Received: 28 July 2021 | Revised: 14 October 2021 | Accepted: 14 October 2021

DOI: 10.1111/epi.17110

Epilepsia®

RESEARCH ARTICLE

Paroxysmal slow wave events predict epilepsy following a first seizure

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Funding information
This research was supported by Israel Science Foundation, Canadian Institute for Health Research; and ERA-NET BIO2, Varda and Boaz Dotan Research Center for Hemato-Oncology Research.

Abstract

Objective: Management of a patient presenting with a first seizure depends on the risk of additional seizures. In clinical practice, the recurrence risk is estimated by the treating physician using the neurological examination, brain imaging, a thorough history for risk factors, and routine scalp electroencephalogram (EEG) to detect abnormal epileptiform activity. The decision to use antiseizure medication can be challenging when objective findings are missing. There is a need for new biomarkers to better diagnose epilepsy following a first seizure. Recently, an EEG-based novel analytical method was reported to detect paroxysmal slowing in the cortical network of patients with epilepsy. The aim of our study is to test this method's sensitivity and specificity to predict epilepsy following a first seizure.

Methods: We analyzed interictal EEGs of 70 patients admitted to the emergency department of a tertiary referral center after a first seizure. Clinical data from a follow-up period of at least 18 months were available. EEGs of 30 healthy controls were also analyzed and included. For each EEG, we applied an automated algorithm to detect paroxysmal slow wave events (PSWEs).

Results: Of patients presenting with a first seizure, 40% had at least one additional recurring seizure and were diagnosed with epilepsy. Sixty percent did not report additional seizures. A significantly higher occurrence of PSWEs was detected in the first interictal EEG test of those patients who were eventually diagnosed with epilepsy. Conducting the EEG test within 72 h after the first seizure significantly increased the likelihood of detecting PSWEs and the predictive value for epilepsy up to 82%.

Significance: The quantification of PSWEs by an automated algorithm can predict epilepsy and help the neurologist in evaluating a patient with a first seizure.

This study was conducted as part of the requirements for an MD degree from the Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev.

[Correction added on 19th December, 2021, after first online publication: The affiliation and present address of "Dan Z. Milikovsky" has been corrected.]

KEYWORDS
biomarker, epilepsy, first seizure, interictal EEG, new onset seizure, paroxysmal slow wave event

1 | INTRODUCTION

Approximately 2%–3% of emergency department (ED) visits are due to epileptic seizures,[1] and approximately one quarter are first time seizures. In the majority of cases, the suspected epileptic event was not observed by trained medical personnel. As such, an accurate diagnosis of whether the patient endured a first isolated event, a first event due to epilepsy, or a seizure mimic (e.g., syncope) can be difficult. An accurate diagnosis is critical for decisions about additional tests, pharmacological treatment, information given to the patient and family, and potential limitations (e.g., driving restrictions). Specifically, the decision regarding initiating antiseizure medication (ASM) depends on the balance between the estimated risk of seizure recurrence, resulting in an increased risk of morbidity and even death,[2,3] and potential side effects due to unnecessary pharmacological intervention. Therefore, an unmet need exists to find objective biomarkers to diagnose epilepsy following a single seizure.

Scalp electroencephalogram (EEG) is a low-cost diagnostic tool available in most medical centers, often routinely performed to assist with decision-making. However, the sensitivity of detecting epileptic discharge by a single EEG evaluation is limited.[4] From this perspective, an EEG-based diagnostic and predictive biomarker to accurately diagnose the seizure-prone patient is of great importance. We focus in our study on describing such a novel EEG-based biomarker in the adult patient population.

Major EEG-based biomarker candidates include abnormal rhythmic oscillations, including high-frequency oscillations (HFOs), slow network activity, and active direct current shifts.[5] Brief HFO events in a spectral range of 80–600 Hz were reported to characterize the focal epileptogenic zones in patients with epilepsy.[6,7] Among children with epilepsy, higher rates of ripple and spike ripple were detected in an early EEG following first seizure.[8] In addition, it was recently reported that the presence of HFOs increases the likelihood of recurrent seizures during the first 2 years after diagnosis.[9]

Abnormal slowing detected through scalp EEG is a well-known finding in patients with temporal lobe epilepsy.[10] Previously, Milikovsky at el. reported EEG slowing in animal models of epilepsy was composed of brief transient episodes of low-frequency network activity, termed paroxysmal slow wave events (PSWEs). Those PSWEs are characterized by median power frequency (MPF) < 6 Hz, and last at least 5 consecutive seconds. In addition, a significantly higher rate of those PSWEs were detected in EEGs obtained from 17 patients with focal epilepsy compared to nine healthy control volunteers. Therefore, it was suggested that PSWEs may function as a useful and reliable indicator for epilepsy.[11] A correlation between the suspected source of PSWEs and the blood–brain barrier dysfunction (BBBD)[11] elicits the hypothesis that interictal events may reflect an epileptogenic cortical network, and predict future ictal events (i.e., epilepsy) following the first seizure.

KEY POINTS

- Detection of high PSWE occurrence in scalp EEG after a first seizure predicts epilepsy
- EEG performed within 72 h following the first seizure improves the likelihood of detecting PSWEs and improves epilepsy prediction

The aim of this retrospective study was to examine to what extent PSWEs can predict epilepsy. We applied the algorithm found in adult patient EEGs within 1–8 days after the first seizure, when clinical follow-up was available for at least 18 months.

2 | MATERIALS AND METHODS

2.1 | Ethics approval

The study adhered to the rules and regulations of the Helsinki Declaration and was approved by the institutional review board of the Rabin Medical Center, Petach Tikva, Israel (0275–20-RMC). Our work was approved as a retrospective clinical study, so the need for consent was waived by the ethics committee. All patient data were fully anonymized before review.

2.2 | Study design

EEEG and clinical data of patients admitted to the ED of the Rabin Medical Center with first seizures were collected retrospectively ($n = 70$). Inclusion criteria were age between 18 and 80 years, ED visit due to suspected

seizure event for the first time, EEG test performed in proximity to the suspected seizure (within 1–8 days; 2.9 ± 2.8 days, minimum 12 h after the seizure event), and availability of follow-up by a neurologist for at least 18 months (38.0 ± 12.1 months, range = 22–80 months). Clinical follow-up data were required to specify whether additional seizures occurred, including a treatment decision on ASM therapy immediately after the first suspected event. The initial diagnosis of a seizure event was made in the ED by a neurology resident and confirmed during admission by a senior neurologist. Patients were followed by general neurologists except for only a fraction by a specialist in epilepsy. Following the first epileptic seizure, the International League Against Epilepsy diagnostic criteria for epilepsy were used to classify patients; 28 patients were diagnosed as suffering from epilepsy after a second epileptic episode, and 15 patients following a single seizure were diagnosed with epilepsy due to brain imaging and EEG results increasing their probability of a further seizure to >60%. Twenty-seven patients were not diagnosed as suffering from epilepsy (single seizure event), and none of the patients was suffering from an epileptic syndrome. Patients with suspected acute symptomatic seizures were excluded. All clinical data were analyzed retrospectively by an epilepsy specialist (F.B.) and all EEGs were clinically reinterpreted by an epilepsy specialist (I.G.). In addition, 30 patients undergoing routine EEG due to unrelated neuropsychiatric diseases were similarly included. These patients were defined as controls and were screened to exclude a diagnosis of psychiatric illness, substance abuse, general medical conditions requiring hospitalization, epilepsy, history of traumatic brain injury, or imaging findings of cerebrovascular diseases, including ischemic and hemorrhagic stroke, or any other conditions requiring anticonvulsants. For comparison, patients were grouped as single seizure patients if no more epileptic seizures occurred in the follow-up period, or epilepsy if at least one more epileptic seizure occurred, independent of ASM treatment. Seizure-free patients treated with ASMs might be patients without epilepsy or epilepsy patients with full control of seizures (via ASMs). Thus, we compared further only patients with a single seizure without ASM treatment on follow-up and those with recurrent seizures.

2.3 | Electroencephalograms

A 19-channel EEG was obtained with a Neurofax-1200 system (Nihon Kohden) and used according to the standard international 10–20 system. Sampling rate was 512 Hz. EEG was recorded for ≥20 min in an awake state with both open and closed eyes.

2.4 | EEG analysis

EEG analysis was performed blinded to subject's clinical data as reported.[9] In short, preprocessing (EDF Browser, https://www.teuniz.net/index.html) included high-pass (1 Hz), low-pass (100 Hz), and notch (45–55 Hz) filters. PSWE analysis was performed using home-developed MATLAB scripts (MathWorks). We used fast Fourier transform (2-s duration, 1-s overlap) to calculate the relative amplitude in six frequency bands (delta, 1–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; beta, 12–20 Hz; low gamma, 20–30 Hz; and high gamma, 30–40 Hz). For PSWE detection, MPF was calculated for each 2-s epoch. PSWEs are defined as periods of MPF of <6 Hz lasting ≥5 s as previously described in animal epilepsy models and in epilepsy patients (Figure 2A).[11] Analysis was performed separately for each electrode. PSWEs were quantified using four parameters: the occurrence per minute, mean MPF, event duration in percent of total recording time, and average number of channels that pick up PSWEs. Average spectrum power and PSWE parameters on all channels were compared between study groups.

2.5 | Statistics

Demographic characteristics were compared using Pearson chi-squared test. Multiple Student *t*-tests followed by Holm–Sidak correction were used to compare both mean relative power for each frequency band and the incidence of PSWEs. For comparison of the relative power or PSWE rates among subgroups (based on received treatment during the follow-up period), two-way analysis of variance was used. For each variable with significant differences among groups, we conducted a receiver operating characteristic (ROC) analysis. Area under the curve (AUC) was calculated to determine the ability of variables to differentiate between groups of patients. Duration and frequency of PSWEs were compared by the Kolmogorov–Smirnov test. Statistical analyses were performed by Prism (GraphPad Software). Logistic regression analyses were carried out by SPSS (IBM). The omnibus test of model coefficients was used to assess the predictive quality of the logistic regression.

3 | RESULTS

3.1 | Participant data

We analyzed the interictal EEGs of 70 patients (age = 49.6 ± 19 years, range = 18–79 years), presenting at the ED for a first epileptic seizure versus those of 30 controls

without neuropsychiatric disorders (age = 55.1 ± 3.1 years, range = 50–60 years, p = .11). During follow-up (38.0 ± 12.1 months, range = 22–80 months), 28 patients (40%) had at least one recurrent seizure, whereas 42 patients (60%) were seizure-free. Follow-up periods differed between the two groups, as patients without recurrent seizures returned to follow-up for 33.9 ± 6.7 months (median = 35 months, range = 22–46 months) and those with recurrent seizures for 44.2 ± 15.5 months (median = 40 months, range = 22–80 months; $p < .05$). Recurrent seizures occurred in 92.8% of patients in the first 18 months following the first seizure (6.2 ± 6.1 months, range = 1–22 months). The fraction of patients administered ASM following the first seizure was similar for the seizure-free group and the group experiencing recurrent epileptic events (35.7% vs. 39.3%, p = .76). Type of epilepsy diagnosed was focal in 64.2%, unknown in 25.7%, and generalized in 10% of patients included. The focal epilepsies were localized as unknown (32.8%), temporal lobe (31.4%), frontal lobe (20%), multifocal (2.8%), and occipital lobe (1.4%). Patients' epilepsy was classified etiologically as structural metabolic (55.7%), unknown (34.3%), and genetic (10%). Two patients included presented with status epilepticus as first seizure. Demographic characteristics such as age, sex, comorbidities, and the time interval between the seizure and the EEG test were not different among groups (Table 1).

TABLE 1 Demographic characteristics of study participants

Characteristic	Seizure-free	Epilepsy	p
N	42	28	
Age, years	48.5 ± 17.8	51.4 ± 20.9	.53
Female, %	35.7	40.7	.67
Seizure to EEG interval, days	2.6 ± 1.5	3.4 ± 4.2	.26
Comorbidities	62.5%	76%	.25
Neurology	12.5%	12%	
Stroke	20%	28%	
Psychiatry	15%	4%	
Substance abuse	12%	6.2%	
Heart disease	8%	9.2%	
Others	12%	12%	
ASM in the ED	35.7%	39.3%	.76
ASM on follow-up	60%	48%	.34
Levetiracetam	25%	4%	
Lamotrigine	7.5%	12%	
Valproic acid	24%	26%	
Epilepsy type (focal/generalized/unknown)	57.1/9.5/33.3	75.0/10.7/14.3	
Etiology (genetic/SM/unknown)	9.5/42.8/47.6	14.3/71.5/14.3	

Note: Comorbidities are listed and separated by different clinical specialties. Neurology: chronic headache, meningioma, glioblastoma, schwannoma, intracranial hemorrhage, and myasthenia gravis. Psychiatric disease: depression, attention-deficit/hyperactivity disorder, autism, schizophrenia, anxiety. Substance abuse: alcohol, cannabis, benzodiazepines.

Abbreviations: ASM, antiseizure medication; ED, emergency department; EEG, electroencephalogram; SM, structural metabolic.

3.2 | Interictal EEG after a first epileptic seizure with cortical slowing

Spectral analysis revealed that interictal EEG of patients with epilepsy was characterized by significantly higher relative amplitude in the delta band (1–4 Hz) and lower relative amplitude in the beta and low gamma bands compared to seizure-free patients (p-values: δ, .006; θ, .981; α, .771; β, .031; low-γ, .010; high-γ, .085) and control participants (p-values: δ, .013; θ, .176; α, .625; β, .039; low-γ, .008; high-γ, .062; Figure 1A; Table 2). No amplitude differences were observed between the control and seizure-free patients ($p > .05$). ROC analyses were performed for control and seizure-free patients (n = 72). AUCs of .69, .65, and .68 were calculated for the relative power in the delta, beta, and low gamma bands (Figure 1B).

Patients were further clustered into subgroups according to the ASMs initiated (yes/no) following the first seizure and before the initial EEG; those diagnosed during the follow-up with epilepsy had increased amplitude in the delta band and lower relative amplitude in the beta and low gamma bands compared to seizure-free patients, regardless of treatment with ASMs (Table 3; Figure 1C). Thus, the use of ASMs during the initial EEG after a first seizure did not influence spectral analysis and delta band relative power at the initial EEG ($p > .05$). Because seizure-free patients treated with ASMs might be healthy patients without epilepsy or epilepsy patients with full control of seizures (via ASMs), an ROC analysis was conducted after excluding this group of patients (δ: AUC = .65, p = .027; β: AUC = .57, p = .043; low-γ: AUC = .68, p = .032; Figure 1D). The relative delta power for each of 19 scalp EEG electrodes is shown (Figure 1E,F). Delta activity was notably diffuse but prominent in temporal electrodes.

3.3 | PSWEs help predict epilepsy

The occurrence of PSWEs in early EEGs, from patients who later reported recurrent seizures was significantly higher (1.32 ± .99 min^{-1}) compared to seizure-free patients (.71 ± .70 min^{-1}, p = .0038) and healthy controls (.58 ± .47 min^{-1}, p = .0005; Figure 2B). Seizure-free patients had a similar occurrence of PSWEs to that of healthy

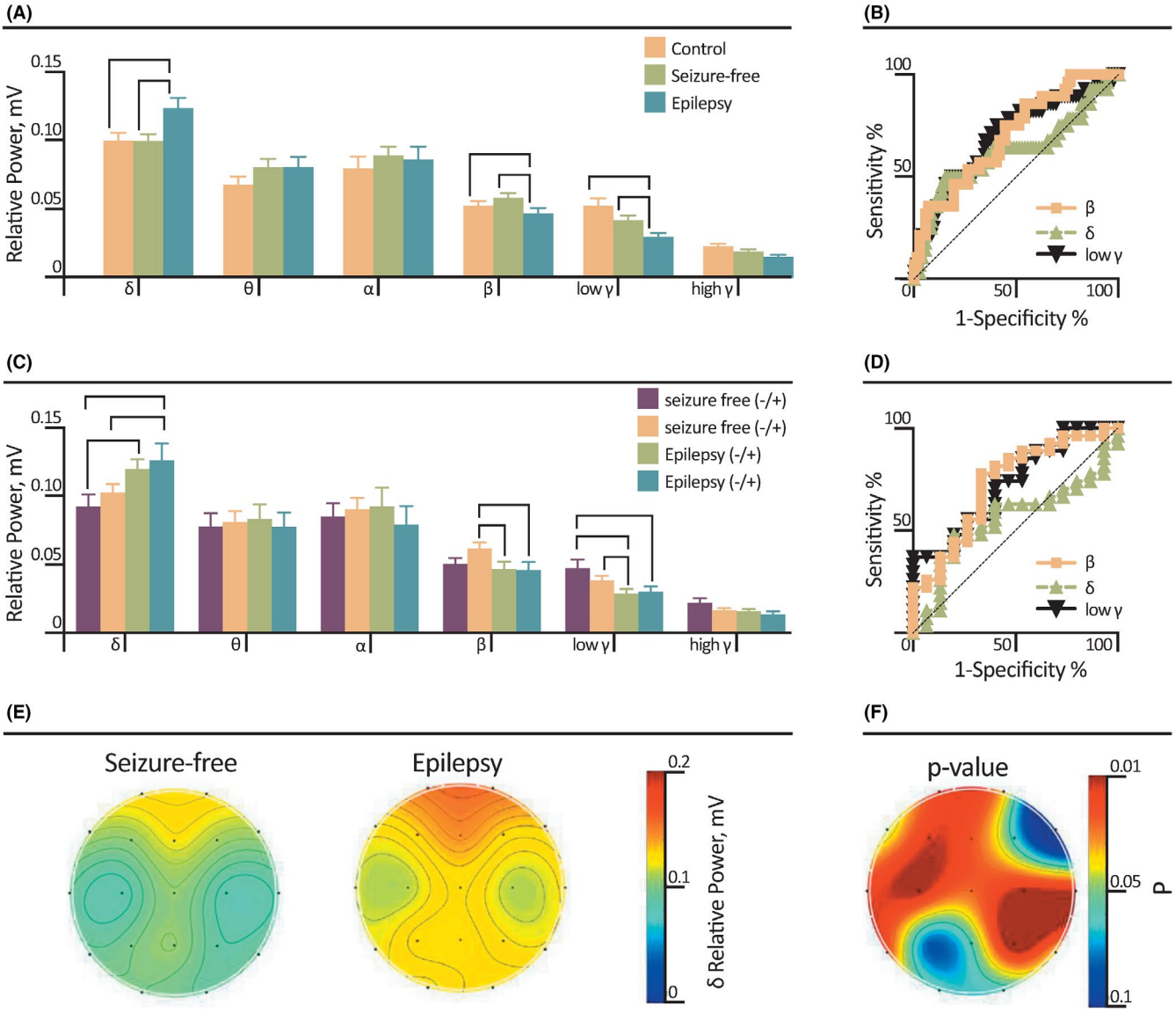

FIGURE 1 Electroencephalogram (EEG) power spectral analysis. (A) The relative amplitude in the frequency bands δ (1–4 Hz), θ (4–8 Hz), α (8–12 Hz), β (12–20 Hz), low-γ (20–30 Hz), and high-γ (30–40 Hz) was calculated. Higher amplitude in the δ band and lower amplitude in the β (12–20Hz) and the low-γ (20–30 Hz) were detected on interictal EEGs of the epilepsy group compared to both seizure-free patients (*p*-values: δ, .006; β, .031; low-γ, .010) and controls (*p*-values: δ, .013; β, .039; low-γ, .008). No significant differences were observed in the θ, α, or high-γ bands ($p > .05$). (B) Receiver operating characteristic (ROC) analysis for the relative amplitudes in the δ (area under the curve [AUC] = .69, $p = .007$), β (AUC = .65, $p = .003$), and low-γ (AUC = .68, $p = .01$) bands revealed poor potential to serve as a biomarker as a single indicator for epilepsy. (C) The spectral changes observed between the seizure-free and the epilepsy patients were not affected by administration of antiseizure medication (ASM; $p > .05$). (D) ROC analysis after excluding patients treated with ASMs compares the relative power in δ (AUC = .65, $p = .027$), β (AUC = .57, $p = .043$), and low-γ (AUC = .68, $p = .032$). (E) The mean δ relative power in each of 19 electrodes for the seizure-free group and epilepsy group. (F) Heat map demonstrates diffuse cortical slowing observed in epilepsy patients

controls ($p = .36$). Thus, for the rest of the analysis, these groups were combined into a seizure-free group ($n = 72$). ROC analysis revealed that PSWEs' occurrence predicted epilepsy with AUC = .72 (Figure 2C). The occurrence of PSWEs was not affected by ASM. For the seizure-free and group, PSWE occurrence were similar with and without ASM use (PSWE: .786 ± .81 min^{-1} vs. .577 ± .48 min^{-1}, $p = .367$) at the time of the EEG. PSWE occurrence was also not affected in the epilepsy group by ASM use (PSWE ASM+: 1.52 ± 1.10 min^{-1} and ASM−: 1.09 ± .82 min^{-1}, $p = .26$; Figure 2D).

Calculating PSWE occurrence for each electrode revealed a significant difference in the number of PSWEs in frontal, temporal, and parietal electrodes (Figure 2E). However, none of the channels served as a single useful predictor of epilepsy (Figure 2F).

TABLE 2 Relative power according to spectral analysis of interictal electroencephalogram

	Control		Seizure-free		Epilepsy	
Frequency	**Mean, mV**	**SD**	**Mean, mV**	**SD**	**Mean, mV**	**SD**
Δ	.1000	.03208	.09964	.03297	.12390	.03846
Θ	.0679	.03262	.08063	.04015	.08086	.0395
A	.0798	.04761	.08932	.04151	.08609	.05039
B	.0524	.01952	.05844	.02157	.04684	.02175
Low-γ	.0525	.03026	.04214	.02127	.03007	.01442
High-γ	.0229	.01053	.01925	.01011	.01528	.00789

TABLE 3 Relative power comparing spectral analysis of interictal electroencephalogram according to medication use

	Seizure-free				Epilepsy			
	ASM−		ASM+		ASM−		ASM+	
Frequency	**Mean, mV**	**SD**	**Mean, mV**	**SD**	**Mean, mV**	**SD**	**Mean, mV**	**SD**
Δ	.0928	.0349	.1034	.0319	.1204	.0254	.1269	.0478
Θ	.0784	.0383	.0819	.0418	.0837	.0393	.0784	.0409
A	.0857	.0379	.0913	.0439	.0931	.0498	.0800	.0519
B	.0511	.0167	.0625	.0231	.0470	.0204	.0467	.0235
Low-γ	.0477	.0260	.0390	.0180	.0293	.0126	.0307	.0162
High-γ	.0226	.0129	.0174	.0079	.0165	.0062	.0143	.0092

Note: For all comparisons between untreated (ASM−) and treated (ASM+) patients, no significant change in relative power was detected ($p > .05$).
Abbreviation: ASM, antiseizure medication.

PSWEs in patients who reported recurrent seizures had a lower MPF and a longer duration, compared to those recorded in the seizure-free group (3.9 ± .64 Hz vs. 3.6 ± .92 Hz, $p < .0001$; 6.7 ± 2.54 s vs. 7.8 ± .07 s, $p < .0001$; Figure 3A,B). Fraction of the total EEG in which PSWEs can be found was significantly higher among patients with epilepsy (11.5% ± 5.54% vs. 22.8% ± 4.37%, $p < .0001$; Figure 3C). A heatmap of the lengths of PSWEs for each electrode is shown for seizure-free patients versus those with epilepsy (Figure 3D). Significant differences were observed in frontal, parietal, and temporal scalp electrodes (Figure 3E).

Timing of performance of the EEG may have had an important impact on the likelihood of detecting abnormal electrical activity.[12] In our cohort, PSWE occurrence was higher in EEGs obtained within 72 h after the first suspected seizure (1.2 ± .13 vs. .4 ± .11 PSWEs/min, $p < .001$; EEG tests of <72 h, $n = 47$ vs. >72 h, $n = 23$, respectively; Figure 3F). Thus, comparing PSWEs in seizure-free patients versus those with epilepsy, who had an initial EEG done within 3 days of the initial event, led to a significant difference in PSWE occurrence (.7 ± .1 vs. 1.7 ± .2, $p < .001$; Figure 3G). ROC analysis for predicting recurrent seizures revealed an AUC of .82 (Figure 3H). By using Youden's index, an optimal cutoff value was .83 events per minute, with sensitivity and specificity rates of 83% and 67%, respectively.[13]

A logistic regression model showed that PSWE occurrence increased the risk of future seizures (odds ratio [OR] =3.56, $p = .009$). Demographic variables (age and sex) and comorbidities did not improve the model. The Pearson coefficient showed a strong correlation between PSWEs and delta band relative power ($r = .89$, $p < .0001$). Only one of these variables was inserted into our model. While including only early EEG tests (<72 h postseizure), the OR was 5.73 for additional seizures ($p = .02$).

4 | DISCUSSION

Our results demonstrate interictal cortical slowing in patients with epilepsy, in accordance with previous studies.[10,14] We show that cortical slowing consists of PSWEs, which are easily detected and quantified by automatic algorithm and may serve as a new tool to estimate the risk of epilepsy. Although transient slow events are observed occasionally in recordings from healthy individuals, our results indicate that low median frequency and long duration PSWEs are likely to be pathological events, more common among patients with epilepsy.

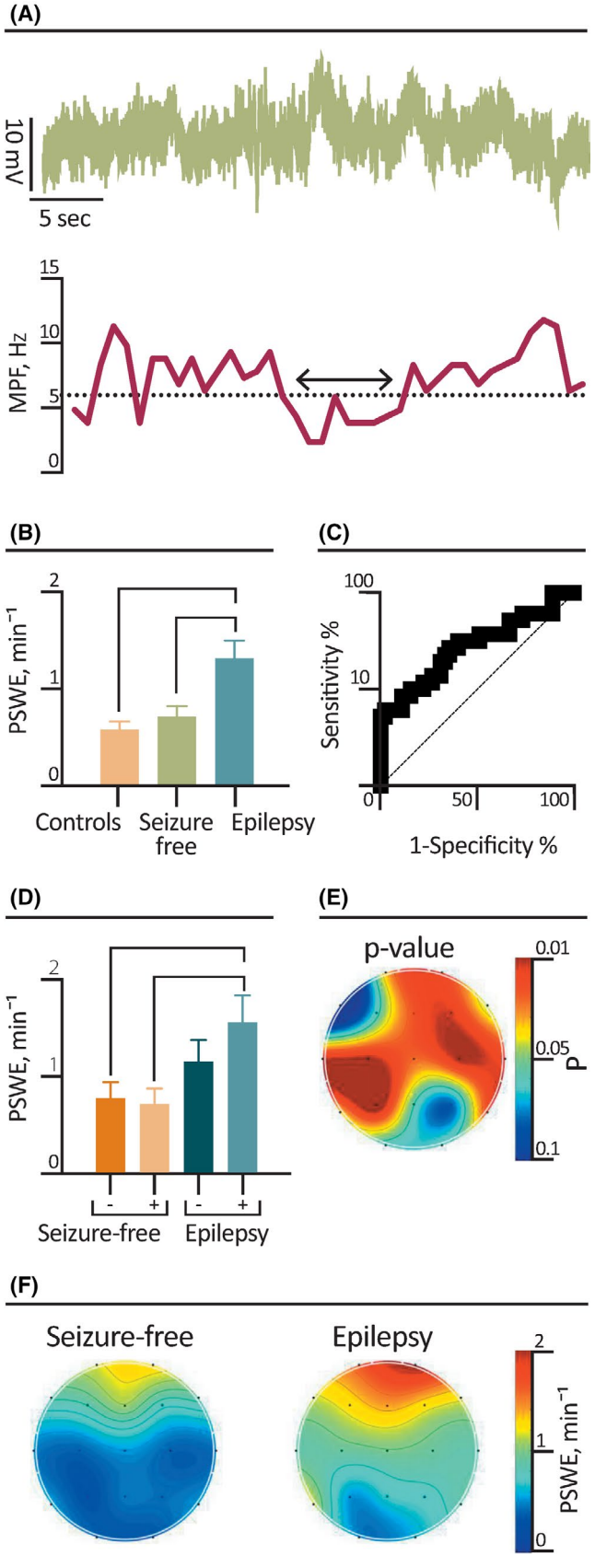

FIGURE 2 Characterization of paroxysmal slow wave events (PSWEs) and the effect of antiseizure medication (ASM). (A) A representative PSWE detected in a segment of interictal electroencephalographic trace obtained for a patient with epilepsy following a first seizure in life is shown. (B) More PSWEs per minute were detected in patients with epilepsy (1.32 ± .18) compared to both controls (.57 ± .08) and seizure-free patients (.7 ± .1; $p < .001$ and $p = .001$). (C) Receiver operating characteristic analysis testing the number of PSWEs per minute detected in patients with epilepsy compared to controls and seizure-free patients combined (area under the curve = .72, $p = .0008$). (D) Following subgrouping according to ASMs use, no difference was observed within the seizure-free patients (.786 ± .81 min^{-1} vs. .577 ± .48 min^{-1}; $p = .367$) or within the patients with epilepsy (1.52 ± 1.10 min^{-1} and ASM−: 1.09 ± .82 min^{-1}; $p = .26$). (E) Topographic heat maps show diffuse PSWEs in 19 scalp electrodes among seizure-free patients versus epileptic patients. (F) Significant differences were observed in frontal, temporal, and parietal electrodes. MPF, median power frequency

PSWE occurrence per minute was higher in frontal, parietal, and temporal electrodes. The correlation between BBBD and focal occurrence of PSWEs was demonstrated in both a human study and an animal model.[11] In contrast, for neurodegenerative diseases such as dementia, PSWEs were detected diffusely in most brain areas. This colocalization suggests that PSWEs may have the ability to expose damaged brain foci, including epileptic zones possibly due to BBBD.[15–17]

The neurological management of patients following a first seizure may be challenging. The risk assessment of additional seizures determines the need to initiate ASMs. Additional factors in decision-making include patients' age, medical background, type of seizure, brain imaging, and EEG results.[18,19] Detection of abnormal brain activity, such as interictal epileptic discharge, is rarely found by routine EEG.[20] Although the utilization of 72-h continuous EEG significantly increases the yield of EEG tests, it is often inaccessible in many centers, as it demands a skilled team and is expensive.[21] PSWE analysis, as shown in our study, can be applied in shorter EEGs, with the potential to improve the interpretation of routine EEGs.

The results are consistent with previous reports, showing that the shorter the interval between a seizure and an EEG test, the better the chances to detect epileptiform activity.[12,22,23] Initial EEG performed up to 3 days following an initial seizure showed significantly higher occurrence of PSWEs, separating the two groups with both sensitivity and specificity (AUC = .82). Early ASM treatment seems not to have influenced PSWE occurrence in our cohort. However, future studies should be designed to specifically assess this question.

Our study is limited by its retrospective design. A randomized controlled trial should be carried out to test the reliability of the novel biomarker. The inclusion of patients with a minimum follow-up of 18 months induces a bias, as patients with recurrent seizures are more prone

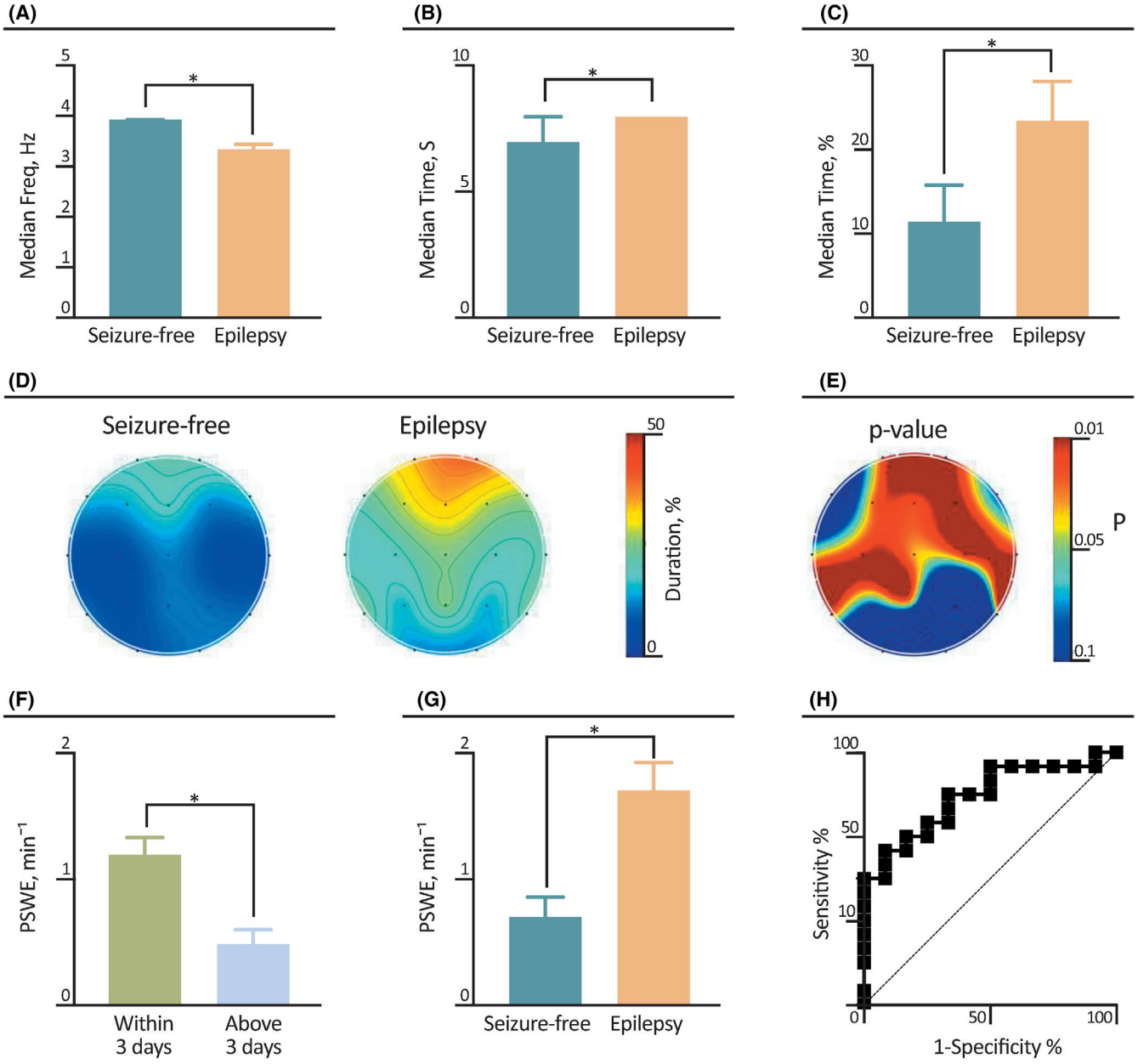

FIGURE 3 Paroxysmal slow wave events (PSWEs) as a biomarker in epilepsy. (A) Median power frequency of PWEs in the epilepsy group and in the seizure-free group. (B) Average duration of PSWEs in epilepsy and seizure-free patients. (C) Fraction of time of the recorded electroencephalogram (EEG) showing PSWE activity. (D) Heat maps demonstrate the overall length of the PSWEs/time of recordings according to 19 scalp electrodes. (E) significant differences were observed in frontal, temporal, and parietal electrodes. (F) Timing of the EEG. Conducting an EEG within 3 days following a seizure increased the occurrence of PSWEs significantly (1.2 ± .13 vs. .4 ± .11; $p < .001$). (G) Occurrence per minute of PSWEs using only EEGs recorded close to the seizure event (the first 3 days). A significant difference between the seizure-free group (.7 ± .1) and the epilepsy group (1.7 ± .2) was seen ($p < .001$). (H) Receiver operating characteristic analysis of seizure-free patients and patients with epilepsy using EEG performed close to the seizure event (<3 days).
* indicates significant difference ($p < .05$)

to seek medical attention and thus might have caused preferred exclusion of patients with only a single seizure. This might be reflected in our patient population by the large fraction of patients with epilepsy. Also, the follow-up period of the two groups differs significantly (33.9 ± 6.7 months, median = 35 months, range = 22–46 months vs. 44.2 ± 15.5 months, median = 40 months, range = 22–80 months, $p < .05$) but as we mentioned, recurrent seizures occurred in 92.8% of patients in the first 18 months following the first seizure (6.2 ± 6.1 months, range = 1–22 months), which minimizes the possibility of missed seizures in the frame of our follow-up period. In addition, a few patients in our cohort received ASM in the ED predating a complete EEG examination. However,

the percent of patients treated with ASM was not different between the groups of patients with or without recurrence of seizures, and we assume that the administration of ASM in the ED did not affect EEG results.

In summary, transient cortical slowing events, PSWEs, can be automatically, efficiently, and reliably detected in routine EEGs; they may represent a dependable new biomarker for epilepsy that can assist the neurologist in deciding on ASM treatment initiation or additional diagnostic tests for patients following a single seizure.

ACKNOWLEDGMENTS

Authors acknowledged the help on the graphic design by Michal Shor.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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How to cite this article: Zelig D, Goldberg I, Shor O, Ben Dor S, Yaniv-Rosenfeld A, Milikovsky DZ, et al. Paroxysmal slow wave events predict epilepsy following a first seizure. Epilepsia. 2022;63:190–198. doi: 10.1111/epi.17110