Clinical Neurophysiology 124 (2013) 1729–1736

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

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

Display of consistent ictal networks in refractory mesial temporal lobe epilepsy

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ARTICLE INFO

Article history:
Accepted 24 March 2013
Available online 29 April 2013

Keywords:
Epilepsy
Hippocampus
Synchrony
Temporal lobectomy
Seizure
EEG
Quantitative EEG

HIGHLIGHTS

- EEG-derived ictal networks were created among subjects with refractory mesial temporal lobe epilepsy using the previously published Synchrony Index.
- Distinct ictal network stages were identified that were consistent across seizures and subjects.
- Synchrony Index values during specific ictal stages were significantly lower in subjects with post-operative seizure freedom.

ABSTRACT

Objective: Exploration of emergent ictal networks was performed in homogeneous subjects with refractory medial temporal lobe epilepsy.
Methods: Maximal Synchrony Index (SI) values were calculated for all electrode pairs for each second during 25 seizures and displayed as connectivity animations. Consistent temporal patterns of SI value and spatial connectivity were observed across seizures and subjects, and used to define a sequence of network stages.
Results: Highest SI values were found in electrodes within the area of surgical resection. Analysis of these electrodes by network stage demonstrated lateral temporal cortex dominance at seizure initiation, giving way to hippocampal synchrony during the major portion of the seizure, with lateral temporal regions re-emerging as the seizure terminated. SI values also corresponded to behavioral severity of seizures, and lower SI values were associated with post-surgical seizure freedom.
Conclusion: SI based methods of network characterization consistently display the intrinsic MTLE ictal network and may be sensitive to clinical features.
Significance: Consistency of EEG-derived network patterns is an important step as network features are applied towards improvement of clinical management. These data confirm consistency of network patterns within and across subjects and support the potential for these methods to distinguish relevant clinical variables.

1. Introduction

One hypothesis to account for the third of patients with refractory mesial temporal lobe epilepsy (MTLE) with continued seizures after epilepsy surgery (Wiebe et al., 2001; Spencer et al., 2005; Barbaro et al., 2009) is that surgery may merely interrupt an epileptic network rather than eliminate a discrete "epileptic focus" (Bear et al., 1996; Bragin et al., 2000; Spencer 2002; Bertram, 2003; Bettus et al., 2009). Understanding emergent network behavior may allow improved treatment selection for individual patients.

Analysis of synchronization of EEG patterns among brain regions is one method for examination of epileptic networks (Iasemidis et al., 1990; Valton et al., 2008; Wendling et al., 2010; Kramer et al., 2010; Ossadtchi et al., 2010). For example, high synchrony has been shown in structures important to seizure initiation (Ding et al., 2006; Warren et al., 2010; Bartolomei et al., 2010; Van Mierlo et al., 2011) and in the context of seizure termination (Schindler et al., 2007; Kramer et al., 2010). Other results suggest that interactions between mesial structures and neocortex are critical to sei-

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1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.03.019

zure initiation (Moran et al., 2001; Wennberg et al., 2002; Bettus et al., 2008; Cadotte et al., 2009; Jiruska et al., 2010).

An important assumption in studies of this type is that there exists an intrinsic ictal network that is consistently demonstrable. Confirmation of this assumption is critical to enabling use of network features for parcellation of individual patients into clinically relevant groups. Consistent features of ictal functional networks have been previously reported in groups of heterogeneous subjects (Kramer et al., 2010) providing insight into principles of ictal physiology but limited in their anatomical interpretation. Evaluation of a more homogenous group, with nearly identical localization and etiology of epilepsy, addresses this issue. The purposes of this study were (1) to identify consistent ictal network spatial patterns within- and across-subjects in a highly selected sample of patients with MTLE with histopathologically-confirmed hippocampal sclerosis and known surgical outcomes and (2) evaluate whether features of these network patterns correspond to relevant clinical variables in this specific population.

2. Methods

2.1. Subjects and seizures

This retrospective, IRB-approved study evaluated patients with pre-operative diagnosis of medically-intractable MTLE who required intracranial monitoring because of insufficient localization after standardized, noninvasive presurgical evaluation including inpatient scalp video-EEG, MRI, neuropsychological battery, and interictal and ictal single-positron emission computerized tomography. Three of four patients had evidence of unilateral hippocampal sclerosis on MRI and all had post-operative histopathological confirmation. All had anterior temporal lobectomy and were followed for at least 2 years.

2.2. Intracranial EEG recording

Patients were implanted with bilateral, eight contact depth electrodes with 1 cm spacing (Adtech, Racine, WI) inserted occipitally, extending through the hippocampus and terminating in the entorhinal cortex. Bilateral subdural strips with 4–8 contacts, spaced 1 cm apart, were placed across anterior, lateral, and posterior frontal lobes and anterior, inferior and lateral temporal lobe regions (Supplementary Fig. S1A). Continuous video-EEG (Grass/Telefactor, Warwick, RI) was recorded at 200 Hz (60 Hz notch filter, high pass 1 Hz, low pass 70 Hz) using a distant, uninvolved subdural electrode as reference (Korzeniewska et al., 2011). All seizures were visually reviewed by a board certified neurophysiologist (GM or MQ) for motion, muscle, or electrical artifact. For each seizure, time and location of electrographic seizure onset and offset, clinical seizure onset time and severity [simple partial (SPS), complex partial (CPS) or secondarily generalized (GTC)], and behavioral state (sleep/wake) were determined. Processed EEG segments began one minute prior to electrographic seizure onset and ended 20 s after seizure termination. Only electrodes targeting similar anatomical regions among all patients were included for quantitative analysis.

2.3. Synchrony Index analysis and display of connectivity animations

The Synchrony Index (SI), a previously described measure of the strength of oscillator coupling (Kiss et al., 2007, 2008), has shown increased values during seizures, maximal in the area of seizure onset (Martz et al., 2008). The value incorporates both the local amplitude coherence of neuronal activity underlying a single electrode and the phase relationships of neuronal activities underlying different electrodes. The SI unifies symmetric, nondirectional, local neuronal coherence at two distinct sites, and the synchronization of their signals, to quantify the induced order between the two regions. Such a combined approach is promising for the identification within EEG data of distinct states driven by inter-regional synchronization changes (Mormann et al., 2005; Kiss et al., 2008).

Coherence of the neurons underlying an electrode, denoted by r, is calculated from the amplitude of the EEG signal at that electrode (relative to a common, uninvolved reference). Phase synchronization between distinct electrodes, denoted σ, is derived using the Hilbert transformation of the full band signal from each electrode. SI is calculated for two electrodes, k and l, as:

$$\mathrm{SI}_{k,l} = \sigma_{k,l}\frac{(r_k + r_l)}{2}$$

where r_k and r_l are the average amplitudes of the respective signals, representing the local coherence, and $\sigma_{k,l}$ is the phase synchronization between the signals (Tass et al., 1998) for a specific time window. Further details on the theory and calculation of SI can be found in a previous study (Kiss et al., 2008).

Customized Matlab (R2009b/ Natick, MA) software was used to calculate SI values over the entire frequency band (1–70 Hz) in non-overlapping one second time bins for every possible pair of electrodes in an iterative fashion. Since the number of interactions among all electrode pairs is large (total = $n \times (n-1)/2$), we determined in preliminary studies that an efficient method of displaying SI connectivity was through "connectivity animations" that allowed direct observation of time-dependent changes across the electrode array (Akiyama et al., 2010). For each electrode at each second, the highest SI value pair was plotted, indicating electrode pairing and magnitude, upon a brain schematic (Supplementary Fig. S1B), thus yielding an animated map of the highest connectivity for each electrode at each second. To demonstrate relative values of SI among electrode pairs, and to highlight statistically significant outlier electrodes, SI amplitude was represented on a normalized 255-bit color scale from low to high (red = highest 5% of SI values) (see representative connectivity animation movies; Supplementary videos S1–S4).

Connectivity animations from every seizure from all patients underwent blinded review. Standard EEG terminology was avoided to distinguish animation from EEG interpretations. "*focality*" was defined as 1–2 electrodes that featured visually increased SI amplitude for $\geqslant$3 s. Changes in SI amplitude occurring simultaneously in >80% of electrodes were considered "*global*". A "*hub*" was defined as a spatial array in which $\geqslant$20% of electrodes were all maximally connected to a single electrode for $\geqslant$3 s.

This process lead to the description of "stages" of SI connectivity based on empiric patterns of SI amplitude and spatial connectivity that were agreed upon by mutual subsequent review by the research group. Stages were correlated with standard visual analysis of EEG, using time zero as the seizure onset as determined by standard EEG analysis. Stage durations were analyzed as per cent time (%*T*), calculated by dividing each stage duration by the total duration of the connectivity animation/EEG sample (= 1 min + seizure + 20 s).

2.4. Statistical analysis

To enable inter-seizure and inter-subject statistical comparisons, several steps were performed for normalization of the maximum SI values used in connectivity animations.

Normalized maximal SI (nMaxSI) = for each electrode at all time points, the maximum SI value (regardless of which other electrode was paired with it for that value at that second) was divided by the largest observed maximum SI score of any electrode within that seizure and subject. The resultant nMaxSI ranged from 0 to 1 (see Supplementary Fig. S3).