

## INSOMNIA

# Wake High-Density Electroencephalographic Spatospectral Signatures of Insomnia

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**Study Objectives:** Although daytime complaints are a defining characteristic of insomnia, most EEG studies evaluated sleep only. We used high-density electroencephalography to investigate wake resting state oscillations characteristic of insomnia disorder (ID) at a fine-grained spatospectral resolution.

**Methods:** A case-control assessment during eyes open (EO) and eyes closed (EC) was performed in a laboratory for human physiology. Participants (n = 94, 74 female, 21–70 y) were recruited through [www.sleepregistry.nl](http://www.sleepregistry.nl): 51 with ID, according to DSM-5 and 43 matched controls. Exclusion criteria were any somatic, neurological or psychiatric condition. Group differences in the spectral power topographies across multiple frequencies (1.5 to 40 Hz) were evaluated using permutation-based inference with Threshold-Free Cluster-Enhancement, to correct for multiple comparisons.

**Results:** As compared to controls, participants with ID showed less power in a narrow upper alpha band (11–12.7 Hz, peak: 11.7 Hz) over bilateral frontal and left temporal regions during EO, and more power in a broad beta frequency range (16.3–40 Hz, peak: 19 Hz) globally during EC. Source estimates suggested global rather than cortically localized group differences.

**Conclusions:** The widespread high power in a broad beta band reported previously during sleep in insomnia is present as well during eyes closed wakefulness, suggestive of a round-the-clock hyperarousal. Low power in the upper alpha band during eyes open is consistent with low cortical inhibition and attentional filtering. The fine-grained HD-EEG findings suggest that, while more feasible than PSG, wake EEG of short duration with a few well-chosen electrodes and frequency bands, can provide valuable features of insomnia.

**Keywords:** high density EEG, power spectrum, resting-state, insomnia, alpha oscillation, beta oscillation, wakefulness, hyperarousal

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## Significance

Whereas round-the-clock hyperarousal is considered characteristic of insomnia, its representation in wake EEG is insufficiently known. We compared the spatospectral properties of high-density wake EEG of 51 people with insomnia and 43 matched controls without sleep complaints. Just as previously reported during sleep, people with insomnia show widespread increased beta power during eyes closed wakefulness. During eyes open, their EEG moreover shows relatively little power in a narrow band in the upper-alpha range. The low correlation between these two features suggests they may reflect distinct processes, respectively high arousal and low inhibition. Future studies may employ these measures to evaluate subtypes of insomnia and relevance for variability in profiles of complaints about sleep and daytime functioning.

## INTRODUCTION

Insomnia is characterized by poor sleep quality, including problems initiating or maintaining sleep, early morning awakening, and nonrestorative sleep.<sup>1</sup> It is accompanied by daytime repercussions<sup>1,2</sup> on mood,<sup>3</sup> energy, and memory,<sup>4</sup> and is among the most common health complaints,<sup>5</sup> affecting approximately 6% of the adult population in its chronic form. Chronic insomnia carries an increased risk of severe, long-lasting health problems, including cardiovascular<sup>6,7</sup> and mood<sup>8</sup> disorders.

Generalized hyperarousal plays a key role in the pathway of the cognitive and behavioral factors leading to chronic insomnia,<sup>9,10</sup> according to recent developments of the neurocognitive model.<sup>11–13</sup> Evidence of hyperarousal has been found across the sleep-wake cycle<sup>12,14</sup> and in the somatic, cognitive, and neurobiological domains,<sup>11</sup> leading to the hypothesis that insomnia is maintained by a continuous, multi-component hyperarousal. Hyperarousal of the central nervous system may result from an imbalance between wake and sleep promoting systems,<sup>10</sup> but could also arise from other structural and functional deviations in emotion and reward regulation systems, interfering with the normally cycling expression of sleep and wakefulness.<sup>15</sup> Local reductions in gray matter volume in the

orbitofrontal cortex have been reported in association with insomnia,<sup>16–18</sup> with sleep fragmentation<sup>19</sup> and with the vulnerability for early morning awakening.<sup>20,21</sup> Given the role of the orbitofrontal cortex in updating the reward value of internal and external stimuli according to the current homeostatic needs, reduced gray matter volume may be involved in the deficient sensing of comfort that has been reported in association with insomnia.<sup>22</sup> Insufficient sensing, integration, and updating of hedonic signals may lead to a reduced orbitofrontal output to the caudate nucleus, a major projection area with an important role in dampening cortical arousal.<sup>23</sup> In accordance with the round-the-clock occurrence of hyperarousal,<sup>9</sup> signatures of hyperexcitability and lack of inhibition are not restricted to the sleep period. Transcranial magnetic stimulation (TMS)-induced hyperexcitability was found to be a trait-like daytime characteristic of insomnia<sup>24</sup>; event-related potentials (ERP) studies revealed signatures of cortical hyperexcitability, during wakefulness<sup>25,26</sup> and sleep onset,<sup>27,28</sup> and signatures of inhibitory deficits, during wakefulness,<sup>28,29</sup> sleep onset,<sup>27,28</sup> and sleep.<sup>29</sup> Accordingly, for a physiological understanding of insomnia it seems of value to focus on the balance between excitatory and inhibitory processes.<sup>30,31</sup>

**Table 1**—Summary of findings in insomnia based on power spectral analysis of the wake electroencephalography.

Study	Participants	Setting	Findings (case vs. control)	Electrodes	Power Spectral Analysis
Wu et al. 2013 <sup>89</sup>	50 PI, 32 controls	Evening EC	NS	C3, C4, Ref: A1+A2	Abs 1 Hz bin, 0.5–32 Hz range
Corsi-Cabrera 2012 <sup>36</sup>	10 young PI, 10 young controls	Wake epochs during the wake to sleep transition period	More frontal beta power, more frontoparietal coupling within beta and gamma	19 electrodes, 10-20 system, Ref: average. Source estimation: VARETA	Abs, beta (17–30 Hz), gamma (31–45 Hz)
Wolynczyk-Gmaj and Szelenberger 2011 <sup>38</sup>	36 PI, 29 controls	First 2 min of 4 sessions from the multiple sleep latency test	Less theta (4–8 Hz), more beta (18–30 Hz)	Average of Fp1, Fp2, Fpz, Ref: between Fz and Cz	Rel, 7 bands (delta, theta, alpha, beta1, beta2, beta3), 1–30 Hz range
Buckelew et al. 2009 <sup>90</sup>	20 students, poor vs. good sleep (n = NR)	EO, EC, audio-listening, mental operation	Sustained theta, not suppressed from EC to task	Cz, Ref: bilateral earlobes	Abs theta (4–8 Hz), beta (13–21 Hz)
Freedman 1985 <sup>35</sup>	12 sleep-onset PI, 12 controls	EO seated, EC in bed	Less alpha (9 Hz), more beta (26–30 Hz in EO, 21 Hz in EC)	C3, O1, Ref: A2	Abs, 1 Hz bin, 0.5–30 Hz range
Hauri 1981 <sup>39</sup>	10 self-reported insomniacs, 10 controls	2 wake noontime sessions	Less SMR	C3, Ref: A2	Abs SMR (12–14 Hz)

PI, primary insomnia; Abs, absolute band power; EC, eyes closed; EO, eyes open; NS, not significant; NR, not reported; Ref, reference; Rel, band power relative to total power; SMR, sensorimotor rhythm.

Currently, insomnia disorder is defined exclusively by subjective reports.<sup>1</sup> A meta-analysis of the sleep macrostructural alterations of insomnia, assessed through polysomnography (PSG)-derived measures, indicates fragmented sleep, reduced slow wave sleep (SWS), and rapid eye movement (REM) sleep.<sup>32</sup> The quantification of the sleep microstructural alterations of insomnia, assessed through power spectral analysis of the sleep electroencephalography (EEG), revealed elevated high-frequency power, a signature of cortical hyperarousal.<sup>33,34</sup> Moreover, power spectral analysis of the wake EEG may also reveal mechanisms of insomnia, because it is known to be a sensitive method to observe cortical dynamics reflecting excitatory and inhibitory processes, related to cognition and vigilance states. A few studies have analyzed the spectrum of wake epochs, recorded before the onset and after the offset of sleep, and consistently found enhanced high frequency power.<sup>35–37</sup>

Other than these wake EEG epochs during recordings in bed, the resting state during wakefulness has received little attention in insomnia research, and the findings have been inconsistent (for an overview, see Table 1). The overall picture of insomnia abnormalities, emerging from the positive findings obtained in these studies, is that of elevated high-frequency spectral power, in a broad beta frequency range,<sup>35,36,38</sup> and decreased low-frequency spectral power, observed in the 4–8 Hz band,<sup>38</sup> at 9 Hz,<sup>35</sup> and in the 12–14 Hz band.<sup>39</sup> Plausible reasons for the poor reproducibility of the findings include small sample sizes, different inclusion criteria, and possible heterogeneity of participants within the studies.

In order to resolve the inconsistencies and gain a better understanding of the wake resting-state brain activity in

insomnia disorder (ID), we undertook a study of adequate sample size, with stringent inclusion criteria, in a standardized setting for data acquisition. We then performed a thorough analysis of the fine-grained spatial and spectral properties of spontaneous oscillations using high-density EEG. Based on the hyperarousal model of insomnia,<sup>9</sup> and based on previous findings of daytime abnormalities of brain structure,<sup>16</sup> function,<sup>23</sup> and excitability,<sup>24</sup> observed in stringently selected homogeneous samples, we expected that the physiological characteristics of insomnia disorder are not restricted to the night; spectral signatures of cortical hyperarousal previously reported in the sleep EEG would therefore also be detectable in the wake EEG.

## METHODS

### Participants and Questionnaires

Participants were recruited through advertisement and through the Netherlands Sleep Registry ([www.sleepregistry.nl](http://www.sleepregistry.nl)).<sup>40</sup> Participants were screened via telephone, and subsequently selected through an intake interview. Exclusion criteria at intake were: any neurological, psychiatric or somatic conditions; the use of sleep medications during the previous 2 mo; previous history of sleep apnea, restless legs syndrome, narcolepsy, overt circadian rhythm disorders or chronic sleep deprivation. The inclusion criteria for the ID group were in accordance to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.<sup>1</sup> Consistent with recommended research assessment of insomnia,<sup>41</sup> we set additional severity criteria, requiring, during the previous 6 mo and more than 3 nights per week, (1) a total sleep time of less than 6.5 h and (2) a sleep onset latency longer than 30 min or wake after

sleep onset longer than 30 min. The controls without sleep complaint (CTRL) group included people who indicated no sleep difficulties.

One hundred two participants participated in the study, and were preliminarily assigned to a group. An additional criterion concerning the insomnia symptoms was set based on the sub-clinical cutoff from the Insomnia Severity Index (ISI).<sup>42</sup> Three participants, originally included in the CTRL group, were excluded (ISI > 7); four participants, originally included in the ID group, were excluded (ISI < 8). One participant was additionally excluded, after data rejection. (See “EEG preprocessing” in the main text and “Electrode and epoch rejection” in the supplemental material).

Fifty-one participants with ID (42 females), aged (range, mean  $\pm$  standard deviation) 21–69,  $50.0 \pm 13.4$  y, and forty-three CTRL (32 females), aged 22–70,  $46.1 \pm 14.9$  y, were finally included in the statistical analysis. Participants completed the Epworth Sleepiness Scale<sup>43</sup> (ESS), a global measure of the propensity to fall asleep during common daytime activities, in order to control for the influence of sleepiness (see supplemental material). Participants were given a 7-day sleep diary (Consensus Sleep Diary, Morning administration<sup>44</sup>) to assess subjective sleep timing and quality. Averages were calculated for: sleep onset latency (SOL), wake after sleep onset (WASO, total time spent awake between the first time asleep and the last awakening), Bedtime (BT—time when participant went to bed), lights-off (time when participant laid in bed and tried to fall asleep), lights-on (time when participant woke up for the last time in the morning), get up time (GUT—time when participant got up and out of bed in the morning), time in bed (TIB—time in minutes from BT to GUT), total sleep time (TST—time spent asleep during TIB), and sleep efficiency (SE, percentage of TIB spent asleep). Volunteers were part of a larger study and participated in more assessments than analyzed and reported here and were paid 200 € for their time and effort to the complete package of assessments. The study was approved by the ethical committee of the VU University Medical Center, Amsterdam, The Netherlands.

### EEG Recordings

Participants were instructed to maintain a regular sleep/wake schedule during 2 w prior to laboratory assessment. Moreover, on the day of laboratory assessment, they were also instructed to refrain from alcohol and drugs and to limit their intake of caffeinated beverages to a maximum of two cups, which were allowed only before 12:00. EEG was recorded between 19:15 and 23:45 pm, according to the convenience of the participant. Participants were seated in an upright position and instructed not to move their head and not to fall asleep, in two wake resting-state conditions: 5 min of visual fixation on a crosshair on a monitor (eyes open, EO), followed by 5 min with eyes closed (EC). High-density EEG (HD-EEG) was recorded using a 256-electrode system, connected to a Net Amps 300 amplifier (Electrical Geodesic Inc., Eugene, OR, input impedance: 200 M $\Omega$ , A/D converter: 24 bits). Electrode impedance was kept below 100 k $\Omega$ . Signals were acquired with a sampling rate of 1,000 Hz and with a Cz reference.

### EEG Preprocessing

All preprocessing steps were coded in MATLAB (The Mathworks Inc., Natick, MA; version 8.3), using the MEEGPIPE toolbox (<https://github.com/meegpipe/meegpipe>). The signals were first filtered in the time domain with a 1D Local Polynomial Approximation filter with adaptive-scale selection from the Local Approximations in Signal and Image Processing (LASIP) toolbox,<sup>45</sup> to attenuate large non-physiological amplitude components (e.g., sudden spikes and slow fluctuations). Signals were subsequently downsampled to 250 Hz with an anti-aliasing filter, and then band-pass filtered using a windowed sinc Type I FIR filter,<sup>46</sup> with cutoffs at 0.75 and 65 Hz, attenuation of –80 dB, transition bandwidth of 0.2 and 5 Hz from each cutoff, respectively. Electrodes, first, and epochs, later, were evaluated for rejection using two similar automated procedures, adaptive for each EEG recording (supplemental material). Further artifacts from physiological (heartbeat, eye movements/blinks, muscle tension) and nonphysiological (power-line and sparse-sensor noise) sources were removed using automated procedures (supplemental material). Importantly with respect to high-frequency EEG investigations, we specifically compensated for signal originating from muscle activity using canonical correlation analysis.<sup>47</sup> Electrodes placed on the neck and face were excluded from further analysis; the remaining 183 scalp electrodes were re-referenced to the common average. We considered it important to evaluate where maximal group differences can be expected in recordings made with a limited number of American Academy of Sleep Medicine (AASM)-recommended electrodes, which are referenced to the contralateral mastoid.<sup>48</sup> In order to do so, we conducted a separate set of analyses after re-referencing each electrode to the contralateral mastoid (supplemental material).<sup>48</sup>

### Relative Spectral Power

For the preprocessed signals of each electrode, spectral power was estimated with a multitaper method (four orthogonal Slepian sequences, frequency smoothing of 0.8 Hz) implemented in the FieldTrip toolbox,<sup>49</sup> over 3-sec epochs with 50% overlap, then averaged across epochs. The relative spectral power was obtained by dividing the power in each of the 116 frequency bins in the 1.5–40 Hz range (resolution 0.332 Hz) by the average over this range. This had two purposes: enhancing frequency specific topographical differences and reducing the influence of sources of variability in broad-band power that were of no interest. Between-electrode variability sources of no interest involve different impedances, contact, and gain. Between-subject variability sources of no interest involve differences in anatomy, skin conductance, and applications of the net. The resulting electrode by frequency bin matrix was used to investigate fine-grained spatio-spectral group differences.

### Overall Low Versus High-Frequency Power Ratio

The most consistent EEG feature previously reported in ID is high power in a broad beta frequency range,<sup>11</sup> which has been interpreted as elevated cortical arousal.<sup>9,35,38,50</sup> In addition, some studies during wakefulness found low power across the lower part of the spectrum in the wake EEG: in the 4–8 Hz band,<sup>38</sup> at 9 Hz,<sup>35</sup> and in the 12–14 Hz band.<sup>39</sup> To obtain a single

measure of these opposite lower and higher frequency deviations, we computed the ratio between the lower (LO, 1.5–16 Hz) and upper (HI, 16–40 Hz) part of the spectrum. The 16 Hz cutoff frequency was chosen at the lower end of the beta band, as defined by Klimesch.<sup>51</sup> The LO/HI ratio measure was calculated both for each electrode and as scalp-average.

### Statistical Analysis: Permutation-Based Inference with Threshold-Free Cluster-Enhancement

Statistical analyses, evaluating group differences on EEG measures, were performed separately for the EO and the EC resting states, with Wilcoxon rank sum tests.<sup>52</sup> No transformation was applied to the data when nonparametric statistics were used. For plotting purposes we applied a log10-transformation. Differences between ID and CTRL were first evaluated for the scalp-averaged outcome measures, followed by separate tests for each electrode. Subsequently, the relative power at the more fine-grained spatio-spectral level was investigated separately for the lower and upper parts of the spectrum (1.5–16 Hz and 16–40 Hz, respectively). Monte Carlo permutations of group membership labels were used to construct the empirical distribution of the null hypothesis that the two groups do not differ at any particular spatial or spatio-spectral bin, respectively at the electrode and electrode by frequency level. Threshold-Free Cluster-Enhancement (TFCE)<sup>53</sup> was used to correct for multiple comparisons while evaluating group differences in relative power: (1) at the electrode level, for the LO/HI ratio; (2) at the electrode by frequency level. TFCE is a nonlinear transformation applied to a set of test statistics that takes into account the intensity in the neighborhood of each value. Compared to the more commonly used cluster-based permutations,<sup>54</sup> it provides better sensitivity over a wider range of signal types, equally enhancing large, narrow effects as well as small, broad effects.<sup>53</sup> Furthermore, it does not require an arbitrary threshold to define clusters, and it provides an integrated score with its relative P value, across all possible thresholds, for each spatial or spatio-spectral bin, while compensating for multiple comparisons. In each run of the Monte Carlo permutations, the maximum absolute value is taken after enhancement of the statistic ( $Z_{\text{tfce}}$ ), to form the null hypothesis distribution. The  $Z_{\text{tfce}}$  relative to the correct group membership is then compared to the null hypothesis distribution, providing the two-sided probability value (P) at each individual spatial or spatio-spectral bin.

### Correlation between Physiological Features of Insomnia

We computed the correlation between the most prominent features of ID that were observed in the exploratory analysis, namely upper alpha in EO and broad beta in EC. To do so, we took a measure for each participant, in EO and EC, respectively the “mean Upper Alpha” and “mean Broad Beta,” by averaging the log 10 of the relative power of all spatio-spectral bins that showed a significant effect of ID (Upper Alpha: 81 bins in the 11–12.7 Hz, involving 26 electrodes; Broad Beta: 1,275 spatio-spectral bins from 16.3 to 40 Hz, involving 124 electrodes). We tested the Spearman correlation between “mean Upper Alpha” and “mean Beta/Gamma,” across all participants, and separately for each group.

### Source Reconstruction and Group Differences at Selected Frequency Bands

To estimate the cortical sources of the relative power at the two frequency bands where we found the largest group differences, in EO and EC, we employed the linearly constrained minimum variance (LCMV) beamforming method,<sup>55</sup> as implemented in Fieldtrip.<sup>49</sup> We used a sparse grid of 90 regions comprising the centroids of all cortical and subcortical areas in the automated anatomical labeling (AAL) parcellation.<sup>56</sup> A regularization parameter of  $\lambda = 0.15$  was used. Prior to the computation of the covariance matrix, EEG signals were filtered separately using a broadband filter (1–40 Hz) and two narrow band filters: upper alpha (11–13 Hz) and beta (16.3–21.7 Hz). Afterward, the broadband power at each source location was used to normalize the source power within each narrow band, following a similar approach to that performed for the scalp data. Finally, the relative source power at each AAL location was compared between controls and patients with insomnia disorder using a two-tailed nonparametric Wilcoxon test. Significant changes in source power are reported at  $P < 0.05$  using Benjamini and Hochberg’s<sup>57</sup> false discovery rate (FDR) procedure to control for multiple comparisons.

## RESULTS

### Participants, Questionnaires, and EEG Recordings

After artifact rejection (supplemental material), two recordings from a participant were excluded due to insufficient length (less than 3 min). The following group statistics are reported in Table 2. Concerning the descriptives, ID and CTRL did not differ significantly in age, nor in sex. Concerning the questionnaires, each participant with ID had, as expected, larger ISI scores than any of the CTRL; ID and CTRL did not differ with respect to the ESS scores. Sleep diaries revealed that ID reported significantly longer SOL and WASO, shorter TST, lower SE, earlier lights-on time and shorter TIB, but did not differ with respect to BT, lights-off and out-of bed time (GUT). The groups also did not differ with respect to the time of the EEG recording.

### Overall Low- Versus High-Frequency Power Ratio

People with ID, as compared to controls, had a lower scalp-average LO/HI RATIO both during EO ( $Z = -1.90$ ,  $P = 0.06$ ) and during EC ( $Z = -2.40$ ,  $P = 0.02$ ), resulting either from less low frequency power, or more high frequency power, or both. Subsequent multiple comparison-corrected electrode-wise evaluation of topographical specificity of these group differences (Figure 1) showed a significantly ( $P < 0.05$ ) lower LO/HI RATIO in ID during EO in 19 electrodes over midline central regions (peak:  $Z = -2.84$ ,  $Z_{\text{tfce}} = -77.94$ ,  $P = 0.04$ ). During EC, people with ID had significantly lower LO/HI RATIO in 85 electrodes distributed over frontal, central and bilateral posterior regions (peak:  $Z = -3.16$ ,  $Z_{\text{tfce}} = -111.21$ ,  $P = 0.03$ ).

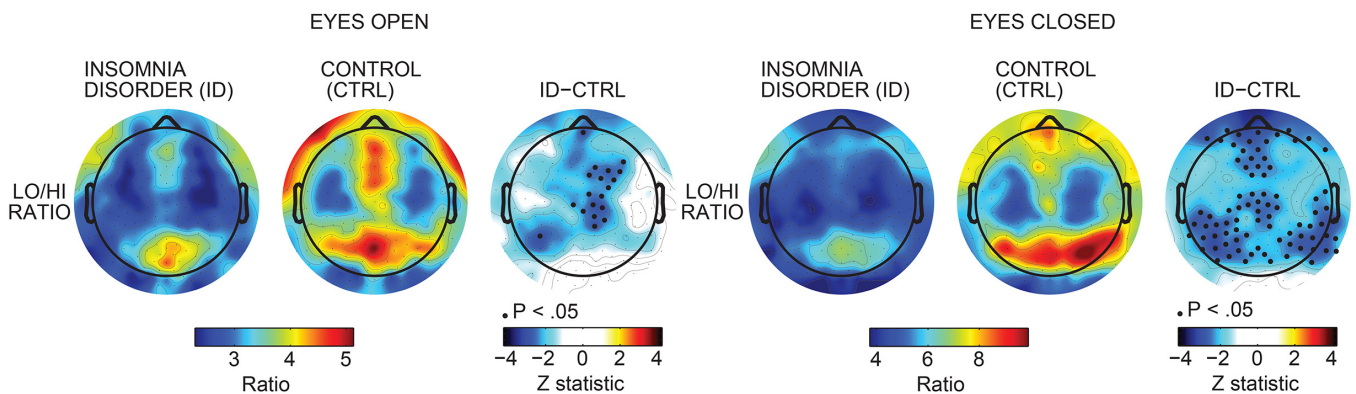
### Fine-Grained Spatio-spectral Power Differences

Figure 2 illustrates that during EO people with ID have less power than CTRL in two narrow upper alpha band spatio-spectral clusters, spanning from 11 to 12.7 Hz, both with maximal

**Table 2**—Demographic variables, questionnaire scores, recording time and averages of sleep diary variables, for insomnia disorder and controls without sleep complaints.

	Insomnia Disorder (n = 51)	Controls (n = 43)	P
Sex, male/female	9/42	11/32	NS
Age, y	21–69, 50.0 ± 13.4	22–70, 46.1 ± 14.9	NS
Insomnia severity index	8–25, 16.0 ± 4.3	0–7, 1.9 ± 1.9	< 0.001
Insomnia disorder duration, y	0.5–54, 21.98 ± 15.16	–	–
Epworth Sleepiness Scale	0–19, 6.32 ± 4.43	1–14, 6.67 ± 3.21	NS
Recording time	19:23–23:37, 21:27 ± 0:57	19:22–23:08, 21:17 ± 1:03	NS
Sleep diary			
SOL, min	1.57–237.14, 41.92 ± 45.	1–30, 13.16 ± 6.78	< 0.0001
WASO, min	1.71–180, 71 ± 46.16	0–69.29, 20.47 ± 17.61	< 0.0001
TST, min	239.00–507.62, 404.24 ± 64.76	393.57–593.57, 480.76 ± 47.93	< 0.0001
Bedtime	21:00–1:18, 23:18 ± 0:52	20:53–2:15, 23:35 ± 1:07	NS
Lights-Off	22:28–1:25, 23:42 ± 0:42	22:03–2:36, 23:56 ± 0:56	NS
Lights-On	3:16–8:51, 6:56 ± 1:06	5:37–10:51, 7:36 ± 0:56	< 0.01
GUT	6:09–11:05, 7:59 ± 1:00	6:00–11:26, 8:04 ± 0:57	NS
TIB, min	261.43–587.86, 434.22 ± 61.72	370.71–556.42, 459.75 ± 43.07	0.03
SE, %	55.45–96.46, 78.25 ± 10.7	84.53–99.28, 93.61 ± 3.52	< 0.0001

Values presented as range, mean ± standard deviation. Bedtime, Lights-Off, Lights-On and GUT express clock time, in hours and minutes. SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; GUT, get up time; TIB, time in bed; SE, sleep efficiency.



**Figure 1**—Imbalance between low and high frequency spectral power in insomnia, during the eyes open (EO) and eyes closed (EC) resting state. As compared to controls without sleep complaints (CTRL), individuals with insomnia disorder (ID) show a low ratio between the power of the lower (1.5–16 Hz) over upper (16–40 Hz) part of the spectrum (LO/HI RATIO). This was most pronounced over midline anterior (prefrontal, frontal, and central) and left parietal regions during EO, and over midline anterior (prefrontal, frontal, central) and bilateral posterior regions (temporal, parietal) during EC. The three maps on the left side show the results for EO, the three maps on the right side the results for EC. Of these triplet maps, the first and the second show the topographical distribution of the within-group median LO/HI RATIO, whereas the third map shows the relative group difference statistic (Z). Electrodes where the P value (derived from the Threshold-Free Cluster-Enhancement procedure) is less than 0.05 are marked with a black dot.

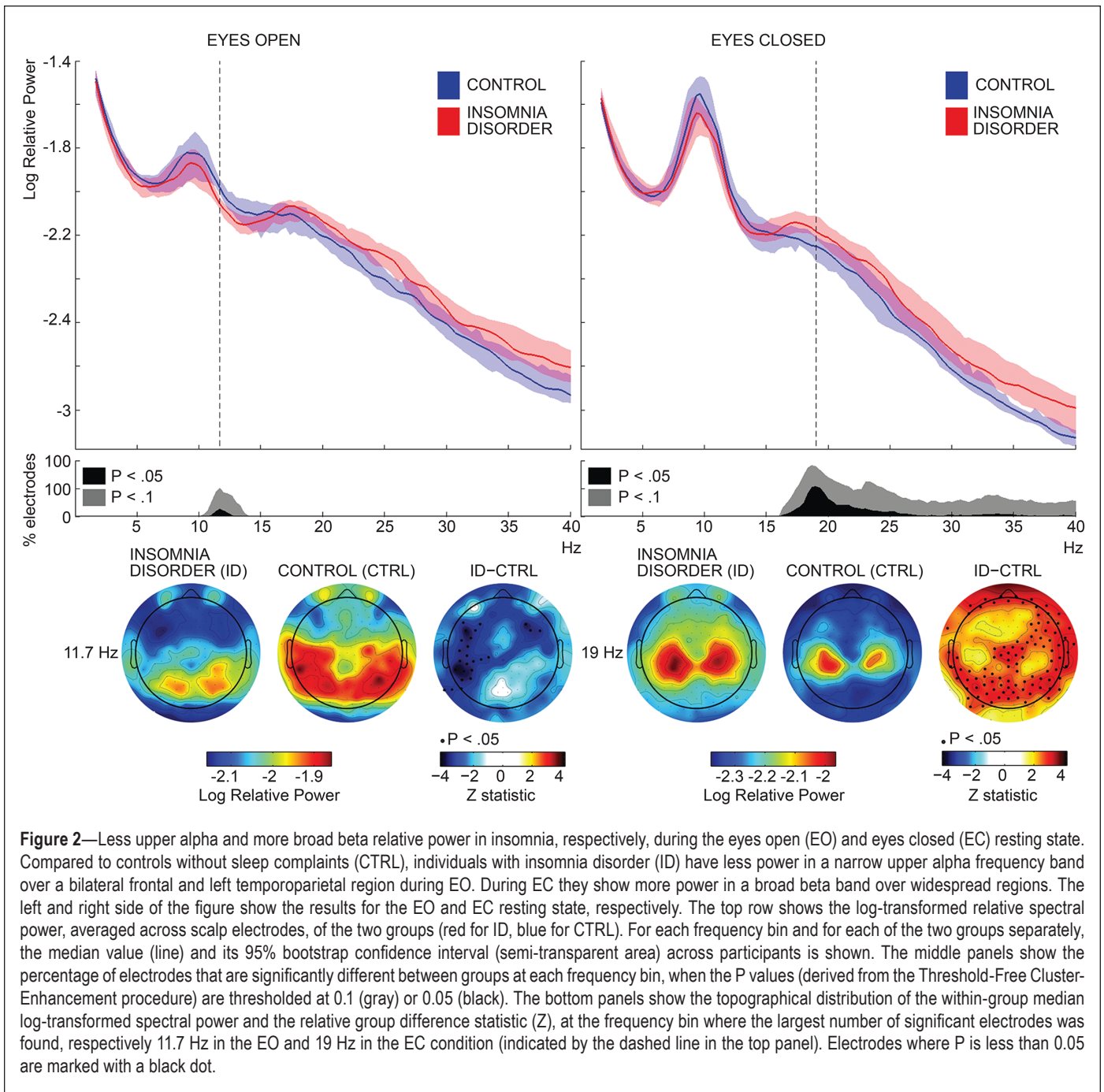
differences at 11.7 Hz. One cluster (69 spatio-spectral bins with  $P < 0.05$ ; peak:  $Z = -4.05$ ,  $Z_{tfc} = -836.78$ ,  $P = 0.03$ ) involved 22 electrodes over left temporal, parietal and frontal regions; the other (12 spatio-spectral bins with  $P < 0.05$ ; peak:  $Z = -3.73$ ,  $Z_{tfc} = -773.76$ ,  $P = 0.05$ ) involved 4 electrodes over the right frontal region.

During EC, people with ID have more power than CTRL in a large high-frequency spatio-spectral cluster spanning from 16.3 to 40 Hz and with maximal differences at 19 Hz. The cluster (1,275 spatio-spectral bins with  $P < 0.05$ , peak  $Z = 3.35$ ,  $Z_{tfc} = 1,541.50$ ,  $P = 0.003$ ) involved 124 electrodes widely distributed across the scalp: at 19 Hz, over prefrontal,

right frontotemporal, central, and bilateral posterior regions; at higher frequencies, from 22 to 25 Hz, over bilateral parietal, prefrontal and frontal, regions; and at even higher frequencies, from 25 to 40 Hz, the cluster involved left parietal, prefrontal, and frontal regions.

#### Correlation between Physiological Features of Insomnia

The correlation between the two main features of ID, “mean Upper Alpha” and “mean Broad Beta”, was negative across all participants ( $\rho = -0.37$ ,  $Z = -3.84$ ,  $P = 0.0002$ ), as depicted in Figure 3. In ID this relationship was more marked ( $\rho = -0.32$ ,  $Z = -2.4$ ,  $P = 0.02$ ) than in CTRL ( $\rho = -0.25$ ,  $Z = -1.7$ ,  $P = 0.09$ ).



**Figure 2**—Less upper alpha and more broad beta relative power in insomnia, respectively, during the eyes open (EO) and eyes closed (EC) resting state. Compared to controls without sleep complaints (CTRL), individuals with insomnia disorder (ID) have less power in a narrow upper alpha frequency band over a bilateral frontal and left temporoparietal region during EO. During EC they show more power in a broad beta band over widespread regions. The left and right side of the figure show the results for the EO and EC resting state, respectively. The top row shows the log-transformed relative spectral power, averaged across scalp electrodes, of the two groups (red for ID, blue for CTRL). For each frequency bin and for each of the two groups separately, the median value (line) and its 95% bootstrap confidence interval (semi-transparent area) across participants is shown. The middle panels show the percentage of electrodes that are significantly different between groups at each frequency bin, when the P values (derived from the Threshold-Free Cluster-Enhancement procedure) are thresholded at 0.1 (gray) or 0.05 (black). The bottom panels show the topographical distribution of the within-group median log-transformed spectral power and the relative group difference statistic (Z), at the frequency bin where the largest number of significant electrodes was found, respectively 11.7 Hz in the EO and 19 Hz in the EC condition (indicated by the dashed line in the top panel). Electrodes where P is less than 0.05 are marked with a black dot.

### Source Reconstruction and Group Differences at Selected Frequency Bands

We reconstructed the sources for the frequency bands that showed the strongest group differences at the scalp level, as described in the Methods section. The upper panels of Figures 4 and 5 show the estimated standardized (Z-scores) relative power at each of the 90 AAL regions for CTRL (left) and ID patients (right), for upper alpha during EO (Figure 4) and for beta during EC (Figure 5). Upper alpha sources comprised occipital, parietal, inferior temporal and midline orbitofrontal regions. For beta, the strongest sources comprised midline motor areas and the precuneus, and a lateralization toward the left was observed with strong sources along left primary sensory and motor areas.

For both frequency bands, differences between ID and CTRL were widespread, consistent with the scalp results (bottom panel of Figure 2). The reduction of power in ID, observed in upper alpha in EO, involved most AAL regions, and was the largest in motor, occipital, and inferior temporal regions, as well as bilaterally in the amygdala and parahippocampal gyri. The increase of power in ID, observed in beta in EC, manifested most strongly bilaterally in motor areas (supplementary motor area and paracentral lobule). The bottom panel of Figures 4 and 5 displays all AAL regions ranked by their Z-statistic for the difference between ID and CTRL (for a summary of AAL region label abbreviation and location, see Table S1 and Figure S4 of the supplemental material). The ranking shows

that the differences between ID and CTRL are rather global, with only small regional differences in significance.

## DISCUSSION

Whereas daytime complaints are a defining characteristic of ID, neurophysiological investigations have focused mostly on sleep. Based on the evidence in ID of a characteristic round-the-clock hyperarousal,<sup>9</sup> and of daytime alterations (detailed in the Introduction) in structure,<sup>16</sup> function,<sup>23</sup> and excitability,<sup>24</sup> we expected that the spectral signatures of cortical hyperarousal previously reported in the sleep EEG would also be detectable in the wake EEG. HD-EEG, assessed during the wake resting state in adequate sample sizes, allowed for a sensitive fine-grained analysis of systematic spatio-spectral differences between people with ID and matched controls.

### Spectral Imbalance in ID

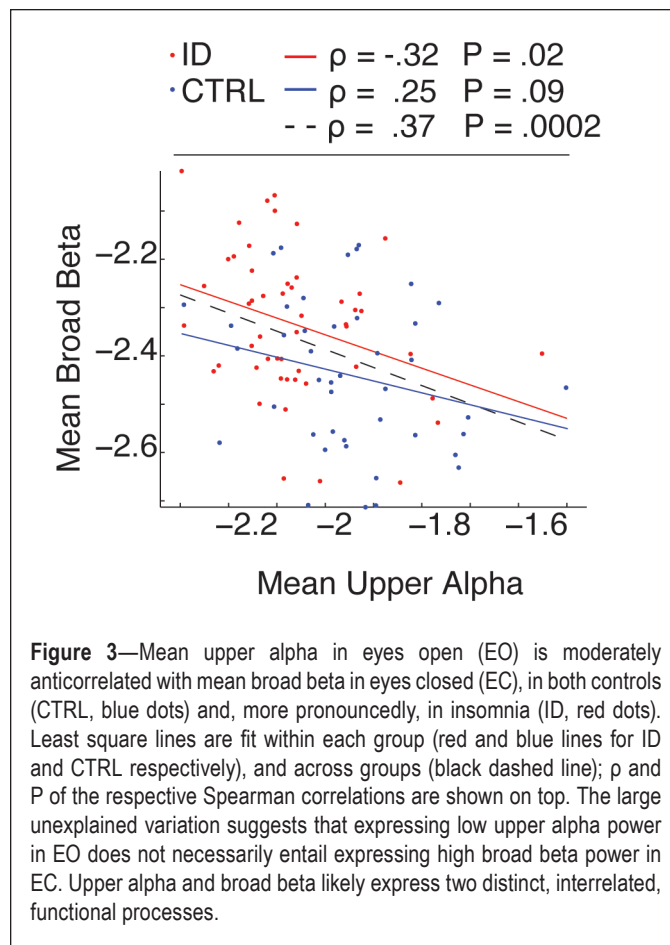
According to the LO/HI RATIO analysis, we found in ID, both in EO and in EC, a shift of the spectral energy from the low frequency range (1.5–16 Hz) to the high frequency range (16–40 Hz). The findings are in agreement with previous reports of reduced low-frequency power,<sup>35,38,39</sup> and increased high-frequency power.<sup>35,36,38</sup> The shift of spectral energy from low to high frequencies is consistent with an altered balance of cortical dynamics, due to either lack of inhibition or hyperexcitation. One of several possible circuits involved in rather global modulation of cortical excitability is the proposed attenuated excitatory input of orbitofrontal neurons to the caudate nucleus—a key structure in moderating the cortical excitability.<sup>23</sup> Other subcortical projections may be of equal importance though: the hyperactivation of the wake-promoting orexin system in the lateral hypothalamus, or the hypofunctionality of the sleep-promoting gamma-aminobutyric acid system in the ventrolateral preoptic nucleus.<sup>9</sup>

Fine-grained spatio-spectral analysis allowed us to further characterize this overall imbalance. The strength and spread across frequencies of the effect of ID on the relative power is different for the two parts of the spectrum. Differences with controls during EO are in the upper alpha range, peaking at 11.7 Hz, and are narrow-band and large in magnitude; whereas during EC they are in the beta range, peaking at 19 Hz, and are broad-band and small in magnitude.

Individual differences in power, in EO upper alpha and in EC broad beta, show a moderate negative correlation. The large unexplained variation suggests that expressing low upper alpha power in EO does not necessarily entail expressing high beta-gamma power in EC. Hence, the two features likely express two distinct, interrelated, functional processes.

### Widespread Spatial Effects

Topographical analysis revealed that the reduction of power in ID in the upper alpha range is mostly expressed in bilateral frontal and left temporoparietal regions during EO (Figure 2); whereas the increase of power in ID in the beta and gamma range is extended over prefrontal, frontal, central, and parieto-occipital regions during EC. Previous work suggested that hyperarousal occurs most pronounced in frontal regions.<sup>58</sup> Although the increase in frontal power in insomnia

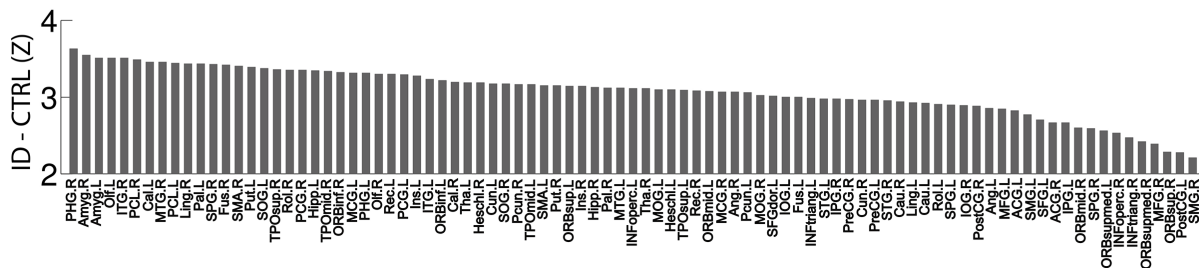
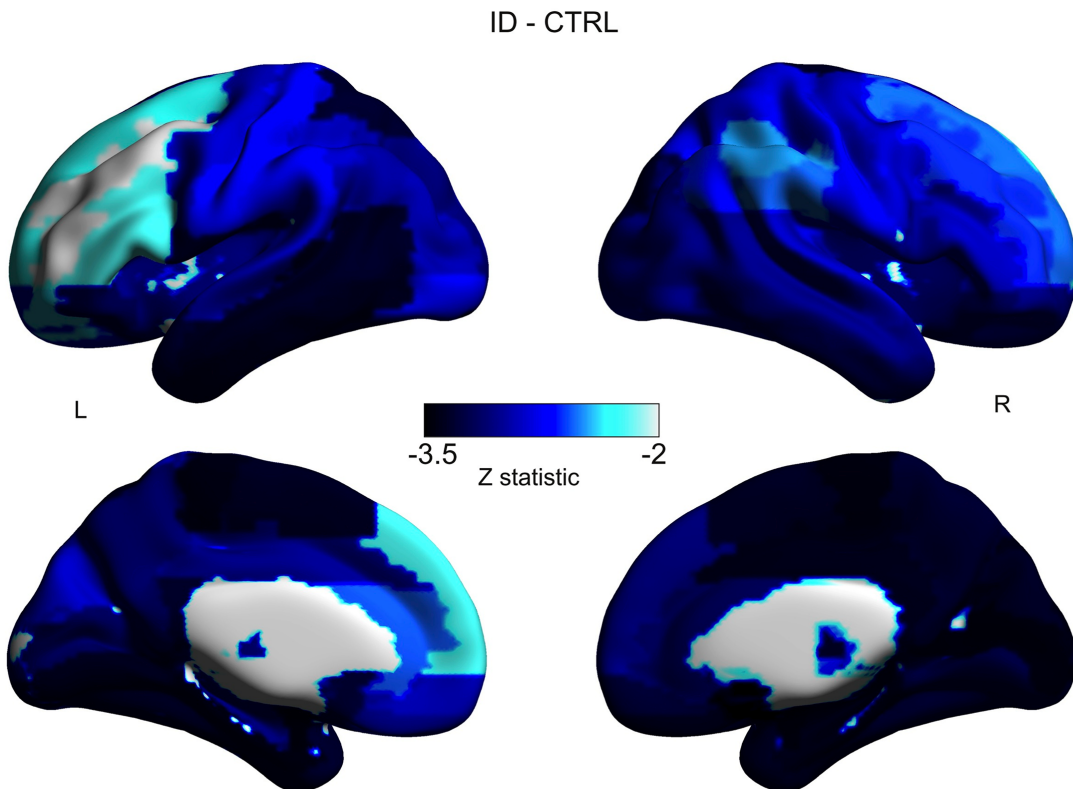
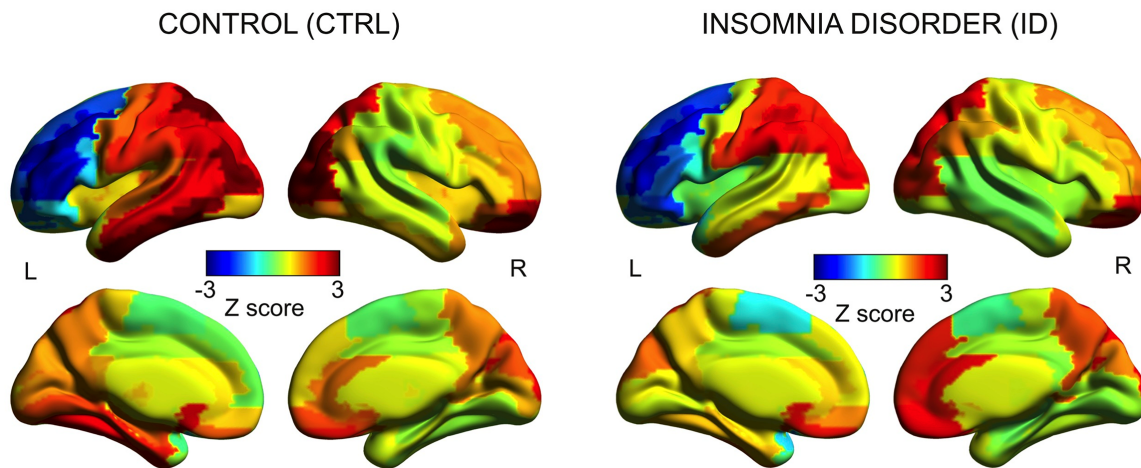


**Figure 3**—Mean upper alpha in eyes open (EO) is moderately anticorrelated with mean broad beta in eyes closed (EC), in both controls (CTRL, blue dots) and, more pronouncedly, in insomnia (ID, red dots). Least square lines are fit within each group (red and blue lines for ID and CTRL respectively), and across groups (black dashed line);  $\rho$  and  $P$  of the respective Spearman correlations are shown on top. The large unexplained variation suggests that expressing low upper alpha power in EO does not necessarily entail expressing high broad beta power in EC. Upper alpha and broad beta likely express two distinct, interrelated, functional processes.

does not reach significance at the specific 19 Hz frequency bin of maximal group difference plotted in Figure 2, significance is reached in the 22–40 Hz range. Group differences are observed widely across the scalp, albeit with different magnitude. Please note that the topographical area where the band-power is maximal does not necessarily coincide with the area where group differences are the largest, because of the variance of the signal or topographical differences between the groups. Group differences may be pronounced at locations with only moderate power, yet less pronounced at locations with the largest power (Figure S3, supplemental material). In spite of the topographies suggestive of spatial specificity (Figure 2), the observed features of insomnia, namely low upper-alpha (11–12.7 Hz) power and high broad beta (16.3–40 Hz) power, actually occurred over widespread areas. Given the stringent multiple comparison correction that we applied, some regions just crossed significance threshold, whereas others simply did not.

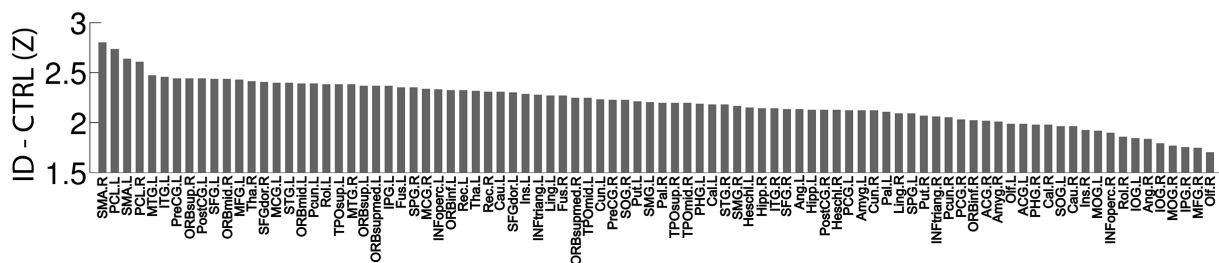
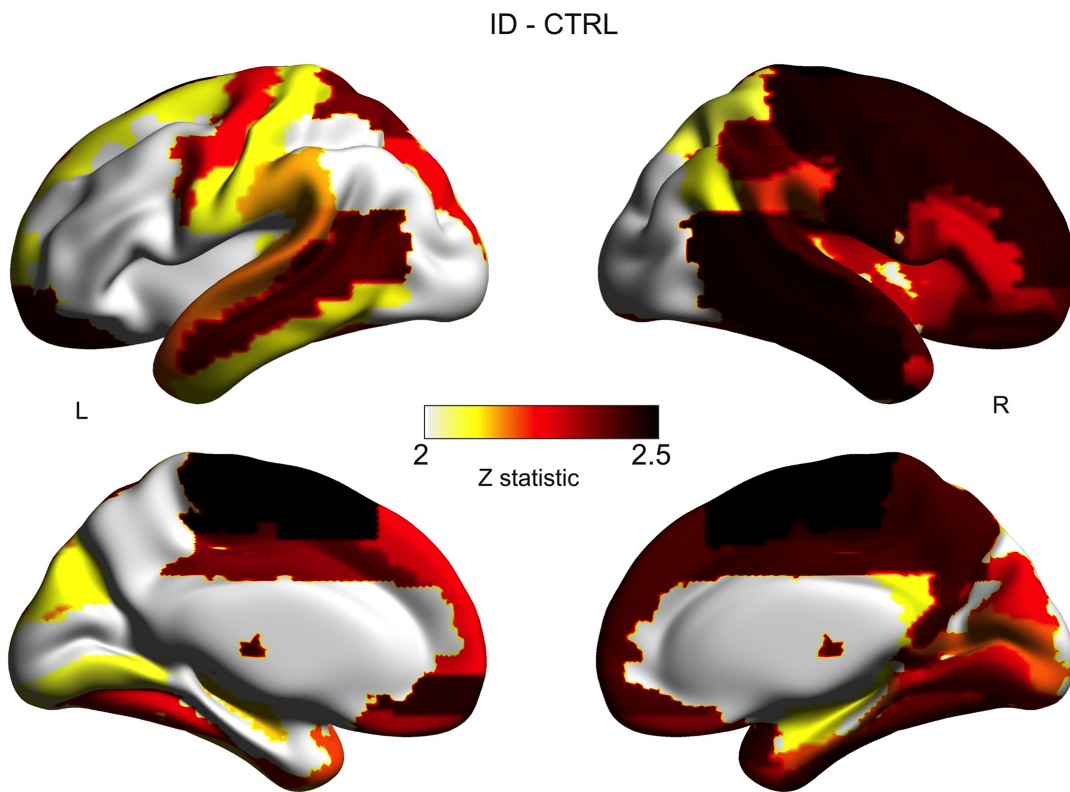
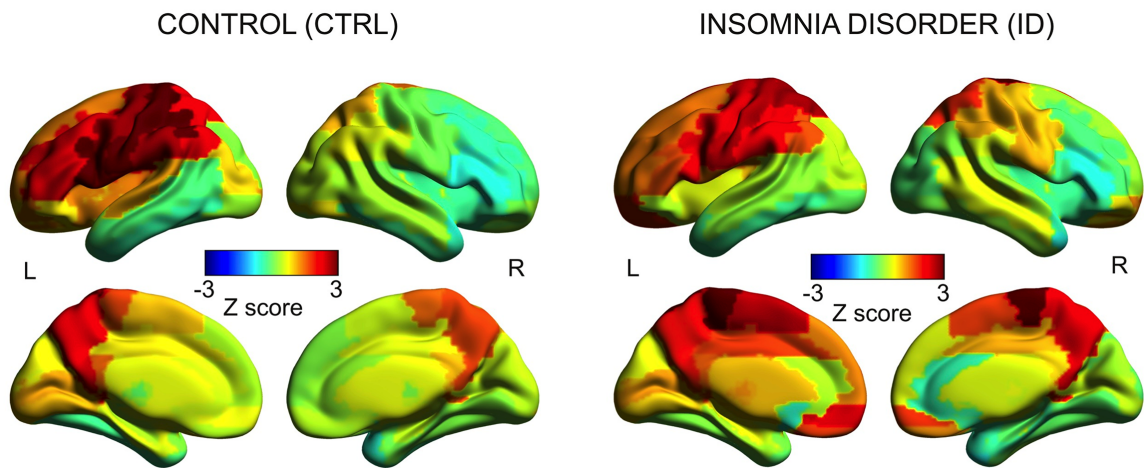
Source estimates confirmed the widespread nature of the group differences, suggesting a global rather than focal origin of scalp profile of low upper alpha power during EO and high beta power during EC, in people with insomnia. This may either indicate that the ID deviations occur across the cortex, or that their locations are highly variable across individuals with ID. An F-test for equality of variances across groups ruled out the second option (supplemental material).

The findings support rather global differences between people with insomnia and controls, in accordance with the proposed



**Figure 4**—Source localization reveals widespread decreases in upper alpha oscillatory power in insomnia during eyes open (EO). Upper panel: distribution of upper alpha sources obtained using linearly constrained minimum variance beamforming, for insomnia disorder (ID, left) and controls without sleep complaints (CTRL, right). Average source power was converted to z-scores for visualization. Middle panel: Automatic anatomical labelling (AAL) template regions where significant ( $P < 0.05$ , Wilcoxon test, Benjamini-Hochberg false discovery rate correction) decreases in upper alpha oscillatory power in ID vs. CTRL were observed. Bottom panel: AAL regions ranked according to the effect size of the upper alpha power decreases in ID versus CTRL (for more information on AAL regions, including abbreviations, please see Figure S4 and Table S1 of the supplemental material).





**Figure 5**—Source localization reveals widespread increases in beta oscillatory power in insomnia during eyes open (EO). Upper panel: distribution of beta sources obtained using linearly constrained minimum variance beamforming, for insomnia disorder (ID, left) and controls without sleep complaints (CTRL, right). Average source power was converted to z-scores for visualization. Middle panel: Automatic anatomical labelling (AAL) template regions where significant ( $P < 0.05$ , Wilcoxon test, Benjamini-Hochberg false discovery rate correction) increases in beta oscillatory power ID versus CTRL were observed. Bottom panel: AAL regions ranked according to the effect size of the beta increases in ID versus CTRL (for more information on AAL regions, including abbreviations, please see Figure S4 and Table S1 of the supplemental material).

global arousal modulatory role of the caudate,<sup>23</sup> and with the diffused alterations resulting from the imbalance between sleep and wake promoting centers within the hypothalamus.<sup>9</sup>

### **Clinical Relevance**

The findings have practical implications for EEG studies in insomnia. Although wake EEG is much easier to assess than PSG, we here show that it still retains useful spatio-spectral information that characterizes ID. Whereas a fine-grained HD-EEG approach similar to what we applied is necessary to uncover such characteristics, these may now be assessed from the AASM montage.<sup>48</sup> Analyses described in detail in the supplemental material show that the F<sub>4</sub>-M<sub>1</sub> bipolar electrode pair can best be evaluated for group differences in upper alpha power around 11.7 Hz during EO. The O<sub>1</sub>-M<sub>2</sub> bipolar electrode pair can best be evaluated for group differences in beta power around 19 Hz during EC. Future studies could investigate whether these features represent trait-like biomarkers of individuals with insomnia or at risk due to family history, or whether they represent state-like signatures that remit after successful intervention. It could moreover be of interest to investigate whether individual differences in these features predict the response to intervention.

Although the findings reported have practical implications for diagnostic and clinical purposes, the findings are also highly relevant for the comprehension of the physiopathology of insomnia. In the following paragraphs, we discuss possible functional correlates of enhanced broad beta and attenuated upper alpha band power, and report converging evidence that ID is characterized by hyperarousal and lack of inhibition of cortical dynamics, which in turn may interfere with cognitive and sensorimotor flexibility.

### **Widespread Enhanced Broad Beta Power and Hyperarousal**

According to the hyperarousal model of insomnia,<sup>11</sup> high power in the broad beta band reflects elevated levels of arousal of the central nervous system and closely matches the hypervigilant cognitive style of insomnia disorder. Cortical arousal is a long-standing interpretation for high frequency EEG activity in insomnia. In an early study,<sup>35</sup> Freedman found high beta power in sleep onset insomnia during rapid eye movement (REM) sleep and non-rapid eye movement (NREM) stage 1 sleep. Recently, a study found high beta power in primary insomnia during resting-state wakefulness,<sup>36</sup> in agreement with our observations; however, when considering the same frequency range (17–30 Hz), we did not only observe the reported frontal effect, but a more widespread effect, that encompassed prefrontal, frontal, central, right temporal, and bilateral posterior regions on the scalp, pointing to global hyperarousal. Source analysis, around the beta frequency where we observed maximal evidence of group differences (19 Hz), confirmed that source-level differences were also widespread. The differences were maximal over sensorimotor cortices, the region were the sources mostly originated from. Furthermore, the differences extended over prefrontal, frontal, right temporal regions of the cortex. These results are suggestive of a global hyperarousal, encompassing sensorimotor, cognitive, and

emotion-regulation systems. In healthy awake volunteers, EEG activity in the beta range is implicated in cognition, attention, and perception.<sup>59</sup> However, pathologically increased beta power is thought to interfere with cognitive and behavioral flexibility, by rigidly maintaining the cognitive and sensorimotor status quo.<sup>60</sup> Follow-up studies have to investigate whether the enhanced beta we observed in the wake EEG of people suffering from ID could be involved in their reportedly hampered ability to disengage from cognitive, sensorimotor and emotional processes.<sup>31</sup>

Although the maximal differences we observed are near the beta peak frequency, our findings extend into the gamma range, up until the last frequency bin we studied (16.3–40 Hz). In healthy awake volunteers, gamma band activity in the range of 30–100 Hz is implicated in learning, focused attention, memory and sensory processing.<sup>61</sup> In one EEG-functional magnetic resonance imaging (fMRI) study,<sup>62</sup> females suffering from ID showed high gamma power during peri-sleep epochs. Gamma power fluctuations were moreover associated with fluctuations in the blood oxygenated level dependent (BOLD) signal in the insula, suggesting pathologically elevated somatosensory awareness and distress. It is tempting to suggest that enhanced beta and gamma power could be involved in cognitive complaints characteristic of ID, including ruminations, worries, racing thoughts and enhanced interoception, exteroception, and self-referential processing.

### **Upper Alpha Role in the Inhibition of Interfering Cognitions**

The functional relevance of attenuated upper alpha power relies on the association of alpha with inhibition. Large amplitude alpha oscillations have been suggested to reflect a state of cortical deactivation or active inhibition.<sup>63</sup> Consistently, in some studies, alpha amplitude is inversely related to cortical excitability.<sup>51,64</sup> In combined EEG-fMRI studies, the BOLD signal in widespread cortical regions is anticorrelated with the estimated localized cortical alpha amplitude.<sup>65</sup> Strong negative BOLD-alpha power correlations are not limited to the occipital cortex, but are also found at cortical sites further away from the generators in the occipital lobe.<sup>66,67</sup> Furthermore, transient periods of high alpha activity are paralleled by a decrease in BOLD connectivity, consistently with the idea that alpha may represent inhibition across a distributed network of cortical areas.<sup>68–70</sup> Whereas source analysis indicated that low power in the upper alpha band in insomnia occurred globally, the difference with controls was most significant in visual, somatosensory, and motor areas. Given the role of alpha oscillations in inhibition, this finding suggests a global insufficiency in inhibition that may show most strongly for sensory and motor processing.

The theoretical framework put forth by Klimesch<sup>52</sup> links specifically the cortical inhibitory role of the upper portion of the alpha range, to the selection and suppression of irrelevant and interfering cognitions.<sup>71</sup> He refers to the inhibitory function of alpha: “large resting power may reflect a person’s ability to build up a highly efficient filter.”<sup>51</sup> Widespread lack of cortical inhibition, paralleled by reduced selectivity of the attentional filter, could therefore leave room for ruminations and interfering cognitions.

In an early neurofeedback experiment, participants with obsessive rumination were trained to modulate alpha power, and indeed an inverse association of alpha power with rumination was found.<sup>72</sup> Given the importance of rumination in insomnia, it would be interesting to investigate whether reduced upper alpha power mediates the tendency to ruminate among people suffering from insomnia, and whether neurofeedback targeting this frequency range could thus alleviate cognitive symptoms in insomnia. Recently, a neurofeedback training successfully enhanced relative power specifically in the upper alpha band, yielding benefits in attention and impulsivity, that are consistent with increased efficiency of the attentional inhibitory filter.<sup>73</sup> It may be possible that the success of neurofeedback training in ID,<sup>39,74–77</sup> targeting the sensorimotor rhythm in the 12–15 Hz range, was partially due to the overlap between this band and the upper alpha band (11–13 Hz), the band where we observed the most impairment in ID. Future neurofeedback studies in insomnia should specifically target the upper-alpha oscillations, where we observed the largest physiological alterations of ID.

In summary, it is tempting to suggest a possible role of attenuated alpha power in the inability to suppress intrusive cognitions<sup>78</sup> and the resulting ruminations that exert a pivotal role in the etiology of ID.<sup>9</sup>

### Control of Possible Confounders

It is unlikely that our finding of enhanced broad beta power is of electromyographic origin. First, we specifically addressed signals originating from muscle activity using canonical correlation analysis.<sup>47</sup> Second, the group-difference effect size, as reflected in the number of significant electrodes, tended to decrease with frequency rather than increase, as it would be expected if the effect was driven by muscular activity under common average reference.<sup>79</sup>

Sleepiness is known to affect the EEG spectral power, in complex ways.<sup>80</sup> The amplitude of spontaneous oscillations in the broad alpha band during eyes open has been shown to be positively related to sleep pressure and fatigue,<sup>81–84</sup> whereas the inverse holds during eyes closed resting state<sup>81,83–85</sup> during wakefulness or the transition to sleep.<sup>80,83</sup> We obtained a measure of momentary sleepiness by quantifying the attenuation of the alpha power, in EC relative to EO, by means of the Alpha Attenuation Index (AAI)<sup>81,86</sup> (supplemental material). We moreover assessed the ESS<sup>43</sup> as a measure of habitual sleepiness. We found no differences between ID and CTRL in either AAI or ESS. It is therefore highly unlikely that our findings involve group differences in either habitual or momentary sleepiness.

Resting state alpha power starts to decrease considerably after the age of approximately 50 y,<sup>87</sup> especially in the upper alpha band. In the current study, the two groups did not differ significantly in age (mean difference = 3.97 y,  $P = 0.22$ ). We then controlled for the possible confounding effect of age, by means of analysis of covariance (supplemental material). The main effect of ID on its electrophysiological correlates remained significant after taking into account the variation entailed by age; furthermore, the interaction of age with ID did not significantly affect the electrophysiological correlates of ID.

Finally, benzodiazepines are known to suppress alpha and increase sigma and beta amplitude.<sup>88</sup> In the current study, use of benzodiazepines was an exclusion criterion.

In summary, we excluded that the groups were different with respect to possible confounders (habitual and momentary sleepiness, age, sex, time of the recording, typical BT and typical GUT).

### CONCLUSIONS

Our findings on the fine-grained spatio-spectral characteristics of the wake resting-state HD-EEG in people suffering from insomnia disorder point to an imbalance of cortical excitation and inhibition, as indexed by a shift in spectral energy from low to high frequencies. During eyes open, people suffering from insomnia show lower power than controls in the upper alpha range, with maximal evidence at 11.7 Hz. This difference with controls is significant only in a narrow band. During eyes closed, people suffering from insomnia show higher power in the broad beta range, with maximal evidence at 19 Hz. This difference with controls extends over a rather broad frequency range. There is no evidence for a localized effect in either condition, as assessed by source-analysis. Furthermore, we provide recommendations on where to best observe these differences on the scalp, using bipolar electrodes of the AASM extended montage. Functional interpretation of the spectral alterations points to hyperarousal and lack of inhibition. The broad-band small increase in the beta range supports hyperarousal of the central nervous system; the narrow-band large reduction in the upper alpha range possibly reflects reduced cortical inhibition and reduced selectivity of the attentional filter.

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