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Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: A study via graph theory

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HIGHLIGHTS

- Effective connectivity and optimal network structure is essential for proper information processing in the brain.
- Functional abnormalities of the brain are found to be associated with the pathological changes in connectivity and network structures.
- Aim of the present study, was to explore the interictal network properties of EEG signals from temporal lobe structures in the context of fronto-temporal lobe epilepsy by graph analysis tools.

ABSTRACT

Objective: It is believed that effective connectivity and optimal network structure are essential for proper information processing in the brain. Indeed, functional abnormalities of the brain are found to be associated with pathological changes in connectivity and network structures. The aim of the present study was to explore the interictal network properties of EEG signals from temporal lobe structures in the context of fronto-temporal lobe epilepsy.
Methods: To complete this aim, the graph characteristics of the EEG data of 17 patients suffering from focal epilepsy of the fronto-temporal type, recorded during interictal periods, were examined and compared in terms of the affected versus the unaffected hemispheres. EEG connectivity analysis was performed using eLORETA software in 15 fronto-temporal regions (Brodmann Areas BAs 8, 9, 10, 11, 20, 21, 22, 37, 38, 41, 42, 44, 45, 46, 47) on both affected and unaffected hemispheres.
Results: The evaluation of the graph analysis parameters, such as 'global' (characteristic path length) and 'local' connectivity (clustering coefficient) showed a statistically significant interaction among side (affected and unaffected hemisphere) and Band (delta, theta, alpha, beta, gamma). Duncan post hoc testing showed an increase of the path length in the alpha band in the affected hemisphere with respect to the unaffected one, as evaluated by an inter-hemispheric marker. The affected hemisphere also showed higher values of local connectivity in the alpha band. In general, an increase of local and global graph theory parameters in the alpha band was found in the affected hemisphere. It was also demonstrated that these effects were more evident in drug-free patients than in those undergoing pharmacological therapy.
Conclusions: The increased measures in the affected hemisphere of both functional local segregation and global integration could result from the combination of overlapping mechanisms, including reactive neuroplastic changes seeking to maintain constant integration and segregation properties.
Significance: This reactive neuroplastic mechanism seeking to maintain constant integration and segregation properties seems to be more evident in the absence of antiepileptic treatment.

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1. Introduction

Epilepsy is a common neurological disorder, characterized by a sudden occurrence of paroxysmal neuronal firing. It is sometimes accompanied (when several causes occur simultaneously, including paroxysmal activity that is highly synchronized, sufficiently prolonged in time and involves a critical neuronal assembly) by clinically evident epileptic attack. It is the most frequently occurring disease of the central nervous system, affecting approximately 1% of the world population. Despite enormous research efforts, the pathogenesis of epilepsy has not completely been elucidated (Timofeev and Steriade, 2004), which hampers both full understanding of the pathophysiology and subsequent treatment.

The clinical diagnosis of epilepsy is based on the criteria of the International League Against Epilepsy (ILAE). A diagnostic interictal electro-encephalogram (EEG) showing 'interictal epileptiform discharges' (IEDs) is obtainable. Unfortunately, while visual EEG inspection is highly specific as a diagnostic tool, it has a relatively low sensitivity, since only 30–50% of patients have IEDs during their first routine EEG (King et al., 1998). Even though this percentage increases with repeated EEG recordings, between 2% and 18% of patients never display IEDs on their EEGs (Marsan and Zivin, 1970; Noachtar and Remi, 2009). To make matters worse, approximately 0.5% of the healthy population shows IEDs that never lead to a clinically evident epileptic attack (Robin et al., 1978; Gregory et al., 1993). Thus, the development of an EEG measure expanding the diagnostic yield of IEDs, whilst preserving high specificity, would be highly valuable.

A relatively new concept in neuroscience is ''functional connectivity''. Functional connectivity in human neuroscience refers to the synchrony of activity in anatomically distinct but functionally collaborating brain regions. For this reason, if two neuronal assemblies are highly correlated in their rhythmic firing activity over time, they are considered functionally connected. This notion refers to the statistical interdependencies (or synchronization) between time series from different brain areas, as measured by electroencephalography (EEG), magnetoencephalography (MEG), or functional magnetic resonance imaging (fMRI). Synchronization of neuronal discharges on one side may be pivotal for optimal brain functioning (Varela et al., 2001). However, it can also reflect abnormal dynamics of hyper-synchronous firing related to epilepsy (Douw et al., 2010). Within this theoretical framework, focal epilepsy is increasingly seen as a 'network disorder' (Kramer and Cash, 2012; Richardson, 2012; Engel et al., 2013).

During the genesis of partial seizures (particularly temporal lobe seizures), it has been observed that the EEG rhythms from involved brain networks are characterized by increased synchronization culminating at the end with a clinical seizure (Lieb et al., 1987; Duckrow and Spencer, 1992; Gotman and Levtova, 1996; Le Van et al., 1998; Bartolomei et al., 2001, 2004, 2005; Schindler et al., 2007). In contrast, few studies have investigated network properties and functioning during the interictal period. An increase of EEG synchrony has been described from cortical surface/grids recordings (Schevon et al., 2007) or from intracerebral recordings in mesial temporal lobe epilepsy (Bettus et al., 2008). In this context, an approach to the characterization of complex networks is the use of the 'graph theory' (Strogatz, 2001; Boccaletti and Pecora, 2006). A graph is a representation of a network, which is expressed by its nodes ('vertices') and connections ('edges'). Graphs can be described by several parameters and particularly by a clustering coefficient (C) and characteristic path length (L). The clustering coefficient is a measure for the local connectedness of the graph, whereas the characteristic path length is an indicator of overall connectedness. It has been shown that graphs with many local connections and a few random long distance connections are characterized by a high clustering coefficient and a short characteristic path length (Watts and Strogatz, 1998). These networks, which acts as intermediaries between an ordered and a random organization, have been defined as ''small world networks''. Such a topology is responsible for high local and global efficiency with low energy and wiring costs (Achard and Bullmore, 2007). Neuronal networks behave as a small world phenomenon, which is also an optimal organization for time-varying dynamic synchronization of neuronal activity among different brain regions (Lago-Fernandez et al., 2000). Graph analysis of structural/anatomical (diffusion MRI and cortical thickness correlation) and functional (fMRI signals and MEG recordings) data have demonstrated a small world configuration in the healthy human brain (Sporns et al., 2000, 2004; Stam, 2004; Sporns and Zwi, 2004; Salvador et al., 2005; Achard and Bullmore, 2007; He et al., 2007; Hagmann et al., 2008; Gong et al., 2009). These small-world properties would be responsible for the high efficiency of the brain information processing, or the efficiency of such an organization being related to cognitive performance (van den Heuvel et al., 2009; Bassett et al., 2009). Along the same lines, alterations of small-world properties have been observed in several brain diseases, shedding light both on their pathophysiology and their behavioral/cognitive consequences (Reijneveld et al., 2007; Bassett et al., 2009; D'Amelio and Rossini, 2012).

In the context of epilepsy, changes in network topology were first described during the ictal period (Ponten et al., 2007; Kramer et al., 2008, 2010; Schindler et al., 2008). More recently, research investigations focused on the interictal period and changes in the graph topology of EEG signals (Chavez et al., 2010; Liao et al., 2010; Horstmann et al., 2010; Bernhardt et al., 2011; Vaessen et al., 2012). Results are not homogeneous. Some studies have reported an increase in clustering and a path length shortening (Chavez et al., 2010; Horstmann et al., 2010; Bernhardt et al., 2011). Others have found a decrease in these network properties (Liao et al., 2010) or a decreased clustering and an increased path length (Vaessen et al., 2012). These discrepancies are probably related to different populations studied at different times (i.e., initial or chronic epilepsies), conditions (i.e., under antiepileptic or drug-free conditions) and with different methodological approaches.

To our knowledge, no previous report has investigated the network's properties during the interictal period in a source's analysis from the EEG scalp recordings in patients with focal fronto-temporal epilepsy. The aim of the present study was a proof of concept for the use of graph theory in investigating the interictal network properties of EEG signals—namely those from epileptic temporal lobe structures—in the context of fronto temporal lobe epilepsy. To this end, the graph characteristics of scalp EEG signals recorded during interictal periods were examined and compared in both hemispheres with respect to an inter-hemispheric marker of healthy subjects.

A corollary endpoint of the present study was also to investigate whether interictal EEGs from patients suffering from MTLE had differing graph characteristics in drug-free or in chronic antiepileptic drugs treatment conditions.

2. Materials and methods

2.1. Participants

A dataset of 17 patients with focal fronto-temporal epilepsy (divided according to the side of focus: 8 left and 9 right) and 48 age-matched healthy subjects was analyzed. Demographic data of the patients are reported in Table 1. To obtain a more reliable