Epilepsy & Behavior 116 (2021) 107767

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Validation of a predictive calculator to distinguish between patients presenting with dissociative versus epileptic seizures

Steven Lenio [a,*], Wesley T. Kerr [b], Meagan Watson [a], Sarah Baker [a], Chad Bush [a], Alex Rajic [a], Laura Strom [a]

[a] Department of Neurology, University of Colorado, Aurora, CO, USA
[b] Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 7 December 2020
Revised 29 December 2020
Accepted 30 December 2020
Available online 2 February 2021

Keywords:
Psychogenic nonepileptic seizures
Functional seizures
PNES
PNEA
Machine learning
External validation

ABSTRACT

Dissociative seizures (also known as psychogenic nonepileptic seizures) are a common functional neurological disorder that can be difficult to distinguish from epileptic seizures. Patients with dissociative seizures provide diagnostic challenges, leading to delays in care, inappropriate care, and significant healthcare utilization and associated costs. The dissociative seizure likelihood score (DSLS) was developed by Kerr and colleagues at UCLA to distinguish between patients with epileptic seizures and dissociative seizures based on clinical and medication history as well as features of seizure semiology. We validated this calculator at the University of Colorado, which is a Level 4 National Association of Epilepsy Center. The DSLS accurately predicted the diagnosis in 81% of patients, despite local variability in the factors associated with epileptic versus dissociative seizures between the two populations. The DSLS can be a useful tool to assist with history taking and may have important utility for clinical decision making with these difficult to distinguish patient populations.

1. Introduction

Dissociative seizures (psychogenic nonepileptic seizures, nonepileptic seizures, functional seizures) are a common occurrence encountered both in the emergency department, general neurologists' offices, and epilepsy centers [1,2]. Dissociative seizures refer to paroxysmal events where patients lose voluntary control of motor, sensory, or cognitive function and can outwardly resemble, and are mistaken for, epileptic seizures. These paroxysmal events also may resemble other physiological phenomena including complex migraine, syncope, and paroxysmal dyskinesia. There is ongoing debate regarding the terminology of dissociative seizures, but for consistency and ease of comparing our results with the work this paper is based on, the term dissociative seizures will be used going forward [3–5].

Estimates of the incidence of dissociative seizures (DS) range from 1.4-4.9/100,000 patients per year, with an estimated 20% of patients referred to epilepsy centers ultimately receiving a diagnosis of dissociative seizures [6,7]. These patients present similarly to patients with epilepsy and regularly create diagnostic dilemmas [8,9]. Delays from first event to reaching a diagnosis of DS average just over 7 years [10–12]. These delays yield burdensome healthcare costs comparable to or higher than drug-resistant epilepsy and can be reduced dramatically with accurate diagnosis [13–15]. Prior work shows that over the 12 months preceding diagnosis, individual patients with DS incurred mean healthcare costs of $4567, compared to $2784 in the 12 months after diagnosis, for a mean total reduction of $1783 [16]. Poor understanding of the etiology of DS, coupled with reliance on a coordinated effort between the often disparate fields of neurology and psychiatry, limit current treatment efforts [17].

Efforts to diagnose DS based on seizure semiology alone are often limited by the reliability of eye-witness report from untrained observers [18]. Direct observation of a typical seizure with simultaneous video-electroencephalography (vEEG) is the gold standard for diagnosis [9,19–21]. Recent work to develop a predictive calculator based on information obtained in an outpatient encounter shows a promising ability to accurately predict whether a patient has DS or epileptic seizures (ES) [22–26]. This paper aimed to validate the dissociative seizure likelihood score (DSLS) developed by Kerr and colleagues at UCLA at an independent institution, as well as evaluate the variation in local patterns of histories of patients referred to two tertiary care centers for seizures [23].

Abbreviations: ES, epileptic seizures; DS, dissociative seizures; DSLS, dissociative seizure likelihood score.

* Corresponding author at: Department of Neurology, University of Colorado Anschutz Medical Campus, 12700 E. 19th Avenue, Aurora, CO 80045|MS B182, USA. Fax: +1 (720) 848 0194.
E-mail address: steven.lenio@cuanschutz.edu (S. Lenio).

https://doi.org/10.1016/j.yebeh.2021.107767
1525-5050/

2. Material and methods

2.1. Data collection methods

Permission was obtained for this chart review study by the Colorado Multiple Institutional Review Board (COMIRB) with a waiver for informed consent on the basis that all clinical information collected was initially obtained as a standard of routine medical care during admission to the epilepsy monitoring unit for either characterization of spells concerning for seizure or pre-surgical evaluation.

Patients with a vEEG confirmed diagnosis or documented diagnosis of DS (documented diagnosis refers to when vEEG was performed outside our system, but the report, not necessarily the raw EEG data, could be reviewed) were identified from a database of consecutive patients referred to the Functional Neurological Disorders Clinic between January 1 2017 and May 15 2019 [27]. All patients with epilepsy were identified from an EEG database with a confirmed diagnosis of epilepsy by vEEG, that were admitted to the University of Colorado (CU) Epilepsy Monitoring Unit (EMU) for video-EEG (vEEG) during the same time period. We randomly selected from this list of patients with epilepsy to create two groups of an equal number of patients with DS and ES. In addition, we included patients with a dual diagnosis of DS and ES during this time period, because of the great clinical importance of this group and relative paucity of data regarding them [28]. We excluded patients with a nondiagnostic EEG and inadequately detailed history on retrospective chart review.

All relevant demographic and clinical data were collected from either an EMU admission note, or the first available neurology intake note in the electronic health record (EHR). If multiple notes were available, the earliest clinical encounter that provided a description of the patient's seizure and pertinent history was used. Clinical variables collected were based on prior work by Kerr and colleagues [22,23,29,30], but also included variables that were of interest at the University of Colorado. These factors are listed in Table 1, which includes the factors of the DSLS (marked by asterisk). Retrospective chart review was performed by three CU Neurology Residents (SL, CB, AR) and one faculty (LS). Statistical analysis on de-identified data was performed by Dr. Kerr.

Table 1
List of historical features, peri-ictal behavior, comorbidities, and medication history studied. Factors included in the DSLS marked by *.

Sex*
Number of Non-psychiatric comorbidities*
Number of current non-anti-seizure, non-psychiatric medications*
History of asthma*
History of migraine*
History of chronic pain
History of diabetes mellitus
History of non-metastatic cancer
Number of current anti-seizure medications
Number of prior anti-seizure medications*
Time since first unprovoked seizure*
Monthly seizure frequency*
Average duration of seizure*
Number of seizure types*
Injury with seizure
Catamenial seizures
Trigger of sleep deprivation*
Aura
Ictal eye closure*
Ictal hallucinations*
Oral automatisms
Incontinence*
Limb automatisms*
Oral automatisms
Ictal tonic-clonic movements
Muscle twitching
Hip thrusting*
Postictal fatigue
Any prior head injury*
Concussion without loss of consciousness
Concussion with loss of consciousness
TBI with loss of consciousness > 30 min
Active opioid prescription
History of psychiatric trauma*
History of sexual abuse*
History of physical abuse
History of rape

2.2. Statistical modeling of patient-reported factors

We analyzed the relationship of patient-reported factors with individual-level predictive statistics. In predictive statistics, we ask if the seizure etiology of an individual patient can be predicted by the pattern of reported factors. This is in contrast to descriptive statistics where we ask if specific factors were associated with a particular seizure etiology on a population level.

For the individual-level predictive statistics, we used three approaches. First, we applied the DSLS directly to the patients seen at the University of Colorado (DSLS*). Second, we used the same patient-reported factors that contribute to the DSLS, but retrained the multivariate piecewise linear logistic regression using leave-one-out-cross-validation from the University of Colorado data alone (UC-DSLS). Due to limited data, we did not re-determine the cutoff of the piecewise linear modeling of time since onset; we used the DSLS cutoffs to determine when longer time since onset did not influence the likelihood of DS [30]. Lastly, we added factors of interest based on trends observed at the University of Colorado to evaluate if these additional factors improved predictive performance and validated this expanded model with leave-one-out cross-validation (UC-DSLS+). All code was written in MATLAB (Mathworks, Natick, MA, USA).

All models were validated with data from patients with either DS alone or ES alone in the University of Colorado dataset. Instead of reporting positive and negative predictive values, we report the predictive value of DS and ES that are defined similarly because our population lacks healthy negative controls. Statistically, the binary comparison of DS versus ES is well posed and well-studied. Simultaneous identification of patients with dual diagnosis of ES and DS is challenging and we report the rate that our scores predicted the patient had ES only.

2.3. Missing data

Due to the retrospective nature of our work, the presence of our studied factors was based on review of clinical notes that did not discuss all studied factors uniformly. With a few exceptions, if a factor was not mentioned, it was assumed to not be present because the authors of the clinical notes may not mention all pertinent negatives if they do not contribute to the overall story of the patient, even if they were asked as part of the interview. The exceptions to this include time from first seizure to vEEG, seizure duration, and seizure frequency because these factors clearly were defined in each patient, even when not discussed. In the development of the DSLS, a multiple imputation model to fill in these data was created based on the UCLA data [31,32]. These UCLA-based multiple imputation models filled in the missing data from the University of Colorado probabilistically based on the best estimate established from collinearity among the observed factors. These models assume conservatively that the probability that these elements were missing completely at random (MCAR), which is defined by the probability of missingness being unrelated to diagnosis, the value of the missing data, or any other measured variable

[31,32]. No information from the University of Colorado was used for multiple imputation. If the probability of missingness was correlated with diagnosis or the missing value, then this approach introduces bias that underestimates the effect of the imputed factor. Based on the available data, it is impossible to evaluate if this bias exists. For additional details regarding the implementation of multiple imputation, see these prior manuscripts [22,29,30].

2.4. Determining significance

To descriptively compare the patient-reported responses, we split the factors into two types: continuous and binary. For binary (yes/no) factors, we compared the prevalence in ES and DS using Fisher exact statistics. For continuous factors, we used heteroskedastic two-sample t-tests, where seizure frequency, seizure duration, and time since seizure onset were considered log-normally distributed. These univariate descriptive statistical comparisons excluded patients where that specific factor was missing (complete case analysis).

We compared the structure and performance of the individual-level predictive models. To compare odds ratios between the DSLS and the model trained using the University of Colorado data, we used heteroskedastic z-tests based on the estimated magnitude and variance of the log odds ratio. While we used leave-one-out-cross-validation to assess performance, we used the full University of Colorado dataset to estimate the odds ratios for these comparisons. We used ad-hoc Wald statistics to determine which factors significantly contribute to the full model. We used two-sample Fisher exact tests to evaluate individual model's performance and Cohen's kappa statistics to compare models' predictions.

2.5. Data availability policy

De-identified raw data and code for this study are available on Mendeley. An online interactive version of the DSLS is linked on SeizureDisorderCenterResearchGroup.org.

3. Results

Age and sex across the 3 groups are summarized in Table 2. The performance of the DSLS*, UC-DSLS, and UC-DSLS+ are summarized in Table 3. The kappa between the DSLS* and the UC-DSLS was 69% (95% CI 60–79%) and the kappa between the DSLS* and the UC-DSLS+ was 57% (95% CI 46–67%). The significant odds ratios from the multivariate logarithmic regression analysis of the University of Colorado population are summarized in Fig. 1. Performance of patients with dual diagnosis of DS and ES is summarized in Fig. 2 and the rate of predicted DS mirrored the pre-test probability of DS in a vEEG dataset.

There are numerous significant differences in the patient-reported factors between the University of Colorado and UCLA datasets, which are summarized in Supplemental Table 1. In addition to these differences in patient-reported factors, due to the varying selection criteria, the prevalence of DS, both ES and DS, and ES differed between the University of Colorado and UCLA datasets (chi-squared 114.17, p-value 9.4×10^{-24}). Specifically, 56% ($n = 135$) and 13% ($n = 31$) of patients had DS and both ES and DS, respectively.

Table 2
Demographics.

	ES ***n*** = 76	DS ***n*** = 135	ES & DS ***n*** = 31
Age (SD)	37 (15)	38 (13)	34 (12)
Female Sex % (*n*)^	45% (34)	79% (107)	67% (22)

^Denotes significant difference with p-value < 0.05 between DS and ES.

Table 3
Performance statistics of DSLS.

Estimate (95% CI)	DSLS*	UC-DSLS	UC-DSLS+
Accuracy	81% (76–86)	84% (78–89)	82% (77–87)
Sensitivity	82% (72–89)	75% (64–84)	79% (70–88)
Specificity	81% (74–87)	89% (83–94)	84% (77–90)
ES-PV	78% (69–86)	80% (70–89)	74% (64–83)
DS-PV	88% (82–93)	86% (80–92)	87% (81–93)
AUC	82% (71–89)	83% (71–90)	82% (71–90)

PV = predictive value. AUC = area under the curve.

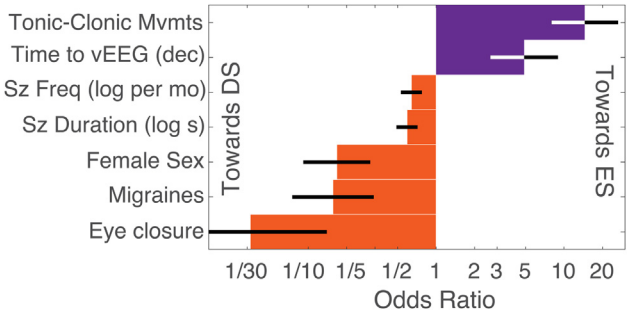

Fig. 1. Multivariate odds ratios of factors in the UC-DSLS found to significantly distinguish between DS and ES using University of Colorado data ($p < 0.05$). Error bars reflect standard error. Bar color reflects if the factor was associated with either ES (purple) or DS (orange). Abbreviations: movements (mvmts), decades (dec), seizure frequency (Sz Freq), month (mo), seconds (s).

Prevalence and univariate comparisons of the studied factors are summarized in supplemental tables 2–4. Numerous factors significantly distinguished between DS and ES in univariate analysis, including chronic pain, opioid use, any prior head injury, history of psychiatric trauma, physical abuse, and sexual abuse among others. Not all of these had a significant conditionally independent association with either DS or ES in the multivariate logarithmic regression analysis. In the University of Colorado data, time since seizure onset, seizure frequency, and seizure duration were missing in 3.1%, 2.3%, and 5.4% of patients with DS, respectively; and 3.3%, 0%, and 6.5% of patients with both ES and DS, respectively; and 5.3%, 1.4%, and 1.4% of patients with ES, respectively.

4. Discussion

This study was an external validation that demonstrated that the DSLS generalized to patients at the University of Colorado. Despite differences in specific factors associated with each seizure type in the University of Colorado population compared to the UCLA population, the overall performance was robust. This robust performance may be due to incorporation of objective data regarding comorbidities, medications, and history, as opposed to relying on seizure semiology alone. Numerous prior papers address the differences in semiology between epileptic and nonepileptic seizures [9,19–21,29,33,34]. Unfortunately, decisions regarding seizure management are often made on the basis of eyewitness reports, and data suggest these reports inadequately describe seizure semiology [18]. Even when viewing videos of seizures, the accuracy of healthcare providers' impression is highly dependent on level of training, with the AUC of 72% for internal medicine physicians and 89% for neurologists [8]. However, among neurologists, interrater agreement was moderate, leading to only 30% of patients with nonepileptic seizures being clinically established by video alone [8,35,36].

There were a number of differences in the prevalence of the factors we studied between the UCLA and University of Colorado (UC)

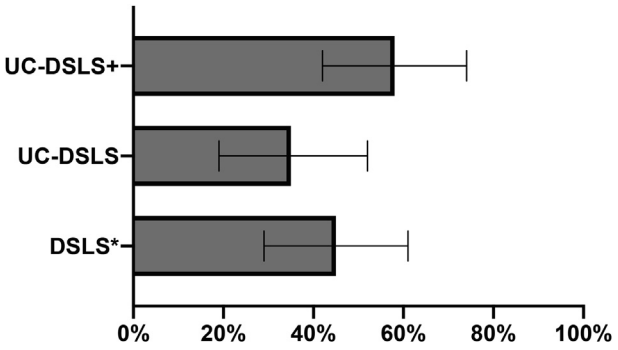

Fig. 2. Calculator predictions for patients with both DS and ES. Percentage of patients with both epileptic and dissociative seizures predicted to have epilepsy by the DSLS*, UC-DSLS, and UC-DSLS+ calculators. Error bars reflect standard error.

data. We independently replicated differences between ES and DS in 9 of the 20 factors of the DSLS. For most factors, the predictive performance and point estimates suggest that similar patterns were seen in the UC population, but some factors were relatively rarely encountered in our sample (supplemental tables 2–4). There were, however, two important differences: number of seizure types and traumatic brain injury (TBI).

In the UCLA population, an increased number of seizure types was associated with DS, whereas it was associated with ES in the UC population. One potential explanation for this finding is the nature in which neurologists record seizure types. At our institution, we typically find two approaches: "lumpers" and "splitters." The "splitters" attempt to record every spell type that has *any* possible difference from other spell types (an extreme example would be including a focal seizure type with left hand tingling as distinct from a seizure type that starts with left hand tingling that then spreads to the elbow), whereas "lumpers" tend to combine seizure types with minor differences that start similarly and share the vast majority of features. The UCLA approach favored "lumping" whereas our results suggest UC providers are more "splitters." Variable approaches to documentation in the setting of a small sample may be contributing to this apparent discrepancy.

History of TBI represents another inflection point between these groups of patients, but unfortunately can be difficult to untangle based on lack of granular descriptions of TBI severity in documentation, as well as relatively broad definitions of the varying severities. Moderate and severe TBI, especially those with significant neuro-imaging abnormalities (subdural hematoma, midline shift, etc), are well-documented risk factors for developing epilepsy [37]. Concussion or mild TBI have been linked to DS in the DSLS and elsewhere, and this association has evoked hypotheses regarding possible pathophysiological mechanisms [38,39]. We did not independently replicate this association between concussion with or without loss of consciousness in the UC population. In contrast, TBI without concussion was found to predict ES in the UCLA population, and indicators for more severe TBI did not significantly contribute to the predictive model. Similarly, TBI with prolonged loss of consciousness (>30 min) predicted ES in the UC population. Further complicating this situation, patients recorded as having "any prior head injury" that included concussion with or without loss of consciousness, severe TBI, or any other recalled head injury without enough details to clearly define, were found by univariate analysis to be more likely to have DS. These varying and evolving definitions of TBI along with unavoidable recall bias make these associations difficult to interpret. Based on these differences, future work is needed to specifically study how TBI is defined and what aspects of TBI are associated with DS as compared to ES. Despite these differences in univariate analyses, the DSLS still proved a powerful tool in distinguishing these populations.

Psychiatric comorbidities, including PTSD, are found at higher rates among patients with DS compared to ES [40]. Due to the unfortunate divide between psychiatry and neurology, neurologists may focus on evaluating the seizures and medical comorbidities, with relatively less emphasis on the psychiatric comorbidities that are common in both DS and ES. This may reflect a lack of training or familiarity with diagnostic criteria for psychiatric illness. Additionally, some patients may be reluctant to reveal the relevant historical details of traumatic events and psychiatric comorbidities at an initial visit before a strong trust and rapport is developed between the patient and provider, which may result in our data underestimating the prevalence of these features in our population. While these factors are important to developing treatment plans for DS, our data and the data used to develop the DSLS showed that detailed evaluation of psychiatric diagnostic criteria may not be necessary for triage. However, inquiring about psychological trauma and sexual abuse was critical to identification of patients with DS. Similarly, even though chronic pain is found at higher rates in patients with dissociative seizures [22,41], we find that patients are often given chronic pain diagnoses (for example, fibromyalgia) without clearly meeting appropriate diagnostic criteria [42]. We found that the number of active opioid prescriptions was associated with DS and DS&ES compared to ES, which may serve as a useful, more objective method of capturing chronic pain in these populations.

The literature is limited regarding patients with dual diagnoses [28]. The reported frequency of patients with a dual diagnosis of DS and ES ranges from 2% to 42%, depending heavily on the study design, with studies aimed at identifying patients with refractory epilepsy undergoing surgical work-up yielding lower frequencies, and those recruiting DS patients, reporting higher frequencies [43]. There are aspects of the clinical presentations of these patients that suggest a combination of two distinct entities which is reflected by exhibiting characteristics of both ES and DS, while some characteristics appear to support a unique pathophysiological phenomenon [22,30]. Similar to how the DSLS performed in the UCLA population, patients with dual diagnosis were not consistently identified as either ES or DS alone. Further work is needed to address this diagnostically and clinically challenging population.

Though we have validated the DSLS's performance outside UCLA despite variations within the populations at UCLA and UC, more work needs to be done to determine how this calculator could and should be used in clinical practice. While the DSLS relies on a standard interview mirroring a neurological history, other written patient-and caregiver-completed questionnaires have been developed and may help inform and supplement the DSLS [24–26]. We suspect that integration of this historical information with neurodiagnostics can assist in considering the diagnosis of DS prior to vEEG [27].

Inpatient hospitalization for vEEG monitoring is expensive and is not available in many countries, including industrialized countries [44,45]. For example, 50% of patients in the United Kingdom who participated in the CODES trial had not undergone vEEG monitoring [46,47]. The typical wait time for an EMU (epilepsy monitoring unit) stay at our institution is 6–8 weeks with an average of 30 patients on the waiting list, yielding effective wait times of up to 12 weeks. However, this wait is short compared to the median of 3 years and average of 7 years from first seizure to vEEG monitoring [11,12].

The primary utility of the DSLS is as a triage tool in instances where EMUs are either underutilized or have limited bed availability. For instance, surgical evaluation for epilepsy is cost-effective and substantially improves quality of life and risk of Sudden Unexpected Death in Epilepsy (SUDEP); therefore, one may initially suggest that epilepsy might take the highest priority [48]. However, as we showed, accurate diagnosis of DS substantially reduces health-

care utilization, and others have shown quality-of-life improvements with treatment as well as increased risk of death in patients with DS [13,47,49]. In fact, patients with DS have the same elevated risk of death as patients with epilepsy, albeit for different reasons [49]. Therefore, if the goal of an EMU is to provide better care to patients with seizures while reducing direct and indirect healthcare costs, it may be appropriate to serve a mixture of patients with epilepsy and dissociative seizures.

At minimum, raising the suspicion for DS early on may improve the delay from first seizure to accurate diagnosis of DS, which has been associated with better outcomes [15]. The targeted epilepsy histories obtained from patients and caregivers are only a small part of the clinical picture. A full medical history, physical exam, and review of diagnostic studies including labs, imaging, and prior EEGs, can and should be used to complement this calculator and increase diagnostic certainty [27]. Future work is needed to integrate this neurodiagnostic testing into evidence-based diagnosis and treatment protocols.

In addition to these well-established diagnostic technologies, the diagnostic accuracy of other technologies like ambulatory EEG, home-based vEEG, patient-provided seizure videos, and wearable devices are promising, but have yet to be established for DS [50]. While the DSLS alone is not accurate enough to replace vEEG, these and other predictive tools may assist in identifying patients that may benefit from referral to therapy as vEEG is nonurgently scheduled, based on a better estimate of the pre-test probability. This can expedite care because, as shown by the substantial delay between diagnosis of DS and initiation of therapy in the CODES trial, there also may be barriers to prompt psychological care [47]. There is some evidence that the psychological interventions frequently employed as part of the treatment plan for DS may have benefit in patients with epilepsy as well, but how to optimize treatment while patients are undergoing this potentially prolonged diagnostic journey remains an important question requiring further research [51–53]. Our group's recent work detailed the feasibility of a group therapy model for patients with dissociative seizures that led to significant reductions in healthcare utilization, as measured by a reduction in neuroimaging of 91%, epilepsy monitoring unit admissions of 95%, emergency room or urgent care visits for seizures of 75%, and a 66% reduction in overall inpatient stays when comparing before and after treatment [13]. As this and other effective treatment strategies for DS are developed, failure to quickly identify patients with DS will not only result in potential unnecessary treatment with ASMs, but also delays to treatments that are effective for DS.

As predictive tools are developed, an important question should be asked: how confident does a clinician need to be in the diagnosis of nonepileptic seizures to forego treatment with an ASM? ASMs can worsen psychiatric comorbidities common in both ES and DS, as well as cause rashes, electrolyte imbalances, effects on the hematopoietic system, and liver and renal dysfunction [54]. Inappropriate withholding of ASMs also may increase the risk of SUDEP, which is a rare but well-known, worst-case outcome of uncontrolled epilepsy [55]. Given the significant risks of either using unnecessary ASMs in patients with DS or not appropriately escalating medical and surgical therapies in patients with ES, the DSLS and other similar predictive approaches are unlikely to ever replace vEEG, and that is not their goal. Instead, future prospective work can evaluate how these objective technologies can be integrated into clinical care to improve patients' morbidity and mortality, while also being cost-effective. Especially as medical care becomes more protocolized, evidence-based clinical decision support tools can be integrated into clinical guidelines to maximize the quality of care that we provide patients.

This study has several important limitations. The nature of a chart review study relies on the ability of numerous providers to accurately elicit, recall, and document the relevant details from their patient encounters. While unsettling for all neurologists, EEG-negative epileptic seizures do exist. Despite the vEEG being considered the gold standard diagnostic test for distinguishing between an epileptic and nonepileptic seizure, it is not infallible [56]. While we use non-EEG criteria to identify scalp EEG-negative epileptic seizures, some of our patients classified as having nonepileptic seizures, may have epileptic seizures with a deep epileptic focus, though this is suspected to be a rare phenomenon. The work at UCLA evaluated 76 separate factors to establish the 20 that contribute to the DSLS, and we focused on the 20 that were included in the DSLS plus other selected factors. Though the factors we added to the DSLS did not substantially improve performance, it remains possible that prospective evaluations including factors not well documented in clinical notes or unique to the University of Colorado population may improve predictive performance.

In addition, this external validation of the DSLS is based on patients who were already referred for vEEG monitoring. While we believe the DSLS has great potential clinical impact, the DSLS needs to be validated in an outpatient population that has not yet been referred for vEEG. The goal of this outpatient validation would be to show that using the DSLS leads to shorter delay to vEEG, and thereby improved quality of life, seizure severity, and ideally healthcare costs.

5. Conclusion

This retrospective, chart review study provides external validation that the DSLS accurately distinguishes between patients with epileptic versus dissociative seizures, with the notable exception of patients with both epileptic and dissociative seizures. The University of Colorado data independently verified the association of 9 of the 20 features in the DSLS (ES associations: tonic clonic movements, longer time since seizure onset, lower seizure frequency, shorter seizure duration; DS associations: female sex, comorbidity of migraine, and ictal eye closure). The University Colorado data differed from UCLA regarding TBI, where the University of Colorado found that severe TBI was associated with epilepsy, and the UCLA data found that TBI without concussion was associated with epilepsy (including TBI more severe than concussion), but concussion was associated with DS. Likely due to the smaller sample size at the University of Colorado, we did not independently verify the significance of the other features in the DSLS. While each of the associations in both datasets had been demonstrated before, this work provides further evidence for a short list of core associations with DS and ES that may be consistent across centers. By identifying these generalizable associations, future work can address common challenges in patients with DS (e.g. high seizure severity as suggested by frequent seizures with long duration) and also design better studies to measure the pathophysiological correlates of DS (e.g. disruption of neurite morphology in DS, independent of the effect of TBI) [39].

In addition to these generalizable associations, the DSLS distinguished between DS and ES with similar accuracy between the UCLA and University of Colorado populations. Therefore, the DSLS's performance may be consistent across comprehensive epilepsy centers. Based on this demonstration of external validity, future work also could explore practical utilization of the DSLS as a triage tool at UCLA, the University of Colorado, and other centers, with the goal of improving patient outcomes as well as healthcare costs.

Declaration of interest and study funding

Drs. Lenio, Kerr, Bush, Rajic, and Strom have clinical responsibilities that include the diagnosis and treatment of patients with epi-

lepsy and nonepileptic seizures. Dr. Kerr receives honoraria from Medlink for articles on this topic. 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.

Funding: This study was partially funded by NIH R25 NS065723.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.107767.

References

[1] Ahmad O, Ahmad KE. Functional neurological disorders in outpatient practice: an Australian cohort. J Clin Neurosci 2016;28:93–6.
[2] Kerr WT, Anderson A, Lau EP, Cho AY, Xia H, Bramen J, et al. Automated diagnosis of epilepsy using EEG power spectrum. Epilepsia 2012;53(11): e189–92.
[3] Asadi-Pooya AA, Brigo F, Mildon B, Nicholson TR. Terminology for psychogenic nonepileptic seizures: making the case for "functional seizures". Epilepsy Behav 2020;104(Pt A):106895.
[4] Beghi M, Peroni F, Cornaggia CM. Reply to: We need a functioning name for PNES: considering dissociative seizures. Epilepsy Behav 2020;109:107084.
[5] Kerr WT, Stern JM. We need a functioning name for PNES: consider dissociative seizures. Epilepsy Behav 2020;105:107002.
[6] Asadi-Pooya AA, Sperling MR. Epidemiology of psychogenic nonepileptic seizures. Epilepsy Behav 2015;46:60–5.
[7] Lesser RP. Psychogenic seizures. Neurology 1996;46(6):1499–507.
[8] Seneviratne U, Rajendran D, Brusco M, Phan TG. How good are we at diagnosing seizures based on semiology? Epilepsia 2012;53(4):e63–6.
[9] Syed TU, LaFrance WC, Kahriman ES, Hasan SN, Rajasekaran V, Gulati D, et al. Can semiology predict psychogenic nonepileptic seizures? A prospective study. Ann Neurol 2011;69(6):997–1004.
[10] Reuber M, Fernández G, Bauer J, Helmstaedter C, Elger CE. Diagnostic delay in psychogenic nonepileptic seizures. Neurology 2002;58:493–5.
[11] Kerr WT, Janio EA, Le JM, Hori JM, Patel AB, Gallardo NL, et al. Diagnostic delay in psychogenic seizures and the association with anti-seizure medication trials. Seizure 2016;40:123–6.
[12] Reuber M, Fernández G, Bauer J, Helmstaedter C, Elger CE. Diagnostic delay in psychogenic nonepileptic seizures. Neurology 2002;58(3):493–5.
[13] Libbon R, Gadbaw J, Watson M, Rothberg B, Sillau S, Heru A, et al. The feasibility of a multidisciplinary group therapy clinic for the treatment of nonepileptic seizures. Epilepsy Behav 2019;98:117–23.
[14] Seneviratne U, Low ZM, Low ZX, Hehir A, Paramaswaran S, Foong M, et al. Medical health care utilization cost of patients presenting with psychogenic nonepileptic seizures. Epilepsia 2019;60(2):349–57.
[15] Walczak TS, Papacostas S, Williams DT, Scheuer ML, Lebowitz N, Notarfrancesco A. Outcome after diagnosis of psychogenic nonepileptic seizures. Epilepsia 1995;36(11):1131–7.
[16] Ahmedani BK, Osborne J, Nerenz DR, Haque S, Pietrantoni L, Mahone D, et al. Diagnosis, costs, and utilization for psychogenic non-epileptic seizures in a US health care setting. Psychosomatics 2013;54(1):28–34.
[17] Baslet G. Psychogenic nonepileptic seizures: a treatment review. What have we learned since the beginning of the millennium? Neuropsychiatr Dis Treat 2012:585.
[18] Mannan JB, Wieshmann UC. How accurate are witness descriptions of epileptic seizures? Seizure 2003;12(7):444–7.
[19] Brigo F, Nardone R, Ausserer H, Storti M, Tezzon F, Manganotti P, et al. The diagnostic value of urinary incontinence in the differential diagnosis of seizures. Seizure 2013;22(2):85–90.
[20] Brigo F, Storti M, Lochner P, Tezzon F, Fiaschi A, Bongiovanni LG, et al. Tongue biting in epileptic seizures and psychogenic events: an evidence-based perspective. Epilepsy Behav 2012;25(2):251–5.
[21] Devinsky O, Gazzola D, LaFrance Jr WC. Differentiating between nonepileptic and epileptic seizures. Nat Rev Neurol 2011;7(4):210–20.
[22] Kerr WT, Janio EA, Braesch CT, Le JM, Hori JM, Patel AB, et al. Identifying psychogenic seizures through comorbidities and medication history. Epilepsia 2017;58(11):1852–60.
[23] Kerr WT, Janio E, Chau AM, Braesch CT, Le JM, Hori J, et al. Objective score from initial interview identifies patients with probable dissociative seizures. Epilepsy Behav 2020;113:107525.
[24] Wardrope A, Jamnadas-Khoda J, Broadhurst M, Grünewald RA, Heaton TJ, Howell SJ, et al. Machine learning as a diagnostic decision aid for patients with transient loss of consciousness. Neurol Clin Pract 2020;10(2):96–105.
[25] Chen M, Jamnadas-Khoda J, Broadhurst M, Wall M, Grünewald R, Howell SJL, et al. Value of witness observations in the differential diagnosis of transient loss of consciousness. Neurology 2019:p. https://doi.org/10.1212/WNL.000.
[26] Trainor D, Foster E, Rychkova M, Lloyd M, Leong M, Wang AD, et al. Development and validation of a screening questionnaire for psychogenic nonepileptic seizures. Epilepsy Behav 2020;112:107482.
[27] Lafrance WC, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach. Epilepsia 2013;54(11):2005–18.
[28] Baroni G, Piccinini V, Martins WA, de Paola L, Paglioli E, Margis R, et al. Variables associated with co-existing epileptic and psychogenic nonepileptic seizures: a systematic review. Seizure 2016;37:35–40.
[29] Kerr WT, Chaud AM, Janio EA, Braesch CT, Le JM, Hori JM, et al. Reliability of reported peri-ictal behavior to identify psychogenic nonepileptic seizures. Seizure 2019;67:45–51.
[30] Kerr WT, Janio EA, Braesch CT, Le JM, Hori JM, Patel AB, et al. An objective score to identify psychogenic seizures based on age of onset and history. Epilepsy Behav 2018;80:75–83.
[31] Rubin DB. Multiple imputation after 18+ years (with discussion). JASA 1996;91:473–89.
[32] Rubin DB. Multiple imputation for non-response in surveys. New York: John Wiley & Sons; 1987.
[33] Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? J Neurol Neurosurg Psychiatry 2010;81(7):719–25.
[34] Chung SS, Gerber P, Kirlin KA. Ictal eye closure is a reliable indicator for psychogenic nonepileptic seizures. Neurology 2006;66(11):1730–1.
[35] Seneviratne U, Ding C, Bower S, Craig S, Leech M, Phan TG. Video-based training improves the accuracy of seizure diagnosis. J Neurol Neurosurg Psychiatry 2014;85(4):466–70.
[36] Erba G, Giussani G, Juersivich A, Magaudda A, Chiesa V, Laganà A, et al. The semiology of psychogenic nonepileptic seizures revisited: Can video alone predict the diagnosis? Preliminary data from a prospective feasibility study. Epilepsia 2016;57(5):777–85.
[37] Xu T, Yu X, Ou S, Liu X, Jinxian Y, Huang H, et al. Risk factors for posttraumatic epilepsy: a systematic review and meta-analysis. Epilepsy Behav 2017;67:1–6.
[38] Popkirov S, Carson AJ, Stone J. Scared or scarred: Could 'dissociogenic' lesions predispose to nonepileptic seizures after head trauma? Seizure 2018;58:127–32.
[39] Goodman AM, Allendorfer JB, Blum AS, Bolding MS, Correia S, Ver Hoef LW, et al. White matter and neurite morphology differ in psychogenic nonepileptic seizures. Ann Clin Transl Neurol 2020;7(10):1973–84.
[40] Salinsky M, Rutecki P, Parko K, Goy E, Storzbac D, O'Neil M, et al. Psychiatric comorbidity and traumatic brain injury attribution in patients with psychogenic nonepileptic or epileptic seizures: a multicenter study of US veterans. Epilepsia 2018;59(10):1945–53.
[41] Benbadis SR. A spell in the epilepsy clinic and a history of "chronic pain" or "fibromyalgia" independently predict a diagnosis of psychogenic seizures. Epilepsy Behav 2005;6(2):264–5.
[42] Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, et al. AAPT diagnostic criteria for fibromyalgia. J Pain 2019;20(6):611–28.
[43] Kutlubaev MA, Xu Y, Hackett ML, Stone J. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: systematic review and meta-analysis of frequency, correlates, and outcomes. Epilepsy Behav 2018;89:70–8.
[44] Kanemoto K, LaFrance WC, Duncan R, Gigineishvili D, Park S-P, Tadokoro Y, et al. PNES around the world: Where we are now and how we can close the diagnosis and treatment gaps-an ILAE PNES Task Force report. Epilepsia Open 2017;2(3):307–16.
[45] Asadi-Pooya AA, Ziyaee F. Outcome of patients with psychogenic nonepileptic seizures with limited resources: a longitudinal study. Seizure 2018;59:1–4.
[46] Cascino GD, Video-EEG Monitoring in Adults. 2002. 43: p. 80-93.
[47] Goldstein LH, Robinson EJ, Mellers JDC, Stone J, Carson A, Reuber M, et al. Cognitive behavioural therapy for adults with dissociative seizures (CODES): a pragmatic, multicentre, randomised controlled trial. Lancet Psychiatry 2020;7 (6):491–505.
[48] Sheikh SR, Kattan MW, Steinmetz M, Singer ME, Udeh BL, Jehi L. Cost-effectiveness of surgery for drug-resistant temporal lobe epilepsy in the US. Neurology 2020;95(10):e1404–16.
[49] Nightscales R, McCartney L, Auvrez C, Tao G, Barnard S, Malpas CB, et al. Mortality in patients with psychogenic nonepileptic seizures. Neurology 2020;95(6):e643–52.
[50] Tatum WO, Hirsch LJ, Gelfand MA, Acton EK, LaFrance WC, Duckrow RB, et al. Assessment of the predictive value of outpatient smartphone videos for diagnosis of epileptic seizures. JAMA Neurol 2020;77(5):593.
[51] Johnsen C, Ding HT. First do no harm: preventing harm and optimizing care in psychogenic nonepileptic seizures. Epilepsy Behav 2020;102:106642.
[52] Reiter JM, Andrews DJ. A neurobehavioral approach for treatment of complex partial epilepsy: efficacy. Seizure 2000;9(3):198–203.
[53] Tang V, Michaelis R, Kwan P, Psychobehavioral therapy for epilepsy. 2014. 32: p. 147-155.
[54] Sankaraneni R, Lachhwani D. Antiepileptic drugs—a review. Pediatr Ann 2015;44(2):e36–42.
[55] Verducci C, Hussain F, Donner E, Moseley BD, Buchhalter J, Hesdorffer D, et al. SUDEP in the North American SUDEP registry. Neurology 2019;93(3):e227–36.
[56] Kapur J, Pillai A, Henry TR. Psychogenic elaboration of simple partial seizures. Epilepsia 1995;36(11):1126–30.