Which epilepsy patients are at risk for psychogenic non-epileptic seizures (PNES)? A multicenter case-control study

Benjamin D. Wissel, BS¹, Alok K. Dwivedi, PhD², Tyler E. Gaston, MD³, Federico J. Rodriguez-Porcel, MD¹, Danah Aljaafari, MD^{4,5}, Jennifer L. Hopp, MD⁶, Allan Krumholz, MD⁶, Sandra M. A. van der Salm, MD, MSc⁷, Danielle M. Andrade, MD, MSc, FRCPC⁴, Felipe Borlot, MD⁴, Brian D. Moseley, MD¹, Jennifer L. Cavitt, MD¹, Stevie Williams, BA⁸, Jon Stone, PhD⁸, W Curt LaFrance Jr, MD, MPH⁹, Jerzy P. Szaflarski, MD, PhD³, Alberto J. Espay, MD, MSc, FAAN¹

¹Department of Neurology and Rehabilitative Medicine, University of Cincinnati, Cincinnati, OH, USA

²Division of Biostatistics & Epidemiology, Department of Biomedical Sciences, Texas Tech University Health Sciences Center, El Paso, TX, USA

³Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA

⁴Division of Neurology, University of Toronto, Toronto, ON, Canada

⁵Department of Neurology, King Fahad Hospital of the University, University of Dammam, Dammam, Saudi Arabia

⁶Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA

⁷Department of Neurology, Academisch Medisch Centrum Universiteit van Amsterdam, Amsterdam, Netherlands

⁸Department of Clinical Neurosciences, The University of Edinburgh, Edinburgh, Scotland, United Kingdom

⁹Departments of Psychiatry and Neurology, Rhode Island Hospital, Brown University,
Providence, RI, USA

Word count: 1,853; Abstract word count: 216; Title character count (with spaces): 115; Tables:
3; Figures: 1; References: 23

Keywords: functional disorders, psychogenic non-epileptic seizures, epileptic seizures, epilepsy

All correspondence to:

Dr. Alberto J. Espay

University of Cincinnati Academic Health Center

260 Stetson St., Suite 2300, Cincinnati, OH 45267-0525, USA

P: 513-558-4035 - F: 513-558-7015

E-mail: alberto.espay@uc.edu

Financial Disclosures

Mr. Wissel has nothing to disclose.

Dr. Dwivedi has nothing to disclose.

Dr. Gaston has nothing to disclose.

Dr. Rodriguez-Porcel has nothing to disclose.

Dr. Aljaafari has nothing to disclose.

Dr. Hopp has received publication royalties from UpToDate.

Dr. Krumholz serves on the editorial board for Clinical EEG and Neuroscience, and has received royalties from UpToDate.

Dr. van der Salm has nothing to disclose

Dr. Andrade has nothing to disclose.

Dr. Borlot has nothing to disclose.

Dr. Moseley serves on an advisory board for UCB Pharma. He also serves on speakers bureaus for UCB Pharma, Cyberonics, and Eisai.

Dr. Cavitt has received funding from NIH, GW Pharmaceuticals, and Neuren Pharmaceuticals.

Mr. Williams has nothing to disclose.

Dr. Stone is supported by an NRS fellowship and NHS Lothian. He runs a free self-help website www.neurosymptoms.org for patients with functional disorders. He has received lecture honoraria from American Academy of Neurology, Merck, British Medical Association and royalties from UpToDate. He carries out expert witness work.

Dr. LaFrance serves on the Epilepsy Foundation Professional Advisory Board; has served as a clinic development consultant for the Cleveland Clinic, Spectrum Health, Emory University and the University of Colorado Denver; and has provided expert medicolegal testimony. Dr LaFrance

receives royalties from Cambridge University Press and Oxford University Press and has received research support from the American Epilepsy Society, the Epilepsy Foundation, the Matthew Siravo Memorial Foundation Inc, the National Institutes of Health, and Rhode Island Hospital.

Dr. Szaflarski received funding from NIH, Epilepsy Foundation of America, Department of Defense, Epilepsy Study Consortium, University of Alabama at Birmingham, Neuroscan Compumedics Inc., Food and Drug Administration, American Epilepsy Society, SAGE Therapeutics Inc., GW Pharmaceuticals, NeuroPace Inc., and Eisai, Inc. He serves or has served as a consultant or on advisory boards for SAGE Therapeutics Inc., Biomedical Systems Inc., GW Pharmaceuticals Inc., Upsher-Smith Laboratories, Inc., and Elite Medical Experts LLC. He serves as an editorial board member for *Epilepsy & Behavior*, *Journal of Epileptology*, *Restorative Neurology and Neuroscience*, *Journal of Medical Science*, *Epilepsy Currents*, and *Folia Medica Copernicana*.

Dr. Espay is supported by the NIH (K23MH092735) and has received grant support from CleveMed/Great Lakes Neurotechnologies, Davis Phinney Foundation, and Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Solvay, Abbott, Chelsea Therapeutics, TEVA, Impax, Merz, Lundbeck, and Eli Lilly; honoraria from TEVA, UCB, the American Academy of Neurology, and the Movement Disorders Society; and publishing royalties from Lippincott Williams & Wilkins and Cambridge University Press.

ABSTRACT

Objective: We sought to examine the clinical and electrographic differences between patients with combined epileptic (ES) and psychogenic non-epileptic seizures (PNES) and age- and gender-matched ES-only and PNES-only patients.

Methods: Data from 138 patients (105 women [77%]), including 46 PNES/ES (39 ± 12 years), 46 PNES-only (39 ± 11 years), and 46 ES-only (39 ± 11 years) were compared using logistic regression analysis after adjusting for clustering effect.

Results: In the PNES/ES cohort, ES antedated PNES in 28 patients (70%) and occurred simultaneously in 11 (27.5%), while PNES was the initial presentation in only 1 case (2.5%); disease duration was undetermined in 6. Compared with ES-only, patients with PNES/ES had higher depression and anxiety scores, shorter-duration electrographic seizures, less ES absence/staring semiology (all $p \leq 0.01$), more ES arising in the right hemisphere, both in isolation and in combination with contralateral brain regions (61% vs. 41%; $p=0.024$, adjusted for anxiety and depression), and tended to have less ES arising in the left temporal lobe (13% vs. 28%; $p=0.054$). Compared with PNES-only, patients with PNES/ES tended to show fewer right-hemibody PNES events (7% vs. 23%; $p=0.054$) and more myoclonic semiology (10% vs. 2%; $p=0.073$).

Conclusions: Right-hemispheric electrographic seizures may be more common among patients with ES who develop comorbid PNES, in agreement with prior neurobiological studies on functional neurological disorders.

1.1. INTRODUCTION

The coexistence of functional (psychogenic) manifestations in patients with organic neurological disorders is well established.¹ However, it is unclear which clinical or electrophysiologic features of organic illnesses predispose to, or modify the expression of, superimposed functional comorbidities. While much has been understood about the neurobiology of patients with psychogenic non-epileptic seizures (PNES),^{2, 3} less is known about those who have comorbid epileptic seizures (PNES/ES).⁴⁻⁹ Patients with combined PNES/ES provide a unique opportunity to evaluate the features that may be associated with the development of functional complications in organic disorders.

While some patients with ES are suspected to have PNES (or vice versa), definite video EEG confirmation for both (mixed diagnosis of ES and PNES) is only reached in about 5% of patients when strict diagnostic criteria are applied.⁴ We sought to conduct a case-control study to compare the characteristics of video EEG-confirmed PNES/ES patients with age- and gender-matched ES-only and PNES-only patients across several epilepsy centers, given the rarity of established dual diagnosis in single centers, in order to answer the following questions: (1) what are the electrographic differences between PNES/ES and ES-only patients, and (2) what are the clinical differences between PNES/ES and PNES-only patients. We hypothesized that (1) ES-related electrographic seizure onset in PNES/ES may more often lateralize to the right hemisphere compared with ES-only patients, based on preliminary evidence suggesting such lateralization of structural and functional cerebral dysfunction in both PNES-only and PNES/ES patients;^{3, 10-12} and (2) the clinical PNES phenotype differs between PNES/ES and PNES-only patients.

1.2. METHODS

1.2.1. Participating Sites

This was a multi-center case-control study conducted at epilepsy monitoring units in the US, Canada, and Europe. Investigators utilized a standardized data collection sheet using de-identified clinical information extracted from electronic medical records. Each local ethical review committee approved this study.

1.2.2. Study population and data collection

We reviewed the records of patients admitted to epilepsy monitoring units from 2010 to 2015 for suspected ES and PNES. Patients with dual diagnosis of PNES and ES were included in order first identified. Once all patients with PNES/ES were identified and their charts abstracted, patients with PNES-only and ES-only were identified and included on the basis of age- and gender-matching in order of appearance on the search list. PNES-only patients were defined by having at least one paroxysmal seizure-like event recorded on vEEG without electrographic changes prior to, during, or immediately after the event. ES-only patients were defined by having at least one typical event with electrographic seizure onset on scalp EEG (ES etiology was not assessed). PNES/ES patients were stringently defined as having video EEG (vEEG) confirmation of both epileptic *and* non-epileptic events. PNES/ES patients were sub-categorized according to whether PNES developed after or simultaneously with ES. Patients who had established care for ES and later developed PNES, or vice versa, were categorized as sequential in onset, while PNES and ES documented within the same year were considered to be of simultaneous onset. All diagnoses were confirmed using most recent medical records. Patients under age 18 or with suspected mixed diagnosis but with vEEG documentation of only one were excluded.

PNES/ES patients were age- and gender-matched to PNES patients without comorbid ES and ES patients without comorbid PNES within the same center. From medical records, we collected demographic information (age, sex), psychiatric comorbidities as provided by the patient during initial interview and without a detailed neuropsychiatric evaluation, and clinical data (seizure stressor/trigger, response to treatment). Ictal EEG data (wave pattern, location of the ictal onset, and propagation) and ictal semiological descriptions made from video-EEG reports (affected body part, side, type of event, and duration of event). PNES and ES semiology were recorded separately. Seizure semiology impressions were extracted from vEEG reports corresponding to the time of the index events.

1.2.3. Statistical Analysis

Data were described using appropriate summary measures for continuous and frequency and proportion for categorical variables. Clinical and EEG variables (except response to treatment) were compared between groups using logistic regression analysis after adjusting for clustering effect. Robust variance was estimated to account for matching. In case of no cell frequency, a Fisher's exact test was used to compare two groups. For ES lateralization with univariate analysis where $p < 0.10$, we conducted multivariable logistic regression analysis after adjusting for significant psychiatric comorbidities obtained in the unadjusted analysis. Only variables that remained significant were retained in the final analysis. In addition, we used a score test for trend analysis of ordinal outcomes, such as response to treatment and EEG duration. P-values of < 0.05 were considered significant. Correction for multiple comparisons was not conducted because of the exploratory nature of the study. All analyses were carried out using STATA 12.1.

1.3. RESULTS

We examined a total of 138 patients (105 women [77%]), including 46 PNES/ES (39 ± 12 years old at enrollment), 46 PNES-only (39 ± 11 years old at enrollment), and 46 ES-only (39 ± 11 years old at enrollment) (Table 1). In the PNES/ES cohort, ES onset antedated PNES in 28 patients (70%) and occurred simultaneously in 11 (27.5%). PNES was the initial presentation in only 1 case (2.5%; onset undetermined in 6). ES-first PNES/ES patients had greater prevalence of multifocal ES onset (31% vs. 0%; $p=0.043$) with a trend for PNES to be more responsive to cognitive-behavioral therapy, measured by number of PNES events ($p=0.064$), compared with simultaneous-onset PNES/ES patients.

1.3.1. PNES/ES vs. ES-only: Clinical Features

Compared with ES-only, patients with PNES/ES had higher proportions of depression ($p=0.006$), anxiety ($p=0.004$) and clinician-identified stressor/triggers ($p=0.025$) (Table 1). Patients with PNES/ES also showed a longer median ES disease duration (20 vs. 12.5 years; $p=0.007$), less absence/staring seizures (9% vs. 41%; $p=0.003$), and a trend for left-hemibody ES presentation (26% vs. 10%; $p=0.077$). Response to antiepileptic treatment and other psychiatric comorbidities were not significantly different between groups.

1.3.2. PNES/ES vs. ES-only: EEG Features

Compared with ES-only, patients with PNES/ES had shorter-duration electrographic seizures on EEG ($p=0.012$, Figure 1A) and disorganized/unclear/other ictal EEG onset (36% vs 10%; $p=0.011$). In the unadjusted analysis, patients with PNES/ES only trended towards more ES arising in the right hemisphere, both exclusively and in combination with other contralateral regions ($p=0.072$), including generalized onset ($p=0.060$), and tended to have less ES arising from the left temporal region (13% vs. 28%, $p=0.054$). After adjusting for age- and gender-

matching and significant univariate variables, including depression and anxiety, patients with PNES/ES had more ES with onset in the right hemisphere, both in isolation and including other contralateral regions ($p=0.024$) and generalized onset ($p=0.034$) (Table 2, Figure 1B).

1.3.3 PNES/ES vs. PNES-only

Compared with PNES-only, patients with PNES/ES spent more time (years) receiving any seizure care ($p<0.001$) and tended to have fewer right-hemibody PNES events (7% vs. 23%; $p=0.054$) and more myoclonic seizure semiology (10% vs. 2%; $p=0.073$). There were no significant differences between group differences in psychiatric comorbidities, response to cognitive behavioral therapy, or body parts involved.

1.4. DISCUSSION

Compared with matched ES-only patients, we found a greater prevalence of right-hemispheric epileptic seizures in patients with comorbid PNES/ES. These were predominantly women whose epilepsy was of longer disease duration and their epileptic seizures were shorter, tending to affect the left hemibody. Furthermore, PNES developed after ES in most cases, in agreement with prior observations,¹³ suggesting that epileptic activity, often including the right hemisphere, may “kindle” later development of PNES.

The pathogenesis of PNES is thought to be related in part to abnormal processing of emotions.¹⁴ The association between emotional regulation and the right hemisphere,¹⁵ and prior evidence pointing toward right hemispheric contribution in the pathogenesis of functional disorders,^{3, 10-12} prompted our search for lateralized abnormalities in a population unique for its potential in providing clues as to the type of abnormal cortical activity that may increase the risk for the

development of functional complications. Our data are in agreement with most previously published reports on lateralized ES in patients with PNES/ES, although some discrepancies exist, in part, due to methodological differences, including lack of matched PNES-only and/or ES-only cohorts, and no vEEG confirmation in some (Table 3). Remarkably, an early report had shown that resection surgery in the right hemisphere independently predicted the subsequent development of PNES in a series of 22 medically refractory ES patients.¹²

Our study has several limitations. We cannot rule out selection biases inherent to patients enrolled in the catchment population of tertiary referral centers, wherein certain epileptic phenotypes may be more likely to be evaluated. Also, epilepsy-monitoring units tend to evaluate PNES and ES patients for different reasons: suspected PNES for diagnostic purposes and medication refractory ES for pre-surgical assessments. Our cohort, thus, may not be representative of the range of ES and EEG localization in the general population. Given that the ES semiology was taken from vEEG reports, manual automatisms could not be reliably excluded from ictal semiology unless specifically denoted in the report. This could have artificially inflated the reported bilaterality of ES presentations, since automatisms are known to be ipsilateral in certain types of ES,¹⁶ and attenuate the statistical differences in lateralization. Furthermore, given the retrospective nature of the study, a structured evaluation of psychiatric comorbidities was unavailable. However, previous studies on ES and PNES have also used patient reports for gathering data on prior psychiatric diagnoses.^{17, 18} Separately, while there was an anticipated female predominance in our PNES/ES cohort, a feature documented in most functional disorders, the gender matching in the ES-only group, by design, may have biased such cohort into ES types more common to females (e.g., cryptogenic localization-related epilepsies),¹⁹ and may have contributed to some of the identified demographic and semiologic

differences. The prespecified matching also prevented the examination of potential gender and age differences between groups, as have been reported using consecutive unselected series of patients (e.g., younger age in PNES/ES than PNES-only).²⁰ Importantly, revealing our hypothesis a priori to all participating investigators may have contributed to a selection bias during matching. Indeed, a systematic review of the literature published between 1965 and 2002 found a higher proportion of left sided symptoms in studies where such laterality was implied in the title of the paper.²¹ Finally, we recognize that PNES is a complex disorder, of which ES laterality may be only one of the predisposing factors. Alternative (unaccounted) factors, including comorbid psychiatric conditions, may have confounded the results.

1.4.1. Conclusions

In summary, our findings lend support to prior evidence regarding the unique clinical and electrographic seizure characteristics of patients with PNES/ES.⁵⁻⁹ Our data suggest that patients with ES may be prone to developing comorbid PNES in the setting of longer disease duration, shorter seizures, and involvement of the right hemisphere. While the stringent inclusion of patients using vEEG confirmation, unlike prior PNES studies,^{8, 9, 22} may have reduced errors associated with misclassification, substantial weaknesses limit the generalizability of this exploratory study. A prospective consecutive cohort study should evaluate the role of pre-morbid personality and psychopathologic features, as well as of antiepileptic treatments, in ES patients with and without later development of comorbid PNES. Such efforts should include deepening the phenotypic characterization of PNES with and without comorbid ES through blinded video recordings and further examining the differential outcome of PNES in those with and without ES, as recently reported.²³

ACKNOWLEDGEMENTS

We thank Ruth Brotherstone, University of Edinburgh, Melissa Tanaka, Rhode Island Hospital, and Yuan Wang, University of Maryland, for their dedication and assistance with the EEG and chart data collection.

Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

BDW: 1B, 1C, 2C, 3A

AKD: 1C, 2A, 2B, 2C, 3B

TEG, FJR-P, DAJ, JLH, AK, SMAvdS, DMA, FB, BDM, JLC, SW, JS, WCL: 1C, 3B

JPS: 1B, 1C, 2C, 3B

AJE: 1A, 1B, 1C, 2C, 3B

Figure Legend

Figure 1. A. ES seizure duration on scalp EEG. PNES/ES duration was significantly shorter in patients with PNES/ES than in patients with ES (trend analysis: $p=0.012$). **B. ES location of electrographic seizure onset on scalp EEG.** Ictal discharges in the right hemisphere exclusively and with other contralateral regions ($p=0.024$) and including generalized ($p=0.034$) were more common in patients with PNES/ES than with ES. Left temporal ictal discharges tended to be more common in patients with ES than with PNES/ES ($p=0.054$).

Table 1. Clinical characteristics for the PNES/ES, PNES-only and ES-only groups

Group	PNES/ES (N=46)		PNES (N=46)	ES (N=46)	p-value	
Event	PNES	ES	PNES	ES	PNES/ES vs. PNES	PNES/ES vs. ES
	N(%)	N(%)	N(%)	N(%)		
Psychiatric comorbidities						
Depression	26(57.8)		21(46.7)	15(32.6)	0.306	0.006
Anxiety	22(47.8)		16(35.6)	9(19.6)	0.164	0.004
Bipolar	3(6.5)		4(8.9)	1(2.2)	0.688	0.343
Psychosis	3(6.5)		1(2.2)	1(2.2)	0.353	0.343
Stressors/triggers	28(66.7)		22(53.7)	19(43.2)	0.097	0.025
Follow-up Duration (yrs)	7.1±8.2		1.3±4.5	6.1±5.5	<0.001	0.306
Body Side Affected by Seizure						
Right	3(7.3)	4(10.5)	9(23.1)	8(20)	0.054	0.274
Left	4(9.8)	10(26.3)	4(10.3)	4(10)	0.936	0.077
Bilateral	34(82.9)	24(63.2)	26(66.7)	28(70)	0.109	0.515
Body Part Affected						
Eye	3(6.8)	3(7.1)	1(2.2)	0(0)	0.334	0.113
Face	6(13.6)	3(7.1)	1(2.2)	4(8.9)	0.089	0.666
Eye-face	3(6.8)	4(9.5)	6(13.3)	5(11.1)	0.346	0.797
Arm	4(9.1)	2(4.8)	5(11.1)	3(6.7)	0.762	0.712
Face-arm	3(6.8)	5(11.9)	1(2.2)	4(8.9)	0.334	0.667
Eye-face-arm	6(13.6)	2(4.8)	3(6.7)	6(13.3)	0.314	0.201
Leg	2(4.6)	-	0(0)	-	-	-
Arm-Leg	4(9.1)	2(4.8)	8(17.8)	2(4.4)	0.179	0.946
Face-Arm-Leg	5(11.4)	4(9.5)	6(13.3)	4(8.9)	0.770	0.921
Eye-face-arm-leg	6(13.6)	10(23.8)	13(28.9)	6(13.3)	0.084	0.198
Mixed	2(4.6)	7(16.7)	1(2.2)	9(20)	0.563	0.681
Seizure Semiology						
Clonic	11(27.5)	4(9.3)	11(23.9)	6(13.0)	0.726	0.601
Tonic	2(5.0)	3(7.0)	6(13.0)	3(6.5)	0.169	0.935
Tonic-Clonic	7(17.5)	22(51.2)	15(32.6)	18(39.1)	0.109	0.276
Atonic	2(5.0)	1(2.3)	5(10.9)	0(0)	0.345	0.483
Myoclonic	4(10.0)	4(9.3)	1(2.1)	3(6.5)	0.073	0.646
Absence/staring	17(42.5)	4(9.3)	14(30.4)	19(41.3)	0.264	0.003
Mixed/Other	16(40.0)	9(20.9)	14(30.4)	10(21.7)	0.388	0.934
Response to Treatment						
No response (reference)	18(52.9)	7(18.4)	12(57.1)	7(16.3)	-	-
Mild/moderate	7(20.6)	14(36.8)	3(14.3)	25(58.1)	0.473	0.363
Marked improvement	3(8.8)	11(29.0)	3(14.3)	9(20.9)	0.670	0.797
Remission of seizures	6(17.7)	6(15.8)	3(14.3)	2(4.7)	0.698	0.279

Comparisons were made between the PNES/ES (only PNES events considered) and PNES-only groups, and the PNES/ES (only ES events considered) and ES-only groups.

Table 2. EEG data in PNES/ES and ES-only groups

	PNES/ES (N=46) N(%)	ES (N=46) N(%)	p-value
EEG Wave Pattern			
Spike	7(16.7)	11(26.9)	0.311
Spike-wave	13(31.0)	16(39.0)	0.443
Polyspike-wave	4(9.5)	6(14.6)	0.455
Disorganized/unclear	5(11.9)	1(2.4)	0.070
Mixed	3(7.1)	4(9.8)	0.683
Other	10(23.8)	2(4.9)	0.069
ES Location of Electrographic Seizure Onset on Scalp EEG			
Right hemisphere alone and bilateral	28(60.9)	19(41.3)	0.072
			0.024*
Left hemisphere alone and bilateral	27(58.7)	29(63.0)	0.673
Right hemisphere including generalized	30(65.2)	21(45.7)	0.060
			0.034*
Left hemisphere including generalized	29(63.0)	31(67.4)	0.658
Generalized	2(4.4)	2(4.4)	1.000
Right frontal	3(6.5)	4(8.7)	0.709
Left frontal	3(6.5)	2(4.4)	0.660
Right frontotemporal	4(8.7)	4(8.7)	1.000
Left frontotemporal	5(10.9)	5(10.9)	1.000
Right temporal	6(13.0)	5(10.9)	0.709
Left temporal	6(13.0)	13(28.3)	0.054
Right temporoparietal	1(2.2)	1(2.2)	1.000
Left temporoparietal	2(4.4)	2(4.4)	1.000
Multiple locations	11(23.9)	5(10.9)	0.088
ES Electrographic Seizure Propagation on Scalp EEG			
Right hemisphere alone and bilateral	7(20.6)	12(32.4)	0.288
Left hemisphere alone and bilateral	6(17.7)	7(18.9)	0.897
Generalized	10(29.4)	5(13.5)	0.113
Right frontal	0(0)	1(2.7)	1.000
Left frontal	0(0)	1(2.7)	1.000
Right frontotemporal	0(0)	1(2.7)	1.000
Left frontotemporal	1(2.9)	1(2.7)	0.952
Right temporal	5(14.7)	7(18.9)	0.658
Left temporal	2(5.9)	4(10.8)	0.467
Multiple locations	5(14.7)	5(13.5)	0.883
No propagation	12(35.3)	12(32.43)	0.797

Comparisons were made between PNES/ES (only ES events considered) and ES-only patients.
 *Multivariable logistic regression analysis after adjusting for age- and gender-matching, depression and anxiety.

Table 3: Assessment of lateralization of PNES in prior studies

Authors	Study design	Comparators	Methods	Outcome	Comments
Devinsky et al. ¹¹	Case-control (n = 79 cases; 122 controls)	PNES/ES, ES-only	Brain MRI, CT, ictal/interictal EEG	Right>Left 43/60* (71%)	Largest consecutive retrospective cohort with strict inclusion criteria
Glosser et al. ¹²	Case series (n = 22)	None	PNES after resective epilepsy surgery	Right>Left 16/22 (73%)	91% anterior temporal lobe resection
Hernando et al. ¹⁰	Case-control (n = 8 cases; 8 controls)	Healthy controls	Diffusion tensor imaging from functional MRI	Right>Left p=0.031	Lateralization only assessed for uncinate fasciculus
Labate et al. ³	Case-control (consecutive, prospective) (n = 20 cases; 40 controls)	Healthy controls	Voxel-based morphometry analysis from brain MRI	Right>Left p<0.05	Lateralization based on cortical atrophy; lack of PNES/ES and ES-only cohorts
Reuber et al. ²²	Case-control (n = 123 cases; 206 controls)	PNES/ES	Brain MRI, interictal EEG	Left>Right 51/157** (33%)	46% of PNES/ES without vEEG confirmation
Reuber et al. ⁹	Case-control (n = 130 cases; 50 controls)	Healthy controls	Interictal EEG	Left>Right 4/9*** (44%)	20% of cohort without ictal vEEG

Only two prior studies evaluated PNES vs. PNES/ES patients.

*Denotes patients with only unilateral lesions (60 out of 79)

**Denotes patients in PNES and PNES/ES groups with detected brain abnormality (157 out of 329)

***Denotes only PNES patients with interictal EEG abnormalities (9 out of 50)

PNES: psychogenic non-epileptic seizures; ES: epileptic seizures

References

1. Stone J, Carson A, Duncan R, et al. Which neurological diseases are most likely to be associated with "symptoms unexplained by organic disease". *Journal of neurology* 2012;259:33-38.
2. van der Kruijs SJ, Bodde NM, Vaessen MJ, et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 2012;83:239-247.
3. Labate A, Cerasa A, Mula M, et al. Neuroanatomic correlates of psychogenic nonepileptic seizures: a cortical thickness and VBM study. *Epilepsia* 2012;53:377-385.
4. Martin R, Burneo JG, Prasad A, et al. Frequency of epilepsy in patients with psychogenic seizures monitored by video-EEG. *Neurology* 2003;61:1791-1792.
5. Asadi-Pooya AA, Emami M. Demographic and clinical manifestations of psychogenic non-epileptic seizures: the impact of co-existing epilepsy in patients or their family members. *Epilepsy & behavior : E&B* 2013;27:1-3.
6. Turner K, Piazzini A, Chiesa V, et al. Patients with epilepsy and patients with psychogenic non-epileptic seizures: video-EEG, clinical and neuropsychological evaluation. *Seizure* 2011;20:706-710.
7. Pillai JA, Haut SR. Patients with epilepsy and psychogenic non-epileptic seizures: an inpatient video-EEG monitoring study. *Seizure* 2012;21:24-27.
8. Hoepner R, Labudda K, May TW, Schondienst M, Bien CG, Brandt C. Distinguishing between patients with pure psychogenic nonepileptic seizures and those with comorbid epilepsy by means of clinical data. *Epilepsy & behavior : E&B* 2014;35:54-58.
9. Reuber M, Fernandez G, Bauer J, Singh DD, Elger CE. Interictal EEG abnormalities in patients with psychogenic nonepileptic seizures. *Epilepsia* 2002;43:1013-1020.
10. Hernando KA, Szaflarski JP, Ver Hoef LW, Lee S, Allendorfer JB. Uncinate fasciculus connectivity in patients with psychogenic nonepileptic seizures: A preliminary diffusion tensor tractography study. *Epilepsy & behavior : E&B* 2015;45:68-73.
11. Devinsky O, Mesad S, Alper K. Nondominant hemisphere lesions and conversion nonepileptic seizures. *The Journal of neuropsychiatry and clinical neurosciences* 2001;13:367-373.
12. Glosser G, Roberts D, Glosser DS. Nonepileptic seizures after resective epilepsy surgery. *Epilepsia* 1999;40:1750-1754.
13. Devinsky O, Sanchez-Villasenor F, Vazquez B, Kothari M, Alper K, Luciano D. Clinical profile of patients with epileptic and nonepileptic seizures. *Neurology* 1996;46:1530-1533.
14. Reuber M. The etiology of psychogenic non-epileptic seizures: toward a biopsychosocial model. *Neurol Clin* 2009;27:909-924.
15. Cancelliere AE, Kertesz A. Lesion localization in acquired deficits of emotional expression and comprehension. *Brain Cogn* 1990;13:133-147.
16. Kotagal P, Luders H, Morris HH, et al. Dystonic posturing in complex partial seizures of temporal lobe onset: a new lateralizing sign. *Neurology* 1989;39:196-201.
17. Szaflarski M, Meckler JM, Privitera MD, Szaflarski JP. Quality of life in medication-resistant epilepsy: the effects of patient's age, age at seizure onset, and disease duration. *Epilepsy & behavior : E&B* 2006;8:547-551.
18. Szaflarski JP, Hughes C, Szaflarski M, et al. Quality of life in psychogenic nonepileptic seizures. *Epilepsia* 2003;44:236-242.

19. Christensen J, Kjeldsen MJ, Andersen H, Friis ML, Sidenius P. Gender differences in epilepsy. *Epilepsia* 2005;46:956-960.
20. Mari F, Di Bonaventura C, Vanacore N, et al. Video-EEG study of psychogenic nonepileptic seizures: differential characteristics in patients with and without epilepsy. *Epilepsia* 2006;47 Suppl 5:64-67.
21. Stone J, Sharpe M, Carson A, et al. Are functional motor and sensory symptoms really more frequent on the left? A systematic review. *Journal of neurology, neurosurgery, and psychiatry* 2002;73:578-581.
22. Reuber M, Fernandez G, Helmstaedter C, Qurishi A, Elger CE. Evidence of brain abnormality in patients with psychogenic nonepileptic seizures. *Epilepsy & behavior : E&B* 2002;3:249-254.
23. Sadan O, Neufeld MY, Parmet Y, Rozenberg A, Kipervasser S. Psychogenic seizures: long-term outcome in patients with and without epilepsy. *Acta Neurol Scand* 2015.

Figure 1 revised