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Pre-seizure architecture of the local connections of the epileptic focus examined via graph-theory

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HIGHLIGHTS

- Graph theory application on brain connectivity is useful to analyze brain information processing.
- Firing abnormalities in synchronized neuronal assemblies are involved in "aberrant" connectivity in pathological processes.
- Excessive binding of "aberrant" connections can progressively lead to electroclinical seizure attacks.

ABSTRACT

Objective: Epilepsy is characterized by unpredictable and sudden paroxysmal neuronal firing occurrences and sometimes evolving in clinically evident seizure. To predict seizure event, small-world characteristic in nine minutes before seizure, divided in three 3-min periods (T0, T1, T2) were investigated.
Methods: Intracerebral recordings were obtained from 10 patients with drug resistant focal epilepsy examined by means of stereotactically implanted electrodes; analysis was focused in a period of low spiking (Baseline) and during two seizures. Networks' architecture is undirected and weighted. Electrodes' contacts close to epileptic focus are the vertices, edges are weighted by mscohere (=magnitude squared coherence).
Results: Differences were observed between Baseline and T1 and between Baseline and T2 in theta band; and between Baseline and T1, Baseline and T2, and near-significant difference between T0 and T2 in Alpha 2 band. Moreover, an intra-band index was computed for small worldness as difference between Theta and Alpha 2. It was found a growing index trend from Baseline to T2.
Conclusions: Cortical network features a specific pre-seizure architecture which could predict the incoming epileptic seizure.
Significance: Through this study future researches could investigate brain connectivity modifications approximating a clinical seizure also in order to address a preventive therapy.

1. Introduction

Epilepsy is characterized by unpredictable and sudden paroxysmal neuronal firing occurrences progressively recruiting larger brain areas and networks and which is time-by-time evolving in clinically evident seizure. Despite enormous research efforts, the pathogenesis of epilepsy as well the turning point from an electrical discharge into a clinically evident attack is not completely clear (Timofeev and Steriade, 2004). Treatments remained mainly pharmacological and less often surgical, although antiepileptic drugs have limitations (Deckers et al., 2003) and fail in about 20–30% of patients to control seizures. In the last years, therapeutic treatment have been suggested as devices based on invasive electrical brain stimulation (Fisher, 2012), drug-delivery (Bennewitz and Saltzman, 2009) or focal-cooling (Rothman, 2009). Most of these

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devices administers continuous stimulation, while others only when seizure activity is detected from chronic and invasive EEG recordings. In this last type of intervention (closed-loop), less stimulation is used reducing side effects of the long term and continuous type (Springer et al., 2006). Stimulation is thought to be more effective in reduction seizures when administered earlier, before the seizure is already developed (Motamedi et al., 2002), but an optimum time to start stimulation has yet to be clarified and the number of false positive (stimulation in absence of risk of attack) and negative (no stimulation despite the risk of attack) episodes are still too high. Such a therapeutic approach could be significantly improved by a better prediction of seizure occurrences to control them and to minimize side effects from unnecessary interventions, but the question of seizure predictability remains an open and still unsolved issue.

Prediction possibility was typically explored from EEG analysis and the main question was to identify changes in EEG preceding seizure onset. During partial seizures' genesis, EEG rhythms are characterized by an increasing of synchronization that culminate in clinical seizure (Bartolomei et al., 1999, 2001, 2004; Schindler et al., 2007). Not many studies analyzed networks' organization during the pre-seizure period (Gadhoumi et al., 2015; Bartolomei et al., 2004), the methods applied for seizure prediction are based on: (i) time-domain and pattern-based features; (ii) frequency domain and time–frequency analysis; (iii) mixed time-domain and frequency-domain; (iv) computation models of neural activity.

Interictal-to-seizure transition may also display changes in spatial organization of the involved neural networks. Therefore, it can be applied graph theory approach to the basis of the "functional connectivity" concept: synchronization of anatomically distinct but functionally linked regions of the brain. Synchronization of neuronal discharges is a pivotal, low-energy consuming and rapidly time-varying mechanism for optimal brain action, but it could represent even the pathological hyper-synchronous firing activity of epilepsy (Douw et al., 2010). Namely, the binding/unbinding of the neuronal assemblies' rhythmic firing in the healthy brain is "fragile" enough to allow rapid and physiological locking-unlocking while both a reduction (dysconnective syndromes) and an excess (dystonias and epilepsy) provoke brain malfunction. From this concept, focal epilepsy is often interpreted as a 'network disorder' due to formation of aberrant connections (Engel et al., 2013).

A recent application of this theory (Ponten et al., 2007) demonstrated that during the seizures, the brain network moved from a more random network interictally to a small-world architecture. Furthermore, in a previous graph theory study of this research group (Vecchio et al., 2015), it was found that the clustering coefficient – that represents functional segregation – and the path length – based on the concept of brain integration – increased in the interictal state in the affected hemisphere, due to the combination of overlapping mechanisms that include reactive neuroplastic changes aiming to maintain both integration and segregation as opposed to aberrant plasticity leading – in case of epilepsy – to hypersynchronization of seizure or spiking state.

Based on the concept that functional neuronal networks adjacent to the epileptic focus (evaluated by stereo-EEG electrodes) is undergoing to time-varying changes in configuration immediately before the seizure, in the present study our aim is to investigate small-world characteristic evaluated nine minutes before the seizure onset divided in three separated periods of three minutes each.

2. Material and methods

2.1. Participants

10 patients with drug resistant focal epilepsy were analyzed. We recruited consecutively, in a period of 6 months, all epileptic patients whom underwent to our observation for pre-surgical invasive evaluation. Demographic data of the patients are reported in Table 1.

All patients were right-handed at Handedness Questionnaire. From each subject informed consent was obtained. StereoEEG was part of the routine pre-surgical invasive evaluation in order to establish the epileptogenic zone (EZ) and its surgical resectability. The non-invasive evaluation included neurological examination, history, magnetic resonance imaging, (MRI), prolonged video-EEG monitoring, interictal and provoked ictal SPECT (single photon emission computed tomography), complete neuropsychological assessment. Intracerebral recordings were obtained by stereotactically permanently implanted electrodes. The structures to be explored were chosen with a non-invasive evaluation. Platinum-iridium electrodes (Microdeep D08, Dixi Medical or Depth electrodes, Alcis) had 5–18 contacts, each of 2 mm length spaced by 1.5 mm, and 0.8 mm in diameter (Table 1). The exact electrodes' location was assessed with individual MRI examination performed after stereotactic implantation. Fig. 1 reports pre- post-surgery MR images in a paradigmatic Patient. Stereo-EEG explored the following cerebral areas: frontal lobe (7 patients), temporal lobe (5 patients) and temporo-parieto-occipital junction (5 patients). In 3 subjects a bihemispheric SEEG implantation was performed.

2.2. Data recordings and preprocessing

The stereo EEG data were registered in a waking rest and no task conditions. For each subjects EEG during a resting (Baseline) period during recurrent seizures were recorded and selected. Nevertheless, for each subject, we analyzed at least 2 clear seizure. The seizure onset was defined as a sudden change of "activity that is distinct from the preceding background, followed by an evolution of this activity in both frequency and amplitude" (Verma and Radtke, 2006) as illustrated in Fig. 2.

Data were analyzed offline with Matlab R2011b software (MathWorks, Natick, MA) and EEGLAB (http://www.sccn.ucsd.edu/eeglab). Four separate time EEG epochs were considered: Baseline, T0, T1, T2. Baseline is represented by epochs at low spiking activity recorded several hours before the seizure, T0 is the time interval (3 min duration) between −9 and −6 min before seizure onset, T1 is the interval of 3 min between −6 and −3 min before seizure, T2 the epochs of three minutes before the seizure onset.

For the visual seizure detection on the sEEG recordings, we used a band-pass 0, 5–70 Hz. Conversely, in the analysis, sEEG signals were filtered with a band-pass 0.1–47 Hz FIR filter at 256 Hz sampling rate frequency. To eliminate interference caused by any type of artifacts, imported data were fragmented in 2 s epochs and reviewed manually by expert Neurophysiologists.

2.3. Functional connectivity analysis

Functional connectivity analysis was obtained by spectral coherence algorithm based on the coupling between two (EEG) signals at all frequency (Vecchio et al., 2014a,b,c; Pfurtscheller and Andrew, 1999). It was computed by an homemade software developed under Matlab (MathWorks, Natick, MA). Hemispheric synchronization of EEG frequency bands of interest was evaluated by magnitude squared coherence (*mscohere*) between each electrode.

Mscohere n that indicates how x corresponds to y at each frequency f. The magnitude squared coherence is a function of $P_{xx}(f)$ and $P_{yy}(f)$ (power spectral densities), and of $P_{xy}(f)$ (cross power spectral density) of x and y: