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Propagation of spike and wave activity to the medial prefrontal cortex and dorsal raphe nucleus of WAG/Rij rats

Magor Lörincz [a], Márta Oláh [a], Péter Baracskay [a], Nora Szilágyi [a,b], Gábor Juhász [a,*]

[a] Neurobiology Research Group of Hungarian Academy of Sciences at Eötvös Loránd University, H-1117 Budapest, Pázmány Péter sétány 1/C, Hungary
[b] Department of Physiology and Neurobiology, Eötvös Loránd University, H-1117 Budapest, Pázmány Péter sétány 1/C, Hungary

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Abstract

Although there is pharmacological evidence for the involvement of the serotonergic system in the expression of spike and wave discharges (SWDs) in experimental absence epilepsy, no direct investigation of this paroxysm in the dorsal raphe nucleus (DRN), one of the main serotonergic nuclei, has been carried out. We have now recorded the EEG simultaneously with local field potentials and unit activity in DRN from WAG/Rij rats, one of the best established models of absence epilepsy during spontaneous SWDs. We have also compared this activity to that in the thalamocortical networks, where SWDs are generated, and in the medial prefrontal cortex (mPFC), as this brain area is reciprocally connected to the DRN. We have found that SWDs propagate to the DRN with a short delay, and that the firing rate of its neurons changes during this type of paroxysm. These results provide the first direct evidence for clear alterations in the firing properties of mPFC and DRN neurons during spontaneous SWDs.

Keywords: Absence epilepsy; Serotonin; Local field potential; Action potential

1. Introduction

Absence seizures, the main feature of absence epilepsy, are characterized by a brief impairment of consciousness associated with 3 Hz, bilateral, synchronous spike and wave discharges (SWDs) in the EEG without post-ictal depression [1]. SWDs are thought to be generated within thalamocortical networks, with this paroxysm appearing first in the somatosensory cortex and then in the thalamus [2]. The involvement of other brain structures, in particular areas rich in dopamine containing cells or afferents [3–5], in the control and modulation of SWDs has also been elucidated. Indeed, the spread of the ictal activity from cortical foci to different nuclei has been suggested to be responsible for the variety of clinical expressions of the seizures (see [6] for a review). Particularly, the following subcortical structures have been associated with involvement in human epilepsy: the thalamus is known to play an important role in motor, sensory, mnemonic, arousal dysfunction and loss of consciousness during seizures [7], its widespread thalamic connections being critical for seizure propagation [8]; the basal ganglia is thought to be involved in ictal dystonia during complex partial seizures [9]; hypothalamic hamartomas can cause gelastic seizures [10] and seizures propagating to the brainstem can also cause loss of consciousness [11].

Experimental results have also suggested the involvement of another brain monoaminergic system, i.e. the serotoninergic system, in the expression of SWDs in WAG/Rij rats [12–15], one of the best established genetic models of typical absence seizures [16]. In particular, administration of 5-HT1A and 5-HT7 receptor antagonists [14] or 5-HT2C agonists [15] has been shown to decrease the occurrence of SWDs.

The majority of serotoninergic cells are located in the brainstem dorsal raphe nucleus (DRN) [17], and innervate numerous forebrain areas, including cortical and thalamic territories [18]. Whereas there are no direct connections from the thalamus back to the DRN, reciprocal connections of the DRN to and from the medial prefrontal cortex (mPFC) have been described [19,20]. In addition, DRN cell firing is modulated both by DRN 5-HT1A autoreceptors [19] and local interneurons [21,22], and is known to correlate with the level of arousal and different sleep stages [23].

* Corresponding author. Tel.: +36 1 2090555x8729; fax: +36 1 3812182.
E-mail address: gjuhasz@dec001.geobio.elte.hu (G. Juhász).

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In this study we have directly tested whether SWDs propagate from the thalamocortical generating networks to the DRN of WAG/Rij rats that were either freely moving or under neurolept analgesia. We also investigated changes in the firing characteristics, temporal dynamics and synchronization of DRN and mPFC neurons during SWDs because of the reciprocal innervation between these two nuclei. The results indicate that SWD activity is present in the mPFC and DRN being reflected by significant changes in the firing properties of these neurons during SWDs.

2. Materials and methods

Experiments were performed in accordance with the guidelines of the European Communities Council Directive (86/609/EEC, 24 November 1986) and the local ethics committee. Male WAG/Rij rats (weight: 250–300 g; age: 10–12 months) were bred in our animal facility, where they were housed under a 12–12 h light–dark cycle with light onset at 07:00 and supplied with water and food *ad libitum*.

2.1. Experiments in freely moving animals

Rats were anaesthetized with halothane (0.8–1%) and placed in a stereotaxic frame. Stainless steel screws (0.8 mm diameter) were placed in the scull over the forelimb region of the primary somatosensory cortex (SS_1FL) (stereotaxic coordinates AP: −2, L: −2 mm) [24], and one over the cerebellum served as ground. A stainless steel plate of 3×5 mm was inserted under the skin over the *masseter muscle* and served as reference. Electrolytically sharpened bipolar tungsten electrodes (diameter: 80 μm; impedance at 1 kHz: 8–12 kΩ) were also implanted in the following areas: thalamic ventro-postero medial nuclei (VPM) (AP: −3.8, L: 2.5, DV: 6 mm), DRN (AP: −8, L: 0, DV: 6.2 mm), ventral part of the medial prefrontal cortex (mPFC) (AP: 2.7, L: 0.6, DV: 5 mm). Electrode tip locations were identified post-mortem in 30 μm cresyl violet-stained serial, coronal sections. Data from rats where electrodes were located outside the target nuclei were discarded.

Recordings began at least ten days after implantation with the rat free to move within a Plexiglas box (50×35×40 cm). Electrical signals were amplified by a Grass 8-10B amplifier and band-pass filtered between 1 and 200 Hz. Local field potentials were recorded both in monopolar (using a stainless steel plate inserted between the masseter muscle and skin with the insulated part facing the muscles as a reference) and in bipolar configuration. Analogue to digital conversion was performed at a sampling rate of 5 kHz using a CED 1401μ type AD converter (Cambridge Electronic Design Ltd, Cambridge, UK). Data were captured using the Spike2 software. The onset and offset of a SWD in the EEG were taken to be the first and last spike–wave complexes, respectively, where the amplitude of the surface negative 'spike' was at least three times the baseline EEG. The frequency domain of neuronal activity was defined by calculating the autospectra of power and frequency (Spike2 software). The temporal relationship between activities of different recording sites was further characterized by cross-correlation analysis. The lag between two compared activities represents the time difference between time zero and the peak of the cross-correlogram.

To quantify the association between the activities of the different brain sites we used cross-wavelet power, the magnitude of the cross-wavelet spectrum. Unlike traditional Fourier methods, wavelet analysis yields a time-frequency mapping of the signal. Its adaptive property makes wavelet decomposition a suitable tool to characterize the oscillatory components of the signal both in time and frequency domains. Morlet wavelet has been chosen for the special purpose of power spectral density estimation. Cross-wavelet power provides a correlation-like measure of the simultaneous occurrences of certain common oscillations [25]. Power spectra were normalized by the total power to allow comparison of activity recorded at different sites. All data are expressed as mean±SD, and two sample Student's *t*-test was used to assess statistical significance.

2.2. Experiments on animals under neurolept analgesia

Local field potentials and extracellular unit activity were recorded under neurolept analgesia [26] using low doses (0.5 ml/kg) of Hypnorm (Janssen, Oxford; fentanyl citrate 0.15 mg/ml; fluanisone 10 mg/ml). Rats ($n=8$) were placed in a stereotaxic frame and all pressure contact points treated with 2% xilocaine. After the scull was exposed, small (0.8 mm diameter) holes were drilled over the target areas. Electrolytically sharpened, Epoxylite insulated pairs of tungsten electrodes (impedance at 1 kHz: 0.5–2 MΩ) were lowered towards the DRN in an 18° medio-lateral angle and the ventral mPFC (AP: 2.7, L: 0.6, DV: 5–6 mm) using a micromanipulator (Model MP285; Sutter Instrument Company, Novato, CA, USA).

Signals were amplified with a Multiamp SMA 1a (Supertech, Hungary) amplifier. SWDs were detected on frontal and parietal EEG which was simultaneously recorded via stainless steel screw electrodes placed in the frontal and parietal bone. Data analogue to digital conversion was performed at a sampling rate of 30 kHz (unit) or 5 kHz (EEG) using a CED 1401μ type AD converter (Cambridge Electronic Design Ltd, Cambridge, UK). Data were stored on a PC hard disc for off-line analysis.

Action potentials were separated from baseline noise using the window discriminator function of Spike2 software. SWDs were defined as in the case of the freely moving animals, while preceding and following fragments of desynchronized EEG were used as control. Discharge rates were calculated from ictal and interictal (pre- and post-ictal) periods of identical length and compared by using paired Student's *t*-test. Neurons recorded for periods shorter than 20 min, or showing changes in spike amplitudes over time, or not located in the target areas were not included in the analysis.

To localize the recording positions, at the end of the experiments recording sites were stimulated using 200–400 ms square wave current pulses (1–10 μA) through the microelectrodes. Rats were deeply anaesthetized with Urethane (1.4 g kg^{-1}) and perfused intracardially with saline and 4% paraformaldehyde. The electrode tract and the recording sites were visualized by means of the Gallyas silver staining method [27].

3. Results

3.1. Propagation of spike–wave activity to mPFC and DRN in freely moving rats

Spontaneous electric activity was recorded from the VPM, SS_1FL, mPFC and DRN in five freely moving WAG/Rij rats. As previously described [2], synchronous episodes of SWDs were observed in SS_1FL and VPM (mean dominant frequencies: 7.6±0.37 Hz, range: 7.02–8.2 Hz [SS_1FL]; 7.72±0.3 Hz, range: 7.4–8.3 Hz [VPM]), that were often accompanied by behavioral arrest and slight movements of the vibrissae. Similar sequences of activity were observed in the mPFC and DRN, although they were of smaller amplitude both in bipolar and monopolar recordings (Fig. 1A). Their dominant frequencies were 7.75±0.58 Hz (range: 6.82–8.82 Hz) in the mPFC and 7.43±0.24 Hz (range: 7.07–7.79 Hz) in the DRN.

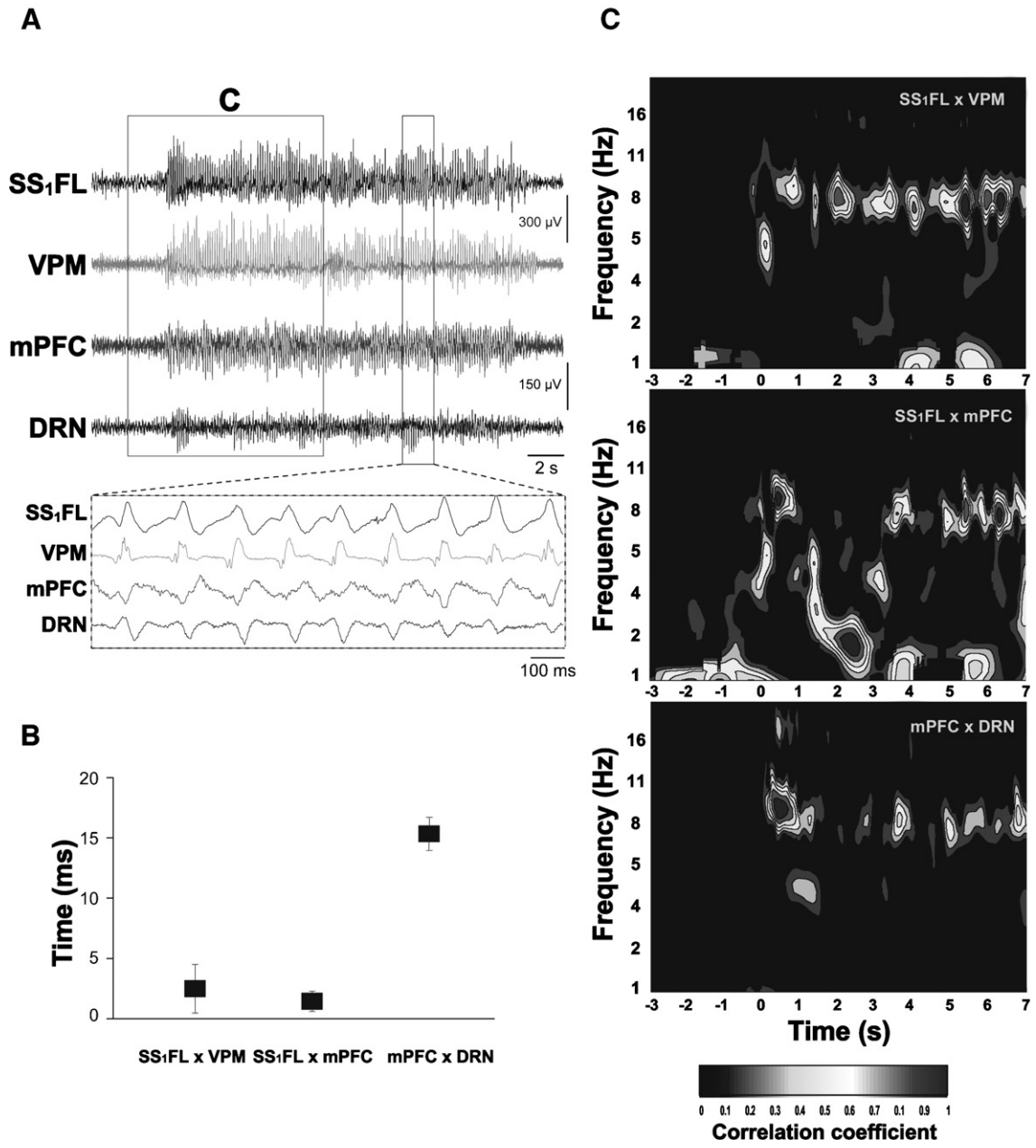

Fig. 1. Propagation of SWDs to the mPFC and DRN of freely moving WAG/Rij rats. (A) Typical example of SWDs recorded in SS_1FL, VPM, mPFC and DRN. At a faster time-base (enlargement of the traces as indicated by dashed lines), individual 'spike' and 'wave' components can be identified in the local field activities of mPFC and DRN. Note that the 'spike' component occurs substantially later in the DRN compared to the other recordings sites (see B). (B) The plot shows the time delay of the 'spike' components between the indicated areas (n=25 SWDs per point). (C) Cross-correlation wavelets between SS_1FL, VPM, mPFC and DRN (from the activity marked by the box in A). Note the persistently high correlation at the SWD dominant frequency between somatosensory and thalamic recordings sites (top plot), the more intermittent correlation between somatosensory cortex and mPFC which is not restricted to the SWD dominant frequency (middle plot), and the overall weak correlation (except at the SWD onset) between mPFC and DRN (bottom plot).

The mean power of the activity recorded in SS_1FL, VPM, mPFC and DRN during episodes of SWDs was significantly higher ($P<0.001$, paired t-test) than that recorded during quiet wakefulness. Furthermore, individual 'spike' and 'wave' components could be identified in mPFC and DRN activities although with some delay with respect to the cortical and thalamic components (see inset of Fig. 1A). Using cross-correlation analysis of 5 SWD episodes (of at least 8 second

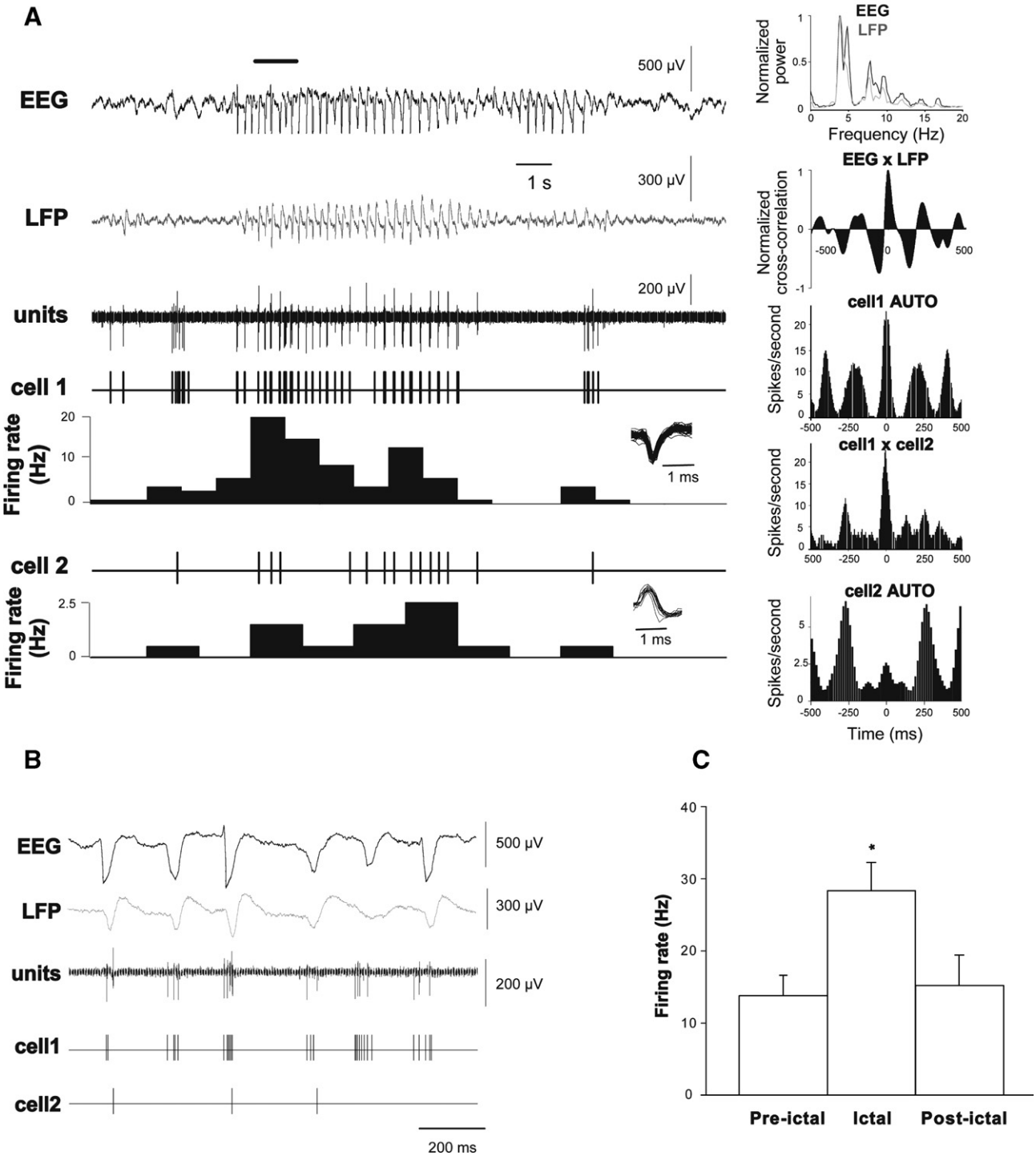

Fig. 2. Local field and unit activity of mPFC during spontaneous spike–wave discharges in neurolept-analgesized rats. (A) Simultaneous frontal EEG, and local field potential and unit recording from the mPFC show correlated activity and increase firing for two recorded units during SWDs. Superimposed action potentials that occurred during this SWDs ($n=85$ and 14 for cell 1 and 2, respectively) are illustrated on the right hand side of the firing rate histograms (bin sizes of 0.5 and 1 s for cell 1 and 2, respectively). The plots on the right hand side are (from top): EEG power spectrum, cross-correlation of EEG and local field potential, and auto- and cross-correlograms of the two units. The sections indicated by the horizontal bar in A are displayed at a faster time-base in B. (C) Average firing rates (before, during and after SWDs) of the 14 neurons that showed an increase in firing rate during SWDs.

duration) from each rat, the largest delay (about 15 ms) was identified between mPFC and DRN 'spike' components, whereas very small delays were present between SS_1FL and both VPM or mPFC (Fig. 1B).

Wavelet analysis indicated a strong correlation between SS_1FL and VPM, which started promptly at the onset of the SWD, remained stable for the duration of the discharge and was restricted to the dominant frequency range (7–9 Hz) of the paroxysm (Fig. 1C, top plot). A high correlation between SS_1FL and mPFC was also evident at the start of the SWD, though particularly in the first half of the paroxysm it was more intermittent and included lower frequencies than that of the SWDs (Fig. 1C, middle plot). Consistent with previous findings studying intracortical coherences [28], substantial correlation at lower frequencies between SS_1FL and mPFC was also present before the start of a SWD (Fig. 1C, middle plot). Finally, a strong correlation between mPFC and DRN was present simultaneously with the onset of the SWD (mean delay: 89.6±27.0 ms), but quickly disappeared to re-emerge at times with a much lower intensity later on during a SWD (Fig. 1C, lower plot).

3.2. Neuronal firing in mPFC and DRN during SWDs in neurolept-analgesized rats

The SWDs recorded in the EEG under this experimental condition were similar to those recorded in freely moving animals with the exception of a lower dominant frequency (5.2± 0.9 Hz, range: 4.3–7.7 Hz, $P<0.001$) (Fig. 2A, top plot on right hand side), as previously reported [26]. To investigate the temporal dynamics between EEG and mPFC and DRN neuronal firing during ictal and interictal states, mPFC and DRN unit activity was recorded in WAG/Rij rats under neurolept analgesia. As in freely moving animals, the local field potential recorded from the mPFC was correlated with the EEG (Fig. 2A).

A clear increase in firing rate was observed in the majority of the recorded layer V mPFC units (14 out of 21, 66%) (Fig. 2A), whereas 7 neurons (out of 21, 34%) did not change their firing during SWDs (data not illustrated). In particular, there was a rapid and marked increase at the onset of a SWD, which was often maintained for a few seconds. Towards the end of a SWD, however, the firing rate of these mPFC neurons declined rapidly,

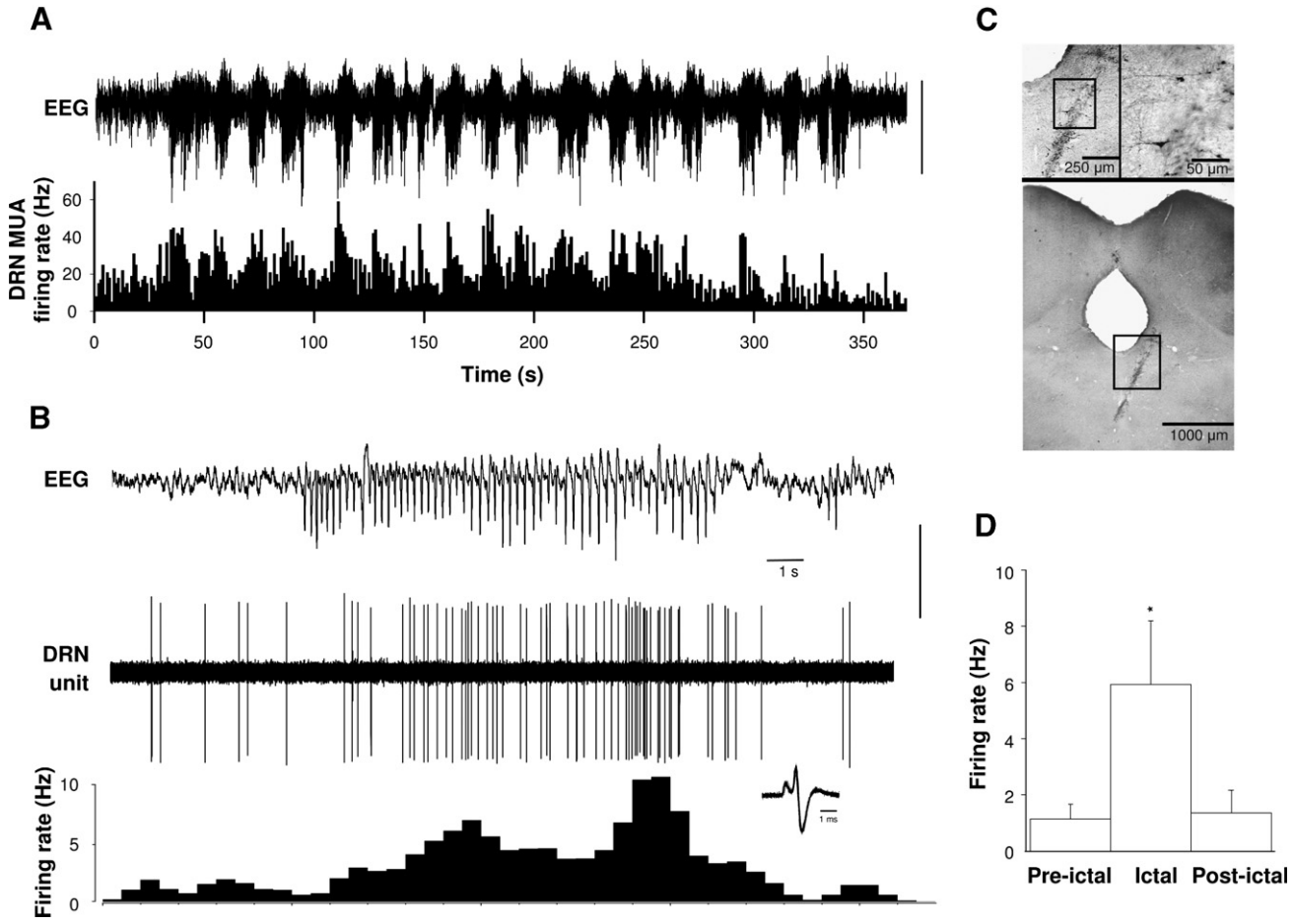

Fig. 3. Unit activity of DRN cells during spontaneous SWDs in neurolept-analgesized rats. (A) Firing rates computed from DRN multiunit activity (MUA) reveals the co-incidence of firing rate increases with SWDs. Calibration bar represents 500 μV. (B) Simultaneous frontal EEG and single unit recording of a DRN cell during a SWD episode. Superimposed action potentials that occurred during this SWD ($n=70$) are illustrated on the right hand side of the firing rate histogram (0.5 s bin size). Calibration bar represents 500 μV for EEG and 200 μV for unit. (C) Histological confirmation of electrode location. The electrode track and exact location of the recordings shown in B are indicated by the presence of argyrophilic cells visible at higher magnifications. (D) Average firing rates (before, during and after SWDs) of the 27 DRN units that showed an increase in firing rate during SWDs.

sometimes even below the baseline level (Fig. 2A). Following the SWD, these units resumed their pre-paroxysm activity, such that there was no significant difference between their pre- and post-ictal firing rates (Fig. 2C). Interestingly, in a subset of mPFC cells (9 out of 21, 42%) a change in firing pattern was also observed during SWDs. These neurons fired bursts of action potentials during SWDs (cell 1 in Fig. 2B), which were phase locked to the 'spike' component of the SWD in the EEG. Following the SWD, the neurons resumed their pre-ictal firing pattern.

The firing rate of the majority (29 out of 38, 76%) DRN neurons from eight rats increased during spontaneously occurring SWDs (Fig. 3). These extensive firing rate increases were evident during each and were never observed in the absence of SWDs (Fig. 3A). Fig. 3B illustrates a representative example of firing rate increase in a DRN neuron during a SWD. The increase in firing rate was evident from the start of the SWD and maintained throughout almost the whole duration of the paroxysm but returned to baseline levels afterwards (Fig. 3B). In contrast to the mPFC, we encountered no DRN unit that changed its firing pattern from interictal tonic firing to burst firing during SWDs. The remaining neurons show either a decrease ($n=5$, 13%) or no change ($n=4$, 11%) in firing rate during SWDs.

4. Discussion

The main findings of this study are that: i) SWDs propagate from thalamocortical networks to the mPFC and DRN, ii) the local field potentials of mPFC and DRN are correlated during SWDs and iii) there are alterations in firing rate and pattern of mPFC unit during SWDs whereas only changes in firing rate occur in DRN cells.

The changes in the local field activities in mPFC and DRN recorded from freely moving rats are not the result of volume conduction for several reasons. Firstly, the spike and wave oscillations observed in the mPFC and DRN were detectable in both monopolar and bipolar recordings, and in the latter case the small tip distance (0.5 mm) ensures recordings of potentials from the local network excluding passive contributions from distal source. The active propagation of spike and wave oscillations is further supported by the variance in the position of cross-correlation peaks (see Fig. 1B). A change in local activity during spontaneous SWDs is also supported by the changes in firing rates and patterns of mPFC and DRN neurons recorded under neurolept analgesia.

Once generated in thalamic–somatosensory cortex networks [2], SWDs rapidly propagate to the mPFC through intracortical connections [29], as there is very little delay in the 'spike' component of the signals between somatosensory cortex and mPFC (see Fig. 1B). It is reasonable to suggest that the synchronized increase in firing rate of the majority of mPFC neurons is then reflected in the altered activity of DRN units, as indicated by the longer delay of the 'spike' component in the latter nucleus (see Fig. 1B).

Our results concerning the increases and decreases in the firing rate of different subsets of DRN neurons during SWDs are consistent with previous observations, where the response of DRN cells to mPFC stimulation was found to be rather complex including both excitation and inhibition [19]. Alternately, these changes in DRN unit firing rates might be related to the two neuronal populations present in this nucleus, i.e. serotoninergic and GABAergic, and/or the complexity of their transmitter receptors (NMDA, AMPA/KA, 5-HT1A, GABAa) [19]. We did not attempt to characterize serotoninergic DRN units on the basis of their electrophysiological properties, as it has been shown that the neurochemical identity of DRN cells, investigated by combined juxtacellular recording followed by immunocytochemical labeling [30], does not always correlate with their basal firing properties.

During neurolept analgesia, the only procedure to record SWDs from head restrained rats, the state of vigilance of the animals is rather stable for long periods of time [31]. In our experiments we have solely encountered drastic and consistent firing rate increases among several mPFC and DRN neurons during SWDs. Furthermore, the firing rate alterations during different levels of vigilance [23] and during anaesthesia [30] are less pronounced than the massive increases during SWDs described in this study. Therefore, it seems improbable that the described firing rate increases during SWDs are caused by a change in the overall state of vigilance of the animals.

WAG/Rij rats are known to possess a prominent intermediate stage of sleep duration which is followed by arousals instead of REM sleep [32]. Most importantly, a recent study has shown a tendency towards a positive correlation between the total SWD time and the thalamic levels of serotonin in WAG/Rij rats [33]. Our findings are consistent with these results, since an increased firing rate among DRN cells during SWDs would result in an enhanced serotonin release in DRN-recipient brain areas. Moreover, serotonin is known to have well defined cellular effects in some of the DRN target nuclei like the cerebral cortex [34] and thalamus [35], two of the main structures involved in the generation of behavioral state dependent rhythms.

In summary, our findings not only describe the involvement of mPFC and DRN in the electrical events leading to the expression of absence epilepsy, but suggest that the complex interactions between absence seizures and serotoninergic system could be the result of the modified activity of DRN cells during these seizures.

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