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Decreased Delta/Beta ratio index as the sleep state-independent electrophysiological signature of sleep state misperception in Insomnia disorder: A focus on the sleep onset and the whole night

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ABSTRACT

Purpose: Sleep State Misperception (SSM) is described as the tendency of Insomnia Disorder (ID) patients to overestimate Sleep Latency (SL) and underestimate Total Sleep Time (TST). Literature exploring topographical components in ID with SSM is scarce and does not allow us to fully understand the potential mechanisms underlying this phenomenon. This study aims to evaluate the existence of sleep EEG topography alterations in ID patients associated with SSM compared to Healthy Controls (HC), focusing on two distinct periods: the Sleep Onset (SO) and the whole night.

Methods: Twenty ID patients (mean age: 43.5 ± 12.7; 7 M/13F) and 18 HCs (mean age: 41.6 ± 11.9; 8 M/10F) underwent a night of Polysomnography (PSG) and completed sleep diaries the following morning upon awakening. Two SSM indices, referring to the misperception of SL (SLm) and TST (TSTm), were calculated by comparing objective and subjective sleep indices extracted by PSG and sleep diary. According to these indices, the entire sample was split into 4 sub-groups: ID +SLm vs HC –SLm; ID +TSTm vs HC –TSTm.

Results: Considering the SO, the two-way mixed-design ANOVA showed a significant main effect of *Groups* pointing to a decreased delta/beta ratio in the whole scalp topography. Moreover, we found a significant interaction effect for the sigma and beta bands. *Post Hoc* tests showed higher sigma and beta power in anterior and temporo-parietal sites during the SO period in IDs +SLm compared to HC –SLm.

Considering the whole night, the unpaired *t*-test revealed in IDs +TSTm significantly lower delta power during NREM, and lower delta/beta ratio index during NREM and REM sleep compared to HCs –TSTm.

Finally, we found diffuse significant negative correlations between SSM indices and the delta/beta ratio during SO, NREM, and REM sleep.

Conclusion: The main finding of the present study suggests that higher SL overestimation and TST underestimation are both phenomena related to diffuse cortical hyperarousal interpreted as a sleep state-independent electrophysiological correlate of the SSM, both during the SO and the whole night.

1. Introduction

In the last decades, the scientific community has shown a significant interest in studying factors associated with subjective sleep perception, that is the individual and unique experience about nocturnal sleep in terms of quality and quantity. Cognitive and electrophysiological factors may affect subjective sleep perception, which is often discordant with objective sleep measures recorded by Polysomnography (PSG; Stephan

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and Siclari 2023). However, the behavioral and physiological mechanisms that determine the subjective experience of falling asleep during the Sleep Onset (SO) and of being deeply asleep during the night remain elusive.

From a clinical standpoint, a better understanding of the physiological basis of sleep perception is relevant in the context of Insomnia Disorder (ID), often characterized by the Sleep State Misperception (SSM) phenomenon. SSM is described as the tendency of ID patients to subjectively overestimate wake periods during the night and to underestimate the Total Sleep Time (TST) despite an objective sleep macrostructure adequately preserved (Baglioni et al., 2014; Edinger and Fins, 1995; Edinger and Krystal, 2003). Given the absence of a clinical consensus and clear indices for the definition of SSM, this ID phenotype has been removed by the last edition of the International Classification of Sleep Disorders (ICSD-3; Anon., American Academy of Sleep Medicine, 2014; Stephan and Siclari 2023). Nevertheless, this phenomenon is widely recognized as ubiquitous among ID patients (Edinger and Krystal, 2003), and understanding the underlying mechanisms is fundamental to characterize ID pathophysiology. Indeed, the cognitive perspective to explain the etiopathogenesis of ID includes SSM as a relevant factor in the severity and maintenance of the disorder. In this cognitive view of ID, patients who underestimate their sleep quantity and quality are at high risk for developing a chronic disease, feeding their excessive worry and distress about sleep, and contributing to increased anxiety and arousal levels in a vicious circle (Harvey and Tang, 2012). Moreover, some evidence shows that a higher SSM degree is related to poorer sleep quality and to a significant presence of psychopathology traits (Moon et al., 2015). This framework makes ID accompanied by SSM one of the most challenging ID phenotypes to treat. It should be noted that a certain degree of mismatch between subjective and objective sleep reports is also observed in good sleepers (Bianchi et al., 2012; Castelnovo et al., 2019; Lecci et al., 2020), more marked when sleep quality worsens (Herbert et al., 2017). In this view, describing the mechanisms underlying SSM is crucial to understanding the physiological processes that return the subjective feeling of being asleep, even in healthy individuals.

At present, the main hypothesis to explain SSM is centered on the concept of cortical hyperarousal, affecting ID patients during wakefulness and sleep. Indeed, several studies in ID suggest that fragmented sleep, characterized by reduced TST and elevated number of awakenings, is associated with higher SSM and represents a significant risk factor in ID to develop SSM (Feige et al., 2008; Parrino et al., 2009; Manconi et al., 2010; Turcotte et al., 2011; Hermans et al., 2019, 2020a, 2020b; Castelnovo et al., 2021; Xu et al., 2022; Berra et al., 2024). Brief but multiple awakenings during the night are remembered and perceived by the patients as a long and unique wake period, leading to the underestimation of the TST (Harvey and Tang, 2012). However, standard PSG macrostructural indices do not seem to capture properly and explain enough the SSM phenomenon, probably caused by the conventionality of this method that considers few scalp electrodes (6 in the standard electroencephalographic [EEG] sleep montage [Berry et al., 2012]) and epochs of extended duration (30 s [Berry et al., 2012]), disregarding the spatial and temporal features of neural activity underlying sleep processes (Stephan and Siclari 2023). Indeed, microstructural and power spectra analysis methods applied to the sleep EEG signals may help investigate SSM in ID, allowing the exploration of electrophysiological changes during the SO and the whole night of sleep.

During the wake-sleep transition, behavioral and cognitive response decay occurs, resulting in several local and frequency-specific electrophysiological changes (Gorgoni et al., 2020). Indeed, during the SO, the synchronized EEG activity spreads from the anterior associative areas to the posterior sensorial cortical regions, accompanied by a centro-parietal increase of the sigma activity and a generalized decrease in the beta frequency range (Marzano et al., 2013; Gorgoni et al., 2019). Studies exploring EEG changes associated with the SSM in ID during the SO, characterized by a significant overestimation of the SL, remarked the relevance of sleep fragmentation (Hermans et al., 2019; Berra et al., 2024) and cortical arousal. Indeed, the degree of the SL misperception (SLm) is related to a pattern of impaired cortical synchronization (i.e., increased beta activity and decreased delta and sigma power in anterior brain areas) during the wake-sleep transition (Marzano et al., 2008). This is in line with recent evidence showing a significant relationship between the SLm index and an EEG pattern during the SO characterized by the presence of stereotyped alpha rhythm in occipital sites, interpreted as the physiological correlate of the unsuccessful attempt of ID patients to disengage from EEG wake activity and to fall asleep (Berra et al., 2024). Moreover, the overestimation of the SL in ID is associated with a specific index of cortical arousal that evaluates the ratio of delta activity relative to the beta during the SO period, namely the delta/beta ratio index (Maes et al., 2014). This state of high cortical arousal, explained by alteration in central nervous system activation (Hsiao et al., 2018), is often accompanied by compromised sensitive and attentional inhibitory processes during the SO (Turcotte et al., 2011), heightened cognitive arousal (i.e., worry, rumination, and intrusive thoughts) and mentation that exacerbate the SSM during the process of fall asleep. However, studies exploring the EEG changes underlying SSM in ID during the SO at present are scarce, and topographical aspects of SLm have been quite neglected.

Considering the whole night of sleep, evidence in EEG spectral features focused on Non-Rapid Eye Movement (NREM) sleep showed that a decreased Slow Wave Activity (SWA; Krystal et al., 2002) and a higher rapid EEG activity (i.e., alpha, sigma, and beta) could be interpreted as electrophysiological correlates of SSM (Perlis et al., 2001; Krystal et al., 2002; Marzano et al., 2008; Krystal and Edinger, 2010; Lecci et al., 2020) and of perception of sleep depth (Stephan et al., 2021). Indeed, these EEG changes were found specifically in ID patients with SSM compared to good sleepers, but not in those ID patients that normoestimated sleep (Krystal et al., 2002). Importantly, using composed indices of EEG activity applicable to characterize cortical arousal, it has been proved that the SSM in ID is related to higher alpha-delta sleep (Martinez et al., 2010) and to lower delta/beta ratio index (Lecci et al., 2020; Xu et al., 2022) during NREM sleep. Moreover, evidence showed that the increased fast EEG activation related to SSM characterized centro-parietal regions during NREM sleep, and the same increase in fast frequencies is cortically widespread during Slow Wave Sleep (SWS; Lecci et al., 2020). The same study showed that in healthy subjects the underestimation of TST was related to faster EEG activity in central scalp derivations during Rapid Eye Movement (REM) sleep, while the TST overestimation was linked to increased SWA during REM sleep (Lecci et al., 2020). Consistently, an interesting line of research in the field of SSM focuses on the role of REM sleep, a sleep stage characterized by increased brain activity with an EEG pattern similar to one observable during wakefulness (i.e., desynchronized EEG activity and experiences of vivid dreams and mentation) that might be perceived and subjectively reported by patients as wake (Riemann et al., 2012; St-Jean et al., 2013; Feige et al., 2018). However, REM spectral changes associated with misperception are scarce in the literature.

The state-of-the-art suggests that SSM in ID might be pinpointed by a pattern of brain cortical arousal. However, literature that explored topographical components in ID with SSM is scarce and does not allow us to understand the physiological mechanisms underlying SSM fully. Since few studies in the literature differentiate ID patients with and without SSM, the electrophysiological changes ascribable specifically to the SSM, and not to the ID pathophysiology in general, are still unknown. Moreover, up to now, no study has assessed topographical EEG changes in ID during SO and their relationship with SSM during this transition period.

Starting from these premises, the present study has been designed to provide a complete overview of sleep electrophysiology associated with SSM. Specifically, this study aimed to evaluate the existence of sleep EEG topography alterations in ID patients associated with SSM compared to Healthy Controls (HC), focusing on two distinct periods of

the night: the SO and the whole night. For this purpose, at first, we compared topographical EEG features between ID patients and HC participants without considering the SSM degree. Then, the same analyses were performed selecting IDs with SSM and HCs without SSM. Finally, we assessed the relationship between EEG topography during the SO and the entire night of sleep, and the level of SSM.

2. Materials and methods

2.1. Participants and experimental procedures

Twenty-two ID patients were recruited at the Sleep Disorder Centre of the San Raffaele Hospital (Milan), and 20 sex and age-matched HCs were recruited in the general population through internet posts and word of mouth. Two IDs and 2 HCs were excluded from the analyses after a visual inspection of the PSG due to technical problems in the recording. Therefore, the analyses were performed on 20 ID patients and 18 HC participants.

The screening procedure to recruit ID patients consisted of an initial visit conducted by a neurologist expert in sleep medicine to assess the patients' eligibility. All ID patients met the clinical criteria for chronic ID according to the ICSD-3 (Anon., American Academy of Sleep Medicine, 2014). Exclusion criteria were i) the presence of dementia, psychiatric, or other sleep disorders; ii) neurological comorbidities; and iii) the intake of drugs or substances interfering with sleep, mood, or affecting the central nervous system. In the case of benzodiazepine, patients had to be drug-free at least 1 week before PSG assessment, while from 2 weeks to a month was requested for antidepressants.

HC participants were selected based on the Insomnia Severity Index (ISI) score of < 8 (Morin et al., 2011; Castronovo et al., 2016), the Epworth Sleepiness Scale (ESS) score of < 10 (Johns, 1991; Vignatelli et al., 2003), and the Pittsburgh Sleep Quality Index (PSQI) score < 5 (Buysse et al., 1989; Curcio et al., 2013) to exclude the presence of ID, excessive daytime sleepiness or any other sleep disorders, respectively. For at least two months, also HCs had to be free of any drug or substance interfering with sleep, mood, or affecting the central nervous system. Moreover, HCs were requested to respect a regular sleep-wake rhythm during the week before the experimental session and complete a weekly sleep log each morning to control their compliance.

In addition to the questionnaires already mentioned, HCs and IDs participants also completed the Beck Depression Inventory (BDI; Beck et al., 1996; Ghisi et al., 2006) and the State-Trate Anxiety Inventory (STAI-Y; Spielberger, 1989).

On the day of the experimental session, each participant came to the Sleep Disorder Center of the San Raffaele Hospital (Milan) between 5.30 and 7:00 p.m. and underwent an ambulatory PSG montage. Sleep monitoring for all subjects was conducted in private homes to record sleep as environmentally friendly as possible and to avoid the first-night effect. Participants were prohibited from drinking caffeinated and alcoholic beverages during the afternoon preceding the sleep recordings. Lights-out time was based on individual habitual bedtime, and participants were allowed to sleep until their spontaneous awakening in the morning. Upon the final awakening (within 15 min), self-reported parameters were collected using sleep diaries. All subjects gave their written informed consent. The study was approved by the Institutional Ethics Committee of the Department of Psychology of the "Sapienza" University of Rome (Protocol number 0,000,573 of the 28/03/2020) and was conducted in accordance with the Declaration of Helsinki.

2.2. Sleep recording

PSG recordings were performed with 19 EEG cortical channels according to the international 10–20 system. The signal was acquired through unipolar derivations referred to averaged mastoids (A1 – A2) and with a filtered system (high-pass filter at 0.5 Hz and antialising low-pass filter at 35 Hz) inclusive of all the canonical EEG frequency ranges: delta (0.5 – 4.75 Hz), theta (5.00 – 7.75 Hz), alpha (8.00 – 12.75 Hz), sigma (12.00 – 15.75 Hz), and beta (16.00 – 24.75 Hz). Electrooculography (EOG) and Electromyography (EMG) of the submentalis muscles were also recorded. EEG, EOG, and EMG channel impedances were kept below 5 kΩ.

An expert sleep researcher manually scored sleep stages and artifact rejection according to the American Academy of Sleep Medicine (AASM) standard criteria on 30-*sec* epochs (Berry et al., 2012). Epochs containing rapid and slow ocular or muscular artifacts were manually rejected. SWS scoring strictly fulfilled the >75 μV amplitude criterion. Cortical arousals were scored when an abrupt shift in EEG frequency occurred, which may include theta, alpha, or frequencies greater than 16 Hz (but not sleep spindles). This EEG frequency shift attributed to the arousal must be equal to or longer than 3 s, and at least 10 continuous seconds of stable sleep must precede any scored arousal. An arousal was scored in REM sleep only if accompanied by a concurrent increase in submental EMG amplitude (Berry et al., 2012). At the end of the sleep scoring, the following macrostructural sleep variables were assessed: i) latencies to stage 2 (that defined the objective SL [oSL]), SWS, and to REM sleep; ii) objective Total Sleep Time (oTST), defined as the sum of time spent in stage 1, stage 2, SWS, and REM sleep; iii) percentage of each sleep stage; iv) Wake After Sleep Onset (WASO, in minutes); v) number of awakenings; vi) number of cortical arousals; vii) Time In Bed (TIB, in minutes); viii) Sleep Efficiency index ($SE = \frac{TST}{TIB} * 100$, expressed in percentage).

2.3. Sleep diaries

Each HC participant completed a week of sleep diary monitoring to ensure healthy wake/sleep habits collecting subjective sleep variables referring to the night just passed. Moreover, HCs and IDs filled out a sleep diary the morning after the PSG recording night. Participants were asked to complete the sleep logs within 15 min of waking up and answer questions about their subjective feelings and memory. Sleep parameters extracted from sleep diaries were i) the subjective SL (sSL) extracted by the question: "*How many minutes did you need to fall asleep?*"; ii) the subjective TST (sTST) referred to the question: "*How many minutes did you sleep overall*?"; iii) number of awakenings during the night; iv) the subjective WASO (sWASO) extracted by the question: "*If you have been waking up during the night, in total, how many minutes have you been awake*?"; v) the subjective TIB (sTIB) extracted by the sum of the score in question: "*What time did you go to bed*?", in question: "*What time did you finally wake up*?", and in question: "*Following your final awakening, after how many minutes did you get out of bed*?"; vi) the subjective SE (sSE) calculated by the ratio of $\frac{sTST}{sTIB} * 100$.

2.4. Sleep state misperception indices

Two SSM indices (Lecci et al., 2020; Maltezos et al., 2023), referring to the SO and the whole night, were calculated by comparing objective and subjective sleep indices extracted by PSG and sleep diary referring to the experimental night.

- SLm index, namely the SSM during the SO, was calculated by the following formula: $\frac{sSL}{oSL} * 100$. Values equal to 100% identified perfect accuracy of the oSL estimation (no discrepancy between subjective and objective estimation); on the other hand, values higher than 100% indicated the overestimation of the oSL.
- Total Sleep Time misperception (TSTm) index, namely the SSM during the whole sleep, was calculated by the following formula: $\frac{sTST}{oTST} * 100$. Values equal to 100% identified perfect accuracy of the oTST estimation (no discrepancy between subjective and objective estimation); on the other hand, values lower than 100% indicated the underestimation of the oTST.

These indices were considered as continuous variables for correlational analyses. However, to test between-group differences and to characterize our sample according to the SSM degree in both moments of the night analyzed (i.e., the SO and the whole night), we used specific cut-offs to split the whole sample into ID misperceptors and HC normoestimators. Indeed, analyses on the SO period were performed in ID subjects that overestimated at least twice the oSL (i.e., SLm index > 200% as arbitrary cut-off) with at least 10 min of oSL (Hermans et al., 2020b) identified as ID +SLm and in HCs that normoestimated their oSL (i.e., SLm index < 200 %) identified as HC –SLm. Analyses on the whole night were performed in ID patients who underestimated their oTST (i.e., TSTm index < 88.31% [Lecci et al., 2020]) identified as ID +TSTm and in HCs that normoestimated the oTST (i.e., TSTm index ranged between 88.31 – 110.43 % [Lecci et al., 2020]) identified as HC –TSTm. The flowchart of participants' enrollment and sample phenotyping is reported in Fig. 1.

3. Quantitative EEG analyses

EEG analyses were carried out using MATLAB R2011b and R2019b.

3.1. Whole night

A quantitative analysis was performed on EEG signals for the entire sleep. Sleep scoring and manual artifact rejection were performed based on 30-*sec* epochs. Since N1 is considered a transitional stage between wakefulness and sleep (De Gennaro et al., 2001), we included only N2 and N3 sleep epochs for the spectral analyses in NREM sleep, considering them stable sleep stages. Sleep power spectra of the 19 cortical derivations were computed separately for NREM (i.e., N2 and N3) and REM sleep by considering the whole recording and through the Fast Fourier transform (FFT) routine for consecutive 4-*sec* periodograms averaged in 30 s epochs, resulting in a frequency resolution of 0.25 Hz. The frequency range considered for this study was 0.5–24.75 Hz. To analyze the 5 canonical frequency bands, adjacent 0.25 bins were collapsed and log-transformed, reducing power EEG data to delta (0.5 – 4.75 Hz), theta (5.0 – 7.75 Hz), alpha (8.00 – 11.75 Hz), sigma (12.00 – 15.75 Hz), and beta (16.00 – 24.75 Hz). The delta/beta ratio index for NREM and REM sleep was also assessed as an electrophysiological index of cortical arousal (Krystal, 2008; Maes et al., 2014).

3.2. Sleep onset

The 5-minute intervals before and after the appearance of the first Sleep Spindle (SS) or K-Complex (KC) were considered as the Pre-SO and Post-SO periods respectively, since the first occurrence of stage N2 (defined as the first appearance of SS or KCs) represents a more reliable and discriminative boundary between wake and sleep than the onset of stage 1, which is considered a transitional stage between wakefulness and sleep (De Gennaro et al., 2001). In line with our previous studies (Marzano et al., 2013; Gorgoni et al., 2019; Annarumma et al., 2024), sleep scoring and artifact rejection were performed based on 12-*sec* epochs, and power spectra were computed separately for Pre- and Post-SO. The SO EEG topography was analyzed for the canonical 5 frequency bands and for the delta/beta ratio during the 5 min Pre and Post the SO as described for the whole night analyses.

4. Statistical analyses

Statistical data analyses were conducted using the JASP program (version 0.16.4.0), MATLAB R2011b and R2019b.

The HC and ID groups, and the sub-groups of HCs without SSM and IDs with SSM, were compared for age (unpaired *t*-test) and gender (Chi-square) to control for significant differences. Moreover, an unpaired *t*-test was employed to evaluate between-group differences in subjective and objective sleep, SSM indices (i.e., SLm and TSTm), and psychological features extracted by questionnaires.

Between-group differences in the EEG whole night topography were computed for each frequency band and for the delta/beta ratio index employing two-tailed unpaired *t*-tests for the 19 cortical channels for NREM and REM sleep separately. According to our aims, the same analyses were performed for the whole sample (ID vs. HC), and to test differences between HCs without TSTm and IDs with TSTm (ID +TSTm vs. HC –TSTm). The False Discovery Rate (FDR; Benjamini and Hochberg, 1995) was applied to α-values to correct for multiple comparisons.

To test group differences in the EEG topography of the SO, for each frequency band and the delta/beta ratio separately, a two-way mixed ANOVA was performed for each scalp derivation, with *Time* (Pre-SO vs. Post-SO) as the within-subject factor, and *Groups* (ID vs. HC, and ID +SLm vs. HC –SLm) as the between-subject factor. To illustrate the topography of the ANOVAs' main effects accounting for their directions, the *t*-values corresponding to each *F*-values were computed (Gorgoni et al., 2015). The difference between the mean values of the levels of each factor defines the sign of each *t*-value. Two-tailed *t*-tests were performed for *Post-Hoc* comparisons in case of significant interactions. The FDR was applied to correct the α-value (Benjamini and Hochberg, 1995).

Possible associations between SSM indices (i.e., SLm and TSTm) and

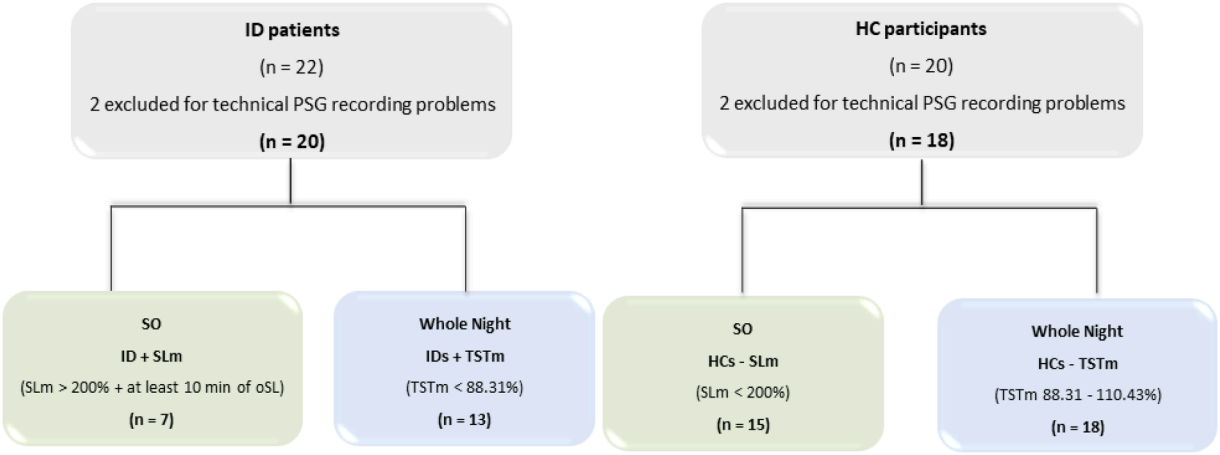

Fig. 1. Sample enrollment and phenotyping based on the Sleep State Misperception during the Sleep Onset (green boxes) and the Whole Night (blue boxes). Abbreviations: Healthy Controls (HC); Insomnia Disorder (ID); Polysomnography (PSG); Sleep Latency misperception (SLm); Sleep Onset (SO); Total Sleep Time misperception (TSTm).

EEG features (i.e., frequency bands and delta/beta ratio index) during the SO and the whole night respectively, were evaluated through Pearson's correlations. Correlational analyses were performed separately for the entire sample of HC participants and ID patients, and in the sub-samples of ID patients with SSM and HCs without SSM. The FDR method was employed to correct for multiple comparisons. Since the SLm and TSTm indices are characterized by opposite tendencies (i.e., higher SSM identified by values < 100 considering the SL, and > 100 considering the TST) the SLm formula was inverted (i.e., $\frac{oSL}{sSL} * 100$) to map the r values for the scalp maps images in order to uniform the direction of the correlations between the frequency bands and the SL and TST misperception indices.

5. Results

5.1. Group-dependent changes in scalp topography: healthy controls vs Insomnia patients

5.1.1. Sample clinical features

Tables 1 and 2 report questionnaires and objective/subjective sleep measures of 18 HC participants (mean age: 41.6 ± 11.9; 8 M/10 F) and 20 ID patients (mean age: 43.5 ± 12.7; 7 M/13 F) similar in age ($t = -0.470$; $p = 0.641$) and gender ($\chi^2 = 0.056$; $p = 0.812$), without considering the SSM phenomenon. ID patients reported a mean disease duration of 12.0 ± 1.7 years. Compared to HCs, IDs reported more severe Insomnia symptoms ($t = -10.440$; $p < 0.001$), higher depressive traits ($t = -2.538$; $p = 0.016$), and higher state (but not trait) anxiety ($t = -2.073$; $p = 0.046$). On the other hand, ID patients and HCs did not differ for diurnal subjective sleepiness and state anxiety ($p > 0.05$).

During the experimental night, compared to HCs, ID patients subjectively reported significantly longer sSL ($t = -2.370$; $p = 0.023$), sWASO ($t = -3.935$; $p < 0.001$), and more subjective awakenings ($t = -2.586$; $p = 0.014$). Moreover, as expected, IDs showed shorter sTST ($t = 4.888$; $p < 0.001$) and worse sSE ($t = 5.036$; $p < 0.001$). The two groups did not differ in hours spent in bed during the night ($t = 1.249$; $p = 0.220$) (Table 2). Moreover, the two groups exhibited significant differences in objective macrostructure sleep features. As expected, ID patients had longer latency to N2 ($t = -3.058$; $p = 0.004$) and objective wakefulness during the night ($t = -4.116$; $p < 0.001$), and more awakenings ($t = -3.551$; $p < 0.001$). Moreover, results revealed that IDs showed higher percentages of N1 ($t = -3.564$; $p = 0.001$) and NREM sleep ($t = -2.588$; $p = 0.014$) than HCs. Conversely, the ID group had a lower REM percentage ($t = 2.588$; $p = 0.014$) and SE ($t = 5.144$; $p < 0.001$) compared to the control group.

ID patients and HC participants did not exhibit significant differences in REM sleep latency, percentages of N2 and SWS, minutes spent in the bed, and numbers of cortical arousal during the night (See Table 2).

Comparing the two groups on the SSM indices, as expected, patients showed significantly higher SLm (HC vs ID: 144.2 ± 60.7 *vs* 487.9 ± 457.4; $t = -3.348$; $p = 0.002$) and TSTm (HC vs ID: 106.9 ± 29.4 *vs* 56.5 ± 46.2; $t = 4.879$; $p < 0.001$) indices compared to HCs (Fig. 2). The boxplots in Fig. 2A showed the presence of three outliers in the ID group identifying patients that strongly overestimated their SL. Actually, the significant between-group differences disappeared when the three outliers were removed ($t = 1.113$, $p = 0.273$) or using the Mann-Whitney non-parametric test ($W = 237.0$, $p = 0.323$).

5.1.2. Sleep onset eeg topography

The EEG regional features of the 5 min Pre- and Post-SO in HCs ($n = 18$) and in IDs ($n = 20$) for the 5 frequency bands and for the delta/beta ratio index are described in Fig. 3. The analysis of macrostructural sleep states before and after the SO showed the absence of any differences between the two samples. Descriptive results showed topographical dynamics expected in the wake-sleep transition in both groups for each frequency band (Fig. 3A) and for the delta/beta ratio index (Fig. 3B). Indeed, the two-way mixed-design ANOVAs *Time* (Post- vs. Pre-SO) x *Groups* (ID vs. HC) revealed a significant principal effect of *Time* for the 5 frequency bands (critic p after FDR correction = 0.034) and for the delta/beta ratio index (critic p after FDR correction = 0.001), showing significant differences between the considered temporal conditions.

Table 1
Self-reported sleep and psychological measures assessed through questionnaires in HCs and IDs.

	HC Means ± SD ($n = 18$)	ID Means ± SD ($n = 20$)	Statistics	p
Gender	8 M/10 F	7 M/13 F	$\chi^2 = 0.056$	0.812
Age	41.6 ± 11.9	43.5 ± 12.7	$t = -0.470$	0.641
Disease Duration (years)	–	12.0 ± 11.0 Range: 1 – 40 y	–	–
PSQI	3.7 ± 1.7	–	–	–
ISI	4.4 ± 2.2	16.9 ± 4.5	$t = -10.440$	< 0.001***
ESS	5.7 ± 3.0	4.4 ± 4.9	$t = 0.931$	0.448
BDI – II	6.5 ± 4.9	12.4 ± 8.5	$t = -2.538$	0.016*
STAI – Y state	36.0 ± 7.5	42.4 ± 10.7	$t = -2.073$	0.046*
STAI – Y trait	42.6 ± 4.6	46.4 ± 7.3	$t = -1.815$	0.079

Significant main effects are in bold. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Abbreviations: Beck Depression Inventory (BDI); Epworth Sleepiness Scale (ESS); Healthy Controls (HC); Insomnia Disorder (ID); Insomnia Severity Index (ISI); Pittsburgh Sleep Quality Index (PSQI); Error (SE); State-Trait Anxiety Inventory (STAI-Y); Years (y).

Table 2
Sleep diaries and polysomnographic measures in HCs and IDs concerning the experimental night.

	HC Means ± SD ($n = 18$)	ID Means ± SD ($n = 20$)	t	p
sSL (min)	11.1 ± 7.1	51.5 ± 71.8	−2.370	0.023*
sWASO (min)	11.7 ± 13.9	147.1 ± 145.2	−3.935	<0.001***
sTIB (min)	477.5 ± 59.2	452.7 ± 62.8	1.249	0.220
sTST (min)	438.9 ± 55.7	276.0 ± 131.0	4.888	< 0.001***
sSE (%)	88.3 ± 6.6	56.2 ± 26.2	5.036	< 0.001***
Subjective Awakenings (n°)	1.5 ± 1.5	4.2 ± 4.2	−2.586	0.014*
oSL (Latency to N2, min)	8.3 ± 6.2	17.8 ± 11.6	−3.058	0.004**
SWS Lat (min)	23.1 ± 9.3	43.0 ± 39.5	−2.089	0.044*
REM Lat (min)	78.5 ± 28.3	100.4 ± 46.1	−1.740	0.090
N1 (%)	5.4 ± 1.7	9.6 ± 4.7	−3.564	0.001**
N2 (%)	47.3 ± 8.0	51.8 ± 10.5	−1.431	0.161
SWS (%)	17.8 ± 6.1	15.0 ± 7.3	1.256	0.217
NREM (%)	70.6 ± 6.0	76.6 ± 7.9	−2.588	0.014*
REM (%)	29.3 ± 6.0	23.3 ± 7.9	2.588	0.014*
oWASO (min)	20.3 ± 17.3	84.1 ± 63.1	−4.116	< 0.001***
oTIB (min)	484.5 ± 69.2	484.2 ± 62.3	−0.018	0.986
oTST (min)	443.8 ± 64.0	364.5 ± 72.8	3.547	0.001**
oSE (%)	91.5 ± 3.7	75.1 ± 13.0	5.144	< 0.001***
Awakenings (n°)	5.8 ± 3.2	10.1 ± 4.0	−3.551	0.001**
Cortical Arousal (n°)	24.1 ± 14.4	32.6 ± 19.0	−1.503	0.142

Significant main effects are in bold. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Abbreviations: Healthy Controls (HC); Insomnia Disorder (ID); non-rapid eye movement (NREM); non-rapid eye movement sleep stage 1 and 2 (N1 and N2); objective Sleep Efficiency (oSE); objective Sleep Latency (oSL); objective Time in Bed (oTIB); objective Total Sleep Time (oTST); objective Wake After Sleep Onset (oWASO); Rapid Eye Movement sleep Latency (REM Lat); Slow Wave Sleep (SWS); Slow Wave Sleep Latency (SWS Lat); subjective Sleep Efficiency (sSE); subjective Sleep Latency (sSL); subjective Time in Bed (sTIB); subjective Total Sleep Time (sTST); subjective Wake After Sleep Onset (sWASO).

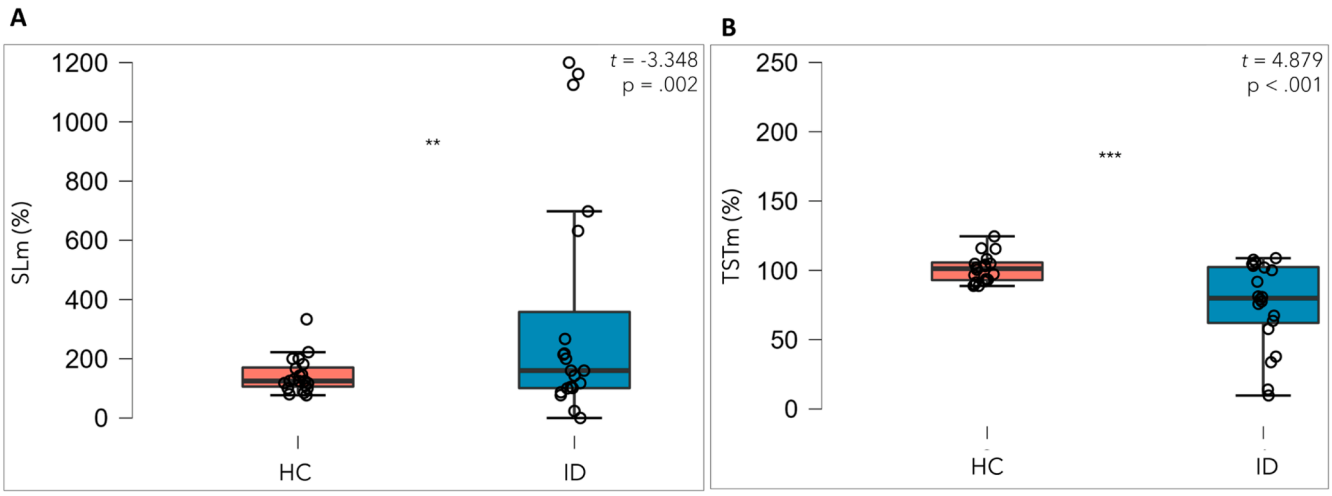

Fig. 2. Results of the comparisons (*t*-test) between HCs (in orange) and IDs (in aquamarine) performed on Sleep State Misperception Measures during (A) the Sleep Onset and (B) the Whole Night.
$^{**}p < 0.01$, $^{***}p < 0.001$.
Abbreviations: Healthy Controls (HC); Insomnia Disorder (ID); Sleep Latency misperception (SLm); Total Sleep Time misperception (TSTm).

Specifically, we found a generalized spectral power increase in the delta, theta, and sigma bands in the Post-SO compared to the Pre-SO period involving all scalp sites. The alpha power increased specifically in frontal electrodes (i.e., F3, Fz, F4). *Vice versa,* a significant general beta power decrease can be observed in all scalp derivation in the Post-SO period (Fig. 3A). Moreover, the delta/beta ratio index during the SO process showed a physiological anterior prevalence of the delta band relative to the beta during the 5 min Post-SO in both groups, more marked in HCs than in IDs (Fig. 3B).

However, the two-way mixed-design ANOVAs *Time* (Post- vs. Pre-SO) *x Groups* (ID vs. HC) revealed no significant main effect of *Groups* or interaction, neither for the EEG frequency bands nor for the delta/beta ratio index.

5.1.3. Whole night eeg topography

Fig. 4 reports the EEG scalp topography maps of the log-transformed EEG power for each frequency band (Fig. 4A) and for the delta/beta ratio index (Fig. 4B) during NREM and REM sleep in HCs ($n = 18$) and IDs ($n = 20$). In both groups, descriptive results depict the typical topographical distribution of each frequency band during NREM and REM sleep. The statistical comparisons (unpaired *t*-tests) show the absence of significant differences between patients and controls for any frequency bands and for the delta/beta ratio index during NREM and REM sleep, albeit it reveals a non-significant tendency of lower values of SWA (i.e., the delta band and the delta/beta ratio index) and greater EEG activity in the sigma and beta bands during NREM sleep in the ID patients group than HCs.

5.2. Group-dependent changes in the sleep onset scalp topography: healthy controls without sleep latency misperception vs. Insomnia patients with sleep latency misperception

According to our second aim focused on the SSM, we analyzed the SO period considering 7 ID subjects (mean age: 49.7 ± 9.9; 3 M / 4 F) that overestimated at least twice the oSL with at least 10 min of oSL and in 15 HCs (mean age: 41.6 ± 11.7; 6 M/9 F) that normoestimated their oSL (SLm index < 200 %). The two groups did not differ for age ($t = -1.573$; $p = 0.131$) and gender ($\chi^2 = 0.121$; $p = 0.905$). Most differences between ID patients +SLm and HC –SLm reflect results considering the whole sample of IDs and HCs. Moreover, PSG data showed further between-group differences revealing in IDs +SLm a higher percentage of N2 sleep ($t = -2.487$; $p = 0.022$) and more cortical arousals ($t = -2.796$; $p = 0.012$) than HCs –SLm (Table S1).

Results of the two-way mixed-design ANOVA *Time* (Post- vs. Pre-SO) *x Groups* (ID +SLm vs. HC –SLm) performed on the 5 canonical frequency bands (Fig. 5A) and on the delta/beta ratio index (Fig. 5B) show a significant main effect of *Time* for all frequency bands except for the alpha frequency range (critic *p* after FDR correction = 0.001), and for the delta/beta ratio index (critic *p* after FDR correction = 0.001) in all cortical derivations. The *Time* effect reflected the physiological EEG changes during the SO already observed in the whole sample analyses. Results also showed a significant main effect of *Groups* for the beta band involving almost all anterior and temporoparietal cortical derivations (critic *p* after FDR correction = 0.023), and for the delta/beta ratio (critic *p* after FDR correction = 0.040) in the whole scalp topography except for F3 channel. Specifically, the *Groups* effect was characterized by a frontal (i.e., Fp1, Fp2, F7, F3, F4, F6) and temporoparietal (i.e., T3, C4, T4, P4, T6) beta increase (Fig. 5A) and by a generalized lower delta/beta power in ID patients +SLm compared to the HC –SLm (Fig. 5B).

Finally, we found a significant (critic *p* after FDR correction = 0.024) interaction effect for the sigma (Fp1, Fp2, and F8) and beta (Fp1, Fp2, F7, F4, F8, T3, C3, C4, T4, P4, and T6) bands. *Post Hoc* tests (Fig. 5C) showed that compared to HC –SLm, ID patients +SLm were characterized by higher sigma (i.e., Fp1, Fp2, and F8) and beta (i.e., Fp1, F7, F4, F8, C4 T3, T4, T6, and P4) power in anterior and temporo-parietal sites during the 5 min Pre-SO. Moreover, during the 5 min Post-SO, IDs +SLm were characterized by an anterior (i.e., Fp1, Fp2, F7, F4, F8, and C4) and temporal (i.e., T3, T4, and T6) increase in the beta activity compared to HC –SLm.

5.3. Group-dependent changes in the whole night scalp topography: healthy controls without total sleep time misperception vs. insomnia patients with total sleep time misperception

According to our aim to test differences between IDs +TSTm and HCs -TSTm, we performed between-group analyses during the whole night considering 13 ID patients (mean age: 46.8 ± 11.2; 4 M/ 9 F) that underestimated their oTST (TSTm index < 88.31% [Lecci et al., 2020]) similar in age ($t = -1.387$; $p = 0.176$) and gender ($\chi^2 = 0.056$; $p = 0.812$) to 18 HCs that normoestimated the oTST (mean age: 41.0 ± 11.5; 8 M / 10 F).

Clinical and sleep features results confirmed findings in the whole sample of IDs and HCs. Moreover, these data pointed to further between-group differences, revealing in IDs +TSTm a higher percentage of N2

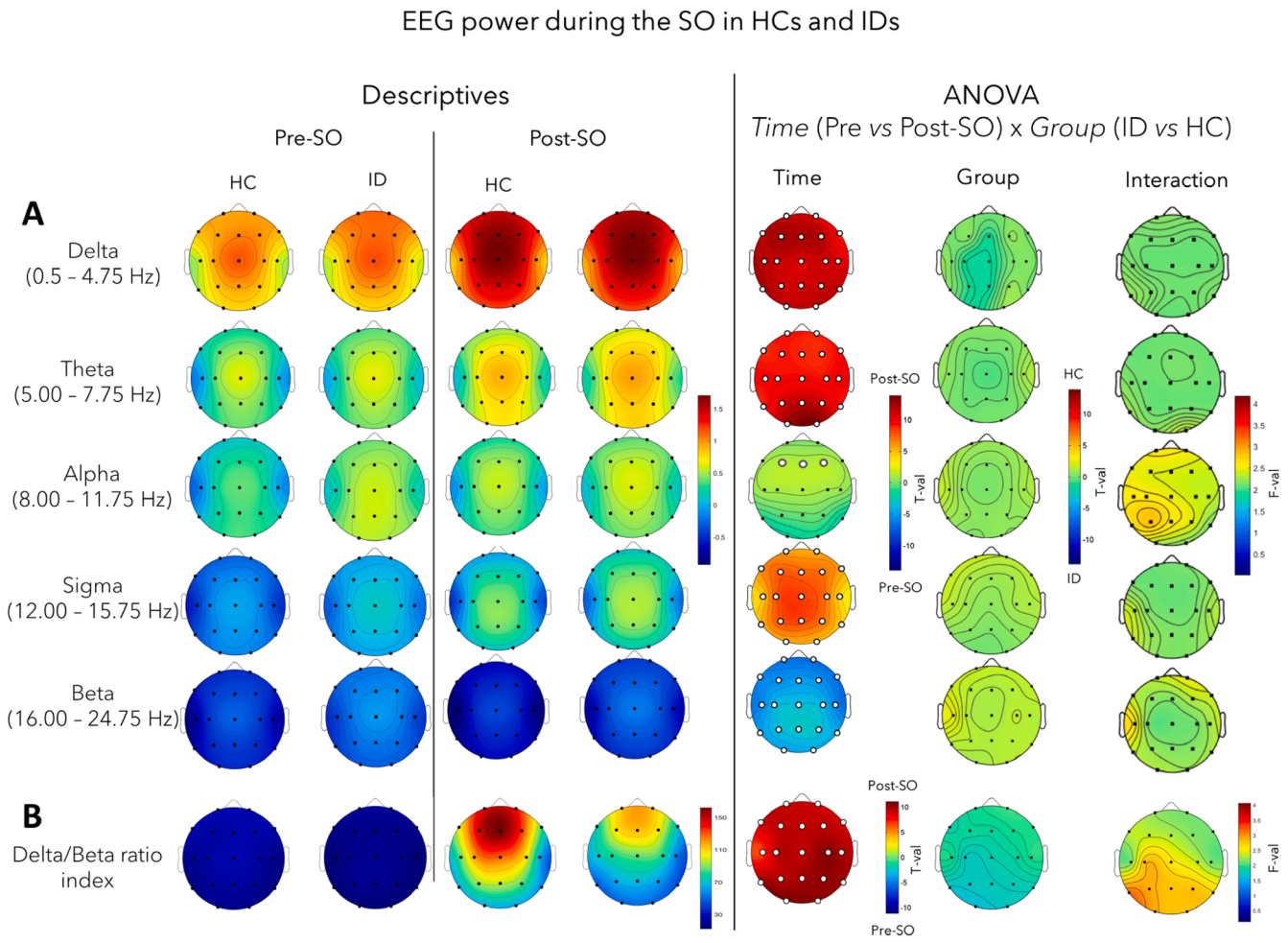

Fig. 3. Topographical scalp maps of the EEG power in the 5 min intervals before and after the SO in HC ($n = 18$) and ID ($n = 20$). The maps are scaled between minimal and maximal values calculated for all the derivations in Pre- and Post-SO in both groups. The maps are based on the 19 unipolar EEG derivations of the international 10 – 20 system with averaged mastoid reference (electrode positions indicated by black dots). Maps are plotted for the following EEG bands: (A) Delta (0.5 – 4.75 Hz); Theta (5.00 – 7.75 Hz); Alpha (8.00 – 11.75 Hz); Sigma (12.00 – 15.75 Hz); Beta (16.00 – 24.75 Hz), and (B) Delta/Beta ratio index. In the right columns are shown results of the two-way mixed ANOVA on each frequency band (A) and on the Delta/Beta ratio index (B) for each scalp derivation, with Time (Pre- vs. Post-SO) as the within-subject factor and Group (ID vs. HC) as the between-subject factor. Results for the main effects of Time and Groups are expressed in *t*-values corresponding to the original *F*-values, aiming to highlight the direction of differences. The sign of each *t*-value was defined by the differences between the mean values of the levels of each factor. Results for the effect of the interaction are expressed in *F*-values. White dots indicate significant differences after the FDR correction (EEG frequency band: critic $p = 0.034$; delta/beta ratio index: critic $p = 0.001$).

sleep ($t = -2.487$; $p = 0.022$), a lower percentage of SWS ($t = 2.131$; $p = 0.041$), and a higher occurrence of cortical arousals during the night ($t = -2.728$; $p = 0.011$) than HCs –TSTm (Table S2).

The regional features of the NREM and REM sleep for each frequency band and delta/beta ratio index are described in Fig. 6. Descriptive maps showed for both groups the physiologically expected EEG course during NREM and REM sleep, already observed in the whole sample analysis.

Moreover, the unpaired *t*-test comparisons revealed that patients ID +TSTm were characterized by a diffuse significantly lower delta power during NREM (critic *p* after FDR correction = 0.035) (Fig 6A) and lower delta/beta ratio index during NREM and REM sleep (critic *p* after FDR correction = 0.034) (Fig 6B) compared to HCs –TSTm. The two groups did not differ for the other frequency bands during NREM sleep and for any frequency band during REM sleep.

5.4. *Correlations between the SLm and electroencephalographic frequency topography during the sleep onset*

To explore the relationship between the SSM and brain EEG activity during the wake-sleep transition, coefficients of linear correlations (Person's r) were calculated between SLm and the 5 canonical frequency bands and delta/beta ratio index during the SO, for the entire sample of HC participants ($n = 18$) and ID patients ($n = 20$), and in the subsamples of HC –SLm ($n = 13$) and ID +SLm ($n = 7$). The SLm formula applied for correlational analyses was inverted (i.e., $\frac{oSL}{sSL} * 100$) in order to uniform the direction of the correlations with the TSTm index.

Results showed no significant correlation between SLm index and EEG frequency band powers during the 5 min Pre- or Post-SO, neither for the whole sample of HCs and ID patients, nor for the subsamples of HC –SLm and ID +SLm. However, significant negative correlations were found between the SLm index and the delta/beta ratio index during the Post-SO interval considering the whole sample ($r \geq -0.522$; critic *p* after FDR correction = 0.011), and the subsample of HC –SLm and ID +SLm ($r \geq -0.589$; critic *p* after FDR correction = 0.011). Specifically, the higher overestimation of the oSL was significantly related to the decrease of the delta/beta ratio index during the 5 min Post-SO, with a frontal topographical pattern (i.e., in HC and HC –SLm: Fp2, F3, Fz, F4, C4, T5, O1; in ID: Fp2, Fz, F4, Fz; in ID +SLm: Fp2, Fz, F4) (Fig. 7 and S1; Tables S3 and S4).

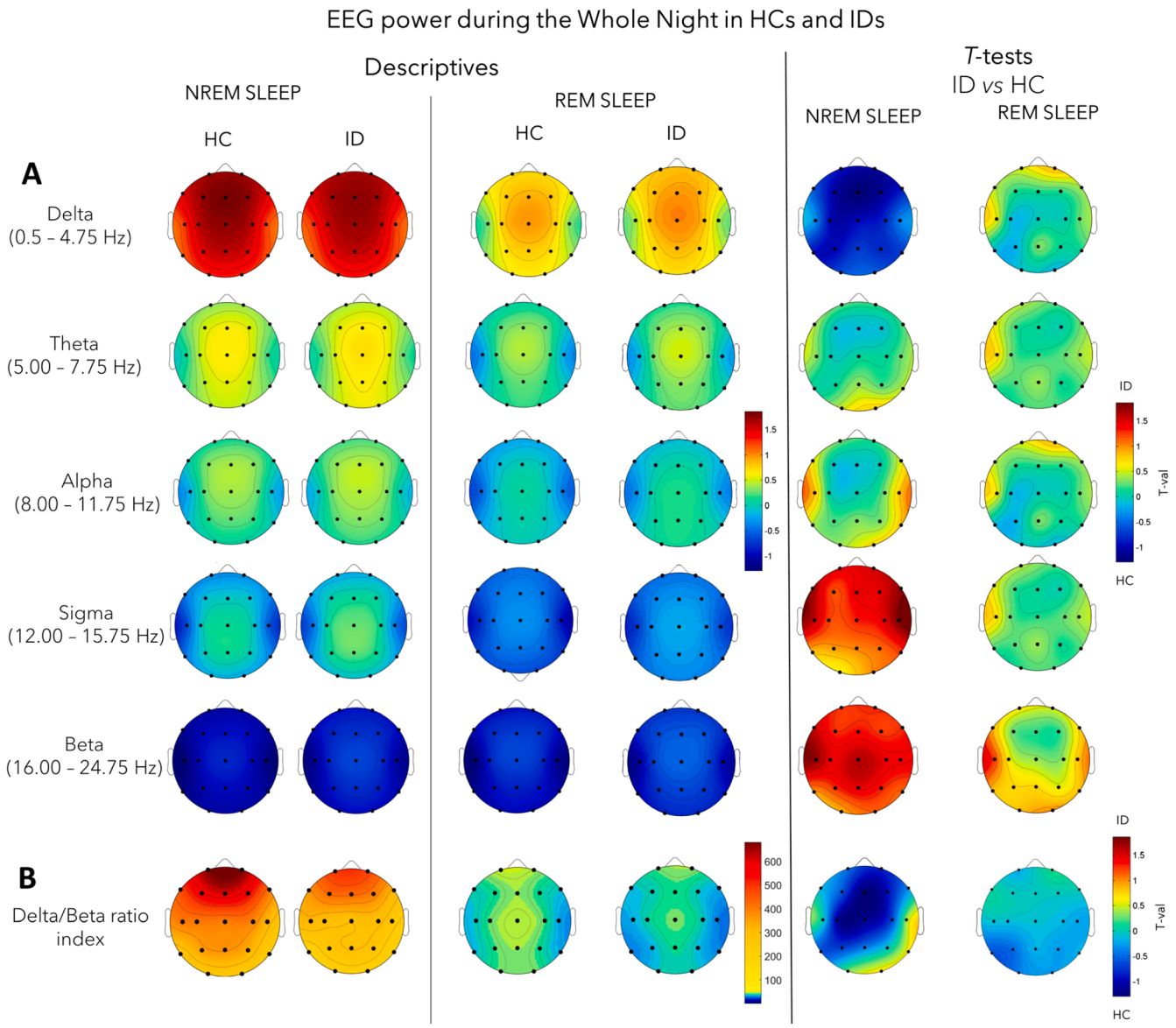

Fig. 4. Topographical scalp maps of the log-transformed absolute EEG power during NREM and REM sleep in HCs ($n = 18$) and IDs ($n = 20$). The maps are scaled between minimal and maximal values calculated for all the derivations in both groups. The maps are based on the 19 unipolar EEG derivations of the international 10 – 20 system with averaged mastoid reference (electrode positions indicated by black dots). Maps are plotted for the following EEG bands: (A) Delta (0.5 – 4.75 Hz); Theta (5.00 – 7.75 Hz); Alpha (8.00 – 11.75 Hz); Sigma (12.00 – 15.75 Hz); Beta (16.00 – 24.75 Hz), and (B) the delta/beta ratio index. The results of the *t*-test on each frequency band for each scalp derivation. Values are expressed in *t*-values: positive *t*-values indicate the prevalence of the ID groups and vice versa. Values are color-coded and plotted at the corresponding position on the planar projection of the scalp surface.

5.5. Correlations between the TSTm and electroencephalographic frequency topography during the whole night

In order to explore the relationship between the SSM and brain EEG activity during the whole sleep, the coefficients of linear correlations (Person's r) were calculated between the TSTm and the 5 canonical frequency bands and delta/beta ratio during the whole night. Correlational analyses were performed separately for the entire sample of HC participants ($n = 18$) and ID patients ($n = 20$), and in the subsamples of HC –TSTm ($n = 18$) and ID +TSTm ($n = 13$).

Considering the whole sample of HC participants and ID patients, significant negative correlations were found exclusively between the TSTm and the delta/beta ratio index during the NREM sleep, both considering the two groups together and separately ($r \geq$ - 0.403; critic p after FDR correction = 0.034). As reported in Fig. 8B (left column) and S2, the higher underestimation of the oTST was related to a diffuse decrease of the delta band relative to the beta considering the two groups together (i.e., in Fig. S2 A, HCs in blu and ID in orange) and the ID patients sample, and with an anterior topographic pattern (i.e., Fp1, Fp2, F7, F3, Fz, F4, C3, Cz) in HC participants (See Table S5).

Moreover, considering the subsample of HC normoestimators and ID misperceptors, significant negative correlations ($r \geq$ - 0.418; critic p after FDR correction = 0.018) were found between the TSTm index and the delta power during the whole NREM sleep for the entire sample but not for the two sub-groups separately. Specifically, as illustrated in Fig. 8A and S3, the higher underestimation of the oTST was significantly correlated to the NREM delta power decreased, with an anterior topographic pattern (i.e., Fp1, Fp2, F3, Fz, F4, F8, Cz) (Table S6).

Moreover, other significant negative correlations were found between the TSTm index and the delta/beta ratio during the whole NREM and REM sleep. Considering NREM sleep, significant negative correlations emerged for the entire sample and for the two sub-groups

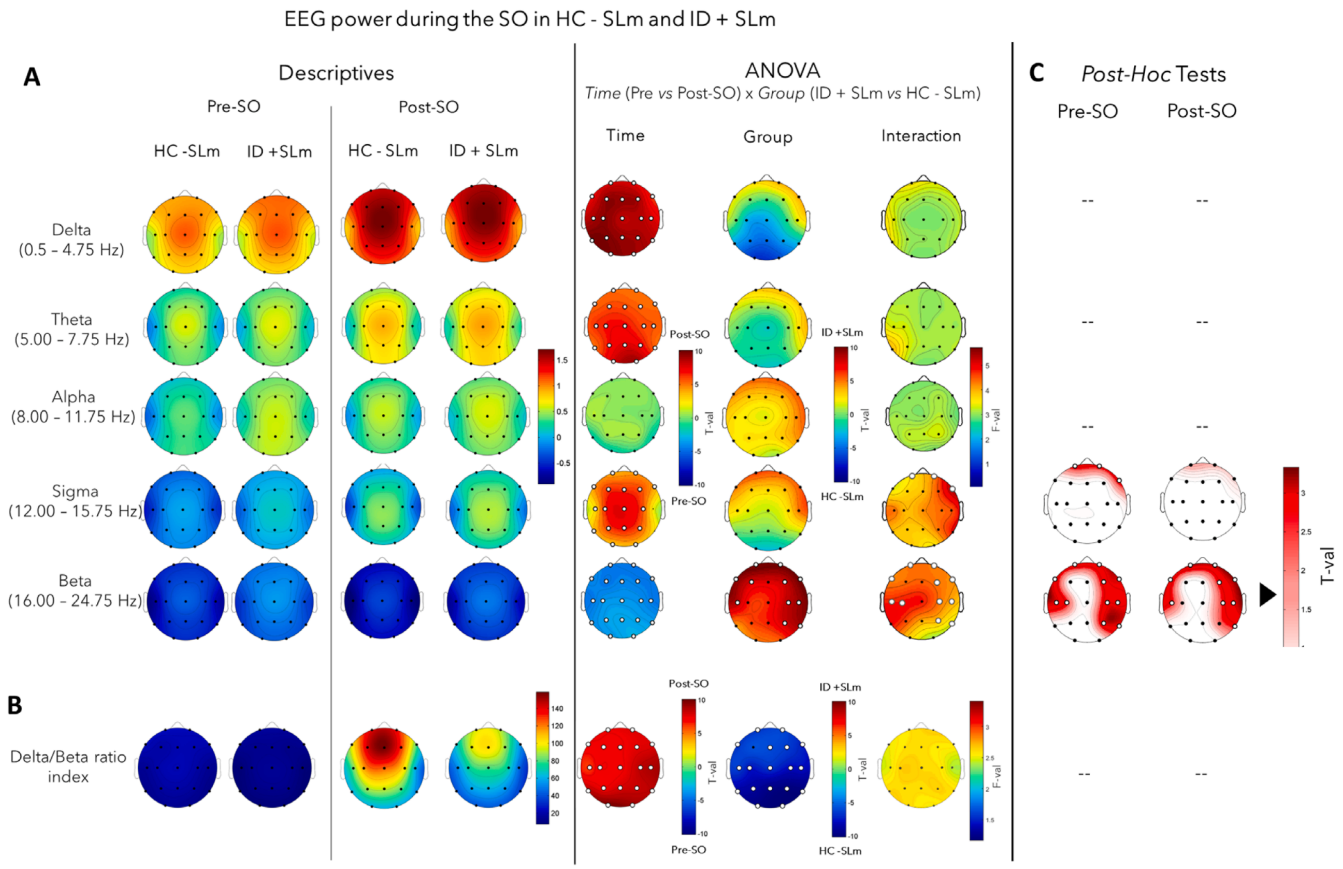

Fig. 5. Topographical scalp maps of the log-transformed absolute EEG power in the 5-minute intervals before and after the SO in HC normoestimators ($n = 15$) and ID overestimators ($n = 7$). The maps were scaled between minimal and maximal values calculated for all the derivations in Pre- and Post-SO in both groups. The maps are based on the 19 unipolar EEG derivations of the international 10 – 20 system with averaged mastoid reference (electrode positions indicated by black dots). Maps are plotted for the following EEG bands: (A) delta (0.5 – 4.75 Hz); theta (5.00 – 7.75 Hz); alpha (8.00 – 11.75 Hz); sigma (12.00 – 15.75 Hz); beta (16.00 – 24.75 Hz), and (B) on the delta/beta ratio index. In the right column are shown results of the two-way mixed ANOVA on each frequency band (A) and on the delta/beta ratio index (B) for each scalp derivation, with *Time* (Pre- vs. Post-SO) as the within-subject factor, and *Groups* (ID +SLm vs HC –SLm) as the between-subject factor. Results for the main effects of *Time* and *Groups* are expressed in *t*-values corresponding to the original *F*-values, aiming to highlight the direction of differences. The sign of each *t*-value was defined by the differences between the mean values of the levels of each factor. Results for the effect of the interaction are expressed in *F*-values. White dots indicate significant differences after the FDR correction different for the 5 canonical frequency bands (*Time* effect: critic $p = 0.001$; *Groups* effect: critic $p = 0.023$; *Interaction* effect: critic $p = 0.024$) and for the delta/beta ratio index (*Time* effect: critic $p = 0.001$; *Groups* effect: critic $p = 0.040$). (C) *Post-hoc t*-tests were performed on the sigma and beta bands during the 5 min Pre- and Post-SO. Colored areas index the derivations in which post hoc analyses were performed. The red color highlights the presence of significant differences ($p \leq 0.05$) indexed by the arrow near the color bar and the white dots.

separately ($r \geq -0.424$; critic p after FDR correction $= 0.040$). Indeed, as illustrated in Fig. 8B and S2, the higher TST underestimation was significantly correlated to the decreased delta/beta ratio index during NREM sleep at all scalp derivations for the whole sample and for the ID patients +TSTm, and with an anterior topographical pattern (i.e., Fp1, Fp2, F7, F3, Fz, F4, T7, C3, Cz) in HCs –TSTm (Table S7). On the other hand, as shown in Fig. 8C and S4, results considering REM sleep show significant negative correlations ($r \geq -0.372$; critic p after FDR correction $= 0.040$) for the entire sample in a single cortical derivation (i.e., T7), and exclusively in the ID sample +TSTm in frontal and central cortical derivations (i.e., F7, F3, Fz, F4, C3, C4) (Table S7).

6. Discussion

What sleep-related physiological processes return in the subjective experience of sleep? How to explain the SSM phenomenon in ID? These points have long been unanswered, and our study aimed to address such questions. Specifically, the present study highlighted the absence of significant differences in EEG topographical features across the wake-sleep transition and the whole night when comparing ID patients and HCs, despite a tendency of decreased SWA and increased faster frequencies in ID patients, which does not reach statistical significance. However, considering the SSM phenomenon, our results showed that ID patients who significantly overestimated their SL (i.e., ID +SLm) were characterized by greater sigma and beta activity in anterior and temporo-parietal sites during the SO period compared to HC without SLm. We also found that IDs underestimating TST (i.e., ID +TSTm) showed a diffuse lower absolute NREM delta power and lower delta/beta power, during NREM and REM sleep. Moreover, this is the first study describing the complete topography of the EEG power correlation with the SSM phenomenon during the wake-sleep transition, showing that the higher SSM significantly correlates to a lower delta/beta ratio index during the 5 min following the SO. Moreover, we extend and confirm previous evidence (St-Jean et al., 2013; Maes et al., 2014; Hsiao et al., 2018; Lecci et al., 2020; Stephan et al., 2021; Xu et al., 2022) showing that the higher underestimation of the TST reported by ID patients is related to a state of cortical hyperarousal, both during NREM and REM sleep. In addition, our correlational analyses between frequency bands and SSM indices, performed both in the whole sample of ID and HC and in the subsamples of ID misperceptors and HC normoestimators, showed that the findings of decreased delta/beta ratio index during the SO and the NREM sleep remain stable into the two clustered samples. On the other hand, the relation between the TST underestimation and the decreased of the delta band during NREM

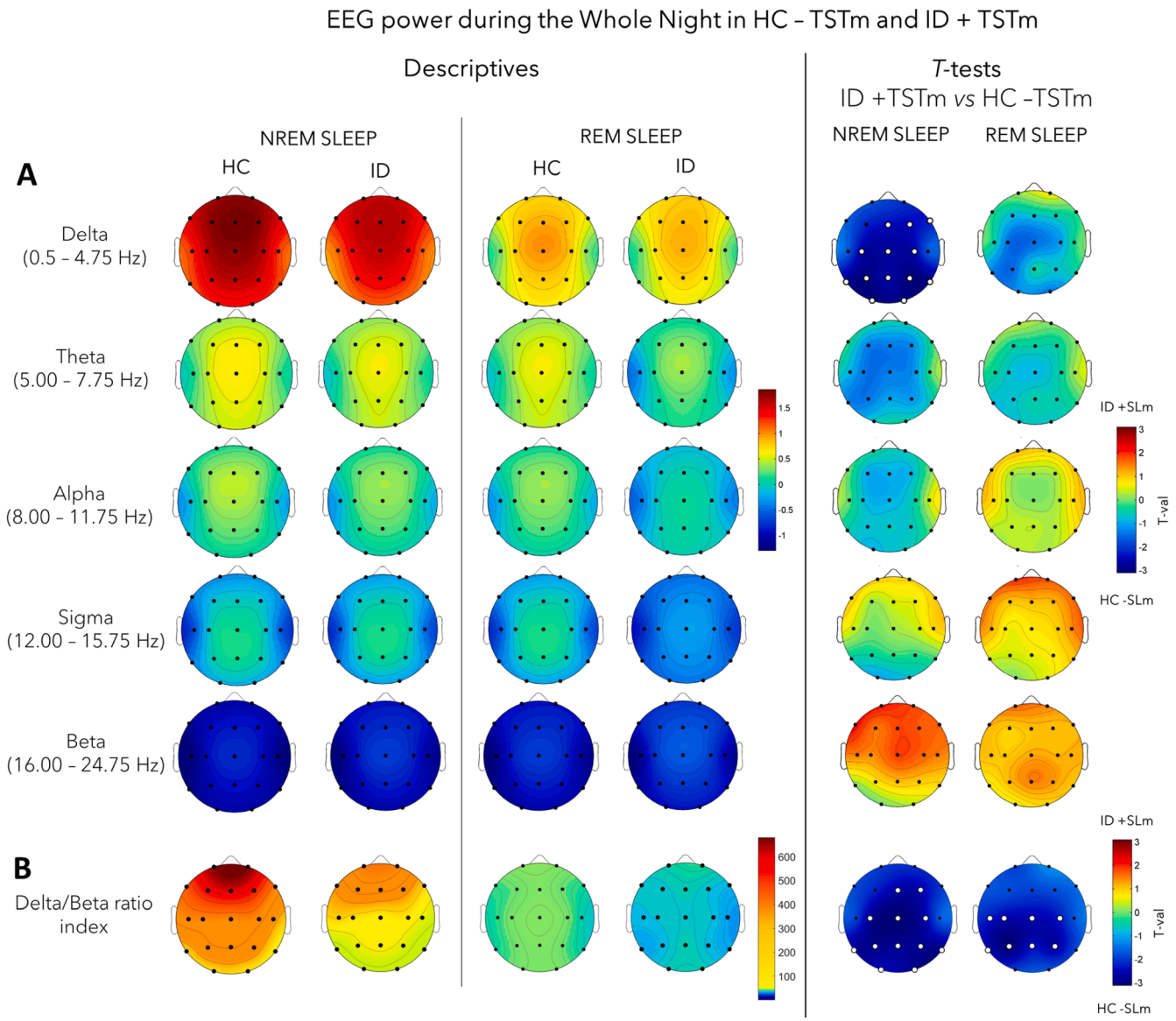

Fig. 6. Topographical scalp maps of the log-transformed absolute EEG power during NREM and REM sleep during the whole night in HC –TSTm ($n = 18$) and ID +TSTm ($n = 13$). The maps were scaled between minimal and maximal values calculated for all the derivations in both groups. The maps are based on the 19 unipolar EEG derivations of the international 10 – 20 system with averaged mastoid reference (electrode positions indicated by black dots). Maps are plotted for the following EEG bands: (A) delta (0.5 – 4.75 Hz); theta (5.00 – 7.75 Hz); alpha (8.00 – 11.75 Hz); sigma (12.00 – 15.75 Hz); beta (16.00 – 24.75 Hz), and (B) on the delta/beta ratio index. In the right column, the *t*-test results on each frequency band (A) and on the delta/beta ratio index (B) for each scalp derivation are shown. Values are expressed in *t*-values: positive *t*-values indicate the prevalence of the ID underestimator group and vice versa. Values are color-coded and plotted at the corresponding position on the planar projection of the scalp surface. White dots indicate significant differences after the FDR correction applied on the NREM delta band (critic $p = 0.035$) and on the NREM and REM delta/beta ratio index (critic $p = 0.034$) separately.

sleep, and the decreased of delta/beta ratio index during REM sleep, emerge exclusively in the misperceptors subsample.

In synthesis, changes in EEG activity highlighted in the present study and summarized in a state of cortical hyperarousal, following the main pathogenetic model of ID (Perlis et al., 1997; Riemann et al., 2010), can be interpreted as the electrophysiological substrate of the SSM phenomenon. Interestingly, our first analysis considering the whole sample of ID patients and HCs, without considering the SSM degree, showed no significant difference in the EEG activity during the SO or the whole NREM sleep. Conversely, changes in EEG activity arose in the analyses performed comparing misperceptors ID patients and normoestimators HC, suggesting that the hyperarousal is directly related to the SSM associated with ID. This relation between SSM and cortical hyperarousal is consistent with changes in macrostructural sleep indices, showing that exclusively in the presence of SSM, ID patients reported significantly lower SWS and higher cortical arousals during the PSG recording night. It is worth noting that, at odds with our findings, most studies conducted in the last 20 years point to a state of cortical hyperarousal during NREM sleep characterizing ID aspecific for misperception conditions (Merica et al., 1998; Perlis et al., 2001; Israel et al., 2012; Spiegelhalder et al., 2012; Riedner et al., 2016; Rezaei et al., 2019). Nevertheless, all these studies, showing NREM sleep characterized by higher EEG frequencies in ID patients compared to HCs, have methodological limitations (i.e., results not corrected for multiple comparisons) reducing the consistency of these findings. On the other hand, according to results reported by Bastien and collaborators (2003), the absence of significant differences between patients and HCs arose in our study is likely due to the drug-free nature of our clinical sample. Indeed, Bastien showed the absence of significant differences in NREM sleep EEG spectral features between ID patients without pharmacological treatment compared to HCs. On the

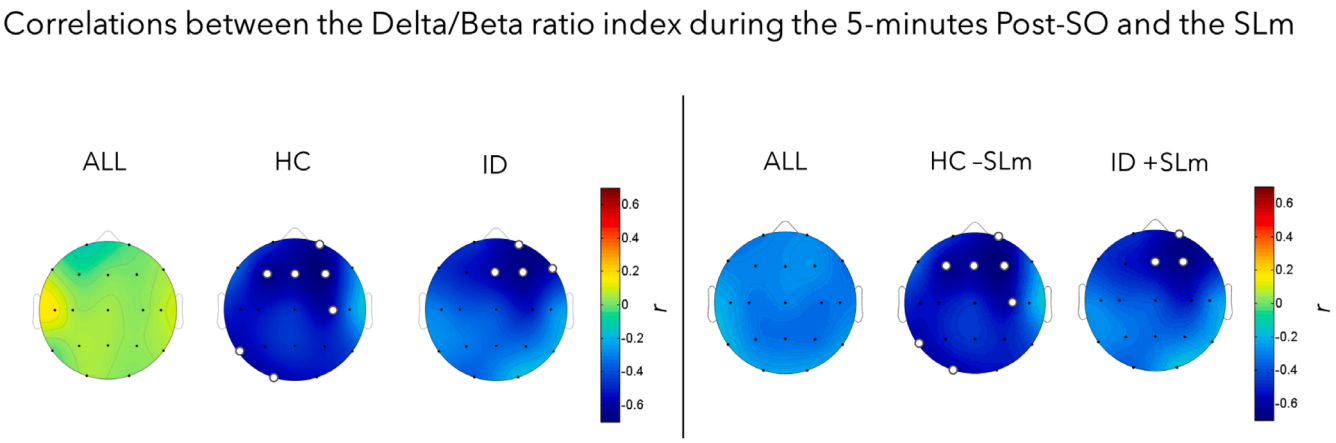

Fig. 7. The topographical distribution of correlation values (Person's r) between the SLm index and the Delta/Beta ratio index during the 5-minute Post-SO interval in the whole sample of HC ($n = 18$) and ID ($n = 20$) in the left column, and in the subsamples of HC –SLm ($n = 13$) and ID +SLm ($n = 7$) in the right column. In order to uniform the direction of the correlations with the TSTm index, the SLm formula applied for correlation analyses was inverted (i.e., $\frac{oSL}{sSL} * 100$). Values are expressed in terms of *r* values: positive values indicate the presence of a positive correlation and vice versa. The alpha level was adjusted to 0.011 after FDR correction for both samples.

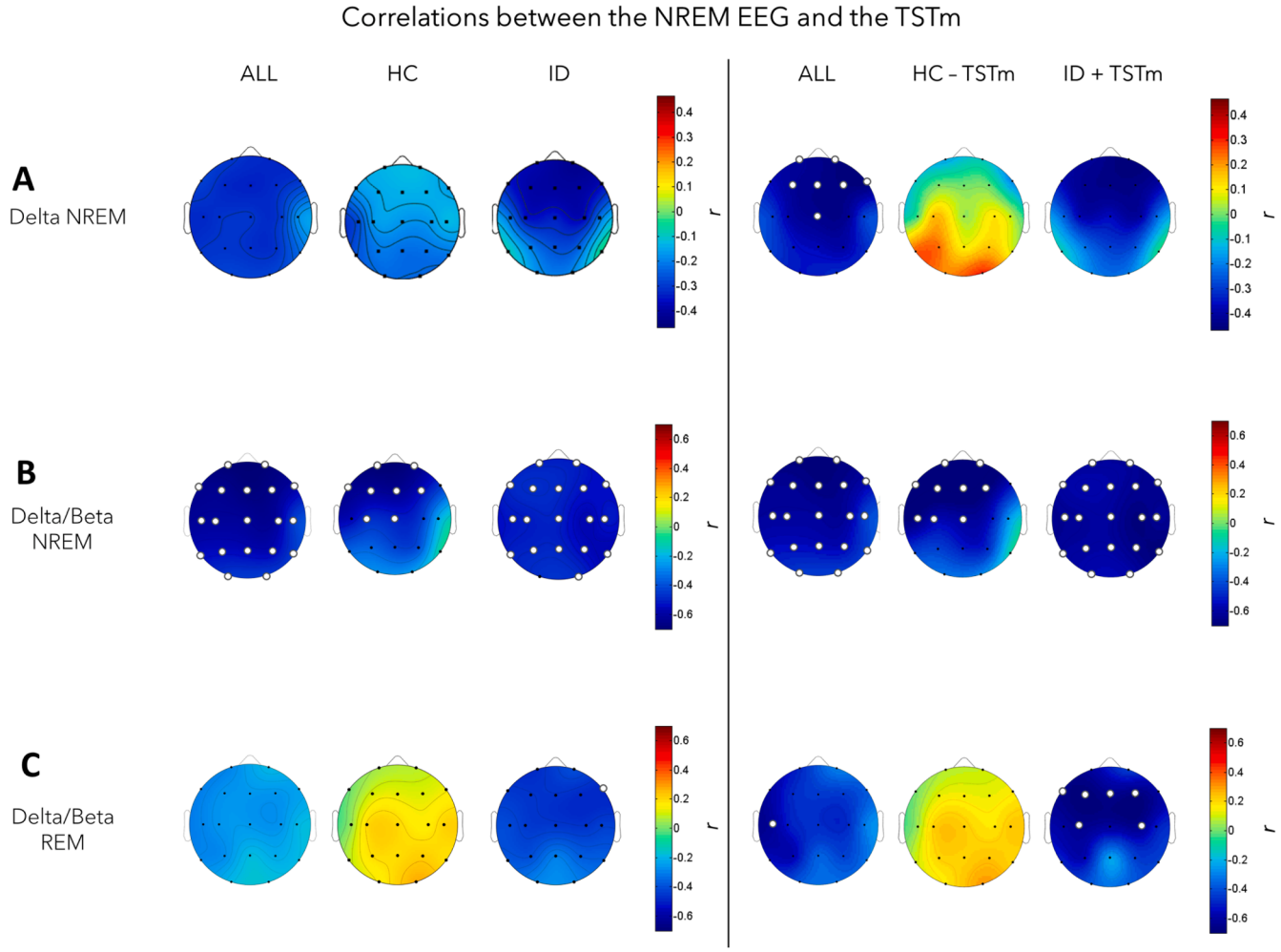

Fig. 8. The topographical distribution of correlation values (Person's r) between the TSTm index and (A) the delta power, (B) the delta/beta ratio index during NREM and (C) REM sleep in the whole sample of HC ($n = 18$) and ID ($n = 20$) in the left column, and in the subsamples of HC –TSTm ($n = 18$) and ID +TSTm ($n = 13$) in the right column. Values are expressed in terms of *r* values: positive values indicate the presence of a positive correlation and vice versa. White dots indicate significant correlations after the FDR correction (delta NREM: critic $p = 0.018$; delta/beta NREM in the whole sample: critic $p = 0.034$; delta/beta NREM and REM in the subsample: critic $p = 0.040$).

other hand, ID patients with benzodiazepine medication showed heightened faster EEG frequency compared to healthy subjects (Bastien et al., 2003). In this view, our findings suggest that cortical hyperarousal may be prominent in the ID phenotype characterized by SSM.

Furthermore, in accordance with our hypothesis, the main finding of the present study was the negative association between the SSM degree (both during the SO and the whole sleep) and the delta/beta ratio index. This is the first topographical evidence of a univocal relationship between the SSM phenomenon and a pattern of cortical arousal during the wake-sleep transition period. Moreover, according to previous literature (St-Jean et al., 2013; Maes et al., 2014; Hsiao et al., 2018; Lecci et al., 2020; Stephan et al., 2021; Xu et al., 2022), these results highlighted that the higher overestimation of the sleep-wake transition period, and the higher underestimation of the TST, are both cognitive phenomena related to the increase of faster and decrease of slower cortical activities. From a functional perspective, faster and slower frequencies are associated with firing- and off-periods of neural activity, respectively. Specifically, rapid frequencies in the range of the beta band reflect a status of autonomic and cortical arousal (Kuo et al., 2016), while SWA is associated with lower brain information integration and with the fading consciousness in the brain characterizing sleep (Tononi, 2008). In this line, our findings indicate that an imbalance between cortical fast and slow frequencies could result in the subjective sleep experience, explaining the SSM phenomenon.

Our results highlighted the topographical features of EEG activity differences between normoestimators HC and misperceptors ID patients. Considering the SO period, according to previous evidence in the general population (Hsiao et al., 2018), we found that ID patients who overestimated their SL were characterized by increased pre-frontal and frontal sigma and beta activities, this last also spreads in central and parietal cortical areas during the 5 min preceding sleep. Moreover, the SL overestimation was significantly related to a decreased delta/beta ratio index during the 5 min Post-SO in the prefrontal and frontal cortices. Prefrontal and parietal regions are involved in attentional processing. Specifically, the prefrontal and frontal lobes play a critical role in executive and control functions (Rossi et al., 2009); on the other hand, the parietal cortex has been associated with sensory integration processes and cognitive functions (Freedman and Ibos, 2018). These two areas constitute the Fronto-Parietal Network (FPN), responsible for cognitive control (Dosenbach et al., 2008), working memory, and top-down goal-directed control processes (Koechlin and Summerfield, 2007). Accordingly, our EEG findings might suggest that sustained high frequencies in these areas during the SO associated with the overestimation of the SL may explain the increased cognitive control during the SO, involving higher levels of information processing and returns in the subjective feeling of wake instead of sleep.

Moreover, our results showed a diffuse decrease of slow frequencies (i.e., delta power and delta/beta ratio index) in misperceptors ID patients compared to normoestimators HC during NREM and REM sleep, which involved all scalp regions. Furthermore, considering NREM sleep, this decrease was related to the SSM degree, with a specific topographical pattern in the two groups. Indeed, the TSTm index was specifically related to the prefrontal and frontal decrease of the delta/beta ratio index in HCs. Conversely, in ID patients, this relationship also affected posterior cortical areas. Even if the low density of our EEG does not provide high spatial resolution, these findings are in line with high-density EEG (Lecci et al., 2020; Stephan et al., 2021) and neuroimaging (Kay et al., 2017; Li et al., 2022) evidence showing that altered activity affecting specifically posterior scalp regions are involved in the SSM phenomenon in ID patients. Accordingly, posterior and parietal cortices are crucially implicated in the arousal system and awareness processes (Laureys et al., 2004; Vogt and Laureys, 2005; Boly et al., 2008; Leech and Sharp, 2014). Specifically, the posterior cingulate cortex activity is altered (i.e., reduced functional connectivity) in states of deep sedation (Fiset et al., 1999) and depends on modifications of consciousness associated with sleep (Horovitz et al., 2008; Samann et al., 2011). Posterior regions, including somatosensory areas and the FPN, are considered critical "*hot zones*" involved in the consciousness experience during sleep (Koch et al., 2016; Siclari et al., 2017), further corroborating the relationship between the SSM phenomenon and the cortical hyperarousal, specifically in posterior regions, observed in our results. Indeed, the decreased SWA in the posterior "*hot zone*" region observed in misperceptors ID as an indicator of cortical hyperarousal, showing a strong relationship with the SSM, may result in a state of heightened awareness during sleep that returns in the SSM phenomenon. Moreover, our findings showed that this posterior "*hot zone*" in ID misperceptor patients is characterized during REM sleep by decreased slow frequencies relative to the faster ones (i.e., the delta/beta ratio index). The topographical distribution of slow waves during NREM and REM sleep is functionally relevant and corresponds to different levels of arousal system activation (Ferrara and De Gennaro, 2011; Bernardi et al., 2019). On the other hand, we showed for the first time a significant relationship between the higher SSM in misperceptors ID and decreased delta/beta ratio index during REM sleep, that involved specifically frontal and central scalp sites. Few studies in the literature showed EEG spectral features during REM sleep underlying ID and specifically the SSM. A "restless REM sleep" pathway, characterized by elevated phasic events during REM sleep (i.e., as correlates of arousal), is the main model recognized to explain ID symptoms and discrepancies between objective and subjective sleep (Feige et al., 2008; Riemann et al., 2012). PSG macrostructural evidence showed a crucial involvement of REM sleep in the SSM phenomenon, which is perceived and memorized by individuals as wake instead of sleep, and exacerbated by ID conditions (Feige et al., 2008). Our findings extend this evidence, emphasizing that the qualitative and quantitative properties of REM sleep, in terms of decreased delta/beta ratio index in frontal and central scalp sites, are strongly related to the SSM phenomenon. REM sleep is characterized by electrophysiological (i.e., faster EEG frequencies) and cognitive processes (i.e., thought-like mentation) similar to a waking state, and the decreased slow frequencies relative to the faster associated with the higher SSM in ID +TSTm sub-sample would explain the bias in sleep perception and memorization that return in the SSM phenomenon. This finding is in line with multiple awakenings evidence showing that ID patients have the predisposition to report a feeling of being awake when they are awakened from an objective REM sleep stage, unlike good sleepers for which objective and subjective sleep coincide (Stepahn & Siclari 2023).

Our findings fit well with the recent conceptualization of SSM advanced by Stephan and Siclari (2023). For several years the SSM clinically observed in ID patients did not have an objective and physiological correlate useful to explain this phenomenon. However, at present, the use of high-resolution techniques able to characterize topographical aspects of sleep, and the recourse to methods to phenotype Insomnia (i.e., sub-typing ID patients according to the misperception degree, within-subject correlations) has allowed to disclose patterns of brain activity related to the subjective feeling of being awake. This enables a theoretical shift from the past, from a conceptualization of SSM based on PSG and sleep macrostructure analyses to a wake intrusion era that characterizes the present and should be developed in the future (Stephan and Siclari 2023).

Taken together, these results may be helpful from a clinical standpoint. Indeed, the possibility of clarifying the specific contribution of physiological mechanisms to the SSM phenomenon could help design specific interventions to modulate SSM in ID patients, reducing the perception of inadequate sleep. SSM-related peculiarities in the topographical expression of the sleep EEG features in ID patients may be considered a possible target for novel non-invasive brain stimulation techniques used to modulate wake and sleep electrophysiology and, in turn, the level of sleep pressure and arousal (Annarumma et al., 2018; Gorgoni et al., 2020). On the other hand, electrophysiological changes related to the SSM, especially during the SO, may be considered in Cognitive Behavioral Therapy for Insomnia (CBT-I) interventions. Indeed, a recent randomized control trial showed that sleep restriction

therapy, which represents the core CBT-I intervention, increased delta power and decreased beta power, manipulating the homeostatic sleep drive (Maurer and Kyle, 2022). In this line, other therapeutic components of CBT-I, such as relaxation and mindfulness training, could affect the brain arousal system, promoting the lowering of the fastest frequencies and improving the subjective experience of sleep quantity and quality (Maurer and Kyle, 2022; Dressle et al., 2023).

From a methodological point of view, this study presents some strengths linked to accurate procedural choices. Indeed, the patients' selection followed strict inclusion/exclusion criteria by selecting drug-free ID patients from the clinical population of a tertiary center. Moreover, the experimental conditions were kept identical in the ID patients and HC groups. The PSG recording for all participants has been conducted at their homes to avoid the first-night effect, which is typically associated with the experience of sleeping in the novel environment of a laboratory. On the other hand, this work has several limitations. The first limitation regards the relatively low sample size, specifically for analyses focused on the between-group differences and correlations related to the SSM. Indeed, we chose to split our whole initial sample of 18 HC and 20 ID patients, based on the sole extreme misperceptors patients and normoestimators HC participants. Even though this choice affects the statistical power of the results, it allows us to characterize the SSM phenomenon considering exclusively patients that strongly misperceive their sleep times. A second limitation regards the presence of three outliers in the ID patients group that largely overestimated the oSL, without which the between-groups differences in the SLm index disappear. This statistical issue may be due to the high intersubject variability in the subjective SL estimation, also reflected in the standard deviation values. However, we have chosen to keep this analysis without removing it from our work, as it is an index that refers to a particular phenomenon such as the SSM in which subjects may report extreme values. Moreover, the interpretation of topographic results, both regarding between-group differences and correlational results, are limited by the low number of electrodes that limits our possibility to make inferences about local sleep changes mediated by the SSM phenomenon. In conclusion, a limitation is the lack of analyses on the cortical dynamics (i.e., functional connectivity during sleep) proper to study altered brain networks underlying SSM in ID. In this line, future studies should apply those levels of analysis to show the complexity of SO and sleep processes as a functional coordination of a cortical fronto-posterior network.

7. Conclusion

The relationship between the topographical EEG changes and the SSM phenomenon during the SO and NREM sleep was explored in ID patients and HCs. The main finding of the present study suggests that the higher SL overestimation and the higher TST underestimation are two phenomena related to a diffuse cortical hyperarousal that may be interpreted as the electrophysiological correlate of the SSM, both during the SO and the whole night. Indeed, the decreased delta/beta ratio index may be interpreted as the sleep state-independent fingerprint of the SSM phenomenon in ID patients, characterizing the SO process, NREM, and REM sleep.

Considering the present findings, assessing topographical sleep EEG features is essential to better understand the neural basis of sleep function, arousal-related processes, and state transitions. Starting from these premises, this study has been designed to provide a thorough description of the electrophysiology associated with different SSM measures, and the proposed methodology would strongly improve knowledge on the neural basis of SSM.

CRediT authorship contribution statement

Elisabetta Fasiello: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maurizio Gorgoni:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Andrea Galbiati:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Marco Sforza:** Writing – review & editing. **Francesca Berra:** Writing – review & editing. **Serena Scarpelli:** Writing – review & editing. **Valentina Alfonsi:** Writing – review & editing. **Ludovica Annarumma:** Writing – review & editing, Formal analysis. **Francesca Casoni:** Resources. **Marco Zucconi:** Resources. **Vincenza Castronovo:** Resources. **Luigi Ferini-Strambi:** Writing – review & editing, Supervision, Resources. **Luigi De Gennaro:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the absence of financial interests/personal relationships which may be considered as potential competing interests.

Data availability

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