Changes in corticocortical and corticohippocampal network during absence seizures in WAG/Rij rats revealed with time varying Granger causality

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A R T I C L E   I N F O

Article history:
Received 11 July 2016
Revised 8 August 2016
Accepted 9 August 2016
Available online xxxx

Keywords:
Absence epilepsy
Spike-and-wave discharge
Granger causality
Feedback loop
Epileptic network
WAG/Rij rat

A B S T R A C T

Purpose: Spike-and-wave discharges (SWDs) recorded in the cortical EEGs of WAG/Rij rats are the hallmark for absence epilepsy in this model. Although this type of epilepsy was long regarded as a form of primary generalized epilepsy, it is now recognized that there is an initiation zone — the perioral region of the somatosensory cortex. However, networks involved in spreading the seizure are not yet fully known. Previously, the dynamics of coupling between different layers of the perioral cortical region and between these zones and different thalamic nuclei was studied in time windows around the SWDs, using nonlinear Granger causality. The aim of the present study was to investigate, using the same method, the coupling dynamics between different regions of the cortex and between these regions and the hippocampus.

Methods: Local field potentials were recorded in the frontal, parietal, and occipital cortices and in the hippocampus of 19 WAG/Rij rats. To detect changes in coupling reliably in a short time window, in order to provide a good temporal resolution, the innovative adapted time varying nonlinear Granger causality method was used. Mutual information function was calculated in addition to validate outcomes. Results of both approaches were tested for significance.

Results: The SWD initiation process was revealed as an increase in intracortical interactions starting from 3.5 s before the onset of electrographic seizure. The earliest preictal increase in coupling was directed from the frontal cortex to the parietal cortex. Then, the coupling became bidirectional, followed by the involvement of the occipital cortex (1.5 s before SWD onset). There was no driving from any cortical region to hippocampus, but a slight increase in coupling from hippocampus to the frontoparietal cortex was observed just before SWD onset.

After SWD onset, an abrupt drop in coupling in all studied pairs was observed. In most of the pairs, the decoupling rapidly disappeared, but driving force from hippocampus and occipital cortex to the frontoparietal cortex was reduced until the SWD termination.

Conclusion: Involvement of multiple cortical regions in SWD initiation shows the fundamental role of corticocortical feedback loops, forming coupling architecture and triggering the generalized seizure. The results add to the ultimate aim to construct a complete picture of brain interactions preceding and accompanying absence seizures in rats.

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1. Introduction

Absence epilepsies are considered as nonconvulsive generalized epilepsies (classification of the International League Against Epilepsy, ILAE) of a presumably genetic etiology [1]. Typical absence seizures mostly occur in children. The absence seizures are brief (-4–20 s) but may occur frequently, sometimes hundreds of times per day. They involve abrupt and transient impairment of consciousness associated with characteristic bilaterally synchronous 3- to 4-Hz spike-and-wave discharges on the EEG [2].

Similar EEG paroxysms, spike-and-wave discharges (SWDs) but of higher frequency (6–8 Hz) appear in rats with a genetic predisposition to absence seizures, such as rats of WAG/Rij (Wistar Albino Glaxo from Rijswijk) strain [3]. Spike-and-wave discharges are accompanied by
behavioral immobility and rhythmic twitching of facial muscles and vibrissae. The responsiveness to mild sensory stimuli is abolished during SWD.

Absence seizures in this animal model have a well defined thalamocortical origin [4,5]. It was shown that SWDs were initiated in a relatively small area of the somatosensory cortex and then generalized over the cortex and within the thalamocortical circuitry [6,7]. Coupling processes (changes in coupling) between the focal area (deep layers of the parietal somatosensory cortex) and some thalamic nuclei were studied to understand mechanisms underlying SWDs [8–11]. The presence of different processes in coupling dynamics associated with SWD was hypothesized in our last studies [12,13]. These processes are not visually apparent on raw EEG recordings, since they take place not in a particular brain structure but between different structures. However, we can try to detect them using time-resolved methods of coupling analysis applied to multichannel time series, such as time-variant adapted nonlinear Granger causality [14].

Spike-and-wave discharges are recorded over the entire cerebral cortex. Fast intracortical spread of seizure activity from the focal region of the somatosensory cortex to other cortical areas is supposed to underlie the large-scale synchronization [6]. Spike-and-wave discharges of typical absence epilepsy are not recorded in the hippocampus or any other limbic structure in epileptic rats [5,15]. However, rats with genetic absence epilepsy demonstrate an increased rate of cerebral glucose utilization in limbic regions [16] and enhanced glutamate levels in the hippocampus [17] and decreased level in thalamus [18]. It has been suggested that the hippocampus, though it is not involved in the expression of typical absence seizures directly, may participate in regulation of the seizure occurrence and/or in restriction of the seizure spread to the limbic circuitry highly susceptible to epileptic excitation [16]. The aim of this work was to study the connectivity between different regions of the cortex (frontal, parietal, and occipital) and between the cortex and hippocampus during initiation, maintenance, and termination of typical absence seizures spontaneously occurring in WAG/Rij rats.

2. Methods

2.1. Animals

This study was performed in accordance with the guidelines of the European Community for the use of experimental animals. Approval of the local ethics committee for animal studies was obtained (RUDEC 2006-064). The animals were used for a pharmacological experiment [19]. In the present study, only baseline data of those animals were reused.

Male WAG/Rij rats were kept under environmentally controlled conditions (ambient temperature = 22 °C, humidity = 40%) in a room with light on from 20:00 to 08:00, with food and water ad libitum. Experiments were carried out during the dark period, during which WAG/Rij rats show maximal occurrence of SWDs [20]. All animals were handled prior to EEG recording. Wistar Albino Glazo from Rijswijk rats, from 8 to 10 months old, were used. All animals of the WAG/Rij strain of this age do express spontaneous SWDs. Animals were housed individually in macrolon cages.

2.2. EEG recording

A permanent set with seven electrodes was implanted under complete isoflurane anesthesia. The coordinates given are in mm, with the skull surface flat and from bregma zero–zero, according to [21]. Four electrodes were placed on the surface of the cortex: frontal cortex (AP + 3.5; L3), parietal cortex (AP − 1.6; L4), and occipital cortex (AP − 6; L − 3.5) and inserted in the hippocampus (AP − 3.5; L2; depth: 3.5). The reference and ground electrodes were placed above the cerebellum. One electrode was aimed at the brainstem, but because of the poor quality of the signal, these data were not used in the study. After surgery, animals were allowed to recover for at least 2 weeks.

Rats were placed into transparent recording cages, connected to an EEG cable that allowed free movements and habituated to the experimental conditions for 12 h. The EEG was filtered (band pass: 0.1 and 100 Hz), digitized with a sample frequency of 512 Hz, and stored for an offline analysis using Windaq system (DATAQ Instruments, Akron, OH, U.S.A.).

2.3. Spectral analysis

An example of a typical SWD is shown in Fig. 1. It is clearly seen that the seizure starts in frontal and parietal areas of the cortex with a frequency of about 11–12 Hz, but then, the frequency drops to 8 Hz in 1–1.5 s. Oscillations in the frontal cortex demonstrate a larger number of higher harmonics (up to 4) than those in the parietal one, where only three first harmonics are seen. Therefore, the signal in the frontal cortex can be interpreted as more nonlinear.

2.4. Granger causality analysis

In order to estimate time-dependent changes of coupling characteristics between different brain areas and especially at the onset and offset of SWD, a time-variant adapted nonlinear Granger causality (GC) approach [14] was used.

The main advantage of GC is that it is less dependent on the amount of experimental data than most other methods of coupling analysis from experimental time series such as EEGs. This is due to parameterization: one has to estimate a small number of coefficients of univariate and bivariate models, rather than multidimensional distributions as for transfer entropy. This gives the opportunity to analyze nonstationary data in a moving window. However, wrong parameterization dramatically suppresses the efficiency of the method, giving either many of false positive results or failures to find actually present coupling. The main problems could be the following: insufficient sampling rate [22], inadequate consideration of signal spectral characteristics [23], and inadequate chosen nonlinear functions [24]. These problems lead to curse of dimensionality (see [25] for example). To solve these problems for the intracortical EEGs, a special structure of an empirical model for absence seizures was developed [26]. This model structure was implemented to develop time-variant adapted nonlinear Granger causality and tested on 4-channel EEGs of WAG/Rij rats [14]. The same empirical model structure is applied here.

The following model parameters were chosen in this work based on previous studies: order of approximating polynomial $P = 2$; dimension of univariate model $D_s = 4$; additional dimension of bivariate model $D_a = 1$; prediction length $\tau = T/4$, where $T$ is the main time scale (for absence seizures, it is approximately equal to 8 Hz); and lag $l$ (distance in data points between values used for state vector reconstruction) $l = T/3$ based on [23].

Calculations of prediction improvement ($PI$) were performed in a moving window of 1-s (512 data points) length which was shifted in time by 0.1 s (51–52 data points).

2.5. Mutual information analysis

To verify the results obtained with Granger causality analysis, the mutual information (MI) function was additionally calculated in a way proposed in [27]. Mutual information measures simultaneous interdependencies between two signals, including nonlinear. In other words, it provides a measurement of information about one signal when measuring the other signal. The analysis was performed in a time window of the same length and with the same shift as prediction improvement. Mutual information is a relatively simple measure in comparison with Granger causality. While it could be less sensitive, it should also be
Then for each averaged dependency seizures in each animal, matching start and ending moments of seizures.

2.6. Statistical analysis

lines should be considered as unreliable. It is possible for this measure too, so the results between gray and black regions at least for some simple processes \[28\], the “ears” effect could be possible for this measure too, so the results between gray and black lines should be considered as unreliable.

2.6. Statistical analysis

Resulting dependencies of \( PI \) on time were averaged across all seizures in each animal, matching start and ending moments of seizures. Then for each averaged dependency \( PI(t) \) the background level \( PI_{bg} \) was established as an average \( PI \) over a 7-s time interval (baseline period, from 10 to 3 s before SWD onset). This period was completely devoid of SWDs. Normalized dependencies were calculated as \( PI_0(t) = PI(t) - PI_{bg} \). The value of \( PI_0(t) = 0 \) corresponds to the baseline level; positive values of \( PI_0 \) correspond to larger coupling than in baseline and negative values to lower coupling. The results were uniform in order to avoid individual differences of animals.

Then, series of \( PI_0(t) \) of different rats were composed together as a 2D array of data points, forming a sample of \( PI_0 \) values for each time point. These data points were analyzed with two-sided Student t-tests to establish differences from zero with p-value <0.05. In order to escape the possibility of Type I errors due to repetitive testing, the Bonferroni-like correction was performed: the p-value was divided by the number of independent (length of 1 s) segments, in which the models for \( PI \) calculation were constructed. Points, for which the results are statistically different from 0 (i.e., from baseline level), are marked either in red (if \( PI_0 > 0 \)) or in blue (if \( PI_0 < 0 \)).

Vertical black lines on \( PI_0(t) \) plots indicate the seizure onset or offset time points; gray vertical lines indicate the length of the moving window, in which Granger analysis was performed (Fig. 2). The results between the black and gray lines have to be considered as unsafe because of the effect of a transition state, when a model is constructed partly from a previous regime, partly from a next one. The results in this interval will not be interpreted. This phenomenon has been studied on etalon oscillators and was named “ears” \[26\]. “Ears” are an increase of \( PI \) when the moving window covers the fast transition from the preictal to the ictal and from the ictal to the postictal phase. Therefore, significant points between the black and gray lines are not taken into account.

As done for \( PI(t) \), dependences \( MI(t) \) for all suitable seizures were averaged per rat, then baseline level was calculated and extracted from \( MI(t) \) dependences, resulting \( MI_0(t) \). Then, the same statistical analysis was performed.

3. Results

Data of 19 rats were used. In a two-hour recording period, a total number of 689 SWDs was observed (18 SWDs per hour per animal in average).

Most channel pairs (except OC → Hp) demonstrated an increase in coupling 3.5–1.5 s before seizure onset (red dots before the first gray line in Fig. 2). The earliest increase in coupling was observed from the frontal region of cortex to the parietal cortex (FC → PC) occurring 3.3 s before the seizure onset, that is 2.3 s before the time moment when the moving window used for Granger causality calculation started to cover the seizure. A bit later (2 s before the window starts to overlap with the seizure), the parietal cortex responded to frontal cortex, so the coupling becomes bidirectional. Then, 1.5 s before the window overlaps the seizure, the coupling from occipital region to the parietal cortex increases. At 0.8 s before the gray line, the bidirectional coupling FC → OC appears. The hippocampus remains mainly passive: there is some coupling from hippocampus to parietal and frontal regions of the cortex just before the window overlaps the seizure, and there is no increase in the direction to the occipital cortex. Involvement of the hippocampus usually can be detected only with Granger causality analysis, because its signal properties, spectral, amplitude, and shape, do not change visibly in most cases.
The mutual information is not sensitive enough to detect the preictal increase in most cases. Significant increase of MI is observed only for Hp–FC pair. The insufficient sensitivity could be the result of two factors: 1) insufficient amount of data (Granger causality is a parametric approach, so it can work for fewer data points) and 2) indirect nature of this measure.

As it can be seen in Fig. 2, all channel pairs showed a significant temporary drop immediately after the SWD onset. In most cases, $P_{0}(t)$ returned to baseline values within the first 3 s of SWD. In 3 cases of 12, the coupling level at the end of seizure remains lower than in baseline: Hp → PC restores 2.2 s before the SWD termination, OC → FC restores 1.7 s before it, and Hp → FC restores only when the moving window overlaps the termination moment. Since coupling can be overestimated because of "ears" effect of the method, one can only guess whether coupling actually restores before the seizure end or not. Mutual information analysis confirms the decoupling effect at the SWD onset in all pairs (Fig. 3).

The red points between gray and black lines seen at the end of seizures (between second gray and second black lines) are insignificant because of "ears" effect [26], as mentioned previously.

Coupling diagrams were constructed to summarize the results of Granger causality of the current study (Fig. 4).

4. Discussion

4.1. Processes in coupling

Analysis of functional connectivity is a useful tool for assessment of dynamic changes in network interactions in different physiological or pathological states. In the present study, we applied Granger causality

![Fig. 2. Dynamics of adapted nonlinear Granger causality. Y-axis: $P_{0}$ averaged over all 19 rats, red points mark that $P_{0}$ is significantly larger than zero; blue points mark that $P_{0}$ is significantly less than zero. X-axis: time. Error bars show the 95% confidence interval. Black vertical lines indicate the seizure onset and offset; gray vertical lines indicate the length of moving window, in which Granger analysis was performed. "Hp" is hippocampus, “FC" is frontal cortex, “PC" is parietal cortex, and “OC" is occipital cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)](image1)

![Fig. 3. Dynamics of mutual information. Y-axis: $MI_{0}$ averaged over all 19 rats, red points mark that $MI_{0}$ is significantly larger than zero; blue points mark that $MI_{0}$ is significantly less than zero. X-axis: time. Error bars show the 95% confidence interval. Black vertical lines indicate the seizure onset and offset; gray vertical lines indicate the length of moving window, in which Granger analysis was performed. “Hp” is hippocampus, “FC” is frontal cortex, “PC” is parietal cortex, and “OC” is occipital cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)](image2)
analysis to corticocortical and corticohippocampal networks to study their interaction during generalized absence seizures (SWDs) spontaneously occurring in WAG/Rij rats.

Existence of different processes, accompanying SWDs, was hypothesized based on the detailed analysis of Granger causality [12,13]. These processes were observed in coupling between different components of the thalamocortical circuitry, which formed feedback loops. Coupling was measured with prediction improvement of Granger causality and by means of mutual information. The important role of networks for epilepsy development was previously mentioned in e.g., [29].

Some precursor activity for absence seizures was detected very early, using power spectrum analysis in humans [30], but with very little statistics. Then, some synchronization measures were also applied to study preictal changes [31,32]. The actual process of SWD initiation was detected as a relatively short in time but significant increase in coupling between some brain structures (cortical and thalamic structures mainly) in the preictal phase, first with nonlinear association analysis [9], then more precisely using Granger causality [14]. Preictal changes in EEGs were also found for another genetic rat model — GAERS [33].

The sequence of involvement of different structures of the thalamocortical circuitry in seizure initiation was described previously [12]. In the current study, the SWD initiation process was characterized by an early preictal (from 3.1 until 1.8 s prior SWD onset) increase in coupling between the frontal, parietal, and occipital areas of the cortex. It is interesting that at the earliest point of detection, driving is occurring from frontal cortex to parietal cortex, and then, shortly afterward, in the opposite direction.

A focal onset of SWDs in the frontal cortex has been shown in patients with childhood absence epilepsy [34–36] though studies in animal models of absence epilepsy suggested the leading role of the somatosensory cortical area in SWD initiation [6]. The results of our present study reveal the earliest preictal driving force originate from the frontal cortical regions of WAG/Rij rats, indicating indeed a more frontal location of SWD-trigger area in this model of absence epilepsy.

Immediately after SWD onset, the temporary decoupling was also observed. We hypothesize that the preictal coupling increase pushes the network over a threshold, so high amplitude oscillations in the form of SWD emerge. After SWD is initiated and assuming that synchrony of oscillations is metabolically cheap [37], it is proposed that only a few elements of the network need to interact (drive) in order to maintain oscillations for a while. The only remaining coupling within the first second of SWD is the driving from the deep cortical layers of the somatosensory cortex to the caudal pole of the reticular thalamus nucleus (RTN) [12]. The driving from frontal cortex to RTN was also the only one which remained significantly higher than baseline level for all considered time moments in [13]. The results of the current study confirm these outcomes; since RTN was not measured in the present study, the drop in coupling is seen in all considered channel pairs.

The decoupling can be considered as an unexpected phenomenon, since activity of remote cortical areas during SWDs is highly synchronous [6]. However, one should mention the difference between synchrony, synchronization, and coupling, since coupling not always leads to synchronization, and synchrony at finite time interval can be achieved because of previous dynamics or by means of common external force but without coupling. One possible mechanism to explain decoupling was discussed in [12], where each brain region is considered as an individual oscillator. Following that hypothesis, the loss of coupling for 1–1.5 s is not critical for seizure maintenance because of a large stock of energy collected in each individual region in the preictal stage. However, this hypothesis does not explain the reason of coupling drop; it only explains why oscillations do not die (different scenarios of oscillation death were found in [38,39]). To clarify mechanisms of decoupling, more studies in different levels of neuron organization are necessary. For instance, one possibility is that mechanisms of “normal coupling” and “pathological coupling” are different. The normal one is present in baseline and preictal phases, but it becomes destroyed by the first spike at the onset. The pathological coupling is gradually increasing throughout the seizure, since different brain areas play different roles in SWDs and their relative impacts in connectivity processes during SWDs are different from their impact during normal activity. Therefore, the coupling level at the end of seizure can be arbitrary in comparison with the baseline coupling level: higher, lower, or similar.

Decoupling should be considered as a reliably detected phenomenon, since it was revealed in 3 different sets of data (19 rats here, 16 rats in [12], and 5 rats in [13]). Also, 2 different measures, nonlinear adapted Granger causality and MI, showed the decoupling.

The maintenance process is reflected in a gradual rise of coupling after the seizure starts, often after decoupling. The current study shows the secondary role of interactions between hippocampus and distinct areas of cortex in seizure maintenance, since coupling occurs at a lower or at
the same level as before the seizure. A primary focus in the somatosenso-
ry cortex was shown to be responsible for generation of typical absence
seizures [6]; an interaction in the corticothalamic circuitry for
the seizure maintenance [6]. This view has been confirmed in
e.g., [9,12]. However, the hippocampus is also thought to be involved;
for instance, targeting the limbic system, one can modulate typical
absence seizures; an enhancement of GABAergic transmission in the
hippocampus reduces the seizures [40]. The review of studies [41]
on the involvement of limbic structures in the modulation of typical
seizures points to thalamohippocampal connections as a way in which
the hippocampus is able to participate in the seizure. Unfortunately,
neither in this review nor in a number of previous studies [9,12,13],
where complex mathematical approaches were applied to reveal the
development of interconnections between brain areas in time, were
activities of the thalamus and the hippocampus measured simultane-
ously. Such a simultaneous measurement was done recently in [42], for
a pharmacological model of absence seizures (gamma-hydroxybutyric
glutamate (GHB) rat model [43]). This study used spectral methods to analyze
the data and found, during the seizures, an increase in coherence
between hippocampus, ventrolateral thalamic nucleus, and parietal
cortex. This finding indeed indicates an involvement of the hippocampus.
But with the used coherence function, it is not possible to answer
the question whether the increase in coherence between the parietal cor-
tex and the hippocampus is a result of a direct corticohippocampal
interaction or the result of indirect interactions via the thalamus.
Our present data suggest that a direct coupling of the hippocampus
with the frontal and parietal cortices plays a role in the initiation and
maintenance of SWDs.

In the termination process, the present analysis did not reveal any
attrition of changes in coupling in considered channel pairs. The results of the current study show that, if the separate termination
process exists, it is narrow localized and specific for brain areas not
considered here.

The results of interaction estimation from occipital cortex to the frontal cortex (OC → FC) in the current study are identical to the results
in [13]; significant increase in the preictal phase (1.5 s before the onset),
then drop down and very slow restoration which lasts until the end of
SWD. The results in the opposite direction are similar, but in the
previous study, the coupling from FC to OC restored to the baseline
level faster than in the current work. So FC in [13] was more responsible
for seizure maintenance. This difference can be a result of different
electrode positions (FC in a previous study was much closer to bregma)
or different animal ages. Also in the current study, the sample size is
larger; 19 rats with 689 seizures in total, while 5 rats with 218 seizures
were studied in [13].

4.2. Conclusion

Thus, the current study has shown the following:

1. Spike-and-wave discharge initiation process is revealed as an
increase in corticothalamic and corticohippocampal interactions
(except hippocampus → occipital cortex) though of different
intensities and different starting times. Involvement of multiple
cortical regions and hippocampus in SWD initiation shows the
fundamental role of coupling feedback loops.

2. The earliest preictal increase in coupling has been shown from the
frontal region of the cerebral cortex to the parietal cortex. This result
suggests that, within the cortex, the earliest changes occur in its
frontal areas.

3. Hippocampus slightly participates in seizure initiation, but it is not
involved in the maintenance or termination of SWDs.

4. After SWD onset, a significant drop in coupling from all cortical areas
and hippocampus to the frontal cortex and from hippocampus to the
parietal cortex is observed.

Acknowledgments

This research was funded by Russian Foundation for Basic Research,
Grants No. 14-04-01184 and 16-34-00203 and Stipendium of President
of Russian Federation for support of young scientists C11-1510.2015.4.

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