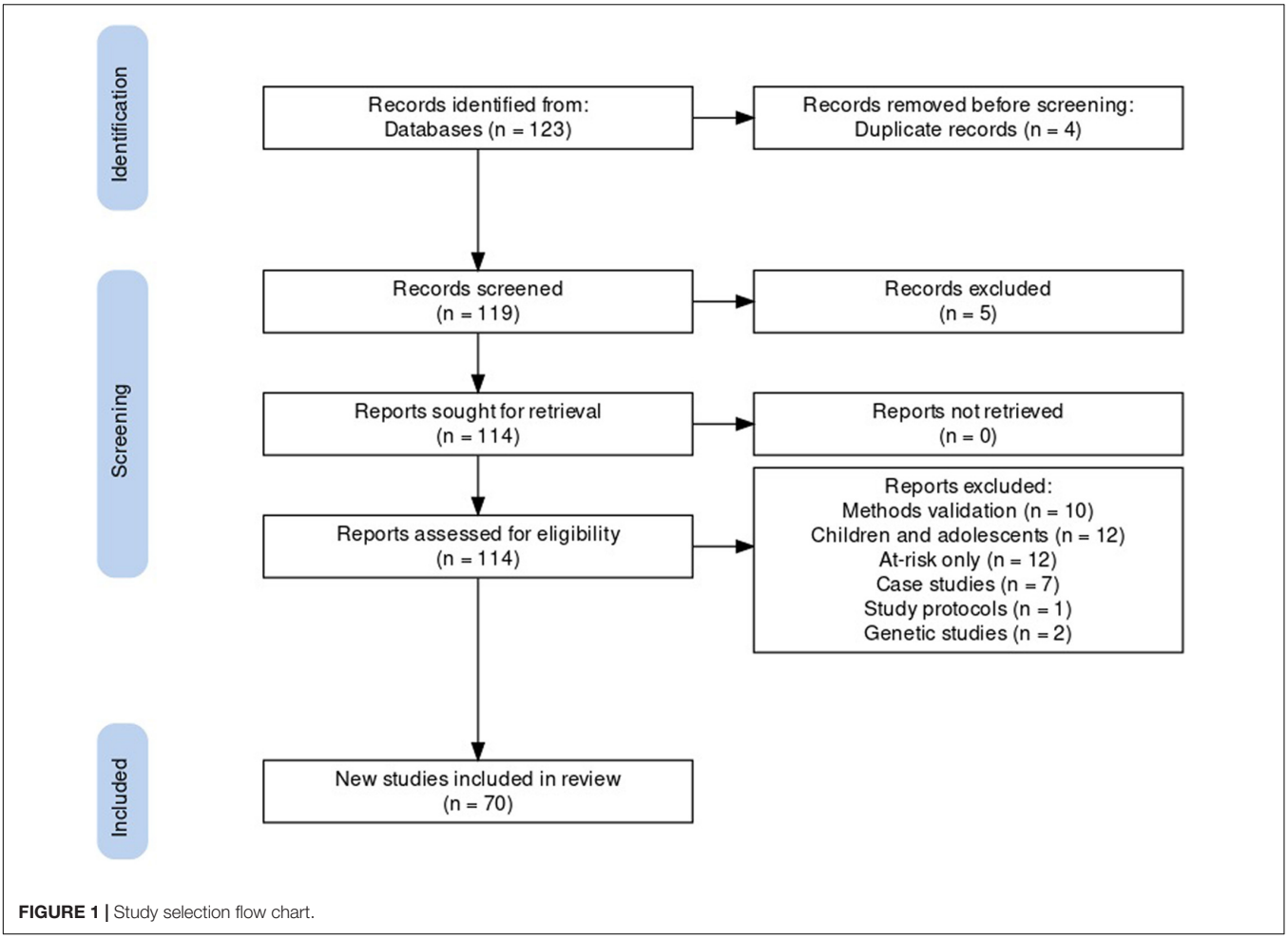

FIGURE 1 | Study selection flow chart.

using actigraphy to validate against PSG), focused on the study of children and adolescents (defined as studies that included individuals under 18 years of age) or were solely conducted in at-risk groups, case studies, descriptions of study protocols, or genetic studies.

Research Questions

In order to address the avenues of investigation of the rest-activity patterns measured through actigraphy, the review was organized by three research questions. First, what are the rest-activity patterns associated with adult BD and how do they differ from those in HCs and other clinical comparison groups? Second, what relationship do these patterns have with other characteristics of BD, including mood, cognition, and neurobiology? Third, what effect do interventions, encompassing both pharmacological and non-pharmacological therapies, have on these patterns in BD?

RESULTS

Study Selection

The database search identified 114 unique articles, of which 70 met systematic review criteria (**Figure 1**). Articles that were excluded from the final list fell into the following categories: methods validation ($n = 10$), the study of children and adolescents ($n = 12$) or at-risk groups ($n = 12$), case studies ($n = 7$), study protocols ($n = 1$), or genetic studies ($n = 2$). To address the three research questions: 41 of the 70 included articles compared actigraphy in BD with that of HCs or other clinical groups; 19 investigated the relationship between rest-activity patterns and different features of BD; and 10 articles assessed the effect of interventions on actigraphy measures in BD. Study characteristics are presented in **Supplementary Table 2**. All rest and activity pattern findings reported in section "Results" are derived from the 70 actigraphy studies.

Consistency in Methods

As demonstrated in **Supplementary Table 2**, actigraphic recording periods varied greatly such that studies collected data from anywhere between 24 h [e.g., (53–55)] and 90 days (56). While 44% ($n = 32$) of studies accounted for the 24-h nature of rest-activity patterns, a further 39% ($n = 28$) focused on recordings during the rest or nighttime period only, and 17% ($n = 12$) focused on those of daytime activity only.

Given the small number of studies and methodological heterogeneity in the studies identified (as evidenced by varying

sample sizes, length of actigraphic recording, devices used, and variables extracted), we did not calculate effect measures for each outcome. The studies were not directly comparable enough to mathematically assess meaningful differences between them. Our results below are based on the findings of each of the studies included in this systematic review.

Question 1: What Are the Rest-Activity Patterns Associated With Adult Bipolar Disorder?

Of 41 articles addressing this question, 49% (n = 20) directly compared rest-activity patterns in persons with BD with those of HCs and 37% (n = 15) included other psychiatric clinical comparison groups, 5% (n = 2) included persons with a diagnosis of insomnia, 2% (n = 1) included persons with childhood attention deficit hyperactivity disorder (ADHD), and 7% (n = 3) included at-risk groups [i.e., non-affected siblings or first or second degree relatives, and those with a previous episode of major depression with sub-threshold mania symptoms (57)] in addition to BD and HC groups.

Rest

In BD, compared to HCs, longer sleep latency and longer sleep duration were most often reported (58–63) and were associated with symptoms of depression (64). Although reported less often, later sleep midpoint was also noted (65). Gershon et al. (60) found that increased sleep latency, as well as wider disruptions in rest continuity including longer wakefulness after sleep onset (WASO) and lower sleep efficiency (SE), were associated with increased negative affect in euthymic BD. They did not detect associations between these rest measures and levels of positive affect in their sample, suggesting the connection between these rest patterns with depression but not mania. Notably, there was a difference in subjective and objective measurements of these rest parameters such that Krishnamurthy et al. (66) found that individuals with BD, compared to HCs, had higher absolute discrepancy between objective and subjective sleep latency, i.e., the BD group self-reported even longer sleep latency than suggested by actigraphy measures, and between subjective and objective TST, i.e., those with BD self-reported significantly lower sleep duration compared to their actigraphy measurement. They, and Gonzalez et al. (67), found that the severity of depressive symptoms was also associated with greater discrepancy between subjective and objective measures of rest, implicating mood state not only in the timing of rest in BD but also in its perception.

To determine whether actigraphy patterns are specific to the depression of BD, studies have also included individuals with MDD, although they have been sparse and inconclusive to date. Robillard et al. performed a series of studies that identified both sleep pattern-related features that were common across depression in BD and MDD, and others that differed suggesting specificity to BD-depression. They observed lower TST and more irregularity of circadian patterns, as measured by a circadian rhythmicity index, to be predictive of worsening verbal memory across groups, suggesting these patterns may be more associated with this cognitive feature in depression than diagnosis (68). However, they observed sleep phase to be more delayed and sleep offset (time of awakening after sleep) to be later in BD-depression than MDD-depression, and that lower SE was predictive of later worsening in manic symptoms (7, 69). In a study that compared BDI, BDII, and MDD, Shou et al. (15) found differences in the average and variability of these subgroups at different times of the day compared to controls. Whereas people with BDII had greater variability during the rest period, those with BDI had lower levels of and greater variability in activity later in the day. These findings also showed specificity for BD because those with MDD did not differ from controls in either average or variability in motor activity at any of the specific time periods or across the whole day (15). These studies suggest that actigraphy may identify specific aspects of current and impending mood symptoms of BD.

A small set of studies compared BD and HC groups to those at risk of developing BD, due to family history or subsyndromal symptom presentation. These studies reinforce the notion of a link between rest disturbances and BD vulnerability. Verkooijen et al. (70) found that later sleep offset (i.e., later time of awakening after sleep) and longer sleep duration across individuals with BD and their non-affected siblings were associated with increased depressive symptoms, suggesting a link between sleep pattern rhythmicity and vulnerability to depression. Ritter et al. (57) observed prolonged sleep latency and difficulties awakening, in both euthymic individuals with BD and those at risk, suggesting that these sleep rhythmicity disturbances may constitute a BD trait. These patterns were significantly different from those in HCs, suggesting that disturbance in rest periods is a characteristic of BD, and could be both an early risk marker for its development and a potential target prior to the initial manic episode. Longitudinal studies are needed to determine whether the rest findings are associated with the development of BD in youths at risk.

Research comparing BD with other clinical groups suggests that diagnostic group status can be predicted with a high degree of accuracy from rest data estimated from actigraphy alone (71). Although studies have suggested that rest disturbances in BD and MDD are quite similar, indicating that sleep fragmentation is an indicator of depression in both groups (72), other research has been able to use actigraphy to distinguish BD from other clinical groups. For instance, delayed onset of rest patterns, as measured by L_5 onset (see **Table 1**), was associated with BPD rather than BD, despite equal levels of depression (73). Of note, a history of ADHD symptoms (in adults with a childhood history of ADHD) was not found to be associated with rest period disturbances in BD (74).

Daytime Activity and Rhythmicity

Despite a limited number of articles on daytime activity levels, findings suggest that abnormal daytime activity patterns are characteristic of BD. In comparison to HCs, individuals with BD who are euthymic and those who have hypo/manic or depressive symptoms have shown lower average daily activity, more periods of daytime napping, and decreased circadian RA, i.e., less differentiation between daytime and nighttime activity levels (16, 54, 75). Studies suggest that the general lowering of daytime activity in BD could be used as a target for therapy (76).

Individuals with BD, compared to HCs, showed higher variability in activity over 24 h (15, 54). In individuals experiencing mania, this increased variability occurred primarily in the morning period, as they displayed reduced autocorrelation during this time (lower correlation of activity counts between subsequent minutes of data collection), differentiating it from depression (77, 78). Of interest, different patterns of variability of activity have been found at different times of the day for BDI and BDII subgroups compared to controls or people with MDD (15). Additionally, compared to HCs, BD mania was associated with a phase advance of around 7 h, while depression was associated with a phase delay of 4 h (79), supporting mood state-related differences in the time of day of activity disturbances. In sum, these studies highlight the importance of timing in the variability of activity, suggesting that timing of activity regulation could be a target for therapy.

Actigraphy differences are also seen when comparing activity patterns in BD to other clinical groups. For instance, similar to findings in comparisons to HC groups, individuals with BD have shown significantly less daytime activity than other mental health service users (80). BD has also been more strongly associated with lower daytime motor activity compared to MDD (81). Individuals with schizophrenia, compared to individuals with BD, had a more complex profile of activity showing more variability at a smaller time scale (54, 77, 78). However, a study of the onset of daytime activity (as measured by M_{10} onset, see **Table 1**) did not distinguish BD from BPD, as both groups had significantly later onset compared to HCs, but did not differ from each other (73, 82). These data suggest that daytime activity patterns may differentiate BD from other major mood and psychotic disorders, although it may be more difficult to distinguish from BPD.

The Contribution of Machine Learning Methods

Building on these findings of differential activity patterns during rest and daytime periods in BD, researchers have also begun to use novel machine learning methods to classify individuals with BD and HCs using actigraphy data, such as 24-h patterns. For instance, using the random forest classifier method, Schneider et al. (56) was able to correctly classify euthymic BD and HCs with a sensitivity of 85% and a specificity of 91%. Krane-Gartiser et al. (83) used a combined rest and activity model to correctly classify 75% of individuals with BD. These tools may also be used to investigate the extent to which the actigraphy features exhibit significant interaction and correlation both within and between domains. For example, Di et al. (84) have applied a dimension reduction technique, Joint and Individual Variation Explained (JIVE), that efficiently deals with multivariate data representing multiple domains that may help to hone in on the core rhythmic patterns underlying BD. Future studies emphasizing longitudinal actigraphy monitoring may be able to better train machine learning algorithms to perform these classifications. This supports the value in using such methods and highlights the potential for such classification tools to be used alongside traditional diagnostic measures.

Question 2: What Relationship Do Rest-Activity Patterns Have With Other Characteristics of Bipolar Disorder?

Nineteen of the 70 included articles addressed this research question. Of these articles, 43% (n = 8) addressed the relationships between rest-activity patterns and specific mood states, 21% (n = 4) investigated the neuroimaging correlates of these patterns, as measured by magnetic resonance imaging, 10% (n = 2) studied the relationship with suicidal thoughts and behaviors, 10% (n = 2) assessed the association with cognition, 6% (n = 1) investigated the relationship with metabolic symptoms, and an additional 10% (n = 2) assessed the relationship between these patterns and coffee, tobacco, and alcohol consumption (85), and characteristics of social support and strain (86).

Rest

Investigations focused exclusively within BD, aiming to understand the relationship between rest patterns and clinical features of BD such as its different mood states, remain limited. Krane-Gartiser et al. (87) found that mood variability in BD during 1 week, measured as significant change on a mood scale adapted from the Systematic Treatment Enhancement Program for Bipolar Disorder study (88), was significantly associated with rest period disturbance. Those in the unstable mood group presented with delayed sleep phase, as well as later and more variable bedtimes and awakening times. Further, Kaplan et al. (89) identified two distinct subtypes of hypersomnia in euthymia using actigraphy: one characterized by "long sleep" or a long TIB rather than a long sleep duration, and the other by "excessive sleepiness." The latter was able to predict later relapse to mania or hypomania. These findings suggest that changes in rest patterns are not only associated with depressive symptoms but may also reflect a wider disruption in underlying neurobiological regulatory mechanisms that may contribute to vulnerability to subsequent episodes.

Notably, disruptions in the rest period have shown associations with adverse outcomes, including preventable risk for early mortality, highlighting the importance of studying rest period disturbances in BD to improve prognosis. Difficulty falling and staying asleep, as well as fragmented sleep, have been associated with a greater history of suicide attempts in euthymic individuals with BD (90) and with suicidal ideation across euthymic, depressed, and hypomanic individuals with BD (91). Associations between fragmented sleep, as well as poor SE, with increased cardiovascular metabolic risk factors have also been found in euthymic BD (92). Environmental and psychosocial factors may be important targets for prevention in euthymia as circadian disruptions are linked to coffee, alcohol, and tobacco consumption (85), and Eidelman et al. (86) found a relationship between instability in rest periods and lack of social support in BD.

Study of associations between actigraphy with cognitive and neuroimaging measures can help to uncover the neurobehavioral mechanisms that contribute to mood and rest patterns. There is growing evidence that disturbances in the rest period in BD, involving both the onset and duration of sleep, are associated

with impaired white matter microstructure, as measured by lower fractional anisotropy, particularly in the genu and body of the corpus collosum and corona radiata (93). Additionally, disturbances in SE and abnormal activity rhythms in euthymic BD were found to be associated with increased functional connectivity in the dorsolateral prefrontal cortex, implicated in working memory processes (94). Though not based on actigraphy measures, a study of cognition in euthymic BD reported significant associations among subjective sleep disturbances, cognitive impairment, and poor work-related outcomes (95). The association between rest and cognition also seems to be linked to specific working memory and attention domains, supported by the neuroimaging associations reported by McKenna et al. (94). Further, Bradley et al. (96) also found that euthymic individuals with BD with abnormal rest patterns performed poorly on tests of sustained attention and working memory compared to those with normal rest patterns and HCs.

Daytime Activity and Rhythmicity

Studies that assess daytime activity patterns within BD report different patterns of activity as indicators of mood state. In Gershon et al. (97)'s study of inter-episode BD, depressive states were found to be distinguished from other mood states by even lower levels of activity, and a later time of activity onset (M_{10} onset). Other studies have reported associations between more irregular activity patterns and a greater severity of manic symptoms (67, 98), and higher baseline activity patterns in BD have been associated with relapse into mania or hypomania (99). Building on this by using predictive modeling, Scott et al. (100) found that daytime activity parameters, including absolute activity, variability markers, autocorrelation, and patterns of regularity, were able to correctly classify BD cases into distinct mood episodes, with particularly high rates for both mania and mixed states. These data suggest that changes in motor activity may be sensitive markers of mood state that could be useful in identifying relapse and measuring treatment response, and that further study of activity patterns in BD may help in the elucidation of mechanisms underlying mood states.

Daytime activity patterns in BD have been associated with adverse clinical outcomes. For example, an earlier onset of daytime activity, as measured by M_{10} onset, suggesting a shortened or disrupted period of rest, was associated with a history of increased suicide attempts in euthymic individuals with BD (90). Further, fragmented profiles of activity as measured by RA and rest duration, were shown to be associated with higher systolic blood pressure (92) and increased alcohol consumption (85). Thus, disrupted daytime activity levels could be indicators of risk for worsening outcomes not only of BD but also the well-established links with cardiovascular disease (101) and substance use disorders (102). These associations with comorbid conditions warrant further investigation through longitudinal studies.

When exploring how daytime activity relates to brain structure and function, studies have found associations with white matter microstructure. An association between lower activity levels with fractional anisotropy in the left bilateral corticospinal tract, a region of the motor pathway, was suggested as a compensatory mechanism for illness-related psychomotor retardation during depressive mood states (103). Verkooijen et al. (93) reported an association between stability in activity patterns with increased fractional anisotropy, particularly in the genu and body of the corpus callosum, and the right anterior corona radiata, which provide connections in brain systems that subserve emotion regulation and behavioral control. Although these findings were not specific to the BD group and were also reported in HCs, they suggest potential links between stability in activity patterns measured by actigraphy and the structural integrity of white matter in brain connections related to motor activity, and emotional and other behavioral regulation. When examining resting state cerebral perfusion, a relationship between cerebral blood flow and daytime activity levels in both euthymic BD and MDD has been reported (104). In both MDD and BD, reduced activity levels were associated with alterations in the middle frontal gyrus and insula, regions implicated in cognitive and emotional functions. In the BD group only, this relationship was further noted in the left precentral gyrus, which subserves motor function (104). Together, these results begin to highlight relationships between patterns of cognitive and emotional processing and motor activity with rest-activity patterns in BD. However, given the small number of studies that have currently investigated these patterns, further investigation combining actigraphy and neuroimaging methods is needed.

Question 3: What Effect Do Interventions Have on Rest-Activity Patterns in Bipolar Disorder?

Ten of the 70 included articles addressed this research question. Of these articles, 60% (n = 6) investigated differences in rest-activity patterns after pharmacological treatment including mood-stabilizing medications (lithium and quetiapine), and 40% (n = 4) investigated differences in these patterns after non-pharmacological treatments including light therapy, cognitive behavioral therapy (CBT), and blue-blocking (BB) glasses. Risk of bias assessment (105, 106) was completed on these interventional studies and can be found in **Supplementary Figure 1**.

Rest

When investigating the response to lithium, a long-standing mood-stabilizing pharmacological treatment for BD, individuals who responded well as assessed by the Retrospective Assessment of Response to Lithium Scale (the Alda scale) were also found to have more regular rest-activity patterns following treatment, as measured by IV and RA (107). Further, when using principal components analysis to classify lithium responders based on their actigraphy parameters, the same investigative group (108) found that circadian rhythmicity markers involving regularity and stability in patterns (RA, IV, IS, as well as M_{10} activity) were able to correctly classify 64% of BD cases as good responders as determined by the Alda scale.

In comparisons of lithium to that of the antipsychotic quetiapine, the latter was associated with improvements in objective sleep parameters, including sleep quality, SE, and WASO, over and above lithium (109). These findings have yet to be replicated. Other studies assessing the role of quetiapine

have found a relationship between rest-activity patterns and later improvements in depression. For instance, Todder et al. (110) found that a rapid and consistent improvement in objective rest parameters (as measured by sleep latency) was observed after 1 week of quetiapine treatment in BD-depression, but that these improvements were not related to changes in depression symptoms at the same time. The researchers found that these objective improvements at week 1 instead predicted longitudinal improvements in depression scores after 4 weeks (111). These results provide objective data supporting longstanding clinical observations that some of the earliest changes during recovery from depressive episodes are changes in activity (112) and that emotional state changes may require additional weeks. This suggests that actigraphy measures of rest patterns may be important in detecting early indicators of improvements in depressive symptoms and antidepressant effects.

A small number of studies have investigated the effect of non-pharmacological therapies targeting rest-activity patterns, including bright light therapy and sleep deprivation therapy. The aim of these therapies is to stabilize or reset the circadian rhythm, either by changing its phase or increasing rhythm amplitude, with the goal of improving symptoms. In Benedetti et al. (113)'s study of individuals with BD depression treated with sleep deprivation therapy alongside morning light therapy for 1 week, two-thirds of subjects responded with a 50% reduction in depressive symptoms and a circadian phase advance. Esaki et al. (114) showed that the timing of light therapy might be relevant to its reported effects on improving rest patterns, as they observed that light exposure at night led to decreased levels of sleep quality – including lower SE, longer sleep onset latency, delayed sleep midpoint, and greater WASO – after 1 week in individuals with BD. The use of blue-light-blocking (BB) glasses (115, 116) has been suggested as a potential treatment to oppose the effect of late night light on circadian patterns in BD. Henriksen et al. (117) found significant improvements in SE, sleep fragmentation, and fewer nights of interrupted sleep, in their BD manic sample treated with BB glasses. Lastly, one study assessing cognitive behavioral therapy for insomnia (CBT-I) with an added component to target sleep inertia (the transitional state between sleep and wake) was found to significantly improve subsequent inertia in euthymic BD (118).

Daytime Activity and Rhythmicity

In a study of lithium and quetiapine in individuals with BD depression, acrophase – or the timing of the peak circadian phase – was found to be delayed by both medications, but the delay was particularly significant for the quetiapine-treated group (119), consistent with previous evidence of a phase-delaying effect of lithium and quetiapine (120, 121). Quetiapine was found to have a more robust effect in shifting this circadian phase over a period of 8 weeks, and, while it seems counter-intuitive that a phase-delaying effect would improve depressive symptoms, this was associated with a reduction in depressive scores (119). These results suggest a related mechanism of regulating depressive mood and stabilizing rest-activity patterns after therapy.

When looking at actigraphy-measured markers of daytime activity during non-pharmacological therapies, the results show a therapeutic benefit but with some differences from pharmacotherapies in the patterns that they alter. For instance, in the two-thirds of individuals with BD depression who responded to sleep deprivation and light therapy over 1 week, Benedetti et al. (113) found that they showed an increase in daytime activity and also a phase advance in the rest-activity rhythm of 57 min. This phase advance after non-pharmacological treatment was also shown in a study of CBT-I with an added component to target sleep inertia, whereby individuals with euthymic BD showed an increase in morning activity levels and improved sleep inertia (118). The therapeutic effects of pharmacotherapies or non-pharmacological therapies associated with phase delays or phase advances suggests the complexity of understanding the effects of differential phase shifting.

DISCUSSION

Summary

Results from this systematic review provide evidence that BD is associated with disruptions in rest-activity patterns including longer sleep duration, longer sleep onset latency (58–63), and lower average daily activity (16, 75) that may be especially associated with depression. BD mania is instead linked to more complex and variable patterns over a shorter temporal scale that can also be predictive of future relapse (54). Different mood episode types are also associated with different profiles of phase-shifting, such that a phase delay is more commonly associated in BD-depression and a phase advance in BD-mania (79). Disruptions in rest-activity patterns are shown to persist during euthymia [e.g., (14, 16, 89)] and there is preliminary evidence that distinct patterns may differentiate BD from other major mood and psychotic disorders, and within subtypes of BD (7, 69, 81). Both pharmacological and non-pharmacological therapies have demonstrated rest-activity pattern stabilization associated with improvements in mood symptoms [e.g., (107, 113)]. However, the mechanisms by which these occur are yet to be fully uncovered. This may be further facilitated by technological and digital advancements provided by actigraphy, allowing the collection of fine-grained, longitudinal, and temporally sensitive parameters while individuals are in their typical environments, and emerging machine learning and other computational strategies to extract maximal information from time series data. The extant literature supports the promise of actigraphy to pave the way for the development of improved early detection, treatment, and prevention methods.

It is important, however, for current limitations to be addressed, including variability in methodology (e.g., the actigraphic variables chosen for analyses, actigraphic recording periods, and small sample sizes) and study sample characteristics (e.g., medication use and age composition) which can impede further meta-analytic work (122). Additionally, future studies should account for variability in daily patterns due to societal

demands (e.g., shift work), in order to consider how such circadian misalignment may lead to artificially fluctuating levels of actigraphic fragmentation (123) that are not representative of rest-activity patterns or endogenous circadian rhythms (124). While meta-analytic work could provide a statistical summary of results, the disparities in study characteristics did not allow for this type of analysis. It is also important to note the inherent limitations in systematic review methodology. This systematic review might exclude relevant literature as, inherent in a systematic review approach, it is bounded by search terms. Of note is the recent expansion in health-related digital technologies available for use on both the research and personal-use market. While we chose not to include commercially available digital technologies in our current review due to their limited specificity and accuracy in reporting rest-activity patterns compared to research-grade devices (51), future research could expand on this as the devices become more ubiquitous in the general population and advancements are made in optimizing their research and clinically oriented utility.

Treatment Implications

Future actigraphy research in BD could not only benefit the work of researchers aiming to further elucidate the neurobiological basis of BD, but also clinicians and patients, who may in the future be able to use real-time and longitudinal monitoring to identify personal rest-activity patterns and warning signs (35, 125). Traditional modes of in-person clinical appointments at the temporal scale of weeks or months can benefit from the use of daily and on-going monitoring through digital technologies and passive activity sensors for their ability to provide longitudinal and prospective data, including interim data that may indicate need for more acute care (34). The use of digital technologies, such as smartphone-based ecological momentary assessment in combination with actigraphy, is gaining traction for its ability to provide complementary information on day-to-day fluctuations in mood and other symptoms, social and other daily functioning, as well as changes in relation to daily stressors and life events (122, 126–128). Further, given the expedited need for remote and digital assessment tools and telehealth provisions that have intensified due to the ongoing COVID-19 pandemic and its associated increase in mood symptoms and disorders (129–131), particularly BD, the additional value of longitudinal monitoring of rest-activity rhythms and its potential to flag possible preceding events for relapse and worsening of symptoms is immense (132–134).

As rest-activity changes can be robust in precipitating mood episodes, and are possible early indicators of impending episodes and of the beneficial effects of treatments, interventions targeted at regulating rest-activity patterns and those that integrate actigraphy over time may be especially effective in treatment and prevention strategies. Interpersonal and Social Rhythm Therapy (IPSRT), which has an SRT component designed to help individuals regularize their rest-activity pattern, is one of the few psychotherapies shown in clinical trials to be effective in treating BD (135–142). The rhythm regularization of IPSRT has been shown to reduce risk of recurrence over 2 years (143) with changes in regularity of daily routines mediating symptomatic outcomes, supporting rhythm regulation as a treatment target with potential for sustained benefits and prognosis improvements. Studies are underway with modified versions of SRT (144), for example a version delivered largely *via* telehealth that has shown promise in reducing mood symptoms and suicide propensity in BD (134).

Future Directions

Combining digital monitoring, and holistic multi-modal assessment of dynamic symptomatology, with neuroimaging and cognitive assessments can help enable the field to uncover the neurobiological mechanisms responsible for the phenotypic presentations of BD. Larger scale studies will be especially helpful in elucidating heterogeneous aspects. As can be seen in **Supplementary Table 2**, several actigraphy devices are available and used for research purposes in clinical populations. Although these devices all estimate body movement through accelerometers on the *x*, *y*, and *z* planes, there can be heterogeneity in the types of actigraphy parameters extracted from the raw data. **Table 1** outlines several different variables that can be referred to, e.g., when reporting disruptions in rest (e.g., SE, WASO, L_5 activity). The field has yet to reach consensus on which parameters are key for our understanding of rest-activity patterns in BD. Going forward, optimal parameters and modalities should be further operationalized to ensure consistency in reporting across studies and to allow for the combined analysis of datasets. It should also be noted that estimating sleep *via* proxy markers, such as L_5, can be problematic because of its derivative nature (73). Collaborative efforts such as those of the Motor Activity Research Network for Health (mMARCH) will also facilitate efforts to use common procedures and methods for data extraction and analysis. For example, a processing pipeline for actigraphy based on the GGIR package that was developed for mMARCH sites (145) extracts features of sleep, physical activity, and circadian rhythmicity, and applies JIVE to capture the joint variation across three domains. Consideration of the joint variation will lead to a better understanding of the interrelationships of rest, activity, and their rhythms within and between days. This package also includes standard methods for handling missing data and non-wear time that has not been systematically presented in most studies of actigraphy in BD. Variability of the features such as IV and IS, which capture regularity in activity patterns within and across days, respectively, as well as circadian features, will be particularly relevant to future studies of BD. These markers are key for their ability to address both rest and activity, as well as highlight the importance of variability across time – two aspects proposed to be fundamental to BD. Further, novel methods to assess this variability are still being developed and could be an important future methodological direction for study in this field (123). For full characterization of sleep, future studies should also use PSG and/or other well-established and more comprehensive sleep measures, as well as capture longer study periods and greater sample sizes.

CONCLUSION

Our use of actigraphy as an avenue of investigation in BD continues to grow and holds enormous potential to transform our current understanding of the nature of BD and its treatment. Using digital technologies to capture temporally sensitive and nuanced change in rest-activity patterns will power our strides toward discovering new phenotypic markers for the illness and to targets for its detection, treatment, and prevention. The promise held by current findings is timely, as sophisticated developments in digital technologies and remote sensors are beginning to enable the collection and meaningful analysis of real-time longitudinal monitoring of complex mood disorders such as BD. Ideally, the guidelines outlined within the future directions section will afford researchers a framework for continued investigation of the temporally sensitive nature of rest-activity patterns, emphasizing the importance of pattern rhythmicity and regularity, with the goal of improving prognosis for those with and at-risk for BD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

PP, AS, and HB contributed to the conception and design of the review. PP and GdQC conducted the systematic search. PP wrote the first draft of the manuscript. GdQC, DG, and HB wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.780726/full#supplementary-material

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