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Enhanced EEG functional connectivity in mesial temporal lobe epilepsy

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Summary
Purpose: To analyze and compare spectral properties and interdependencies of intracerebral EEG signals recorded during interictal periods from mesial temporal lobe structures in two groups of epileptic patients defined according to the involvement of these structures in the epileptogenic zone (EZ).
Methods: Interictal EEG activity in mesial temporal lobe (MTL) structures (hippocampus, entorhinal cortex and amygdala) was obtained from intracerebral recordings performed in 21 patients with drug-resistant mesial temporal lobe epilepsy (MTLE group). This group was compared with a ''control'' group of patients (non-MTLE group) in whom depth-EEG recordings of MTL show that seizures did not start from the MTL. Comparison criteria were based on spectral properties and statistical coupling (nonlinear correlation coefficient h^2) of MTL signals.
Results: Power spectral density analysis showed a significant decrease in the theta frequency sub-band ($p = 0.01$) in the MTLE group. Nonlinear correlation (h^2) values were found to be higher in the MTLE group than in the NMTLE group ($p = 0.0014$). This effect was significant for theta, alpha, beta and gamma frequencies. Correlation values were not correlated with the frequency of interictal spikes (IS) and significant differences between groups were still measureable even when spikes were suppressed from analyzed EEG periods.
Discussion: This study shows that, during the interictal state, the EZ in MTLE is characterized by a decrease of oscillations in the theta sub-band and by a general increase of signal interdependencies. This last finding suggests that the EZ is characterized by network of neuronal assemblies with a reinforced functional connectivity.

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Introduction

Focal (or partial) epilepsies are characterized by recurrent seizures generated in an abnormal region of the brain, the epileptogenic zone (EZ). Approximately 1/3 of cases are resistant to antiepileptic drugs. In this situation, surgical resection of the EZ is the only therapeutic option able to suppress seizures or, at least, to significantly reduce their frequency. The localization and the definition of the EZ are therefore crucial issues in epileptology and are addressed through detailed analysis of anatomo-functional data acquired in epileptic patients during pre-surgical evaluation. Among investigation methods used during this evaluation, intracerebral exploration remains the only way to directly record the electrophysiological activity (depth-EEG) from brain structures and to formulate hypotheses about their potential involvement in epileptogenic processes. In this context, a large number of studies have been dedicated to the analysis of depth-EEG signals. Based of the estimation of interdependences (i.e. statistical coupling) between signals recorded from distinct sites, some reports have demonstrated that the areas involved in the generation of seizures (defining the EZ) are characterized by synchronous oscillations at seizure onset (Bartolomei et al., 2005, 2001b, 2004, 1999; Duckrow and Spencer, 1992; Gotman and Levtova, 1996; Le Van Quyen et al., 1998; Lieb et al., 1987). The ''synchronization'' of activities recorded from brain structures is therefore an important phenomenon that may be used for identifying epileptogenic networks (i.e. promoting the initiation of seizures). Other studies based on nonlinear associations in multivariate signals (Guye et al., 2006) have also reported that long distance functional connectivity is dramatically altered during seizures, or indicated that the topology of networks changes as ictal activity develops (Ponten et al., 2007).

In contrast, knowledge about the properties of electrophysiological signals recorded from the EZ during interictal periods remains elusive. It is usually observed that brain structures involved in the EZ produce abnormal transient electrophysiological (interictal spikes). However, the spectral characteristics of depth-EEG signals as well as the properties of the ''functional connectivity'' of involved networks are poorly described.

Generally speaking, the analysis of statistical couplings between signals generated from distant sites has been proposed as an approach to assess this functional connectivity. For instance, in cognitive studies, synchronization processes in the theta frequency band has been associated with memory processes (Sarnthein et al., 1998; Stam et al., 2002a). Synchronization in the gamma band has been shown to relate to the representation of complex information in conscious perception (Csibra et al., 2000; Micheloyannis et al., 2003; Rodriguez et al., 1999; Tallon-Baudry and Bertrand, 1999) and also to memory processes (Fell et al., 2003; Summerfield and Mangels, 2005; Tallon-Baudry et al., 2001).

Functional connectivity may also serve as a potentially useful marker of brain disease (Cordes et al., 2001; Lowe et al., 1998; Salvador et al., 2005; Stam et al., 2002b; Uhlhaas and Singer, 2006).

It is indeed expected that diseases inducing changes in synaptic efficiency may alter the communication within and between neuronal networks and thus, induce neurological disturbances. In the field of epilepsy, two studies have recently shown an increase of the ''local synchrony'' calculated from monochannel signals (using the autocorrelation function) (Monto et al., 2006) or from multichannel signals (using the mean phase coherence method) (Schevon et al., 2007), in the vicinity of the epileptogenic zone. In these studies, recordings were performed from a neocortical ''focus'' using intracranial grids and led authors to suggest that functional connectivity could be altered during the interictal state of partial epilepsies.

In the present study, we investigated the spectral properties and the possible changes in functional connectivity affecting the mesial temporal region in patients with MTLE.

Intracerebral EEG signals were collected in patients with MTLE undergoing presurgical evaluation. They were recorded from the mesial temporal structures using stereoelectroencephalography (SEEG). Moreover, in order to confront quantities measured in MTLE with those obtained under ''normal'' condition, we also studied depth-EEG signals recorded from mesial structures in patients in whom the EZ was localized outside the mesial temporal lobe.

Methods

Patients

Patients undergoing pre-surgical evaluation of drug-resistant epilepsy were retrospectively selected in the database of our epilepsy unit (CHU Timone, Marseille) for the present study.

All patients had a comprehensive evaluation including detailed history and neurological examination, neuropsychological testing, conventional presurgical MRI, surface EEG and depth-EEG recording (stereo-EEG using intracerebral electrodes implanted according to a stereotactic approach) as previously reported (Bartolomei et al., 2002; Guye et al., 2006).

Patients were selected for the present study if they satisfied the following criteria: (i) a clearly localized, unilateral epileptogenic zone defined by the regions primarily involved in seizures (generally characterized by a fast ictal discharge at onset) and (ii) at least two mesial temporal lobe structures explored by intracerebral electrodes.

Patients were divided into two groups depending on the participation of the mesial regions at seizure onset:

(i) The first group, denoted by the acronym ''MTLE'', included patients ($n = 21$) with seizures that initially involved mesial temporal lobe.
(ii) The second group, denoted by the acronym ''NMTLE'', included patients ($n = 14$) with a non-mesial temporal lobe epilepsy. These patients had frontal lobe epilepsy ($n = 5$), lateral temporal lobe epilepsy ($n = 4$) and occipital lobe epilepsy ($n = 5$).

Table 1 gives a summary of the patient's data.

SEEG recordings

Depth-EEG recordings were performed according to the stereo-electroencephalographic approach in which intracerebral multiple contact electrodes (10—15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) are placed intracranially according to Talairach's stereotactic method (Talairach et al., 1974). The positioning of electrodes was established in each patient based upon hypotheses about the localization of the epileptogenic zone formulated from available non-invasive information. The implantation