Time-frequency dynamics during sleep spindles on the EEG in rodents with a genetic predisposition to absence epilepsy (WAG/Rij rats)

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ABSTRACT

Sleep spindles are known to appear spontaneously in the thalamocortical neuronal network of the brain during slow-wave sleep; pathological processes in the thalamocortical network may be the reason of the absence epilepsy. The aim of the present work is to study developed changes in the time-frequency structure of sleep spindles during the progressive development of the absence epilepsy in WAG/Rij rats. EEG recordings were made at age 7 and 9 months. Automatic recognition and subsequent analysis of sleep spindles on the EEG were performed using the continuous wavelet transform. The duration of epileptic discharges and the total duration of epileptic activity were found to increase with age, while the duration of sleep spindles, conversely, decreased. In terms of the mean frequency, sleep spindles could be divided into three classes: 'slow' (mean frequency 9.3 Hz), 'medium' (11.4 Hz), and 'fast' (13.5 Hz). Slow and medium (transitional) spindles in five-month-old animals showed increased frequency from the beginning to the end of the spindle. The more intense the epilepsy is, the shorter are the durations of spindles of all types. The mean frequencies of 'medium' and 'fast' spindles were higher in rats with more intense signs of epilepsy. Overall, high epileptic activity in WAG/Rij rats was linked with significant changes in spindles of the transitional type, with less marked changes in the two traditionally identified types of spindle, slow and fast.

Keywords: Sleep spindles, absence epilepsy, time-frequency analysis, continuous wavelet transform, instantaneous frequency dynamics

1. INTRODUCTION

Sleep spindles are essential electroencephalographic (EEG) hallmarks of non-REM sleep that associated with burst firing in thalamocortical neuronal network.[1,2] Sleep spindles are known to originate from the thalamus, whereas cortex is responsible for the synchronization and propagation of sleep spindles.[3] The American Academy of Sleep Medicine (AASM) determines sleep spindles as "a train of distinct waves with frequency 11–16 Hz (most commonly 12–14 Hz) with a duration of more than 0.5 seconds".[4] The frequency of sleep spindles is one of the most important parameters used for their identification in EEG.[5,6] In humans, there is a clear predominance of the two spindle types, ∼12 Hz and ∼14 Hz, which were distinguished by spatiotemporal dynamics.[2,7,8] In rats, the frequency of sleep spindles is 8–14 Hz and tend to be slightly lower than in humans:[5,9] the frequency of anterior sleep spindles is 10–11 Hz and the frequency of posterior spindles is 12.4 Hz. In the present paper we examined variability of intra-spindle frequency in rats and determined whether or not sleep spindles can be classified in slow ∼10–12 Hz and fast ∼14 Hz, similar to humans.

In the middle of the last century Gibbs and Gibbs[7] noted an additional spindle type ∼10 Hz that was commonly seen as sleep deepened. Later the existence of ∼10 Hz spindle type became controversial, as long as

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~10 Hz spindle oscillations were considered as a forerunner of 6–10 Hz rhythmic activity during transition between sleep stages 2 and 3.[8] However, ~10 Hz sleep spindles were common in more than 50% of epileptic patients with various seizure types.[10,11] Eventually frequency of sleep spindles tend to decrease in patients with neurological and sleep–related disorders. For instance, in patients with obstructive sleep apnea syndrome, the frequency of sleep spindles was 11.9 Hz versus 12.9 Hz in healthy control group.[6] It is likely that disturbances in thalamo-cortical network in absence epilepsy consequently result in changes of sleep spindles, therefore time-frequency analysis of sleep spindles may provide information on pro-epileptic changes in thalamo-cortical mechanisms.

In animals, sleep spindles are abundant during slow-wave sleep, and their frequency 7–14 Hz[12] tend to be slightly lower than in humans. Sleep spindles in animals are of particular interest because sleep spindles can be transformed in epileptic spike-wave discharges (SWD) under specific pharmacological conditions (injections of pentobarbital and penicillin under anesthesia).[1,13,14] Epileptic transformation of sleep spindles was investigated in cats (a model of feline generalized epilepsy) and led to the conclusion that sleep spindles and SWD emerge from the same thalamo-cortical neuronal network.[11,14,15] SWD are electroencephalograpic manifestation of absence seizures and other generalized idiopathic epilepsies.[16] Nowadays it is well known that SWD are caused by the impairment of thalamo-cortical network mechanisms (mostly cortical part),[15,17] suggesting that some disturbances of physiological sleep spindle oscillations may specifically correlate with absence epilepsy. In other words, time-frequency structure of sleep spindles may change as absence epilepsy progresses. Previously in WAG/Rij rat model of absence seizures we found an abnormal spindle type which combined some properties of epileptic discharges (pro-epileptic spindles).[18–20] In this study we analyzed sleep spindles in EEG in adult WAG/Rij rats using the Morlet-based wavelet transform and noted large inter-subject variation of spindle frequencies: the averaged frequency of sleep spindle varied from 12.1 Hz to 14.1 Hz.[19] In addition to that, there were substantial frequency variations within one spindle train (intra-spindle frequency variation) and between different sleep spindles in one subject (intra-subject variation). In the present paper, we discuss non-stationary features of sleep spindles, i.e. that the frequency content and the amplitude of sleep spindles change with time.

As a non-stationary signal, sleep spindle could be characterized by "instantaneous" frequency. The latter is a time-varying parameter that defines the location of the signal's spectral peak as it varies with time.[21] Continuous wavelet transform has several advantages over traditional FFT that are crucial for time-frequency analysis of unperiodic and non-stationary signals, such as EEG.[22] First, in the wavelet space, EEG signal power is distributed throughout time and frequency domains that enables tracking frequency dynamics over time. Second, adjust able parameters in wavelet spectra provide the best time-frequency representation of signals that cannot be achieved with other methods of time-frequency analysis (i.e. empirical mode analysis, windowed Fourier transform, Gabor-Wigner transform).

Sleep spindles are of particular interest to specialists in clinical and basic neuroscience, because sleep spindle oscillations has long been known to associate with absence seizures (spike-wave discharges in EEG[14,15]). Some inbreed rat strains are prone to develop SWD spontaneously. For example, WAG/Rij rat strain has a genetic predisposition to absence seizures.[23] The current paper uses WAG/Rij rats as a genetic model of absence epilepsy. Considering the fact that SWD result from an impaired functioning of thalamo-cortical network,[11,15,17] we assume that time-frequency structure of sleep spindles might also be impaired due to disturbances in thalamo-cortical network as absence epilepsy progresses.

Sleep spindles in rats display maximum amplitude in the frontal cortical area,[5,9,24] and the present study is focused in anterior spindles. Previously we found that about 10% of anterior sleep spindles in WAG/Rij rats were characterized by abnormal features and considered as pro-epileptic.[18,20,25] In the current paper we examined putative changes of sleep spindles in WAG/Rij rats during a short period of life (between 5 and 7 months of age) when seizure activity is rapidly aggravating in comparison with the age-match non-epileptic control Wistar rats.[26,27]

2. MATERIALS AND METHODS

In order to monitor age-dependent changes in sleep spindle activity, EEGs were recorded in six male WAG/Rij rats and six Wistar rats in two successive sessions: at the age of 7 and 9 months. The experiments were conducted in accordance with the legislations and regulations for animal care and were approved by the Ethical Committee

on Animal Experimentation of the Institute of Higher Nervous Activity and Neurophysiology RAS. A recording electrode was implanted epidurally over the frontal cortex (coordinates: AP +2 mm and L 2.5 mm relatively to the bregma) for the reason that sleep spindles showed their amplitude maximum in this zone. Ground and reference electrodes were placed over the two symmetrical sides of the cerebellum. EEG recordings were made in freely moving rats continuously during a period of 24 h. EEG signals were fed into a multi-channel differential amplifier via a swivel contact, band-pass filtered between 0.5–200 Hz, digitized with 400 samples/second/per channel. Only frontal EEG data were used for time-frequency analysis (because sleep spindles showed maximum amplitude in the frontal channel), while occipital and parietal EEGs were used to facilitate determining the state of vigilance, in particular, slow wave sleep.

Epochs of artifact-free EEG during slow-wave sleep were extracted from raw EEG for automatic detection of sleep spindles and the further time-frequency analysis.

Sleep spindles and SWD were investigated in the frontal EEG for the reason that they both displayed amplitude maximum in this (anterior) area. SWD were detected visually as a sequence of repetitive high-voltage negative spikes and negative waves that lasted longer than 1 sec; amplitude of SWD exceeded background more than three times. The number and duration of SWD were scored in 6-hour interval during dark phase. Sleep spindles were recognized in EEG as 8–14 Hz waves with characteristic waxing-waning morphology and symmetrical waveform, whose amplitude exceeded background level at least twice. The continuous wavelet transform (CWT)[22] was used for time-frequency analysis of sleep spindles in EEG. The CWT, $M(f,t)$, was obtained by convolving the EEG signal, $x(t)$, with the basis function (complex Morlet wavelet) (Eqs. (1) and (2))

$$M(f,\kappa) = \sqrt{f} \int_{-\infty}^{+\infty} x(t)\eta_0^*\left((t-\kappa)f\right)], dt, \tag{1}$$

where '*' denotes complex conjugation, the parameter f corresponds to the 'wavelet' frequency of oscillating processes, κ is the time shift, and $\eta_0(t)$ is the basic complex function ('mother' wavelet) of wavelet transform. We used complex Morlet wavelet as the basis function

$$\eta_0(t) = \pi^{-0.25} \exp\left(j\Omega t\right) \exp\left(-0.5t^2\right), \tag{2}$$

where Ω is the central frequency.

In the present study, we considered $\Omega = 2\pi$ that resulted in optimal time-frequency resolution of the transformed EEG signal. Fig. 1a demonstrates EEG recording of WAG/Rij rat with two typical sleep spindles and the corresponding Morlet-based wavelet spectrum. The modulus of the CWT, $|M(f,t_0)|$, characterizes signal intensity associated with the frequency f at the given time moment t_0. We introduce wavelet energy distribution (a scalogram), $E(f)$, in the time interval $[t-h/2,\, t+h/2]$ (for example, in the time interval corresponding to a certain oscillatory event in EEG with the duration h):

$$E(f) = \frac{1}{h} \int_{t-h/2}^{t+h/2} M^2(f,t)\, dt. \tag{3}$$

Scalogram represents a wavelet power spectrum similar to the Fourier power spectrum.

For automatic detection of spindle-like events in EEG, we employed a specific wavelet-based algorithm.[18–20,28] This method is based on measurements of the wavelet energy in the predetermined frequency band, $[f_1, f_2] = [9, 16]$ Hz being characteristic for sleep spindles

$$m(t) = \frac{1}{f_2 - f_1} \int_{f_1}^{f2} M^2(f,t)\, df. \tag{4}$$

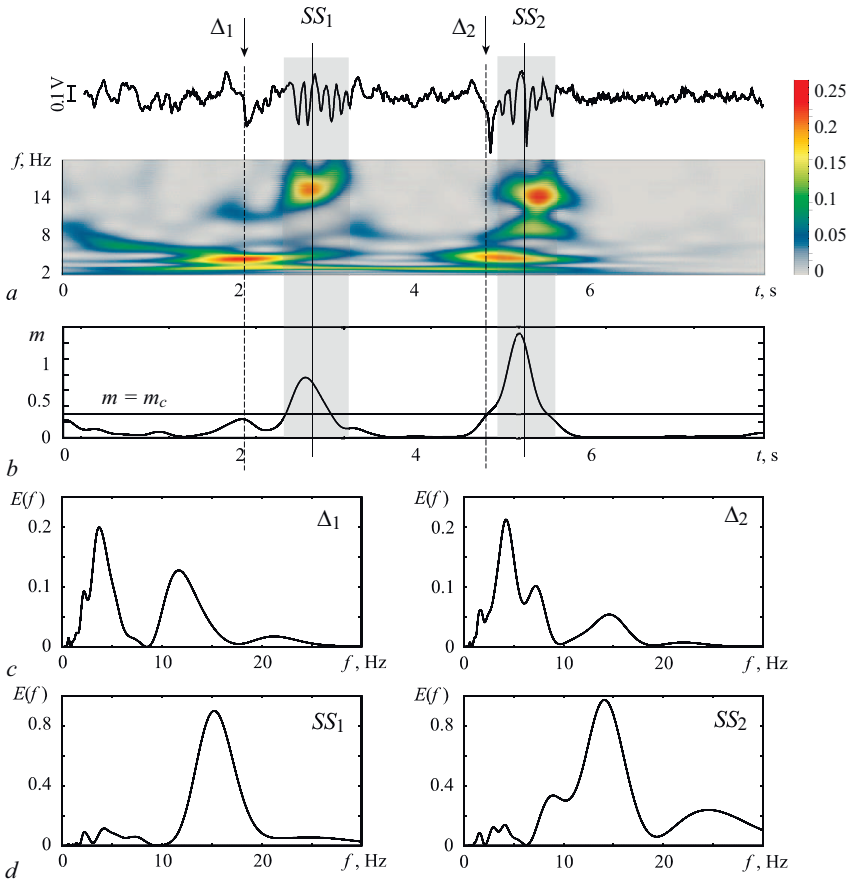

Figure 1. Principle of the wavelet-based system for automatic pattern detection in EEG. Fig. a shows an example of EEG recording with two sleep spindles SS1 and SS2 (shown by grey boxes) and the corresponding Morlet-based wavelet spectrum. Curve in the Fig. b displays distribution of the wavelet energy $m(t)$ measured in the 9–16 Hz frequency range. Sleep spindles are recognized under the condition that the wavelet power in a certain frequency band $[f_1, f_2]$ exceeds the threshold value m_c. Fig. c,d show distributions of the wavelet energy, $E(f)$, as measured in 2-4 Hz (delta) precursor activity preceded sleep spindles (marked by arrows and dotted line in Fig. a, b) (c) and in sleep spindles oscillations (d). $E(f)$ indicates that peak frequencies of these oscillatory phenomena are well allocated to the background EEG and correspond to 2–4 Hz and 10–15 Hz frequency bands. In the case of delta-precursor, the distributions demonstrate peaks in both delta band (2–4 Hz) and sleep spindle frequency band (10–15 Hz). The second high-frequency peak corresponds to the beginning of sleep spindles which follows brief episodes of delta precursor activity

Wavelet power, $m(t)$, in specific frequency bands, $[f_1, f_2]$, was computed by means of CWT and used in automatic detection system as criteria for selective identification and localization of the sleep spindles. For this purpose the power $m(t)$ in the selected frequency band was averaged within the temporal window T,

$$\bar{m}(t) = \frac{1}{T} \int_{t-T/2}^{t+T/2} m(\tau)\, d\tau \tag{5}$$

and the obtained value was compared with the empirically defined threshold, $\bar{m}(t) = m_c$. The presence of sleep spindle was recognized under the condition that $\bar{m}(t) > m_c$. This method provided specific discrimination of sleep spindles in the background EEG by an increase of cumulative wavelet power, $m(t)$, in the frequency band $[9, 16]$ Hz. The accuracy of detections was about 90–95% in both WAG/Rij and Wistar rats.

In order to determine the end point of each oscillation, we defined the averaged wavelet power, m_b, of EEG background intervals. The value of m_b was compared with the wavelet power as measured in analyzed

frequency band $[f_1, f_2]$, $m(t)$. Termination of sleep spindle events was assigned when the following criterion was met: $\bar{m}(t) < 2m_b$. This requirement also allowed avoiding false detections of short spindle-like events with the duration less than 0.3 s.

Fig. 1b illustrates the procedure of automatic discrimination of the investigated EEG oscillatory patterns (sleep spindles). Typical energy distributions, $E(f)$, of the sleep spindles are shown in Fig. 1d. It is clearly seen that peaks of the wavelet energy distributions are observed at the frequencies corresponding to the range of 9–16 Hz. Due to these peaks we can automatically determine sleep spindles in EEG using the above described method of automatic allocation of EEG oscillatory patterns. Thus, the time-frequency structure of sleep spindles is typical and very stable for all spindle-like patterns. Note that such frequency structure is observed for the spindle-like patterns of various duration (from 0.2 s to 1.5 s), at the same time the majority of allocated automatically sleep spindles had a duration from 0.3 s to 0.7 s. Therefore we considered as sleep spindles all automatically allocated spindle-like patterns with the duration longer than 0.3 s.

Let us note that sleep spindles are preceded the events of delta activity whose typical wavelet energy distributions are shown in Fig. 1c. Together with the sleep spindles, these delta-precursors in the EEG are the K-complexes.

3. TIME-FREQUENCY ANALYSIS OF SLEEP SPINDLE OSCILLATIONS

Time-frequency characteristics of the investigated phenomena were studied in EEG recordings using CWT described in the previous section. For the time-frequency analysis and observation of the dynamics of the dominant frequency during oscillatory events in EEG we used the numerical method of construction of 'skeletons' of wavelet surfaces.[29] In this case we analyzed the instantaneous wavelet energy distribution $E(f)$ for the fixed time moments $t = t_0$ and found all the local maxima of $E(f)$: $E_{max,k} = \max[E(f)]$.

After this we found the largest peak in the wavelet energy distribution at the considered time moment $t = t_0$ and determined the main frequency, f_b, corresponding to the largest maximum. This frequency was considered as the basic frequency of oscillations in EEG and plotted in 'skeletons' of wavelet surfaces. Let us note, that there is only one dominate frequency, f_b, at each time moment which is presented in skeletons in Fig. 2. In fact, the skeleton is the dependence of the instantaneous basic frequency from the time and allows conveniently representing and tracking the dynamics of instantaneous frequency, $f_b(t)$, in the EEG recordings. In this paper, for the time-frequency analysis we exploited only skeletons of wavelet surfaces and did not use the wavelet spectra that are allowed automated data processing. Using the skeleton we can easy define both extreme frequency values at the beginning (f_1) and the end (f_2) of spindle train and mean frequency, f_{mean}, of sleep spindles.[29]

In Fig. 2, the wavelet spectra and the corresponding skeletons of wavelet surfaces are shown for the sleep spindles with typical dynamics of basic frequency: (a) with increasing frequency from the beginning to the end of spindle, and (b) with diminishing frequency. One can easily see that the skeleton plot is very effective tool for analyzing time-frequency peculiarities of oscillatory events in EEG.

4. FREQUENCY-SPECIFIC GROUPS OF SLEEP SPINDLES

Time-frequency analysis was performed in sleep spindles automatically selected in EEG by the wavelet-based system. In total, about 500 sleep spindles were studied in Wistar and 300 sleep spindles in WAG/Rij rats (35–50 spindles per animal per age). The mean frequency of sleep spindles in WAG/Rij rats was lower than in non-epileptic Wistar rats and it did not change with age. At the age of 7 months, frequency of sleep spindles in WAG/Rij rats was 11.2 Hz and at the age of 9 months – 11.3 Hz. In Wistar rats, it was 13.2 Hz for both ages.

The incidence of absence seizures in WAG/Rij rats increased in the period between 7 and 9 months of age: the number of SWD increased from 19 ± 24 to 40 ± 41 and the total duration of seizure activity increased from 125 ± 202 s to 317 ± 327 s. Wistar rats did not develop any SWD. Mean duration of sleep spindles in WAG/Rij and Wistar rats displayed different age-related dynamics. In 7-months old Wistar rats, sleep spindles lasted 0.406 ± 0.148 s (mean $\pm$ s.d. here and below) and their duration increased to 0.437 ± 0.168 s at the age of 9 months. In WAG/Rij rats, mean duration of sleep spindles did not change with age (0.388 ± 0.107 s and 0.371 ± 0.075 s in 7– and 9–months old animals, correspondingly).

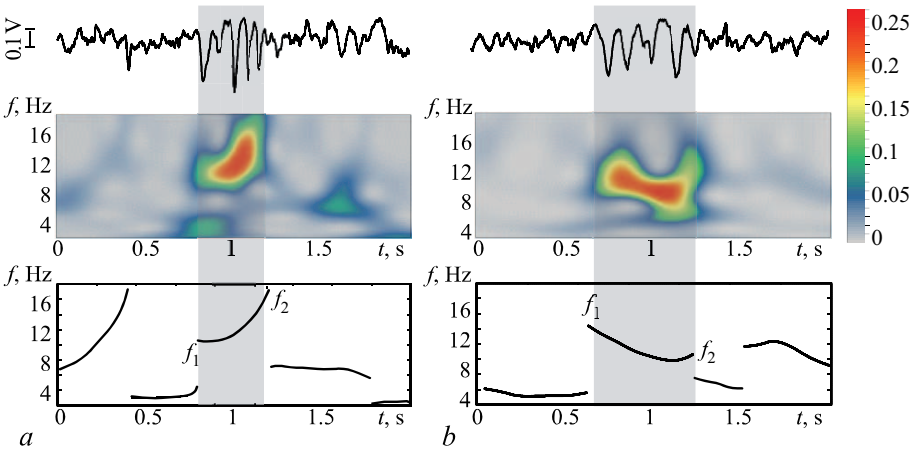

Figure 2. Wavelet spectra and 'skeletons' of wavelet surfaces of sleep spindles illustrating instantaneous dynamics of intra-spindle frequency: mean frequency (f_{mean}) and extreme frequency values at the beginning (f_1) and the end (f_2) of spindle train. Fig. (a) corresponds to the sleep spindle with growth of frequency from the beginning to the end of event ($f_{mean} = 13.8$ Hz), and (b) – with decreasing frequency (13.1 Hz)

Therefore in WAG/Rij rats, age-related increase of seizure activity did not affect basic parameters of sleep spindles (duration and frequency). We further examined age-related and seizure-related changes of time-frequency structure of sleep spindles using 'skeletons' of wavelet surface. First step was to analyze dynamics of intra-spindle frequency from the beginning (f_1) to the end (f_2) of a spindle train. Second, to study the mean frequency (f_{mean}) of sleep spindles.

Statistical distribution of the mean frequencies of sleep spindles was not normal (Kolmogorov-Smirnov test) with noticeable multimodality. This fact has been known from the literature: in humans, spindles showed two spectral peaks 12 Hz and 14 Hz (slow and fast spindles),[2,7,8] similar to rats.[5,9] In the present study we analyzed distribution of the mean frequency of sleep spindles. Noteworthy is that mean frequencies were not centered around one or two bands, moreover $\sim$ 12 Hz did not seem to be the central frequency in both WAG/Rij and Wistar lines. Considering peaks in distribution histograms (Fig. 3), sleep spindles can be divided in several groups: 'slow' (8–10.4 Hz), 'medium' (or 'transitional') (10.5–12.4 Hz) and 'fast' (12.5–14.4 Hz) spindles. Sleep spindles, whose frequency was beyond the spindle rage (14.5–16 Hz), comprised an 'extra' spindle type.

Mean frequency of the 'slow' sleep spindles was 9.3–9.8 Hz, in 'medium' spindles — 11.4–11.6 Hz, 'fast' — 13.2-13.4 Hz and 'extra' spindles — 14.9–15.3 Hz. Fig. 3 shows percentage of each spindle type in Wistar and WAG/Rij rats. In 7-months old WAG/Rij rats, percentage of 'slow' and 'medium' sleep spindles was higher than in Wistar rats, but percentage of 'extra' sleep spindles was lower. At the age of 9 months, percentage of 'slow' spindles in WAG/Rij rats was higher than in Wistar rats, but percentages of 'fast' and 'extra' spindles were lower (see Fig. 3). About two-thirds of sleep spindles in Wistar rats appeared with a frequency higher than 12.5 Hz (62%, 'fast' and 'extra' spindle class). This kind of sleep spindles was rather rare in WAG/Rij (21% in 7-months old WAG/Rij rats, where only 8% comprised 'extra' spindle). According to GLM analysis, there were no age-related changes in percentage of distribution of sleep spindles across spindle types. However, there was a significant interaction 'strain' * 'spindle type' ($F_{3;87} = 21.0$, $p<0.0001$), suggesting that relative amount of frequency-specific spindle types differed in the two rat strains and did not change with age. Post-hoc test showed that 'slow' and 'medium' spindles were more numerous in WAG/Rij rats than in Wistar, but 'fast' and 'extra' spindles – less numerous (both p's<0.05).

In wavelet 'skeletons' (Fig. 2), majority of sleep spindles displayed gradual changes in dominant frequency in the ascending or descending manner. In order to analyze this intra-spindle frequency dynamics, we measured instantaneous frequency at the beginning (f_1) and at the end (f_2) of each spindle event. In Wistar rats, sleep spindles showed an increase of intra-spindle frequency from the beginning to the end, and this effect became more pronounced with age (the difference between f_1 and f_2 in 9-months animals was larger than in 7 months

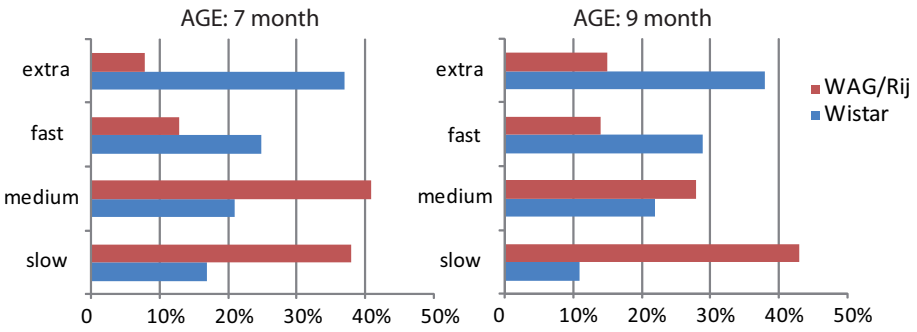

Figure 3. Percentage of frequency-specific spindle types in WAG/Rij and Wistar rats

old rats). An increase of intra-spindle frequency varied in different spindle types: it was significant in 'medium' and 'fast' spindles, but not obvious in 'slow' and 'extra' spindle types.

In opposite to Wistar rats, the instantaneous frequency for WAG/Rij rats did not change in the time course of sleep spindles, i.e., $f_2 = f_1$ (Fig. 3). The intra-spindle frequency dynamics in WAG/Rij rats was absent in both age groups and in all spindle types.

5. CONCLUSION

This study examines time-frequency characteristics of sleep spindles during late ontogenesis (from 7 to 9 months of age) in non-epileptic Wistar and epileptic WAG/Rij rats. The incidence of absence seizures in WAG/Rij rats increased from 7 to 9 months of age, however, neither duration, nor frequency of sleep spindles were changed. In Wistar rats, mean duration of sleep spindles increased with age, but their frequency did not. In WAG/Rij rats at the age of 7 and 9 months, instantaneous frequency remained constant during a spindle event. There were no age-related changes in time-frequency profile of sleep spindles in WAG/Rij rats, despite progressive development of seizure activity. Even in younger animals, in which absences were less frequent and severe, frequency of sleep spindles was lower than in non-epileptic control and intra-spindle frequency was constant during a spindle event. These data suggest that (i) low frequency of sleep spindles and (ii) the lack of intra-spindle frequency dynamics might be used as biomarkers for early (perhaps, preclinical) stage of absence epilepsy

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