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Application of adaptive nonlinear Granger causality: Disclosing network changes before and after absence seizure onset in a genetic rat model

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HIGHLIGHTS

- Cortico-thalamic network associations were analyzed in rats with absence epilepsy.
- The outcomes of linear and adaptive nonlinear Granger causality were compared.
- Adaptive nonlinear measures were more sensitive to preictal changes of associations.
- Nonlinear interdependencies increased 1-1.5 s prior to seizure onset.

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ABSTRACT

Background: Advanced methods of signal analysis of the preictal and ictal activity dynamics characterizing absence epilepsy in humans with absences and in genetic animal models have revealed new and unknown electroencephalographic characteristics, that has led to new insights and theories.
New method: Taking into account that some network associations can be considered as nonlinear, an adaptive nonlinear Granger causality approach was developed and applied to analyze cortico-cortical, cortico-thalamic and intrathalamic network interactions from local field potentials (LFPs). The outcomes of adaptive nonlinear models, constructed based on the properties of electroencephalographic signal and on statistical criteria to optimize the number of coefficients in the models, were compared with the outcomes of linear Granger causality.
Results: The nonlinear adaptive method showed statistically significant preictal changes in Granger causality in almost all pairs of channels, as well as ictal changes in cortico-cortical, cortico-thalamic and intrathalamic networks. Current results suggest rearrangement of interactions in the thalamo-cortical network accompanied the transition from preictal to ictal phase.
Comparison with existing method(s): The linear method revealed no preictal and less ictal changes in causality.
Conclusions: Achieved results suggest that this proposed adaptive nonlinear method is more sensitive than the linear one to dynamics of network properties. Since changes in coupling were found before the seizure-related increase of LFP signal amplitude and also based on some additional tests it seems likely that they were not spurious and could not result from signal to noise ratio change.

1. Introduction

Absence epilepsy is non-convulsive generalized epilepsy of unknown etiology. Clinically, absence seizures appear as an abrupt and brief impairment of consciousness (absence), when ongoing activity is interrupted, responsiveness is decreased, and mental functioning is impaired. Electroencephalographically, absence seizures are manifested as paroxysmal electrical

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activity consisting of generalized 3–4 Hz spike–wave discharges (SWD) (Panayiotopoulos, 2001).

Spike-and-wave paroxysms appear spontaneously in rat strains with a genetic predisposition to absence epilepsy, such as GAERS (Genetic Absence Epilepsy Rats from Strasbourg) and WAG/Rij (Wistar Albino Glaxo from Rijswijk). These two rat strains, GAERS and WAG/Rij, have been validated as reliable genetic animal models of human absence epilepsy, and they are widely used in basic research toward mechanisms involved in the pathogenesis of this disease (Vergnes et al., 1987; Marescaux et al., 1992; Coenen and van Luijtelaar, 2003; Depaulis, 2006).

In WAG/Rij rat model, later also in GAERS, it was found that a specific cortical area in the somatosensory region initiates spontaneous SWD (Meeren et al., 2002; Polack et al., 2007), and that cortical mechanisms effectively control and drive widespread cortico-cortical and cortico-thalamic networks during absence seizures (van Luijtelaar and Sitnikova, 2006; David et al., 2008; Lüttjohann et al., 2012). The transition from the preictal to the ictal phase is characterized by changes in associations within the cortico-thalamo-cortical neuronal network. Previously we examined the spatiotemporal synchronization of the thalamo-cortical system in WAG/Rij rats by means of EEG coherence (Sitnikova and van Luijtelaar, 2006), and also the strength and directionality of cortico-thalamic relationships by means of Granger causality (Sitnikova et al., 2008). These analyses confirmed that especially the onset of SWD seems a rather abrupt process in persons with absence epilepsy (Panayiotopoulos, 2001). However, other signal analytical approaches demonstrated the existence of preictal activity immediately before the onset of SWD both in persons with absence epilepsy (Inouye et al., 1994; Gupta et al., 2011) and in rats (Meeren et al., 2002; van Luijtelaar et al., 2011a; Lüttjohann et al., 2012; Lüttjohann and van Luijtelaar, 2012), perhaps in agreement with preictal neuronal firing in the deep cortical layers (Polack et al., 2007). Prediction of seizure activity from local field potentials (LFP) or surface EEG is a challenging problem that encourages specialists in physics and mathematics to develop new approaches of EEG data analysis (Mormann et al., 2007) that might be extremely relevant from a clinical perspective.

In comparison with traditional methods of network analysis, such as cross-correlation, coherence, phase synchronization, Granger causality may detect weak or hidden coupling, which not necessarily lead to synchronization, and defines next to changes in coupling strength also changes in the direction of coupling within a network. Granger causality was developed originally to detect the presence and direction of coupling between two systems (Granger, 1969). It takes into account the past state of one time series in order to predict the present state of the second time series. In his original paper, Granger (1969) used only linear predictive (autoregressive) models; new nonlinear models were successfully applied more recently (Bezruchko and Smirnov, 2010; Wang, 2007). Granger causality method is based on the idea to use competing models with optimal predictive abilities. The choice of the appropriate parameters in the model (parameterization) is important: even in linear Granger causality, the choice of the dimension of the model (the number of points in the past that are used for prediction) has a large impact on its predictive abilities. In nonlinear models, the type and number of nonlinear terms is also important. The proposed method actually depends on specific parameters of data, first on frequencies. As it was shown by Sysoeva et al. (2012), changing method parameters linked with frequency alters sensitivity and specificity of the method (number of real couplings that were not detected and number of false positive findings respectively). In this work used values of these parameters correspond to best specificity with as good sensitivity as possible.

If we need to construct vector time series from scalar observables (this usually refers to complex neurophysiologic signals, like EEG or LPF data), embedding takes place. Therefore parameters of embedding also become parameters of Granger causality method, for instance to determine the optimal number of time lags (Packard et al., 1980). Finally, when a prediction model is constructed, prediction length (the distance in time between time series point to be predicted and time series point(s) used for prediction) becomes another parameter of the model.

Wrong parameterization may cause false results: too simple models lead to missing couplings (Chen et al., 2004; Smirnov and Bezruchko, 2012; Sysoev et al., 2010; Sysoeva et al., 2012), too complex and universal models lead to unreliable estimates of model coefficients and often - to spurious causality. However it is possible to improve the methods by adapting the model structure to the experimental data: this implies that properties of the experimental data are used to set parameters of the model, in which case less coefficients can be used. Finally, a shorter length of time series can be used for model construction, given the opportunity to have a higher temporal resolution while applying Granger causality in a moving time window. Here we developed and applied this new approach called adaptive Granger causality to LFP data recorded in vivo by means of intracranial electrodes implanted in the cortex and thalamus in WAG/Rij rats. In particular, we investigated the dynamics of cortico-cortical, cortico-thalamic and thalamo-thalamic network interactions at the transition from preictal to ictal phase and compared results of linear and adaptive nonlinear estimation of Granger causality.

2. Methods

2.1. Animals and LFP data acquisition

Experiments were performed in five male 11–12 month old WAG/Rij rats. The recordings were done at the Department of Biological Psychology, Radboud University Nijmegen in accordance with the European Communities Council Directive (86/609/EEC). Experiments were approved by the Ethical Committee on Animal Experimentation of Radboud University Nijmegen. Distress and suffering of animals were minimal.

Rats were implanted, under complete inhalation anesthesia (isoflurane), with two standard tripolar electrode sets (Plastics One MS-333/2-A, Plastic Products, Roanoke, USA). There were stainless steel insulated wire electrodes with non-insulated tip (diameter 0.2 mm). Two epidural electrodes were located epidurally over the frontal (AP 2; L 2.5) and occipital (AP −7; L 6) cortical areas, skull flat. Two depth electrodes were implanted in the ventroposteromedial nucleus of thalamus (VPM, AP −3.5; L 2.5; H 7.2) and in the rostral pole of the reticular thalamic nucleus (RTN, AP −1.5; L 2.2; H 7.2). All coordinates are given in mm relative to bregma (Paxinos and Watson, 2006). Recording electrodes were implanted unilaterally at the right hemisphere. Ground and reference electrodes were placed symmetrically over both sides of the cerebellum. Electrodes were permanently attached to the rat's skull with dental cement.

After the surgery, animals were allowed to recover during at least ten days. During this recovery period, animals received post surgery care and their weight was monitored. Upon completion of the recording sessions, rats were deeply anesthetized with overdose of sodium pentobarbital (200 mg/kg i.p.) and their brains were stained with Nissl. Electrode positioning was verified using the atlas of the rat brain (Paxinos and Watson, 2006).

Recordings were performed in freely moving rats in a Faraday cage. Each recording session lasted from 5 to 7 h during the dark period of the day–night cycle. LFP signals were fed into a multi-channel differential amplifier, filtered between 1 and 200 Hz, digitized with 1024 samples/s/per channel (CODAS software) and stored on hard disk.