Stereotypy of psychogenic nonepileptic seizure-like events compared to temporal lobe seizures: a quantitative analysis of ictal events captured during Video EEG monitoring

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Abstract

***Objective*: The overarching goal of the current study was to study the features of stereotypy in temporal lobe seizures (TLS) and psychogenic nonepileptic seizures (PNES) in four different domains: duration, type, sequence and continuity of ictal behaviours.**
***Methods*: Video-EEG (VEEG) data from 20 TLS patients and 20 PNES patients admitted to the Stanford Epilepsy Center were retrospectively analysed. *A priori,* a set of 59 possible ictal behaviours was defined. Each behaviour was analysed for its duration, sequence, and continuity using quantified measures.**
***Results*: A total of 138 seizures were analysed (90 PNES, 48 TLS). Median duration of PNES (143 s) was significantly longer than TLS (68 s) (P=0.002), and PNES exhibited greater duration variability (P=0.005). The density of "pauses" within a seizure (time-lag during which ictal behaviours cease) was significantly greater in PNES comparing to TLS (P=0.012). Moreover, the presence of 2 "pauses" during an episode determines a 69% probability of the seizure being non-epileptic, and only a 30% probability of being epileptic.**
***Conclusion*: While different degrees of stereotypy can be seen in TLE seizures and psychogenic seizure-like events, we found that event duration and fluctuating pattern of ictal behaviour (i.e., "on-off" pattern with pauses of behaviour during ictal event) are reliable predictors of an event being psychogenic in etiology.**

KEY WORDS: **stereotypy, psychogenic nonepileptic seizures, temporal lobe seizures, differential diagnosis, video-EEG and PNES.**

Introduction

Since the early days of neurology, the existence of psychogenic nonepileptic seizure-like events (PNES) has been acknowledged but never clearly understood. These events have been given many names including hysterical spells (1) and pseudoseizures (2) in an attempt to describe their mysterious etiology. Yet, we are still in search for a definitive explanation as to why patients exhibit these seizure-like events and a method by which to differentiate them from epileptic seizures (ES) (3). Several semiological features - taken together - might be helpful in the differential diagnosis and are useful in clinical practice: for instance, eye closure is common in PNES but rare in ES, while lateral tongue biting and incontinence are more common in epileptic seizures (3-5).
While semiological features have been studied in ES and PNES, the issue of stereotypy of events has not been compared systematically between the two. For decades it has been clear to most neurologists that ES is stereotypical in nature, i.e., certain ictal behaviors occur reliably and in a similar order during the patient's seizures. For instance, a patient with TLE is often witnessed to start seizures with rising nausea which proceeds with staring and lip smacking (6). By comparison, nonepileptic events are commonly thought to share a more variable course and a wider phenotypic spectrum (7). Contrary to this common belief, some have argued that PNES can be highly stereotypic and that the feature of stereotypy is not reliable in differentiating the ES and PNES from each other (8, 9). However, the lack of a uniform and comprehensive definition of the concept of stereotypy, in addition to the paucity of quantified and systematic analysis of ictal behaviour, have been major drawbacks in this context. The current study was designed to provide a systematic analysis of ictal behaviour in ES and PNES using data captured during in-patient video EEG monitoring. For ES, we selected events

captured in patients with confirmed temporal lobe epilepsy (TLE) since the ictal behaviour in this group is well established (6, 10). For PNES we selected events that were determined to be unequivocally psychogenic in nature based on EEG analysis and comprehensive in-patient psychiatric evaluation of the patients. Stereotypy was studied using quantified measures in four different domains: duration, type, sequence and continuity of ictal behaviour. 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. We believe that our findings will have practical importance in everyday clinical practice and will enhance our ability to make accurate differential diagnosis.

Methods

Patients

Retrospective video-EEG data of 20 patients with psychogenic nonepileptic seizures (PNES) and 20 patients with temporal lobe epilepsy (TLE) who underwent monitoring at the Stanford Epilepsy Center (Stanford University, California, USA) were included in the study. The diagnosis of PNES was made at a regular consensus meeting of our Institution by a panel of expert epileptologists after review of the clinical history, EEG recording and seizure semiology as observed on video recording. The following criteria, based on previous expert-consensus (9, 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; 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). Patients with mixed disorders (co-occurrence of epileptic and nonepileptic seizures in the same patients) were excluded from analysis. The rationale of choosing patients with temporal lobe epilepsy was threefold: 1) ictal origin and propagation in TLS is well-established (6, 10); 2) TLS involve a complex set of behaviours, ranging from motionless staring to semipurposeful motor activity and psychic phenomena, that can be easily mistaken for psychogenic events on clinical grounds (4); 3) deep temporal lobe seizures, 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 Ethics Committee of the Stanford Hospital and Clinics.

Coding Patient Videos

Before the beginning of the study, the Authors compiled a list of 59 ictal behaviours in 3 major areas (motor, language and autonomic disturbances) that would most likely be present in any seizure episode (Fig. 1). The list was reviewed by all evaluators to ensure that there would be consistency in coding. All videos were viewed from start to finish without interruptions to allow the evaluator to note the major motor behaviours that would be coded. During the second viewing, evaluators recorded the behaviours of the patient prior to the seizure episode, onset time of the seizure, onset time and duration and description of each major behaviour, details of any indication of patient awareness during the episode, and termination time of the seizure.

Data analysis

Repeated Ratio

To evaluate the semiologic variability of ictal behaviours across seizures in each patient, the Repeated Ratio (RR) was measured:

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

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

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 behaviours cease. Only intervals longer than 2 seconds were considered as pauses. A 5 and 10 seconds cut-off 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 will probably allow more pauses to occur.

Overlapped density

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

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

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

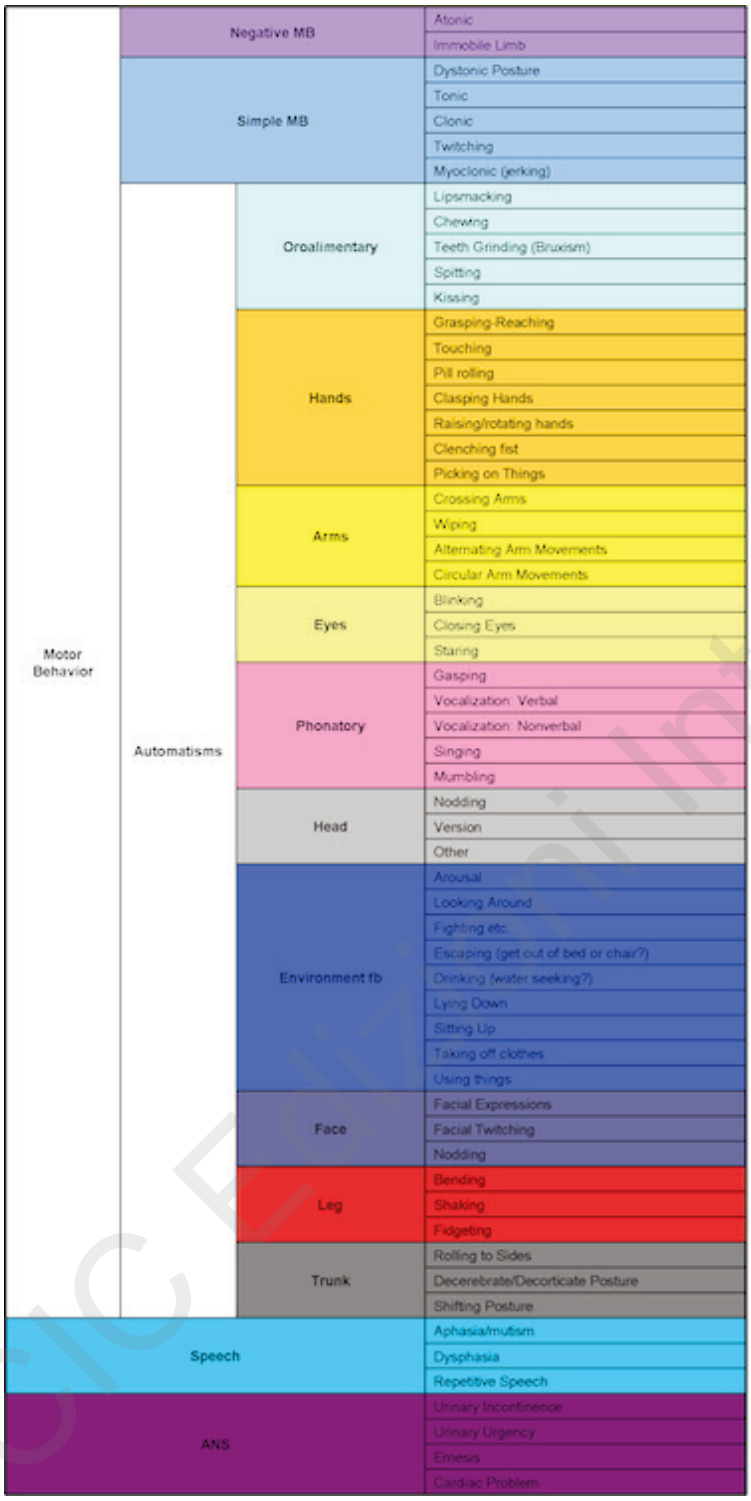

Figure 1 - Set of 59 ictal behaviours in 3 major areas (motor, language and autonomic disturbances) that would most likely be present in any seizure episode. The list was designed a priori in order to code the patients' seizures.

Statistical analysis

Statistical analysis was done by comparing two groups (TLS patients and PNES patients). First, the one-sample Kolmogorov-Smirnov test was used to check whether the data set 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.

Results

Demographic Characteristics

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

Seizures number and type

A total of 138 seizures were recorded. 938 behaviours in 22 behavioural categories were coded from 90 seizure events in the PNES population and 426 behaviours in 17 behavioural categories from 48 seizure events in the ES population. Since the number of patients was equal in the two groups, the number of seizures per patient differed (*P*=0.004). PNES patients had a median of 4 seizures during the hospital stay (interquantile range of 4.5) whereas ES patients had 1.5 seizures (interquantile range of 2). On average, each PNES patient exhibited 5 unique behaviours over the course of all coded seizures while each ES patient exhibited 4.5 unique behaviours. The difference did not reach statistical significance (*P*=0.307).

PNES have longer seizure duration and greater duration variability than TLS patients

Seizure duration between the two groups differed significantly. We observed longer events and more duration variability in the PNES population. Median duration in PNES was 143.5 seconds (interquartile range of 215 seconds) while TLS lasted a median of 68 seconds (interquartile range of 49 seconds) (Fig. 2). The difference reached statistical significance (*P*=0.002).

To answer the question of seizure duration consistency between ES and PNES patients, we calculated the intra-patient 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. 18 patients in the PNES group and 10 patients in the ES group satisfied the above-mentioned criteria. Accordingly, the mean event duration for PNES patients who had at least 2 seizure events was 181.2 seconds compared to the TLS mean duration of 76 seconds. PNES patients had a significantly (*P*=0.005) higher coefficient of variation of 0.54 compared to TLS patients (0.35) (Fig. 3).

PNES patients exhibit an "on-off" pattern during seizure more commonly than ES patients

The density of "pauses" (defined as time intervals within a seizure without ictal behaviours) 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 Figure 4 and the graph of the two distributions in Figure 5.

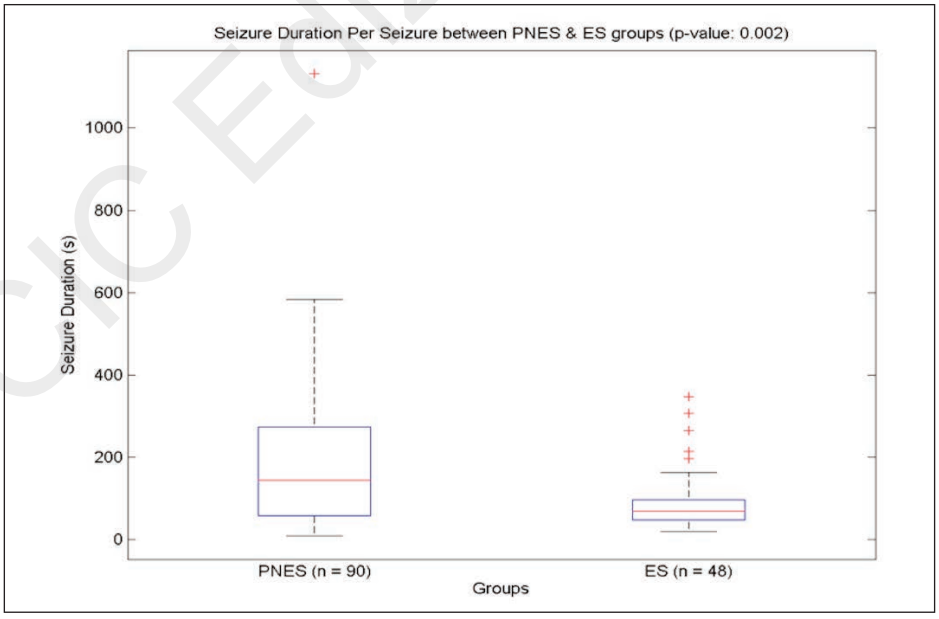

Figure 2 - Seizure duration between the two groups. Median duration in PNES was 143.5 seconds while TLS lasted a median of 68 seconds (P=0.002).

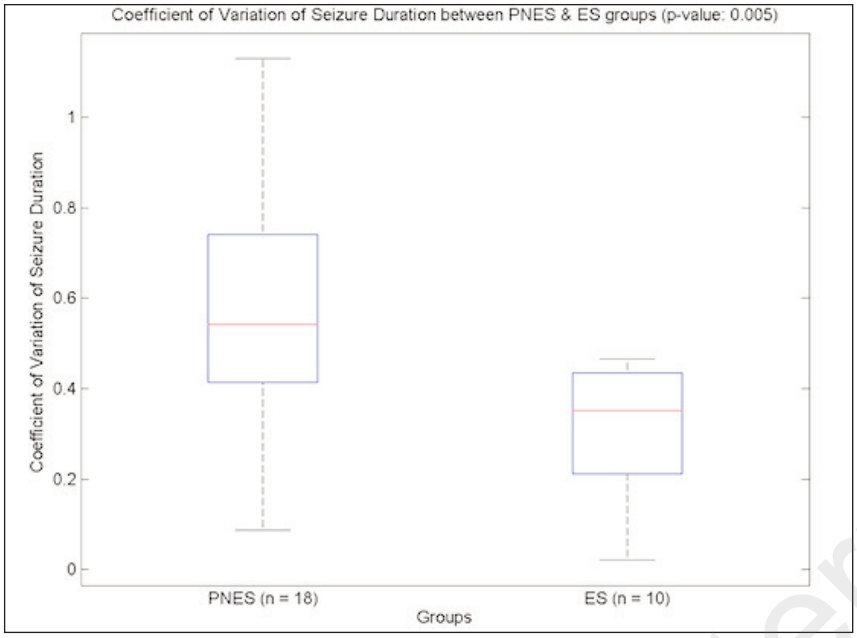

Figure 3 - Duration variability in TLS and PNES patients. PNES patients had a significantly higher coefficient of variation compared to TLS patients (P=0.005).

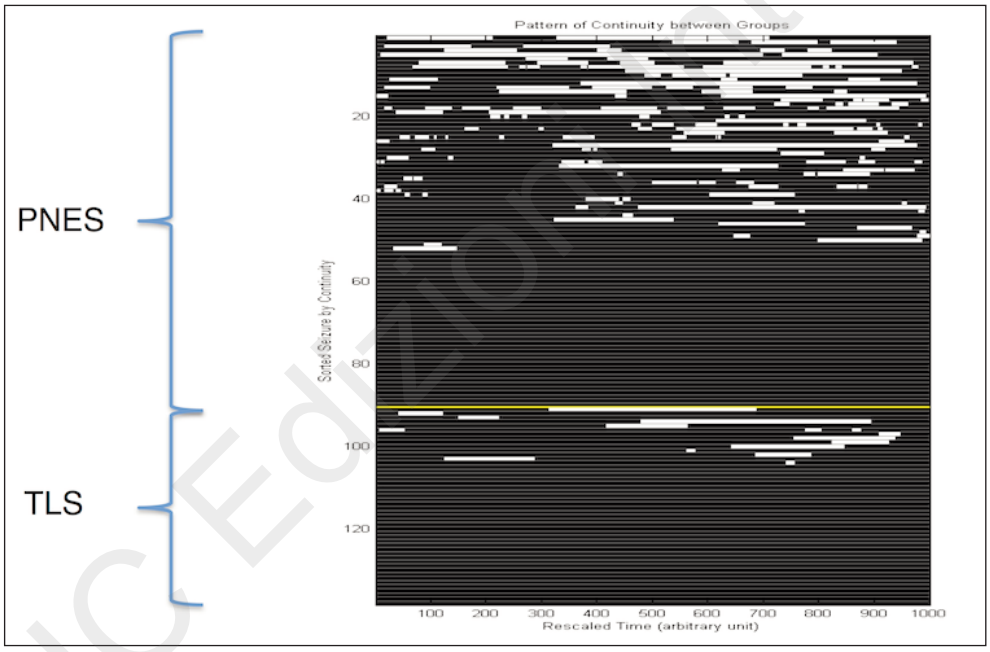

Figure 4 - Schematic representation of all the seizures in the two groups (rows) with their "free-spots" (blank spots) corresponding to "pauses" (defined as time-lag during which ictal behaviours cease). PNES (upper quadrant) show significantly higher number of "pauses" than TLS (lower quadrant). Moreover, the presence of 2 "pauses" during an episode determines a 69% probability of the seizure being non-epileptic, and only a 30% probability of being epileptic.

Conclusions

This is the first study examining the features of stereotypy in ES and PNES using a VEEG-based systematic and quantitative approach. By analysing the duration, sequence and continuity of the various behaviours that together constitute a seizure, we were able to assess the degree of ictal stereotypy within and across patients.

Our study shows that TLS typically last approximately one minute (68 seconds), while PNES usually last more than twice as long (143.5 seconds). This observation is in accordance with the previous finding of PNES duration usually longer than 2 minutes (14, 15) and ES characteristically less than 2 minutes (14-16). Moreover, we found that the duration of a PNES is more variable than that of an ES, with a higher coefficient of variation.

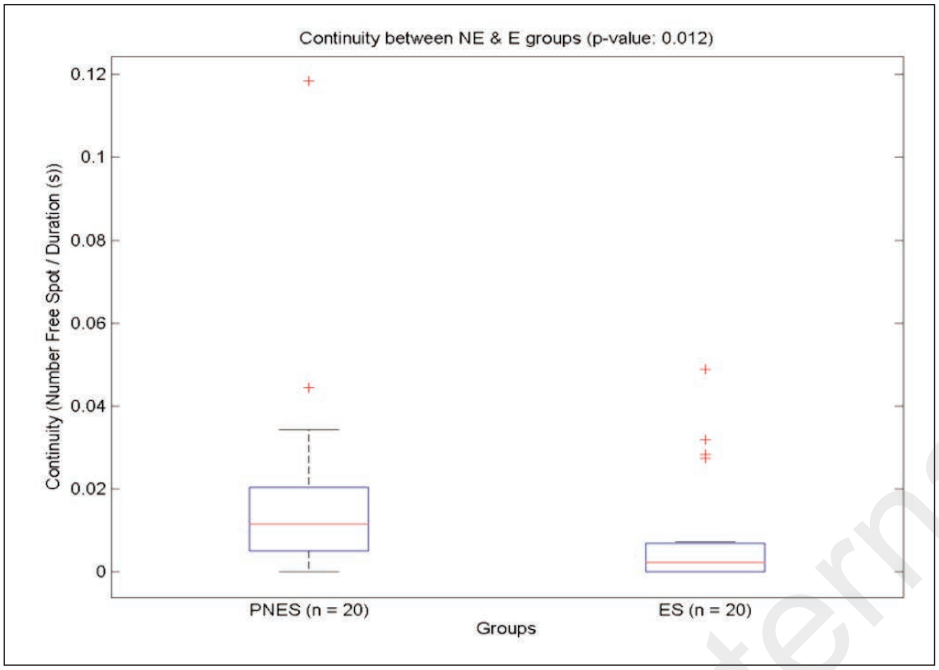

Figure 5 - The density of "pauses" (time intervals within a seizure without ictal behaviours) was higher in PNES than in TLS (P=0.0121).

Epileptic and nonepileptic seizures differed in our study in one key feature, namely the continuity of ictal behaviour. 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" behaviour (17), a feature rarely observed in epilepsy. This feature could be helpful in the differential diagnosis between the two conditions. In conclusion, seizure duration and ictal behaviours fluctuation ("on-off" pattern) distinguish PNES from TLS.

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Disclosure

The Authors report no disclosures relevant to the manuscript.

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