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Functional brain connectivity from EEG in epilepsy: Seizure prediction and epileptogenic focus localization

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ABSTRACT

Today, neuroimaging techniques are frequently used to investigate the integration of functionally specialized brain regions in a network. Functional connectivity, which quantifies the statistical dependencies among the dynamics of simultaneously recorded signals, allows to infer the dynamical interactions of segregated brain regions. In this review we discuss how the functional connectivity patterns obtained from intracranial and scalp electroencephalographic (EEG) recordings reveal information about the dynamics of the epileptic brain and can be used to predict upcoming seizures and to localize the seizure onset zone. The added value of extracting information that is not visibly identifiable in the EEG data using functional connectivity analysis is stressed. Despite the fact that many studies have showed promising results, we must conclude that functional connectivity analysis has not made its way into clinical practice yet.

Contents

Abbreviations: ADT, adaptive DTF; AED, antiepileptic drug; AIC, Akaike's Information Criterion; APDC, adaptive PDC; AR, autoregressive; DC, directed coherence; DCM, dynamic causal modeling; DTF, directed transfer function; ECoG, electrocorticography; EEG, electroencephalography; ESI, EEG source imaging; EZ, epileptogenic zone; ffADTF, full-frequency ADTF; ffDTF, full-frequency DTF; FINE, first principle vectors; fMRI, functional MRI; GCI, Granger causality index; HD EEG, high-density EEG; iADTF, integrated ADTF; iAPDC, integrated APDC; ICA, independent component analysis; iDTF, integrated DTF; IED, interictal epileptiform discharge; IEEG, intracranial EEG; IFCN, International Federation of Clinical Neurophysiology; ILAE, International League Against Epilepsy; iPDC, integrated PDC; IPI, initial precipitating insult; IVEM, invasive video/EEG monitoring; L, lateral; LGS, Lennox-Gastaut syndrome; LM, lateral–medial; M, medial; MEG, magnetoencephalography; MI, mutual information; ML, medial–lateral; MRI, magnetic resonance imaging; MVAR, multivariate autoregressive; PC, partial coherence; PDC, partial directed coherence; PET, positron emission tomography; PLI, phase lag index; PLV, phase locking value; SBC, Schwarz's Bayesian Criterion; SDTF, short-window DTF; SEEG, stereo EEG; SOZ, seizure onset zone; SPECT, single photon emission computed tomography; SVEM, scalp/video EEG monitoring; swADTF, spectrum weighted ADTF; TE, transfer entropy; TLE, temporal lobe epilepsy.

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1. Introduction

Epilepsy is a neurological disorder characterized by recurrent seizures. During the seizures there is abnormal excessive firing of neurons in the brain resulting in diverse symptoms such as staring, muscle stiffness (tonic movements), muscle spasms (clonic movements) and impaired consciousness. The unpredictability of when seizures occur dramatically impacts the life of patients with epilepsy. Therefore, seizure prediction can help to warn patients and to improve their quality of life. Seizure prediction aims at predicting an upcoming seizure before the clinical manifestation of the seizure occurs. If antiepileptic drugs do not result in adequate treatment of the patient, a possible treatment is the surgical resection of the epileptogenic focus, i.e. the region in the brain responsible for causing the seizures. This makes the localization of the epileptogenic focus of utmost clinical importance. The aim of epileptogenic focus localization is to provide information on the location and delineation of the epileptogenic focus to the epileptologists in order to support their decision making.

Electroencephalography (EEG) is the most important technique for the diagnosis and treatment follow-up in epilepsy patients. EEG records the electric field generated by the neurons in the brain with high temporal resolution (order of ms). It is used to classify the type of seizures and to localize the epileptogenic focus. Because brain areas are highly interconnected, many (distant) brain regions are potentially involved during a seizure. This makes the localization of the epileptogenic focus from ictal EEG recordings a true challenge.

Three decades ago, functional neuroimaging was mainly used to establish functional segregation as a principle of organization in the human brain, addressing how specific brain regions are used to execute specific tasks (Friston, 1994). Lately functional neuroimaging is used to study functional integration rather than segregation: the integration of functionally specialized brain regions is investigated. How these intercommunications take place and which brain regions are involved is addressed in the research domain of brain connectivity. Brain connectivity can reveal pathways between brain regions or reveal how information is processed, sent to, received by or shared between different brain regions.

In this review paper we discuss how functional brain connectivity obtained from EEG recordings can be used to localize the epileptogenic focus. Because of the growing appreciation that a single focus may not be the best way of understanding the pathophysiology underlying seizure activity we emphasize the role of networks or distributed processing in epilepsy. We start by giving a general introduction on epilepsy and the treatment of epilepsy patients. Afterwards we introduce functional connectivity measures, discuss the conceptual difference between them and draw attention to important issues during the functional connectivity analysis. We give an overview how these functional connectivity measures can be used to predict seizures and localize the epileptogenic focus. In the last section we discuss the current state of use of functional brain connectivity in clinical practice and suggest possible future directions.

2. Epilepsy

2.1. Definition, prevalence and incidence

Epilepsy is one of the most common neurological disorders affecting roughly 0.5–1% of the population worldwide. Epilepsy is characterized by recurrent, unprovoked seizures (Fisher et al., 2005), defined as the manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurons in the brain (Blume et al., 2001). During a seizure, a sudden burst of uncontrolled electrical activity occurs within a group of neurons in the cerebral cortex (Sörnmo and Laguna, 2005). Epilepsy is usually diagnosed after a person has experienced at least two unprovoked seizures that were not caused by some known condition like alcohol withdrawal or extremely low blood sugar.

Epilepsy can develop at any age, but the incidence of epilepsy is highest during the first years of life and after the age of 65. During the adult years the incidence is the lowest (Jallon, 2006). In many cases the precise etiology of epilepsy in a specific patient is unknown. Nevertheless, many factors can cause epilepsy: genetic factors, head trauma, tumors, stroke, dementia, meningitis, prenatal injury, oxygen deprivation and many more. This is called the initial precipitating insult (IPI) generating a symptomatic form of epilepsy. The process in which epilepsy develops until spontaneous seizures occur is called epileptogenesis.

2.2. Seizures

Epilepsy can be divided into two subtypes based on the location in the brain where the seizures start from and how it propagates. On the one hand, seizures in primary generalized epilepsy begin with a widespread electrical discharge that involves the entire brain. On the other hand, partial seizures begin with an electrical