NeuroImage 82 (2013) 564–573

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Are high frequency oscillations associated with altered network topology in partial epilepsy?

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ARTICLE INFO

Article history:
Accepted 10 June 2013
Available online 17 June 2013

Keywords:
Functional connectivity
Network analysis
Graph theory
High frequency oscillations
Temporal lobe epilepsy

ABSTRACT

Neurophysiological studies have reported functional network alterations in epilepsy, most consistently in the theta frequency band. Highly interconnected brain regions (so-called 'hubs') seem to be important in these epileptic networks. High frequency oscillations (HFOs) in intracranial EEG recordings are recently discovered biomarkers that can identify the epileptogenic area and are thought to result from altered neuronal interactions. We studied whether the epileptogenic zone (identified by HFOs and seizure onset zone) is associated with pathological hubs. Bilateral depth electrode recordings from the hippocampus and amygdala were available from twelve patients suspected of temporal lobe epilepsy. HFOs, classified as ripples (80–250Hz) and fast ripples (250–500Hz), and epileptiform spikes were marked for all patients in a five-minute epoch of slow-wave sleep. For each channel, we computed hub-measures from a period without epileptiform spikes and found that the epileptogenic zone was associated with a decreased hub-value in the theta frequency band. The amount of HFOs, especially fast ripples, was negatively correlated with the hub-value per channel. Results from post-hoc analyses of other frequency bands, particularly the broad- and gamma frequency band, pointed in the same direction as the results for the theta frequency band. These findings suggest a pathological functional 'isolation' of the epileptogenic zone in the interictal state.

Introduction

Partial epilepsy is increasingly seen as a 'network disorder' despite its focal character (Engel et al., 2013; Kramer and Cash, 2012; Richardson, 2012). Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy and often associated with mesial temporal sclerosis (MTS) (Engel, 1996). MTS is characterized by a progressive hippocampal cell loss and, consequently, reorganization of adjacent mesial structures (Bernasconi et al., 2005; Kalviainen et al., 1997) and (extra-) temporal structures (Gross et al., 2006; Mueller et al., 2006; Weber et al., 2007). This reorganization is likely to contribute to epileptogenicity (Heinemann, 2004) with emerging pathological networks (Blumcke et al., 2012).

Studies have used connectivity measures to relate structural abnormalities in TLE with brain functioning. Functional imaging (Bettus et al., 2009; Laufs et al., 2007; Mankinen et al., 2011; Pittau et al., 2012; Voets et al., 2012) and intracranial EEG recordings (Bettus et al., 2008; van Dellen et al., 2009) revealed an altered functional connectivity in the pathological temporal lobe regions and distant, functionally related, regions. A method used to characterize the overall organization of structural and functional networks is network analysis (Bullmore and Sporns, 2009; Reijneveld et al., 2007; Rubinov and Sporns, 2010; Stam and van Straaten, 2012). Network analysis provides a theoretical framework to model complex systems, such as the brain, as a collection of nodes (i.e. brain regions) and edges (i.e. connections between brain regions). Healthy brain networks have a so-called 'small-world' topology (Bullmore and Sporns, 2009; Stam, 2010): an adequate balance between local segregation (high clustering coefficient) and global integration (short average path length). In partial epilepsy, a disturbed local segregation and/or global integration is present, leading to a less efficient network topology (Horstmann et al., 2010; Liao et al., 2010; van Dellen et al., 2009; Vlooswijk et al., 2011). These changes appear most prominent in the theta frequency band (4–8 Hz) (Bettus et al., 2008; Douw et al., 2010a, 2010b; van Dellen et al., 2012). Highly interconnected nodes within epileptic networks or so-called 'hubs' are

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http://dx.doi.org/10.1016/j.neuroimage.2013.06.031

thought to reflect pathological tissue that may have a central role in the altered network organization (Wilke et al., 2011) and may be responsible for the fast spreading epileptic activity within a network in the ictal state (Bonifazi et al., 2009; Morgan and Soltesz, 2008; Ortega et al., 2008). It is unknown to what extent the epileptogenic zone itself is reflected by local changes in the interictal functional network.

The seizure onset zone (SOZ) and interictal epileptiform spikes (the irritative zone) represent the potential epileptogenic area in clinical practice. Recently, high frequency oscillations (HFOs) have been proposed as a more reliable marker of the epileptogenic zone (Bragin et al., 1999b; Jacobs et al., 2008; Staba et al., 2007; Urrestarazu et al., 2006; Worrell et al., 2004). The surgical removal of regions generating HFOs turned out to be a better predictor of seizure freedom than spikes or the SOZ (Akiyama et al., 2011; Jacobs et al., 2010; Wu et al., 2010). HFOs are divided into ripples (80–250 Hz) and fast ripples (250–500 Hz) and are thought to arise from distinct neurophysiological mechanisms: ripples are associated with the rhythmic firing of interneurons, whereas fast ripples represent co-firing of pathological interconnected principle neurons (Bragin et al., 1999a; Bragin et al., 2002). Another theory suggests that fast ripples result from the out-of-phase firing of neurons (Ibarz et al., 2010). It has been a topic of debate whether HFOs, especially fast ripples, themselves induce a pathological epileptic network or are simply a by-product of epileptogenic tissue. The spatial relation between HFOs and network organization and the presence of pathological hubs can help solve this pathophysiological puzzle.

We use a network analytical approach to investigate how the epileptogenic zone is reflected in focal network alterations in patients suspected of TLE. Both HFOs and the SOZ are used to define the epileptogenic zone. We hypothesize that brain tissue associated with the epileptogenic zone, identified by HFOs and the SOZ, is differently connected within the functional network compared to brain regions not associated with the epileptogenic zone.

Methods

Patient selection

Between 2004 and 2008, 60 patients underwent depth electrode placement as a pre-surgical work-up for selective surgery at the Montreal Neurological Institute. The electrophysiological recording was performed for clinical reasons. From this group, patient inclusion criteria for this study were: (1) the availability of bitemporal depth EEG recordings from both the amygdala and hippocampus, and (2) the availability of conclusive clinical intracranial EEG reports. In this study we chose to focus on the amygdala and hippocampus electrodes only to enable group wise comparison. The Montreal Neurological Institute and the Hospital Research Ethics Committee approved this study. All patients signed an informed consent.

Depth electrode recordings

Between 6 and 10 depth-electrodes were placed stereotactically in each patient, using an image-guidance system (SNN Neuronavigation System, Mississauga, Canada). For this study, we only included the depth-electrodes aimed at the amygdalae and hippocampi in the eventual analysis. The electrodes were manufactured onsite (9 contacts per electrode, contact surface = 0.8 mm^2) as described earlier (Jacobs et al., 2008; Urrestarazu et al., 2006). The electrode tips were placed in the amygdala and the hippocampus in both hemispheres. A reference electrode was placed intracranially on the parietal lobe. The sample frequency was 2000 Hz with an amplifier band-pass filter at 0.5–500 Hz. All signals were recorded and viewed using Harmonie (Stellate, Montreal, Canada). For each electrode, seven consecutive bipolar channels were analyzed. The outer channel (bipolar recording 8–9) was excluded from the analysis, because of the presence of artifacts in most patients. Fourteen bipolar channels in each hemisphere were available for analysis for all included patients (Fig. 1).

Marking events and defining SOZ

Five minutes of slow-wave sleep, interictal depth electrode EEG-recordings at least four hours away from any seizure activity were selected. Fast ripple, ripple and spike events were manually marked. We selected the events from slow wave sleep, as the rates of HFOs and spikes are highest during slow-wave sleep (Bagshaw et al., 2009). To accomplish consensus about the markings, two reviewers (J.J. and M.Z.) separately marked the first minute of each EEG-recording. An inter-observer agreement was calculated using Cohen's kappa coefficient. A Cohen's kappa coefficient >0.5 was interpreted as a sufficient agreement. We identified HFOs by displaying data with the maximum time resolution (0.6 s, 1200 Hz) and splitting the computer display vertically as previously described (Jacobs et al., 2008, 2009). On the left display, an 80 Hz high-pass filter was used, and on the right display a 250 Hz high-pass filter. An event visible on the left display, and not on the right display, was marked as a ripple. An event visible on the right display was considered a fast ripple. We marked events as HFOs if at least four consecutive oscillations were present. Two events were considered separate, when at least two non-HFO oscillations were seen in between. Considering the variability between patients in the number of HFOs, we expressed the number of HFOs per channel in a percentage to optimize group wise comparison. In this normalization the number of HFOs per channel was divided by the number of HFOs per patient. The SOZ was identified in the EEG-channels showing the first ictal activity during EEG-recording by a clinical neurophysiologist (F.D.), who was blinded for the selection of HFOs and spikes.

Functional connectivity

We selected four epochs of 8.19 s each (4096 samples) per patient during awake, eyes closed and rest conditions to assure stable EEG dynamics for the calculation of functional connectivity (Douw et al., 2010a; van Dellen et al., 2012; van Diessen et al., 2013). The depth EEG was recorded at 2000 Hz and down sampled to 500 Hz. In the selected epochs during wakefulness with eyes closed, some HFOs occurred in several patients, especially in the deeper hippocampal channels, because their rate of occurrence often exceeded 1 per second. We focussed on selecting epochs without epileptiform spikes, free of motion-induced artifacts and if possible with a low number of HFOs, especially those that occurred in only one channel at a time. Next, epochs were converted to ASCII files for further analysis with Brainwave software (authored by C.J.S.; available at http://home.kpn.nl/stam7883/brainwave.html). Functional connectivity was computed from each selected epoch by means of the Phase Lag Index (PLI) (Stam et al., 2007). A PLI value per channel was obtained from each epoch and the average PLI (over four epochs) was used for further analysis. The PLI measures the phase coupling between two signals, while precluding volume conduction as a confounding factor by disregarding a phase difference of zero. As a result, PLI is less sensitive to confounding by common sources than other functional connectivity measures (Stam et al., 2007). The PLI ranges from 0 to 1. A PLI of 0 indicates no phase coupling between signals, or coupling with a phase difference centered on $0 \pm \pi$ radians. A PLI of more than 0 indicates a certain phase coupling. An index of the asymmetry of the phase difference distribution can be obtained from a time series of phase differences $\Delta\Phi(t_k)$ in the following way:

$$PLI = |\langle sign[\Delta\Phi(t_k)]\rangle|$$

in which $<>$ denotes the average over time t. A detailed description of the calculation and specifications of PLI can be found elsewhere (Stam and Reijneveld, 2007). The strength of the PLI was calculated for each