Clinical Neurophysiology 127 (2016) 2992–2999

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

The role of sub-hippocampal versus hippocampal regions in bitemporal lobe epilepsies

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ARTICLE INFO

Article history:
Accepted 21 June 2016
Available online 1 July 2016

Keywords:
Entorhinal cortex
Bilateral temporal epilepsy
SEEG
Surgery
Epileptogenicity Index

HIGHLIGHTS

- Epileptogenicity distribution of bilateral versus unilateral TLE was evaluated with SEEG.
- Unilateral TLE patients displayed epileptogenicity mostly in hippocampal structures.
- Bilateral TLE patients displayed epileptogenicity mostly in subhippocampal regions.

ABSTRACT

Objective: We aimed at better delineating the functional anatomical organization of bitemporal lobe epilepsy.
Methods: We studied the epileptogenic zone (EZ) by quantifying the epileptogenicity of brain structures explored by depth electrodes in patients investigated by stereoelectroencephalography (SEEG). We compared 15 patients with bilateral mesial temporal lobe epilepsy (BTLE) and 15 patients with unilateral mesial temporal lobe epilepsy (UTLE). This quantification was performed using the 'Epileptogenicity Index' (EI).
Results: Age at epilepsy onset, and epilepsy duration, were not statistically different in both groups. UTLE patients more frequently displayed maximal epileptogenicity in hippocampal structures, whereas BTLE patients had maximal values in subhippocampal areas (entorhinal cortex, temporal pole, parahippocampal cortex).
Conclusions: Our results suggest different organization of the EZ in the two groups.
Significance: BTLE was associated with more involvement of subhippocampal regions, a result in agreement with known anatomical connections between the two temporal lobes.

1. Introduction

Bitemporal lobe epilepsies (BTLE) are characterized by seizures arising independently or starting simultaneously from the two temporal lobes (So et al., 1989) and are a major source of concern in the context of epilepsy surgery. The suspicion of BTLE is a usual indication for depth electrode exploration in temporal lobe epilepsy (TLE) (Diehl and Luders, 2000). Previous studies have shown that BTLE may account for ~20% of TLE patients explored by depth EEG (Hirsch et al., 1991). Anterior temporal lobectomy is often proposed when a majority of seizures arise from one side (So et al., 1989; Hirsch et al., 1991) but cognitive risks are significant and

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http://dx.doi.org/10.1016/j.clinph.2016.06.021
1388-2457/

outcome is generally less favorable. Factors contributing to bilaterality in TLEs are unclear. No specific etiological factors have been significantly correlated to BTLE (So et al., 1989; Hirsch et al., 1991; Lim et al., 1991; Sirven et al., 1997). From experimental models of mirror foci, it has been suggested that bilaterality could be due to a secondary epileptogenesis process (Morrell, 1991). However, somewhat against this hypothesis is the observation that bilaterality has not been clearly correlated with epilepsy duration or age at onset (Steinhoff et al., 1995).

In the present work we aimed at studying the functional anatomy of the epileptogenic zone (EZ) in patients undergoing bilateral SEEG exploration for mesial TLE. We particularly wished to establish whether the anatomo-functional structure of the EZ is different in patients presenting unilateral versus bilateral TLE. In particular, it has been suggested that some structural factors (notably hippocampal sclerosis) may influence bilaterality (Duckrow and Spencer, 1992). In addition, interhemispheric connectivity linking subhippocampal regions (rhinal cortices including entorhinal cortex, perirhinal cortex and parahippocampal cortex) appear to be stronger than connections between the two hippocampi in humans (Gloor, 1997; Adam, 2006). It is not known however if the pathophysiology of BTLE affects the subhippocampal regions more than the hippocampus.

To gain insight into this question, we analyzed data obtained in patients explored by SEEG and presenting either BTLE or unilateral TLE (UTLE). The epileptogenicity of mesio-temporal brain structures was estimated using the Epileptogenicity Index (EI), a method previously described to quantify the epileptogenic zone networks (Bartolomei et al., 2008, 2010).

2. Methods

2.1. Patient selection and SEEG recordings

Patients with either BTLE or UTLE explored by SEEG were selected for this study. BTLE were defined as patients whose habitual seizures were characterized by independent mesial temporal onset from each side (more than 20% of seizures) or bilateral onset (discharge affecting both mesial temporal structures with latency of less than one second). UTLE were defined as patients whose seizures started from a unilateral mesial temporal region during the SEEG video recordings. We retained for this study only patients having undergone bilateral exploration with at least one contralateral mesiotemporal electrode. Since BTLE is relatively less prevalent than UTLE, we collected data from 15 consecutive patients with BTLE recorded in four French epilepsy centers (Marseille, Lyon, Lille, Toulouse). These patients were compared with 15 UTLE patients investigated in the presurgical epilepsy unit at the Timone hospital in Marseille during the same period. These patients had strictly unilateral onset of temporal lobe seizures during SEEG recordings. After surgical procedures most of the patients with UTLE were seizures free (Table 1). In case of seizure relapse after surgery, residual seizures were recorded and were located in the same side, thus excluding an unsuspected BTLE revealed in these cases.

All patients had SEEG implantation including exploration of the hippocampal region (anterior hippocampus, aHip and/or posterior hippocampus, pHip), sub-hippocampal regions (entorhinal cortex, EC), posterior part of the para-hippocampal gyrus (pPHG), amygdala (Amy) and temporal pole (TP).

All patients had SEEG after a comprehensive evaluation including detailed history and neurological examination, routine brain MRI, video-EEG recordings. Most of them also had positron emission tomography (FDG-PET), ictal and/or interictal single-photon emission computed tomography (SPECT) imaging, and neuropsychological testing.

SEEG exploration was carried out during long-term video-EEG monitoring, as part of our patients' normal clinical care. Recordings were performed using intracerebral multiple contact electrodes (5–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracranially according to Talairach's stereotactic method (Bancaud et al., 1965; Guenot et al., 2001). The targeting of electrodes was established in each patient based upon available non-invasive information and hypotheses about the localization of the epileptogenic zone. Video-EEG recording was prolonged as long as necessary for the recording of several habitual seizures.

SEEG signals were sampled at 256 Hz or 512 and recorded on a hard disk using no digital filter. Habitual spontaneous seizures or seizures induced by low frequency (bipolar stimulation, 1 Hz, 2 ms pulse width, intensity range: 0.3–1.5 mA) electrical stimulation were analyzed. All available seizures (mean 5.2, range 2–11) were analyzed in the BTLE group (as seizure patterns greatly varied from one seizure to another), and a minimum of 2 seizures (mean: 3.13, range 2–7) analyzed in the UTLE group.

2.2. Signal analysis: definition and computation of the Epileptogenicity Index (EI)

Our study was based on the determination of the "Epileptogenicity Index" (EI). This quantification has been proposed in order to characterize the propensity of a given brain structure to generate a 'rapid discharge' (the high frequency oscillations observed during the transition between ictal and interictal activity) and takes into account the delay of appearance of this discharge with respect to seizure onset (Bartolomei et al., 2008, 2010, 2011) (for details see Supplementary material). The purpose of this index is to provide quantified information about the behavior of brain structures recorded from signals they generate during the seizure process. This index summarizes two pieces of information into a single quantity: (1) whether or not the recorded brain structure is involved in the generation of a high frequency discharge (beta and gamma range) and (2) when involved, whether or not this rapid discharge is delayed with respect to rapid discharges generated by other structures. A normalized value is used ranging from 0 to 1. If there is no involvement of the brain structure, the EI = 0 whereas if the brain structure generates a rapid discharge and the time to seizure onset is minimal, the EI = 1. An EI between 0 and 1 corresponds to secondary involvement of the brain structure concerned (for detailed methodology see (Bartolomei et al., 2008)).

In practice, we use a semi-automatic approach: using a handy graphical user interface, the user can easily inspect and validate automatically detected change points indicating the accurate onset of rapid discharges. From this validation performed on a "structure-by-structure" basis, the EI is then computed.

We determined the EI values from signals recorded in distinct structures (7 or 8 in each patient) including all mesial temporal regions available in our patients. A structure was considered as being highly epileptogenic when its EI value was $\geqslant 0.4$, according to previous reports (Bartolomei et al., 2010). Generally, the implantation strategy favored one side with a complete set of explored regions. We therefore quantified the EZ from the predominantly explored side.

The SEEG signals from the following regions were analyzed in each selected patient: anterior hippocampus (aHip), posterior hippocampus (pHip); entorhinal cortex (EC); internal part of the temporal pole (iTP); parahippocampal cortex (pPHG) and amygdala (A).

2.3. Statistical analysis

Statistical analysis was performed to assess potential links between the bilateral or unilateral nature of the related epilepsy and EZ location/organization, as well as several clinical and