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Research Report

On–off intermittency of thalamo-cortical oscillations in the electroencephalogram of rats with genetic predisposition to absence epilepsy

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ABSTRACT

Spike-wave discharges (SWD) are electroencephalographic hallmarks of absence epilepsy. SWD are known to originate from thalamo-cortical neuronal network that normally produces sleep spindle oscillations. Although sleep spindles and SWD are considered as thalamo-cortical oscillations, functional relationship between them is not obvious. The present study describes temporal dynamics of SWD and sleep spindles as determined in 24 h EEG recorded in WAG/Rij rat model of absence epilepsy. SWD, sleep spindles (10–15 Hz) and 5–9 Hz oscillations were automatically detected in EEG using wavelet-based algorithm. It was found that non-linear dynamics of SWD fitted well to the law of 'on–off intermittency'. Sleep spindles also demonstrated 'on–off intermittency', in contrast to 5–9 Hz oscillations, whose dynamics could not be classified as having any known type of non-linear behavior. Intermittency in sleep spindles and SWD implies that (1) temporal dynamics of these oscillations are deterministic in nature, and (2) it might be controlled by a system-level mechanism responsible for circadian modulation of neuronal network activity.

1. Introduction

Sleep spindles are among the most numerous spontaneous oscillations that are abundantly present in electroencephalograms (EEG) during non-REM sleep in humans and in animals (reviewed in De Gennaro and Ferrara, 2003). Sleep spindles can be recorded at the cortical surface, and also in the thalamus as brief episodes of 9–14 Hz oscillations. Basic electrophysiological studies have shown that sleep spindle oscillations are triggered by the reticular thalamic nuclei, spread throughout the thalamus and propagated to the cortex (for Refs see: Destexhe and Sejnowski, 2001; Steriade, 2003). Thalamo-cortical neuronal circuit, which normally produces sleep spindles, under certain conditions[1] could give rise to epileptic spike-wave discharges, SWD (Gloor, 1968; Steriade et al., 1993a; Kostopoulos, 2000). SWD are electroencephalographic hallmarks of generalized

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Abbreviations: SWD, spike-wave discharges; CWT, continuous wavelet transform
[1] This can happen when neuronal network synchronization becomes too high (hyper-synchronization), or when cortical neurons express too strong excitation (hyper-excitation) in response to thalamic input.

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idiopathic epilepsies, such as absence epilepsy and other syndromes. Typical 3 Hz SWD could be seen in childhood absence epilepsy or 'pyknolepsy' (Panayiotopoulos, 1997).

Reciprocal relationship between sleep spindles and SWD was first established in pharmacological models of epilepsy. It was found that spindle oscillations were gradually transformed into SWD after local or systemic injections of penicillin that acted as GABAergic antagonist and led to an increase of cortical excitation (Gloor, 1968; Steriade et al., 1993a; Kostopoulos, 2000). In other words, SWD were derived from spindle-like oscillations under experimental conditions. Further investigations in drug-free animals with genetic predisposition to absence epilepsy raised some doubts about the intimate relationship between sleep spindle oscillations and SWD (Pinault et al., 2006; Sitnikova, 2010). For example, in WAG/Rij rat model of human absence epilepsy (Coenen and van Luijtelaar, 2003), time–frequency characteristics of spontaneous SWD differed from that in sleep spindles as measured in cortex and thalamus (e.g., Sitnikova, 2010). In addition to that, SWD and sleep spindles are associated with different neuronal processes and different neurotransmission mechanisms (Sargsyan et al., 2007).

It is well known that sleep spindles and spontaneous SWD (but not pharmacologically induced seizures) are characterized by similar temporal distribution across sleep-waking cycle. In particular, both EEG events are predominant in drowsy state and in transition from wakefulness to sleep (e.g., Drinkenburg et al., 1991; Steriade, 2003; van Luijtelaar and Bikbaev, 2007). Sleep spindles are abundant during slow-wave sleep (SWS); and circadian dynamics of SWD also positively correlates with the dynamics of SWS, as it was demonstrated in WAG/Rij rat model of absence epilepsy (Drinkenburg et al., 1991). In human patients, absence epilepsy sometimes dismissed as simple 'daydreaming'. Absence epilepsy might be considered as a sleep-related disorder, inasmuch as SWD more often appear when the level of vigilance is low, e.g., passive wakefulness, drowsiness and light slow-wave sleep in animal models (Lannes et al., 1988; Drinkenburg et al., 1991; Coenen and van Luijtelaar, 2003), as well as in epileptic patients (Kellaway, 1985; Sadleir et al., 2011). Altogether this implies that occurrence of sleep spindles and SWD could be controlled by a common circadian timing mechanism that regulates sleep–wake cycle.

Relationship between SWD, sleep spindles and mechanisms of sleep is very complicated and it is not well understood. Despite the fact that absence epilepsy common physiological substrate non-sleep, absence seizures might be initiated by wake-related processes (reviewed in Pinault and O'Brien, 2005; Halász and Kelemen, 2009). In particular, in Genetic Rats with Absence Epilepsy (GAERS), "SWDs develop from *wake-related* 5–9 Hz oscillations, which are distinct from spindle oscillations (7–15 Hz)" (Pinault et al., 2006; p. 209). 5–9 Hz oscillations originate from the cortex ('*launched by corticothalamic neurons*', Pinault et al., 2006), in opposite to sleep spindles, whose pacemaker is well known to be located in the thalamus (Steriade et al., 1993a). Spontaneous medium-voltage 5–9-Hz oscillations usually present in EEG during awake immobility, but they do not always lead to spike-and-wave discharges (Pinault et al., 2001). In addition to that, 5–9-Hz oscillations can be recorded in non-epileptic rats and never give rise to SWD (Pinault et al., 2001). Despite considerable progress made in elucidating the cellular mechanisms of 5–9-Hz oscillations, temporal dynamics of these oscillations have not been investigated so far.

The current paper examines three kinds of thalamo-cortical oscillatory patterns, SWD, sleep spindles and 5–9 Hz oscillations, in respect to their intrinsic time–frequency structure and global dynamics. Continuous 24 h EEG recordings were obtained in freely moving WAG/Rij rats. EEG analysis was performed by means of the continuous wavelet transform. Nonlinear dynamics of spindles and SWD were statistically evaluated based on the theory of intermittency. Briefly stated, intermittency in nonlinear oscillatory systems is known to be associated with aperiodic switching between so-called static behavior and chaotic bursts (Platt et al., 1993; Heagy et al., 1994). In EEG, static behavior can be considered as long-lasting periods of desynchronized state, and chaotic bursts — as various kinds of oscillatory events. In the human EEG, intermittent behavior is known to characterize dynamics of spontaneous alpha-range activity 8–13 Hz in healthy subjects (Gong et al., 2007), as well as seizure activity in patients suffering from intractable partial epilepsy (Velazquez et al., 1999). A particular type of intermittent behavior, *on–off* intermittency, is manifested as an abrupt shift between synchronized and desynchronized states in dynamic systems (Boccaletti et al., 2002; Hramov and Koronovskii, 2005), suggesting that the same intermittent mechanism might underlie temporal dynamics of synchronized oscillations synchronous thalamo-cortical oscillations in EEG, such as SWD, sleep spindles and 5–9 Hz oscillations.

2. Results

2.1. *Time–frequency properties of sleep spindles, 5–9 Hz oscillations and SWD*

Time–frequency characteristics of the investigated phenomena were studied in frontal EEG recordings using continuous wavelet transform (CWT, see Section 4.2). This analysis was aimed to define the spectral features that would explicitly characterize each class of the investigated EEG patterns; these features were also used as selection criteria in the automatic detection system (Section 4.3).

Criteria for assessing sleep spindles in EEG derived from animal EEG research (Terrier and Gottesmann, 1978; Steriade et al., 1993a; van Luijtelaar, 1997). In WAG/Rij rats, sleep spindles represented a sequence of 8–14 Hz waves, they were characterized by twofold increase in amplitude as compared to EEG background, had waxing–waning morphology and minimal duration of 0.5 s. According to Morlet-based wavelet analysis (Eq. (3)), sleep spindles in WAG/Rij rats showed a marked increase wavelet power in 10–15 Hz (Fig. 1*a,c*). Wavelet spectrum of sleep spindles was often contaminated with additional low-frequency components (Fig. 1) and high-frequency bursts (occasional spikes). There were substantial frequency fluctuations within one spindle train (i.e., intra-spindle frequency variation) and mean frequency of different sleep spindles also varied (i.e., between-spindle frequency variations). The averaged frequency of sleep spindle per rat