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Physiological and pathological high-frequency oscillations have distinct sleep-homeostatic properties

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ABSTRACT

Objective: The stage of sleep is a known modulator of high-frequency oscillations (HFOs). For instance, high amplitude slow waves during NREM sleep and the subtypes of REM sleep were shown to contribute to a better separation between physiological and pathological HFOs. This study investigated rates and spatial spread of the different HFO types (physiological and pathological ripples in the 80–250 Hz frequency band, and fast ripples above 250 Hz) depending on time spent in sleep across the different sleep cycles.

Methods: Fifteen patients with focal pharmaco-resistant epilepsy underwent one night of video-polysomnography during chronic intracranial EEG recording for presurgical epilepsy evaluation. The HFO rate and spread across the different sleep cycles were determined with an automatic HFO detector. We built models to explain the observed rate and spread based on time in sleep and other variables i.e. sleep stage, delta band and sigma band activity, and slow wave amplitude. Statistical significance of the different variables was determined by a model comparison using the Akaike information criterion.

Results: The rate of HFOs depends significantly on the accumulated time of sleep. As the night advanced, the rate of pathological ripples and fast ripples decreased during NREM sleep (up to 15% per hour spent in the respective sleep stages), while the rate of physiological ripples increased during REM sleep (8% per hour spent in REM sleep). Interestingly, the stage of sleep but not the sleep cycle determined the extent of spread of HFOs, showing a larger field during NREM sleep and a more restricted field during REM sleep.

Conclusion: The different dependence with sleep time for physiological and pathological ripples is in keeping with their distinct underlying generating mechanisms. From a practical point of view, the first sleep cycle seems to be best suitable for studying HFOs in epilepsy, given that the contrast between physiological and pathological ripple rates is largest during this time.

1. Introduction

High-frequency oscillations >80 Hz (HFOs), which can be divided into ripples (80–250 Hz) and fast ripples (>250 Hz), are a new biomarker of epilepsy (see review of Frauscher et al., 2017, submitted). Of note, ripples and even fast ripples have been described to occur also in normal cortical areas, such as the paracentral cortex, the hippocampus, and the occipital cortex (Axmacher et al., 2008; Blanco et al., 2011; Nagasawa et al., 2012; Melani et al., 2013; Alkawadri et al., 2014; von Ellenrieder et al., 2016; Nonoda et al., 2016). Traditional markers (ripple rate per minute, power, duration, and amplitude) as well as the relation to epileptic activity, presence of task-induced HFOs, or oscillatory EEG background activity are unable to successfully separate physiological from pathological HFOs (Nagasawa et al., 2012; Matsumoto et al., 2013; Melani et al., 2013; Wang et al., 2013; Kerber et al., 2014; Alkawadri et al., 2014; Malinowska et al., 2015).

The stage of sleep modulates the occurrence of HFOs. They have highest rates during NREM sleep, and lowest rates during REM sleep (Staba et al., 2004; Bagshaw et al., 2009; Dümpelmann et al., 2015; Sakuraba et al., 2016). Sleep can separate physiological from pathological HFOs (Frauscher et al., 2015, 2016; von Ellenrieder et al., 2016; Nonoda et al., 2016). For instance, HFOs occurring in normal cortical areas (physiological HFOs) are coupled to a different phase of the high amplitude slow wave compared to HFOs occurring in the epileptogenic zone (pathological HFOs) (Frauscher et al., 2015). Also, there is a difference in the coupling of physiological and pathological HFOs to the two subtypes of REM sleep: Pathological HFOs are maximally suppressed during phasic REM sleep compared to tonic REM sleep, whereas physiological HFOs show the opposite behavior with higher rates during

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phasic compared to tonic REM sleep (Frauscher et al., 2016). These studies suggest that the coupling to sleep transients might be useful to separate physiological from pathological HFOs. For instance, adding the coupling to slow waves increases the discrimination between physiological and pathological HFOs (von Ellenrieder et al., 2016).

Visual HFO identification is traditionally performed in five-minute segments of NREM sleep (Zelmann et al., 2009). It is currently not known during which sleep cycle these segments should be best selected, as the distribution of HFOs depending on time in sleep across the night has not been investigated so far. Given the dependence of HFO rates with the stage of sleep, slow wave amplitude, delta band activity, sleep spindles, and type of REM sleep (Frauscher et al., 2017 submitted), we speculated that rates of the different HFO types might also change across the different sleep cycles throughout the night, which is not solely explained by the stage of sleep.

It is also unknown if the different sleep stages and cycles influence or modulate the spatial spread, or field, of HFOs. Based on findings of interictal epileptic discharges (IEDs), which were shown to be more widespread during NREM sleep and more focally restricted during REM sleep (Sammaritano et al., 1991), it is tempting to speculate that HFOs might also have a wider field during NREM sleep as opposed to REM sleep. This study analyzed if rates and spatial spread of physiological and pathological ripples, and fast ripples depend on the time in sleep and vary across the sleep cycles, beyond the dependence with the stages of sleep.

2. Material & methods

2.1. Patient selection

We selected patients with pharmaco-resistant focal epilepsy who underwent combined scalp-intracerebral EEG recording (S-EEG electrodes) for presurgical epilepsy evaluation at the Montreal Neurological Institute and Hospital between October 2013 and January 2015, and one night of video-polysomnography during the S-EEG investigation. We included patient recordings which had at least one channel in the physiological region and one channel in the pathological region (see definitions below), as we aimed to evaluate both physiological and pathological HFOs. Exclusion criteria were: (i) scalp EEGs with IEDs (spikes, sharp waves, or polyspike waves with or without after discharge slow wave) or widespread pathologic slowing during wakefulness making correct sleep staging ambiguous or impossible; and (ii) presence of secondarily generalized seizures during the 12 h, or focal seizures (symptomatic or asymptomatic, habitual or non-habitual) during the 6 h prior to or during the evaluated night of sleep recording.

Thirty patients underwent intracerebral EEG with at least one night of video-polysomnography, and 15 were included in the current project according to the selection criteria. Reasons for exclusion were occurrence of focal seizures during the 6 h prior to or during the evaluated night of sleep recording ($n = 6$), absence of normal EEG channels ($n = 6$), and scalp EEGs making sleep staging ambiguous or impossible ($n = 3$). Table S1 of the Supplementary File A provides information on the demographic, neuroimaging, and electroclinical findings of the patient group. This study was approved by the Montreal Neurological Institute and Hospital Review Ethics Board. All patients signed an ethical board approved written informed consent prior to study participation.

2.2. Scalp and intracerebral EEG recordings

Intracerebral EEG electrodes were implanted stereotactically using an image-guided system. Table S1 of the Supplementary File A provides the investigated cortical sites. Scalp EEG was obtained with subdermal thin wire electrodes at positions F3, F4, Fz, C3, C4, Cz, P3, P4, and Pz. In the night of the sleep recording, which was at least 72 h after implantation, additional electrodes for electrooculography and electromyography of the chin and the flexor digitorum superficialis muscles were used. The EEG signal was high-pass-filtered at 0.1 Hz, low-pass-filtered at 500 Hz, and sampled at 2000 Hz. EEG were recorded using the Harmonie EEG system (Stellate, Montreal, Canada). Sleep was scored manually in 30 s epochs in the scalp EEG by a sleep expert (Berry et al., 2012).

Intracerebral EEG channels were classified as channels in the physiological region or channels in the pathological region. Channels in the physiological region had normal EEG activity (absence of IEDs and of non-epileptic abnormalities during the complete intracranial recording, usually lasting 2–3 weeks), were located in brain regions with no structural abnormalities as revealed by high-resolution MRI, and were outside the seizure-onset zone (i.e. showing the first unequivocal ictal intracranial EEG change at seizure onset of both habitual and non-habitual seizures, see Spanedda et al., 1997). Channels in the pathological region included channels inside the irritative zone (i.e. with IEDs) and channels in the seizure-onset zone. Channels displaying non-epileptic abnormalities, artifacts interfering with the identification of HFOs, or channels outside the brain were excluded. Suitable channels were selected independently by two electrophysiologists.

2.3. HFO detection

HFOs were automatically detected looking for an increase in power with respect to the background in narrow frequency bands and with a duration longer than four oscillations plus the effective response time of the filters (equi-ripple FIR filters of order 508, more details in von Ellenrieder et al., 2012, 2016). Ideally, a human reviewer should verify the results of an automatic detector, but in this case, such an approach was not practical, since the whole night was investigated. For this reason, and since muscle activity and movement artifacts could lead to an increase of false positives in the HFO detection, we excluded wake and stage N1 sleep from the analysis.

We studied the subject-level *rate* of HFOs, defined by the number of occasions in which an HFO is detected in one channel or several channels simultaneously, i.e. when HFOs are detected simultaneously in several channels, it counts as one subject level event. We also studied the HFO spatial *spread*, defined as the number of channels in which HFOs are detected during each subject-level event. When studying the spread of HFOs, we excluded all the subject-level events that involved channels in the physiological and pathological regions, since in such cases it was not possible to determine if the ripple was pathological or physiological.

2.4. Variables included in the model

The primary variable of interest is the time spent in sleep in any given sleep stage. Other variables that could lead to HFO rate and spread changes were included in the model as well. These secondary variables are the respective sleep stages (REM, N2, and N3), the slow wave amplitude, the delta band activity, and the sigma band activity (10–16 Hz). The slow wave amplitude is the average amplitude of the slow waves detected in 30 s epochs used in the sleep scoring, defining slow waves as oscillations of the band pass filtered signal (0.5–4 Hz) with consecutive zero crossings separated by 0.5 to 2 s. See von Ellenrieder et al. (2016) for more details on the filters and slow wave detection algorithm. The delta band and sigma band activity was computed as the root mean square value of the band pass filtered signal during the same 30 s epochs (elliptic IIR filters of order 5, 0.2 dB ripple in the pass band 40 dB attenuation in the stop bands, 0.5–4 Hz and 10–16 Hz respectively). All the variables were computed for the scalp channels F3-C3 and F4-C4 and averaged, then modified to have zero mean in each analyzed sleep stage and/or patient, and all the variables except the accumulated time were normalized to have unit variance in each patient. The accumulated time was expressed in hours.