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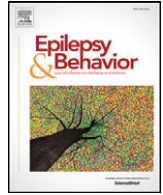
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## Diagnostic implications of review-of-systems questionnaires to differentiate epileptic seizures from psychogenic seizures

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### ABSTRACT

**Objective:** Early and accurate diagnosis of patients with psychogenic nonepileptic seizures (PNES) leads to appropriate treatment and improves long-term seizure prognosis. However, this is complicated by the need to record seizures to make a definitive diagnosis. Suspicion for PNES can be raised through knowledge that patients with PNES have increased somatic sensitivity and report more positive complaints on review-of-systems questionnaires (RoSQs) than patients with epileptic seizures. If the responses on the RoSQ can differentiate PNES from other seizure types, then these forms could be an early screening tool.

**Methods:** Our dataset included all patients admitted from January 2006 to June 2016 for video-electroencephalography at UCLA. RoSQs prior to May 2015 were acquired through retrospective chart review ( $n = 405$ ), whereas RoSQs from subsequent patients were acquired prospectively ( $n = 190$ ). Controlling for sex and number of comorbidities, we used binomial regression to compare the total number of symptoms and the frequency of specific symptoms between five mutually exclusive groups of patients: epileptic seizures (ES), PNES, physiologic nonepileptic seizure-like events (PSLE), mixed PNES plus ES, and inconclusive monitoring. To determine the diagnostic utility of RoSQs to differentiate PNES only from ES only, we used multivariate logistic regression, controlling for sex and the number of medical comorbidities.

**Results:** On average, patients with PNES or mixed PNES and ES reported more than twice as many symptoms than patients with isolated ES or PSLE ( $p < 0.001$ ). The prospective accuracy to differentiate PNES from ES was not significantly higher than naïve assumption that all patients had ES (76% vs 70%,  $p > 0.1$ ).

**Discussion:** This analysis of RoSQs confirms that patients with PNES with and without comorbid ES report more symptoms on a population level than patients with epilepsy or PSLE. While these differences help describe the population of patients with PNES, the consistency of RoSQ responses was neither accurate nor specific enough to be used solely as an early screening tool for PNES. Our results suggest that the RoSQ may help differentiate PNES from ES only when, based on other information, the pre-test probability of PNES is at least 50%.

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### 1. Introduction

Early and efficient differentiation of psychogenic nonepileptic seizures (PNES) from epileptic seizures (ES) is critical to the successful treatment of both conditions [1–3]. Accurately characterizing the subtype of seizures in each patient helps physicians choose a medication

that is most likely to reduce or eliminate seizures, and avoid the unnecessary risks of medications that are not likely to be effective [2,4–6]. Despite this, 50–90% of patients diagnosed ultimately with PNES were treated initially with anti-seizure medications (ASMs) [3,7], potentially delaying time to definitive diagnosis [8] while exposing patients to iatrogenic adverse effects. The most effective treatment of PNES is cognitive-behavioral-informed therapy to address the underlying psychological stressors that contribute to their seizures [9,10]. Diagnosing PNES earlier results in reduced cost and better short and long-term seizure control [2,4,5,11,12]. Unfortunately, the average delay from first

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seizure to diagnosis of PNES is over 8 years [8]. Given this clinical scenario, high quality, low cost, and objective screening tools to identify patients at risk for PNES are needed.

A major challenge in identifying the etiology of seizures as early as possible is the development of evidence-based methods that differentiate seizure types based on standardized information acquired early in the patient assessment. Almost all clinics ask patients to fill out standardized review-of-systems questionnaires (RoSQ) before they speak to a physician; evidence that these are effective in diagnosis of seizures is promising but limited [13,14]. Patients with PNES experience increased somatic sensitivity, as evidenced by medically unexplained symptoms and reporting more disability for less severe symptoms [1, 12,13,15,16]. Additionally, most frequently, PNES are a component of conversion disorder in which patients convert psychological stressors into somatic symptoms or findings, one of which can be seizures [3, 12,17]. However, conversion disorder frequently presents with other positive findings including pain, fatigue, lethargy, myalgias, constipation or diarrhea [3]. These symptoms may not be severe enough to warrant medical attention or treatment, but they are reported on RoSQs.

There is retrospective evidence that RoSQs may help identify patients at risk for PNES [13,14]. In a small dataset with many different formats of RoSQs, Robles and colleagues demonstrated recently that patients who noted >17% of symptoms on RoSQs were more likely to have PNES than ES with an area under the receiver operating curve (AUC) of 84% [13]. Their sample size was limited, however, by inconsistent availability of RoSQs in the electronic health record. Recently, Asadi-Pooya and colleagues also demonstrated that an alternate type of RoSQ achieved an AUC of 67% with a cut-off of 3 of 10 positive organ systems [14]. We extended their work by studying a larger retrospective dataset at an independent institution, as well as a dataset in which RoSQs were collected prospectively from almost every patient admitted for video-electroencephalographic (vEEG) monitoring, the definitive diagnostic modality for most patients with PNES [1]. We also controlled for sex and the total number of medical comorbidities to better describe effect of RoSQ responses, independent of these confounders. Additionally, we addressed how patients with mixed PNES plus ES, physiologic non-epileptic seizure-like events (PSLE), and inconclusive vEEG monitoring respond to RoSQs. This provides a more complete understanding of the differential diagnosis for seizures and the potential role of RoSQs in differentiating these populations.

## 2. Methods

Our patient population included all patients admitted to the UCLA adult vEEG monitoring unit between January 2006 and June 2016. Diagnosis was expert clinical opinion based on clinical history, physical exam, vEEG, and structural & diffusion magnetic resonance imaging; fluorodeoxyglucose-positron emission tomography magnetoencephalography and single-photon emission computed tomography also were used in some patients. We placed patients in five mutually exclusive categories: psychogenic nonepileptic seizures (PNES), physiologic nonepileptic seizure-like episodes (PSLE), epileptic seizures (ES), mixed nonepileptic & epileptic seizures, and inconclusive monitoring. We recognize that these are heterogeneous populations with many important subtypes, but the description of subtypes within PNES and ES is outside the scope of this article. Throughout this manuscript, we will specify mixed seizures when referring to any patients with both PNES and ES. We chose to keep patients with mixed PNES plus ES separate from patients with PNES because, while both have PNES, there is insufficient evidence to suggest that the mechanism and risk factors for PNES are the same in these populations [18]. Inconclusive monitoring occurred when patients did not experience sufficient characteristic events during monitoring to yield a definitive diagnosis.

Our population included two groups: retrospective patients (January 2006–April 2015) and prospective patients (May 2015–June 2016). We do not refer to these groups as “training” and “validation” because they

differ from traditional training and validation sets in machine learning. The function of the retrospective group was to generate objective criteria for using RoSQs to differentiate between PNES and ES, whereas the function of the prospective group was to validate how well these criteria function in a real-world, unselected dataset.

Records from patients prior to May 2015 were acquired through retrospective chart review. In the retrospective patient group, patients or their caregivers filled out RoSQs in the outpatient neurology waiting room prior to their appointment or at home as part of the admission packet sent to them prior to vEEG admission. If the patient had not filled out their RoSQ prior to vEEG, they were given another form during admission and the form was collected by nursing staff. RoSQs from patients admitted after April 2015 were collected in person within 48 h of vEEG admission by an interviewer. If the patient had not filled out the form, the patient was provided another form and the interviewer returned later to collect the form. The goal of including an interviewer in the prospective group was to reduce the potential for selection bias from missing data. To assess the potential for selection bias, we report the leave-one-patient-out area under the receiver operating curve (AUC) of our predictive algorithm on the retrospective group.

For patients with multiple available RoSQs, the earliest standard form was used. RoSQs collected after conclusive vEEG monitoring were excluded. If retrospective patients were re-admitted during the prospective period (e.g. due to an inconclusive first admission), they were excluded from the prospective analysis and, if necessary, their diagnosis was updated in the retrospective dataset. Because the first available RoSQ was used, there was no difference between the RoSQ data for patients that required more than one admission to yield a definitive diagnosis. Readmission reduced the frequency of inconclusive monitoring in the retrospective group. Age was recorded as the age at the time of RoSQ completion.

All patients or their caregivers filled out a standardized 78-item review of system questionnaire (see Supplemental Fig. 1). Two minor variations of the standard form were accepted, one of which omitted 3 items (75 total items), and the other omitted the same 3 items while splitting one item into two separate items (76 total items). All forms listed the same 14 organ systems. These standardized forms were used across all UCLA neurology providers. Caregivers' responses were used when the patient was unable to fill out the form due to physical or intellectual disability.

We analyzed the RoSQ responses using both population-level descriptive statistics and individual-level predictive statistics. For the population level analysis, the retrospective and prospective datasets were combined (for analysis of each dataset separately, see Supplemental Information). For all analyses, we controlled for patient sex and the number of medical comorbidities. For the descriptive analysis, controlling for confounders differentiated the effect of etiology on RoSQ responses conditionally independent from the effect of sex and medical comorbidities. For the predictive analysis, controlling for confounders demonstrated the additive value of RoSQ past that of knowing the patient's sex and medical comorbidities. A linear correction for age did not have a significant impact on the results (analysis not shown).

Descriptive multivariate binomial regression was used to determine if the total percent of positive responses or the likelihood of a positive response to each specific question differed between the 5 diagnostic categories on a population level. Inclusion of patients with inconclusive monitoring improved our ability to estimate and control for the effect of patient sex and number of comorbidities but otherwise had no effect on the results of the other 4 diagnostic categories. False discovery rate multiple testing correction was applied to analysis of each specific complaint. We also display the frequency of each diagnostic subclass, based on the number of RoSQ symptoms.

Predictive multivariate logistic regression was used to determine if the percent of positive RoSQ symptoms could differentiate between individual patients with PNES and ES. Patients with mixed ES plus PNES, PSLE, and inconclusive monitoring were excluded from predictive

analysis. All predictive models were trained using the retrospective dataset alone and performance was assessed on the prospective dataset. Predictive performance was compared to the naïve assumption that all patients had ES, to the performance of the 17% cut-off proposed by Robles and colleagues, and to a predictive approach similar to what was done by Asadi-Pooya and colleagues [13,14]. Comparison to a naïve assumption is more conservative than a comparison to a random classifier with accuracy of 50% because it takes into account the prevalence difference between PNES and ES.

To assess the performance of the Robles and colleagues cut-off, we used the combined retrospective and prospective database because, with respect to the Robles and colleagues' analysis, our retrospective cohort was an out-of-sample dataset. To compare our results directly to Robles and colleagues, we also report the cut-off that maximized the average of sensitivity and specificity without controlling for sex and the number of comorbidities.

To simulate the RoSQ used by Asadi-Pooya and colleagues, we grouped symptoms based on organ systems according to their form and considered the system positive if any symptom within the system was noted. Their RoSQ questions were of the form: “do you have any X problems”, where X indicated the lay term for the organ system. While this does not match their exact methods of collecting RoSQ information, it is the closest simulation of their methods that was possible with our data. Because our dataset did not have equal numbers of patients with PNES and ES, and was not matched for sex and age, we re-determined the systems-based cut-off for PNES versus ES using the retrospective dataset controlling for sex and assessed the performance on the prospective dataset (linear corrections for age had no effect, analysis not shown). To compare our results directly to their 3 or more cut-off, we report the systems-based cut-off that maximized the average of sensitivity and specificity after controlling for sex.

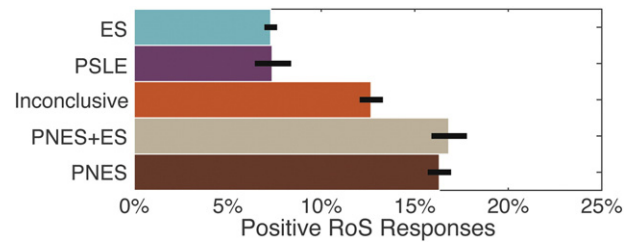
All patients consented for the use of their records in research, and the UCLA Institutional Review Board approved this study. This work is consistent with Declaration of Helsinki. De-identified raw data and code for this study is available at <http://www.brainmapping.org/MarkCohen/research.html>.

### 3. Results

No significant differences in any of the studied measures were found between the retrospective and prospective datasets with a few exceptions (Supplemental Table 1,  $p > 0.1$ ). The rate of inconclusive monitoring significantly increased in the prospective dataset (2.4% vs 30%,  $p = 3 \times 10^{-22}$ ) and the rate of an epilepsy diagnosis significantly decreased (69% vs 46%,  $p = 10^{-7}$ ). RoSQs were available from 36% (405/1126) of patients in the retrospective group and 85% (190/224) of patients in the prospective group (Fisher exact test,  $p < 0.001$ ). The shorter, minor variation of the RoSQ form was used more frequently in the retrospective dataset than the prospective dataset (72% (293/405) vs 8% (15/190), Fisher exact test,  $p < 0.001$ ). Consistent with previous literature, there were demographic differences between the diagnostic subclasses (Table 1).

**Table 1**  
Demographic information about included patients. Abbreviations: Confidence Interval (CI), psychogenic nonepileptic seizures (PNES), physiologic nonepileptic seizure-like episode (PSLE), epileptic seizures (ES).

Diagnosis	Count	Age (years) min (95% CI) max	% female	# comorbidities (95% CI)
PNES	122	13 (37–44) 88	76	(2.7–4.1)
PNES + ES	28	13 (31–43) 63	61	(1.3–2.7)
Inconclusive	68	15 (37–46) 84	65	(1.5–2.8)
PSLE	9	34 (38–61) 86	67	(1.8–8.0)
ES	368	6 (33–37) 78	53	(1.0–1.4)
All patients	595	6 (35–39) 88	59	(1.6–2.1)



**Fig. 1.** Overall percent ROSQ response by diagnostic class. Expected percent symptoms reported on RoSQ in each population, controlling for sex and number of comorbidities using binomial regression. Error bars reflect standard error.

#### 3.1. Population-level statistics

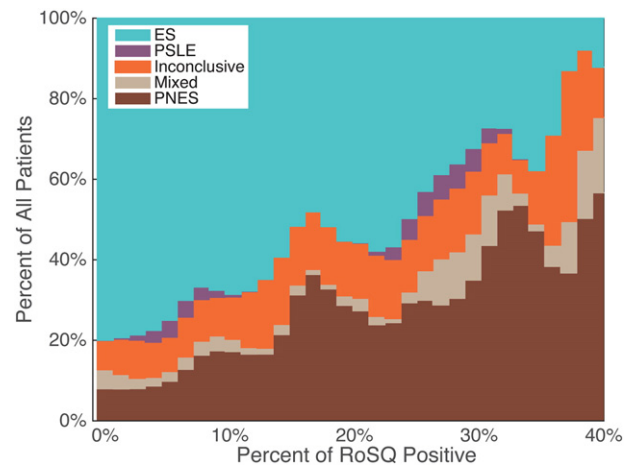
Controlling for sex and number of medical comorbidities, patients with PNES or mixed seizures reported a higher percentage of RoSQ symptoms than patients with ES or PSLE (Fig. 1,  $z > 14$ ,  $p < 10^{-16}$ ). There were no significant differences between ES and PSLE ( $z = 0.10$ ,  $p = 0.92$ ) or PNES and mixed ( $z = 0.56$ ,  $p = 0.58$ ). Patients with inconclusive monitoring were significantly different from all other populations ( $|z| > 5.3$ ,  $p < 10^{-7}$ ). Sex and number of medical comorbidities explained a significant amount of the variation in positive responses (female sex: 95% CI odds 1.23–1.32,  $p < 10^{-15}$ ; comorbid: 95% CI odds per comorbidity 1.076–1.087,  $p < 10^{-16}$ ).

The percent of each diagnostic subclass that responded with similar percent positive symptoms is visualized in Fig. 2. A full-width, half-max of 3% was chosen to visualize the full complexity of data efficiently while assuming that a difference of less than three symptoms was not meaningful. A direct comparison between patients with PNES and ES is visualized in Supplemental Fig. 2. A version of these figures including only retrospective patients is in Supplemental Fig. 3.

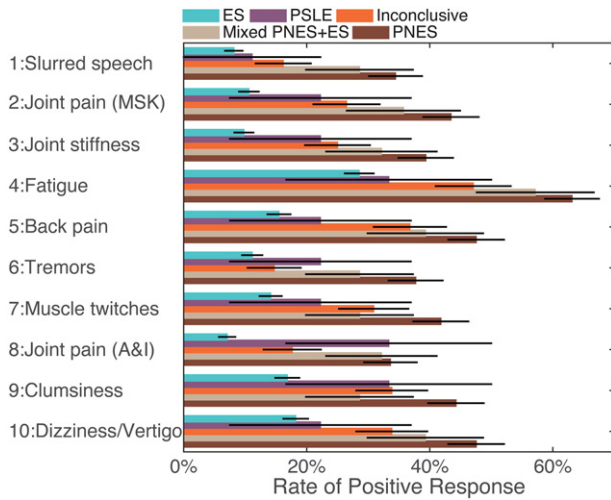
Controlling for sex and number of medical comorbidities, patients with PNES noted 52 of the 78 symptoms more frequently than patients with ES ( $q < 0.05$ , FDR corrected). The top 10 significant symptoms are displayed in Fig. 3. A list of all symptoms appears in Supplemental Table 2 and Supplemental Fig. 4. The prevalence of each system in the Asadi-Pooya and colleagues categories appears in Supplemental Table 3.

#### 3.2. Individual-level statistics

Based on the retrospective dataset, increasing percent RoSQ symptoms, female sex, and increasing number of comorbidities were all



**Fig. 2.** Diagnostic class based on RoSQ percent. Percent of patients in each diagnostic subtype based on percent positive RoSQ symptoms using combined dataset. Data smoothed full-width half-max 3%.



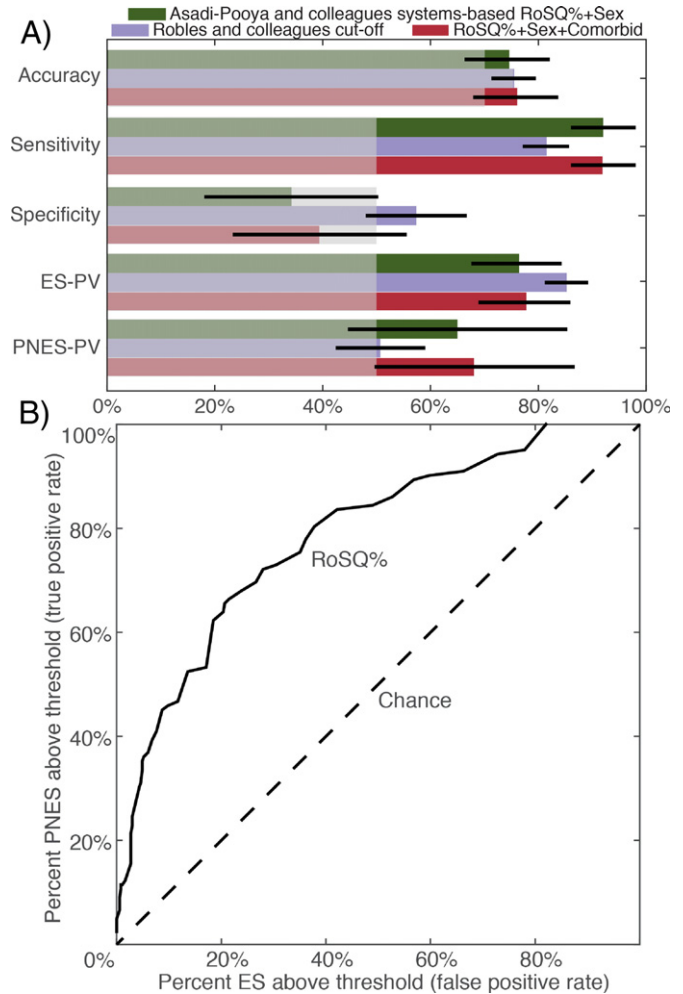
**Fig. 3.** Top 10 symptoms that differ between PNES and ES. Ranking determined by Wald-test between patients with PNES and ES, controlling for sex and number of comorbidities using logistic regression. Joint pain appeared twice in both the musculoskeletal (MSK) and allergy & immunology (A&I) sections. Error bars reflect standard error.

associated positively with PNES as compared to ES ( $p < 0.03$ , model summary in Supplemental Table 4). The interaction of female sex with percent RoSQ symptoms was not associated significantly with either PNES or ES (Wald,  $z = -1.18$ ,  $p = 0.23$ ). The prospective performance of this model, the Robles and colleagues 17% cut-off, and the Asadi-Pooya and colleagues systems approach are shown graphically in Fig. 4A. For numerical values of performance seen in Fig. 4A, please refer to Supplemental Table 5. The only significant difference on any performance measure between Robles and colleagues' cut-off and our model was in sensitivity (Fisher exact test, sensitivity 82% vs 92%, respectively,  $p < 0.05$ ; all other performance statistic differences had  $p > 0.1$ ). There were no significant differences between our model and the Asadi-Pooya systems approach (Fisher exact test,  $p > 0.1$ ).

The accuracy of a naïve assumption that diagnosed all patients with ES was 70% (88/126) and 75% (368/490) on the prospective dataset and combined datasets, respectively. The accuracy of all RoSQ-based methods was not significantly higher than the accuracy of this naïve assumption ( $p > 0.10$ ). The only binary-choice summary statistic that was significantly higher than both a chance classifier that predicted 50% of patients have PNES and the naïve assumption that all patients have ES was the predictive value of epilepsy using the Robles and colleagues 17% cut-off (85% vs 75%, binomial exact test,  $p < 0.05$ ). The epilepsy predictive value of our model and the Asadi-Pooya and colleagues approach did not differ from the naïve assumption (78% and 76% vs 75%,  $p > 0.1$ ). All PNES predictive values, sensitivities, and specificities were not significantly higher than both the chance classifier and naïve assumption.

The receiver-operating curve (ROC) of percent symptoms based on the combined dataset appears in Fig. 4B (AUC 77.0%). The leave-one-patient-out AUC on the retrospective group was 83% (95% CI 77–89%) compared to prospective AUC 74% (95% CI 63–84%,  $p = 0.76$ ). When symptoms were grouped by system, the AUC was 78% on the combined dataset. Attempts to differentiate PNES from ES using a combination of specific RoSQ symptoms, grouped responses to specific systems, or principle components of symptoms did not yield significant results (analysis not shown).

The cut-off that maximized the average of sensitivity and specificity in our retrospective dataset was 14.7% (balanced accuracy: 75%, sensitivity for ES: 92%, specificity for PNES: 37%). The systems-based cut-off that maximized the average of sensitivity and specificity in our retrospective dataset was 4 or more positive systems (balanced accuracy: 73%, sensitivity for ES: 78%, specificity for PNES: 30%).



**Fig. 4.** Performance statistics of individual-level predictions. A) Performance of binary prediction of patients with PNES vs ES based on Robles and colleagues 17% cut-off, and on our model including percent RoSQ symptoms, sex, and comorbidities. Error bars reflect exact binomial standard error. Shading reflects performance of a naïve assumption that all patients have ES or chance classifier. See Results for detailed description of significant differences. Abbreviations: predictive value (PV). B) Receiver-operating curve using the percent RoSQ symptoms alone to differentiate between patients with PNES and ES in the combined dataset. AUC 77%.

#### 4. Discussion

Review of system questionnaires provide unequivocally important information about patients' current symptoms and provides insight for how their disease affects their quality of life. Our results highlight the difference between population level and individual level statistical inference. On a population level, RoSQ responses highlight substantial differences between patients with psychogenic seizures and other organic causes of seizure-like events. However, this information was neither reliable nor consistent enough to differentiate between patients with PNES and ES on an individual level. Therefore, RoSQs should not be used solely as early screening tools to identify patients at risk for PNES without considering other information.

##### 4.1. Population-level inferences

On a population level, patients with PNES with and without comorbid ES reported greater than two times more RoSQ symptoms than patients with ES only and those with PSLE, after controlling for sex and number of comorbidities. In addition to our larger sample, these results suggest that patients with mixed PNES and ES may be similar to patients with PNES only. All patients with PNES therefore may have increased

somatic sensitivity, somatic dysfunction, or increased disability or distress caused by somatic symptoms [13,17,19]. This increased somatic sensitivity has been used to explain why patients with PNES tend to be diagnosed with more medical conditions [18,20–22]. By controlling for the number of comorbidities, we showed that this increase in comorbidities does not explain the increased number of RoSQ symptoms. This may reflect how patients with PNES report distress due to both minor symptoms covered on RoSQs as well as symptoms consistent with other medical conditions.

Our finding that patients with PNES responded more frequently to 52 of the 78 symptoms than patients with ES is consistent with the hypothesis that the hypersensitivity or conversion symptoms are present in all organ systems. One of the most general symptoms, fatigue, was reported in over 60% of patients with PNES, but was also reported in 30% of patients with ES. These multiple symptoms certainly reduce quality of life [19,23,24].

More specifically, musculoskeletal and joint pain was a common component of PNES, as evidenced by four of the top 10 symptoms relating to pains. The association of chronic pain with PNES is well established [21,25–28]. The prevalence of vestibular and coordination problems suggested by the presence of slurred speech, clumsiness, dizziness, and vertigo in the top 10 may be related to increased reported side-effect burden in PNES [29]. When viewed together with tremors and muscle twitches, these symptoms may represent common neurologic complaints of lower severity than seizures. This is consistent with the definition of conversion disorder of translating psychological stressors into neurological symptoms. Patients' belief prior to accurate diagnosis may be that they have a neurologic condition that causes multiple symptoms, one of which is seizures.

Conversion disorder can manifest as a wide array of symptoms and signs, as shown here by a diffuse elevation in the number of RoSQ symptoms. However, patients are unable to determine which symptoms are caused by conversion disorder and which are due to other conditions. Therefore, appropriate treatment of PNES should address both the seizures and the psychological challenges that may be expressed through other somatic complaints [9,10,12].

#### 4.2. Individual-level inferences

When a provider reviews a RoSQ, the patient's RoSQ responses should not change his or her base assumption that the patient with seizures probably has ES because ES are much more prevalent than PNES. In our combined dataset, this base assumption would diagnose 75% of patients correctly. Obviously, this practice would misdiagnose all patients with PNES, but our results suggest that there is no RoSQ response cut-off that would improve upon this overall diagnostic accuracy substantially, even if we grouped symptoms by systems. In particular, a pan-positive RoSQ with >60% symptoms marked occurred so rarely in patients with PNES (6/122) that it did not impact the overall accuracy. Even if providers focus on individual RoSQ symptoms or systems, the responses were not consistent enough to improve upon the base assumption that most patients have ES. Further, the lack of a significant interaction between RoSQ response and sex suggests that we did not find sufficient evidence to suggest that RoSQs should be interpreted differently in men and women.

This does not suggest that RoSQs provide no diagnostic information. As evidenced by the data in Figs. 2 and 4A, and by the high predictive value for ES of few RoSQ symptoms, if few symptoms were noted on the RoSQ then the likelihood of PNES was low. Therefore, RoSQ responses could reduce potential concern for PNES. However, the predictive value is not high enough to rule-out PNES completely. Additionally, patients with mixed ES plus PNES mirrored the results of patients with PNES alone. Therefore, a response pattern similar to PNES does not exclude the possibility of co-morbid epilepsy.

The comparison of our results with those of our colleagues suggests that the diagnostic utility of RoSQs depends upon the pre-test

probability of PNES. Our conclusion that RoSQs are not diagnostic in isolation is appropriate when considering the population of all patients admitted for monitoring where the pre-test probability of PNES was 25%. The difference between our approach and the approach of our colleagues is that they artificially set the pre-test probability to 50% by using a dataset with equal numbers of patients with PNES and ES [14] or maximizing the average of sensitivity and specificity [13]. Our high AUC of 77% and the similarity of our cut-offs with theirs suggest that if the pre-test probability of PNES is raised to 50% then the RoSQ may be useful in identifying patients at risk for PNES.

Pre-test probabilities of PNES can be modified based on the clinical context or clinical judgment regarding risk factors. The population with the lowest pre-test probability, 6%, is comprised of patients admitted to vEEG for pre-surgical assessment [30]. The wide population of adults presenting for outpatient seizures has a pre-test probability of 5–20% [31,32]. This probability rises slightly to 15–20% for adults referred to epilepsy treatment centers [33,34]. In these contexts where the pre-test probability of PNES is low, our results suggest that RoSQs do not provide diagnostic information.

One context where the pre-test probability of PNES is as high as 50% is in patients admitted to vEEG for differential diagnosis [30]. These patients have already been referred for the gold-standard diagnostic assessment, so RoSQs could not serve as an early screening tool or decision support tool to identify patients that should be referred. Therefore, the primary context for where RoSQs may be helpful is in patients that have risk factors for PNES including history of sexual abuse, significant psychiatric comorbidity, or atypical seizure semiology. While experienced clinicians can use their experience and judgment to qualitatively estimate pre-test probabilities of PNES, future work is necessary to estimate pre-test probabilities objectively in the context of these and other risk factors. Therefore, we did not find evidence that RoSQs should be used routinely as screening tools to identify patients at risk for PNES.

#### 4.3. Future directions & limitations

Given that the average diagnostic delay from first seizure to definitive diagnosis of PNES is 8.6 years [8], objective methods to identify patients at risk for PNES are necessary to assist in triaging patients quickly towards more definitive diagnosis with vEEG. This prospective validation of one possible early screening tool illustrates how it can be difficult to identify patients with PNES reliably. After an objective-screening tool has been validated prospectively in a vEEG population, the tool also would need to be confirmed in an outpatient setting, where the prevalence of PNES may be lower.

Additionally, as we highlight here, the diagnostic dilemma of seizures is not as simple as differentiating ES from PNES; one must consider the less prevalent conditions of PSLE and mixed ES plus PNES. The population of patients with inconclusive vEEG monitoring is difficult to study, because there is no definitive diagnosis. If we consider inconclusive patients to be a mix of patients with and without PNES, then using only RoSQ responses, our results suggest that 60% of inconclusive patients had PNES or mixed ES plus ES. This suggests that patients with inconclusive monitoring represent a roughly even mix of ES and PNES and provides further evidence that inconclusive monitoring should be interpreted as non-diagnostic as compared to negative. By reporting the population-level statistics for patients with PSLE, mixed ES plus PNES, and inconclusive monitoring, we begin to describe these patients that often are excluded from other studies.

One potential limitation of this work is the difference in rate of inconclusive monitoring between the retrospective and prospective datasets. The rate of inconclusive monitoring in the retrospective dataset likely was reduced by re-admitting patients, whereas patients who initially had inconclusive monitoring in the prospective time period had not been re-admitted yet. The inclusion of patients with inconclusive monitoring in analysis does not interfere with the conclusions

regarding the other diagnostic categories. Additionally, the relative percent of patients with PNES as compared to ES did not change between the retrospective and prospective groups; therefore, the difference in the relative percent of ES compared to all patients likely was driven by the inconclusive group. The admission criteria, diagnostic criteria and, to our knowledge, patient population of our center did not change in the past year; therefore, the minor differences between the retrospective and prospective groups likely represents natural variation in patient samples.

#### 4.4. Conclusion

Novel, objective methods to assist in the differentiation between patients with PNES and epilepsy are needed to reduce time to diagnosis, reduce risk of iatrogenic adverse effects, and reduce cost while improving quality of life and long-term seizure outcomes. Our analysis of a large, unselected dataset with definitive seizure diagnoses confirms the knowledge that patients with PNES experience many more symptoms across multiple organ systems as compared to patients with epilepsy. While physicians should be alert to that these symptoms are common in the PNES population, the diagnosis of an individual patient is not shifted substantially by this result without consideration of other information that raises the suspicion of PNES considerably.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.yebeh.2016.11.002>.

#### Conflicts and ethical publication

Drs. Engel, Stern, and Kerr have clinical responsibilities that include the diagnosis and treatment of patients with epilepsy and nonepileptic seizures. The remaining authors have no declared conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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