High-Frequency Oscillations in the Normal Human Brain

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Objective: High-frequency oscillations (HFOs) are a promising biomarker for the epileptogenic zone. It has not been possible, however, to differentiate physiological from pathological HFOs, and baseline rates of HFO occurrence vary substantially across brain regions. This project establishes region-specific normative values for physiological HFOs and high-frequency activity (HFA).

Methods: Intracerebral stereo-encephalographic recordings with channels displaying normal physiological activity from nonlesional tissue were selected from 2 tertiary epilepsy centers. Twenty-minute sections from N2/N3 sleep were selected for automatic detection of ripples (80–250Hz), fast ripples (>250Hz), and HFA defined as long-lasting activity > 80Hz. Normative values are provided for 17 brain regions.

Results: A total of 1,171 bipolar channels with normal physiological activity from 71 patients were analyzed. The highest rates of ripples were recorded in the occipital cortex, medial and basal temporal region, transverse temporal gyrus and planum temporale, pre- and postcentral gyri, and medial parietal lobe. The mean rate of fast ripples was very low (0.038/min). Only 5% of channels had a rate > 0.2/min HFA was observed in the medial occipital lobe, pre- and postcentral gyri, transverse temporal gyri and planum temporale, and lateral occipital lobe.

Interpretation: This multicenter atlas is the first to provide region-specific normative values for physiological HFO rates and HFA in common stereotactic space; rates above these can now be considered pathological. Physiological ripples are frequent in eloquent cortex. In contrast, physiological fast ripples are very rare, making fast ripples a good candidate for defining the epileptogenic zone.

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High-frequency oscillations (HFOs), comprised of ripples (80–250Hz) and fast ripples (>250Hz), are a promising biomarker for the epileptogenic zone.[1] Despite this potential, ripples and even fast ripples have also been reported in normal cortical areas.[2–5] HFOs are likely generated by multiple, possibly not exclusive, mechanisms occurring at the cellular and network level, with interneurons playing a complex role.[6]

The issue of separating physiological from pathological HFOs is important, but not easy to address, and so far, all studies have found a large overlap in their properties and none has managed to correctly separate the two entities.[3,5,7–13] One challenge in the interpretation of HFO rates is that different brain regions generate highly variable rates of physiological HFOs,[5] and that region-specific normative indices for HFOs are lacking. A new type of semicontinuous/continuous high-frequency activity (HFA) exceeding 80Hz has been described to occur in certain healthy brain regions.[4] This pattern showed a high prevalence in the hippocampus and occipital lobe, two regions in which spontaneous HFOs of physiological nature have been described. In keeping with this finding, Kerber and colleagues found that HFOs occurring in an oscillatory background activity might be suggestive of physiological activity.[8]

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The lack of normative values for both HFO rates and longer-lasting HFA is mainly explained by: (1) the relatively rare placement of electrodes in healthy brain tissue and the difficulty in identifying healthy brain regions; (2) the lack of standardization for electrode placement, compared to scalp EEG, resulting in problems accumulating data from multiple individuals, as sometimes even in the case of patients with the same type of epilepsy the implantation schemes are heterogeneous; and (3) the finding that even in large tertiary epilepsy referral centers such as the participating sites, only approximately 15 to 20 patients are implanted during a 1-year period. This multicenter project aimed to establish region-specific normative values for physiological HFO rates as well as HFA. Once a statistical distribution of physiological HFO rates is established for a region, it becomes possible to define a rate that is most likely to be pathological. This atlas will be an open resource available for augmentation and consultation on the web (http://mni-open-ieegatlas.research.mcgill.ca). It was realized using the LORIS data platform developed at the Montreal Neurological Institute (MNI).[14]

Subjects and Methods

Selection of Intracranial Electroencephalographic Recordings

Recordings of patients who underwent intracerebral stereoencephalographic (S-EEG) investigation as part of their clinical epilepsy surgery evaluation at the MNI or the Department of Neurology of Grenoble-Alpes University Hospital (CHUGA), and whose awake recordings were selected for the development of an atlas of normal region-specific EEG during wakefulness,[15] were screened for inclusion.

Recordings had to fulfill the following inclusion criteria: (1) presence of channels with normal activity; such channels are not common[16]; a channel with normal activity is defined as a channel localized in normal tissue as assessed by magnetic resonance imaging (MRI), outside the seizure-onset zone, without at any time of the circardian cycle interictal epileptiform discharges (according to the clinical report of the complete implantation evaluation and a careful investigation of 1 night of sleep), and that shows the absence of overt slow-wave anomaly; (2) presence of peri-implantation imaging for exact localization of individual electrode contacts; (3) availability of at least 1 sleep recording obtained after a minimum of 72 hours after insertion of S-EEG electrodes, and at least 12 hours after a generalized tonic–clonic seizure, 6 hours in the case of focal clinical seizures, or 2 hours in the case of purely electrographic seizures[16]; and (4) use of a minimum sampling frequency of 512Hz. The protocol for this study received prior approval from the MNI Institutional Review Board (15-950-MP-CUSM). The MNI recordings were acquired with Harmonie EEG amplifiers (Stellate, Montreal, Quebec, Canada) at a sampling rate of 2kHz, using 2 types of depth electrodes, commercial DIXI electrodes and homemade MNI (HM) electrodes.[15] The CHUGA recordings were acquired with Micromed EEG amplifiers (Micromed, Treviso, Italy) at sampling rates of 512 and 1,024Hz, using the same type of DIXI electrodes as at the MNI. The analysis was performed in bipolar channels, formed by neighboring contacts in each electrode; a secondary analysis was performed in the recording referential montage.

Coregistration and Anatomical Localization of Electrodes and Electrode Contacts

Registration to stereotaxic space and anatomical localization of electrodes was performed, as described in our previous work.[15,17–20] As a Web-accessible resource, the Open MNI iEEG Atlas (https://mni-open-ieegatlas.research.mcgill.ca), has been made available via the LORIS neuroinformatics platform developed at the MNI.[14] For open consultation and dissemination of this atlas, LORIS customizations enable selection, visualization, filtering, and download of intracranial EEG signal files as well as brain region-based groups of channels. Additional visualization tools within the platform provide a spectrum visualizer and 3-dimensional overlay of signal coordinates on an anatomical template atlas, augmented with signal metadata.

Selection of EEG Sections and Analysis

We visually selected 20-minute sections from N2/N3 sleep[21] in the first sleep recording performed at least 72 hours after implantation (in 15 of 71 patients, sections of <20 minutes were identified with a minimum of 10.5 minutes, median = 16.2 minutes). Ripples were defined by a frequency between 80 and 250Hz, fast ripples by frequency > 250Hz. The boundary frequency of 250Hz was chosen following the recommendation in the literature.[1,22] HFOs were automatically detected using a previously validated algorithm,[5,23,24] implemented in MATLAB (MathWorks, Natick, MA). Given the number of data and to guarantee reproducibility of the data,[25] we chose to fully automatically detect HFOs. The code of the detector is provided at https://mni-open-ieegatlas.research.mcgill.ca. After automatic detection, the EEG was reviewed in standard EEG time scale for artifacts during HFO markings.

Grouping Regions for HFO Rate Analysis

The original atlas provided a segmentation with 66 regions in the cortical gray matter.[15] We merged some of these regions to increase the number of channels per region and hence the reliability of the results. Regions were merged if they were in the same lobe, either in the lateral or in the mesial cortex, they were neighboring regions, and there was no statistical evidence that the distribution of the HFO rates in the channels of the regions was different (2-sample Kolmogorov–Smirnov test).

High-Frequency Activity

We studied the presence of HFA in the different brain regions. To define HFA, we obtained the amplitude of the signal (root mean square value) in 100-millisecond steps for 12 different frequency bands in the 80 to 500Hz range, increasing in bandwidth between 10 and 18% in each step, and avoiding second

and third harmonics from the power-line frequencies (80–88, 88–98, 102–118, 122–145, 155–178, and 182–215Hz for channels with 512Hz sampling rate, and additional bands 215–248, 252–285, 285–330, 330–380, and 380–435Hz for channels sampled at 1,024Hz and 435–500Hz for channels sampled at 2,000Hz). In all cases, we used finite impulse response filters of order 508 and transition bands of 10Hz. For each channel, the values in each band were normalized by the mean value of all the intervals in the band. Then, the 95th percentile of the normalized amplitude was computed among all the channels for each frequency band, to be used as a threshold. The presence of HFA was defined in each channel and frequency band by identifying intervals with amplitude higher than this threshold and computing their duration relative to the total duration of the recording. A nominal value of 5% HFA would be expected in every channel and frequency band if the HFA were distributed equally among channels.

Statistical Tests

We compared median ripple rates between 2 groups with Bonferroni-corrected Wilcoxon rank sum tests. To determine statistical significance of fast ripples per region, we compared the number of channels with fast ripples in each region to the number expected if the channels with fast ripples were uniformly distributed among all the regions (binomial distribution). For comparing average duration of HFA in different regions, we performed a label permutation test, randomly permuting the labels identifying the region of each channel 1 million times, with Bonferroni correction for multiple comparisons.

Results

Ripples

A total of 1,171 bipolar channels recording from the gray matter of 71 patients were analyzed (this represents 18.8% of the total channels). From these channels, 617 corresponded to CHUGA patients with DIXI electrodes, 582 recorded at a sampling rate of 512Hz and 35 at 1,024Hz. The remaining 554 channels corresponded to MNI patients, all recorded at 2,000Hz, 300 of them with DIXI electrodes and 254 with HM electrodes. Figure 1 shows the location of the channels in MNI space, as the midpoint between the adjacent bipolar channel contacts. A total of 53,079 ripples were detected in 22,720 minutes of EEG recorded from the 1,171 channels.

Electrode Type, Epilepsy Center, and Sampling Rate. First, we compared the ripple rate between both centers. Because the ripple rate depends on the brain region, all rate comparisons were made by matching channels in the same regions. Results are shown in Figure 2. Comparing 346 channels pairs from CHUGA and MNI, we found a statistically significant difference in their distributions. The median rate in the CHUGA channels was 1.15 ripples per minute compared to 0.75/min in the MNI channels ($p < 10^{-4}$). To determine the reason for this difference, we compared the rate in 186 channel pairs of MNI patients recorded with either DIXI or HM electrodes. We found an even more important difference, with median rates of 1.05 and 0.35/min, respectively ($p < 10^{-4}$). To further investigate the reason for the difference in rates, we repeated the comparison using a referential montage instead of a bipolar montage. The referential montage was chosen because for each channel the contact characteristics (material and surface area) of each electrode type are maintained, but the difference in intercontact distance between electrode types has no impact, as the reference is far away from the contact for both electrode types. We found no statistical difference in 204 channels pairs with a median rate of 0.65/min for the DIXI electrodes and 0.55/min for the HM electrodes ($p = 0.11$), suggesting that the main cause for the difference in the bipolar case is the intercontact distance.

Another source of difference in ripple rate between the centers could be the sampling rate. We found no significant difference between the rates in the 35 CHUGA channels recorded at 1,024Hz and channels in matching regions recorded at 512Hz (median = 0.75 and 1.0/min, respectively, $p = 0.66$). Further evidence that the sampling rate does not play a significant role was obtained when comparing 248 channel pairs recorded with DIXI electrodes at MNI (2,000Hz) and CHUGA (1,024 and 512Hz); the median rates were 1.1/min for CHUGA channels and 1.0/min for MNI channels ($p = 0.45$; see Fig 2D).

Regional Distribution of Ripples. Given the difference between DIXI and HM electrodes and the much larger number of DIXI electrodes, we analyzed the regional distribution of ripple rates measured with the DIXI electrodes. There were 42,800 ripples detected in the 17,140 minutes of EEG recorded from these 917 channels from 53 patients. The mean ripple rate was 2.5/min, median = 1.05/min, 95th percentile = 9.6/min. Figure 3 provides the false-positive rate when using the HFO rate to classify channels as either physiological or pathological. The curves show the proportion of physiological channels that would be incorrectly classified as pathological as a function of the HFO rate threshold used for the classification.

Following the criteria given in the Subjects and Methods section, the regions of the original brain segmentation were joined into 17 larger regions with homogeneous distribution of rates within them. The number of recording channels for each region is presented in Table 1. Among the 917 DIXI channels, there were 561 channels in the left hemisphere and 356 in the right hemisphere. No statistical evidence was found for a difference between 352 pairs of channels in the same regions but different

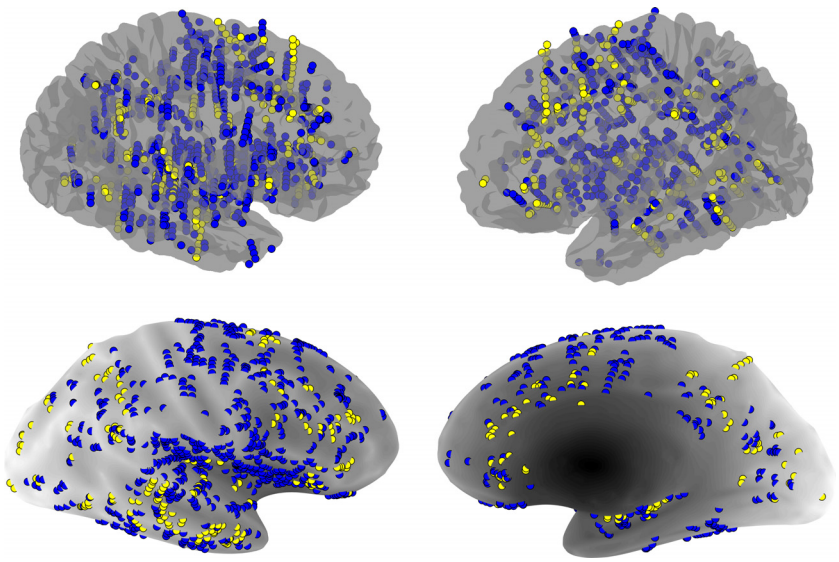

FIGURE 1: Location of recording channels in a semitransparent brain (top), and on the inflated cortex (bottom). The dots correspond to the midpoint between the 2 contacts of bipolar channels. Blue dots indicate 917 channels from DIXI electrodes (Grenoble-Alpes University Hospital and Montreal Neurological Institute [MNI]), and yellow dots correspond to 254 channels recorded with homemade MNI electrodes (left: lateral view, right: medial view).

hemispheres. As shown in Figure 2E, the median rate in the left hemisphere channels was 1.0/min and in the right hemisphere channels was 1.1/min (p = 0.29). Looking at each region separately there were no significant differences either. The region with the highest disparity between the left and right hemispheres was the transverse temporal gyrus and planum temporale, with a median rate almost 3 times higher in the left hemisphere compared to the right hemisphere (median left = 2.4/min in 27 channels, median right = 0.84/min in 8 channels, p = 0.51).

The mean, median, and 95th percentile of the ripple rate in each region are presented in Table 1. Figure 4 shows the rate of each channel and the 95th percentile for each region. The regions with the highest physiological ripple rates are the mesial and lateral occipital cortex, the mesial and basal temporal region, the transverse temporal gyrus and planum temporale, and the primary sensorimotor cortices, followed by the medial and superior parietal regions. Table 2 shows the values measured by HM electrodes in the same regions (for regions with at least 10 electrodes). The data show a similar ordering of the regions based on their rate, but with lower absolute values (except the 95th percentile of the lateral occipital lobe rate).

Stability of Ripple Rates. We identified 33 patients for whom we had non–rapid eye movement (NREM) recordings of a later sleep cycle in the same night, and analyzed 20-minute segments during this different cycle. We analyzed 494 channels from 33 patients and found that the ripple rate was highly correlated in both segments (Pearson rho = 0.95, 95% confidence interval = 0.94–0.96, $p < 10^{-4}$). To determine whether the difference we found was relevant, we compared the difference in rate between segments to the difference between each of the retested channels and other channels in the same brain region during the originally tested segment. In all the retested channels, the rate difference between both segments at different times was not significantly different from the rate difference between the channel and other channels in the same brain region during the original 20-minute segment (minimum uncorrected p value among 494 channels was 0.08, Wilcoxon rank sum test).

Fast Ripples

A total of 404 fast ripples were detected in 10,380 minutes of intracerebral EEG recorded from 519 channels from 34 patients (channels with 2kHz sampling rate and low-pass filter with cutoff frequency at 600Hz, shown in Fig 5). About 78% of the fast ripples (314) had a frequency < 310Hz. Figure 6 shows the spectrum for all HFOs recorded in channels sampled at 2kHz. There was no indication of a discontinuity at 250Hz or any other frequency that would indicate a difference between the arbitrary ripple and fast ripple classification for physiological HFOs.

The median fast ripple rate was zero; 73% (379 of 519) of the channels had no fast ripples at all. The overall mean rate was 0.039 per minute (or 1 fast ripple every 26 minutes). Only 5% (27/519) of the channels had a rate of at least 0.2 per minute (1 fast ripple every 5 minutes). None of these channels was in the vicinity of an MRI lesion/cavity, and 50% of the channels were in a

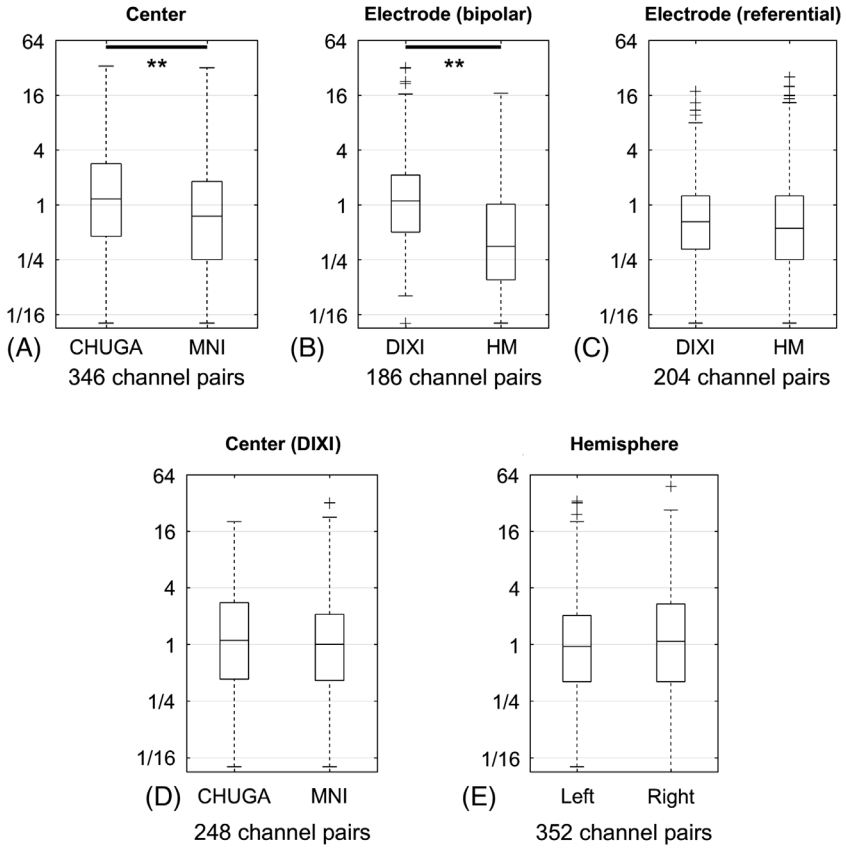

FIGURE 2: Median ripple rates in 2 groups of channels paired according to their location. Horizontal lines indicate the median, boxes extend from the 25th to the 75th percentile, and crosses indicate outliers of a log-normal distribution. **Significant difference in the median with $p < 0.001$. (A) The recorded ripple rates are significantly different between the 2 centers. (B, C) Within the Montreal Neurological Institute (MNI) recordings, there is a significant difference in the ripple rate recorded with DIXI electrodes and homemade MNI (HM) electrodes for bipolar channels, but not for referential channels, indicating that the difference is likely due to the intercontact distance and not due to the material or surface area of the contacts. (D) When restricting the MNI results to channels recorded with DIXI electrodes, there are no significant differences between centers. (E) Among the 917 channels recorded with DIXI electrodes at both centers, no difference was found in the rate between left and right hemispheric channels. CHUGA = Grenoble-Alpes University Hospital.

different lobe than the seizure-onset zone, whereas only 5% were close to the seizure-onset zone. Channels with rates < 0.2 per minute were not further analyzed, as such low rates could be false positives of the automatic detector.

When comparing the fast ripple rate in DIXI versus HM electrodes, the median rate is null in both cases and the difference in the distribution of rates was not statistically significant. Thus, we decided to analyze the results of both types of electrodes together.

Results are shown in Figure 5. Channels with fast ripple rates > 0.2/min were located in the lateral (3/17) and medial (6/14) occipital lobe, hippocampus (5/24), transverse temporal gyrus (2/5), superior frontal gyrus and frontal pole (3/28), superior temporal gyrus (3/83), temporal pole and planum temporale (1/5), supplementary motor cortex (1/8), superior temporal gyrus (1/15), precuneus (1/21), and middle frontal gyrus (1/71). However, only the first 4 regions had a number of channels with a rate > 0.2/min, significantly higher than expected by chance (binomial distribution, with the number of channels of the region and probability parameter 27/519 = 0.052). These regions are also the 4 regions with the highest proportion of channels showing a rate > 0.2/min and with the highest maximum rates: hippocampus (5 channels with rates of 3.1, 0.8, 0.8, 0.8, 0.8/min), medial occipital lobe (6 channels with rates of 1.5, 0.6, 0.5, 0.4, 0.2, 0.2/min), lateral occipital lobe (3 channels with rates of 0.4, 0.3, 0.2/min), and transverse temporal gyrus (2 channels with rates of 0.4, 0.2/min). The maximum rate in the remaining regions was 0.3/min or lower (see Fig 5). It must be noted that the coverage of the central regions was quite poor, with no channels in the postcentral gyrus, and only 5 channels in the precentral gyrus.

High-Frequency Activity

HFA was investigated in the 1,171 available channels, grouped per region. The mean value of the percentage of

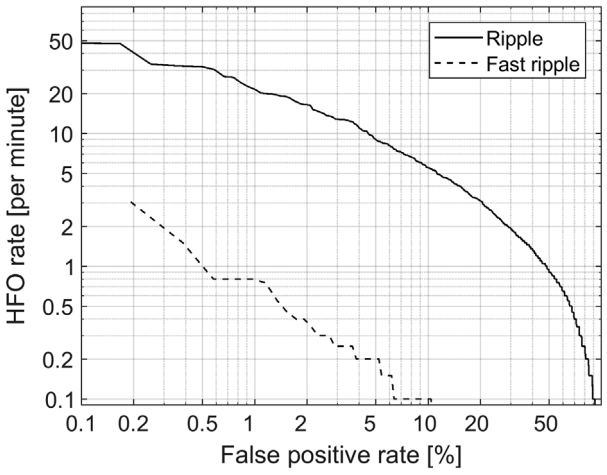

FIGURE 3: False-positive rate when using the high-frequency oscillation (HFO) rate to classify channels as either physiological or pathological. The curves show the proportion of physiological channels that would be incorrectly classified as pathological as a function of the HFO rate threshold used for the classification. Results for ripples are shown with a solid line, and for fast ripples with a dashed line.

time with HFA is shown in Figure 7. A permutation test with 1 million region label permutations and Bonferroni correction indicated that the HFA was significantly higher than expected by chance in the medial occipital lobe in all the bands of the 80 to 435Hz frequency range (maximum = 9.2% in the 122–145Hz band), the pre- and postcentral gyri in the whole tested frequency range 80 to 500Hz (maximum = 7.4% in the 182–215Hz band), the transverse temporal gyrus and planum temporale in the range from 80 to 215Hz (maximum = 7.0% in the 122–145Hz band), and the lateral occipital lobe in the 80 to 145Hz frequency range (maximum = 6.9% in the 122–145Hz band). No other region showed a significant amount of HFA, including the mesiotemporal region.

Forty-five channels had HFA for >10% of the time, 18 of them in the pre- and postcentral gyri (maximum = 17.4%), 13 in the medial occipital lobe (maximum = 16.3%), 9 in the transverse temporal gyrus and planum temporale (maximum = 14.4%), 3 in the lateral occipital lobe (maximum = 12.9%), and 2 in the supplementary motor cortex (maximum = 10.5%).

Discussion

This multicenter study established quantitative normative values for physiological ripples (80–250Hz), fast ripples (>250Hz), and HFA, using a common stereotactic framework, to separate normal physiological from abnormal pathological activity. The major outcomes are that (1) knowing the physiological rates of HFOs in every brain region allows the definition of rates that are too high to be physiological and should therefore, statistically, be pathological; (2) ripples are frequent in brain areas corresponding to eloquent cortical areas and rare outside these regions; whereas (3) fast ripples and HFA are rare in both eloquent and noneloquent areas.

Selection of Channels from Presumably Normal Brain Regions

We are aware that selecting "true" normal cortex is a challenging task, as we analyze EEGs from epileptic patients. In most of them, however, some electrodes need to be placed in nonepileptogenic zones apparently devoid of structural or physiological anomalies. These electrodes help to define the limits of surgical resection. Also, normal superficial neocortical regions are recorded as a result of the need to reach a deep structure with a multicontact electrode. Selecting the most normal brain regions in these patients is as close as we can get to creating an atlas of normal intracerebral EEG. To ensure as much as possible the selection of channels with normal physiological EEG activity, we followed a strict protocol that involved the consensus of 2 epileptologists.[15] We were able to select approximately 18% of all channels. Even if channels from pathological regions might have slipped through our careful screening, this is unlikely to have occurred for many, and the large number of channels in each region makes it likely that our average results are representative of normal brain. Moreover, even if selected channels were not in close vicinity of lesional tissue or the seizure-onset zone, we cannot exclude that some of the HFOs that are assumed to be physiological are actually pathological HFOs generated by remote pathologically interconnected neuron clusters.[26] One study, however, compared HFO rates in 2 nonepileptic patients versus the non–seizure-onset zone of epilepsy patients; the study did not reveal significant differences.[27]

Ripples Are Frequent in Eloquent Cortical Areas

Physiological ripples are frequent in eloquent cortex, with the highest rates in the occipital and sensorimotor cortices, and in the mesiotemporal region, followed by the medial and superior parietal regions. Our results agree with the few previous studies providing information on some of these regions using smaller numbers of patients, and targeting different research questions.[2–5]

There are different hypotheses for the relevance of physiological HFOs and HFA in eloquent cortex. Previous work supported the concept that HFOs are associated with phasic increases of neural activity during slow-wave oscillations.[12] It was suggested that such patterned activity in the sleeping brain could play a role in offline processing of cortical networks and memory consolidation.[28–31]

TABLE 1. Cortical Regions Classified by Rates of Ripple (Ripples per Minute)

Region	Channels, n	95% Rate	Median Rate	Mean Rate
Medial occipital lobe	23	24	8.8	10.9
Lateral occipital lobe	18	21.5	1.5	5.4
Medial and basal temporal region	60	19.5	1.6	4.2
Transverse temporal gyrus and planum temporale	35	15.1	2.2	4.9
Pre- and postcentral gyri	112	14.9	2.2	4.4
Medial parietal lobe	28	12.6	2.1	3.4
Superior parietal lobule	17	8.4	3.5	4.1
Superior temporal gyrus	38	8.1	2	3.2
Supplementary motor cortex	32	5.8	1.5	2.2
Medial frontal cortex (including medial segment of superior frontal gyrus)	28	4.7	0.6	1.1
Inferior parietal lobule	94	4.1	0.8	1.4
Central operculum and opercular part of inferior frontal gyrus	55	4	0.6	1.1
Superior, middle, and orbital frontal gyri and anterior part of inferior frontal gyrus	191	3.5	1.1	1.4
Insula	62	2.7	0.3	0.8
Middle and inferior temporal gyrus, temporal pole, and planum polare	79	2.7	0.5	0.8
Anterior and middle cingulate gyrus	31	2	0.3	0.6
Frontal operculum	14	1.2	0.5	0.7

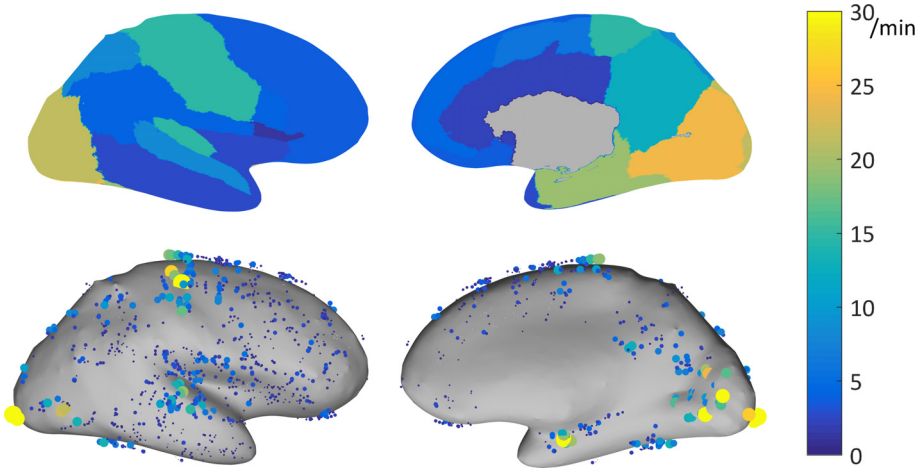

FIGURE 4: Physiological ripple rate results for bipolar channels recorded with DIXI electrodes, represented on the inflated cortex. Top: 95th percentile of the physiological ripple rate per brain region. Bottom: rate of the individual channels. Each dot represents a channel, the size and color indicate its ripple rate (left: lateral view, right: medial view).

Apart from their significance during sleep, it is known that some brain areas present heightened levels of HFA in the gamma and ripple range that actually drops during a task. For the default mode network, spontaneous levels of 50 to 150Hz activity drop when the patient begins to process a stimulus. This was proposed as the electrophysiological

TABLE 2. Ripple Rates (per Minute) in the Different Brain Regions for DIXI and HM Electrodes

	DIXI Electrodes				HM Electrodes			
Region	**Channels, n**	**95th Percentile**	**Median Rate**	**Mean Rate**	**Channels, n**	**95th Percentile**	**Median Rate**	**Mean Rate**
Medial occipital lobe	23	24	8.8	10.9	10	30.3	6.3	11.6
Medial and basal temporal region	60	19.5	1.6	4.2	15	5.5	1.7	29
Medial parietal lobe	28	12.6	2.1	3.4	25	7.3	1.6	2.5
Superior parietal lobule	17	8.4	3.5	4.1	13	4.2	1	2.1
Superior temporal gyrus	38	8.1	2	3.2	10	3.6	0.3	0.7
Inferior parietal lobule	94	4.1	0.8	1.4	19	1.7	0.3	0.7
Superior, middle, and orbital frontal gyri and anterior part of inferior frontal gyrus	191	3.5	1.1	1.4	48	2.9	0.2	0.6
Middle and inferior temporal gyrus, temporal pole, and planum polare	79	2.7	0.5	0.8	54	1.4	0.4	0.5
Anterior and middle cingulate	31	2	0.3	0.6	28	0.7	0.2	0.3

HM = homemade at Montreal Neurological Institute.

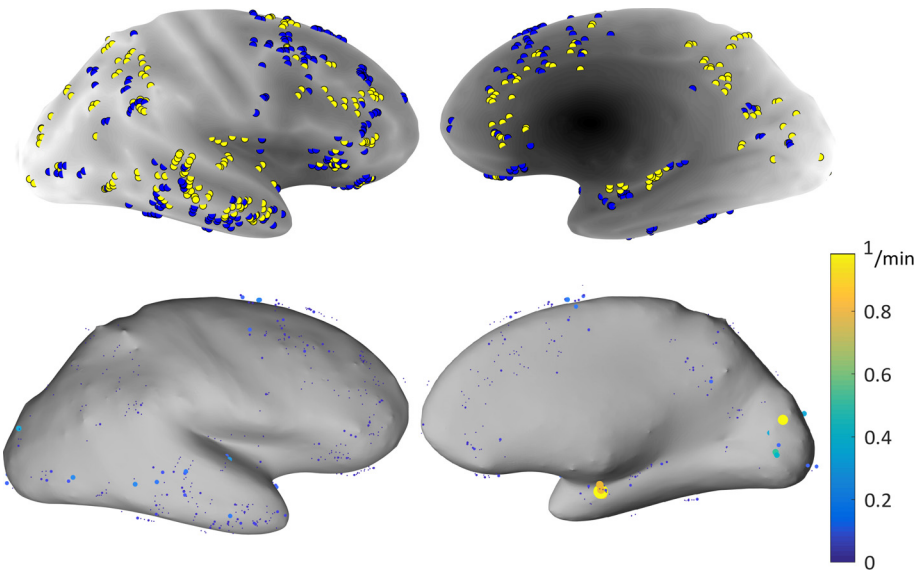

FIGURE 5: Location of recording channels used to analyze fast ripples on the inflated cortex (top). The dots correspond to the midpoint between the 2 contacts of bipolar channels. Blue dots indicate 265 channels from DIXI electrodes (Grenoble-Alpes University Hospital and Montreal Neurological Institute [MNI]), and yellow dots correspond to 254 channels recorded with homemade electrodes (MNI). Fast ripple rates recorded in each individual channel are shown (bottom). Each dot represents a channel; the size and color indicate its fast ripple rate (left: lateral view, right: medial view).

equivalent of the negative blood oxygen level-dependent.[32,33] There have also been reports suggesting the existence of resting levels of HFOs/HFA that also vanish or decrease during involvement in a task. Their generation has been related to local balance of excitation and inhibition, interneurons being a likely key player in their generation. Interestingly, the

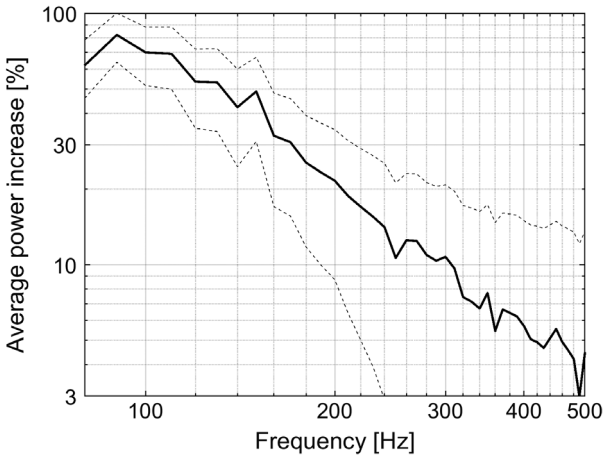

FIGURE 6: Average increase of the power spectral density during all high-frequency oscillations (HFOs) recorded in channels sampled at 2kHz, relative to the average of the background in the same channels. The solid line corresponds to the mean, and the dashed lines indicate the standard error of the mean. There is no indication of a discontinuity at 250Hz (or any other frequency) that would indicate a difference between the ripple and fast ripple classification for physiological HFOs.

inhibitory system is largely γ-aminobutyric acidergic (GABAergic), so the concentration or receptor density of GABA, which differs across brain areas, might be related to the spatial pattern of spontaneously occurring HFA.[34,35]

Regions identified with higher ripple rates correspond to cortical regions that have a higher degree of myelination.[36,37] Interestingly, a magnetoencephalographic study suggested that myeloarchitecture supports connectivity across all bands.[38]

Physiological ripples are ubiquitous in normal regions, with particularly high rates in eloquent cortex. This is important to remember when using ripples to delineate the epileptogenic zone. Future research should apply the region-specific cutoffs proposed here, considering rates below these thresholds to be normal. This should enhance the specificity of ripple rates to predict surgical seizure outcome on a channel level, even if it does not help separate individual physiological from pathological ripples. The usefulness of this approach is underlined by a paper investigating anatomic variation of HFO rates and amplitudes inside and outside the seizure-onset zone.[39]

Fast Ripples Are Very Rare in Both Eloquent and Noneloquent Cortical Areas

Only 5% of all channels had 1 fast ripple every 5 minutes; these channels were also located in eloquent cortex. These findings are in keeping with work done in a smaller number of patients and brain regions.[5,10] For most cases, the

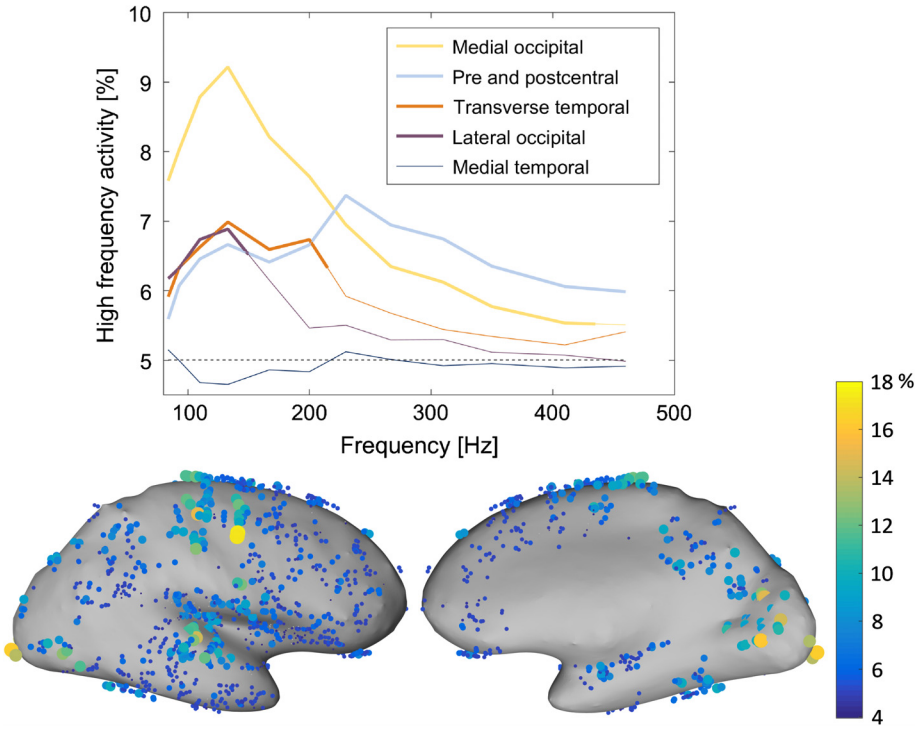

FIGURE 7: Results of high-frequency activity (HFA). Top: average content of HFA in the channels of 5 different brain regions. The lines show the mean value, among all the channels of each region, of the percentage of time that the channels exhibit HFA, as a function of the frequency. Only 4 regions showed a significant increase (frequency range of significant increase is indicated by thicker lines); the medial temporal region is included for comparison. The black dotted line indicates the 5% level, average of all the channels. Bottom: HFA content in each of the 1,171 channels on the inflated cortex. Each dot represents a channel, and its size and color indicate the percentage of time with HFA in the channel. A few channels exhibit HFA up to 17% of the time (left: lateral view, right: medial view).

frequency of these physiological fast ripples exceeded only slightly the upper limit of 250Hz for normal ripples (80% have a frequency < 310Hz). This suggests that these rare events are not functionally distinct from ripples. We conclude that the presence of fast ripples is specific for the epileptogenic zone.

Physiological HFA in Eloquent Cortex

The current study showed that HFA is present in the mesial and lateral occipital lobe, pre- and postcentral gyri, and transverse temporal gyrus and planum temporale. Previous work showed a peculiar pattern of oscillatory HFA lasting longer than ripples. This activity was interpreted as physiological and present in only certain brain areas.[4,8] In contrast to Melani and colleagues,[4] we did not find increased HFA in the hippocampus. We explain this difference by a different channel selection process; we discarded channels with epileptic activity and those being part of the seizure-onset zone, whereas the Melani study included all channels. Whether this is the sole explanation awaits further confirmation.

Features to Separate Physiological from Pathological HFOs

The current work analyzed region-specific rates of HFOs in presumed physiological channels. Previous literature has attempted to differentiate pathological from physiological HFOs by considering their coupling with epileptic spikes,[7] the background EEG activity,[8] task-induced HFOs,[3,9] the anatomical location of implanted electrodes,[7,10,11] more classical neurophysiological features including amplitude, duration, spectral frequency, and rate,[10,11] and their interaction with different features of sleep, such as sleep slow waves and phasic rapid eye movement (REM) sleep.[5,12,13,23,40] None of these features, however, was sufficient to separate physiological from pathological HFOs, as they showed significant overlap. Whether the combination of different features including region-adjusted HFO rates might better delineate the epileptogenic zone remains to be investigated.

Factors Influencing HFO Rates

Before combining data for this project, we performed subanalyses for intercenter and interelectrode differences and found differences in HFO rates depending on the intercontact distance in analyses with bipolar montages. This was demonstrated by the finding that the same analyses using a referential montage showed that the rate difference was no longer significant. We also corroborated that HFO rates are independent of the contact size.[41] Despite differences in absolute rates between both electrode types, the order of regions with highest HFO rates remained stable.

We used one of the validated HFO detectors.[5,23,24] It is likely that rates would change with a different detection algorithm. For this reason, we provide the code for the algorithm used and the data from this study are available on the website. These options make the definition of physiological rates of HFOs provided by the atlas independent of the detector.

It is likely that HFO rates would differ if assessed during wakefulness, or N1 or REM sleep.[23,42,43] We opted a priori to analyze HFO rates during N2 and N3 sleep, as artifacts interfering with ripple and fast ripple identification are low during NREM sleep and research in epilepsy has focused on this stage for analysis of HFOs.[1]

Interhemispheric Differences in Regional HFO Rates

The region with the highest disparity between the left and right hemispheres was the transverse temporal gyrus and planum temporale, with a median rate almost 3 times higher in the left than in the right hemisphere. This difference did not reach significance. Increasing the number of channels could lead to a significant difference. Whether this becomes also true for other left and right hemispheric regions will only be answered when the current data pool grows.

Conclusion and Future Prospects

This atlas provides region-specific normative values for physiological HFOs and HFA in a common stereotactic space. Physiological ripples are particularly frequent in eloquent cortical areas. In contrast, physiological fast ripples and HFA are very rare, even in eloquent cortex, which makes them better candidates for defining the epileptogenic zone. Some cortical regions are not yet fully covered, and we intend to allow the atlas to grow by inclusion of data (from the original centers and from other qualified centers) and to continue the current project prospectively. Ultimately, this atlas will provide thresholds of physiological HFO rates and HFA resulting in increased specificity of HFOs for delineating the epileptogenic zone and hence leading to better postsurgical seizure outcomes. This atlas will be an open resource available for augmentation and consultation (http://mni-open-ieegatlas.research.mcgill.ca).

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Author Contributions

B.F., N.v.E., and J.G. contributed to the conception and design of the study; all authors contributed to the acquisition and analysis of data; B.F., N.v.E., and J.G. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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