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A systematic study of stereotypy in epileptic seizures versus psychogenic seizure-like events

Alberto Vogrig [1], Jen Chun Hsiang [1], Jacqueline Ng, Joshua Rolnick, Jessica Cheng, Josef Parvizi *

Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA

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ABSTRACT

Objective: The objective of this study was to quantify the features of stereotypy in epileptic seizures and compare it with that of stereotypy in psychogenic nonepileptic seizure-like events (PNES) confirmed by video-electroencephalography (VEEG) monitoring.
Methods: Video-electroencephalography monitoring records of 20 patients with temporal lobe seizures (TLS) and 20 with PNES were retrospectively reviewed (n = 138 seizures, 48 TLS and 90 PNES). We analyzed the semiology of 59 behaviors of interest for their presence, duration, sequence, and continuity using quantified measures that were entered into statistical analysis.
Results: We identified *discontinuity* as the parameter that was clearly distinct between PNES and epileptic TLS events: there were significantly more frequent pauses of behavior (i.e., "on–off" pattern) in PNES compared with TLS ($P = 0.012$). The frequency of pauses during an event was diagnostic of PNES events. For instance, the presence of 2 "pauses" during an episode determines a 69% probability of the seizure being nonepileptic. Moreover, PNES events had significantly greater duration (143 s) than TLS events (68 s) (excluding outliers, $P = 0.002$) and greater duration variability from one event to another in the same subject ($P = 0.005$).
Significance: Our work provides the first quantified measure of behavioral semiology during epileptic and nonepileptic seizures and offers novel behavioral measures to differentiate them from each other.

1. Introduction

Psychogenic nonepileptic seizure-like events (PNES) are paroxysmal clinical phenomena that resemble epileptic seizures (ES), but have a different etiology. The differential diagnosis between these two conditions is, at the same time, challenging and imperative: both share several clinical features in common; scalp electroencephalography (EEG) can be either normal in patients with epilepsy or abnormal in patients with PNES; and no single observation allows a high degree of certainty for differentiating between the two conditions [1–3]. A further complication is that patients with PNES may also manifest ES at a nonnegligible rate (10%) [4,5]. Given the huge medical and social costs of epilepsy misdiagnosis [6], further clinical and video-EEG (VEEG) diagnostic criteria are needed.

For decades, it has been clear to most neurologists that epileptic events are stereotype, i.e., certain ictal behaviors occur reliably and in a similar order during the patient's seizures. For instance, a patient with temporal lobe seizures (TLS) is often witnessed to start seizures with rising nausea which proceeds with staring and lip smacking [7]. By comparison, nonepileptic events are commonly thought to share a more variable course and a wider phenotypic spectrum [8]. Contrary to this common belief, some have observed that PNES behaviors can also be highly stereotypical and that the feature of stereotypy is not a reliable factor to distinguish epileptic and PNES events from each other [9,10]. However, the lack of a uniform and comprehensive definition of the concept of stereotypy, along with the paucity of quantified and systematic analysis of ictal stereotypy, has been major drawbacks in this context.

The current study was designed to provide a systematic analysis of ictal stereotypy in TLS and PNES using data captured during inpatient VEEG monitoring. By doing so, we aimed to provide clarity in the controversy about the presence or lack of stereotypy in PNES as a distinguishing feature of epileptic from nonepileptic seizures.

2. Material and methods

2.1. Patients

The study analyzed retrospectively a consecutive series of 20 patients with PNES admitted to the Stanford Medical Center (Stanford University, California, USA), a level IV Epilepsy Center, between 2008 and 2010. For each patient with PNES, a control was recruited by selecting from the list of consecutive patients with TLE (same time period), when the following criteria were matched: sex and age (±5 years). This type of recruitment was maintained until matching of the two groups was achieved.

* Corresponding author at: Department of Neurology and Neurological Sciences, Stanford University, 300 Pasteur Drive, Stanford, CA, USA.
E-mail address: jparvizi@stanford.edu (J. Parvizi).
[1] These authors contributed equally to this work.

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The diagnosis of PNES was made by a panel of expert epileptologists and psychiatrists after comprehensive review of the patient's video and EEG recordings. The following criteria, based on previous expert consensus [10,11], were used to diagnose PNES: (1) at least one single typical clinical event captured on VEEG, (2) EEG did not show any concomitant ictal activity or postictal slowing, (3) no evidence of any alternative neurological diagnosis, and (4) neuropsychiatric evaluation of the patient and their review of ictal events confirmed the diagnosis of PNES. The diagnosis of epilepsy was performed according to the International League Against Epilepsy (ILAE) definition and classification [12]. Episodes with or without preservation of consciousness were included. Patients with mixed disorders (co-occurrence of epileptic and nonepileptic seizures in the same patients) were excluded from the analysis. The rationale for choosing patients with TLE was threefold: 1) ictal origin and propagation in TLS is well-established [7]; 2) TLS involve a complex set of behaviors, ranging from motionless staring to semipurposeful motor activity and psychic phenomena, that can be easily mistaken for psychogenic events on clinical grounds [2]; and 3) deep TLS, like frontal lobe seizures, do not always generate an ictal epileptiform pattern [13], thus requiring clinical criteria to perform a correct diagnosis. Relevant medical records were noted and reviewed for demographic information. The present study was approved by the Stanford Hospital Institutional Review Board.

2.2. Behavioral coding

Before the beginning of the study, we compiled a list of 59 ictal behaviors in 3 major areas (motor, language, and autonomic disturbances) that would most likely be present in any seizure episode. The list was reviewed by all evaluators to ensure that there would be consistency in coding. All videos were viewed frame by frame from start to finish allowing the evaluator to note all the behaviors (Fig. 1) that would be coded. Evaluators recorded the type of behavior, time of onset and duration of each behavior, and the length of the entire ictal event. In both ES and PNES cases, the onset of ictal episode was defined on the video-EEG files by clinicians caring for the patients.

2.3. Data analysis

To evaluate the degree of stereotypy, data were analyzed in four axes: duration, sequence, type, and continuity of ictal behaviors (Fig. 2). The four aspects of stereotypy represented behavioral elements that could be objectively measured. ***Duration*** of a behavior was measured by recording the start and stop of a given behavior (listed in Fig. 1). ***Sequence*** referred to the measure of consistency which was measured by observing the order by which each behavior manifested itself in temporal relationship to the others. ***Type*** of clinical behavior was quantified as "typical" if it was present in more than 50% of the seizures in a given patient. The proportion of typical versus unique behaviors was measured for all the patients who had at least 2 recorded seizures. ***Continuity*** of an ictal event was quantified as the inverse measure of the density of behavioral "pauses" during a seizure.

2.3.1. Consistency of sequential pattern

Fig. 3 graphically presents the concept of consistency of sequential pattern (CSP). In order to measure the order of appearance of specific behavioral features, we measured CSP, which was defined as:

$$\mathrm{CSP} = C_{pc}/N_{pc}$$

C_{pc}: mean consistency value in each paired category
N_{pc}: number of different paired categories

Every semiologic category was matched with each one of the others in order to observe if their appearance follows a particular order or occur randomly.

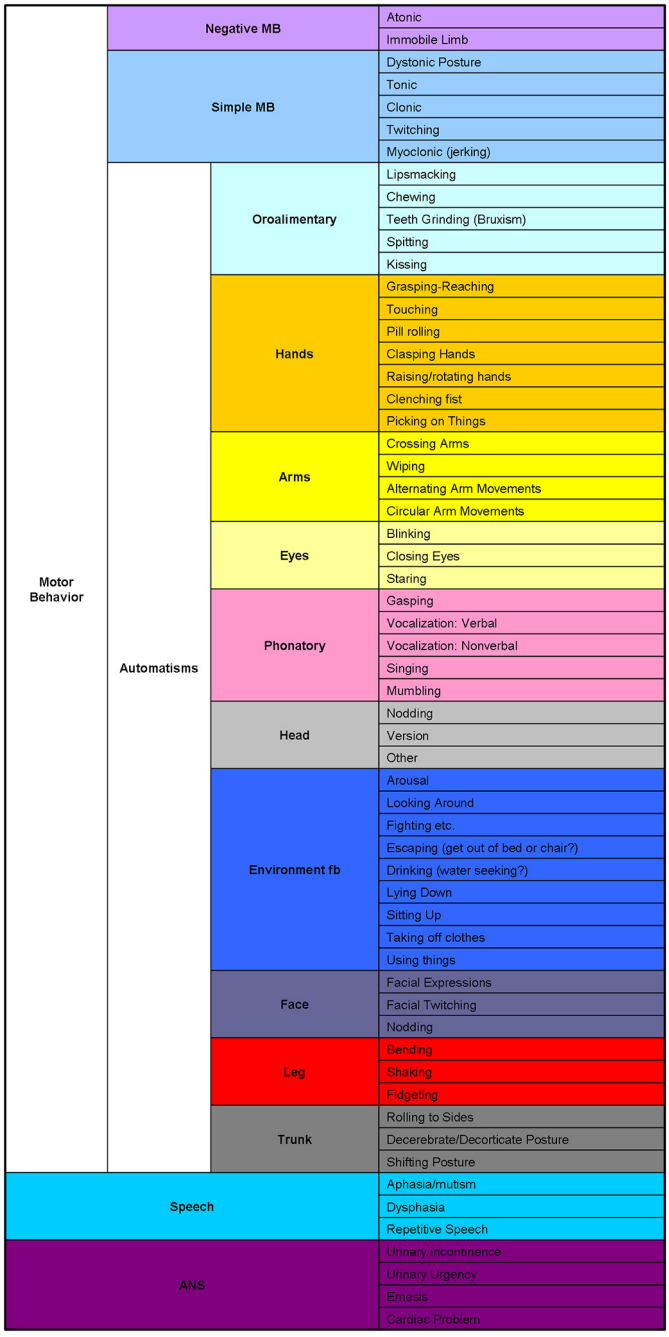

Fig. 1. Set of 59 ictal behaviors in 3 major areas (motor, language, and autonomic disturbances) that would most likely be present in any seizure episode. The list was designed a priori in order to code the patients' seizures.

Since the number of seizures could be small, the result was adjusted by Laplace's rule of succession.

$$C_{pc} = \frac{|(2 \times N_{A\to B}) - N_{A\leftrightarrow B}|}{N_{AB}}$$

$N_{A\to B}$ is the number of paired categories in one particular order. $N_{A\leftrightarrow B}$ is the number of paired categories in both orders (A→B and B→A). N_{AB} is $N_{A\leftrightarrow B}$ plus the number of pairs in which A and B appear at the same time.

To the matter of this analysis, only pairs that appear in more than one seizure were taken into account.

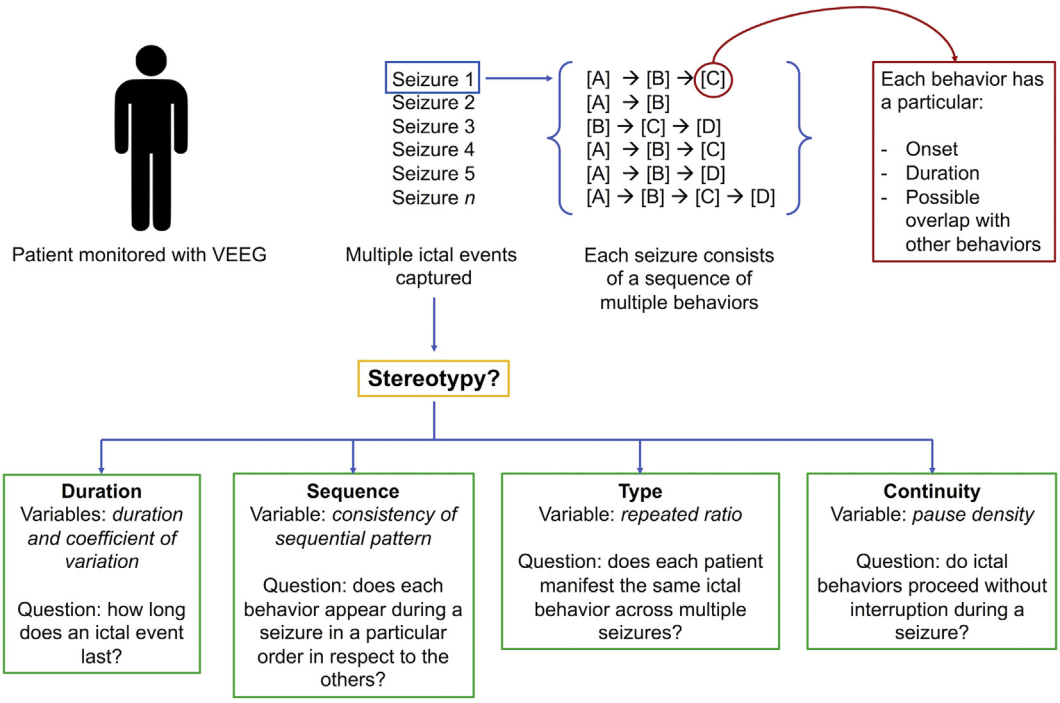

Fig. 2. Schematic presentation of the study design.

2.3.2. Repeated ratio

To evaluate the semiologic variability of ictal behaviors across seizures in each patient, the repeated ratio (RR) was measured:

$$RR = N_{freq}/N_{uniq}$$

N_{freq} indicates the number of behaviors that appears more than 50% of the time across all seizures in each patient. Since the number of seizures could be small, the result is adjusted by Laplace's rule of succession. N_{uniq} is the number of unique categories per patient. For this analysis, we excluded patients who only had a single seizure during the recording.

2.3.3. Overlapped density

In order to quantify the amount of time within a seizure during which multiple ictal behaviors appear at the same time, the "overlapped density" (OD) was measured:

$$OD = T_{over}/D$$

T_{over} is the time lag during which multiple behaviors manifest simultaneously in a seizure. D is the duration of the seizure.

2.3.4. Pause density

To quantify the continuity of each seizure, the "pause density" (PD) was measured. Pause was defined as the time lag within a seizure during which ictal behaviors ceased. Only intervals longer than 2 s were considered as pauses. A 5 and 10 s cutoff were also tested in order to avoid potential biases in the results.

$$PD = N_p/D$$

N_p is the number of pauses during each seizure. D is the duration of each seizure.

The density rather than N itself was used, because longer duration would probably allow more pauses to occur.

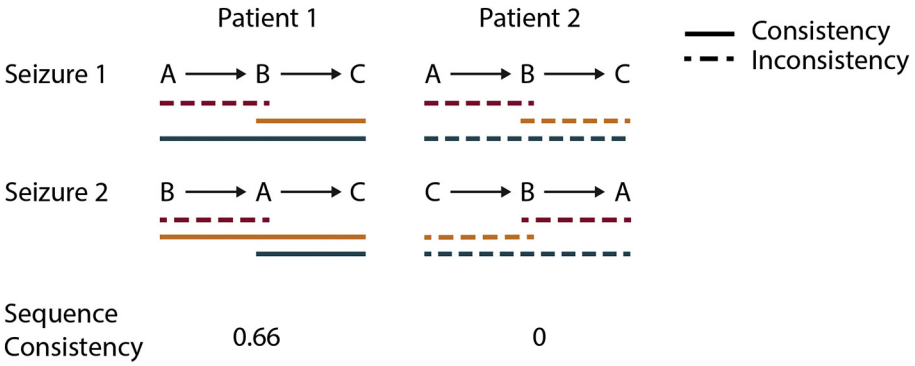

Fig. 3. Schematic representation of the concept of "sequence consistency" adopted in the present study (A, B, C: hypothetical ictal behaviors). Two seizures were measured for each hypothetical patient. Each of the red, orange, or green line indicates a pair of two ictal behaviors. Red is A and B. Green is A and C. Orange is B and C. If the order of the paired ictal behaviors between seizures is inconsistent, it is denoted as a dot line. Vice versa, if the order is the same, it is a solid line.

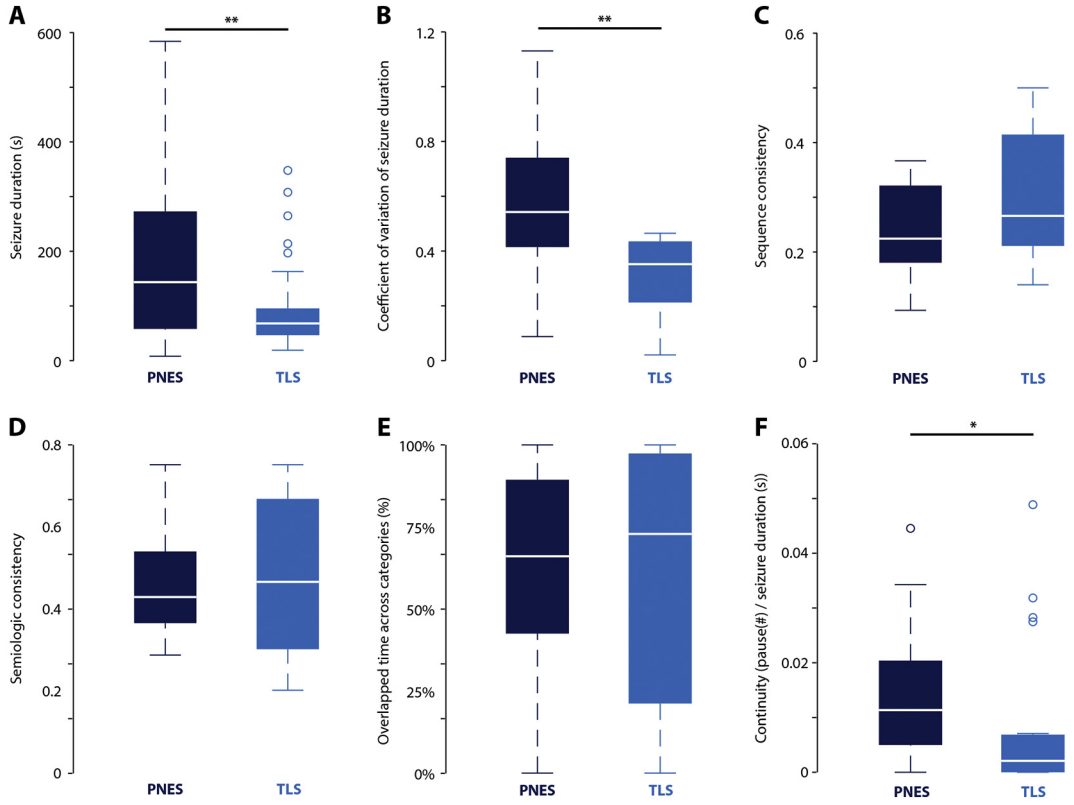

Fig. 4. (A) Seizure duration between the two groups. Median duration in PNES was 143.5 s while TLS lasted a median of 68 s ($P = 0.002$, adjusted $P = 0.012$ for the false discovery rate). (B) Duration variability in patients with TLS and PNES. Patients with PNES had a significantly higher coefficient of variation compared with patients with TLS ($P = 0.005$, adjusted $P = 0.015$). (C) Consistency in the sequence of ictal behaviors and (D) consistency in type of ictal behaviors (calculated by the "repeated ratio", RR) did not differ between the two groups ($P = 0.327$, adjusted $P = 0.491$ and $P = 0.665$, adjusted $P = 0.665$, respectively). (E) The time within a seizure during which multiple ictal behaviors occur (calculated by the "overlapped density") also did not differ between the two groups ($P = 0.617$, adjusted $P = 0.665$). (F) The density of "pauses" (time intervals within a seizure without ictal behaviors) was higher in PNES than in TLS ($P = 0.0121$, adjusted $P = 0.024$).

2.4. Statistical analysis

Statistical analysis was done by comparing the two groups (TLS and PNES events). First, the one-sample Kolmogorov–Smirnov test was used to check whether the dataset follows the normal distribution. If the normality of the distribution was respected, a two-sample *t*-test was subsequently applied. In the case the data samples of the two groups possessed different variances, Satterthwaite's approximation was applied to test the null hypothesis. If the data violated the assumption of normal distribution, Wilcoxon rank sum test, a nonparametric analysis, was applied to examine whether two samples are independent. None of the stereotypy parameters was found to follow the normal distribution. Thus, instead of showing the mean and standard deviation of each comparison, the median and quantile were used to illustrate the distribution of the data. MATLAB (MathWorks, USA) was used to process the combined data from Excel (Microsoft, USA) and to conduct statistical analysis. Since we conducted 6 metrics to compare between patients with TLE and PNES, to avoid the issue of multiple comparisons, we adjusted the *P* value of each comparison by false discovery rate following Benjamini & Yekutieli procedure [14].

3. Results

3.1. Demographic characteristics

The patients in the two groups were age- and gender-matched. The median age in the group with PNES was 31.5 years and 35.5 in the group with TLS ($P = 0.244$), and 80 and 70% of the patients were female in the group with PNES and TLS, respectively ($P = 0.465$).

3.2. Seizures number and type

A total of 138 seizures were recorded. Nine hundred thirty-eight behaviors in 22 behavioral categories were coded from 90 seizure events in the population with PNES and 426 behaviors in 17 behavioral categories from 48 seizure events in the population with TLS. Since the number of patients was equal in the two groups, the number of seizures per patient differed ($P = 0.004$). Patients with PNES had a median of 4 seizures during their hospital stay (interquantile range of 4.5) whereas patients with TLE had 1.5 seizures (interquantile range of 2). On average, each patient with PNES exhibited 5 unique behaviors over the course of all coded seizures while each patient with TLS exhibited 4.5 unique behaviors. The difference did not reach statistical significance ($P = 0.307$).

3.3. PNES have longer seizure duration and greater duration variability than TLS

Seizure duration between the two groups differed significantly. We observed longer events and more duration variability in the population with PNES. Median duration in PNES was 143.5 s (interquartile range of 215 s) while TLS lasted a median of 68 s (interquartile range of 49 s) (Fig. 4-A). The difference reached statistical significance ($P = 0.002$).

To answer the question of seizure duration consistency between TLS and PNES cases, we calculated the intrasubject variation in the duration of seizures for patients who had at least 2 observed seizures (in order to calculate the standard deviation and, afterwards, the coefficient of variation). Using this metric, each patient's mean event duration was used as a data point. Eighteen patients in the group with PNES and 10 patients

in the group with ES satisfied the abovementioned criteria. Accordingly, the mean event duration for patients with PNES who had at least 2 seizure events was 181.2 s compared with the TLS mean duration of 76 s. Patients with PNES had a significantly ($P = 0.005$) higher coefficient of variation of 0.54 compared with patients with TLS (0.35) (Fig. 4-B).

3.4. TLS did not show a significant difference in sequence consistency compared with PNES

Value of consistency (0: no consistency; 1: completely consistent) was calculated for the two groups. Epileptic seizures showed a value of 0.26 whereas PNES had a value of 0.22 ($P = 0.327$). This means that the consistency in the sequence in which every behavior appear with respect to each other was not significantly higher in patients with epilepsy (Fig. 4-C).

3.5. Consistency did not differ between populations with PNES and TLS

Consistency in the type of ictal behaviors (calculated by the RR previously defined) did not differ between the two groups ($P = 0.665$) (Fig. 4-D). The time within a seizure during which multiple ictal behaviors occur (calculated by the "overlapped density") also did not differ between the two groups ($P = 0.617$) (Fig. 4-E).

3.6. PNES events have more pauses

The density of "pauses" (defined as time lag during which ictal behaviors cease) was higher in PNES (median value: 0.011; interquantile range of 0.015) than in TLS (median value: 0.002; interquantile range of 0.007), and the difference was statistically significant ($P = 0.0121$). We provide a schematic representation of all the seizures in the two groups with their "free-spots" in Fig. 5 and the graph of the two distributions in Fig. 4-F.

Based on our data, the presence of 2 "pauses" during an episode determines a 69% probability of the seizure being nonepileptic and only a 30% probability of being epileptic.

4. Discussion

We provide a detailed analysis of ictal stereotypy in ES and PNES using a VEEG-based systematic and quantitative approach. By analyzing the duration, type, sequence, and continuity of the various behaviors that together constitute a seizure, we were able to assess the degree of ictal stereotypy within and across patients.

To date, several semiological features have been helpful in the differential diagnosis of PNES and TLS events. For instance, eye closure is common in PNES, while lateral tongue biting and incontinence are rarely encountered in nonepileptic seizures [1–3]. There is major agreement on many of these distinguishing semiological characteristics, except for the important issue of stereotypy. For decades, it was clear to most neurologists that ES is often stereotypic in nature, while it was thought that nonepileptic events share a more variable course and a wider phenotypic spectrum [8]. Contrary to common belief, recent studies demonstrated that the clinical manifestations of PNES could be highly stereotypic and that the feature of stereotypy is not reliable in differentiating the two categories [9,10]. This apparent inconsistency could be explained by the following: 1) a different definition of the concept of stereotypy adopted (most of the studies consider a seizure to be stereotypic if belonging to the same semiologic category across seizures [10,15]; factors such as type of onset/offset, duration, intensity fluctuation, type of behaviors, and semiologic variability were not considered); 2) the fact that multiple PNES classifications exist [10,15–21], each one with a different number and type of categories included (it appears logical to think that the greater the number of semiologic categories adopted, the less likely the probability for a seizure to belong to the same category across multiple episodes); 3) only a mild to moderate interrater reliability for classifying PNES was demonstrated using 5 proposed classification schemes [22]; and 4) a lack of quantified data on ictal behaviors.

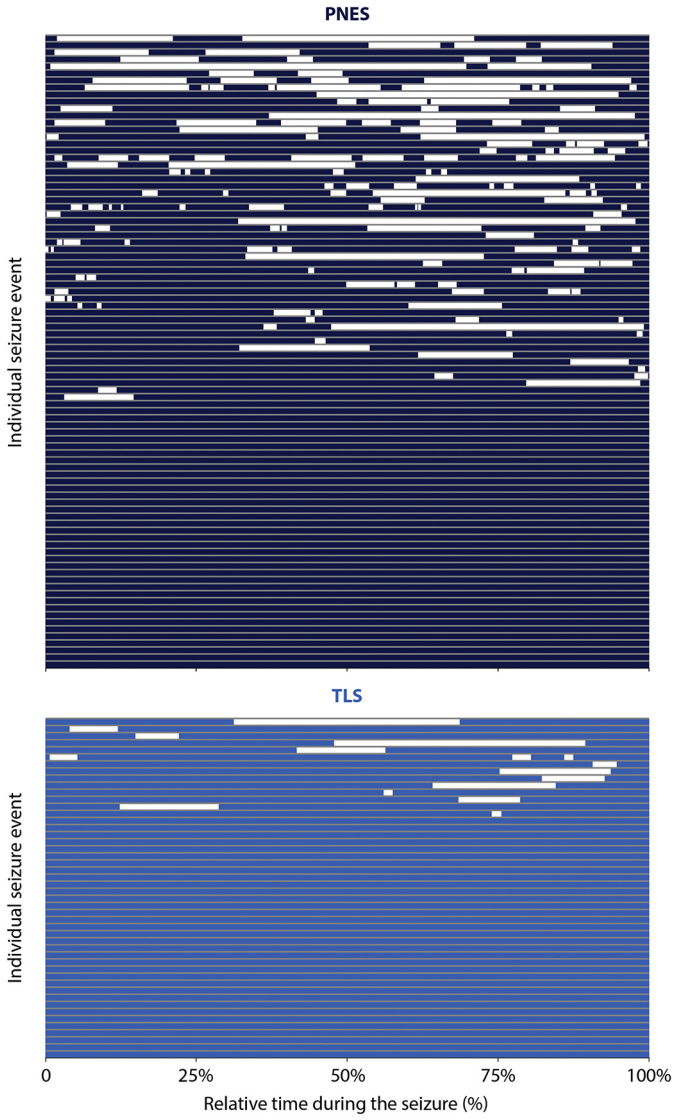

Fig. 5. Schematic representation of all the seizures in the two groups (rows) with their "free-spots" (blank spots) corresponding to "pauses" (defined as time lag during which ictal behaviors cease). Psychogenic nonepileptic seizure-like events (upper quadrant) show significantly higher number of "pauses" than TLS (lower quadrant). Moreover, the presence of 2 "pauses" during an episode determines a 69% probability of the seizure being nonepileptic and only a 30% probability of being epileptic.

Currently, two main semiologic classification systems for PNES are used in clinical practice. The first one [10] classifies psychogenic seizures into six categories: 1. rhythmic motor, 2. hypermotor, 3. complex motor, 4. dialeptic, 5. nonepileptic auras, and 6. mixed. By adopting this system, all PNES events belonged to the same semiologic type in 82% of adult patients in one study [10], 85% of cases in a study involving a pediatric population [20], and in all patients (100%) examined in a very recent work that provide also an assessment of the type of movements and anatomical regions involved [23]. However, different results were obtained using the second classification system [15,16], which comprises four distinct classes: 1. generalized motor, 2. akinetic, 3. subjective symptoms, and 4. focal motor. In fact, in the latter, 71.5% of the patients showed either inter- or intraclass variability, whereas seizures were stereotypical in only 28.5% [15].

The problem inherent in classification systems is the arbitrary subdivision of complex phenomenological data into a limited number of fixed categories, which would not capture every behavioral aspect involved

in the feature of stereotypy. Belonging to the same semiologic category does not imply the exact same seizure (e.g., the appearance of "hand shaking" and "leg movements" in two PNES episodes, both "focal motor", does not imply that the two are stereotypic). Moreover, seizures typically do not consist of a single but several motor and nonmotor manifestations and subjective sensations, with a peculiar onset, offset, sequence, overlap, and duration.

An alternative method of studying ictal stereotypy is the use of a quantified approach and applying ad hoc algorithms in the analysis of behavioral data, while comparing the same findings to behaviors exhibited by another group of subjects with EEG-documented epileptic events. These are the main novel methodological aspects adopted in the present study. We analyzed ictal behaviors in PNES and TLS through 4 axes: duration, type, sequence, and continuity. Our study shows that TLS typically last approximately 1 min (68 s), while PNES usually last more than twice as long (143.5 s). This observation is in accordance with the previous finding of PNES duration usually longer than 2 min and ES characteristically less than 2 min [24–26]. However, we are mindful that these observations were made in epileptic events that were not occurring in the context of status epilepticus.

More importantly, we found that the duration of a PNES event is more variable than that of an ES, with a higher coefficient of variation. Epileptic and nonepileptic seizures differed also in another key behavioral feature, namely the continuity of ictal behavior. Based on our data, the presence of "pauses" within a seizure is a distinctive characteristic of PNES. Our data provide final confirmation of the previous observation that PNES exhibit an "on–off" behavior [27], a feature rarely observed in epilepsy.

Limitations of the present study include the following:

- the lack of quantification of interrater reliability of the rating method applied to code the clinical episodes,
- the absence of observations of long-term changes on clinical semiology.

Moreover, we are aware that these results need to be confirmed in other form of epilepsy (frontal, parietal, or occipital epilepsies).

Prospective studies involving automated measures of ictal behaviors (e.g., computer-aided video analysis) could provide definitive conclusions on how to distinguish between PNES and ES.

In conclusion, our phenomenological data provide novel observations about the stereotypy of ictal behaviors in patients with PNES and TLS. While we confirmed that both groups demonstrate certain degrees of stereotypy, we discovered that the fluctuating pattern of ictal behavior (i.e., duration variability and the "on–off" pattern of events with frequent pauses of behavior during ictal event) is reliable predictor of an event being psychogenic in etiology. We believe that our findings will have practical importance in everyday clinical practice and will enhance our ability to make accurate differential diagnosis.

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Disclosure

The authors report no disclosures relevant to the manuscript.

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