Neural complexity and the spectral slope characterize auditory processing in wakefulness and sleep

Sigurd Alnes¹, Lea Bächlin¹, Kaspar Schindler², and Athina Tzovara¹

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Abstract

Auditory processing and the complexity of neural activity can both indicate residual conscious-ness levels and differentiate between states of arousal. However, how measures of neural signal diversity, or complexity, manifest in evoked activity, and, more generally, how the electrophys-iological characteristics of auditory responses change in states of reduced consciousness, remain under-explored. Here, we tested the hypothesis that measures of neural complexity and the spectral slope would discriminate stages of sleep not only in spontaneous EEG, but also in auditory-evoked responses. High-density EEG was recorded in 21 participants to determine the spatial relationship between these measures, and between spontaneous and auditory-evoked signals. Results showed that the complexity and the spectral slope in the 2-20 Hz range discriminated between sleep stages and had a high correlation in sleep. In wakefulness, complexity was strongly correlated to the 20-40 Hz spectral slope. Auditory stimulation resulted in reduced complexity in sleep compared to spontaneous activity and modulated the spectral slope in wakefulness. These findings demonstrate the persistence of electrophysiological markers of arousal during both spontaneous and evoked EEG activity and have direct applications to studies using auditory stimulation to probe neural functions in states of reduced consciousness.
Wake
Evoked
NREM2
NREM3
Spontaneous
REM

Spectral slope (20 - 40 Hz)

Lempel-Ziv complexity

A
B
C
D
E

r=0.72, p<0.01
r=0.67, p<0.01
r=0.71, p<0.01
r=0.89, p<0.001
r=0.87, p<0.001
r=0.86, p<0.001
r=0.71, p<0.01
r=0.67, p<0.05

A B C
D E
Lower Higher
LZ complexity (a.u.)
1.1 0.7 0.9 1.0 0.8
Spontaneous Evoked
t-values
20 -20 0 10 -10
Spontaneous Evoked
Wake NREM2 NREM3 REM
Difference

LZ complexity (a.u.)
A. LZ complexity and spectral slope (2-20 Hz)

B. LZ complexity and spectral slope (20-40 Hz)

- Wake
- NREM2
- NREM3
- REM

Steeper slope as complexity increases
Flatter slope as complexity increases

Pearson's r

-1.00 -0.75 -0.50 -0.25 0 0.25 0.50 0.75 1.00

Spontaneous Evoked Spontaneous Evoked
Lower Higher
LZ complexity (a.u.)
1.1 0.7 0.9 1.0 0.8

Slow-wave density (sws/minute)
20 0 10 15 5

Pearson's r
-0.8 -0.4 0.0 0.4 0.8

A

B

C

D

E

F

Spectral slope (2-20 Hz)

Spectral slope (20-40 Hz)

r=0.64, p<0.05

r=0.69, p<0.05

r=0.48, p=0.09

r=0.50, p=0.09

r=0.32, p=0.78

r=0.24, p=0.78

Lower
Higher
LZ complexity (a.u.)
0.7 0.8 0.9 1.0 1.1

Slow-wave density (sws/minute)
0 5 10 15 20

Pearson's r
-0.8 -0.4 0.0 0.4 0.8
<table>
<thead>
<tr>
<th>Stage</th>
<th>Time (hh:mm, M ± SEM)</th>
<th>Epochs (M ± SEM)</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>Wake sessions</td>
<td>1:50 ± 0:13</td>
<td>1644 ± 173</td>
<td>20</td>
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<tr>
<td>NREM2</td>
<td>2:48 ± 0:06</td>
<td>3162 ± 308</td>
<td>15</td>
</tr>
<tr>
<td>NREM3</td>
<td>1:18 ± 0:06</td>
<td>1812 ± 158</td>
<td>15</td>
</tr>
<tr>
<td>REM</td>
<td>0:36 ± 0:08</td>
<td>925 ± 176</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 1 Descriptive statistics of stages included in subsequent analyses.
Table 2 Post-hoc comparisons of LZc and spectral slope values between sleep/wake states, in the spontaneous and auditory-evoked EEG. All sleep/wake states were significantly different for LZc and the spectral slope in the 2-20 Hz range, in both the spontaneous and evoked EEG. In the 20-40 Hz range, the spectral slope was different between wake and all sleep stages, and between NREM3 and REM sleep. Values reported as (t, p) value pairs for each contrast. Statistically significant differences are marked in bold (p < 0.05).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Spontaneous</th>
<th>Evoked</th>
</tr>
</thead>
<tbody>
<tr>
<td>NREM2</td>
<td>12.5, 1.12e-13</td>
<td>18, 7.53e-18</td>
</tr>
<tr>
<td>NREM3</td>
<td>5.3, 1.13e-10</td>
<td>8.6, 7.3e-6</td>
</tr>
</tbody>
</table>

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<tr>
<th>Stage</th>
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<td>NREM3</td>
<td>5.3, 1.13e-10</td>
<td>8.6, 7.3e-6</td>
</tr>
</tbody>
</table>

**Note:** This table represents post-hoc comparisons of LZc and spectral slope values between sleep/wake states, in the spontaneous and auditory-evoked EEG. All sleep/wake states were significantly different for LZc and the spectral slope in the 2-20 Hz range, in both the spontaneous and evoked EEG. In the 20-40 Hz range, the spectral slope was different between wake and all sleep stages, and between NREM3 and REM sleep. Values reported as (t, p) value pairs for each contrast. Statistically significant differences are marked in bold (p < 0.05).
<table>
<thead>
<tr>
<th>Stage</th>
<th>Lempel-Ziv complexity</th>
<th>Spontaneous M ± SD</th>
<th>Evoked M ± SD</th>
<th>Contrast M ± SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake</td>
<td></td>
<td>0.4 ± 0.04</td>
<td>0.4 ± 0.03</td>
<td>-1.30 ± 0.21</td>
<td>-1.30</td>
<td>0.21</td>
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<tr>
<td>NREM2</td>
<td></td>
<td>0.27 ± 0.02</td>
<td>0.26 ± 0.02</td>
<td>-10.62 ± 5.88e-8</td>
<td>-10.62</td>
<td>5.88e-8</td>
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<tr>
<td>NREM3</td>
<td></td>
<td>0.21 ± 0.02</td>
<td>0.19 ± 0.02</td>
<td>-12.59 ± 1.00e-8</td>
<td>-12.59</td>
<td>1.00e-8</td>
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<tr>
<td>REM</td>
<td></td>
<td>0.34 ± 0.02</td>
<td>0.3 ± 0.02</td>
<td>-18.94 ± 3.01e-10</td>
<td>-18.94</td>
<td>3.01e-10</td>
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<thead>
<tr>
<th>Stage</th>
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<tr>
<td>Wake</td>
<td>-0.78 ± 0.20</td>
<td>-0.83 ± 0.18</td>
<td>-0.52 ± 1.22e-5</td>
<td>-0.52</td>
<td>1.22e-5</td>
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<tr>
<td>NREM2</td>
<td>-1.95 ± 0.14</td>
<td>-1.95 ± 0.15</td>
<td>0.63 ± 0.54</td>
<td>0.63</td>
<td>0.54</td>
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<tr>
<td>NREM3</td>
<td>-2.69 ± 0.22</td>
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<tr>
<td>REM</td>
<td>-1.41 ± 0.14</td>
<td>-1.45 ± 0.14</td>
<td>-2.94 ± 0.02</td>
<td>-2.94</td>
<td>0.02</td>
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</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Spontaneous M ± SD</th>
<th>Evoked M ± SD</th>
<th>Contrast M ± SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake</td>
<td>-1.68 ± 0.88</td>
<td>-1.63 ± 0.86</td>
<td>5.11 ± 2.46e-4</td>
<td>5.11</td>
<td>2.46e-4</td>
</tr>
<tr>
<td>NREM2</td>
<td>-2.59 ± 0.31</td>
<td>-2.57 ± 0.33</td>
<td>0.62 ± 0.54</td>
<td>0.62</td>
<td>0.54</td>
</tr>
<tr>
<td>NREM3</td>
<td>-2.38 ± 0.29</td>
<td>-2.35 ± 0.29</td>
<td>1.87 ± 0.16</td>
<td>1.87</td>
<td>0.16</td>
</tr>
<tr>
<td>REM</td>
<td>-2.73 ± 0.49</td>
<td>-2.78 ± 0.51</td>
<td>-1.68 ± 0.16</td>
<td>-1.68</td>
<td>0.16</td>
</tr>
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</table>

Table 3: Comparison of spectral slope and LZc values between the spontaneous and auditory-evoked EEG. LZc was modulated by auditory stimulation in all sleep stages, and not in wake. In the 2-20 Hz range, the spectral slope was steeper in the evoked than in the spontaneous EEG, while in the 20-40 Hz range, the slope was flatter in the evoked EEG, compared to the spontaneous. Statistically significant (p < 0.05) differences marked in bold.
Neural complexity and the spectral slope characterize auditory processing in wakefulness and sleep

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Keywords: 1/f; EEG; Consciousness; Evoked; Spontaneous
Abstract

Auditory processing and the complexity of neural activity can both indicate residual consciousness levels and differentiate between states of arousal. However, how measures of neural signal diversity, or complexity, manifest in evoked activity, and, more generally, how the electrophysiological characteristics of auditory responses change in states of reduced consciousness, remain under-explored. Here, we tested the hypothesis that measures of neural complexity and the spectral slope would discriminate stages of sleep not only in spontaneous EEG, but also in auditory-evoked responses. High-density EEG was recorded in 21 participants to determine the spatial relationship between these measures, and between spontaneous and auditory-evoked signals. Results showed that the complexity and the spectral slope in the 2-20 Hz range discriminated between sleep stages and had a high correlation in sleep. In wakefulness, complexity was strongly correlated to the 20-40 Hz spectral slope. Auditory stimulation resulted in reduced complexity in sleep compared to spontaneous activity and modulated the spectral slope in wakefulness. These findings demonstrate the persistence of electrophysiological markers of arousal during both spontaneous and evoked EEG activity and have direct applications to studies using auditory stimulation to probe neural functions in states of reduced consciousness.
Introduction

The human brain has an astonishing capacity of processing stimuli of the environment even in the absence of overt signs of consciousness. The integrity of the auditory processing network has been linked to the depth of anesthesia (Nourski et al., 2018), the presence of residual consciousness in patients with disorders of consciousness (Gui et al., 2020; Laureys, 2000), and to the chances of coma patients to regain consciousness (Aellen et al., 2022; Alnes et al., 2021; Liu et al., 2022; Morlet & Fischer, 2014; Robinson et al., 2003). During sleep, processing of auditory stimuli is largely preserved (Blume et al., 2018; Ruby et al., 2008; Wislowska et al., 2022), although the amplitude, latencies, and frequency content of auditory-evoked potentials (AEPs) change according to the state of sleep (Andrillon et al., 2016; Wislowska et al., 2022).

In parallel to studying AEPs, a large body of literature assessing quantitative measures of conscious processing has focused on measures of neural information content, or complexity (Casali et al., 2013; Sarasso et al., 2015). In states of reduced consciousness, spontaneous neural activity typically loses information content (Sarasso et al., 2021; Tononi & Edelman, 1998). At the level of electroencephalography (EEG), information content can be quantified in two main ways: (a) via measures of neural complexity, assessing how regular a signal is across time (Casali et al., 2013; Schartner et al., 2017), or (b) via measures of the steepness of EEG power spectra, assessing the speed of decay in 1/f EEG dynamics (Donoghue et al., 2020; Pritchard, 1992).

Both of these measures have been studied in a large body of literature measuring spontaneous neural activity in the absence of sensory stimulation (Frohlich et al., 2022; Lendner et al., 2020; Mateos et al., 2018; Medel et al., 2022; Miskovic et al., 2019; Nicolaou & Georgiou, 2011; Schartner et al., 2015, 2017; Timmermann et al., 2019). In spontaneous activity, neural complexity tends to decrease when conscious processing is reduced, such as during propofol anesthesia (Medel et al., 2022; Schartner et al., 2015; Varley et al., 2021), deep sleep (Abásolo
et al., 2015; Andrillon et al., 2016; Mateos et al., 2018; Nicolaou & Georgiou, 2011), and epileptic seizures (Mateos et al., 2018). In sleep in particular, complexity of neural activity decreases compared to wakefulness (Abásolo et al., 2015; Andrillon et al., 2016; González et al., 2022; Mateos et al., 2018; Nicolaou & Georgiou, 2011), and it is lower in non-rapid eye movement (NREM) than in rapid eye movement (REM) sleep (Abásolo et al., 2015; Andrillon et al., 2016; Mateos et al., 2018; Nicolaou & Georgiou, 2011). The reduction in complexity of spontaneous EEG signals during NREM sleep relative to wakefulness or REM may be due to slow wave activity (0.5 – 4 Hz), which exhibits strong stereotypical patterns (Adamantidis et al., 2019; González et al., 2022; Massimini et al., 2004).

Similar to neural complexity, the spectral slope of the EEG power spectrum is also sensitive to changes in consciousness levels, such as those occurring during sleep (Höhn et al., 2022; Lendner et al., 2020; Miskovic et al., 2019) and anesthesia (Colombo et al., 2019; Lendner et al., 2020). The spectral slope is computed in either low (generally below 20 Hz), or high frequencies (generally between 20-45 Hz) (Alnes et al., 2021; Colombo et al., 2019; Gyurkovics et al., 2022; Höhn et al., 2022; Lendner et al., 2020). During sleep, the spectral slope tends to be steeper than in wake irrespective of frequency range (Höhn et al., 2022; Lendner et al., 2020). In the higher frequency range, the decay of the spectral slope is steeper during REM compared to NREM sleep (Höhn et al., 2022; Lendner et al., 2020), while in lower frequencies (generally below 20 Hz) it is flatter in REM relative to NREM (Höhn et al., 2022; Miskovic et al., 2019). The spectral slope, in particular in higher frequency ranges, has been previously linked to the excitation to inhibition (E/I) balance (Gao et al., 2017).

Despite numerous assessments of neural complexity and the spectral slope during spontaneous EEG activity in wake and sleep, there are only few studies assessing these two measures in evoked activity, following auditory stimulation. Neural complexity decreases in the auditory-evoked relative to the spontaneous EEG, predominantly during NREM sleep, and
more subtly in wakefulness (Andrillon et al., 2016), possibly as a result of an auditory-evoked increase in temporal structure of EEG signals. The very few attempts to quantify changes in the spectral slope with respect to auditory stimulation focus on the wake EEG and show that the spectral slope in low frequencies steepens following auditory stimulation, or attentional demand (Gyurkovics et al., 2022; Waschke et al., 2021). Notably, in deeply unconscious and acute coma patients, the complexity of AEPs is not always lower than that of conscious controls (Aellen et al., 2023; Alnes et al., 2021), as one could expect based on previous studies of resting-state activity (Abásolo et al., 2015; Mateos et al., 2018; Medel et al., 2022; Schartner et al., 2015; Varley et al., 2021). Instead, AEPs exhibit higher or lower complexity in coma patients compared to conscious controls (Alnes et al., 2021). It therefore remains unknown whether in states of reduced consciousness neural complexity and the spectral slope follow similar changes after auditory stimulation as during spontaneous neural activity.

Here, we focused on sleep as a controlled and reversible model for assessing neural dynamics in states of reduced consciousness (Tivadar et al., 2021). Our main aim was to investigate whether neural complexity and the spectral slope are modulated by sleep/wake states in similar ways following auditory stimulation as during spontaneous activity. We also aimed to characterize the spatial distribution of these measures across the scalp, using high-density EEG, which to date is under-explored, as the vast majority of studies have either limited spatial resolution, focus on single EEG signals, or collapse all spatial information (Alnes et al., 2021; Andrillon et al., 2016; Colombo et al., 2019; Frohlich et al., 2022; Gyurkovics et al., 2022; Höhn et al., 2022; Miskovic et al., 2019; Schartner et al., 2015; Timmermann et al., 2019). We hypothesized that (1) both the spectral slope and complexity would discriminate between stages of wake and sleep, not only during spontaneous activity but also in the auditory-evoked EEG, (2) the spectral slope and complexity following auditory stimulation would be strongly correlated in sleep and wakefulness, similar to what has been shown in spontaneous EEG activity in
sleep (Höhn et al., 2022), anesthesia (Medel et al., 2022) and in evoked activity in coma (Alnes et al., 2021) and wakefulness (Alnes et al., 2021; Höhn et al., 2022), and that (3) complexity would be reduced and the spectral slope become steeper in the auditory-evoked EEG compared to spontaneous activity. Additionally, we performed exploratory analyses to assess the topographical distribution of changes in spectral slope and complexity induced by wakefulness and sleep, in relation to slow wave activity.

Methods

Participants

Twenty-one participants (13 women; M_{age} ± S_{age}, 25.5 ± 3.4 years) took part in the experiment. Participants gave written informed consent and reported normal or corrected-to-normal vision, normal hearing, and no previous neurological or psychiatric disorder. Participants were instructed to sleep no more than four hours the night preceding the recording, and abstain from caffeine, alcohol, and any drugs for the last 24 hours before coming to the lab. The study was approved by the Ethics Committee of the canton of Bern, Switzerland. Participants arrived at the lab in the evening and were discharged the next morning.

Study Design

Auditory stimulation was presented before, during, and after overnight sleep. Participants were presented with pairs of auditory stimuli where a pure tone (554.37, 739.99, 932.33, 1244.5 Hz) was followed by a natural or man-made sound, with a constant 700 ms interval. The duration of the inter-trial interval (before each pure tone) was drawn randomly from a uniform distribution between 1300 and 1700 ms, such that there was at least 1000 ms of silence between a sound (300 ms duration) offset and the onset of the subsequent pure tone. In the context of the present study, we focused on AEPs following the pure tones, as their physical
characteristics are directly comparable to stimuli used in previous studies assessing auditory-evoked potentials in other states of reduced consciousness, such as coma (Alnes et al., 2021; Fischer et al., 2004; Pfeiffer et al., 2018; Tzovara et al., 2013). Sounds had a duration of 100 ms with a 5 ms on- and off-ramp and were sampled at 44.1 kHz.

**Experimental Procedure and EEG Acquisition**

Upon arriving in the lab on the evening of the recording, participants were fitted with a sensor net after giving informed written consent and performing their pre-bedtime routines. Next, participants were provided with noise isolating in-ear earphones (Etymotic Research, Inc. ER4-SR) through which the auditory stimuli were presented. They next performed a session of wake EEG. Then participants were offered a sleep opportunity and asked to relax and ignore the sounds that were presented throughout the night. Participants were woken up in the morning and performed the same wake EEG session as before going to sleep.

EEG was recorded with 256-electrode HydroCel geodesic sensor nets for long-term monitoring and a GES 300 amplifier (Electrical Geodesic Inc., EGI, Eugene, OR). Data was recorded at a 1000 Hz sampling rate with electrode Cz serving as online reference. To enable an accurate marking of the onset of auditory events on the EEG recording, the analogue auditory signal presented to participants was also passed to a Physio16 input box (EGI) connected to the GES 300 amplifier.

**EEG Preprocessing**

Data preprocessing and analysis was done in Python 3.9.7 using the MNE-Python toolbox (version 0.23.4). Data was first downsampled to 500 Hz, filtered between 1 and 40 Hz and channels with artifacts were manually identified. Independent component analysis was performed on the remaining electrodes. Components reflecting muscle artifacts and cardiac
activity were removed, as well as eye-blink and saccade components from wake sessions, and
components reflecting rapid eye-movements from sleep sessions. Next, we performed interpo-
lation of noisy electrodes (M_{bad} ± SD_{bad}, 23.8 ± 13.8 electrodes per participant). The recordings
were then average-referenced and epoched to two different epoch types. The first (“Spontane-
ous”) was extracted from -500 to 0 ms relative to pure tones’ onset, and the second 0 to 500
ms relative to pure tones’ onset (“Evoked”) (See Figure 1 for Grand Average AEPs across
participants). As it is common practice in the field of EEG, baseline correction was applied to
the stimulation condition epochs, using the -50 to 0 ms time-period, but all results were repli-
cated without baseline correction. The resulting epochs were visually inspected, and noisy
epochs were rejected. Finally, a subset of electrodes on the chin and neck (N = 83 electrodes)
were excluded from analyses, as they were contaminated by muscle artifacts in the wake re-
cordings.

Sleep Scoring and Sleep Stage Selection

EEG data were scored offline in 30 second epochs according to the AASM criteria
(Berry et al., 2020) by two scorers (Example hypnogram: Figure 1C; Summary sleep statistics:
Table 1). Sleep-scoring was performed using a sub-set of electrodes, corresponding to the
equivalent electrodes to F3, F4, C3, C4, O1, and O2 on the 256-electrode HydroCel geodesic
sensor net (Luu & Ferree, 2005), referenced to their contralateral mastoid. Only participants
with at least 100 trials in a sleep stage were included in analyses of that sleep stage (Table 1
for descriptive statistics).

EEG Data Analysis

Spectral slope. To compute the spectral slope per condition and sleep stage, we first
estimated the power spectral density for each participant and channel. The power spectral
density was calculated using Welch's method as implemented in the MNE Python toolbox (Gramfort et al., 2013), and as in previous studies using similar experimental stimuli (Alnes et al., 2021; Cusinato et al., 2022). Next, the spectral slope was obtained independently for the 2-20 and 20-40 Hz ranges using the specparam toolbox (Donoghue et al., 2020) and following previous work estimating the spectral slope in spontaneous and evoked EEG data (Cusinato et al., 2022). In particular, the two frequency bands of 2-20 and 20-40 Hz were chosen to obtain a better local fit by avoiding a ‘knee’ around 20 Hz observed in previous studies estimating the spectral slope in scalp EEG data (Alnes et al., 2021; Colombo et al., 2019; Cusinato et al., 2022).

**Lempel-Ziv complexity.** We employed Lempel-Ziv complexity (LZc; Lempel & Ziv, 1976) to quantify the complexity of EEG signals during spontaneous and auditory-evoked activity using a similar approach as in previous EEG studies (Aellen et al., 2023; Alnes et al., 2021; Brito et al., 2020). LZc is a measure of the compressibility of a signal obtained by calculating how many unique sequences exist within it, thus providing an index of how complex the signal is. To obtain one LZc score for each participant and electrode, we concatenated the epochs belonging to the same condition and sleep stage per participant and binarized each channel according to whether the amplitude was above or below the median value of the channel at each time-point. We next quantified the number of unique subsequences in the binarized sequence, giving us a raw LZc score. LZc scores was normalized by the mean LZc score of 50 randomly shuffled versions of the same binarized signal. Randomly shuffling the binary sequence maximizes the number of unique subsequences for a sequence of given length (Brito et al., 2020), and the reported, normalized, LZc score is therefore a measure of how complex a signal is relative to its maximum obtainable complexity.

**Slow-wave density.** Slow-waves were detected on each EEG channel separately using the single-channel slow-wave detection algorithm of the YASA Toolbox (Vallat & Walker,
The continuous average-referenced EEG signal of each period of NREM sleep, resampled to 100 Hz, was used for slow-wave detection. Similar to the procedure described in other reports (Nir et al., 2011), we band-pass filtered the EEG signal between 0.5 and 4 Hz and detected slow-waves based on their negative peak, defined as individual half-waves in the EEG with a negative deflection lasting 0.25 to 1 second between consecutive zero-crossings. Following visual inspection of the data, we removed outliers by excluding slow-wave candidates with a peak-to-peak amplitude outside the 50 - 350 µV range. Slow-wave density was operationalized as the average number of slow-waves per minute in NREM3 sleep, obtained by dividing the final number of slow-waves identified in NREM3 with number of minutes spent in the sleep stage. The detection of slow wave activity was focused exclusively on NREM3, where slow waves are most likely to occur, with the goal of linking local slow waves to measures of neural complexity and synchrony.

**Statistical analysis.** We used linear mixed effects models with a random intercept for each participant to investigate differences in spectral slope and LZc between sleep stages, to account for varying number of participants reaching each sleep stage and for the dependency of stage within participants: \( VALUES \sim stage + (1 \mid participants) \), where \( VALUES \) was the spectral slopes in either the 2-20 or 20-40 Hz range, or the LZc, for each participant in each of the stages (Wake, NREM2, NREM3, REM), in either the evoked or spontaneous EEG condition. Post-hoc contrasts between pairs of wake/sleep stages, or between the spontaneous and evoked EEG within a wake/sleep stage, were performed using two-sided paired sample t-tests. False Discovery Rate (FDR) correction was applied to all p-values to correct for multiple comparisons across electrodes. To reduce the risk for false positives, we employed a criterion of \( p < 0.01 \) along with FDR correction in all our analyses.
Results

Participants were presented with auditory stimuli in wakefulness and sleep (Figure 1). AEPs in wakefulness were characterized by typical EEG components, occurring around 100 ms after sound onset, with a negative polarity in central electrodes (Figure 1B). During NREM, AEPs showed slower responses, with the most prominent peaks at later latencies, between 150 and 250 ms after sound onset (Figure 1B), while during REM, auditory responses were lower in amplitude.

Spectral Slope and Lempel-Ziv Complexity in Wake and Sleep

We first investigated whether there were systematic differences in the spectral slope in the 2-20 Hz or 20-40 Hz range, and in LZc, among wake and sleep stages (Wake, NREM2, NREM3, REM). LZc was higher in wake than during sleep, and different between sleep stages, with an ordering of wake > REM > NREM2 > NREM3, in both the evoked and spontaneous EEG activity (Figure 2A, full and empty circles for evoked and spontaneous, respectively). We first investigated whether there was an effect of sleep/wake state on LZc, using a linear mixed-effects model, and found a main effect of sleep/wake in both the spontaneous EEG and AEPs (Figure 2A; spontaneous: $F(3, 41) = 166.94, p < 0.001$; evoked: $F(3,41) = 184.97, p < 0.001$).

Likewise, the spectral slope in the 2-20 Hz range showed a main effect of sleep/wake state both for spontaneous EEG activity and AEPs (Figure 2D; spontaneous: $F(3,41) = 415.48, p < 0.001$; evoked: $F(3,41) = 405.65, p < 0.001$). Similarly, the slope in the 20-40 Hz range also showed a main effect of state (Figure 2E; spontaneous: $F(3,41) = 16.38, p < 0.001$; evoked: $F(3,41) = 19.66, p < 0.001$). The 2-20 Hz range slope was steeper for NREM3 compared to NREM2, REM and Wake, while the 20-40 Hz slope was shallower in wake, followed by NREM2/3 which were at similar ranges, and then REM sleep where it was steeper (Figure 2D/E).
Post-hoc contrasts (reported in Table 2) revealed that LZc was significantly different between all pairs of sleep/wake states for both spontaneous and evoked activity and followed an ordering of: NREM3 < NREM2 < REM < Wake (Figure 2A; Table 2). The spectral slope in the 2-20 Hz range followed the same order, also for both spontaneous and evoked activity, and was also significantly different between all pairs of sleep/wake states (Figure 2D; Table 2). The 20-40 Hz spectral slope was significantly flatter for wake compared to all sleep stages (Figure 2E; Table 2), and significantly flatter in NREM3 compared to REM, both for spontaneous and evoked activity (Table 2).

The Relationship Between Spectral Slope and LZc Differs Between Sleep and Wakefulness

We next calculated the correlation between LZc and the spectral slope, in order to investigate the relationship of these two measures. During wakefulness, there was no correlation between LZc and the spectral slope in the 2-20 Hz range (Figure 2B; spontaneous: $r = 0.15$, $p = 0.52$; evoked: $r = 0.27$, $p = 0.28$). However, a strong and significant correlation was observed between LZc and the 20-40 Hz spectral slope: participants with higher complexity had flatter 20-40 Hz slope (Figure 2C; spontaneous: $r = 0.67$, $p < 0.01$; evoked: $r = 0.66$, $p < 0.01$). Contrary to wakefulness, there was no significant correlation between LZc and the spectral slope in the 20-40 Hz range for any stage of sleep (Figure 2C; NREM2 spontaneous: $r = -0.46$, $p = 0.11$; NREM2 evoked: $r = -0.48$, $p = 0.11$; NREM3 spontaneous: $r = -0.009$, $p = 0.97$; NREM3 evoked: $r = -0.07$, $p = 0.9$; REM spontaneous: $r = -0.49$, $p = 0.11$; REM evoked: $r = 0.55$, $p = 0.11$). However, there was a strong and statistically significant positive correlation between LZc and the 2-20 Hz spectral slope for all sleep stages (Figure 2B), including NREM2 (spontaneous: $r = 0.89$, $p < 0.001$; evoked: $r = 0.72$, $p < 0.01$), NREM3 (spontaneous: $r = 0.86$, $p < 0.001$; evoked: $r = 0.87$, $p < 0.001$), and REM sleep (spontaneous: $r = 0.67$, $p < 0.05$; evoked: ...
r = 0.71, p < 0.01). In summary, during sleep, LZc was strongly and positively correlated to the 2-20 Hz spectral slope, while in wakefulness, to the 20-40 Hz spectral slope.

Spectral Slope and Complexity in the Spontaneous Versus Evoked EEG

In the abovementioned analyses, spontaneous and evoked activity showed similar modulations by sleep/wake states. In the following, we directly tested the effects of auditory stimulation on LZc and the spectral slope. LZc did not differ between the evoked and spontaneous EEG in wakefulness (t(19) = -1.30, p = 0.21; Figure 2A; Table 3). By contrast, in all sleep states, we observed a significant decrease in the complexity of EEG signals following auditory stimulation compared to spontaneous activity (Figure 2A; Table 3 for a detailed description of statistical tests). However, we observed a steepening of the 2-20 Hz spectral slope of AEPs relative to the spontaneous wake EEG (t(19) = -6.52, p < 0.001; Figure 2D; Table 3). The 2-20 Hz spectral slope did not differ between the auditory-evoked vs. spontaneous EEG in any of the investigated stages of sleep (Figure 2D; Table 3). Similarly, there was no stimulation-related modulation of the spectral slope in the 20-40 Hz range during sleep, while a slight, however, statistically significant, flattening of the slope was observed in wakefulness following auditory stimulation (t(19) = 5.11, p < 0.001; Figure 2E; Table 3).

Spatial Correlates of Complexity and the Spectral Slope

After establishing global characteristics of LZc and the spectral slope in wake and sleep, we next explored their spatial correlates, taking advantage of the high-density EEG montage. To this aim, instead of averaging each of the studied measures across electrodes, we contrasted spontaneous to post-stimulation values for each electrode separately. In wake, posterior electrodes had lower LZc than frontal and temporal electrodes, while, across sleep stages, LZc was highest in temporal electrodes, and had a remarkable reduction in frontal electrodes (Figure 3).
Considering each electrode separately, 9/173 electrodes, primarily centrally located, had a significantly different LZc in wakefulness between the spontaneous and evoked EEG (Figure 3; max p < 0.01, FDR-corrected). In all stages of sleep, all of the included electrodes had a significant reduction in LZc post-auditory stimulation relative to the spontaneous EEG (Figure 3; NREM2: max p < 0.01; NREM3: max p < 0.001; REM: max p < 0.001, FDR-corrected), mirroring the strong effect of auditory stimulation observed when averaging LZc values over all electrodes during sleep (Figure 2; Table 3).

The spatial distribution of the spectral slope values in the 2-20 Hz range (Figure 4A) strongly resembled that observed for LZc in sleep (Figure 3). Across all sleep/wake states, there was a flattening of the slope in temporal electrodes. This was accompanied by a steepening in frontal electrodes in wake and NREM sleep, which was specific to electrodes close to the midline in wake. Wake was also characterized by a steepening of the slope in the 2-20 Hz range in central electrodes, which was not observed in sleep (Figure 4A). In the 20-40 Hz range, there was a tendency towards a flatter spectral slope in temporal electrodes relative to other regions across all sleep/wake states, which was however less pronounced in REM (Figure 4B).

Contrasting the spontaneous and evoked EEG, we observed a steepening of the 2-20 Hz spectral slope in wakefulness in the vast majority of EEG electrodes following auditory stimulation (Figure 4A; 99/173 electrodes; max p < 0.01, FDR-corrected). In sleep, however, no electrodes showed a significant difference in their 2-20 Hz spectral slope between spontaneous and evoked EEG. In the 20-40 Hz spectral slope, there was no single-electrode significant difference between the spontaneous and evoked EEG, neither in wake nor in any stages of sleep (Figure 4B).

We next investigated the spatial relationship between LZc and the spectral slope, in both the spontaneous and evoked EEG. In NREM2, the 2-20 Hz spectral slope was significantly and positively correlated to LZc for 153/173 electrodes in the spontaneous EEG (Figure 5A;
max $p < 0.01$, FDR-corrected), and for 99/173 electrodes in the post-stimulation period (Figure 5A; max $p < 0.01$, FDR-corrected). A similar positive correlation between 2-20 Hz slope and LZc was also found for NREM3 (Figure 5A; spontaneous, evoked; 172/173 (max $p < 0.01$), 171/173 (max $p < 0.01$) electrodes, FDR-corrected), and a weaker, albeit still present, relationship was found for REM sleep (Figure 5A; spontaneous, evoked; 24/173 (max $p < 0.01$), 64/173 (max $p < 0.01$) electrodes, FDR-corrected). In wakefulness, we found the weakest relationship between LZc and the spectral slope of any state in the 2-20 Hz range, with 17/173 electrodes having a significant correlation in the auditory-evoked EEG (Figure 5A; max $p < 0.01$, FDR-corrected), and none in the spontaneous signal (Figure 5A).

We next examined single-electrode correlations between LZc and the 20-40 Hz spectral slope and found that no electrodes had a statistically significant correlation in NREM2, NREM3, or REM sleep (Figure 5B), for neither the spontaneous nor the evoked EEG. In wakefulness, there was a strong correlation between LZc and the 20-40 Hz slope in both the spontaneous (Figure 5B; 148/173 electrodes, max $p < 0.01$, FDR-corrected) and the evoked EEG (137/173 electrodes, max $p < 0.01$, FDR-corrected), as would be expected considering the strong correlation between the two measures when averaging across all electrodes (Figure 2C).

**Slow-Wave Density**

Last, we focused on NREM3 sleep, that is characterized by prominent slow oscillatory activity, and tested whether the steeper 2-20 Hz slope and lower LZc that was observed in frontal EEG electrodes, could be explained by the local density of slow-wave activity. To this aim, we calculated the slow-wave density, operationalized as the average number of slow-waves per minute, for each electrode and participant in NREM3 sleep. On average, the slow-wave density was particularly pronounced in frontal EEG electrodes, strongly resembling the topography of LZc (Slow-wave topography: Figure 6D,E; LZc topography: Figure 3). We
found no correlation between slow-wave density and the 2-20 or 20-40 Hz spectral slope neither in the spontaneous nor the evoked EEG (Figure 6B;C). By contrast, we found a significant negative correlation between LZc and slow-wave density (Figure 6A), both on the spontaneous (r = -0.71, p < 0.05, FDR-corrected) and evoked (r = -0.65, p <0.05, FDR-corrected) EEG, suggesting that participants with higher slow wave density had lower complexity in their EEG signals.

We additionally investigated the topographic distribution of the relationship between LZc and the slow wave density. We found a negative significant correlation for 74/173 electrodes in the spontaneous and 37/173 electrodes in the evoked EEG (p < 0.01, FDR-corrected). The electrodes showing this negative correlation between LZc and slow wave density were identified in two distinct clusters, a fronto-central and a parietal-occipital one (Figure 6F).

**Discussion**

Our study examined the variation of the spectral slope and LZc across wakefulness and sleep stages and assessed how these measures are affected by auditory stimulation. We showed that neural complexity can distinguish between sleep/wake states based on both spontaneous and auditory-evoked EEG activity. Following auditory stimulation, LZc reduced during sleep but not wakefulness. The 2-20 and 20-40 Hz spectral slope became flatter in the spontaneous compared to the evoked EEG in wakefulness but did not significantly change in any of the studied sleep stages. The correlation between LZc and the spectral slope was strong, but dependent on the frequency range of the spectral slope calculation and the state, with LZc correlating with the spectral slope in the 2-20 Hz range during sleep and in the 20-40 Hz range during wakefulness. Lastly, we found no evidence of electrode-specificity in either the relationship between LZc and the spectral slope or the auditory-evoked modulation of either measure. Our results show that although neural complexity and the spectral exponent are modulated by auditory
stimulation, this modulation is negligent when compared to overall changes induced by sleep/wake states.

Information Content in Auditory-Evoked Potentials

The field of consciousness research has mainly focused on two ‘schools’ for evaluating neural functions in conditions of reduced consciousness. The first consists of assessing sensory neural responses to external stimuli, typically by measuring the latency and presence or absence of AEP components (Binder et al., 2017; Nourski et al., 2018; Perrin et al., 1999; Pfeiffer et al., 2018; Ruby et al., 2008; Sculthorpe et al., 2009; Tivadar et al., 2021). NREM sleep AEPs are characterized by higher amplitude components, occurring at greater latencies than wake AEPs (Arzi et al., 2021; Colrain & Campbell, 2007; Yang & Wu, 2007). To this, we add that sleep AEPs also have a reduced neural complexity and a steeper slope relative to wakefulness.

The second school of quantitative measures of consciousness assesses instead the information content of spontaneous neural activity in the absence of sensory input (Casali et al., 2013; Frohlich et al., 2022; Sarasso et al., 2021; Schartner et al., 2017). This line of work has shown that when consciousness diminishes, for instance during sleep, anesthesia, or in disorders of consciousness, the complexity of spontaneous neural activity is diminished (Andrillon et al., 2016; Mateos et al., 2018; Medel et al., 2022; Schartner et al., 2015, 2017), while the spectral exponent typically flattens (Colombo et al., 2019; Lendner et al., 2020; Medel et al., 2022). To this line of research our results add that the reduction of complexity observed in NREM can be explained by the density of local slow wave activity.

Overall, our work aims at bridging these two fields investigating consciousness measures, by showing that metrics of information content can be applied similarly to the evoked as to the spontaneous EEG, while retaining their sensitivity in tracking changes in the sleep/wake cycle. Currently, only few studies have investigated how measures of neural
information content are altered by evoked activity following auditory stimulation (Andrillon et al., 2016; Bola et al., 2018), which represents a significant gap. Andrillon et al. (2016) showed that LZc is reduced relative to baseline in an early and comparable time-period as our study, following onset of spoken words across sleep/wake states, while Bola et al. (2018) found that LZc was lower while wake participants listened to speech than during a resting period. By employing auditory stimulation via pure tones, we show that this effect is not only present for stimuli with high information content, such as spoken words. In addition, we show that an auditory-evoked, and frequency-range specific effect, exists in the spectral slope of the EEG.

Evidence of the prognostic and diagnostic value of quantification of AEPs and neural information content for assessing consciousness levels, or the integrity of neural functions in reduced consciousness conditions is growing (Aellen et al., 2023; Alnes et al., 2021; Bekinschtein et al., 2009; Benghanem et al., 2022; Colombo et al., 2019; Comanducci et al., 2020; Liu et al., 2022; Morlet & Fischer, 2014; Pfeiffer et al., 2018). Measures based on information content can differentiate levels of consciousness (Casali et al., 2013), while both measures based on information content and AEPs are promising as prognostic tools for patients with disorders of consciousness (Alnes et al., 2021; Liu et al., 2022; Pfeiffer et al., 2018; Tzovara et al., 2013). Recent work has shown that in acute coma, the complexity of auditory-evoked EEG responses, and the power spectral decay can be either higher or lower than that of healthy and conscious controls (Alnes et al., 2021), opposite to what one would have expected based on studies evaluating the complexity or spectral slope of spontaneous neural activity (Lendner et al., 2020; Medel et al., 2022; Miskovic et al., 2019; Schartner et al., 2015; Timmermann et al., 2019). Here, we show that neural information content reflective of sleep/wake state is not obfuscated by AEPs and that diagnostic and prognostic tools leveraging both approaches simultaneously could be considered.
In our analyses, we observed that the spectral slope, both in the 2-20 and 20-40 Hz range, flattened after auditory stimulation in wakefulness, but not during sleep. Conversely, global LZc across the scalp did not differ between the spontaneous and evoked EEG in wakefulness, while it decreased LZc following auditory stimulation across sleep stages. This is in line with previous reports, showing that auditory stimulation decreases LZc in NREM sleep (Andrillon et al., 2016). Others have also reported a decrease of complexity after auditory stimulation in wakefulness (Andrillon et al., 2016; Bola et al., 2018), which we have also observed in our data, in central electrodes. The difference in modulation of LZc in sleep and wake may arise from the large-amplitude ERP components, observed specifically in NREM sleep, such as stimulus-elicited k-complexes (Colrain & Campbell, 2007), producing a widespread response and leading to less stochasticity in the auditory-evoked relative to the spontaneous EEG in sleep. This is in line with the observation that the reduction in LZc following auditory stimulation in sleep was not constrained to any specific region but was instead reflected in a general reduction of LZc across the scalp.

Neural Complexity Differentiates Between Sleep Stages in Evoked and Spontaneous Activity

Our finding that LZc decrease from wake to NREM sleep is corroborated by previous results in spontaneous EEG (Aamodt et al., 2021; Andrillon et al., 2016; Schartner et al., 2017), while comparable results have also been found using other measures of complexity in humans (Burioka et al., 2005) and rats (González et al., 2022). We hypothesized that the reduced LZc in NREM sleep may be linked to slow-wave activity, leading to less variation in the EEG signal, an interpretation supported by the increase in delta power observed in NREM sleep (González et al., 2022). As expected, we found a statistically significant correlation between slow-wave density and LZc in NREM3. Participants with greater slow wave density were the ones
having lower complexity in their spontaneous and evoked NREM3 EEG signals. This effect was driven by two distinct clusters of frontal and parietal electrodes. The increase of LZc in REM relative to NREM could be linked to the re-emergence of a more wake-like EEG (Cirelli & Tononi, 2015; González et al., 2022).

**Disassociation Between the Spectral Slope in the 2-20 and 20-40 Hz Range**

Our analyses of the spectral slope focused on two different ranges: 2-20 and 20-40 Hz, following previous reports of a change in the rate of the PSD decay around 20 Hz (Colombo et al., 2019; Robinson et al., 2001). In our case, the spectral slope in the 2-20 Hz range decreased from wake to REM to NREM, whereas the spectral slope in the 20-40 Hz range differentiated between wake and all sleep stages, as well as between REM and NREM3 sleep. This is in line with previous studies that have proposed the spectral slope as a metric for differentiating sleep/wake states (Höhn et al., 2022; Lendner et al., 2020; Miskovic et al., 2019). The high sensitivity of the 2-20 Hz spectral slope at differentiating between sleep stages is in accordance with previous studies showing that the spectral slope in relatively low frequency ranges becomes increasingly negative from wake to REM to NREM2 to NREM3 (3-45 Hz: Höhn et al., 2022; 0.5-35 Hz: Miskovic et al., 2019). This is not surprising, as the lower frequency range encompasses EEG frequency bands that are sensitive to sleep stages, such as slow-waves (typical in NREM3; 0.5-4 Hz) and sleep spindles (typical in NREM2; 9-16 Hz) (Adamantidis et al., 2019; Massimini et al., 2004; Nir et al., 2011). The flattening of the spectral slope from NREM2/3 to REM sleep in the 2-20 Hz range may be attributed to a re-emergence of more wake-like brain activity, similar to what was observed for LZc (Cirelli & Tononi, 2015). By contrast, the 20-40 Hz spectral slope in sleep only discriminated between NREM3 and REM, and between wake and sleep. It has been proposed that the spectral slope in the 20-40 Hz range may reflect the E/I balance. Pyramidal cell activity is reduced in sleep and particularly in REM
sleep (Niethard et al., 2016), which would reduce the E/I balance, and may be indexed by a steepening of the spectral slope in the higher frequency range (Gao et al., 2017). Future studies should formally test links between the spectral slope and the E/I balance in sleep.

**Relation Between LZc and the Spectral Slope and Topographic Distribution**

The spectral slope in the 2-20 Hz range strongly correlated with LZc across NREM2, NREM3, and REM sleep, as expected given the similar ordering of values across sleep stages for both measures and their similar topographical distribution. This correlation may indicate that both measures reflect similar EEG sleep characteristics, as demonstrated by previous research in rats, where low-frequency activity contributed to the variation in complexity across sleep stages (González et al., 2022).

These findings are in accordance to previous reports (Höhn et al., 2022) albeit with a much lower density EEG montage, of 11 electrodes. Different from our results, Höhn et al. (2022) also found a correlation to LZc in the spectral slope in their higher frequency range (30-45 Hz) in NREM sleep, as well as a negative correlation between LZc and the slope in the same frequency range. One key difference is that our study had a high-density montage, which requires a much stricter correction for multiple comparisons, over a much larger set of electrodes.

**Limitations and Perspectives**

The current analysis is using sleep as a model for reduced consciousness (Sculthorpe et al., 2009; Strauss et al., 2015), but lacks ground truth, a common issue in studies relating level of consciousness to electrophysiological measures. Future studies should investigate links between evoked and spontaneous activity in other states of reduced or absent consciousness. Additionally, as auditory stimulation was presented throughout overnight sleep, we cannot exclude the possibility that it may have induced changes in sleep architecture. However, our
results in spontaneous (baseline) activity very closely mirror previous reports of complexity and spectral slope in sleep, in terms of direction of effects and range of reported values (Andrillon et al., 2016; Höhn et al., 2022; Lendner et al., 2020; Miskovic et al., 2019; Schartner et al., 2017), suggesting that auditory stimulation did not change the fundamental properties of the sleep EEG signals that we studied here. Last, future studies should evaluate whether our present results would translate in clinical populations with disorders of consciousness, with simultaneous assessments of evoked and spontaneous EEG, in order to advance the quest for markers of conscious processing.

Summary

Our work showed that both neural complexity and the spectral exponent discriminated between wake and sleep states, with the spectral slope discriminating more strongly between sleep/wake states in the 2-20 Hz range. LZc was reduced following auditory stimulation during sleep. However, the auditory-evoked reduction was still negligent with respect to the overall modulation of LZc by sleep/wake. Our results suggest that measures of information content of EEG signals applied to evoked activity are helpful in investigations of consciousness and can be applied in evoked or spontaneous EEG signals to probe neural functions in unconscious states.
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Methodology: SLA, AT
Resources: KS, AT
Supervision: AT
Visualization: SLA
Writing – original draft: SLA, AT
Writing – review & editing: SLA, LZMB, KS, AT

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.
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1 Tables
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Table 1 Descriptive statistics of stages included in subsequent analyses.
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**Table 2** Post-hoc comparisons of LZc and spectral slope values between sleep/wake states, in the spontaneous and auditory-evoked EEG. All sleep/wake states were significantly different for LZc and the spectral slope in the 2-20 Hz range, in both the spontaneous and evoked EEG. In the 20-40 Hz range, the spectral slope was different between wake and all sleep stages, and between NREM3 and REM sleep. Values reported as (t, p) value pairs for each contrast. Statistically significant differences are marked in bold (p < 0.05).
**Table 3** Comparison of spectral slope and LZc values between the spontaneous and auditory-evoked EEG. LZc was modulated by auditory stimulation in all sleep stages, and not in wake. In the 2-20 Hz range, the spectral slope was steeper in the evoked than in the spontaneous EEG, while in the 20-40 Hz range, the slope was flatter in the evoked EEG, compared to the spontaneous. Statistically significant (p < 0.05) differences marked in bold.
1 Figures
Figure 1 (A; B) Grand average spontaneous EEG activity (A) and AEPs (B) in wakefulness (top), NREM2 (second from top), NREM3 (third from top), and REM (bottom) sleep. The plotted topographies display EEG signals averaged across participants at peaks following auditory stimulation in wakefulness (95; 190 ms), NREM2 (80; 180 ms), NREM3 (60; 200 ms), and REM (60; 180 ms) sleep. The same time-points are displayed for the topographies of spontaneous EEG signals for consistency. Global field power (GFP) is shown in green. The shaded area in the (B) evoked EEG plot indicates the onset and duration of the presented auditory stimuli. (C) Example hypnogram from one participant in this study.
Figure 2 The spectral slope and LZc across sleep/wake states in the auditory-evoked and spontaneous EEG. (A) LZc varied systematically between sleep/wake states in both the spontaneous and evoked EEG. Similarly, the spectral slope was significantly different between states, in both the (D) 2-20 and (E) 20-40 Hz range. Across both the spontaneous and evoked EEG, (B) the spectral slope in the 2-20 Hz range correlated with LZc across sleep stages, but not in wakefulness, while (C) the spectral slope in the 20-40 Hz range correlated with LZc in wakefulness, but not in sleep.
Figure 3 Topographical map of LZc in the spontaneous and auditory-evoked EEG. Values are normalized to keep the same scale across states and between the spontaneous and evoked EEG. LZc decreased in 9/173 electrodes in wakefulness following auditory stimulation. (p < 0.01, FDR-corrected).

In all sleep stages, 173/173 electrodes showed a significant reduction in sleep in the evoked compared to the spontaneous EEG (p < 0.01; FDR-corrected).
Figure 4 Topographical map of the spectral slope in the (A) 2-20 Hz and (B) 20-40 Hz range in the spontaneous and auditory-evoked EEG. Values are normalized per stage and frequency band. (A) In the 2-20 Hz range, the spectral slope was steeper in the auditory-evoked than in the spontaneous EEG across 99/173 electrodes (p < 0.01, FDR-corrected). In sleep, no electrodes show a statistically significant change in spectral slope in the 2-20 Hz range (p >= 0.01, FDR-corrected). (B) Likewise, in the 20-40 Hz range, there was no difference between the spontaneous and evoked EEG, neither for wake nor any stages of sleep (p >= 0.001, FDR-corrected).
Figure 5 Topographical map of the correlation between LZc and the spectral slope in the (A) 2-20 Hz and (B) 20-40 Hz range. Electrodes with a significant correlation between the two measures are marked with white dots (p < 0.01, FDR-corrected). Darker red color indicates that complexity increases as the slope flattens, and darker blue color indicates complexity increases as the slope steepens. (A) Between LZc and the spectral slope in the 2-20 Hz range, there were few or no electrodes correlating in wake (spontaneous: 0/173; evoked: 17/173), a strong correlation in the direction of greater complexity as the slope flattened in NREM2 (spontaneous: 153/173; evoked: 99/173) and NREM3 (spontaneous: 172/173; evoked: 171/173). In REM, the correlating electrodes were more fronto-centrally located (spontaneous: 24/173; evoked: 64/173). (B) The spectral slope in the 20-40 Hz range tended to flatten as complexity increased in wake electrodes (spontaneous: 148/173; evoked: 137/173), and no relationship was observed between the two measures in any sleep stage.
Figure 6 Association between slow-wave density and LZc and the spectral slope in NREM3 sleep. (A) LZc and slow-wave density correlated in both the spontaneous (r = 0.69, p < 0.05) and evoked (r = 0.64, p < 0.05) EEG, with a trend towards greater complexity as slow-wave density decrease. (B; C) The spectral slope did not correlate with slow-wave density in neither the 2-20 nor 20-40 Hz range. (D; E) Topographical map of (D) LZc and (E) slow-wave density in the spontaneous EEG during NREM3 sleep. (F) Topographical distribution of the correlation between LZc and slow-wave density in the spontaneous EEG during NREM3 sleep. Electrodes with a statistically significant correlation are marked as white dots (74/173 electrodes, p < 0.01, FDR-corrected). Sws/minute: Slow-waves per minute.