Intracerebral dynamics of sleep arousals: a combined scalp-intracranial EEG study

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Abstract

As an intrinsic component of sleep architecture, sleep arousals represent an intermediate state between sleep and wakefulness and play an important role in sleep-wake regulation. They have been defined in an all-or-none manner, whereas they actually present a wide range of scalp-electroencephalography (EEG) activity patterns. It is poorly understood how these arousals differ in their mechanisms. Stereo-EEG (SEEG) provides the unique opportunity to record intracranial activities in superficial and deep structures in humans. Using combined polysomnography and SEEG, we quantitatively categorized arousals in non-rapid eye movement sleep into slow wave (SW) and Non-SW arousals based on whether they co-occurred with a scalp-EEG SW event. We then investigated their intracranial correlates in up to 26 brain regions from 26 patients (12 females). Across both arousal types, intracranial theta, alpha, sigma, and beta activities increased in up to 25 regions (p<0.05, d=0.06-0.63), while gamma and high frequency (HF) activities decreased in up to 18 regions across five brain lobes (p<0.05, d=0.06-0.44). Intracranial delta power widely increased across five lobes during SW arousals (p<0.05 in 22 regions, d=0.10-0.39), while it widely decreased during Non-SW arousals (p<0.05 in 19 regions, d=0.10-0.30). Despite these main patterns, unique activity was observed locally in some regions such as the hippocampus and middle cingulate cortex, indicating spatial heterogeneity of arousal responses. Our results suggest that Non-SW arousals correspond to a higher level of brain activation than SW arousals. The decrease in HF activities could potentially explain the absence of awareness and recollection during arousals.

Significance Statement

Intrinsic to sleep architecture, sleep arousals play an important role in sleep-wake regulation. They are defined in an all-or-none manner, whereas they actually present various scalp electroencephalography (EEG) patterns. Using simultaneous scalp and intracranial EEG in humans, we analyzed the intracranial activity during two types of arousals marked on scalp EEG, quantitatively categorized by whether they co-occurred with a scalp-EEG slow wave (SW). Non-SW arousals present prevalent low-voltage fast activity, while SW arousals exhibit high-voltage slow waves alongside fast activities. This work represents the first intracranial study of different types of NREM sleep arousals and provides a comprehensive description of local brain activities during both arousal types, serving as a foundation for future studies investigating regional behaviors during sleep-wake transition.

Introduction

Intrinsic to sleep architecture, sleep arousals are transient periods of increased vigilance level that occur around a hundred times every night without the sleeper's awareness or recollection (Schieber et al., 1971; Halász et al., 1979; Mathur and Douglas, 1995). They reflect an intermediate state between sleep and wakefulness and are defined as the shift of brain activity to higher frequencies in the scalp electroencephalogram (EEG) (Peter-Derex et al., 2015; Berry et al., 2020). Functionally, they may play a crucial role in sleep-wake regulation and allow the brain to respond to important environmental cues while preserving sleep continuity. (Boselli et al., 1998; Halasz et al., 2004; Bonnet and Arand, 2007; Latreille et al., 2020).

Sleep arousals have been defined as an all-or-none phenomenon (ASDA, 1992; Berry et al., 2020); however, arousals during non-rapid eye movement (NREM) sleep exhibit a wide range of activity patterns that differ in the amount of slow wave (SW) activity observed on the scalp EEG (Schieber et al., 1971; Halász, 1998; Parrino et al., 2006). "Fast" arousals present prevalent low-voltage fast activity, while "slow" arousals exhibit high-voltage SWs alongside fast activities. Despite the importance of arousals in sleep structure, the intracranial mechanisms leading to the scalp EEG manifestation of different arousal types remain poorly understood.

Previous studies provided partial insights to this question: from "slow" to "fast" arousals, a weak to strong modification of muscle tone and cardiorespiratory rates was reported, suggesting that different arousal types represent a continuous spectrum of physiological

activation and share a common brainstem involvement (Sforza et al., 1999, 2000; Terzano et al., 2002; Azarbarzin et al., 2014). Recent studies using stereo-EEG (SEEG) provided further insight. These recordings, performed exclusively in the presurgical evaluation of patients with focal drug-resistant epilepsy, offer the unique opportunity to record superficial and deep structures with high spatiotemporal resolution. They further enable the evaluation of high frequency activity which is difficult to distinguish on the scalp. When combined with polysomnography (PSG) and capitalizing on the channels without epileptic activity, SEEG can provide a thorough description of the intracranial activity underlying physiological sleep oscillations (Frauscher et al., 2020; von Ellenrieder et al., 2020). Using this method, homogeneous activity was discovered in the thalamus during NREM arousals, suggesting a common subcortical correlate underlying all arousal types (Peter-Derex et al., 2015). In contrast, highly heterogeneous activity was found across different cortical regions (Nobili et al., 2011; Peter-Derex et al., 2015; Ruby et al., 2021), indicating the activity variations during NREM arousals have a predominantly cortical origin. However, previous studies were limited as they did not differentiate between different arousal types and had small sample sizes ranging from 4 to 8 patients (Nobili et al., 2011; Peter-Derex et al., 2015; Ruby et al., 2021). Investigating the regional activities during different arousal types is crucial to understanding the nature of sleep arousals. It could also offer valuable insights into the neural activity during pathological sleep-wake transitions such as NREM parasomnias.

In this study, we quantitatively categorized NREM sleep arousals into SW arousals and Non-SW arousals based on whether they co-occurred with a scalp-EEG SW event, and

investigated their intracranial correlates in up to 26 brain regions from 26 patients. We explored: (a) the regional activities during sleep arousals; (b) the intracranial differences between the two arousal types, and (c) the influence of sleep homeostatic pressure on their overnight occurrence. We hypothesized: (a) due to the heterogeneous cortical activity observed previously, NREM arousals will show region-specific patterns (Nobili et al., 2011; Peter-Derex et al., 2015; Ruby et al., 2021); (b) Non-SW arousals represent a higher level of cortical activation than SW arousals as assessed by their activity change, given the higher autonomic modifications reported previously (Sforza et al., 1999, 2000; Terzano et al., 2002; Azarbarzin et al., 2014); and (c) “slow” arousals are more likely to occur during the first half of the night when the sleep pressure is high (Terzano et al., 2002).

Materials and Methods

Patient selection

We reviewed medical charts of 55 consecutive patients (30 males, 25 females) with drug-resistant focal epilepsy, aged 16 years or older, who underwent combined intracerebral SEEG and PSG recordings as part of their presurgical epilepsy evaluation at the Montreal Neurological Institute and Hospital between October 2013 and October 2021. If a patient underwent more than one SEEG evaluation, the most recent evaluation was used. Exclusion criteria were: (a) absence of SEEG channels with normal physiological activity; (b) absence of a well-identified seizure-onset zone (SOZ); (c) unreliable sleep and arousal scoring; (e) presence of an electro-clinical seizure during the selected night of combined SEEG-PSG recordings; (d) NREM arousal index (number of arousals per hour) exceeds

the normative range (Mitterling et al., Sleep 2015). If asymptomatic electrographic seizures were present, a 30-min window, starting 15 min before the seizure onset and ending 15 min after the seizure offset, was excluded from the analysis. This study was approved by the Montreal Neurological Institute and Hospital Review Ethics Board (2014-183).

Intracranial and scalp EEG recordings

Depth MNI (9 contacts, 0.5-1 mm in diameter, separated by 5 mm; 10 patients) or DIXI (10-15 contacts, 2 mm in diameter, separated by 1.5 mm; 18 patients) electrodes were implanted stereotactically using an image-guided system (ROSA Robotic, Indiana, United States or Medtronic Stealth, Minnesota, United States). The scalp EEG was recorded with subdermal thin wire electrodes at positions F4, C4, P4, F3, C3, P3, Fz, Cz, and Pz (except for 1 patient who had only F4, C4, F3, C3, 1 patient who had only Fz, Cz, and Pz; and 1 patient who did not have F3). Electrooculography (EOG) and chin electromyography (EMG) electrodes were applied prior to the night of the sleep recording. Scalp EEG channels were assessed using a bipolar montage, instead of the standard referential mastoid montage, as done in our previous studies. The reasons are (i) the mastoid electrode was not feasible for all patients due to the locations of implanted SEEG channels and risk of contaminating the EEG activity with epileptic activity and slow wave anomalies; (ii) bipolar montage was best suited for our study purpose to highlight local sleep activity (Frauscher et al., 2015; Frauscher et al., 2020; Latreille et al., 2020; Peter-Derex et al., 2023b).

SEEG recordings were sampled at 2 kHz using the Harmonie EEG system (Stellate, QC, Canada) for recordings prior to 2017, and the Neuroworkbench EEG system (Nihon Kohden, Japan) for recordings obtained in 2017 and later. EEG signals were high-pass filtered at 0.1 Hz and low-pass filtered at 500 Hz in the Harmonie EEG system, and high-pass filtered at 0.08 Hz and low-pass filtered at 600 Hz in the Neuroworkbench EEG system. Intracranial channels were assessed in the bipolar montage with the neighboring contacts on the SEEG electrode.

Selection and localization of intracranial channels

Only SEEG channels with normal brain activity were included in the analysis; these were determined by a procedure described in our previous work (Frauscher et al., 2018a). Briefly, these channels are located outside the seizure onset zone, inside normal tissue as assessed by MRI, do not show interictal epileptic discharges throughout the SEEG investigation, and do not show a significant slow-wave anomaly.

All patients underwent post-implantation imaging for anatomical localization of individual channels, which were determined using a procedure described previously (Drouin et al., 2016; Frauscher et al., 2018a). SEEG channels were then grouped into 38 anatomical regions that were condensed from a brain segmentation template, which originally included 66 regions in the cortical grey matter (Landman et al., 2012). Certain regions were merged to increase the number of channels in each region which ultimately resulted in 38 anatomical regions (Frauscher et al., 2018b). We then combined the same regions from both hemispheres to increase the number of channels available per region, as there

is no evidence suggesting that there are differences in EEG power spectra between hemispheres (Frauscher et al., 2018a). Finally, we excluded any region that contained less than 3 channels or were available in less than 3 patients.

Sleep and arousal scoring

Sleep scoring was performed manually in 30-s epochs using the scalp EEG, blind to SEEG data, by a board-certified neurophysiologist (B.F.), according to the American Academy of Sleep Medicine (AASM) criteria (Berry et al., 2020). Arousals are defined as an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) lasting at least 3 s, with at least 10 s of stable sleep preceding the change (Berry et al., 2020). The end of arousals was determined as either the clear reappearance of a sleep pattern, including the disappearance of rapid activities and the reappearance of a slower background rhythm, sleep features (vertex waves, spindles) or, for arousals preceding an epoch of wakefulness, by the onset of this epoch.

Unambiguous sleep arousals were manually scored by a board-certified neurophysiologist (L.P-D.) on Fz-Cz and, in five patients on F3-C3, Cz-Pz, or Fz-P4 due to artifacts in Fz-Cz, including those preceding awakenings or stage shifts. We then randomly selected 10% of the arousals of each patient and created the same number of non-arousal events, which are segments placed randomly during the non-arousal part of the recordings and which had an identical duration as the selected arousals. After that, the arousals and non-arousals were independently scored by two board-certified neurophysiologist (B.F. and C.A.) without knowledge of the markings by L.P-D. The kappa

values were 76.8% between L.P-D. and B.F. and 89.2% between L.P.D. and C.A.. These rates were considered excellent in the clinical context (Kaufman and Rosenthal, 2009).

Temporal windows of interest

We assessed the scalp-EEG and intracranial activity during three temporal windows, the arousal onset, arousal body, and arousal offset (Fig. 2). The temporal windows were defined using the scalp-EEG marking of arousals and the intracranial activities were computed using these time windows. The arousal onset was defined as the first 3-s window of the arousal, because (1) this was used in previous studies on sleep arousals (Peter-Derex et al., 2015, Ruby et al., 2021); (2) American Sleep Disorders Association (ASDA) defined the minimum duration of arousals to be 3 s (ASDA, 1992). The arousal body was defined as the period immediately after the onset until the end of the arousal. The division into the arousal onset and body was based on the observation of a strong delta increase at the beginning of some arousals compared to the arousal body (Peter-Derex et al., 2015). To explore the intracranial activities during the return to sleep immediately after the arousal, we defined the 3-s window after the end of the arousal as the arousal offset. Since sleep arousals are defined as a transient change in the current brain state, the baseline segment for arousal onset, body, and offset was selected individually for each arousal from every channel, instead of having a same baseline for all arousals. They were defined as the 10-s period of continuous sleep from -12 s to -2 s where 0 s is the arousal start time. The duration of 10 s was decided based on the AASM criteria which states that at least 10 s of stable sleep must precede the arousal (Berry et al., 2020). We chose to end the baseline at -2 s with respect to the arousal onset because

previous studies reported that delta activity increased in certain cortical areas during the 1-2 s before the onset of arousals on the scalp EEG (Nobili et al., 2011; Peter-Derex et al., 2015). Excluding the 2 s prior to arousals thus avoided the potential contamination of the baseline segment by early intracranial activity associated with arousals.

Arousal selection

For this study, 1646 sleep arousals from NREM stages N2 and N3 were included and analyzed together as NREM arousals. Because we wanted to study delta activity (0.5-4 Hz) which included frequencies at 0.5 Hz during the arousal body, we only included arousals with a duration of 5 s or longer to ensure that the arousal body lasted for at least 2 s. We thus excluded arousals which were shorter than 5 s (n = 18% of all included arousals). We further excluded arousals whose baselines occurred in a different sleep stage to the arousal itself (n = 6%), crossed two sleep stages (n = 3.4%), or overlapped with another arousal (n = 1.6%), so that the activity change during the arousals was not affected by the inherent changes in brain activity that occur during the transition between different sleep stages.

Classification of arousals

We classified arousals into slow wave (SW) and non-SW arousals. If the arousal intersected temporally with a SW event detected on any of the scalp channels specified below, it was classified as a SW arousal. If there was no co-occurring SW event, the arousal was defined as a Non-SW arousal.

Slow wave detector

SW events were automatically detected on scalp channels Fz-Cz, F3-C3, C3-P3, F4-C4, C4-P4, Cz-Pz during N2 and N3 sleep. Using a bipolar montage reduces the overall EEG amplitude compared to the referential montage. This reduction significantly impacts SW activity, with the potential for an up to 75% decrease in the Fz-Cz channel compared to C4-M1 (Kemp et al., 2013). As a result, we adjusted the amplitude detection criteria for SW events as done in our previous work (Latreille and Avigdor et al.,2023). In brief, the data was first filtered within the 0.3-4 Hz range and all successive positive-to-negative zero crossings were identified. We then included SW with a duration of 0.125-3 s. After that, we lowered the amplitude thresholds by 50-60% to account for the potential decrease of EEG amplitude in a bipolar montage. Visual confirmation was then performed independently by neurophysiologists, blinded to the patients' diagnosis, on a subset of patients with randomly selected arousals. Based on the visual assessment, the peak-to-peak amplitude was set at 40 µV and the negative peak amplitude was set at 20 µV to ensure the best detection of SW events (Latreille and Avigdor et al., 2023).

Quantification of activity changes during arousals

Both the scalp EEG and SEEG signals were bandpass filtered at 0.3-300 Hz. The scalp EEG signal was additionally preprocessed with a 60 Hz notch filter. To quantify the activity change during each temporal window, we computed the ratio of the mean band power during the time window of interest versus that during the baseline, in the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), sigma (10-16 Hz), beta (17-30 Hz), gamma (30-80 Hz), and high frequency (HF) (80-250 Hz) ranges. The power spectral density (PSD) was

estimated using the Welch method (Hamming window, 2 s window length, 50% overlap). Note that the PSD of gamma and HF activity was only computed on the SEEG signal but not on scalp EEG, as these activities were challenging to distinguish from the muscle artifacts on the scalp which would lead to unreliable quantification. All signal processing and power spectrum analyses were performed using the software Brainstorm (Tadel et al., 2011).

We further explored the sleep-related and wake-related properties of every region in each time window (TW) of interest (onset, body, and offset) by computing the wake-related ratio defined as the average of theta, alpha, and beta activity ratio (the ratio means: power during the TW of interest/power during baseline) versus the delta activity ratio during the time window of interest. This measure is based on previous findings that delta activity is associated with sleep and theta, alpha, and beta activities are associated with wakefulness (Berger, 1929; Jasper and Penfield, 1949; De Gennaro et al., 2001; Cote et al., 2002; G Buzsáki, 2011; Adamantidis et al., 2019). It allows us to explore whether the brain region becomes more sleep-related or wake-related during sleep arousals relative to the pre-arousal baseline.

Statistical analysis

Overnight distribution and duration of arousals

We computed the arousal indices of SW and Non-SW arousals during the first and second half of the night in each patient. We then conducted a repeated-measure

ANOVA with two within factors: arousal type (SW, Non-SW arousals) and part of sleep (first half, second half).

We compared the duration of the two types of arousals using the Mann-Whitney U test for nonparametric data. The effect size Cliff's *d* was computed.

Activity changes during arousals

To analyze the intracranial activity changes during each arousal type, the power ratio (power during TW of interest/power during baseline) of individual frequency bands, as well as the wake-related ratio, from all channels in each anatomical region was pooled from all patients. Similarly, to analyze the scalp EEG activity changes during each arousal type, the power ratio from the channels on which the arousals were marked was pooled from all patients.

After that, the pooled ratios were natural-log transformed to approximate a normal distribution. Since each patient had different numbers of every arousal type and different numbers of channels in each region, the distribution was weighted according to the number of data points that each patient contributed to the dataset, in order to ensure the distribution mean was not biased by a specific patient (Peter-Derex and Avigdor et al., 2023a). A one-sample *t*-test against zero was then performed to assess (1) whether there was a significant intracranial activity change in each region during arousals ($\alpha < 0.05$); (2) whether there was a significant scalp activity change ($\alpha < 0.05$), and (3) in terms of wake-

related ratio, whether the change in fast activity (theta, alpha, and beta) is significantly higher than the change in delta activity, or the opposite.

All P-values were corrected with the false discovery rate procedure. For intracranial analysis of the individual bands, 7 frequency bands *x* 3 TW *x* (26 regions for SW arousals and 25 regions for Non-SW arousals) = 7 *x* 3 *x* 26 + 7 *x* 3 *x* 25 = 1071 P-Values were corrected in total. The P-values of the wake-related ratio was corrected separately: 3 *x* 26 + 3 *x* 25 = 153 P-Values were corrected. For scalp EEG analysis, 7 *x* 3 + 7 *x* 3 = 42 P-Values were corrected for individual bands, and 1 *x* 3 + 1 *x* 3 = 6 P-Values were corrected separately for the wake-related ratio.

If the activity change after correction was statistically significant, the effect size Cohen's *d* of the one-sample *t*-test of each region was computed. A positive effect size of individual frequency bands means an activity increase in the region, and vice versa. Regarding wake-related ratio, a positive value means a stronger activity change in the theta to beta activity range compared to that in the delta range, and vice versa. Small, medium and large effect sizes were suggested as Cohen's *d* = 0.2, 0.5 and 0.8, respectively.

Activity comparisons between arousal types

To directly compare the activities between two arousal types, we conducted a Welch's *t* test between SW and Non-SW arousals using the data of all channels in each brain region during each time window ($\alpha < 0.05$). P-values were corrected with the false discovery rate procedure (25 regions x 2 arousal types x 3 time window = 150 pairs of P-Values

corrected for each frequency band). Effect sizes were then computed in Cohen's *d* for significant comparisons.

Results

Patient and arousal information

Twenty-six patients (12 females) with a mean age of 35.5 ± 11.2 years met our selection criteria and were therefore included (Fig. 1). Patient demographic and clinical characteristics are provided in Table 1. We included 613 SW arousals and 563 Non-SW arousals (Fig. 2). After the anatomical localization of the SEEG channels, we identified a total of 26 regions to study SW arousals and 25 regions to study Non-SW arousals (Fig. 3).

The median duration of SW arousals was 8.2 s (range 5.0-25.3 s) and 7.5 s (range 5.0-25.4 s) for Non-SW arousals. The duration of Non-SW arousals was significantly shorter than that of SW arousals (Mann-Whitney U test, U = 374520, $p = 0.02$, Cliff's $d = 0.54$).

The two-way repeated measure ANOVA revealed no significant main effects or interactions, indicating that SW and Non-SW arousals did not distribute differently across the night (Main effect of arousal type: $F(1,25) = 0.145$, $p = 0.707$; Main effect of half of sleep: $F(1,25) = 3.467$, $p = 0.074$; Interaction between two factors: $F(1,25) = 0.272$, $p = 0.607$).

Delta activity shows a widespread increase during SW arousals and a widespread decrease during Non-SW arousals

The intracranial delta activity during the two arousal types aligns with the scalp EEG delta activity even in medial and deep brain regions. During SW arousals, we reported an early widespread increase in delta band power across all five brain lobes that became more locally confined to temporo-parietal regions during the body (onset and body: $p < 0.05$ in 22 and 5 regions; $d = 0.10\text{-}0.39$ and $d = 0.05\text{-}0.15$) (Fig. 4, Table 2, Table 3). On the scalp, we observed a similar increase during the onset and no change during the body (onset: $p < 0.05$, $d = 0.31$; body: $p > 0.05$).

During Non-SW arousals, we observed an increase in delta activity across five brain lobes during the onset, followed by a widespread decrease across the five lobes during the body (onset increase: $p < 0.05$ in 11 regions, $d = 0.10\text{-}0.29$; body decrease: $p < 0.05$ in 19 regions; $d = 0.10\text{-}0.30$) (Fig. 4, Table 2, Table 3). On the scalp, delta activity similarly showed an increase during the onset and a decrease during the body ($p < 0.05$, $d = 0.15$ and 0.11).

During the arousal offset, delta power decreased after both arousal types across all the five brain lobes (SW arousals: $p < 0.05$ in 18 regions, $d = 0.10\text{-}0.69$; Non-SW arousals: $p < 0.05$ in 21 regions, $d = 0.12\text{-}0.32$) (Fig. 4, Table 2, Table 3). These patterns showed on the scalp as no change during the SW arousal offset ($p > 0.05$) and a decrease during the Non-SW arousal offset ($p < 0.05$, $d = 0.27$).

By directly comparing the activities between SW and Non-SW arousals, we observed that delta activity in many regions across the five lobes differed significantly between the two arousal types ($p < 0.05$ for all, $d = 0.12 – 0.50$) (Table 4).

Theta, alpha, sigma, and beta activities show widespread increases during both arousal types

During both arousal types, theta, alpha, sigma, and beta power increased in many regions across all five brain lobes during the onset. As the arousals progressed into the body phase, theta, alpha, and sigma activities continued to increase, albeit in fewer regions, while beta activity expanded to increase in more regions. After that, during the offset, theta, alpha, and sigma activity decreased widely across the five lobes, while beta activity returned to baseline in the majority of regions (Fig. 5, Table 2, Table 3).

In detail, for SW arousals, theta, alpha, sigma, and beta power increased in 19, 25, 22, and 10 regions during the onset ($p < 0.05$ for all, $d = 0.06$-0.60, $d = 0.04$-0.30, $d = 0.06$-0.34, and $d = 0.06$-0.25). After that, theta, alpha, and sigma increased in 11, 16, and 19 regions during the body, while beta increased in 19 regions ($p < 0.05$ for all, $d = 0.06$-0.28, $d = 0.07$-0.23, $d = 0.08$-0.25, and $d = 0.06$-0.33). During the offset, theta, alpha, and sigma power widely decreased in 17, 15, and 15 regions ($p < 0.05$ for all, $d = 0.07$-0.43, $d = 0.06$-0.23, $d = 0.08$-0.25), while beta activity returned to baseline in most of the regions.

Similarly, theta, alpha, sigma, and beta activity increased in 9, 16, 14, and 12 regions across the five lobes during the Non-SW arousal onset ($p < 0.05$ for all, $d = 0.11$-0.27, d

= 0.09-0.63, d = 0.08-0.47, and d = 0.08-0.40). After that, theta, alpha, and sigma power increased in 4, 10, and 9 regions ($p < 0.05$ for all, d = 0.10-0.20, d = 0.10-0.49, d = 0.11-0.37), while beta increased in 16 regions during the body ($p < 0.05$ for all, d = 0.11-0.45). Then, theta, alpha, and sigma activities showed a widespread decrease across five lobes in 19, 17, and 20 regions ($p < 0.05$ for all, d = 0.09-0.35 and d = 0.12-0.49), while beta activity returned to baseline in all regions except two.

The comparison of the activities between the two arousal types revealed that the increase in theta, alpha, sigma, and beta activities was lower during SW arousals than NW arousals in multiple temporo-parieto-occipital regions ($p < 0.05$ for all, d = 0.14 – 0.42). In addition, the decrease of theta, alpha, and sigma activities was weaker in many regions across the five brain lobes during the offset of SW arousals ($p < 0.05$ for all, d = 0.13 – 0.68), while beta activity during offset did not differ between the two arousal types (Table 4).

Note, that these increases were not explained by the number of channels in the respective brain regions. The general intracranial activity pattern also manifested on the scalp EEG.

Gamma and HF activities decrease in many regions during both arousal types

Across both arousal types, gamma and HF activities decreased in many regions across the five brain lobes during the onset. They then continued to decrease during the body, only in fewer regions. During the offset, they continued to decrease or returned to baseline (Fig. 6, Table 2, Table 3).

In detail, during SW arousals, gamma and HF activity decreased in 17 and 18 regions during the onset ($p < 0.05$ for all, $d = 0.07$-0.44 and $d = 0.10$-0.43). They then decreased primarily in fronto-parieto-occipital regions during the body ($p < 0.05$ in 7 and 10 regions, $d = 0.06$-0.28 and $d = 0.09$-0.24).

Regarding Non-SW arousals, we observed an early decrease in gamma and HF activity both in 11 regions across the five lobes during onset ($p < 0.05$ for all, $d = 0.13$-0.39 and $d = 0.14$-0.34). After that, 4 and 7 regions showed a decrease in gamma and HF activity during the body ($p < 0.05$ for all, $d = 0.10$-0.24 and $d = 0.12$-0.27). During the offset, gamma power returned to baseline except in the parietal operculum ($p < 0.05$, $d = 0.18$), while HF activities continued to decrease in 5 temporo-parietal regions ($p < 0.05$, $d = 0.11$-0.27).

Comparing the activities between SW and Non-SW arousals showed that gamma and HF activities only differed in less than five regions across the five lobes between the two arousal types ($p < 0.05$ for all, $d = 0.15 – 0.44$) (Table 4). The gamma decrease in the inferior occipital gyrus and occipital pole was weaker during SW arousals ($p < 0.05$, $d = 0.27$), and the HF decrease in the cuneus was stronger during the onset of SW arousals ($p < 0.05$, $d = 0.44$).

SW arousals show sleep-related properties during the onset, while Non-SW arousals show persistent wake-related properties

We further explored whether different brain regions became more sleep-related or wake-related compared to the pre-arousal baseline (Fig. 7, Table 2, Table 3). SW arousals showed a widespread sleep-related activity pattern during the onset, which then turned to a widespread wake-related pattern during the body (onset and body: $p < 0.05$ in 17 and 21 regions, $d = 0.05$-0.36 and $d = 0.05$-0.50). During the offset, 15 regions were wake-related ($p < 0.05$, $d = 0.09$-0.35).

Non-SW arousals showed a wake-related activity pattern throughout their duration. Across all five lobes, 12 regions across the five lobes were wake-related during the onset and 24 regions were wake-related during the body ($p < 0.05$ for all, onset: $d = 0.11$-0.34; body: 0.15-0.55).

A similar pattern as described for the SEEG manifested on the scalp EEG. Regarding SW arousals, we observed a sleep-related activity pattern during the onset and a wake-related pattern during the body and offset ($p < 0.05$ for all, $d = 0.12$, 0.27, 0.12). For Non-SW arousals and their offset, a wake-related pattern was observed during the body and offset ($p < 0.05$, $d = 0.27$ and 0.23).

The wake-related property was weaker during SW arousals than Non-SW arousals in up to 15 regions across the five lobes ($p < 0.05$, $d = 0.10$-0.72).

Intracranial activity during sleep arousals exhibit spatial heterogeneity

While the intracranial activity of each frequency band exhibited a general pattern across brain regions which was also observed on the scalp EEG, multiple regions exhibited unique activities (Fig. 4,5,6,7). Throughout SW arousals, the parietal operculum, hippocampus, planum temporale, and middle cingulate cortex showed no increases in delta activity; in fact, the parietal operculum, planum temporale, and middle cingulate even showed a decrease during the body ($p < 0.05$ for all, $d = 0.18$, $d = 0.28$, and $d = 0.40$). The middle cingulate also showed no increase in the theta, alpha, sigma, or beta bands ($p > 0.05$). In addition, the fusiform and parahippocampal gyri, hippocampus, amygdala, middle temporal gyrus, superior temporal gyrus, and posterior insula showed no decreases in neither gamma nor HF band power, but only an increase in HF power in the middle temporal gyrus ($p < 0.05$, $d_{onset} = 0.26$, $d_{body} = 0.31$), superior temporal gyrus ($p < 0.05$, $d_{body} = 0.20$), and posterior insula ($p < 0.05$, $d_{onset} = 0.12$, $d_{body} = 0.24$). Interestingly, the parietal operculum and planum temporale showed a unique wake-related activity pattern during the onset ($p < 0.05$, $d = 0.13$ and 0.35), coexisting with other sleep-related regions.

For Non-SW arousals, the hippocampus, amygdala, and posterior insula showed no increases in theta, alpha, sigma, or beta power; instead, theta activity decreased in the hippocampus and amydala ($p < 0.05$ for all, hippocampus: $d_{onset} = 0.43$, $d_{body} = 0.34$; amygdala: $d_{body} = 0.53$;). In gamma and HF bands, the supplementary motor cortex, hippocampus, amygalda, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, posterior cingulate, and posterior insula showed no change throughout Non-SW arousals ($p > 0.05$).

Discussion

Although sleep arousals have been defined as an all-or-none phenomenon, they actually present a wide range of scalp EEG activity patterns. With the unique set-up of combined SEEG-PSG, we categorized NREM arousals into SW arousals and Non-SW arousals and studied their intracranial activities. Our main findings were (a) across both arousal types, theta to beta activities showed a widespread increase across many brain regions, while gamma and HF activities decreased in many regions; (b) delta activity increased widely during SW arousals, whereas it decreased widely during Non-SW arousals; (c) a sleep-related activity pattern dominated the onset of SW arousals, while a wake-related pattern persisted throughout Non-SW arousals; and (d) despite a common arousal signature, unique activity was observed locally in some regions, indicating spatial heterogeneity of arousal responses.

Intracranial EEG signature across the different arousal types

Across all arousal types, theta, alpha, sigma, and beta activities increased in up to 25 regions. No previous studies investigated activity patterns during different arousal types, but our result is consistent with previous findings in fronto-parietal regions during spontaneous and nociceptive-induced NREM arousals (Nobili et al., 2011; Peter-Derex et al., 2015; Ruby et al., 2021). It also aligns with previous results in fronto-temporo-parietal regions during confusional arousals, a NREM parasomnia (Flamand et al., 2018). Scalp-EEG findings showed as well that the occipital alpha power increases during behavioral arousals (Setzer et al., 2022). We proposed the widespread theta to beta

increase indicates a higher vigilance state during all arousal types, because these frequency bands have been suggested as wake-related (Berger, 1929; Jasper and Penfield, 1949; G Buzsáki, 2011; Adamantidis et al., 2019).

We also found gamma and HF activities decreased in up to 18 regions across the five brain lobes. In the only study that explored activities in frequency range >30 Hz during arousals, gamma power decreased in the hippocampus and increased in the prefrontal cortex (Ruby et al., 2021), which is different from our results of no change in the hippocampus and a decrease in frontal regions. This discrepancy may result from the different durations between arousals and awakenings which were also analyzed in their study. Compared to NREM sleep, activities > 30 Hz has higher power during wakefulness in the fronto-temporo-occipital regions (Cantero et al., 2004; Mikulan et al., 2018). This is consistent with our HF increase in the temporal lobe, but contrasts with our HF decrease in other regions and the widespread gamma decrease. Given that the intracranial increase of >30Hz activity across four lobes was associated with memory processing and cognitive tasks (Burke et al., 2014; Kucewicz et al., 2014; Greenberg et al., 2015; Lundqvist et al., 2016; Castelhano et al., 2017; Dickey et al., 2022; Liu et al., 2022), the widespread gamma and HF decrease may explain the absence of awareness and recollection during arousals.

Differences across the various arousal types

The two arousal types showed distinct intracranial delta activities and wake-related properties. SW arousals showed a widespread delta increase and sleep-related

properties during onset, while Non-SW arousals showed a widespread delta decrease and wake-related properties. The early sleep-related properties of SW arousals may reflect their sleep-preserving properties. This result also confirms our hypothesis that Non-SW arousals represent a higher level of cortical activation than SW arousals which may indicate a higher probability of awakening. While we initially hypothesized "'slow' arousals are more likely to occur during the first half of the night when the sleep homeostatic pressure is high, the result suggests that the occurrence of SW and Non-SW arousals may not be heavily influenced by sleep homeostatic pressure.

Interestingly, we further observed a simultaneous increase in delta (associated with sleep) and theta alpha, beta (associated with wakefulness) activity in over 20 regions during SW arousals. This is a significant finding because the paradoxical coexistence of these activities was also reported in fronto-parietal regions during confusional arousals, a type of NREM parasomnia when individuals present wake-like behavior without memory or awareness (Mahowald and Schenck, 2005; Terzaghi et al., 2009). Notably, a recent study showed that the scalp EEG activity does not differ between arousal periods with simple and complex movements (Mainieri et al., 2022). Therefore, the intracranial activity pattern of SW arousals might help us understand the pathology underlying NREM parasomnias. Future studies are needed to investigate the temporal dynamics of two arousal types and how SW arousals may be prolonged to and associated with abnormal behaviors in parasomnias.

Intracranial activity after sleep arousals

574 During the post-arousal offset, delta, theta, alpha, and sigma activities widely decreased
575 compared to baseline, while beta, gamma, and HF activities returned to baseline in many
576 regions. This aligns with previous scalp EEG findings in the delta, theta, sigma, alpha,
577 and beta band power (Bruce et al., 2011). Since sleep depth - defined as the difficulty to
578 wake up - positively correlates with delta power assessed on scalp EEG (Neckelmann
579 and Ursin, 1993; Berry et al., 1998; Younes et al., 2020), our results indicate many regions
580 showed lighter sleep immediately after arousals than pre-arousal periods. This effect is
581 important, since during sleep disorders associated with sleep fragmentation such as
582 obstructive sleep apnea, arousals may not only disrupt brain activity during sleep but also
583 lighten sleep and facilitate further arousals, which were known to occur more frequently
584 as sleep depth decreases (Terzano et al., 2000, 2002, 2005, Nobili et al., 2011). We wish
585 to distinguish the sleep depth here from the subjectively perceived sleep depth, which
586 was recently shown to decouple with delta power (Stephan et al., 2021).
587
588 **Spatial heterogeneity of sleep arousals**
589 We reported heterogeneous activity across brain regions during sleep arousals, which
590 aligns with previous research (Peter-Derex et al., 2015). These results showed despite
591 having a common intracranial signature, sleep arousals show local properties which
592 supports the notion that sleep is a locally regulated phenomenon (Huber et al., 2004;
593 Krueger et al., 2008; Ferrara and De Gennaro, 2011). The local properties of sleep were
594 also reported for other sleep oscillations such as spindles, K-complexes, and sawtooth
595 waves (Frauscher et al., 2015a; Latreille et al., 2020; Frauscher et al., 2020). Among all
596 the regions that showed unique activities, the following four are of particular interest. First,

the middle cingulate cortex exhibiting no increase in theta to beta activity during SW arousals aligns with what was observed during confusional arousals (Flamand et al., 2018). This structure was found to link to affective, motor, and somatosensory networks in humans (Oane et al., 2020). Second, the hippocampus showing no increases in delta power during both arousal types is in line with previous research during physiological and confusional arousals (Flamand et al., 2018; Ruby et al., 2021). Third, the parietal operculum, which showed a delta decrease during both arousal types, contains the secondary somatosensory cortex (Meyer et al., 2016). Lastly, the gamma and HF increase in the superior and middle temporal gyrus during SW arousals was associated with auditory attention and language tasks (Thampratankul et al., 2010; Nelson et al., 2017; Nourski et al., 2017; Omigie et al., 2019). The delta decrease in the parietal operculum and HF increase in the temporal lobe might allow the brain to process important somatosensory and auditory information from the environment, since arousals could be induced by nociceptive and auditory stimulation.

Strengths and potential limitations

This work represents the first intracranial study of different types of NREM sleep arousals. Our dataset is currently the largest intracranial dataset of sleep arousals with a wide brain coverage in humans. Using a wide frequency band analysis, we identified the intracranial signatures of arousals without *a priori* hypotheses, especially in the HF range (80-250 Hz) that remained unexplored in past works. Additionally, our registration of channel positions to a common stereotaxic space allowed us to include channels with physiological activity

from all patients. These strengths allowed us to provide a comprehensive description of the local brain activities across both arousal types.

Our dataset did not contain autonomic or behavioral measures, which would expand the picture of physiological activation during arousals. We also acknowledge the potential limitation of using data from patients with epilepsy, the only group where prolonged intracranial recordings are performed. However, we selected channels with physiological activity and excluded nights with electroclinical seizures. Although antiseizure medication might modify sleep architecture (Jain and Glauser, 2013; Shvarts and Chung, 2013), the scalp EEG features of our included arousals were similar to those observed in healthy subjects (Bonnet and Arand, 2007; Azarbarzin et al., 2014). It could be interesting to explore in future work the aperiodic component that was recently shown to differ among the various states of vigilance and see if there are changes in the background preceding SW and non-SW arousals (Donoghue et al., 2020; Lendner et al., 2020).

In conclusion, while SW and Non-SW arousals correspond to different levels of brain activation, they both reflect a heightened vigilance state with the decrease in high frequencies potentially explaining the absence of awareness and recollection of these events. SW arousals notably present similar intracranial patterns to NREM parasomnias and could potentially help us understand the underlying pathology.

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Figure and table legends

Figure 1. Flowchart of patient selection.

Figure 2. Schematic of temporal windows of interest and arousal types. Representative examples of SW and Non-SW arousals taken from patients # 9 and 24 are shown, recorded on the scalp EEG and SEEG. Arousals were marked on the scalp EEG using Fz-Cz for patients # 9 and Cz-Pz for patient #24. The remaining channels are SEEG channels. The onset, body, and baseline segments are indicated by the dashed lines and arrows. The yellow marking represents the arousal segment. The NREM sleep stage before and after the arousal was indicated above each example. Here, the SW arousal exhibits delta activity throughout its onset and body with superimposed fast activity, while the non-SW arousal shows fast activity throughout. Abbreviations: POPer: parietal operculum; AnG: angular gyrus; PCing: posterior cingulate; ITG: inferior temporal gyrus; ACing: anterior cingulate gyrus; Tri IFG: triangular part of the inferior frontal gyrus; Fus & PHG: fusiform and parahippocampal gyrus; Orb IFG: orbital part of the inferior frontal gyrus; GR & OG: gyrus rectus and orbital gyri; MFC: medial frontal cortex.

Figure 3. Localization of channels with physiological activity. (a) Number of channels with physiological activity that were selected in each anatomical region for SW arousals. (b) Number of channels with physiological activity in each region for Non-SW arousals. (c) Number of channels included in each region for the two arousal types. Regions are listed in the following order: frontal lateral, frontal mesial, temporal lateral, temporal mesial, insula, parietal lateral, parietal mesial, occipital mesial and occipital lateral areas. The

channels for each region were grouped together from both hemispheres. There were 26 and 25 regions used to study SW and non-SW arousals.

Figure 4. Delta activity widely increases during SW arousals and widely decreases during Non-SW arousals. The color represents the effect size of the change in delta band power relative to baseline on the scalp EEG (bar) and SEEG (brain visualizations) during the arousal onset, body, and offset of SW and Non-SW arousals. Red represents an increase in delta power while blue represents a decrease in delta power. Regions that were available in <3 patients are marked in grey and regions with no significant change in delta power are in black. We observed that many regions showed a delta increase during SW arousals and the onset of Non-SW arousals, yet many regions showed a delta decrease during the body of Non-SW arousals.

Figure 5. Theta, alpha, sigma, and beta activities increase in many regions during the two arousal types. The color represents the effect size of the change in theta, alpha, sigma, and beta band power relative to baseline on the scalp EEG (bar) and SEEG (brain visualizations) during the arousal onset, body, and offset of SW and Non-SW arousals. Red represents an increase in the band power while blue represents a decrease in band power. Regions that were available in <3 patients are marked in grey and regions with no significant change in band power are in black. We observed that many regions showed an increase in theta, alpha, sigma, and beta activity during two types of arousals which turned to a decrease or returned to baseline afterward.

Figure 6. Gamma and HF activities decrease in many regions during the two arousal types. The color represents the effect size of the change in gamma and HF band power relative to baseline on the scalp EEG (bar) and SEEG (brain visualizations) during the arousal onset, body, and offset of SW and Non-SW arousals. Red represents an increase in the band power while blue represents a decrease in band power. Regions that were available in <3 patients are marked in grey and regions with no significant change in band power are in black. We observed that many regions showed a decrease in gamma and HF activity during two types of arousals which continued to decrease or returned to baseline afterward.

Figure 7. SW arousals show sleep-related properties during the onset while Non-SW arousals are wake-related throughout. The color represents the effect size of the wake-related properties on the scalp EEG (bar) and SEEG (brain visualizations) during the arousal onset, body, and offset of SW and Non-SW arousals. Red represents a stronger activity change in the theta, alpha, and beta frequency range than delta, while blue represents the opposite. Regions that were available in <3 patients are marked in grey and regions with no significant change in band power are in black. We observed that sleep-related responses occurred during the onset of SW arousals, while wake-related responses persisted throughout Non-SW arousals. We also observed coexistence of sleep-related and wake-related regions during the onset of SW and Non-SW arousals.

Table 1. Patient demographics and clinical information. Abbreviations: Medication abbreviations: AM = amitriptyline; BRV = Brivaracetam; CBZ = carbamazepine; CLO =

clonazepam; LAC = lacosamide; LAM = lamotrigine; LEV = levetiracetam; LOR = lorazepam; OXC = oxcarbazepine; PER = perampanel; PHE = phenytoine; TPM = topiramate; VEN = venlafaxine; VPA = sodium valproate; ZNS = zonisamide. Anatomical abbreviations: ACing = anterior cingulate; AIns = anterior insula; Amg = amygdala; AnG = angular gyrus; CC = calcarine cortex; COper = central operculum; Cu = cuneus; FOper = frontal operculum; Fus & PHG = fusiform and parahippocampal gyrus; GR & OG = gyrus rectus and orbital gyri; HPC = hippocampus; IOG & OP = inferior occipital gyrus and occipital pole; ITG = inferior temporal gyrus; L, left; LG & OFG = lingual gyrus and occipital fusiform gyrus; MCing = middle cingulate; MFC = medial frontal cortex; MFG = middle frontal gyrus; mPG = medial segment of precentral gyrus; mSFG = medial segment of superior frontal gyrus; MTG = middle temporal gyrus; Orb IFG = orbital part of inferior frontal gyrus; Oper IFG = opercular part of inferior frontal gyrus; PCing = posterior cingulate; PCu = precunus; PG: precentral gyrus; PIns = posterior insula; POper = parietal operculum; PT = planum temporale; R, right; SMC = supplementary motor cortex; SMG = supramarginal gyrus; SPL = superior parietal lobule; STG = superior temporal gyrus; Su & M OG = superior and middle occipital gyri; TP & PP = temporal pole and planum polare; TTG = transverse temporal gyrus; Tri IFG = triangular part of inferior frontal gyrus.

Table 2. P-values of scalp-EEG and SEEG activity during SW arousals relative to baseline. The table shows the P-values of delta, theta, alpha, sigma, beta, gamma, HF power, and wake-related ratio during arousal onset, body, and offset of SW arousals, relative to baseline. The first row shows the scalp-EEG activity and the rest shows the

SEEG activity in each region. P-values < 0.001 are marked with ***; 0.001 ≤ p < 0.01 are marked with **; 0.01 ≤ p < 0.05 are marked with *.

Table 3. P-values of scalp-EEG and SEEG activity during Non-SW arousals relative to baseline. The table shows the P-values of delta, theta, alpha, sigma, beta, gamma, HF power, and wake-related ratio during arousal onset, body, and offset of Non-SW arousals, relative to baseline. The first row shows the scalp-EEG activity and the rest shows the SEEG activity in each region. P-values < 0.001 are marked with ***; 0.001 ≤ p < 0.01 are marked with **; 0.01 ≤ p < 0.05 are marked with *.

Table 4. Comparisons of scalp-EEG and SEEG activities between SW and Non-SW arousals. The table shows the effect size (Cohen's d) of the direct comparisons of delta, theta, alpha, sigma, beta, gamma, HF power, and wake-related ratio during arousal onset, body, and offset between SW and Non-SW arousals. The first row shows the scalp-EEG activity and the rest shows the SEEG activity in each region. Comparisons with P-values < 0.001 are marked with *** after the effect size; the ones with 0.001 ≤ p < 0.01 are marked with **; and the ones with 0.01 ≤ p < 0.05 are marked with *. To help interpret the positive and negative sign of the effect size: If the band power increases during both arousal types, a positive effect size means the increase during SW arousals is stronger; If the power decreases during both arousal types, a positive effect size means the decrease during SW arousals is weaker; If the band power increases during SW arousals and decreases during Non-SW arousals, the effect size (with p < 0.05) will be positive.