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Looking for complexity in quantitative semiology of frontal and temporal lobe seizures using neuroethology and graph theory

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Epileptic syndromes and seizures are the expression of complex brain systems. Because no analysis of complexity has been applied to epileptic seizure semiology, our goal was to apply neuroethology and graph analysis to the study of the complexity of behavioral manifestations of epileptic seizures in human frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE). We analyzed the video recordings of 120 seizures of 18 patients with FLE and 28 seizures of 28 patients with TLE. All patients were seizure-free >1 year after surgery (Engel Class I). All patients' behavioral sequences were analyzed by means of a glossary containing all behaviors and analyzed for neuroethology (*Ethomatic* software). The same series were used for graph analysis (*CYTOSCAPE*®). Behaviors, displayed as nodes, were connected by edges to other nodes according to their temporal sequence of appearance. Using neuroethology analysis, we confirmed data in the literature such as in FLE: brief/frequent seizures, complex motor behaviors, head and eye version, unilateral/bilateral tonic posturing, speech arrest, vocalization, and rapid postictal recovery and in the case of TLE: presence of epigastric aura, lateralized dystonias, impairment of consciousness/speech during ictal and postictal periods, and development of secondary generalization.
Using graph analysis metrics of FLE and TLE confirmed data from flowcharts. However, because of the algorithms we used, they highlighted more powerfully the connectivity and complex associations among behaviors in a quite selective manner, depending on the origin of the seizures. The algorithms we used are commonly employed to track brain connectivity from EEG and MRI sources, which makes our study very promising for future studies of complexity in this field.

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1. Introduction

In patients with TLE, the most common form of focal epilepsy in adulthood, previous semiological studies of epileptic seizures using neuroethological tools have shown great potential to reveal localizing and lateralizing signals, such as the presence of epigastric aura, the lateralization value of dystonias, the impairment of consciousness and speech during ictal and postictal periods, and the development of secondary generalization [1,2]. The neuroethology–SPECT correlation in TLE was an effective tool to reliably evaluate ictal behavior and the functionally associated brain areas. However, our data did not confirm the association of ipsilateral basal ganglia hyperperfusion with contralateral dystonic posturing, as described in the literature. Nevertheless, we demonstrated that ipsilateral basal ganglia hyperperfusion is associated with contralateral upper limb automatisms and also with the lack of contralateral cephalic version [1].

The second most common form of focal epilepsy, frontal lobe epilepsy (FLE), represents approximately 20% of patients admitted to epilepsy surgery programs [3]. The diverse spectrum of ictal behavioral phenomenology of patients with frontal lobe seizures has received far less attention than that of those with temporal lobe seizures. The typical clinical manifestations includes contralateral clonic movements, unilateral or bilateral tonic motor activity, as well as complex automatisms [4]. In

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order to better define the localization and limits of the epileptogenic zone (EZ), various diagnostic tools such as semiological seizure analyses, electrophysiology, and neuroimaging are used [5]. Altogether, these important clinical, electroencephalographic (EEG), and neuroimaging data may help to define which cerebral circuit or network is responsible for the seizure generation while also evidencing its propagation and guiding potential surgical treatment and outcome.

Semiological analysis of clinical seizures has been well documented by many authors [6–13], and the highly heterogeneous behavioral repertoire suggests the activation of variable brain regions and the spreading of their activation to adjacent areas. Some of these studies (mostly about TLE) have intended to standardize the terminology [2,14,15] or to quantify human epileptic seizure behaviors [2,14–17]. A detailed analysis of the ictal semiology can often provide lateralizing or localizing signs that disclose valuable information about the location of the EZ and the pathways potentially involved in seizure propagation [18].

Methodologies based on the description of seizures by the percentages of signs and symptoms may be found in various reports [6,8,9,19]. Wieser [13] pioneered the use of cluster analysis to correlate groups of signs and symptoms and to verify the sequence of behaviors occurring during complex partial seizures in patients with TLE. Subsequently, Kotagal et al. [10,16] also applied cluster analysis to characterize temporal and frontal lobe epileptic seizures. Manford et al. [17] combined cluster analysis and flowchart representation to differentiate TLE from FLE and to correlate the topography of MRI lesion with ictal behaviors. An interesting aspect of the latter report was the seizure representation as flowcharts, with ictal behaviors displayed in a sequential way and the temporal progression of the seizures represented by arrows between behaviors. At some point, this is similar to what we have used already (see below) with seizure analysis in TLE [2].

Neuroethology is a combination of ethology – the comparative study of behavior – and neurophysiology or neurobiology — the study of central nervous system functioning. Neuroethological analysis, from flowcharts built based on frequency, duration, and interaction between behaviors, has been successfully applied and validated in animal models of epilepsy by Garcia-Cairasco and co-workers since 1983 [20–22]. Dal-Cól et al. [2] applied this neuroethological method to a highly selected group of patients with mesial temporal lobe epilepsy (mTLE) for the first time, revealing some localizing and lateralizing signs, such as the presence of epigastric aura, lateralization value of dystonias, and impairment of consciousness and speech during ictal and postictal periods. One advantage of this method is the possibility to analyze all behaviors developed by the patient during the entire seizure, whereas in other methods, the analysis is restricted to only one behavior or to a group of behaviors [8,10,23].

The neuroethological analysis applied to mTLE in humans [2] was further correlated with SPECT findings [1] to evaluate which cerebral areas were or were not recruited during seizures. Although the power of such neuroethological studies is high, we are far from characterizing behavioral sequences with measurements that are nonlinear quantifications of the complexity associated with the expression of epileptogenic brain circuits. This, in fact, has been applied with much more frequency to functional imaging/EEG connectivity [24,25]; however, there is no single study, as far as we know, proposing such evaluations to semiology data, even though this is the final common pathway of brain activity.

For that reason, more recently, we have been exploring the use of graph theory [24,25] as another neuroethological analysis method [26] because of the variety of available software, the huge amount of different measurements that can be calculated, and also the widespread applicability of these methods to neuroscience and brain pathologies (including the epilepsies) and their diagnostic tools [27].

Based on the previous findings of Dal-Cól and colleagues [2] and Bertti et al. [1], as well as on the widely described features of TLE and FLE seizures, the main objectives of the present study were to apply and to validate neuroethological methods, flowchart and graph representation of the analysis of preictal, ictal, and postictal signs and symptoms of patients with FLE compared with those with TLE.

2. Methods

2.1. Patients

We retrospectively studied a group of patients successfully operated on (Engel Class I; [28]), with previous pharmacoresistant FLE (120 seizures) or TLE (28 seizures). Subjects underwent presurgical evaluation and surgery between 1997 and 2006 at the Epilepsy Surgery Center of the Ribeirão Preto School of Medicine (CIREP/FMRP), University of São Paulo, Brazil. All patients signed an informed consent form, allowing the use of images for research purposes, following recommendations and approval of the Ethics Commission of the Institution (protocol 13528/2010 and 782/1998).

The presurgical workup included high-resolution MRI acquired from a 1.5-T Siemens Magneton Vision (Erlangen, Germany) machine; long-term video-EEG monitoring; ictal and interictal SPECT; and neurological, psychiatric, neuropsychological, and socioeconomic evaluations. During video-EEG, medication was either tapered or discontinued. Patients with FLE were selected according to the following criteria: (1) medical history and seizure semiology consistent with FLE, diagnosed by the presurgical workup, (2) presurgical seizures acquired during the video-EEG monitoring at our institution, and (3) more than 6 years of age. Patients with TLE were selected according to the following criteria: (1) medical history and seizure semiology consistent with mTLE, (2) unilateral interictal epileptiform discharges over the anterior and mesial temporal regions, (3) presence of hippocampal sclerosis and no other lesion on MRI, and (4) ictal and interictal SPECT scans. Patients with abnormal neurological and neuropsychological examinations suggesting other brain diseases were excluded. For more details, see [1].

2.2. Video recording and analysis

Video-EEG recordings were performed on a digital EEG system (*Vangard System, version 9.1, Cleveland Clinic Foundation*) through scalp electrodes placed according to the International 10–20 System of Electrode Placement and through additional frontal intermediate electrodes of the International 10–10 System. *Hewlett-Packard workstations* (*Model 715/64*) were used for EEG data acquisition and analysis. Video images were obtained through *Panasonic WV-GL704* video cameras and recorded on a *Super-VHS Panasonic AG5700* videocassette player. Video editions were performed on a *Super-VHS Panasonic AGA96* videocassette player. All videos were captured and digitalized through a video card *Pinnacle DC10plus®*, *Studio 8®* software, and observed in an *Intel® Core™ i5* computer using *Virtualdub* 1.4d or *Windows Media Player*.

Only the videotaped seizures with clear image and sound were evaluated and submitted to neuroethological analysis. Behaviors were identified according to a previous TLE semiological dictionary [2]. New behaviors presented by patients with FLE were added to this dictionary (see Supplementary Table 1 with glossary). Seizure onset and termination were defined based on semiological data obtained during seizure analysis. Electroencephalography time marks were considered only when the clinical seizure onset or seizure termination was not clear by semiology. Clinical seizure onset was defined as the time when the patient indicated the occurrence of an aura by pushing the seizure alarm button (or attempting to do so) or when the first unequivocal behavioral change was observed. Clinical seizure termination was defined as the relaxation phase immediately after a secondarily generalized seizure or the recovery of consciousness or ending of tonic or dystonic postures for partial seizures.

Each seizure was observed as many times as necessary, including frame-by-frame analysis. Behaviors were mutually exclusive, i.e., each moment corresponded to only one behavior. All seizures were analyzed

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