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Identifying seizure clusters in patients with psychogenic nonepileptic seizures

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ABSTRACT

The present study explored how seizure clusters may be defined for those with psychogenic nonepileptic seizures (PNES), a topic for which there is a paucity of literature. The sample was drawn from a multisite randomized clinical trial for PNES; seizure data are from participants' seizure diaries. Three possible cluster definitions were examined: 1) common clinical definition, where ≥3 seizures in a day is considered a cluster, along with two novel statistical definitions, where ≥3 seizures in a day are considered a cluster if the observed number of seizures statistically exceeds what would be expected relative to a patient's: 1) average seizure rate prior to the trial, 2) observed seizure rate for the previous seven days.

Prevalence of clusters was 62–68% depending on cluster definition used, and occurrence rate of clusters was 6–19% depending on cluster definition. Based on these data, clusters seem to be common in patients with PNES, and more research is needed to identify if clusters are related to triggers and outcomes.

1. Introduction

Psychogenic, nonepileptic seizures (PNES) are paroxysmal episodes that can resemble epileptic seizures but that have psychological underpinnings [1]. Though often similar in manifestation, PNES are differentiated from epileptic seizures in that PNES are not associated with EEG epileptiform (i.e., patterns indicating epilepsy) correlates with their events [1]; thus, PNES are classified as a somatic symptom disorder of the conversion type (i.e., see Smith [2]). Although dissimilar in etiology, both epileptic and psychogenic seizures can occur in clusters or bouts [3,4]. In particular, evidence indicates those who have epileptic seizure clusters have poorer outcomes relative to those who do not have clusters [5]. Currently, there is a paucity of research concerning seizure clustering in those with PNES — including the operationalization of clusters. Operationalization of clusters in PNES is especially difficult given that there is no theoretical basis of clustering (known to the authors) occurring in the PNES literature, from which an operational definition may be derived. Because PNES clusters are observed clinically, but there is no definition, research from the epilepsy literature [4] could be used to help inform the study and operationalization of seizure clusters for the population with PNES.

Seizure clusters are often defined in the epilepsy literature as three or more seizures occurring within 24-h [6–11]. This definition was first introduced by Haut et al. [12], who observed that epileptic seizures occurring within 8 h of each other were more likely to be concordant (i.e., same hemisphere foci) than discordant. Though the three or more threshold definition is clear and easy to implement in practice, the reasoning behind this cluster definition may not extend to PNES; what's more, this and other threshold-based definitions do not take into account a patient's relative seizure presentation. One consequence of using a threshold definition is patients who typically present with repeated bouts of three or more seizures in a day will always be considered as having clusters, while relative increases in their seizure frequency will go unrealized.

Other studies have employed various statistical models to find evidence for epileptic seizure clustering. These models evaluate if a patient's seizure occurrence deviates from what would be expected due to randomness alone [13–15]. One weakness with this approach is these statistical models provide evidence only for the presence of clustering, but seizure clusters themselves are not individually identified as events. Because a cluster itself is not identified as an event with these models, it is difficult to evaluate the improvement of clusters over time. In addition, these studies also used modeling approaches that assumed a patient's seizure rate remained constant. Though seizure frequency may remain stationary for some, this cannot be assumed for many patients, such as those receiving therapy or those who have

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been enrolled in a treatment trial and who may be experiencing a change in their baseline seizure frequency. For these patients, seizure frequency may be affected by a treatment effect, a placebo effect or a Hawthorne effect. Whether existing definitions of cluster from the epilepsy literature may inform a theoretical basis for PNES have not been established, and that many of these definitions are either too vague or not realistic for PNES, another model of seizure cluster, separate from those used in epilepsy, could be considered.

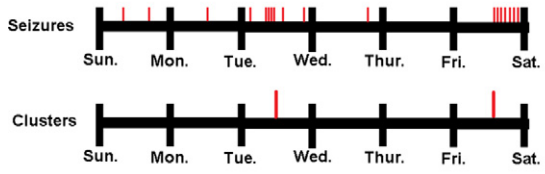
As noted previously, although the occurrence of seizure clusters is acknowledged in the PNES literature, what is not provided in the literature is description and theory concerning the nature of clusters for PNES, thus making their operationalization difficult. Nevertheless, it could be argued that a fundamental feature of a cluster is the notion that a cluster event occurs when the frequency of seizures observed in a specific interval of time is "higher" than what would be expected. Obviously, what is "higher" and what is "expected" are vague and debatable, but the general notion remains: the frequency of seizures occurring would be relatively higher than some objective (e.g., a patient's past seizure rate) or subjective (i.e., a patient's perceived seizure rate) reference of count.

It could also be argued that other features of a cluster might include a qualitative increase in severity of symptoms, increased duration of given seizures, decreased duration between seizure events, or increased impact to functioning and subjective distress relative to single seizure events. However, how these features relate to the concept of a cluster is difficult to parse out when considering that PNES themselves can vary in intensity, duration, symptomatology, impact, and context, not only between patients, but even within patients.

Finally, what a cluster may be and the limitations of how we are able to observe them must be considered. Specifically, how clusters are operationalized is limited to how individual seizure events are observed and documented. For instance, because seizures are often self-reported in daily diaries; the exact times and even frequencies of seizures cannot be assumed to be precise or accurate due to recall bias and memory decay. Seizure frequency (for epilepsy or PNES) outside of the seizure monitoring unit (SMU) will not be documented with the same precision as that observed in the SMU. As illustrated in Fig. 1a, we would hypothesize that a cluster is several seizures occurring relatively closely in time, distinguished by single seizure events occurring relatively distantly in time. Because self-reported seizure data recorded on seizure diaries are not documented with the level of detail of the SMU, also presented in Fig. 1a is our hypothesized approximation of how a cluster could be observed, using daily seizure diaries.

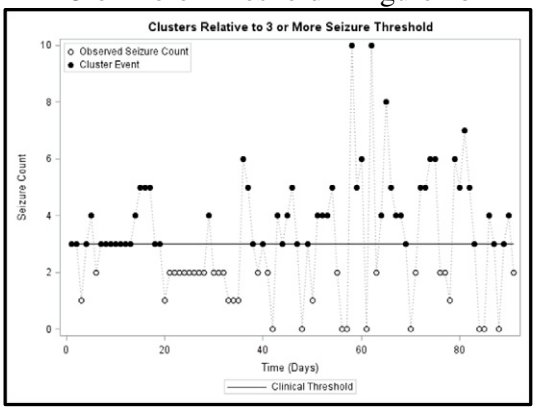
The aim of the current study was to present an operationalization of PNES clusters with the aforementioned considerations in mind. Here, a cluster is operationalized using the frequency of seizures observed in a given day. Intensity, duration, impact to functioning and distress are not included as part of the operationalization because these are also features of the seizures themselves, which vary not only between patients but also within patients. Thus, in order to allow for comparisons across patients, our definition of cluster is based on the unit of the seizure itself, however it is defined for the patient. In addition, seizure frequency also varies between patients, so no threshold of seizure frequency would apply to all patients. Therefore, a cluster is defined not as a frequency of seizures, but rather a frequency of seizures occurring in a day that exceeds what would be subjectively or objectively expected for a given patient. Finally, our proposed method of operationalizing clusters provides clinicians a method by which clusters may be observed with data that are commonly available in clinical practice; namely, daily seizure diaries.

Example week of a patient – Figure 1a

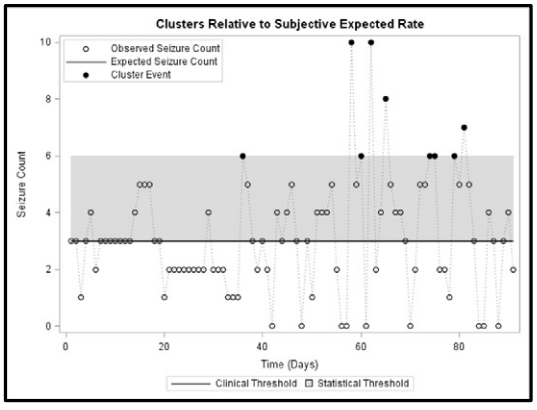


Seizures (top): seizure events during a day, during the week (red lines)
Cluster (bottom): cluster events during the week (red lines), assuming a patient's expected seizure rate is 3

3 or more Threshold – Figure 1b



Subjective – Figure 1c



Seven – Figure 1d

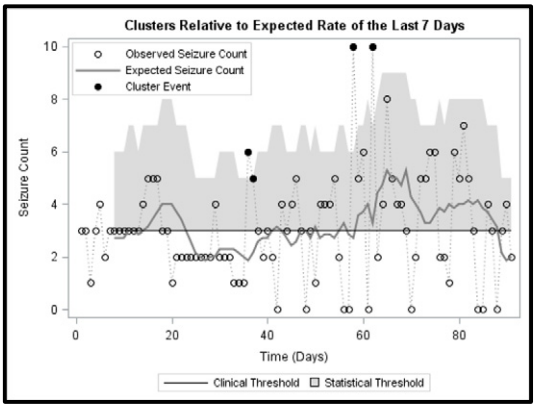


Fig. 1. All three seizure cluster definitions for a single patient over the span of the trial. 1. X-Axes are "Time" in days 2. Y Axes are "Seizure counts" 3. Hollow circles are seizure counts 4. Filled circles are identified clusters 5. Gray areas denote statistical cutoff for a cluster being identified 6. Black line denotes the 3 or more threshold 7. Expected counts are dark gray lines 8. All using 3 or more seizure requirement 9. Note: This patient was selected because their subjective rate was approximately 3 seizures per day, thus providing a direct comparison with the threshold definition of 3 seizures or more. 10. Note that the threshold definition identifies the most cluster events and the seven definition the fewest.