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Identification of the epileptogenic zone of temporal lobe epilepsy from stereo-electroencephalography signals: A phase transfer entropy and graph theory approach

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ABSTRACT

The aim of this research is to apply an approach based on phase transfer entropy (PTE) and graph theory to study the interactions between the stereo-electroencephalography (SEEG) activities recorded in multilobar origin, in order to evaluate their ability to detect the epileptogenic zone (EZ) of temporal lobe epilepsies (TLE). Forty-three patients were included in this retrospective study. Five to sixteen (median = 12) multilead electrodes were implanted per patient, and, for each patient, a sub-set of between 10 and 32 (median = 22) bipolar derivations was selected for analysis. The leads were classified into the onset leads (OLs), the early propagation leads (EPLs), and the rest of the leads (RLs). The results showed that a significantly different dynamic trend of the out/in ratio (more obvious in the gamma band) distinguishes the OLs from RLs in the 23 patients who were seizure-free not only during the ictal event (significant elevation), but also during the inter-,pre-, late-ictal periods, and especially in the post-ictal (sharp decline) state. However, in the 20 patients who were not-seizure-free, the differences between the OLs and RLs during the post-ictal period were not found in any frequency band. The dynamic trend was used to predict surgical outcome, and the results showed that the sensitivity was 91% and the specificity was 70%. In brief, this study indicates that our approach may add new and valuable information, providing efficient quantitative measures useful for localizing the EZ.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common type of pharmacoresistant epilepsy in adults, and it is frequently successfully treated by surgery, although long-term relapses in up to 58% of cases suggest insufficient network disruption (Coito et al., 2015). Although it primarily affects the temporal lobes, TLE is thought to be a network disease with widespread extratemporal effects. One or both hippocampi are commonly involved in TLE, and this is often visible as hippocampal sclerosis on structural MRI. Hippocampal involvement can also occur in TLE without hippocampal sclerosis in neocortical TLE, in temporal 'plus' epilepsies, and even in extra-temporal epilepsies (Barba et al., 2007; Haneef et al., 2014).

In most TLE with hippocampal sclerosis, the extent of the surgical resection can be defined by noninvasive presurgical investigation (Gnatkovsky et al., 2014). Nonetheless, the identification of epileptogenic zone (EZ) boundaries in patients with equivocal TLE and in imaging negative cases requires invasive recordings. However, stereo-electroencephalography (SEEG) registers electrical activity from a very confined region, and this may lead to false localization of the ictal onset zone. This is likely if there is no clear distinction among ictal onset patterns corresponding either to the ictal onset zone proper or to areas of ictal spread (Singh et al., 2015).

The EZ represents the minimum amount of cortex that must be resected (inactivated or completely disconnected) to achieve seizure freedom (Panzica et al., 2013). The non-negligible rate of failure in epilepsy surgery brings evidence that the question of the definition of the EZ is still unsolved and that progress must still be made to determine the epileptogenicity of the brain regions in a patient-specific context (Bartolomei et al., 2008).

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The visual inspection of SEEG signals does not allow full advantage to be taken of the intrinsic properties of the epileptogenic network, so more sophisticated diagnostic methods are required (Varotto et al., 2012). Phase transfer entropy (PTE) is a novel, information theory–-based measure of directed connectivity. It exhibits many characteristics that make it especially suitable for connectomics analysis of electroencephalography (EEG) data (Lobier et al., 2014; Dauwan et al., 2016).

However, regardless of the method used to evaluate connectivity, such an approach may not be sufficient to grasp the full complexity of the brain as a network (Varotto et al., 2012). Graph theory (Boccaletti et al., 2006) is currently widely used to analyze the structure and evolution of complex networks in a quantitative manner (Varotto et al., 2012; Stam, 2014). In recent years, some efforts have been made to develop the approach based on graph theory for improving the identification of the EZ, since the study of the topological properties of the networks has strongly improved the study of brain connectivity mechanisms (Panzica et al., 2013). However, these are still qualitative studies (Varotto et al., 2012; Wilke et al., 2010; Van Mierlo et al., 2013; Antony et al., 2013).

In this study, we apply a quantitative approach based on PTE and graph theory to study the dynamics of the interactions between the SEEG activities recorded in the multilobar origins, which are characterized by the involvement of a complex epileptogenic network of a group of patients with TLEs, to evaluate their ability to detect the EZ. Our primary hypothesis is that the electrical net outflow of epileptogenic zone in gamma band changes dynamically from the inter-, pre-, early- and late-ictal periods to the post-ictal period, especially rise in the early-ictal section and decline in the post-ictal section. Our minor hypothesis is that the above-mentioned regularity should be tenable regardless the types of TLEs and the types of SEEG onset patterns, but the details may be different.

2. Material and methods

The study was approved by the ethics committee of Sanbo Brain Hospital, Capital Medical University, where it was carried out from May 2015 to December 2016. Informed consent was obtained from the patients or legal guardians.

2.1. Patients

Subjects for this retrospective study included patients with drug-resistant focal seizures of suspected temporal lobe origin at the Sanbo Brain Hospital in Beijing between January 2012 and January 2016, and who were candidates for epilepsy surgery but required diagnostic depth electrode studies because results from non-invasive tests were inconclusive.

All patients had a comprehensive evaluation, including detailed history and neurological examination, neuropsychological testing, routine magnetic resonance imaging (MRI), surface EEG, seizure semiolgoy and SEEG. Patients were selected for the present study if they satisfied the following criteria: (i) absence of any detectable lesion at mesial temporal lobe on MRI, with the exception of hippocampal sclerosis; (ii) no history of epilepsy surgery; (iii) SEEG recordings showing that seizures involved at least mesial and/or neocortical temporal lobe structures; (iv) surgery performed according to SEEG results, taking into account anatomical constraints; and (v) at least 1 year of postoperative follow-up. According to the criteria, 43 patients with drug-resistant TLE were selected from a series of 180 cases. Five to sixteen (median = 12) multilead electrodes were implanted per patient in temporal and extratemporal areas, depending on the suspected origin and region of early spreading of seizures.

The population consisted of 24 males and 19 females, aged 12.2–39.4 years (see the clinical findings in Table 1). Epilepsy-onset age ranged from 1 to 31 years. Eight patients (29%, 8/28) with mesial TLE and one patient (7%, 1/15) with neocortical TLE had experienced febrile convulsions in childhood. Four patients (14%, 4/28) with mesial TLE and eight patients (53%, 8/15) with neocortical TLE had normal MRI scans.

Hippocampal sclerosis was identified radio-graphically and later confirmed pathologically in 17 cases with mesial TLE without early extratemporal propagation (74%, 17/23), 0 case in the patients with the other types of TLEs. One case with mesial TLE and one case with neocortical TLE showed hippocampal sclerosis on MRI, but this could not be confirmed pathologically. One case showed pathological hippocampal sclerosis, which was not identified radio-graphically. Different types of anatomical lesions were found in 24 cases, including 1 ganglioglioma, 2 type IIb focal cortical dysplasias (FCD), 3 type IIa FCDs, 10 type Ib FCDs, 2 type Ia FCDs, and 6 other lesions.

The seizure-onset zone (SOZ) was defined as the depth electrode contacts showing the first unequivocal ictal intracranial EEG change. Seizure early propagation was defined as a clear seizure discharge, starting 0.5–5 s after seizure onset and recorded outside the SOZ (Perucca et al., 2014). There were 20 patients who had early propagation on SEEG after seizure onset. Four ictal onset patterns were identified across the 43 seizures: low-voltage fast activities (12 cases, 28%); low-frequency high-amplitude periodic spikes (11 cases, 26%); spike or polyspike fast discharges (15 cases, 33%); and spike- or sharp-and-wave rhythmic activities (5 cases, 12%).

In the 25 patients with mesial TLE, surgery consisted of a tailored resection, including at least the temporal pole and mesio-temporal lobe structures (amygdala, hippocampus, and para-hippocampal gyrus). The posterior limits of the temporal neocortical resection varied according to SEEG results. A selective amygdalo-hippocampectomy was performed in the other three patients (No. 1, 21 and 24) with mesial TLE, and two (No. 21 and 24) patients with mesial TLE with early extratemporal propagation were operated on twice, since seizures recurred rapidly. In the 15 patients with neocortical TLE, individualized surgical planning was performed according to SEEG and imaging results, and one (No. 37) of the patients with neocortical TLE with early extratemporal propagation underwent two episodes of electrode implantation and two operations.

Postoperative seizure status, according to Engel's classification (Engel, 1993), showed that 20 mesial TLE patients without early extratemporal propagation were in class I (87%, 20/23), whereas only 1 mesial TLE patient with early extratemporal propagation was in class I (20%, 1/5); 5 neocortical TLE patients without early extratemporal propagation were in class I (63%, 5/8), whereas 3 neocortical patient with early extratemporal propagation was in class I (43%, 3/7); and 10 patients with low-frequency high-amplitude periodic spikes (91%) and 13 (80%) with spike or polyspike fast discharges were in class I, whereas only 5 with low-voltage fast activities (50%) and 1 with spike- or sharp-and-wave rhythmic activities (20%) were in class I.

2.2. SEEG recordings

The SEEG exploration was performed using intracerebral multiple-contact electrodes (Huake-Hengsheng Medical Technology, China; 8–16 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracranially with the aid of a stereotactic ROSA robotic device (Medtech). The SEEGs were recorded using a common reference electrode (Nicolet™ system; 128-channels; sampling rate: 512 Hz). The SEEG recording was carried out during long-term video-EEG monitoring to record several of the patient's habitual seizures, following complete or partial withdrawal of antiepileptic drugs. We used bipolar derivation to avoid possible contamination deriving either from a not completely inactive common reference or from interference due to a volume conduction effect.

A patient management conference was then held for each individual, after enough seizures were recorded (at least three to five seizures), to discuss the results and implications of the SEEG study and to decide collectively on a plan for resection. Subsequent to this