Experimental Neurology 251 (2014) 30–38

Contents lists available at ScienceDirect

Experimental Neurology

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

Dynamic modulation of epileptic high frequency oscillations by the phase of slower cortical rhythms ☆

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ARTICLE INFO

Article history:
Received 25 April 2013
Revised 24 October 2013
Accepted 29 October 2013
Available online 5 November 2013

Keywords:
Cross-frequency coupling
Epilepsy
High frequency oscillations
HFOs
Seizure
Intracranial EEG
Networks

ABSTRACT

Pathological high frequency oscillations (pHFOs) have been proposed to be robust markers of epileptic cortex. Oscillatory activity below this frequency range has been shown to be modulated by phase of lower frequency oscillations. Here, we tested the hypothesis that dynamic cross-frequency interactions involving pHFOs are concentrated within the epileptogenic cortex. Intracranial electroencephalographic recordings from 17 children with medically-intractable epilepsy secondary to focal cortical dysplasia were obtained. A time-resolved analysis was performed to determine topographic concentrations and dynamic changes in cross-frequency amplitude-to-phase coupling (CFC). CFC between pHFOs and the phase of theta and alpha rhythms was found to be significantly elevated in the seizure-onset zone compared to non-epileptic regions ($p < 0.01$). Data simulations showed that elevated CFC could not be attributed to the presence of sharp transients or other signal properties. The phase of low frequency oscillations at which pHFO amplitudes were maximal was inconsistent at seizure initiation, yet consistently at the trough of the low frequency rhythm at seizure termination. Amplitudes of pHFOs were most significantly modulated by the phase of alpha-band oscillations ($p < 0.01$). These results suggest that increased CFC between pHFO amplitude and alpha phase may constitute a marker of epileptogenic brain areas and may be relevant for understanding seizure dynamics.

Introduction

The human brain is intrinsically organized into dynamic cell assemblies supported by synchronous neuronal oscillations at various frequencies (Buzsaki, 2010). This oscillatory activity is thought to result in rhythmic fluctuations in neuronal excitability, creating temporal windows for inter-regional communication (Fries, 2005). Frequency-specific oscillations may subserve perceptual binding (Fries, 2005), synaptic plasticity (Buzsaki and Draguhn, 2004), and the coordination of distinct brain regions (Lachaux et al., 2005). Low-frequency rhythms modulate activity over large spatial regions and across long temporal windows, whereas high frequencies are restricted to small regions and short temporal windows (Canolty and Knight, 2010; von Stein and Sarnthein, 2000). Interactions among neural oscillations at different frequency bands have accordingly been proposed to regulate neural processing occurring across multiple spatiotemporal scales (Canolty and Knight, 2010; Lakatos et al., 2005).

The regulation of neural activity and inter-regional communication through cross-frequency coupling (CFC) has been the subject of considerable recent interest. Slow rhythms have been shown to co-exist with fast, transient oscillations (Buzsaki and Draguhn, 2004) and the phase of low frequency theta rhythms has been reported to modulate the power of high gamma activity (80–150 Hz) (Canolty et al., 2006). CFC may also generalize to interactions among oscillations in other frequency bands (Lakatos et al., 2005; Palva et al., 2005). Two principal forms of cross-frequency interactions have been proposed: (a) amplitude-independent phase synchrony; and (b) nested

☆ Funding: This work was supported by the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship, the CIHR Bisby Fellowship, The Hospital for Sick Children Foundation Student Scholarship Program, The Hospital for Sick Children Centre for Brain and Behaviour, the EpLink program of the Ontario Brain Institute, and the Wiley Family and Jack Beqaj Funds for Epilepsy Surgery Research.

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http://dx.doi.org/10.1016/j.expneurol.2013.10.019

oscillations reflecting the locking of high frequency amplitude to lower frequency oscillations (Vanhatalo et al., 2004). Less characterized amplitude–amplitude interactions have also been reported (Shirvalkar et al., 2010). CFC has been implicated in a variety of cognitive functions, (Sederberg et al., 2003) suggesting that it represents a physiological process regulating cortical processing.

Epilepsy is a disorder of neuronal synchrony within specific networks, resulting in recurrent, unprovoked seizures. One increasingly recognized feature of epileptic cortex is its tendency to express excessive pathological high frequency oscillations (pHFOs; pathological ripple frequencies: 80–150 Hz; pathological fast-ripple frequencies > 200 Hz) (Akiyama et al., 2011; Jacobs et al., 2010; Ochi et al., 2007). Epileptic pHFOs are thought to occur through different mechanisms than their physiological counterparts, which are discrete oscillations at less than 100 ms generated by perisomatic inhibitory interneuron activity (Mann et al., 2005). PHFOs may represent out-of-phase firing of neural assemblies in the absence of physiologically-relevant inhibitory and/or regulatory mechanisms (see Jefferys and colleagues for review (Jefferys et al., 2012)). Resection of cortical areas expressing pHFOs has been associated with improved seizure outcomes (Akiyama et al., 2011; Jacobs et al., 2010; Ochi et al., 2007). Recent studies have also suggested that the epileptic cortex may also demonstrate atypical cross-frequency interactions (Alvarado-Rojas et al., 2011; Cotic et al., 2011; Vanhatalo et al., 2004) and that these cross-frequency interactions may themselves predict seizure onset (Alvarado-Rojas et al., 2011) and occur in regions demonstrating high inter-regional epileptic network connectivity (Cotic et al., 2011). The phase of low frequency signals reflects fluctuations in neuronal excitability (Canolty and Knight, 2010), and has also been shown to modulate the occurrence of interictal epileptic activity during sleep (Vanhatalo et al., 2004).

It remains unclear, however, whether CFC during seizures is concentrated in the epileptogenic zone, or whether ictal CFC dynamics are related to progression of seizures or pHFOs. Furthermore, the clinical utility of CFC in the localization of epileptogenic cortex for pre-surgical planning has not been determined. Using electrocorticographic (ECoG) collected from 17 children with focal medically-refractory epilepsy secondary to focal cortical dysplasia (FCD), we first tested the hypothesis that excessive CFC involving pHFOs is concentrated within the epileptogenic cortex. Second, we evaluate whether these topographically specific increases in CFC were strongest during seizures and investigated the frequencies at which ictal CFC within epileptogenic brain areas was most reliable. Data simulations were performed to evaluate whether observed CFC increases were attributable to true phase–amplitude coupling or other signal characteristics. Finally, we also tested the hypothesis that reliable cross-frequency phase–amplitude relationships would vary with seizure progression to study the role of CFC in ictal dynamics.

Methods

Subjects

Analysis was performed on data obtained from seventeen consecutive children with medically-intractable localization-related epilepsy secondary to FCD undergoing pre-surgical invasive monitoring as well as simulated signals (Supplementary Fig. S1). The subjects included 9 males and 8 females with a mean age of 9.9 years (range 5–16 years) and a mean epilepsy duration of 4.8 years (range 1–11 years). A comprehensive description of the subjects' clinical demographics and epilepsy syndromes is presented in Table 1. Individual seizure morphology, including spectral characteristics are presented in Supplementary methods (Supplementary Figs. S2 and S3). This research was approved by the Hospital for Sick Children Research Ethics Board.

Electrocorticographic recording and processing

The technique of subdural grid implantation has been previously described (Benifla et al., 2009). Data were recorded from subdural grids of 4-mm diameter electrodes embedded in a silicone elastomer sheet with interelectrode distances between 8 and 10 mm. In addition, strip and depth electrodes were implanted, as clinically indicated. Patients underwent digitally recorded intracranial video-EEG using a Harmonie system (Stellate, Montreal, QC, Canada) with a sampling rate of 1 kHz and an anti-aliasing filter at 300 Hz (Butterworth, −20 dB/oct) applied prior to sampling. An averaged reference electrode was selected from two channels in an inactive area of the grid. These represent the same sampling criteria employed to identify pHFOs clinically using multiple band frequency analysis, as previously published (Ochi et al., 2007). An ictal and interictal epoch was selected for each participant. The former was selected by clinical electrophysiologists based on ECoG tracings, correlated with seizure activity on video-EEG, whereas the latter were chosen at least 2 h apart from ictal activity. Ictal epochs varied in length according to seizure duration, whereas interictal epochs were uniformly 2 min in duration. The seizure-onset zone was defined as the electrodes with earliest ictal activity (namely, focal fast waves). The "early spread zone" was classified as secondary areas of seizure

Table 1
Clinical and demographic information for 17 children included in the study.

Subject	Sex	Age (years)	Epilepsy duration (years)	Seizure semiology	Resection location	Size of SOZ[a]	Histopathology
A	M	16	6	SPS	Frontal	13	FCD IB
B	F	12	6	(1) SPS; (2) CPS; (3) SGS	Frontal	29	FCD IIA
C	M	13	6	CPS	Frontal	10	FCD IIB
D	F	13	11	(1) GTC; (2) CPS	Frontal	11	FCD IIB
E	M	15	2	(1) GTC; (2) SPS	Parietal	6	FCD IIB
F	M	5	4	CPS	Parietal	19	FCD IIB
G	F	14	4	(1) SPS; (2) GTC	Parietal	13	FCD IIB
H	M	4	1	CPS	Parieto-occipital	7	FCD IIB
I	M	15	3	(1) CPS; (2) GTC	Fronto-temporo-parietal	2	Suspected FCD
J	M	7	6	GTC	Frontal	1	FCD IIB
K	F	13	10	(1) CPS; (2) SPS	Peri-rolandic	11	FCD IIB
L	F	14	8	(1) SPS; (2) GTC	Peri-rolandic	17	Suspected FCD
M	M	16	7	CPS	Temporal	22	Suspected FCD
N	F	6	4	(1) CPS; (2) SPS; (3) SGS	Fronto-temporal	3	Suspected FCD
O	M	6	3	(1)CPS; (2) SGS	Frontal	8	FCD IIB
P	M	17	8	(1) SPS; (2) GTC	Peri-rolandic	4	FCD IIB
Q	M	6	1	(1) CPS; (2) GTC	Frontal	1	FCD IIA

CPS — complex partial seizures; GTC — secondarily generalized tonic–clonic seizures; SGS — secondarily generalized seizures; SPS — simple partial seizures; SOZ — seizure-onset zone; FCD — focal cortical dysplasia.

[a] As defined by the number of iEEG electrodes involved.