Feasibility Study of the Time-variant Functional Connectivity Pattern during an Epileptic Seizure

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Abstract. Epilepsy is a neurological disorder characterized by seizures, i.e. abnormal synchronous activity of neurons in the brain. Intracranial ElectroEncephaloGraphy (iEEG) is the recording of brain activity at a high temporal resolution through electrodes placed within different brain regions. Intracranial electrodes are used to access structures deep within the brain and to reveal brain activity which is not displayed in scalp EEG recordings. In order to identify pattern of propagation across brain areas, a connectivity measure named the Adapted Directed Transfer Function (ADTF) has been developed. This measure reveals connections between different regions by exploiting statistical dependencies within multichannel recordings. The ADTF can be derived from the coefficients of a time-variant multivariate autoregressive (TVAR) model fitted to the data. We applied the ADTF to 26 iEEG signals recorded during a subclinical seizure to identify the propagation of electrical activity specific to epilepsy. We showed the feasibility of detecting the propagation pattern during the epileptic seizure. The leading region seen in the pattern was consistent with post-operative results. We proved that connectivity patterns derived from iEEG recordings can provide useful information about seizure propagation and may improve the accuracy of the pre-surgical evaluation in patients affected by refractory epilepsy.

Keywords: Adapted DTF; Time-Variant Autoregressive Model; Functional Connectivity Pattern; Epileptic Seizure

1. Introduction

Epilepsy is one of the most common chronic neurological diseases and is characterized by recurrent epileptic seizures. Epilepsy is usually diagnosed after a person has had at least two seizures that were not caused by some known medical condition like alcohol withdrawal or extremely low blood sugar. An epileptic seizure is defined as the manifestation(s) of epileptic (excessive and/or hyper synchronous), usually self-limited activity of neurons in the brain [Blume et al., 2001]. During a seizure a sudden burst of uncontrolled electrical activity occurs in a group of neurons of the cerebral cortex [Sörnmo and Laguna, 2005].

Though recent advances in neuroscience enable us to better understand high level brain processes, the precise interaction between different brain regions in epileptic patients is not yet revealed. The intracranial ElectroEncephaloGraphy (iEEG) recordings monitor the electrical activity of brain regions by electrodes placed on subdural cortical layers (strips) or inserted deep within the brain (depth electrodes). Intracranial electrodes are used to reveal brain activity which is not seen on scalp EEG recordings.

Brain connectivity gives better insight into the information flows between brain regions. Knowledge about interaction is important for better understanding diseases. It can reveal changes in the neural pattern characteristic for the disease. Three types of connectivity are defined in the brain. Structural connectivity refers to the direct anatomical connections in the brain. Functional connectivity refers to statistical dependency between activities of different regions, regardless of any underlying anatomical connection. Effective connectivity is defined as the influence that one neuronal system exerts over another [Friston et al., 1993].

The functional connections between brain regions can be investigated by applying measures of connectivity or information flow to the iEEG recordings. These measures exploit statistical

dependencies between the iEEG signals leading to a functional connectivity pattern. The Directed Transfer Function (DTF) [Kaminski et al., 2001] is such a parametric multivariate time-variant analysis technique that estimates the indirect (cascade flows) directional information flow between multiple signals in the frequency domain. The Adaptive Directed Transfer Function (ADTF) [Wilke et al., 2008] is the extension of the DTF proposed to deal with non-stationary signals such as an epileptic seizure. The functional connectivity pattern obtained when the ADTF is applied to the iEEG recordings shows the information flows between different regions at specified frequencies and how they change over time. In this study the feasibility of detecting the information flows within the brain during an epileptic seizure is investigated.

2. Information flow in multivariate systems

In order to obtain the information flow in the system a multivariate autoregressive (MVAR) model can be fitted to the measured signals. MVAR models assume that the signals are stationary in the considered time window. To overcome this issue we let the parameters of the autoregressive model vary in time. This time-variant multivariate autoregressive (TVAR) model with time varying parameters allows us to investigate non-stationary signals such as an epileptic seizure. The ADTF is constructed out of the coefficients of the TVAR model and shows the information flows in the frequency domain over time between the signals.

2.1. Time-variant Autoregressive Model

The time-variant multivariate autoregressive model assumes that the value of a vector $\mathbf{X} = [x_1 \ x_2 \ \dots \ x_K]^T$, containing K signals, at time n can be linearly predicted from p previous samples of the same vector as:

$$\mathbf{X}(n) = \sum_{i=1}^{p} \mathbf{A_i}(n)\mathbf{X}(n-i) + \mathbf{E}(n) \tag{1}$$

where $\mathbf{X}(n)$ is the signal matrix at time n which contains K signals, p is the order of the TVAR model, $\mathbf{A_i}(n)$ is the model coefficient matrix (K by K) for delay i at time n and $\mathbf{E}(n)$ is the prediction error matrix at time n.

The coefficients of the TVAR model are estimated using Kalman filtering. The Kalman filter is an algorithm for estimating the state of a state space model with a system equation (Eq. 2) and measurement equation (Eq. 3) [Arnold et al., 1998]:

$$\mathbf{z}_k = \mathbf{G}_{k,k-1}\mathbf{z}_k + \mathbf{w}_k \tag{2}$$

$$y_k = \mathbf{F}_k \mathbf{z}_k + v_k \tag{3}$$

where $\mathbf{z}_k$ is the state vector of the system, $\mathbf{G}_{k,k-1}$ is the state transition matrix, $\mathbf{w}_k$ is the process noise with zero mean and covariance matrix $\mathbf{W}_k$, $\mathbf{F}_k$ is the measurement matrix, v_k is the measurement noise with zero mean and variance V_k and y_k is the output signal.

The estimated coefficients of the TVAR model constructed out of this state space model vary over time which eventually leads to a time dependent transfer matrix of the process: $\mathbf{H}(f,n)$. The time-variant transfer matrix of the process is the inverse of the Fourier transformation of the model coefficient matrix in Eq.1.

2.2. Adaptive Directed Transfer Function

The normalized Adaptive Directed Transfer Function (ADTF) [Wilke et al., 2008] is the time dependent version of the DTF [Kaminski et al., 2001] and is based on the time-variant transfer matrix of the process.

$$\gamma_{ij}{}^2(f,n) = \frac{\left|\mathbf{H}_{ij}(f,n)\right|^2}{\sum_{k=1}^{K}\left|\mathbf{H}_{ik}(f,n)\right|^2} \tag{4}$$

where $\gamma_{ij}^{2}(f,n)$ is the normalized ADTF, $\mathbf{H}(f,n)$ is the time dependent transfer matrix of the TVAR process and K is the number of signals.

The normalized ADTF represents the fraction of information flow from signal j to signal i with respect to the total incoming flow to signal i and it detects direct and indirect directional connections over time. The values of the normalized ADTF are in the interval [0, 1].

3. Material and Method

3.1. Dataset

We consider a dataset recorded during the pre-surgical evaluation of a patient with refractory epilepsy. The dataset contains 26 intracranial electrodes displaying 4 regions of interest. The patient had an amygdalo-occipital depth-electrode with 12 contact points implanted in the left hippocampus (LH1- LH12), two subdural strips (electrodes fixated on a plastic patch), with 4 contact points each, on the left temporal-basal area (anterior: LTA1-LTA4 and posterior: LTM1-LTM4) and a subdural strip with 6 contact points was placed on the left temporal-lateral area (LTP1-LTP6). The intracranial signals during a subclinical seizure are depicted in Fig. 1. The patient underwent a selective amygdalo-hippocampectomy and has been seizure free since then.
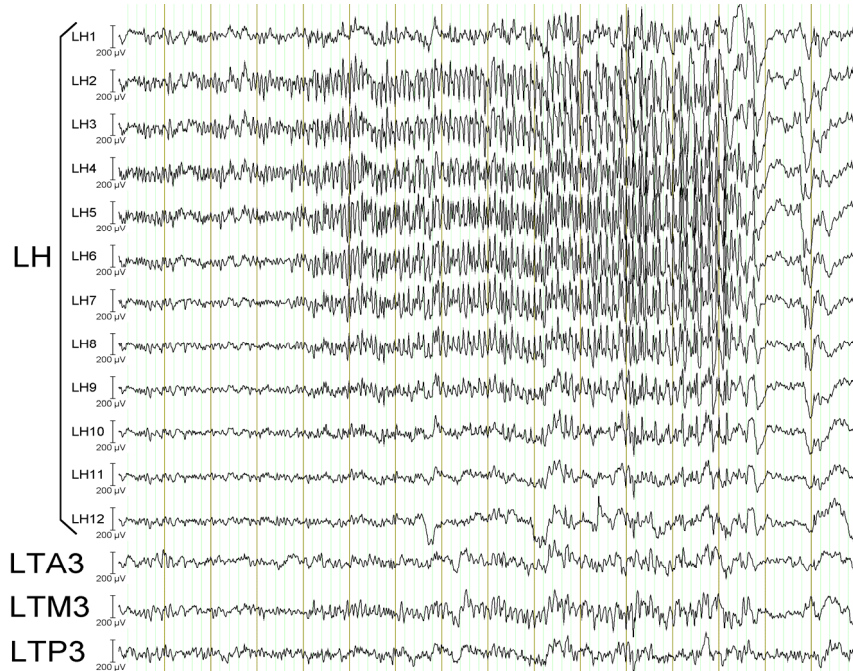
Figure 1. The intracranial signalslduring the subclinical seizures: LH: depth electrode in left hippocampus, LTA: left temporal-basal area anterior, LTM: left temporal-basal area posterior, LTP: left temporal-lateral area.

3.2. Method

We considered an EEG epoch of approximately 16 seconds, sampled at 256Hz. The data is preprocessed using Analyzer2 ® (Brain Products, Munich, Germany). The signals were band-pass filtered (0.5–30Hz) and normalized. The normalization of the data is necessary because false detection of influences can be caused by differences in variance between the signals, leading to spurious, directed influences from the process with low variance to the processes with significantly higher variances [Winterhalder et al., 2005]. For each electrode the spectrogram was calculated (Hamming window of 512 samples).

A TVAR model using the Kalman Filtering algorithm was fitted to the 26 signals. The model order was determined through simulations on an EEG fragment of 1 second by minimizing the residual energy. A model order of 10 was found and kept constant over time. The coefficients of the TVAR were used to compute the ADTF between 0.5Hz and 30Hz. At each time point we weighted the ADTF with the power spectral density (PSD) of the signal j, normalized with respect to maximum energy

across channels over the considered time window. An empirical minimal threshold is applied to the ADTF of 0.1 before weighting to remove spurious connections.

4. Results

Figure 2 shows the spectrogram of one channel from each group of electrodes. We found similar spectrograms for the electrodes belonging to the same group. The fundamental frequency of the epileptic activity, and its harmonics, are clearly visible in LH (Fig.2a) and LTM (Fig.2c), decreasing from 13Hz to 6Hz. The fundamental frequency of the seizure appears also in the PSD of LTA3 (Fig.2b) but not in PSD of LTP (Fig.2d).
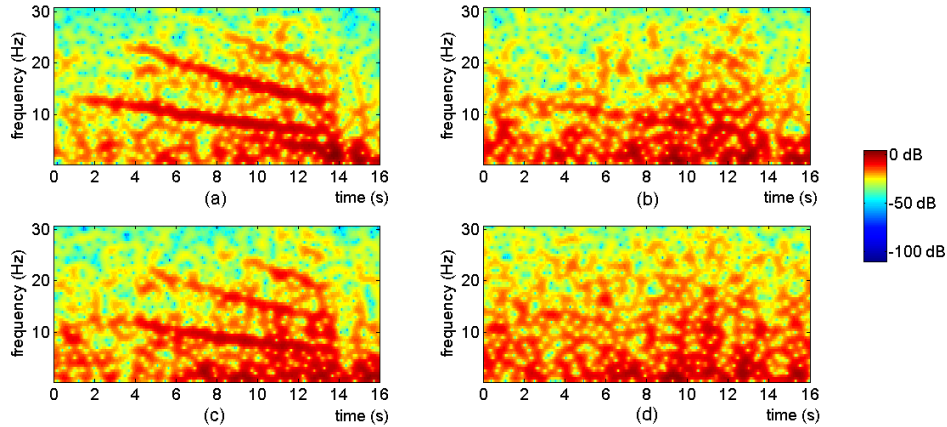
Figure 2. *The Power Spectral Density (PSD) of the intracranial EEG signals in dB. (a) PSD of LH2; (b) PSD of LTA3; (c) PSD of LTM3 and (d) PSD of LTP3.*

Figure 3 shows the results of the weighted-ADTF analysis of the intracranial EEG channels during the subclinical seizure. When considering the 4 groups of electrodes (LH, LTA, LTM, LTP) we found a flow of information from LH to LTM and with lower magnitude to LTA and LTP (Fig.3a). When considering only the leading group of electrode (LH) the most important flows arise from LH4, LH5 and LH6 to the other electrodes. The information flow spreads from LH4 and LH5 symmetrically to the other contact points with a magnitude that decreases according to the increase in distance from the focus LH4-LH5 (Fig.3b).

5. Discussion and conclusions

In this work we used an energy weighted ADTF to identify the connectivity pattern of intracranial EEG signals. This weighting highlights the connectivity at prominent signal frequencies. The normalization of the PSD may be a drawback when high energy artifacts are present in the signals. However intracranial EEG is less affected by artifacts making the weighting more robust.

The results obtained by our method are concordant with post-surgical finding. The group of electrodes leading the epileptic activity can easily be identified through the inspection of the weighted-ADTF and coincides with the surgical removed area. Moreover, the high number of contact point allows us to identify a smaller leading area. Therefore the weighted-ADTF may add information during the pre-surgical evaluation of a patient.

We proved the feasibility of investigating the propagation pattern through weighted-ADTF during a subclinical seizure and the benefit of incorporating a priori information about the frequency content of the data.
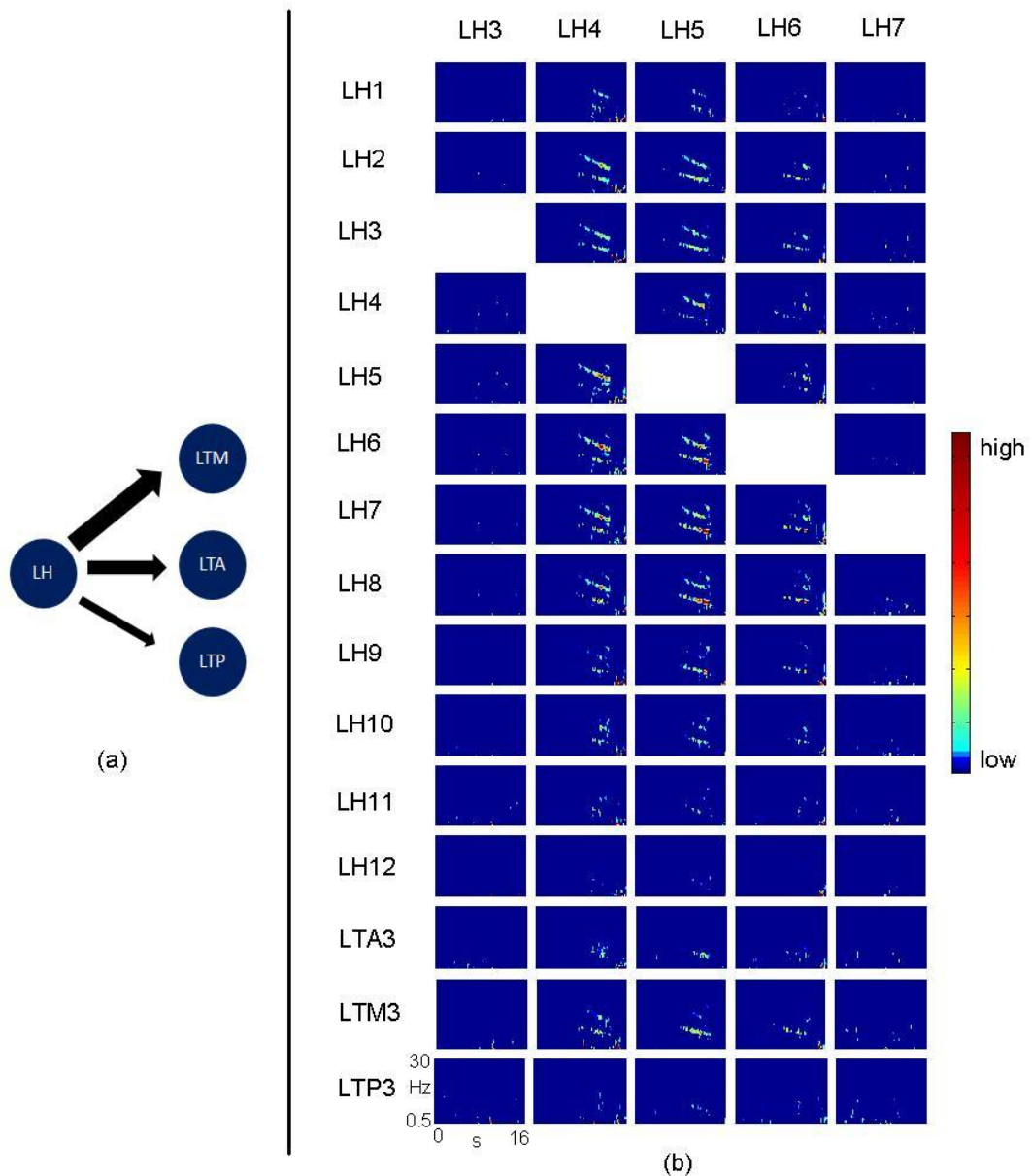
Figure 3. *Connectivity pattern of the intracranial EEG signals. (a) Propagation pattern during the subclinical seizure. The size of the arrows is proportional to the amount of information flow. (b) Weighted DTF value showing the information flow from LH3-LH7 to LH1-LH12, LTA3, LTM3 and LTP3 from 0.5 to 30Hz over 16s subclinical seizure. The color depicts the amount of information flow.*

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