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Electroencephalographic precursors of spike-wave discharges in a genetic rat model of absence epilepsy: Power spectrum and coherence EEG analyses

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Summary Periods in the electroencephalogram (EEG) that immediately precede the onset of spontaneous spike-wave discharges (SWD) were examined in WAG/Rij rat model of absence epilepsy. Precursors of SWD (preSWD) were classified based on the distribution of EEG power in *delta—theta—alpha* frequency bands as measured in the frontal cortex. In 95% of preSWD, an elevation of EEG power was detected in *delta* band (1—4 Hz). 73% of preSWD showed high power in *theta* frequencies (4.5—8 Hz); these preSWD might correspond to 5—9 Hz oscillations that were found in GAERS before SWD onset [Pinault, D., Vergnes, M., Marescaux, C., 2001. Medium-voltage 5—9 Hz oscillations give rise to spike-and-wave discharges in a genetic model of absence epilepsy: in vivo dual extracellular recording of thalamic relay and reticular neurons. Neuroscience 105, 181—201], however, *theta* component of preSWD in our WAG/Rij rats was not shaped into a single rhythm. It is concluded that a coalescence of *delta* and *theta* in the cortex is favorable for the occurrence of SWD. The onset of SWD was associated with strengthening of intracortical and thalamo—cortical coherence in 9.5—14 Hz and in double *beta* frequencies. No features of EEG coherence can be considered as unique for any of preSWD subtype. Reticular and ventroposteromedial thalamic nuclei were strongly coupled even before the onset of SWD. All this suggests that SWD derive from an intermixed *delta—theta* EEG background; seizure onset associates with reinforcement of intracortical and cortico—thalamic associations.

Introduction

Absence seizures in humans and in animal models of absence epilepsy begin abruptly and unpredictably. There are no obvious clinical or electroencephalographic signs, by which absence seizures can be anticipated or reliably predicted,

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whereas only some less specific disturbances could be visualized in the background EEG immediately before the onset of spike-wave discharges (SWD). In humans, seizure-precursor activity is referred to as '*poorly developed epileptiform discharges*' (Inouye et al., 1990). It has been shown that in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), SWD are preceded by medium-voltage 5—9 Hz oscillations (Pinault et al., 2001). The presence of this pro-epileptic 5—9 Hz rhythmic activity (Pinault et al., 2001) has never been confirmed in other animal models of absence epilepsy, including WAG/Rij[1] rat strain, which most closely resembles GAERS strain in many respects (Danober et al., 1998; Depaulis and van Luijtelaar, 2005). Therefore, we cannot exclude a possibility that 5—9 Hz oscillatory precursors of SWD are merely an epiphenomenon characterizing GAERS strain. In the present study we examine EEG activity in WAG/Rij rats in order to figure out weather SWD in WAG/Rij rats are also anticipated by the same 5—9 Hz oscillations or similar oscillatory EEG patterns.

Medium-voltage 5—9 Hz oscillations are known to precede SWD during a specific behavioral state, in which animals were awake, but less alert (sitting in a safe environment and not anticipating any imminent stimulus). 5—9 Hz oscillations often appear in the EEG of non-epileptic rats therefore, this EEG pattern can hardly be considered as exclusive predictor of absence epilepsy (Pinault et al., 2001; Pinault, 2003). Even in GAERS, 5—9 Hz oscillations are not always followed by SWD. Broadly speaking, 5—9 Hz rhythmic activity in rodents is rather 'normal', i.e., this physiological EEG pattern is not fairly associated with absence epilepsy. It seems also obscure why 5—9 Hz oscillations never encourage absence seizures in non-epileptic animals.

It is well accepted that SWD are generated in a strongly coupled cortico—thalamo—cortical network, which comprise neocortex, specific thalamus and reticular thalamic nucleus, RTN (e.g., Gloor et al., 1990; Steriade, 2003; Destexhe and Sejnowski, 2001). When neuronal synchronization in this network becomes abnormally high, the cortex recruits the thalamus primarily through the RTN (Buzsáki et al., 1988; Avanzini et al., 2000); this entails hypersynchronous generalized SWD (e.g., Sitnikova and van Luijtelaar, 2006). Several recent investigations in animal models of absence epilepsy cast doubts about the primary involvement of the RTN (Timofeev and Steriade, 2004; Meeren et al., 2002, 2005; Pinault, 2003; Pinault et al., 2006; van Luijtelaar and Sitnikova, 2006). In particular, it is shown that the neocortex, rather than the thalamus, plays a crucial role in initiation and synchronization of SWD (Meeren et al., 2002; Timofeev and Steriade, 2004). Another aspect of absence epilepsy is an impairment of membrane properties of neurons, for example, hyperpolarization-activated cation Ih-current, in the somatosensory cortex in WAG/Rij rats (Strauss et al., 2004; Kole et al., 2007) and in the corresponding thalamic regions (Budde et al., 2005) that underlie neuronal hyperexcitability and prompt occurrence of absence seizures. The basic intrinsic neuronal mechanisms of absence epilepsy are reviewed in several papers (e.g., Crunelli and Leresche, 2002; Manning et al., 2003; van Luijtelaar and Sitnikova, 2006). In general, absence epilepsy is accompanied by abnormalities thalamo—cortical system, such us deep injuries in ion channels, membrane properties, neurotransmitter systems and, finally, by disturbances of neuronal network interactions. In the current paper we examine cortico—thalamo—cortical network associations with the aid of EEG coherence.

Cellular mechanisms of medium-voltage 5—9 Hz oscillations have been investigated in anesthetized and non-anesthetized GAERS (Pinault, 2003; Pinault et al., 2006). Some important outcomes are as follows: firstly, absence-related 5—9 Hz oscillations were generated mostly in the somatosensory part of the thalamo—cortical system. Secondly, neurons in layer IV of the somatosensory cortex started firing at 5—9 Hz a few milliseconds earlier than neurons in the corresponding specific and reticular thalamic nuclei. Thirdly, cortical neurons were capable to modulate membrane potentials of thalamic neurons throughout dense cortico—thalamic synaptic interactions. All this confirms that layer IV cortical neurons largely affect neuronal activity in functionally related thalamic nuclei. After receiving initial signal from the somatosensory cortex, the cortico—thalamo—cortical network may enter a pro-epileptic state and may produce 5—9 Hz seizure-precursor rhythm that is consequently followed by SWD. It is hypothesized that, in epileptic animals, 5—9 Hz pro-epileptic oscillations give rise to SWD due to the impairment of cortico—thalamo—cortical network associations. Our study aims to access dynamic changes of synchronization in this network that accompany transition from seizure-precursor activity (preSWD) into SWD. For that purpose, we measure EEG coherence between two cortical areas (frontal and occipital channels), ventroposteromedial nucleus (VPM, somatosensory relay thalamic nucleus) and reticular thalamic nucleus before and just after the onset of SWD.

In the current paper, we address the following questions: (1) phenomenology of preSWD by characterizing their amplitude-frequency parameters in EEG as measured in the cortex and in the thalamus (incl. the VPM and RTN); (2) relationship between electrographic properties of preSWD and subsequent seizure activity; (3) cortico—thalamo—cortical network associations during preSWD and in subsequent SWD with the aid of EEG coherence.

Methods

Animals

EEG records were made in five male WAG/Rij rats (11—12-month-old, body weigh 320—360 g). Animals were born and raised at the laboratory of the Department of Biological Psychology of the Radboud University Nijmegen (The Netherlands). They were kept in pairs in standard cages with food and water available *ad libitum* and 12—12 h light—dark cycle (white light on at 18:00). After surgery, housing conditions were the same except that rats were housed individually. 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 Rad-

[1] WAG/Rij rats with genetic predisposition to absence epilepsy are widely used as a reliable animal model of this disease (e.g., van Luijtelaar and Coenen, 1986; Coenen and van Luijtelaar, 2003).