BURDEN OF ILLNESS IN PEOPLE WITH EPILEPSY: FROM POPULATION-BASED STUDIES TO PRECISION MEDICINE

EDITED BY: Adam Strzelczyk, Karl Martin Klein and Felix von Podewils

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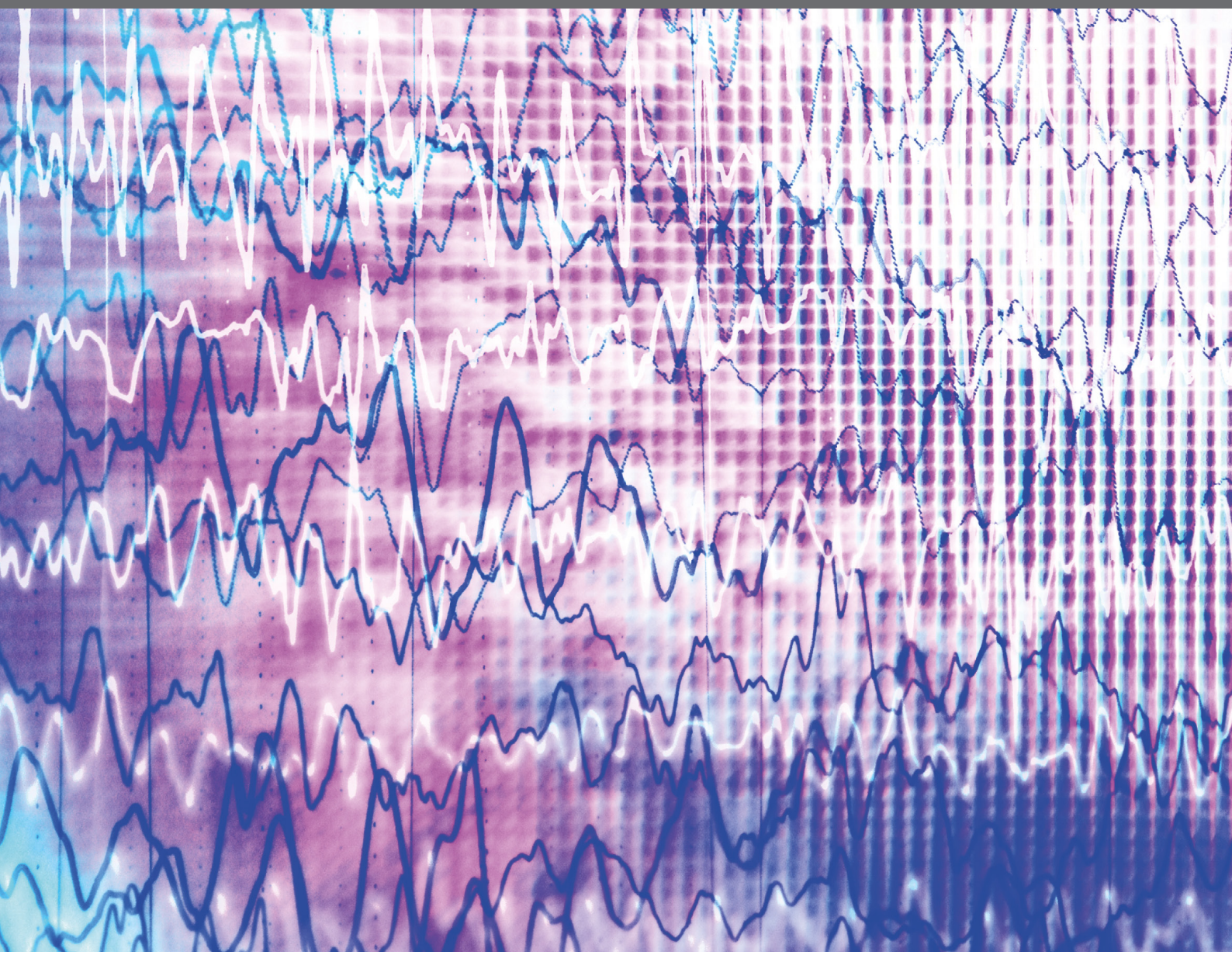

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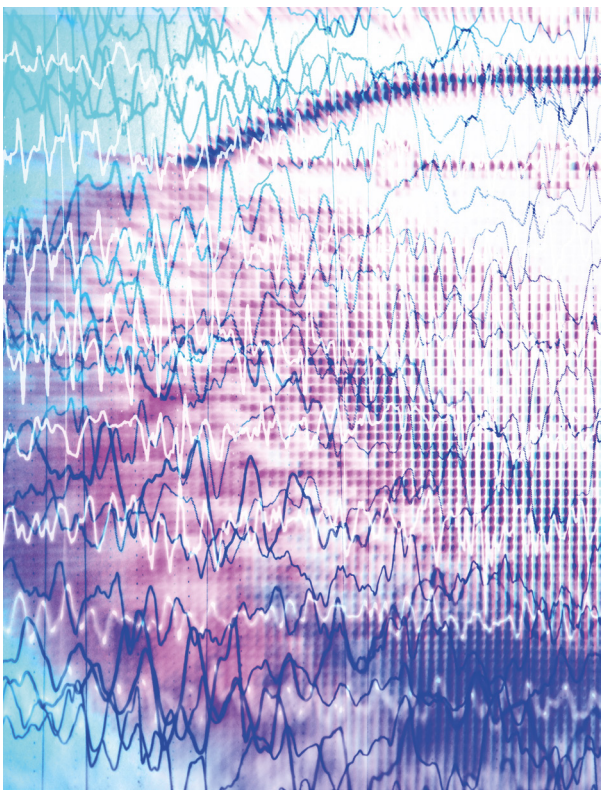
BURDEN OF ILLNESS IN PEOPLE WITH EPILEPSY: FROM POPULATION-BASED STUDIES TO PRECISION MEDICINE

Topic Editors:
Adam Strzelczyk, Goethe-University Frankfurt, Germany
Karl Martin Klein, University of Calgary, Canada
Felix von Podewils, Ernst-Moritz-Arndt University Greifswald, Germany



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Epilepsy is a common and chronic neurological disease that is characterized by recurrent seizures which impose a major burden on patients, their caregivers, and society. Worldwide more than 39 million people are affected by epilepsy.

The aim of this Research Topic was to provide evidence that personalized translational epilepsy research will benefit patients through targeted experimental, clinical and network research.

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EDITORIAL
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Editorial: Burden of Illness in People With Epilepsy: From Population-Based Studies to Precision Medicine

Adam Strzelczyk[1,2,3]*, *Karl Martin Klein*[1,3,4] and *Felix von Podewils*[5]

[1] Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, Goethe-University Frankfurt, Frankfurt am Main, Germany, [2] Epilepsy Center Hessen and Department of Neurology, Philipps-University Marburg, Marburg, Germany, [3] LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe-University Frankfurt, Frankfurt am Main, Germany, [4] Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada, [5] Epilepsy Center Greifswald and Department of Neurology, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany

Keywords: epilepsy, seizure, anticonvulsant, antiepileptic drug (AED), quality of life, imaging

Editorial on the Research Topic

Burden of Illness in People With Epilepsy: From Population-Based Studies to Precision Medicine

Epilepsy is a common and chronic neurological disease that is characterized by recurrent seizures which impose a major burden on patients, their caregivers, and society (1, 2). The aim of this Research Topic was thus to provide evidence that personalized translational epilepsy research will benefit patients through targeted experimental (3), clinical and network research (4, 5). There is a fast growing number of publications that deal with personalized or precision approaches for the treatment of epilepsy, **Figure 1**.

People with epilepsy face disease-specific restrictions concerning self-sufficiency, mobility, career choice, family planning, and other social aspects (6, 7). An analysis of patients with severe drug-refractory epilepsy showed a seven-fold increase in mortality, along with high costs and frequent epilepsy-related accidents and injuries (Strzelczyk et al.). The authors used a German health insurance database to administer a top-down approach, drawing patients from a representative cohort and matched them to a cohort that was not affected. Comorbidities, like depression and vascular disorders, were significantly increased in patients with epilepsy (Strzelczyk et al.). Focusing on epilepsy-related accidents and injuries, Willems et al. used a bottom-up approach in a cross-sectional study, and it showed that there was a possibility of a reduced quality of life and increased depression scores in affected patients (Willems et al.). The presented data in both studies fits well with other recent burden-of-disease studies that showed the costs for hospital treatment and anticonvulsants as being major cost drivers (8–11) and that persisting seizures were also associated with a reduced quality of life (12, 13).

While the use of newer anticonvulsants may be associated with increased costs, it also has the potential to significantly reduce the seizure burden. Brivaracetam is the latest anticonvulsant that has been approved as an add-on therapy for the treatment of focal-onset seizures (14). A single-center study from Marburg in Germany (Zahnert et al.) shows promising post-marketing results in a cohort of mainly drug-refractory patients, while another multi-center study focused on patients with epileptic encephalopathies (Willems et al.). In both studies, 50% responder rates of 35 to 45% were achieved, which were well in line with other postmarketing results (15–17).

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Fernando Cendes,
Universidade Estadual de Campinas, Brazil

***Correspondence:**
Adam Strzelczyk
strzelczyk@med.uni-frankfurt.de

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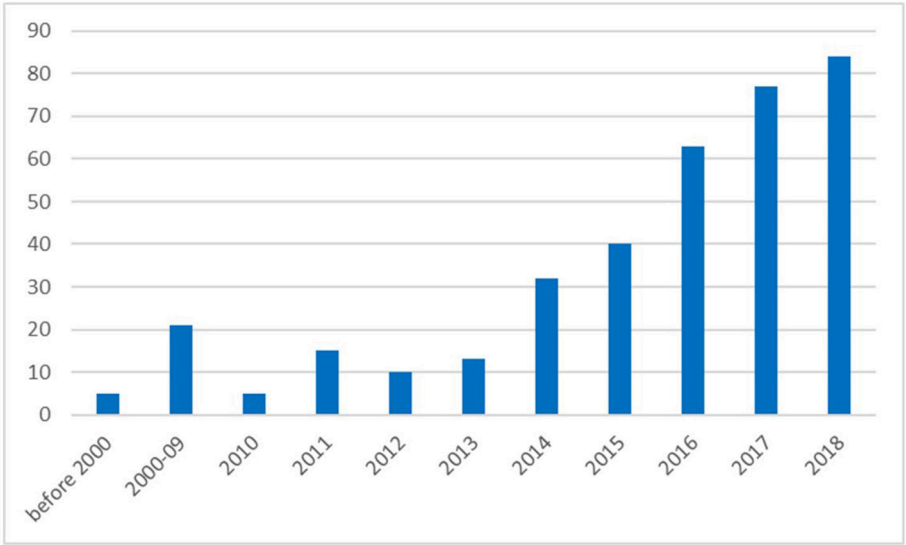

FIGURE 1 | Number of publications listed in PubMed referring to search terms "Epilepsy" and "personalized" or "precision medicine" (PubMed query on September 13th 2018).

The initial response to anticonvulsants is explored in patients with newly diagnosed epilepsy, and showed that the initial 6-month response, as well as the number of seizures prior to treatment and brain-imaging abnormalities, are important prognostic factors (Xia et al.).

Lifestyle-dependent factors are important, especially in genetic generalized epilepsies. Until now, it was unclear as to whether alcohol consumption has an impact on epilepsy in these patients (18). Even if the risk is generally increased in patients with epilepsy, patients with genetic generalized epilepsies have a particularly high risk of alcohol related-seizures after the consumption of a large amount of alcohol. This can also be attributed to accompanying factors, such as altered sleep architecture or impaired adherence to antiepileptic medication (Hamerle et al.).

The genetic architecture of common non-lesional focal epilepsies was evaluated in a study that uses a customized panel of 21 well-known focal epilepsy genes (Tsai et al.). The study revealed that only 1.85% (11/593 patients) carried pathogenic or likely pathogenic variants in these genes, and this indicated that other yet to be discovered genes play a role as well.

Comorbidities, such as cognitive issues, are often present in patients with epilepsy (19). Gorny et al. showed that not all scales that were used to assess global cognitive function, work reliably in patients with epilepsy.

Structural abnormalities associated with clinical and neuropsychological characteristics in genetic epilepsies was evaluated in two studies on juvenile myoclonic epilepsy (JME) using MRI diffusion tensor imaging (DTI), and in benign childhood epilepsy, with centrotemporal spikes (BECTS), which used the graph theory analysis based on the cortical gyrification index, respectively (Domin et al.; Jiang et al.). In JME, the extent of microstructural abnormalities within the subcortical networks, including cortico-cortical, thalamo-frontal, and cortico-spinal connections, determined the clinical manifestation and subtype of JME in the individual patient, such as photoparoxysmal responses or seizures with predominant motor symptoms (Domin et al.). In contrast, abnormal cortical folding that was mainly in the central region is presumably the neuroanatomical basis for BECTS (Jiang et al.). The findings of both studies are important steps for the establishing of the pathophysiological concepts found in genetic epilepsies.

A step forward in the care for people with epilepsy could be through the introduction of technological therapies. Page et al. pointed out in their perspective article that there has been an increase in patient-triggered interventions, a finding based on automated monitoring of indicators and risk factors facilitated by technological advances. The main goal of such interventions would be the reduction of epilepsy-related mortality with SUDEP (Sudden Unexpected Death in Epilepsy) being the main reason for epilepsy-related deaths (20, 21).

An important point on this road is the development of an automatic computer-based detection algorithm of seizures. In their review, Baumgartner et al. described the use of potential bio signals, such as scalp EEG, ECG, and surface EMG, which can be combined for an algorithm and implemented into devices. The daily work of clinicians may be significantly improved by the use of an automated long-term EEG review. This was described by Koren et al. as an automatic critical care EEG pattern detection method that would be helpful in reducing review times.

This Research Topic presents a compilation of different studies which increases the visibility of the high burden associated with epilepsy, along with providing some directions as to how personalized or precision approaches may help

to overcome this burden. In the coming years we will see a dramatic increase in personalized or precision medicine, **Figure 1**, that will significantly contribute to the management of epilepsy.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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The Burden of Severely Drug-Refractory Epilepsy: A Comparative Longitudinal Evaluation of Mortality, Morbidity, Resource Use, and Cost Using German Health Insurance Data

Adam Strzelczyk[1,2], Claudia Griebel[3], Wolfram Lux[4], Felix Rosenow[1,2] and Jens-Peter Reese[5]*

[1] Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, Goethe University, Frankfurt am Main, Germany, [2] Epilepsy Center Hessen, Department of Neurology, Philipps-University Marburg, Marburg, Germany, [3] LivaNova Deutschland GmbH, München, Germany, [4] HGC GesundheitsConsult GmbH, Düsseldorf, Germany, [5] Institute of Health Service Research and Clinical Epidemiology, Coordinating Center for Clinical Trials, Philipps-University Marburg, Marburg, Germany

Purpose: To evaluate long-term outcome of three years and treatment patterns of patients suffering from severely drug-refractory epilepsy (SDRE).

Methods: This analysis was population-based and retrospective, with data collected from four million individuals insured by statutory German health insurance. ICD-10 codes for epilepsy (G40*) and intake of anticonvulsants were used to identify prevalent cases, which were then compared with a matched cohort drawn from the population at large. Insurance data were available from 2008 to 2013. Any patient who had been prescribed with at least four different antiepileptic drugs (AEDs) in an 18-month period was defined as an SDRE case.

Results: A total of 769 patients with SDRE were identified. Of these, 19% were children and adolescents; the overall mean age was 42.3 years, 45.4% were female and 54.6% male. An average of 2.7 AEDs per patient was prescribed during the first follow-up year. The AEDs most commonly prescribed were: levetiracetam (53.5%), lamotrigine (41.4%), valproate (41.3%), lacosamide (20.4%), and topiramate (17.8%). During 3-year follow-up, there was an annual rate of hospitalization in the range 42.7 to 55%, which was significantly higher than the 11.6–12.8% ($p < 0.001$) for the matched controls. Admissions to hospital because of epilepsy ranged between 1.7 and 1.9 per year, with an average duration for each epilepsy-caused hospitalization of 10–11.1 days. The number of comorbidities for SDRE patients was significantly increased compared with the matched controls: depression (28% against 10%), vascular disorders (22% against 5%), and injury rates were also higher (head 16% against 3%, trunk and limbs 16% against 8%). The 3-year mortality rate for SDRE patients was 14% against 2.1% in the matched cohort.

Conclusion: SDRE patients are treated with AED polytherapy for all of the 3-year follow-up period. They are hospitalized more frequently than the general population and show increased morbidity levels and a sevenfold increase in mortality rate over 3 years. Further examination is required of ways in which new approaches to treatment could lead to better outcomes in severely affected patients.

Keywords: seizure, morbidity, epidemiology, population-based, secondary data analysis

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Edited by:
Antonio Gil-Nagel, Hospital Ruber Internacional, Spain

Reviewed by:
Jose F. Tellez-Zenteno, University of Saskatchewan, Canada
Rafael Toledano Delgado, Hospital Ruber Internacional, Spain

****Correspondence:***
Adam Strzelczyk
strzelczyk@med.uni-frankfurt.de

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INTRODUCTION

Epilepsy, a chronic neurological disorder, is not only common, but also burdensome both for individuals and for society. First diagnosis triggers costs in regard to diagnostic procedures, inpatient admission, and patient's loss of income (1, 2). Patients may experience social stigma, have restricted employment opportunities, and suffer impairment to the quality of life of both themselves and their caregivers. Subsequently, indirect and intangible costs result as early as the first seizure or the first diagnosis occurs (3–9).

For most patients, treatment with anticonvulsants will be necessary over a long period, and—despite optimal medical treatment—up to 30% of patients will incur refractory (10–13). Due to the high amount of total costs associated with a refractory course of disease, such drug-refractory epilepsy requires sound economic evaluation (14–19). In addition, uncontrolled seizures are often accompanied with an increased risk of psychiatric comorbidities, such as depression, and an increase in morbidity, such as falls and injuries as direct consequence of seizures, as well as an increased overall mortality from sudden unexpected death in epilepsy (SUDEP) and accidents (20–23).

Drug-refractory epilepsy is defined as the occurrence of uncontrolled seizures despite two tolerated and appropriately chosen antiepileptic drugs (AEDs) used either in combination or as monotherapies (11). Repeated changes in AEDs during disease course are a hallmark of drug-refractory epilepsy. Patterns of AED prescription changes were used to define patients with uncontrolled seizures in the database. In order to be able to study patients with severely drug-refractory epilepsy (SDRE), we chose patients who had used a minimum of four different AEDs in an 18-month period. This study's purpose is the examination of long-term (3-year) follow-up, between 2008 and 2013, of SDRE patients. Data were sourced from the German Health Risk Institute (HRI) research database (24) containing details of four million Germans insured by statutory health insurance (Gesetzliche Krankenversicherung). This top-down approach allows for the examination of a high number of patients affected by epilepsy in Germany.

MATERIALS AND METHODS

This is a retrospective longitudinal analysis of secondary data carried out on the research database of the German HRI providing access to the details of approx. four million individuals (5% of the total population of Germany) covered by statutory health insurance (24). The sample was so designed as to be representative of the population of Germany by age and gender. The analysis proceeds from the perspective of costs that must be met by statutory health insurance in Germany. Data available were anonymous at the patient level, but included diagnosis, admissions as inpatients, practitioner consultations, medication used, and other items covering the use of a healthcare service. In Germany, physicians' claims must be submitted at the end of each quarter, so that there are four time units for each year in the dataset and each of these units represents a period of 3 months. In total, 24 quarters in the insurance years 2008–2013 were available. The study was granted approval by the ethics committee of the University of Frankfurt. STROSA guidelines (Standardized Reporting Of Secondary data Analyses) were followed (25).

Identification of Study Population Affected by SDRE

Records with codes for epilepsy (G40*) from the ICD-10-GM (10th revision of the International Statistical Classification of Diseases and Related Health Problems, German Modification, www.dimdi.de) were used to identify patients with epilepsy. Since, at the level of the third and fourth digits, epilepsy codes between the ICD-10 and ICD-10-GM systems show no discernible difference, ICD-10 is the term used throughout this article. The ICD-10 coding has already been used in Canada and Germany to identify cases of epilepsy and status epilepticus and demonstrated sensitivity and positive predictive value up to 98% (26–32).

Since no ICD-10 code exists for refractory epilepsy, we added to the need for a confirmed G40* diagnosis the prescription of at least four different AEDs matching ATC-codes N03A in an 18-month period sometime between 2009 and 2010. The reason for choosing a cutoff of four different AEDs was to reflect the definition of drug-refractoriness laid down by the ILAE, and to exclude patients who had become free from seizures following prescription of two AEDs in combination following the previous failure of one different drug, while the 18-month period was chosen as a sufficient time period for the titration of the dose of three AEDs (11, 12). These criteria for the definition of SDRE were put together in a preliminary retrospective analysis of records of epilepsy patients. For each insured person, the date of prescription of the fourth AED decided what the 3-year follow-up period would be, with the previous year acting as baseline. We did not determine an epilepsy syndrome on the basis of only ICD-10 diagnoses, due to the complications afforded by mixing classification of seizure with syndrome classification. In addition, no precise correspondence exists between the ICD-10 codes for epilepsy and the epilepsy syndrome and the International League Against Epilepsy classification of seizures, as defined in the 1980s, and nor is there such correspondence with the most recent concepts and terminologies for seizure and epilepsy classification that were revised in 2009 and 2017 (33–35).

Cost Calculations

Cost evaluation applied a top-down approach of costs covered by statutory health insurance. Inpatient care costs were derived from the German Diagnosis Related Groups (G-DRG; www.g-drg.de), with costs calculated for the single baseline year and for the three follow-up years (i.e., 2011, 2012, and 2013). Inpatient costs were assumed to be specific to epilepsy where the primary ICD-10 was either G40 (epilepsy) or G41 (status epilepticus). Previous studies will provide more details of how costs were calculated (15, 18, 36).

Statistical Analysis

To comply with regulations concerning data protection, management and analysis of all data was conducted by the use of anonymous patient codes. The number of admissions as an inpatient, the number of comorbidities, and the degree of mortality were all compared with a cohort that represented the general

population matched by both age and gender at a ratio of 20:1 where $n = 15{,}380$. None of the matched patients had a diagnosis of epilepsy, to detect excess resource utilization, morbidity, and mortality. Age and gender distribution are provided in Figure S1 in Supplementary Material. Differences between SDRE patients and matched controls were assessed using chi-square tests, and Kaplan–Meier methodology was adopted for comparison for survival of SDRE patients with matched controls. p-Values were two-sided in all cases and were accepted as statistically significant <0.05. Since the study was planned to have an explorative nature, no further adjustment for multiple testing was performed.

RESULTS

Identification of SDRE Patients

We identified 769 patients meeting our definition of SDRE. Of those, 54.6% were male, mean age was 42.3 years, standard deviation (SD) was 21.9, and 19% ($n = 146$) were either children or adolescents below the age of 18 years; 61.3% of patients ($n = 471$) were of working age and 19.8% ($n = 152$) were older than 65 years.

Prescription Patterns

The time between prescription of the first three AEDs and prescription of the fourth AED varied with a mean latency of 212 days (SD 136.2). During the 3-year follow-up period, each patient received an average of 5.3 AEDs (SD 1.6), with the most commonly prescribed being: levetiracetam (56.6%, $n = 435$ during the 3 years of follow-up); lamotrigine (44.6%, $n = 343$); valproate (43.4%, $n = 334$); lacosamide (25.4%, $n = 195$); and topiramate (19.1%, $n = 147$). Further details are shown in **Figure 1**. More recently introduced AEDs, such as lacosamide, were prescribed twice during follow-up, as compared to baseline ($p < 0.001$); in contrast to that, carbamazepine ($p < 0.001$) and oxcarbazepine ($p = 0.004$) prescriptions fell significantly during follow-up. Perampanel was approved in 2012 and prescriptions increased from 0.4% of patients during the second follow-up year to 6.2% in the third follow-up year, which put this drug ahead of gabapentin, retigabine, and eslicarbazepine and showed a very rapid adoption rate. Further details are available in **Figure 2**.

Benzodiazepines were prescribed in a large percentage of patients, with lorazepam being prescribed at least once for 284 patients (36.9%) in the three follow-up years, followed by diazepam ($n = 217$, 28.2%), clobazam ($n = 192$; 25.0%), and clonazepam ($n = 113$; 14.7%).

Other drugs that were prescribed to SDRE patients at least once during the three follow-up years included: antibiotics (e.g., cefuroxime 20.5%); pain medication (e.g., ibuprofen 40.3%; metamizole 35.5%); antidepressants (citalopram 10.9%); proton pump inhibitors (pantoprazole 29.6%, omeprazole 20.4%); and neuroleptics (risperidone 7.9%; melperone 7.7%). Further information is contained in Table S1 in Supplementary Material.

Hospitalization and Outpatient Visits

The overall number of patients who were admitted to hospital at least once during the three follow-up years was 568 (73.9%) (total admissions: 2,403; mean number of admissions per hospitalized patient: 4.2; total number of days in hospital, 23,346; mean stay 9.7 days). Of this total of 568, at least one admission was due to epilepsy in the case of 353 patients (total number of epilepsy-related admissions: 1,002, mean number of admissions per patient: 2.8; total number of days in hospital 10,474, mean stay 10.5 days). **Figure 3** provides a summary of annual outpatient

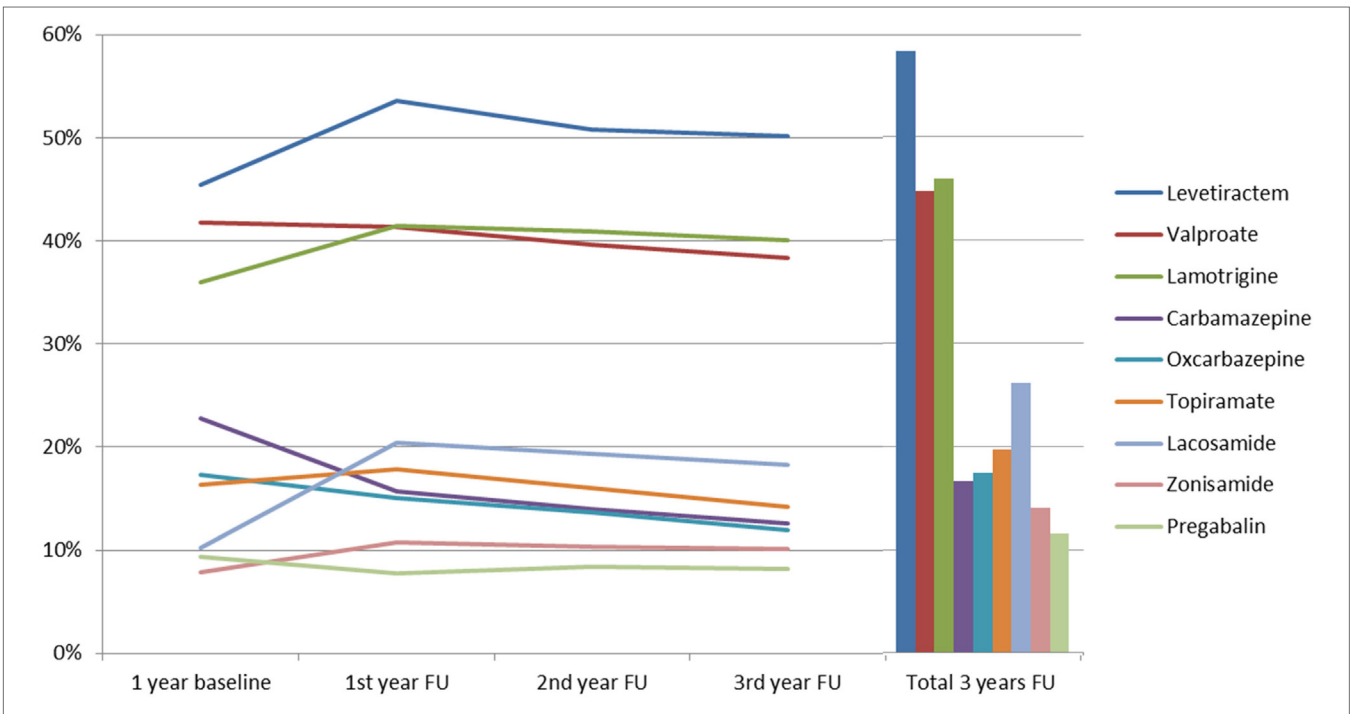

FIGURE 1 | Prescription patterns of the anticonvulsants most used among severely drug-refractory epilepsy patients (FU, follow-up).

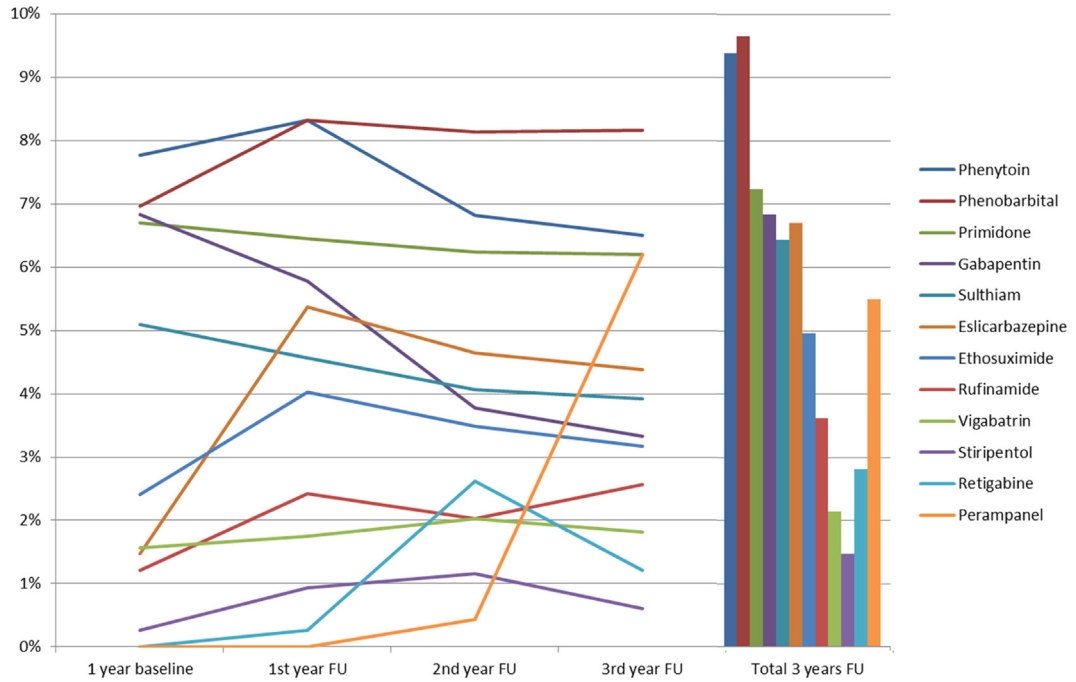

FIGURE 2 | Prescription patterns of anticonvulsants of which <10% were used among severely drug-refractory epilepsy patients (FU, follow-up).

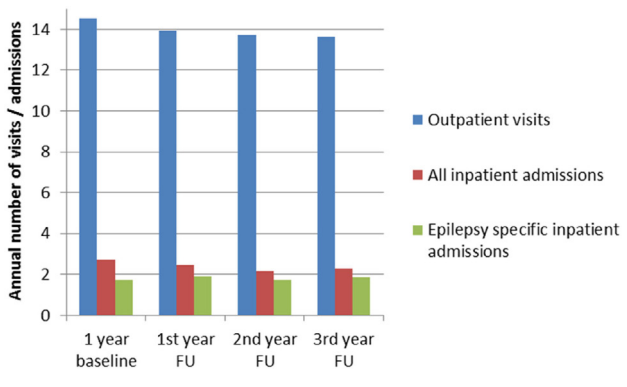

FIGURE 3 | Annual inpatient admissions, epilepsy-specific admissions, and outpatient visits during baseline and FU in patients with epilepsy (FU, follow-up).

visits, annual overall admissions to hospital, and annual admissions to hospital for courses related to epilepsy.

Epilepsy-related hospital admissions per annum averaged from 1.7 to 1.9, and the epilepsy-related length of stay averaged from 10 to 11.1 days per annum. The rates of annual admission for complex treatment of epilepsy ("Komplexbehandlung Epilepsie" OPS 8-972.x) averaged from 6% to 6.8%, and at least one such complex treatment during the three follow-up years was provided to 13.6% (105/769) of patients. Annual rates of admission for non-invasive video-EEG-monitoring [OPS 1-210 (37)] averaged from 1.6% to 3.2%; 5.7% (44/769) of patients had at least one such non-invasive monitoring during the three follow-up years, while invasive monitoring was performed in five (0.6%) patients [OPS 1-211 (37)]. Brain surgery (OPS 5-010) was performed in 4% of the patients (31/769), while annual rates ranged between 1.5 and 2.1%. Within the three follow-up years, 94 patients (12.2%) were hospitalized as a result of a status epilepticus.

In the three follow-up years, annual rates of hospitalization ranged from 42.7% to 55%, which was a significant increase compared to the matched controls (11.6–12.8%, $p < 0.001$). Four thousand two hundred and ninety-seven (27.9%) of controls were hospitalized at least once in the three follow-up years; the total number of admissions among controls was 8,461 representing a mean number of admissions per matched hospitalized control of 1.97. Their total days spent in hospital amounted to 63,179, resulting in an average length of stay of 7.5 days.

Annual outpatients visits ranged between 13.6 and 14.0 contacts per year, see **Figure 3**. General practitioners were seen between 4.9 and 5.0 times per year by 94–96% of the SDRE patients. Neurologists were seen 2.9–3 times a year by 29–30% of the patients and neuropsychiatrists (Nervenarzt) were seen 3.4–3.5 times a year by 38–42% of the patients. Neuropediatricians were seen 2.1–2.2 times a year by 2.9–3.3% of the patients. Radiologists were seen 1.2–1.4 times a year by 19.6–23.2% of the patients. Prescription of AEDs was performed mainly by general practitioners (52–58% per year) ahead of neurologists (24–25% per year) and neuropsychiatrists (Nervenarzt: 35–36% per year).

Comorbidities and Mortality

The number of comorbidities in the SDRE group was significantly higher than in the control group, see **Figure 4**. Depression was diagnosed in 28% in the first year of follow-up compared to

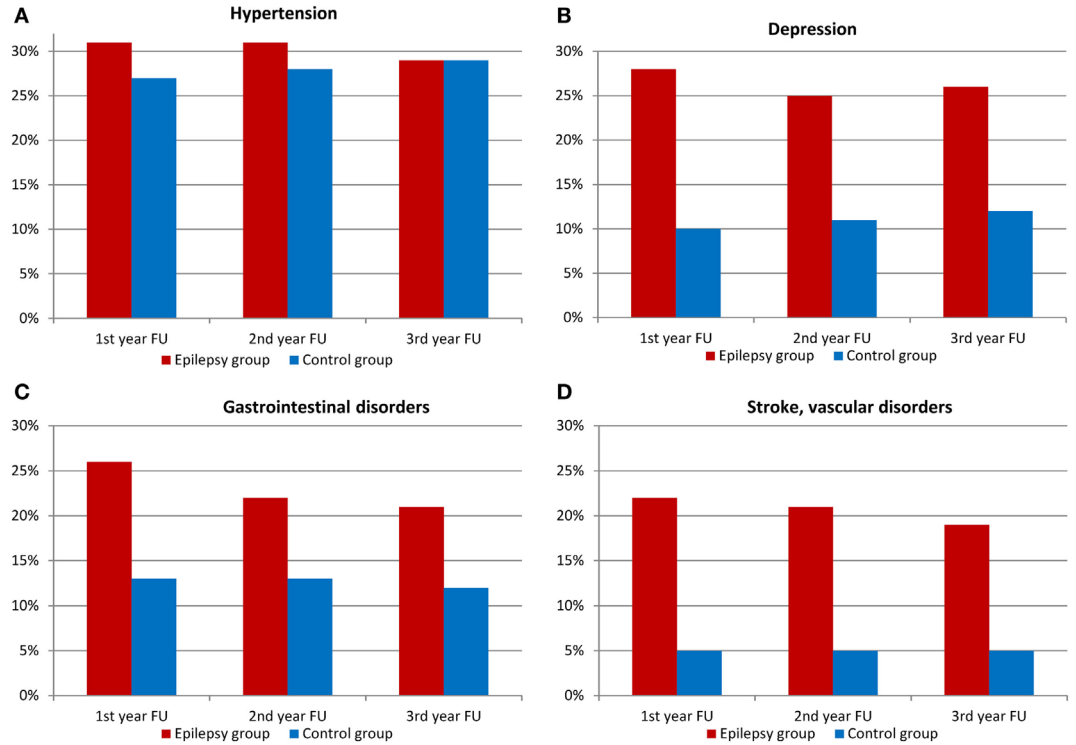

FIGURE 4 | Comorbidities among patients with epilepsy and control group (FU, follow-up). **(A)** Hypertension, **(B)** depression, **(C)** gastrointestinal disorders, and **(D)** stroke, vascular disorders.

10% in the general population ($p < 0.001$). Further psychiatric comorbidities comprised organic mental disorders (ICD-10 F06) in 24.8%, somatoform disorders (ICD-10 F45) in 20.8%, and personality and behavioral disorders (ICD-10 F07) in 19.6%.

Other conditions were gastrointestinal disorders (26 against 13%, $p < 0.001$) and vascular disorders (22 vs. 5%, $p < 0.001$). As **Figure 4** shows, hypertension distribution showed no difference. SDRE patients were also more likely to suffer injuries, with 16% suffering head injuries compared with 3% of the control cohort ($p < 0.001$) and injuries to trunk and limbs also at 16%, compared, in this case, with 8% in general population ($p < 0.001$), please refer to **Figure 5** for details. Table S2 in Supplementary Material shows the details of ICD-10 coding in inpatient and outpatient settings during the three follow-up years.

Mortality rate of SDRE within 3 years was 14%, compared with the matched cohort's 2.1% ($p < 0.001$). **Figure 6** uses the Kaplan–Meier method to show survival times. SDRE patients' mortality rate was at its highest (7.8%) during the first follow-up year.

Costs

The annual direct costs of treating SDRE patients totaled to between €12,925 and €14,639 during the three follow-up years. The annual inpatient treatment costs were between €4,880 (37% of total direct costs) and €6,110 (42%). Annual medication costs were between €4,565 (35%) and €5,294 (38%). **Figure 7** gives details of the costs, both at the baseline year and in follow-up years.

DISCUSSION

This is the first nationwide study using health insurance data analyzing the long-term treatment patterns, costs, and mortality of SDRE patients in Germany. It shows the high burden imposed on SDRE patients in the form of higher consumption of resources, comorbidities, injuries, and mortality when compared to matched cohort drawn from the population at large.

Prescription patterns for 2011, 2012, and 2013 from this study demonstrate an increased use of newer anticonvulsants. The study has also confirmed findings from other studies on prescription patterns in drug-refractory patients who used a top-down approach (38–40). Comparison of these prescription patterns with previous German studies carried out in 2003 (15), 2008 (18), 2009 (38), 2011 (8, 41), and 2012 (9) show a significant increase in the use of "newer" AEDs and a marked reduction in enzyme-inducing anticonvulsant prescriptions. Since 2008, German guidelines recommend that the first choice for monotherapy in focal epilepsy should be lamotrigine or levetiracetam and that anticonvulsants with drug–drug interactions should not be used. Recent studies show that German prescription patterns for anticonvulsants follow these recommendations with marked reduction in prescription of carbamazepine and phenytoin, that is largely in line with the current guidelines (9, 31, 42). Benzodiazepines were used commonly in our SDRE cohort; however, we cannot

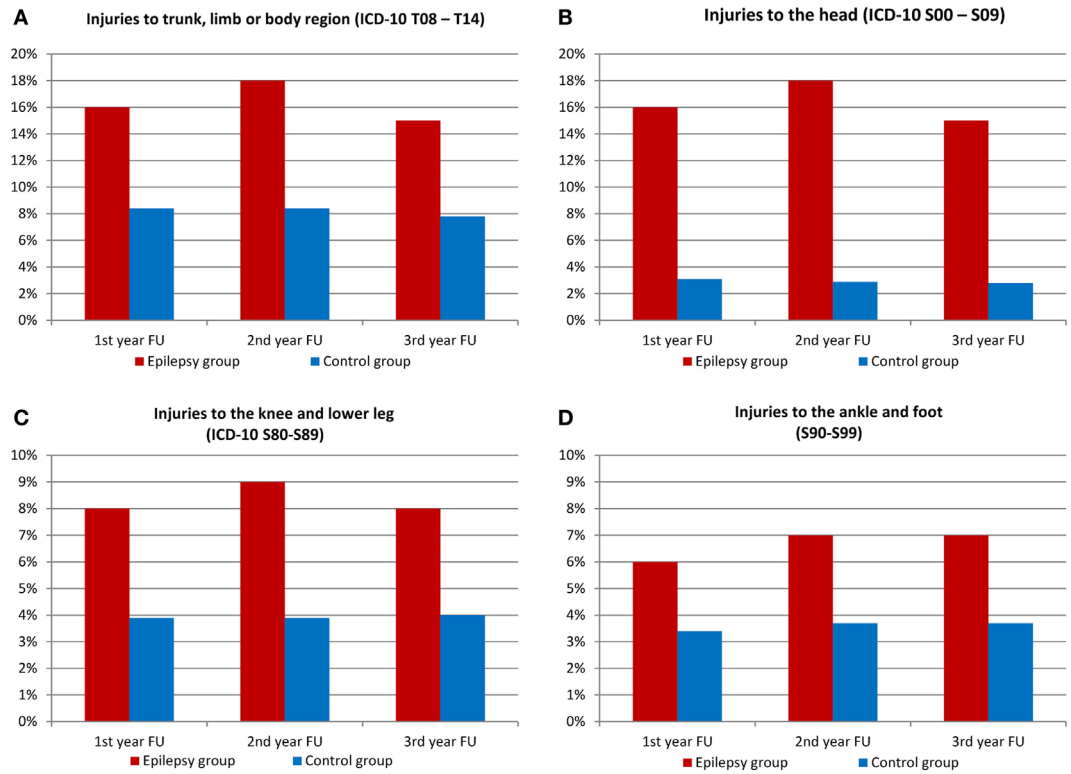

FIGURE 5 | Injuries among patients with epilepsy and control group (FU, follow-up). **(A)** Injuries to trunk, limb, or body region (ICD-10 T08–T14), **(B)** injuries to the head (ICD-10 S00–S09), **(C)** injuries to the knee and lower leg (ICD-10 S80–S89), and **(D)** injuries to the ankle and foot (S90–S99).

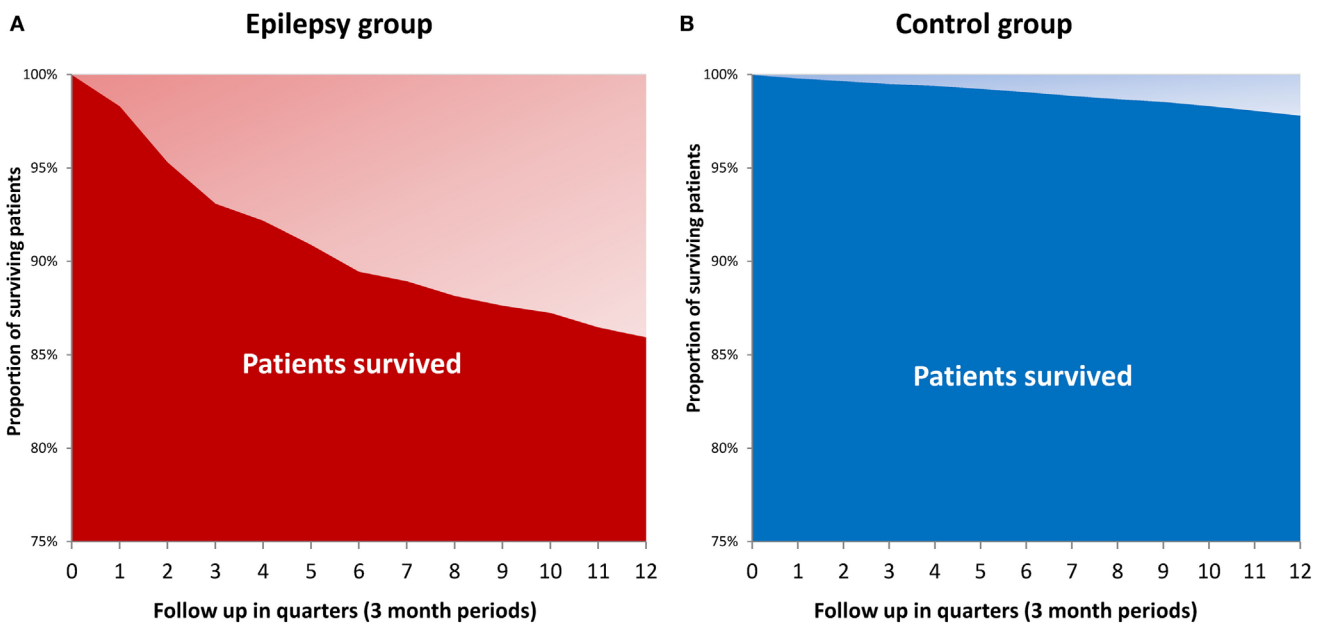

FIGURE 6 | Mortality among patients with epilepsy **(A)** and control group **(B)**.

differentiate in detail which benzodiazepines were prescribed for rescue therapy, ongoing anticonvulsive treatment, or use in depression or anxiety disorders.

Our study suggests a possible undertreatment of SDRE patients. Only 13.6% of patients had specialized inpatient epilepsy treatment, and the proportion of patients admitted to presurgical

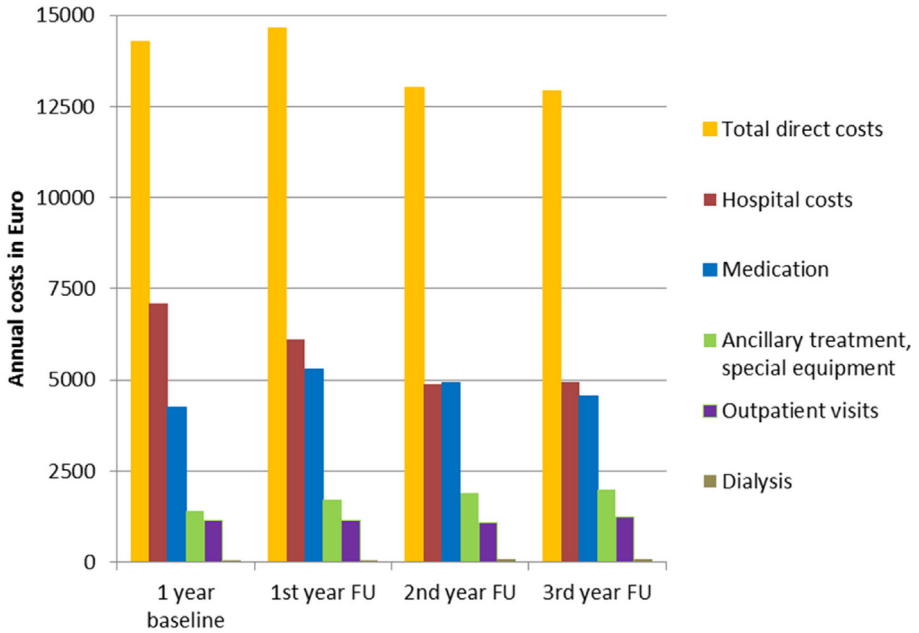

FIGURE 7 | Annual inpatient treatment, medication, ancillary treatment, special equipment, outpatient visits, and dialysis costs, separately and as total direct costs.

evaluation through video-EEG-monitoring was 5.7%, even fewer (37, 43). A substantial proportion of 30–40% of the patients did not attend a neurologist or neuropsychiatrist during each year of follow-up. Despite the AED polytherapy in these patients, anticonvulsive therapy was not prescribed by a neurologist or neuropsychiatrist. It can be inferred from these low percentages that therapeutic and diagnostic options may be underused. Due to the underutilization of specialist care, some patients might have suffered from a SDRE. There are difficulties in gaining access to epilepsy centers and surgery programs for epilepsy; this seems in line with other studies that have shown that referral takes 15–20 years on average (44–48). Evaluation at an epilepsy center of patients who had been referred showed that only 30% came with magnetic resonance imaging (MRI) that conformed to the guidelines and was sufficient, whereas this was not the case in 70% of the referred patients. In 10%, MRI had not been carried out (49). Studies to be carried out in future should also follow-up treatment of SDRE patients and should pay particular attention to such aspects of the guidelines as: what information about their disease has been provided to patients (48, 50); and what access refractory patients have to the comprehensive care that epilepsy centers can provide or to the provision of epilepsy nurses and/or epilepsy counseling services to patients with a low access threshold (51, 52).

The mortality rate of SDRE in patients within 3 years was 14%, which is seven times the rate for a control population matched for age and gender. The increased mortality is high and in line with a recently published, matched nationwide study from Denmark reporting mortality among epilepsy patients of more than 10% 3 years after diagnosis of epilepsy (53). Causes of death among people with epilepsy are manifold. The risk of a SUDEP is up to 9.3 per 1,000 person-years in a refractory population (54). Given such SUDEP risk, we would expect a crude number of around 18–20 SUDEP cases during the 3 years of follow-up in our cohort, which covers approximately 2,200 person-years. Studies of SUDEP lifetime risks have shown that, even in an unselected epilepsy patient cohort, onset at one year of age leads to an 8% SUDEP risk by age 70. That risk falls to 7.2% if the epilepsy began at 15 years of age, and to 4.6% for a starting age of 30 years (23). A study carried out in Finland on long-term mortality rates in epilepsy that begins in childhood followed 245 patients for 40 years (20). A total of 60 patients (24%) died, which was three times the rate that would be expected in a cohort from the general population adjusted for age and gender. Active epilepsy and a remote symptomatic cause correlated with mortality. In total, 33 deaths (55%) were epilepsy-related, with SUDEP present in 18 cases (30%), seizure (either definite or likely) in 9 (15%), accidental drowning in 6 (10%), and status epilepticus in 4 (7%). Mortality resulting either from injuries or from status epilepticus might also suggest an explanation of mortality in our study, which shows an increase in the number of injuries and that status epilepticus was responsible for 12.2% of the epilepsy population being hospitalized. There is a mean mortality association between 15 and 20% with status epilepticus (32, 55–57). The high number of injuries appearing in our study confirms the results of previous studies (58–61). An American study of 52 patients suffering from refractory focal epilepsy showed that injury in 21% of temporal lobe epilepsies and 8% in extratemporal epilepsies had occurred in the year previous to the survey (61). Temporal lobe epilepsy showed a 57% lifetime prevalence of injuries with a 22-year average duration, while, for extratemporal epilepsies, this lifetime prevalence was 17% and the duration of the disease 17 years. Comparing interviews with patient records showed that injuries were

documented in only 45% of cases and that whether documentation occurred depended on how severe the injuries were (61). A prospective European study on disease and injury used friends and relatives as a control for 12 years (58) and found that the likelihood of accident and injury in the epilepsy patients was 21%, compared with 14% for the controls (58). There was a correlation between number of injuries and seizure frequency (58). The continuing significance of injuries caused by seizures as a serious and persistent problem in cases of childhood onset epilepsy was confirmed by a population-based study conducted by the Nova Scotia Childhood Epilepsy cohort (59). In a follow-up averaging 24 years, 11% of patients (52/472) experienced one or more serious injuries, with the total of injuries being 81. Of these, the most frequently reported were lacerations requiring sutures (30%), fractures (19%), broken teeth (14%), concussions (10%), and burns (5%). Also reported were one drowning that proved fatal, two near-drownings, one severe eye injury, and three dislocations of the shoulder. As before, the risk factors were symptomatic generalized epilepsy and intractable epilepsy. Most injuries occurred during the patient's normal daily activities. They occurred at any stage in the patient's life and were judged as not easily preventable. In line with our results on vascular and gastrointestinal disorders, studies on somatic comorbidities in epilepsy patients show an increase in stomach/intestinal ulcers, stroke, urinary incontinence, bowel disorders, migraine, Alzheimer's disease, and chronic fatigue (62, 63). Overall, our study's high mortality figures can, therefore, be seen to confirm the findings of previous studies (20, 53). A significant proportion may be related to epilepsy as a result of SUDEP, status epilepticus, or injuries.

Our results show that the total direct costs of treatment of SDRE patients amounted to between €12,925 and €14,639 per annum in the three follow-up years, exceeding the annual average cost of €3,011 for any insurant in Germany (64). The main constituents of the direct cost were inpatient costs, amounting to 37%, 42% of the total direct costs, and cost of medication, which came to between 35 and 38%; these percentages did not change over time, which demonstrates that there is a need for increased levels of healthcare services for SDRE patients. Studies of cost of illness (2) show hospitalization costs to be less subject to change than medication costs. Hospitalization costs continue to be a major element of total costs, and this confirms the results of other top-down studies from Denmark (65) and the United States of America (66, 67). Evaluating large cohorts, as has been the case with this study, allows data to be captured from cost-intensive patients presenting infrequently to hospital [as, for example, with status epilepticus (68–70) or for video-EEG monitoring or epilepsy surgery (71)]. Smaller, bottom-up studies are more likely to overlook these patients.

While this study was designed with great care, it nevertheless has limitations of the sort such studies cannot escape. Top-down studies are able to include all epilepsy patients, regardless of whether they could take part in field studies, but there is still difficulty in identifying mortality and injury as definitely caused by or connected to epilepsy. Mortality can be due to underlying causes, such as stroke, traumatic brain injury, or malignancies. Difficulties also remain in the categorization of costs between, for example, costs directly related to epilepsy and costs connected with comorbidities. Even though the control group was age and gender matched, it would have been useful to have a match by propensity score so that the impact of comorbidity could be minimized (72). It is possible to explore what impact or influence epilepsy and anticonvulsive therapy have on such comorbidities as osteoporosis and depression, both of which, whether separately or in combination, have the potential to increase mortality, injury frequency, and consumption of resources. It is also possible that our results have been affected by matters of methodology and/or by the SDRE definition used. These possible effects include the origin of the information from health insurance database, since definitive patient information at the chart level is not available from such records due to data protection rules. AEDs might have been discontinued due to adverse events and not due to refractoriness. Therefore, we cannot provide sensitivity and specificity values for the definition used. Classifying SDRE by means of an algorithm based on treatment is perhaps insufficiently precise.

CONCLUSION

This study's significance arises from analysis of health insurance data based on a sample population for longitudinal analysis of SDRE patients; this is the first time that this has been done. Future analysis should explore ways in which new approaches to treatment could improve outcomes for severely affected patients.

ETHICS STATEMENT

This study was carried out in accordance with the Declaration of Helsinki. As this study used anonymous insurance data written informed consent was not obtained. The protocol was approved by the ethics committee of the University of Frankfurt. We confirm that we have read Frontiers in Neurology position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

AUTHOR CONTRIBUTIONS

AS and CG generated the research idea and concept. WL acquired and analyzed the data. AS, CG, WL, FR, and JPR made critical revisions for important intellectual content and interpreted the data. AS wrote the manuscript. AS, CG, WL, FR, and JPR approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fneur.2017.00712/full#supplementary-material.

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Incidence, Risk Factors and Consequences of Epilepsy-Related Injuries and Accidents: A Retrospective, Single Center Study

Laurent M. Willems[1], Nina Watermann[2], Saskia Richter[2], Lara Kay[1], Anke M. Hermsen[1], Susanne Knake[2], Felix Rosenow[1,2] and Adam Strzelczyk[1,2]*

[1] *Department of Neurology, Epilepsy Center Frankfurt Rhine-Main, Goethe University Frankfurt, Frankfurt, Germany,*
[2] *Department of Neurology, Epilepsy Center Hessen, Philipps University of Marburg, Marburg, Germany*

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****Correspondence:***
Laurent M. Willems
laurent.willems@kgu.de

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Introduction: This study was designed to evaluate risk factors and incidence of epilepsy-related injuries and accidents (ERIA) at an outpatient clinic of a German epilepsy center providing healthcare to a mixed urban and rural population of over one million inhabitants.

Methods: Data acquisition was performed between 10/2013 and 09/2014 using a validated patient questionnaire on socioeconomic status, course of epilepsy, quality of life (QoL), depression, injuries and accidents associated with seizures or inadequate periictal patterns of behavior concerning a period of 3 months. Univariate analysis, multiple testing and regression analysis were performed to identify possible variables associated with ERIA.

Results: A total of 292 patients (mean age 40.8 years, range 18–86; 55% female) were enrolled and analyzed. Focal epilepsy was diagnosed in 75% of the patients. The majority was on an antiepileptic drug (AEDs) polytherapy (mean number of AEDs: 1.65). Overall, 41 patients (14.0%) suffered from epilepsy-related injuries and accidents in a 3-month period. Besides lacerations ($n = 18$, 6.2%), abrasions and bruises ($n = 9$, 3.1%), fractures ($n = 6$, 2.2%) and burns ($n = 3$, 1.0%), 17 mild injuries (5.8%) were reported. In 20 (6.8% of the total cohort) cases, urgent medical treatment with hospitalization was necessary. Epilepsy-related injuries and accidents were related to active epilepsy, occurrence of generalized tonic-clonic seizures (GTCS) and drug-refractory course as well as reported ictal falls, ictal loss of consciousness and abnormal peri-ictal behavior in the medical history. In addition, patients with ERIA had significantly higher depression rates and lower QoL.

Conclusion: ERIA and their consequences should be given more attention and standardized assessment for ERIA should be performed in every outpatient visit.

Keywords: epilepsy, seizure, falls, laceration, accident

INTRODUCTION

Epilepsy is a common and chronic neurological disorder that affects about 39 million people worldwide (1, 2). People with epilepsy are subject to social and vocational stigma, have only restricted access to the labor market and significantly reduced employment opportunities (3). Moreover, quality of life (QoL) is significantly reduced for themselves and their caregivers (4–9). Active epilepsy with persisting seizures is associated with loss of consciousness, uncontrolled movements, falls or periictal abnormal behavior may predispose to accidents and injuries such as burns, contusions, lacerations or fractures (10–12).

A prospective longitudinal analysis from Finland on 245 children with epilepsy since 1964 showed a significantly increased age- and sex-adjusted mortality. During the 40-year follow up, 60 (24%) subjects died and 33 (55%) of these events were attributed to the underlying epilepsy. Besides sudden unexpected death in epilepsy (SUDEP) and status epilepticus, epilepsy-related injuries and accidents (ERIA), such as peri-ictal drowning, were common causes of death. Within this cohort, pneumonia, cardiovascular diseases and suicide have been reported as most frequent causes of death not related to seizures or epilepsy (13–15). ERIA were shown to be a major cost factor for hospitalizations among patients with epilepsy (16). One major problem with ERIA is unreported cases in daily practice. If not investigated in detail, it can be assumed that approximately 50% of ERIA are falsely not documented as seizure-related in medical documentation (17).

The main aim of our study was to assess the frequency and types of ERIA in a cohort of consecutive patients with epilepsy using a validated questionnaire (18) and to search for variables associated with ERIA. Improved screening parameters for ERIA may help in reducing the frequency and severity of ERIA. A second aim was to assess QoL and depression as possible consequences of ERIA.

PATIENTS AND METHODS

Study Settings, Patients and Design

This study was performed as a survey at the epilepsy outpatient clinic of the University Hospital Marburg. The University Hospital Marburg is a large multispecialty tertiary care hospital in the center of Germany that provides healthcare to a population of over 1,000,000 inhabitants. Marburg is located within the postal code area 35, which was used previously for a population-based estimation of the incidence of status epilepticus and different cost-of-illness studies (3, 19–21). After receiving written informed consent, all adult epilepsy patients aged 18 years or older were eligible. Socioeconomic data and information on injuries or accidents as well as on QoL were accessed between 10/2013 and 09/2014 using a validated questionnaire (18). Patients were asked to complete the questionnaire concerning their individual epilepsy related experiences during the last 3 months. The diagnosis was based on the definitions proposed by the International League Against Epilepsy and the International Bureau for Epilepsy (22) and was provided by the treating physician. Any patient with at least one seizure during the last 12 months at enrolment was classified as having an "active epilepsy." Patients were excluded when the diagnosis of epilepsy could not be determined without doubt. The study had the approval of the local ethics committee.

Variables Associated With Epilepsy-Related Injuries and Accidents

Specification of epilepsy syndromes as well as information regarding intake of AEDs was assessed by the attending physician. The following factors were identified as possible parameters influencing injuries or accidents in patients with epilepsy according to published literature (18): patient age, duration of epilepsy, sex, epilepsy syndrome, postictal patterns of behavior as well as seizure frequency and semiology (loss of consciousness, nocturnal seizures). Abnormal postictal behavior patterns were classified in line with the guidelines of the German employers' liability insurance association (Unfallversicherung, DGUV 250-001), which classifies seizures with abnormal postictal behavior as "high risk" for related injuries or accidents at work (23). Refractory epilepsy was classified according to ILAE definitions (24). Moreover, different sociodemographic and clinical characteristics were documented.

Changes in Mood and Quality of Life Due to ERIA

To evaluate the psychological aspects of ERIA, various established neuropsychological inventories were assessed using already established questionnaires: To measure health related QoL, the QOLIE31 score (Quality of Life in Epilepsy Inventory) (25) and EQ5D score (Euro Quality of Life) were used (26). For EQ5D, both relevant parameters, i.e., overall TTO (time trade-off) and VAS (visual analog scale), were determined (26). To evaluate health-related depression, NDDI-E (Neurological Disorders Depression Inventory for Epilepsy) (27) and BDI-II (Becks Depression Inventory) were used (28). As an independent parameter, ABNAS (A-B Neuropsychological

TABLE 1 | Epilepsy syndromes within the cohort.

Epilepsy syndrome (*n* = 292)	% (*n*)
Focal epilepsy	75.0 (219)
TLE	49.0 (143)
FLE	10.6 (31)
Other lobes	5.1 (15)
Multilobar	4.5 (13)
Other/cryptogenic	5.8 (17)
Idiopathic generalized epilepsy	19.5 (57)
IGE with grand mal on awakening	0.3 (1)
JME (Janz syndrome)	4.8 (14)
Juvenile absence epilepsy	1.7 (5)
Other	12.7 (37)
Unclassified	5.5 (16)

TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy.

TABLE 2 | Sociodemographic and clinical characteristics of the entire cohort and for patients with focal and idiopathic generalized epilepsies.

		Total *n* = 292	Focal epilepsy *n* =219	IGE *n* =57	*p*-value
Age in years[a]		40.8 ± 15.6	43.1 ± 15.5	31.4 ± 12.5	<0.001[b]
		Range:18–86	Range: 18–86	Range: 18–63	
Disease duration in years[a]		14.2 ± 19.8	14.3 ± 14.1	14.7 ± 13.6	0.881[b]
		Range: 0.1–63	Range: 0.1–63	Range: 0.1–55	
Sex					
Male		45.2 (132)	46.1 (101)	40.4 (23)	0.121[c,d]
Female		54.9 (160)	53.9 (118)	59.7 (34)	
Anticonvulsants	Mean no of AED	1.6 (±0.8)[a]	1.7(±0.8)[a]	1.5 (±0.6)[a]	
		% (n)	*% (n)*	*% (n)*	
	No AEDs	1.7 (5)	0.18 (4)	0.3 (1)	0.958[c]
	Monotherapy	48.3 (141)	45.7 (100)	54.4 (31)	
	2 AEDs	34.6 (101)	34.7 (76)	38.6 (22)	
	≥3 AEDs	15.4 (45)	17.8 (39)	7.0 (4)	
Seizures		% (*n*)	% (*n*)	% (*n*)	
Seizure freedom >1 year		32.2 (94)	29.2 (64)	45.6 (26)	0.019[c]
Active epilepsy		67.8 (198)	70.8 (155)	54.5 (31)	

[a]*Mean ± standard deviation.*
[b]*p-value calculated using T-Test.*
[c]*p-value calculated using chi2-test.*
[d]*Male vs. female.*

TABLE 3 | Prescription pattern of anticonvulsant drugs within the cohort.

AED	% Total patients (*n*)
Levetiracetam	53.1 (155)
Lamotrigine	35.6 (104)
Valproate	16.1 (47)
Carbamazepine	11.6 (34)
Lacosamide	11.6 (34)
Zonisamide	9.2 (27)
Oxcarbazepine	7.5 (22)
Perampanel	6.2 (18)
Topiramate	3.8 (11)
Pregabalin	2.4 (7)
Gabapentin	1.7 (5)
Clonazepam	1.0 (3)
Primidone	1.0 (3)
Ethosuximide	1.0 (3)
Phenobarbital	0.7 (2)
Eslicarbazepine	0.3 (1)
Stiripentol	0.3 (1)
Methsuximide	0.3 (1)
Phenytoine	0.3 (1)
Piracetam	0.3 (1)
Percentage of "old" AEDs[a]	28.8%
Percentage of enzyme-inducing AEDs[a]	13.7%

[a]*Enzyme-inducing AEDs: carbamazepine, phenobarbital, primidone, and phenytoin; "old" AEDs: valproate, carbamazepine, phenobarbital and phenytoine.*

Assessment Schedule) was assessed (29). Liverpool Adverse Events Profile (LAEP) was measured to detect AED-specific aspects in QoL (30, 31).

Data Entry and Statistical Analysis

Data entry and analysis were performed using the File Maker Pro 8.5 database (Filemaker Inc., Santa Clara, CA, USA). A double-entry procedure was employed to assure a high level of data accuracy. Statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). For the calculation of variables that potentially influence injuries and accidents in patients with active epilepsy, a chi-square test following Pearson and Benjamini-Hochberg-Adjustment was used to exclude multiple testing bias (32, 33). In addition, regression analysis was performed. *P*-values < 0.05 were considered as significant.

RESULTS

Sociodemographic and Clinical Characteristics

We enrolled 292 patients with epilepsy and a mean age of 40.8 years (SD ± 15.6; range 18–86 years). Gender ratio was nearly balanced with 55% female patients. Two-thirds of patients (67.8%) had an active epilepsy with at least one seizure within the last 12 months. The majority of 75% ($n = 219$) suffered from focal epilepsy (FE), 19.5% ($n = 57$) from an idiopathic generalized epilepsy (IGE) and, in 5.5%, the epilepsy syndrome was reported as unclassified; details are presented in **Table 1**. Between the two cohorts with IGE or FE, there were no significant differences in gender distribution, number of AED or seizure freedom. The mean age in the IGE cohort was significantly younger. Detailed information of sociodemographic and clinical characteristics for all patients and the FE and IGE cohorts are displayed in **Table 2**.

The five most frequently prescribed AEDs were levetiracetam (LEV, 53.1%), lamotrigine (LTG, 35.6%) and valproate (VPA,

TABLE 4 | Overview of patients with epilepsy-related injuries and accidents (ERIA, $n = 41$).

Epilepsy			Patient	Semiology				Potential associated factors				Injuries and accidents					
Duration (y)	FE/IGE	AEDs (n)	Decade of life	SPS	CPS	sGTCS	pGTCS	Ictal falls	Ictal loss of consciousness	Abnormal postictal behavior	Sleep-associated seizures	Fracture	Burn	Laceration	Sprain/bruise	Mild injuries	Hospitalization required
–	FE	3	61–70					x	x			x		x			x
0.1	IGE	1	11–20				x	x	x					x			
0.1	FE	1	31–40	x		x		x	x							x	x
0.1	IGE	1	21–30				x	x	x							x	
1	FE	1	51–60					x	x						x		x
1	FE	1	51–60			x		x	x			x					x
1	FE	2	51–60			x		x	x						x		
1	FE	3	21–30		x	x		x	x						x		
1	FE	1	11–20	x		x		x	x						x		
2	FE	3	61–70		x			x	x			x	x				x
2	FE	2	31–40	x				x	x	x					x	x	
4	FE	1	11–20	x		x		x	x							x	x
5	FE	1	61–70	x		x		x	x							x	x
5	IGE	1	11–20		x				x					x			
6	FE	2	31–40		x			x	x	x				x			
7	FE	2	31–40			x		x	x	x				x			
7	IGE	2	41–50	x				x	x							x	
7	FE	1	11–20			x	x		x		x				x		
7	FE	3	41–50			x		x	x	x				x			
8	FE	2	21–30	x				x	x			x					
10	IGE	3	21–30			x			x	x			x	x		x	x
11	FE	3	21–30	x				x	x	x		x		x			x
11	FE	1	21–30	x		x										x	
11	FE	3	31–40	x				x	x	x						x	x
11	FE	3	21–30	x		x		x							x		
13	FE	2	51–60	x				x	x	x				x		x	
13	FE	3	31–40	x				x	x	x				x			x
13	FE	0	41–40	x		x		x	x					x			x
18	FE	3	31–40	x				x	x	x						x	
18	IGE	1	21–30	x		x		x	x					x			
22	FE	3	41–50				x	x	x					x		x	
26	FE	1	31–40			x			x	x	x					x	x
27	FE	3	41–50			x		x	x	x						x	
28	FE	3	41–50	x				x	x	x						x	
29	IGE	2	31–40	x		x		x	x			x		x			x
29	FE	2	41–50			x		x	x					x	x		
37	FE	3	41–50	x		x		x	x							x	x
41	FE	3	51–60	x				x	x	x			x	x			x
48	IGE	4	41–50	x		x		x	x					x		x	
53	FE	1	51–60					x	x					x			
55	FE	3	61–70		x			x	x						x		x

AEDs, anticonvulsant drugs; SPS, simple partial seizures; CPS, complex partial seizures; sGTCS, secondary generalized tonic-clonic seizures; pGTCS; primary generalized tonic-clonic seizures; mild injuries: biting of lips and tongue, small scrapes, mild contusion, myogelosis, aching muscles.

TABLE 5 | Frequency and clinical characteristics of patients with epilepsy-related injuries and accidents ($n_{total} = 292$, $n_{ERIA} = 41$).

		Epilepsy related injuries and accidents					
		No ***n*** **(%)**	**Yes** ***n*** **(%)**	**Total**	**Chi-square**	***p*-value**	***p*-value corrected**
Age	≥50years	82 (87.2)	12 (12.8)	94	0.2310	0.631	0.688[c]
	<50 years	166 (85.1)	29 (14.9)	195			
Duration of epilepsy	≥10 years	114 (84.4)	21 (15.5)	135	0.4000	0.527	0.688[c]
	<10 years	128 (87.1)	19 (12.9)	147			
Sex	Male	110 (84.6)	20 (15.4)	130	0.2784	0.598	0.688[c]
	Female	138 (86.8)	21 (13.2)	159			
EPILEPSY SYNDROME							
Focal epilepsy		184 (84.8)	33 (15.2)	217	0.8103	0.368	0.688[c]
IGE		51 (89.5)	6 (10.5)	57			
NEWLY DIAGNOSED EPILEPSY[a]							
	Yes	16 (84.2)	3 (15.8)	19	0.0429	0.836	0.688[c]
	No	232 (85.9)	38 (14.1)	270			
SEIZURE FREQUENCY							
Seizure free > 1 year	Yes	91 (96.8)	3 (3.2)	94	13.8347	<0.001	0.006[c]
	No	157 (80.5)	38 (19.5)	195			
No GTCS > 1 year	Yes	179 (92.3)	15 (7.7)	194	20.1980	<0.001	0.006[c]
	No	69 (72.6)	26 (27.4)	95			
Refractory epilepsy[b]	Yes	57 (76.0)	18 (24.0)	75	8.0117	0.005	0.02[c]
	No	191 (89.3)	23 (10.7)	214			
SEIZURE SEMIOLOGY							
Ictal falls	Yes	169 (82.4)	36 (17.6)	205	6.2858	0.012	0.036[c]
	No	77 (93.9)	5 (6.1)	82			
Ictal loss of consciousness	Yes	198 (83.5)	39 (16.5)	237	5.2314	0.022	0.044[c]
	No	48 (96.0)	2 (4.0)	50			
Inadequate peri-ictal behavior	Yes	44 (75.9)	14 (24.1)	58	4.3352	0.017	0.036[c]
	No	202 (88.2)	27 (11.8)	229			
Nocturnal seizures only	Yes	6 (75.0)	2 (25.0)	8	0.8299	0.362	0.688[c]
	No	240 (86.3)	38 (13.7)	278			

[a] *Newly diagnosed epilepsy, new onset epilepsy with ≥ 2 seizures within the last 12 months.*
[b] *According to ILAE guidelines, IGE, idiopathic generalized epilepsy; GTCS, generalized tonic clonic seizure.*
[c] *Adjusted for multiple testing using Benjamini-Hochberg-Adjustment.*

16.1%) followed by carbamazepine (CBZ) and lacosamide (LCM) (each 11.6%). A wide variability of newer AEDs (second and third generation) were used, while 28.8% of prescribed AEDs were so called "old" substances like VPA, CBZ, phenobarbital (PB) and phenytoine (PHT). Only 13.7% of the AEDs had enzyme-inducing properties (i.e., CBZ, PB, primidone, PHT). For a more detailed listing, please refer to **Table 3**.

Clinical Characteristics of Patients With Epilepsy-Related Injuries and Accidents

In total, 41 patients (14.0%) suffered from epilepsy-related injuries and accidents (ERIA) within the 3-month observation period. Of these, 20 patients (6.8% of total cohort) required hospitalization. Out of a total of 292 patients, two independent injuries were reported in two cases and one patient suffered from three independent injuries. Besides lacerations ($n = 18$, 6.2%), abrasions and bruises ($n = 9$, 3.2%), fractures ($n = 6$, 2.1%) and burns ($n = 3$, 1.0%), 17 other mild injuries (5.8%) were reported. Among the patients with injuries, 48.8% were male, the mean age was 39.2 years (SD ± 14.1, range 18–67 years). Mean disease duration in patients with ERIA was 14.7 years (SD ± 15.2, range 0.1–40 years). Only one patient in this group reported no AED therapy, 14 participants (14/41; 34.2%) were under anticonvulsant monotherapy, 26 reported taking two or more AEDs (63.4%), and the mean number of AEDs was 2.0 (SD 1.0, range 0–4). The majority of seizure-related injuries was observed in patients suffering from generalized tonic-clonic seizures ($n = 24$, 58.5%, i.e., bilateral tonic-clonic seizures). Another 14 patients (34.2%) reported predominantly simple partial seizures (SPS, i.e., focal seizures with preserved awareness) or complex partial seizures (CPS, i.e., focal onset seizures with impaired awareness); in three cases (7.3%), the habitual seizure type was not stated. In nearly all cases (40 of 41 patients, 97.6%) suffering from ERIA, certain semiological features were reported. Most of the injured patients reported ictal loss of consciousness ($n = 39$, 95.1%) or ictal falls ($n = 36$, 87.8%) or both ($n = 35$, 85.4%). Isolated peri-ictal abnormal behavior ($n = 14$, 34.2%) was less often seen in patients with ERIA, but several patients reported

TABLE 6 | Changes in mood and quality of life due to epilepsy-related injuries and accidents ($n_{total} = 292$, $n_{ERIA} = 41$).

		Epilepsy related injuries and accidents					
		No	**Yes**	**Total**	**Chi-square**	***p*-value**	***p*-value corrected**
DEPRESSION							
BDI	Depression (Score ≥ 14)	41 (75.9)	13 (24.1)	54	5.3325	0.021	0.021[a]
	No depression (Score < 14)	207 (88.1)	28 (11.9)	235			
NDDI-E	Major depression (Score ≥ 13)	34 (72.3)	13 (27.7)	47	9.7522	0.002	0.003[a]
	No major depression (Score < 13)	154 (90.1)	17 (9.9)	171			
		All patients	**Patients with ERIA**	**Patients without ERIA**	***p*-value**		
QUALITY OF LIFE							
QOLIE-31	Overall T (mean ±SD)	48.1 ± 10.8	38.9 ± 9.0	49.2 ± 10.4	<0.001	0.002[a]	
	Range	17–68	22–56	17–68			
EQ5D	VAS (mean ± SD)	66.7 ± 19.3	56.0 ±19.1	68.4 ± 18.7	<0.001	0.002[a]	
	Range	10–100	10–90	20–100			
MEDICATION							
LEAP	Total (mean ± SD)	39.9 ± 10.8	39.2± 10.9	44.6 ± 9.3	0.007	0.008[a]	
	Range	19–64	19–64	26–63			
OTHERS							
ABNAS	Total (mean ± SD)	24.0 ± 16.7	35.8 ±17.9	22.2 ± 15.7	<0.001	0.002[a]	
	Range	range 0–72	range 1–72	range 0–63			

NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; BDI, Becks depression inventory; QOLIE31, Quality of Life in Epilepsy Inventory; ABNAS, A-B Neuropsychological Assessment Schedule; EQ5D, Euro Quality of Life; LEAP, Liverpool Adverse Events Profile; a adjusted for multiple testing using Benjamini-Hochberg-Adjustment.

periictal abnormal behavior in association with ictal falls and ictal loss of consciousness ($n = 12$, 29.3%). Only two patients with ERIA reported to suffer from sleep-bound seizures only (4.9%). For a detailed list of all patients that reported ERIA see **Table 4**.

Variables Associated With Epilepsy-Related Injuries and Accidents

Reported sociodemographic and clinical characteristics were analyzed as potential variables associated with ERIA. Comparing patients with ($n = 41$, 14.0%) to patients without ($n = 251$, 86.0%) ERIA, we identified an active epilepsy ($p < 0.001$), regular GTCS ($p < 0.001$) and a refractory course of disease ($p = 0.005$) as variables associated with ERIA using a univariate analysis. Moreover, ictal falls ($p = 0.012$), ictal loss of consciousness ($p = 0.022$) and inadequate postictal behavior ($p = 0.017$) were significantly increased in patients suffering ERIA. After *post hoc* multivariate analysis all reported parameters remained significant. No difference was determined for patient age, duration of epilepsy, gender, epilepsy syndrome or sleep-related seizures in our cohort; for details please refer to **Table 5**. Multiple regression analysis revealed a strong positive correlation of ERIA with active epilepsy ($p = 0.006$, $B = 0.140$), all other tested characteristics (i.e., age, sex, disease duration, seizure semiology, epilepsy syndrome, refractive epilepsy) did not reach levels of significance.

Epilepsy-Related Injuries and Accidents are Accompanied by a Decreased Quality of Life (QoL)

People suffering from ERIA reported significantly more symptoms indicative of a manifest depression (BDI ≥ 14 [$p = 0.021$], NDDIE ≥ 13 [$p = 0.002$]). Patients with ERIA (overall T 38.9 ± 9.0) had a significant lower (QoL) compared to patients without ERIA (overall T 49.2 ± 10.4 [$p < 0.001$]) in QOLIE-31. Regarding each single item of the QOLIE-31 inventory, patients with ERIA showed a significantly increased seizure worry ($p \leq 0.001$) and decreased overall QoL ($p < 0.001$), emotional well-being ($p = 0.001$) and energy level ($p = 0.019$) as well as cognitive ($p < 0.001$) and social functions ($p < 0.001$). Medication effects did not reach any level of significance in QOLIE-31 ($p = 0.68$), even if the results for Liverpool Adverse Events Profile (LEAP) were significantly different between patients with and without ERIA ($p = 0.006$). Similar results for QoL were obtained in EQ5D Score [VAS (visual analog scale) 56.0 ±19.1 vs. 68.4 ±18.7, $p < 0.001$]. In addition, ABNAS showed a significant distinction between patients with (22.2 ± 15.7) and without ERIA (35.8 ± 17.9, $p < 0.001$). After *post hoc* multivariate analysis all reported parameters remained significant. For a detailed statistical analysis of QoL and depression scores please refer to **Table 6**.

TABLE 7 | Standardized assessment and management of variables associated with ERIA.

(1) Structured assessment of ERIA	(2) Individual evaluation of variables associated with ERIA	(3) Development of individual avoidance strategies for ERIA
Medical history	**Seizure semiology**	**Information and consultation**
Short-term: *"Have you had any injury or accident since the last visit?"* *"Was this injury related to an epileptic seizure"*	Generalized tonic clonic seizures[b] Status epilepticus[a] Peri-ictal falls[b] Peri-ictal loss of consciousness[b] Peri-ictal inadequate behavior[b]	Average risk for ERIA Individual risk for ERIA due to Medical history Seizure semiology Epilepsy syndrome Possible consequences
Long-term: *"Have you ever had an injury or accident that was related to an epileptic seizure?"*	**Epilepsy syndrome**	**Avoiding strategies**
	Active epilepsy[b] Refractory epilepsy[b]	Safe surrounding Information of caretakers Early detection of seizures
Examination		**Auxiliary means**
"Where have you got this scar/wound from?" *"Was the injury related to an epileptic seizure?"*		Protective helmets Hip protectors In-house-emergency calls Wearables Seizure dog

ERIA epilepsy-related injuries and accidents.
[a] *Variables associated with ERIA proposed by other publications.*
[b] *Variables associated with ERIA according to our cohort.*

DISCUSSION

This study analyzed in detail a cohort of epilepsy patients in Germany showing the high burden imposed on patients due to ERIA. In addition, patients with ERIA showed a decreased QoL and increased depression rates. Our results are in line with other studies on ERIA, showing that number and frequency of injuries and accidents are significantly increased in epilepsy patients compared to matched controls. However, there are certain limitations of the study design (e.g., a missing epidemiologic approach) that may display limitations of the acquired data and findings. The finding that most enrolled patients had focal and active epilepsy may also affect the comparability with other studies.

In a large database study published in 2010, 8,890 subjects with epilepsy were analyzed, resulting in a 1-year incidence of one or more injuries in 20.6% of patients with and 16.1% of patients without epilepsy ($p < 0.001$) (34). Active epilepsy and refractory course of disease, as demonstrated in our cohort, are variables associated with ERIA. Within the 3-month observation period, 41 of 292 patients (14.0%) reported ERIA. The most common symptoms were lacerations ($n = 18$, 6.2%) followed by abrasions and bruises ($n = 9$, 3.1%), fractures ($n = 6$, 2.1%) and burns ($n = 3$, 1.0%). In 20 cases, urgent medical treatment and hospitalization was necessary. These results are well in line with previously published data on ERIA from a pilot study from 2008 among our outpatients (18, 35) and other international publications reporting ERIA in children, adolescents and adults with epilepsy in Nigeria, the United States, Australia and the UK (34, 36–41). In addition, a study reporting on 52 patients with refractory focal epilepsy led to comparable results with epilepsy-related injuries in 21% of cases with TLE and 8% with other focal epilepsies within a mean disease duration of 22 and 17 years. Lifetime prevalence of ERIA was estimated to 57%. Moreover, this study reported that only 45% of ERIA in general, and especially severe ones, had been documented (17). This is in contrast to another study with 247 enrolled patients showing a rather low frequency for ERIA of 1 per 44 patient years and which claimed a minor severity for the most reported cases (41).

Another prospective study analyzed ERIA using a control group of healthy relatives, showing that epilepsy patients have a 21% higher likelihood to harm themselves over a 1–2 year observation period, however, mainly mild and trivial injuries were reported (42). In children aged 2–16 years, ERIA were reported in 4.7% (43) and children with epilepsy were shown to have a 18–23% increased risk of fracture, a 49% increased risk of thermal injury and more than twice the risk of poisoning from medicinal products (39). Differences between the mentioned studies are probably due to diverging study designs (prospective vs. retrospective), different cohort characteristics and may be influenced by local factors as well as awareness and ascertainment issues. ERIA are commonly underreported and there is a high estimated number of underreported cases (17). The high frequency of ERIA in our study can be attributed to the targeted questions and precise documentation reducing underascertainment.

The vast majority of patients reporting ERIA (96.0%) presented specific ictal features and we were able to identify a significant correlation between ERIA with epilepsy characteristics and semiological aspects. Variables associated with ERIA were active epilepsy, drug-refractory course as well as reported ictal falls and ictal loss of consciousness or abnormal peri-ictal behavior in the medical history. These findings are similar to the results of past studies (18). Moreover, the presence of GTCS was significantly associated with ERIA, which is in line with previous studies, in which over 80% of ERIA

occurred during GTCS (41). Additionally, we were able to show a significant coherence between ERIA and abnormal peri-ictal behavior, which was previously controversially discussed (18). Patients with frequent and prolonged ictal auras seem to be at lower risk, which is probably based on the possibility of informing bystanders, calling for help and creating a secure surrounding. As another high-risk subgroup, individuals with active epilepsy could be identified. There was no significant difference in the occurrence of ERIA between patients with FE or IGE, which is surprising because of the common presence of GTCS in patients with IGE. Overall, 75% of IGE patients presented with GTCS compared to 51% with FE in an ERIA cohort (40).

A second focus of our study was to assess QoL and depression as possible consequence of ERIA using a battery of neuropsychological inventories (BDI-II, NDDIE, EQ5D, QOLIE-31, ABNAS, and LEAP) that have been already established and validated in patients with epilepsy (25–29). Subjects reporting ERIA showed significantly increased depression rates and had a lower QoL, which has not been reported so far. The association of lower QoL and a trend to depression with drug-refractory epilepsy has been already shown (12, 27, 28, 31, 44, 45) and ERIA might be associated or rather aggravate these aspects. However, this study was not designed to further analyse and correlate these aspects. Also, adverse effects due to AEDs were significantly higher in patients with ERIA.

The most practical solution to injury prevention is a better seizure control (40, 41). However, this may not be achieved, especially in patients with drug-refractory epilepsies who have been shown to be a high-risk group for ERIA. Therefore, another focus should aim at reducing the risk for ERIA. We propose a prophylactic pathway focusing on three major aspects: (1) identifying high risk patients by a standardized assessment of ERIA, (2) optimising antiepileptic therapy, and (3) developing individual safety assessments to reduce the future risk of ERIA (see **Table 7**). Individual safety assessments may contain information and education on the risks and consequences of ERIA, possibilities to avoid injuries (behavior, early detection) and suggestions for auxiliary means (helmets, hip protectors, in-house emergency calls, wearables). Even if the majority of epilepsy-related injuries and accidents occur at home (88%) and not in a public space (10%), a professional and epilepsy-specific assessment of the actual or aspired profession and the concomitant work environment seems to be unavoidable, hence, the fact that only 2% of epilepsy-related injuries and accidents occur at work (46, 47).

CONCLUSION

ERIA, as well as their clinical consequences, are an underreported but highly relevant aspect in the treatment of patients with active epilepsy. Moreover, ERIA might be associated or rather aggravate neuropsychological symptoms such as depression or decreased QOL in this severely affected subgroup of patients with epilepsy. However, ERIA are only sporadically considered in the development of tailored anti-epileptic therapies. More effort should be spent on the identification and assessment of ERIA or patients at risk as well as on prevention and general education on this topic to increase patient safety, satisfaction and QoL.

AUTHOR CONTRIBUTIONS

LW and AS generated the research idea, study design, and concept. NW, SR, and AS acquired the data. LW and AS analyzed the data and drafted the work. LW, NW, SR, LK, AH, SK, FR, and AS made critical revisions for important intellectual content and interpreted the data. LW and AS wrote the manuscript. LW, NW, SR, LK, AH, SK, FR, and AS approved the final manuscript.

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Brivaracetam in the Treatment of Patients with Epilepsy—First Clinical Experiences

Felix Zahnert, Kristina Krause, Ilka Immisch, Lena Habermehl, Iris Gorny, Izabella Chmielewska, Leona Möller, Anna M. Weyand, Peter M. Mross, Jan Wagner, Katja Menzler† and Susanne Knake†*

Department of Neurology, Universitätsklinikum Gießen und Marburg, Philipps University of Marburg, Marburg, Germany

Objectives: To assess first clinical experiences with brivaracetam (BRV) in the treatment of epilepsies.

Methods: Data on patients treated with BRV from February to December 2016 and with at least one clinical follow-up were collected from electronic patient records. Data on safety and efficacy were evaluated retrospectively.

Results: In total, 93 patients were analyzed; 12 (12.9%) received BRV in monotherapy. The mean duration to follow-up was 4.85 months (MD = 4 months; SD = 3.63). Fifty-seven patients had more than one seizure per month at baseline and had a follow-up of more than 4 weeks; the rate of ≥50% responders was 35.1% (n = 20) in this group, of which five (8.8%) patients were newly seizure-free. In 50.5% (47/93), patients were switched from levetiracetam (LEV) to BRV, of which 43 (46.2%) were switched immediately. Adverse events (AE) occurred in 39.8%, with 22.6% experiencing behavioral and 25.8% experiencing non-behavioral AE. LEV-related AE (LEV-AE) were significantly reduced by switching to BRV. The discontinuation of BRV was reported in 26/93 patients (28%); 10 of those were switched back to LEV with an observed reduction of AE in 70%. For clinical reasons, 12 patients received BRV in monotherapy, 75% were seizure–free, and previous LEV-AE improved in 6/9 patients. BRV-related AE occurred in 5/12 cases, and five patients discontinued BRV.

Conclusion: BRV seems to be a safe, easy, and effective option in the treatment of patients with epilepsy, especially in the treatment of patients who have psychiatric comorbidities and might not be good candidates for LEV treatment. BRV broadens the therapeutic spectrum and facilitates personalized treatment.

Keywords: brivaracetam, levetiracetam, epilepsy, treatment, side effects

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***Correspondence:**
Susanne Knake
knake@med.uni-marburg.de

†These authors have contributed equally to this work.

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INTRODUCTION

More than 30% of patients with epilepsy are refractory to medication with antiepileptic drugs (AEDs) (1, 2), although pharmaceutical treatment options have expanded steadily over the last 20 years. While many AEDs have similar potency with regard to seizure control, they often vary with regard to tolerability and side effects, which have the most important impact on treatment compliance and thus on seizure control (3, 4). Brivaracetam (BRV) is the latest AED, which was approved in Germany in February 2016 as an adjunctive treatment of partial-onset seizures with and without secondary generalization in patients aged 16 years or older (5). Similar to levetiracetam (LEV), it mainly targets

synaptic vesicle protein 2A, but more selectively and with a 15- to 30-fold increased affinity (6, 7). Clinical trials have demonstrated a significant reduction of seizure frequency after the initiation of BRV, with ≥50% responder rates ranging from 30.3 to 55.8% (8–15). At a dose of 100 mg/day, the amount of seizure-free patients was sevenfold compared to placebo (16). During those trials, the overall efficacy of BRV was greater in LEV-naïve patients. In previous clinical studies, treatment-emergent adverse events (AE) of BRV occurred in 54.2% of the patients. The most common AE were irritability, fatigue, asthenia, somnolence, headache, paresthesia, and dizziness (13, 16–18). Compared to LEV, the occurrence of AE and seizure control was similar, with a significantly higher incidence of dizziness in BRV (18). However, behavioral adverse events (BAE) are common in LEV (19) and they accounted in one study for 40.4% of discontinuations of LEV therapy (3). In the therapeutic range of 50–200 mg BRV per day, BAE such as anxiety, aggression, depression, or others occurred in 5.0–12.3% (5). In a small, open-label prospective exploratory study, a direct switch from LEV to BRV led to a reduction of BAE in 27/29 patients, making BRV a promising treatment option in patients with LEV-associated BAE (20).

So far, long-term post-marketing observations can provide further important insight into the efficacy and tolerability under real-life conditions. Here, we report post-marketing experience with BRV.

PATIENTS AND METHODS

Data were retrospectively collected from in- and outpatients of the Epilepsy Center Hessen, Germany, who received BRV treatment after its approval and introduction to the German market between February 2016 and December 2016. All patients who had at least one clinical follow-up were included. Based on a decision of the local IRB, patients do not have to be consented for retrospective data analysis.

The effect of BRV on seizure frequency and tolerability was assessed. Data were collected at baseline (BL) (i.e., initiation on BRV) and at each of the follow-up visits, usually after 3 and 6 months. Data on concurrent anticonvulsant medication, seizure frequency, initiation, and termination of treatment as well as AE were identified from electronic patient records.

Responder rates were assessed at the most recent follow-up in patients on BRV who had seizure frequencies of ≥1 per month at BL and a follow-up of at least 4 weeks. Patients were classified as seizure-free when no seizures occurred during the entire observation period.

Analyses of AE were separated into two different subgroups: behavioral AE, including psychiatric AE such as depression and anxiety, and non-behavioral AE, including AE such as dizziness, cognitive decline, and others.

To compare the tolerability of LEV and BRV, we analyzed the reoccurrence and persistence of LEV-associated AE, which either had emerged on LEV in medical history, leading to the discontinuation of LEV, or were present on LEV at BL. The number of LEV-related AE (LEV-AE) was compared with the number of the same LEV-AE reoccurring under BRV in each respective patient using repeated measures *t*-tests.

RESULTS

A total of 93 patients who received BRV during the observation period and who had at least one follow-up visit were identified and included in the analysis.

Demographic Characteristics

For demographic characteristics of the study population, see **Table 1**. In the subpopulation eligible for the analysis of seizure frequencies, the mean length of the observation period was 5.3 months (MD = 5.5 months, SD = 4.1 months). A direct switch from LEV monotherapy to BRV monotherapy was performed in 12 patients (12.9%). Patients had received 6.3 AEDs on average since their first diagnosis of epilepsy (MD = 5 AEDs, SD = 3.7). Four (4.3%) patients were initiated on a further AED other than BRV within the observation period.

Seizure Frequencies and Responder Rates

Responder rates at the most recent follow-up (average 5.3 months after first BRV prescription) were determined in 57/93 patients (**Figure 1**). The rate of ≥50% responders was

TABLE 1 | Patients' characteristics.

Characteristic	**Baseline (BL), *n* = 93**
Age (years), M (SD)	43.9 (17.3)
Sex, *n* (%)	
– Male	58 (62.4)
– Female	35 (37.6)
Epilepsy duration (years), M (SD)	19.3 (14.7)
Epileptic seizure profile	
– Idiopathic generalized, *n* (%)	3 (3.2)
– POS, *n* (%)	90 (96.8)
Period of follow-up (months), M (SD)	4.85 (3.6)
Number of previous AEDs, M (SD)	6.3 (3.7)
Number of AEDs concomitant to BRV, M (SD)	1.7 (1)
Psychiatric comorbidity	42 (45.2)
BRV daily dose in mg	***n* = 93 (%)**
50	26 (28)
100	55 (59.1)
150	4 (4.3)
200	8 (8.6)
Concomitant AEDs in >5% of patients	***n* = 93**
Lamotrigine	32
Lacosamide	25
Valproate	17
Zonisamide	14
Oxcarbazepine	13
Topiramate	12
Perampanel	8
Pregabalin	5
Vagus nerve stimulation	7
BRV monotherapy	12
LEV medication at BL	***n* = 93 (%)**
LEV intake at BL	47 (50.5)
– immediate switch to BRV	43 (46.2)
– gradual switch	4 (4.3)
LEV in (past) medical history	87 (93.5)
LEV naïve	6 (6.5)

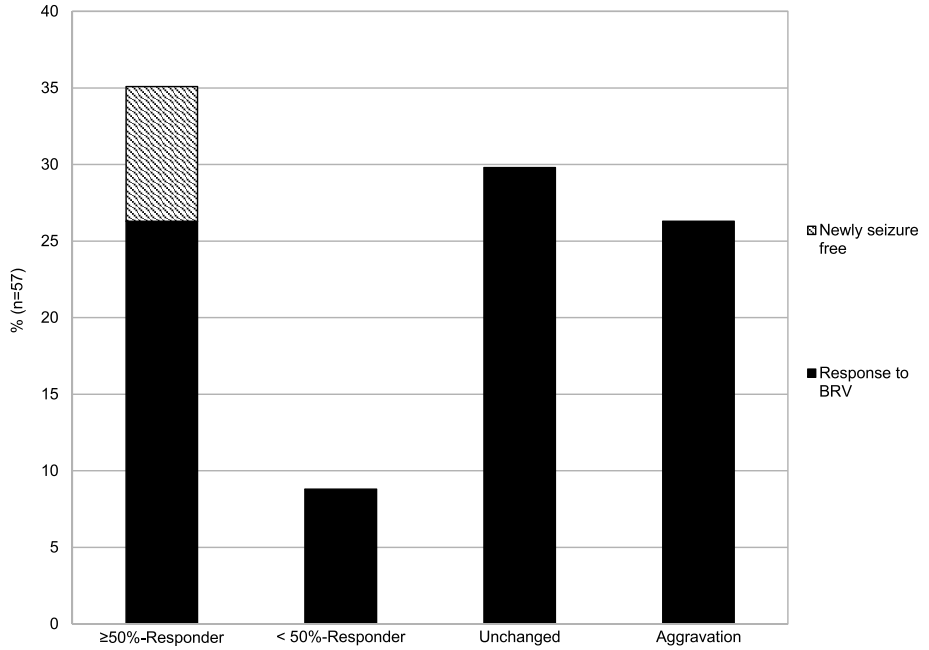

FIGURE 1 | Change in seizure frequency after initiation of BRV treatment.

35.1% ($n = 20$), of which five (8.8%) patients became seizure-free. The rate of <50% responders was 8.8% ($n = 5$), while seizure frequency remained unchanged in 29.8% ($n = 17$). An aggravation of seizure frequency occurred in 26.3% ($n = 15$) of patients. Overall seizure freedom was achieved in 27/93 patients (29%). Status epilepticus was observed in four (4.3%) patients under BRV treatment.

Due to sample size, we did not investigate seizure frequencies and responder rates in LEV-naïve patients ($n = 6$) separately.

Treatment-Emergent AE and Discontinuation Rates

Overall, AE during BRV intake occurred in 37 (39.8%) patients. BAE and NBAE were observed in 21 (22.6%) and 24 (25.8%) patients, respectively.

Adverse events reported in >5% of patients were irritability, depression, fatigue ($n = 7$, 7.5%), aggression ($n = 6$, 6.5%), and cognitive decline ($n = 5$, 5.4%). For other AE, see **Table 2**.

The discontinuation of BRV was reported in 26/93 patients (28%). Reasons for the discontinuation of BRV are listed in **Table 3**. Two patients (2.2%) requested to discontinue AED therapy entirely. The mean duration from BRV initiation to discontinuation was 3.19 months (MD = 3 months, SD = 2.6). The most frequent AE leading to discontinuation was aggression ($n = 4$, 4.3%).

In 12/15 patients (80%) who had a follow-up after BRV discontinuation, a clinically meaningful reduction of AE was observed.

An immediate switchback to LEV was performed in 10/26 patients who discontinued BRV. Of these patients, eight were followed up: seven (87.5%) of those showed clinical improvement.

TABLE 2 | The number of total AE during BRV therapy (overall AE under BRV) and the number of AE that were associated with previous LEV treatment at BL (LEV-AE at BL) and under treatment with BRV ([a]LEV-AE on BRV at the most recent follow-up).

AE	Overall AE on BRV, $n = 93$ (%)	LEV-AE at BL, $n = 36$ (%)	LEV-AE on BRV[a], $n = 36$ (%)
Drug-related AE	37 (39.8)	36 (100)	12 (33.3)
Behavioral AE	21 (22.6)	31 (86.1)	10 (27.8)
Irritability	7 (7.5)	9 (25)	3 (8.3)
Depression	7 (7.5)	10 (27.8)	3 (8.3)
Aggression	6 (6.5)	9 (25)	3 (8.3)
Agitation	2 (2.2)	5 (13.9)	2 (5.6)
Psychosis	2 (2.2)	3 (8.3)	1 (2.8)
Listlessness	1 (1.1)	2 (5.6)	0 (0)
Anxiety	1 (1.1)	1 (2.8)	0 (0)
Lability of affect	1 (1.1)	0 (0)	0 (0)
Hysteria	1 (1.1)	0 (0)	0 (0)
Non-behavioral AE	24 (25.8)	12 (33.3)	3 (8.3)
Fatigue	7 (7.5)	6 (16.7)	1 (2.8)
Cognitive deficit	5 (5.4)	4 (11.1)	2 (5.6)
Dizziness	3 (3.2)	2 (5.6)	1 (2.8)
Sleep disturbance	3 (3.2)	3 (8.3)	0 (0)
Reduced consciousness	1 (1.1)	0 (0)	0 (0)
Weight loss	1 (1.1)	0 (0)	0 (0)
Other	12 (12.9)	2 (5.8)	1 (2.8)

Multiple indication were possible.

Note that some patients suffered multiple AE. Cognitive deficit was not objectified and mirrors subjective impressions by the patient. AE classified as "other" were non-severe NBAE, respectively, occurring in one patient only.

LEV-Associated AEs

More than half of the patients (57/93) had AEs under LEV treatment before, either in their prior medical history ($n = 21$), or at

actual BL ($n = 36$). In this population, 44/57 (77.2%) patients reported either a clinically meaningful reduction or no reemergence of previous LEV-AE under BRV at all.

Out of 36 patients suffering from LEV-AE at BL, 24 (66.67%) experienced a clinically meaningful reduction in AE by switching to BRV. Comparison of the mean number of LEV-AE at BL and the most recent follow-up on BRV for each respective patient revealed a significant reduction of an average of 1.08 AE ($p < 0.001$, $M_1 = 1.56$, $SD_1 = 0.91$; $M_2 = 0.47$, $SD_2 = 0.81$) (**Figure 2**).

The mean number of LEV-AE was reduced significantly in patients who were immediately switched from BL on LEV to BRV ($n = 32$) ($p < 0.001$, $M_1 = 1.56$, $SD_1 = 0.95$; $M_2 = 0.5$, $SD_2 = 0.84$).

Significant reductions in LEV-BAE were observed between BL on LEV and the most recent follow-up on BRV ($n = 31$; $p < 0.001$, $M_1 = 1.26$, $SD_1 = 0.63$; $M_2 = 0.39$, $SD_2 = 0.67$), and a similar reduction was observed in patients experiencing LEV-NBAE at BL ($n = 12$; $p = 0.001$, $M_1 = 1.4$, $SD_1 = 0.67$; $M_2 = 0.42$, $SD_2 = 0.9$). The aggravation of LEV-AE occurred in four patients (4.3%).

Patients who were not currently on LEV treatment, but who had discontinued LEV in the past due to AE ($n = 21$), reported a significantly smaller amount of those LEV-associated AEs after being treated with BRV ($n = 21$; $p < 0.001$, $M_1 = 1.4$, $SD_1 = 0.75$; $M_2 = 0.19$, $SD_2 = 0.51$). Here, similar results emerged regarding BAE ($n = 15$; $p < 0.001$, $M_1 = 1.47$, $SD_1 = 0.74$; $M_2 = 0.2$, $SD_2 = 0.56$) and NBAE ($n = 6$; $p = 0.013$, $M_1 = 1.33$, $SD_1 = 0.52$; $M_2 = 0.17$, $SD_2 = 0.41$). Only 2/21 (9.5%) patients experienced a reoccurrence of LEV-associated AE.

TABLE 3 | Reason for discontinuation of BRV therapy.

Discontinuation due to	$n = 93$ (%)
AE	19 (20)
– BAE	12 (12.9)
– NBAE	11 (11.8)
Lack of seizure control	14 (15.1)
– Status epilepticus	4 (4.3)
Wish to discontinue therapy at all	2 (2.2)

Monotherapy

Within our study population, 12/93 patients received BRV in monotherapy, based on individual therapeutic decisions and on individual medical reasons. Here, the mean observation period was 4.6 months (SE = 0.8, SD = 2.7; median = 4 months) and the mean number of AEDs prescribed in prior anamnesis was 2.1 (SE = 0.3, SD = 1.2, median = 2).

In this subpopulation, freedom from seizures was achieved in 9/12 (75%) patients.

In 6/9 (66.67%) patients, LEV-AE from BL were reduced to a clinically and statistically significant extent (n = 9; $p = 0.011$, $M_1 = 2.3$, $SD_1 = 1$; $M_2 = 1$, $SD_2 = 1.3$). Overall, AE occurred in 5/12 patients (41.7%), the most common (in >10%) being irritability and agitation ($n = 2$, 16.7%).

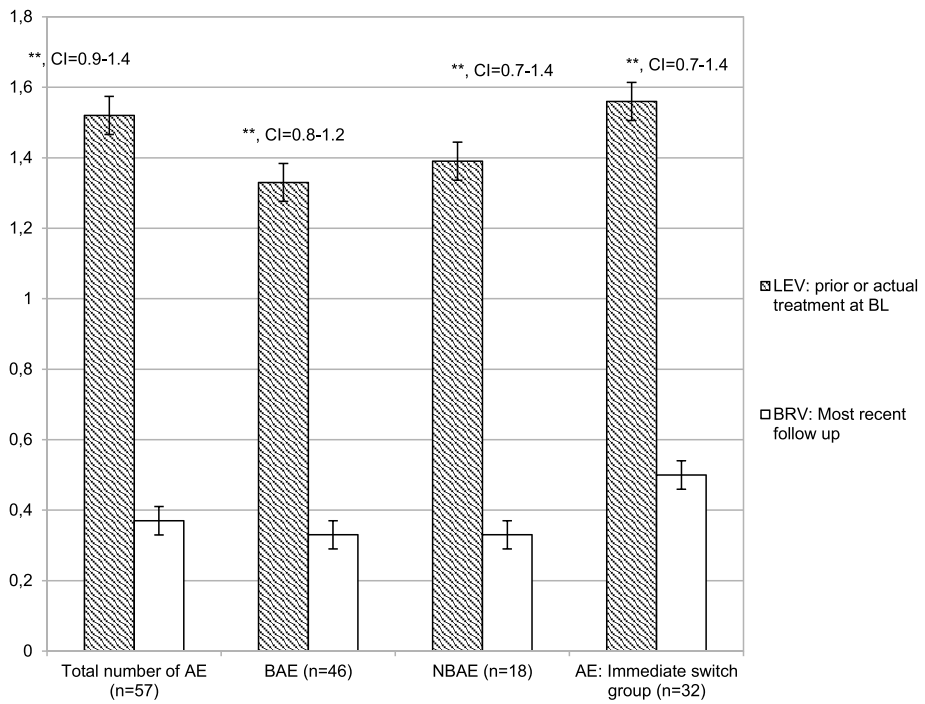

FIGURE 2 | Number of adverse events: [total number and number of behavioral and non-behavioral adverse events (AE)] under Levetiracetam (LEV) treatment and under brivaracetam (BRV) treatment in the subpopulation of patients who ever (actual or in prior treatment) had AE under LEV medication. Thirty-two patients had been switched immediately from LEV to BRV. $^{**}p < 0.001$, and error bars indicate the mean error.

Five of these 12 patients (41.7%) discontinued therapy with BRV, with a mean duration of therapy until discontinuation of 3.65 months (SE = 1.5, SD = 3.3, median = 3.5 months). Two patients (16.7%) discontinued due to BAE, and two stated that they wished to discontinue therapy entirely. Non-behavioral AE accounted for three discontinuations. Again, multiple, simultaneously occurring AE leading to discontinuation were common.

DISCUSSION

Our primary objective was to assess seizure control and tolerability in patients under BRV treatment.

We found that treatment with BRV can effectively reduce seizure frequency in patients with epilepsies with a ≥50% responder rate of 35.1 and 8.8% of patients being newly seizure-free.

Data are consistent with results from earlier trials (27.8–55.8%), and our rate of patients newly free of seizures (8.8%) was within the range of previously described rates (3–14.9%) (8–14, 21, 22). An exacerbation of seizure frequency occurred in 26.3%. This rate may not be surprising, considering the highly selective group of patients with a long history of treatment-resistant epilepsy resulting in a comparatively high number of previously prescribed AEDs. Responder rates on BRV were comparable to post-marketing experiences with other recently introduced AEDs such as Perampanel (PER; ≥50% responder rate in the largest three trials: 27–50%) or Lacosamide (LCM; ≥50% responder rate: 18–69%). The same did also apply to rates of seizure-free patients (PER: 14–17% in the largest three trials; LCM: 3–33%), as in the present study, 29% were seizure-free with 8.8% being newly seizure-free (23, 24).

Within our study population, AE on BRV were common and occurred in 39.8% of patients, which is consistent with the findings of a retrospective clinical study (37%) and slightly lower than indicated by the findings of a pooled analysis of phase IIb and phase III trials (54.2%) (13, 21).

In a meta-analysis of previous clinical trials, AE significantly associated with BRV compared to placebo were somnolence, dizziness, fatigue, and irritability, with an incidence of 12.4, 9.6, 7.7, and 2.8%, respectively (16). In another pooled analysis, the most common AE overall were headache (20.9%), dizziness (17.5%), somnolence (15.2%), nasopharyngitis (13.2%), fatigue (11.3%), and convulsion (10.6%) (13). In this study, the safety profile of BRV differed from the above data. While in previous studies, the most common BAE (irritability, insomnia, depression, and anxiety) occurred in only 2–3% of patients (16), BAE emerged more frequently under BRV (22.6%) in our study population. In our analysis, depression, irritability and fatigue (7.5% each), and aggression (6.5%) were the most frequently reported AEs. Dizziness, one of the most common AEs from previous studies, only occurred in 3.2%, and somnolence was observed in only one patient (1.1%). One major reason for the higher rate of BAE in our data might be that BRV was initiated in patients who mostly had psychiatric comorbidities (45.2%) or who were prone to behavioral side effects and had already discontinued LEV due to BAE. Unlike some other AEDs, BRV did not cause metabolic syndrome or weight gain (25).

As previous studies suggested, the effects on seizure frequency seemed strongest in patients who were LEV-naïve (16). Hence, the safety and efficacy of BRV administered in monotherapy is of great interest. The administration of BRV as the first anticonvulsive treatment in patients is yet to be examined. In our data, monotherapy with BRV appeared safe and was well tolerated with a reduction of LEV-associated AE in the majority of patients, supporting previously described experiences (22). Patients on monotherapy had less severe epilepsy and were previously on another monotherapy. Switching to BRV was mainly performed due to behavioral side effects or psychiatric comorbidities and not due to a lack of seizure control. This explains the greater proportion of seizure-free patients than in the overall study population.

In patients who were switched from LEV to BRV, a reduction of AE was observed. AEs, which had led to LEV discontinuation in the past, rarely reemerged under therapy with BRV.

Our findings indicate that BRV has a safety profile that is distinct from LEV, making it a useful alternative to enhance adherence to therapy with AEDs. Especially for patients who are not eligible for LEV use, BRV might be a therapeutic option, opening a chance to achieve sufficient seizure control.

These results are consistent with the findings from previous studies where a reduction of LEV-associated BAE was described (20, 22).

An immediate switch from LEV to BRV was safe and reduced LEV-associated AE in the majority of patients. Switching back from BRV to a prior anticonvulsive medication, especially LEV, was safe, and AEs as well as increases in seizure frequency emerging under BRV seem at least partially reversible this way. Due to the sample size, further studies investigating the pharmacokinetics and the clinical impact of a fast and direct switch of anticonvulsive medication are of interest.

Limitations

The use of retrospective data obtained by a review of the patient charts and from a standard patient anamnesis in daily clinical practice might potentially introduce individual bias. This might stem from the neurologists' individual evaluations and interpretations, as well as the variable comprehensiveness of patient self-reports. However, these results mirror conditions in clinical practice, where the clinician mostly relies on patient self-report, and standardized data are not always available.

Results in analyses for subgroups such as patients on monotherapy or immediate switchback to LEV might consolidate with reanalysis once more data become available. Larger, prospective, and multicenter trials of these subgroups would be desirable.

CONCLUSION

Therapy with BRV seemed safe and well tolerated. An immediate switch from LEV to BRV was easy and safe and reduced LEV-associated AE. However, behavioral and non-behavioral AEs occurred under BRV treatment. In case of newly occurred AE on BRV, a direct switchback to LEV was safe. Single patients

were treated for individual reasons with BRV monotherapy, which seemed safe and achieved seizure freedom in 9/12 patients.

In summary, we demonstrated that BRV might be a promising option for the treatment of epilepsies, especially for those patients who suffer from side effects of LEV therapy. BRV seems to offer the chance to improve therapeutic effectiveness and broadens the therapeutic spectrum to facilitate personalized treatment.

ETHICS STATEMENT

For the local IRB, the ethics committee of the Department of Medicine, Philipps University Marburg, extra ethical approval is not needed, if data are collected retrospectively; any patients in our University Hospital agree upon admission that data might later be used anonymously for research purposes.

AUTHOR CONTRIBUTIONS

FZ contributed to conception, acquisition of data, analysis and interpretation of data, and manuscript drafting. KK participated in data analysis, manuscript drafting, and revision. II, IC, JW, LH, AS, IG, AW, PM, and LM contributed to data collection and manuscript revision. KM contributed to study conception, data analysis, and draft writing. SK contributed to study conception, data analysis, and draft writing.

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Efficacy, Retention, and Tolerability of Brivaracetam in Patients With Epileptic Encephalopathies: A Multicenter Cohort Study From Germany

Laurent M. Willems[1], Astrid Bertsche[2,3], Frank Bösebeck[4], Frauke Hornemann[3], Ilka Immisch[5], Karl M. Klein[1], Susanne Knake[5], Rhina Kunz[6], Gerhard Kurlemann[7], Lisa Langenbruch[8], Gabriel Möddel[8], Karen Müller-Schlüter[9], Felix von Podewils[6], Philipp S. Reif[1], Bernhard J. Steinhoff[10], Isabel Steinig[1], Felix Rosenow[1,5], Susanne Schubert-Bast[1,11†] and Adam Strzelczyk[1,5†]*

[1] Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, Goethe University Frankfurt, Frankfurt, Germany, [2] Department of Neuropediatrics, University of Rostock, Rostock, Germany, [3] Centre of Pediatric Research, Hospital for Children and Adolescents, Leipzig, Germany, [4] Epilepsy Center Rotenburg, Agaplesion Diakonieklinikum Rotenburg, Rotenburg, Germany, [5] Epilepsy Center Hessen and Department of Neurology, Philipps-University, Marburg, Germany, [6] Epilepsy Center Greifswald and Department of Neurology, Ernst-Moritz-Arndt-University, Greifswald, Germany, [7] Department of Neuropediatrics, Westfälische Wilhelms-University, Münster, Germany, [8] Epilepsy Center Münster-Osnabrück, Department of Neurology with Institute of Translational Neurology - Epileptology, Westfälische Wilhelms-University, Münster, Germany, [9] Epilepsy Center for Children, University Hospital Neuruppin, Brandenburg Medical School, Neuruppin, Germany, [10] Kork Epilepsy Center, Kehl-Kork, Germany, [11] Department of Neuropediatrics, Goethe University Frankfurt, Frankfurt, Germany

Objective: To evaluate the efficacy and tolerability of brivaracetam (BRV) in a severely drug refractory cohort of patients with epileptic encephalopathies (EE).

Method: A multicenter, retrospective cohort study recruiting all patients treated with EE who began treatment with BRV in an enrolling epilepsy center between 2016 and 2017.

Results: Forty-four patients (27 male [61%], mean age 29 years, range 6 to 62) were treated with BRV. The retention rate was 65% at 3 months, 52% at 6 months and 41% at 12 months. A mean retention time of 5 months resulted in a cumulative exposure to BRV of 310 months. Three patients were seizure free during the baseline. At 3 months, 20 (45%, 20/44 as per intention-to-treat analysis considering all patients that started BRV including three who were seizure free during baseline) were either seizure free ($n = 4$; 9%, three of them already seizure-free at baseline) or reported at least 25% ($n = 4$; 9%) or 50% ($n = 12$; 27%) reduction in seizures. An increase in seizure frequency was reported in two (5%) patients, while there was no change in the seizure frequency of the other patients. A 50% long-term responder rate was apparent in 19 patients (43%), with two (5%) free from seizures for more than six months and in nine patients (20%, with one [2 %] free from seizures) for more than 12 months. Treatment-emergent adverse events were predominantly of psychobehavioural nature and were observed in 16%.

Significance: In this retrospective analysis the rate of patients with a 50% seizure reduction under BRV proofed to be similar to those seen in regulatory trials for focal epilepsies. BRV appears to be safe and relatively well tolerated in EE and might be considered in patients with psychobehavioral adverse events while on levetiracetam.

Keywords: levetiracetam, epileptic encephalopathies, epilepsy, seizure, anticonvulsants

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***Correspondence:**
Adam Strzelczyk
strzelczyk@med.uni-frankfurt.de

[†] These authors have contributed equally to this work.

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INTRODUCTION

Brivaracetam (BRV), the second substance in the racetam class of anti-epileptic drugs (AEDs), was approved in the EU and USA in 2016 as adjunct therapy for epilepsy with focal onset seizures whether or not secondary generalization is present. Promising results concerning efficacy, tolerability and safety of BRV were demonstrated in a number of clinical trials (1–7). Like levetiracetam (LEV) BRV primarily acts as inhibitory ligand at the synaptic vesicle protein 2A (SV2A). Compared to LEV, BRV shows a 30-fold increased affinity to its structural target (8–12). Switching patients from LEV to BRV at a ratio of 10:1 to 15:1 may reduce adverse drug events in patients who respond well to LEV but develop drug-related sedation or BAEs (behavioral adverse events) (1, 7, 13).

Epileptic encephalopathies (EE) are a heterogeneous group of epilepsy syndromes (14, 15) in which epileptic activity leads to progressively greater levels of cognitive and behavioral impairment as it would be expected only as a result of the underlying structural or genetic pathology. According to ILAE guidelines (International League Against Epilepsy), common EE syndromes with characteristic electroclinical manifestations are Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS), West Syndrome (WS) and EE with continuous spike-and-wave during sleep (CSWS). In addition, there is a heterogeneous group of diseases with metabolic, or structural aetiologies predisposing the development of EEs, such as Landau-Kleffner Syndrome (LKS), Tuberous Sclerosis Complex (TSC) or Unverricht-Lundborg Syndrome (UVR). Moreover, several epileptogenic mutations like *SCN9A*, *KCN2A* or *GRIN-2B* have been shown to be associated with EE in their course of disease. The majority of EE patients develop refractory epilepsies and suffer from relapsing seizures of heterogeneous semiologies. Frequent hospitalization associated with the need for extended medical and nursing care place major social, interpersonal, and economic burden on patients, caregivers and society (14–18).

The purpose of this multicenter study was to evaluate efficacy and tolerability of BRV in patients with EE.

PATIENTS AND METHODS

A retrospective data analysis with EE patients who received at least one dose of BRV between 2016 and 2017 was performed at eight German epilepsy centers (Frankfurt, Greifswald, Kork, Leipzig, Marburg, Münster, Neuruppin, and Rotenburg/Wümme). There is no third party funding or sponsoring to report. This study was approved by the ethics committee. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed (19).

The average seizure frequency of the last three months prior to the initiation of BRV was accepted as the baseline frequency. Three, 6 and 12 months retention rates were calculated. Terminal remission defined patients reaching seizure freedom throughout the subsequent follow up periods. For the purposes of this study, a 25% seizure reduction was assumed if seizure frequencies declined by 25 to 50% compared to the baseline whereas a 50% seizure reduction described a reduction of the seizure frequency above 50%. Patients who showed less than a 25% seizure reduction were assumed to be non-responders. A seizure increase was defined as any increase of seizure frequencies greater 25%. Further details of analysis and the definition of BAEs are available in Steinig et al. (20). Data acquisition was performed using anonymised, standardized reporting forms and statistical analysis by IBM SPSS Statistics, Version 22.0 (IBM Corp, Armonk, NY, U.S.A.). Kaplan-Meier survival curves were used to estimate retention time; Chi-Square and log-rank tests were used for statistical analysis with p-values <0.05 treated as statistically significant.

RESULTS

Patient Characteristics at Baseline

Forty-four patients (27 male; 61% male), mean age 28.8 years ($\pm$14.2, range 6-62, nine children or adolescents $<$18 years [21%]), were included in this study. The most frequent aetiologies of EE in our cohort were LGS ($n = 20$, 45.5%), TSC ($n = 3$, 6.8%), UVR ($n = 2$, 4.5%), and CSWS ($n = 2$, 4.5%). Moreover, several patients displayed other well-defined syndromes associated with EE, such as DS, AS and Neuronal Ceroid Lipofucinosis (each $n = 1$, 2%) or epileptogenic mutations, such as *SCN9A*, *KCN2A* and *GRIN-2B* (each $n = 1$, 2%). Mean epilepsy duration at baseline was 24.4 $\pm$ 15 years (median 23; range 0–57 years). Epilepsy onset was at a mean age of 4.4 $\pm$ 6.3 years (median 2; range 0–27 years). In 18 patients (40.9%), mRS (modified Rankin Scale) of 3–5 indicated moderate to severe impairment. Mean AED number at start of BRV was 2.9 $\pm$ 0.9 (median: 3, range: 1–4 AEDs). The most frequently prescribed drugs at baseline were: valproate (VPA, $n = 27$, 61%); LEV ($n = 24$, 55%); lamotrigine (LTG, $n = 24$, 55%); clobazam (CLB, $n = 18$, 41%); carbamazepine (CBZ, $n = 14$, 32%), topiramate (TPM, $n = 14$, 32%), and zonisamide (ZNS, $n = 14$, 32%). A drug refractory course was present in all patients, they have failed a mean number of 4.4 $\pm$ 4.3 AEDs in the past (median 3.5, range 0–17; current AEDs not included). A total of 37 patients (84.1%) had exposure to LEV during their lifetime. Details are presented in **Table 1**.

The mean monthly seizure frequency during baseline period was 54.9 $\pm$ 76.9 (median 30, range 0–400). In three patients (6.8%) no seizures during baseline period were reported, however, they were switched due to TEAE (Treatment Emergent Adverse Event) under LEV or another AED. Focal onset seizures with preserved awareness were reported in three patients (7%), while 20 patients (46%) suffered from focal onset seizures with impaired awareness. 27 patients (61%) described focal onset seizures evolving into bilateral tonic-clonic seizures. Atypical absence seizures were reported by 14 (32%) and myoclonic seizures by 18 patients (41%). In addition, 20 patients (46%) described other generalized seizure types, such as tonic or atonic seizures.

Treatment With Brivaracetam

The initial daily dosage of BRV for patients who were not taking LEV at start of BRV varied between 25 mg and 100 mg (mean 66.3 mg $\pm$ 26.0 mg, median 50 mg). Median titration time was 6

days (mean 13.7 ± 15.8 days), the target dose ranged between 100 mg and 200 mg (mean 138.5 ± 50.6 mg, median 100 mg). The total number of patients switching from LEV to BRV at a median 15:1 ratio (mean 16.2:1, range 5:1 to 50:1) was 24 (55%), of whom 21 switched overnight and three overlapped LEV and BRV. Patients switched from LEV to BRV at an initial dose in the range 25 mg to 300 mg (mean 122.1 ± 72.1 mg, median 100 mg), with a target dose in the range 60 mg to 300 mg (mean 175.2 ± 70.1 mg, median 187.5 mg).

Retention, Responder Rate, and Seizure Free Patients

The probability that a patient would still be on BRV treatment after 3 months was 65%, respectively 52% after 6 months and 41% after 12 months. The most common reasons for discontinuing BRV were lack of efficacy ($n = 12$, 27%), adverse events ($n = 5$, 11%); or both ($n = 2$, 5%).

At 3 months, 20 (45%, 20/44 as per intention-to-treat analysis considering all patients that started BRV including three who were seizure free during baseline) were either seizure free ($n = 4$; 9%, three of them already seizure-free at baseline) or reported at least 25% ($n = 4$; 9%) or 50% ($n = 12$; 27%) reduction in seizures. There was no change in the frequency of seizures in 21 patients (48%), an increase in seizure frequency was reported in two (5%) patients. In one patient response was not well quantifiable. **Table 2** shows the response according to clinical characteristics.

A 50% long-term responder rate was apparent in 19 patients (43%), with two (5%) free from seizures for more than 6 months and in nine patients (20%, with one [2%] free from seizures) for more than 12 months. The mean exposure time to BRV was 211 days, ranging from one day to 24 months (median 140 days). The total exposure time to BRV in this study was 310 months. Retention rates were calculated and plotted using the Kaplan–Meier survival curves for all patients (**Figure 1A**) and depending on the LEV to BRV switch (**Figure 1B**). No significant difference was observed between patients who started on BRV and those who switched from LEV (log-rank p-value: 0.515). At the final follow-up, the daily BRV dose ranged from 50 mg to 300 mg (mean 131.5 ± 86.2 mg, median 150 mg); three patients (6.8%) had a daily dose greater than 200 mg.

Treatment-Emergent Adverse Events

TEAEs were reported in seven (16%) patients while being treated with BRV. There were six (14%) cases of BAE, one (2 %) of somnolence and one (2%) of bruxism. BAE were observed in four patients that had had BAE while exposed to LEV ($n = 4/18$), while two patients had BAE on BRV who had had no BAE on LEV or were not exposed to LEV in the past ($n = 2/26$, $p = 0.35$). Details are presented in **Table 3**.

TABLE 1 | Clinical and sociodemographic characteristics of the cohort ($n = 44$).

Age (years)	
Mean ± SD	28.3 ± 14.5
Median	26.0
Range	3–62
Mean age at onset of epilepsy (years)	
Mean ± SD	4.4 ± 6.2
Median	2.0
Range	0–27
Epilepsy duration (years)	
Mean ± SD	24.4 ± 15.0
Median	23.0
Range	0–57
Sex	*n* (%)
Male	27 (61.4)
Female	17 (38.6)
Number of concomitant AEDs at start of BRV	
Mean ± SD	2.9 ± 0.9
Median	3.0
Range	1–4
Previously failed AEDs (without current)	
Mean ± SD	4.4 ± 4.3
Median	3.5
Range	0–17
Seizure semiology	*n* (%)
Focal onset seizures with preserved awareness	3 (6.8)
Focal onset seizures with impaired awareness	20 (45.5)
Focal to bilateral tonic-clonic seizures	27 (61.4)
Myoclonic seizures	18 (40.9)
Atypical absence seizures	14 (31.8)
Other generalized seizures	20 (45.5)
Syndrome/etiology	*n* (%)
Lennox-Gastaut-Syndrome (LGS)	20 (45.5)
Tuberous sclerosis complex (TSC)	3 (6.8)
Unverricht-Lundborg-Syndrome (UVR)	2 (4.5)
Continuous Spike Waves in Sleep (CSWS)	2 (4.5)
Dravet-Syndrome	1 (2.3)
SCN9A mutation	1 (2.3)
Neuronal Ceroid Lipofuscinosis (NCL)	1 (2.3)
KCN2A mutation	1 (2.3)
GRIN-2B mutation	1 (2.3)
RBFOXI mutation	1 (2.3)
Angelman-Syndrome	1 (2.3)
other	10 (22.7)

AED, anti-epileptic drug; SD, standard deviation; BRV, brivaracetam.

DISCUSSION

This multicenter retrospective study examined the efficacy of BRV and its tolerability in a cohort of 44 EE patients who represent a severely affected subgroup with usually drug refractory epilepsy and frequent seizures (15, 21). The burden placed on these patients, their caregivers and society makes outcome research in patients with EEs relevant and important. New AEDs including cannabidiol and fenfluramine are being developed for some EE patient subgroups (14–17) and there are few precision medicine approaches for single syndromes leading to EE, such as everolimus in TSC or ketogenic diet in Glut1-deficency. To date, there is only insufficient information on the efficacy and tolerability of BRV in this special subgroup. Data on this cohort, with aggregated 310 month exposure to BRV

TABLE 2 | Clinical characteristics and outcome on 3-months-follow-up ($n = 43$, response in 1 patients not quantifiable).

	Patients	Non responders	>25% response	>50% Response	Subgroup of seizure free patients
	n			% *(n)*	
Total	43	53.5 (23)	9.3 (4)	37.2 (16)	9.3 (4)
SEX					
Male	26	50.0 (13)	3.8 (1)	46.2 (12)	15.4 (4)
Female	17	52.6 (10)	15.8 (3)	21.1 (4)	0.0 (0)
AGE RANGE					
<18 years	9	44.4 (4)	11.1 (1)	44.4 (4)	22.2 (2)
≥18 years	34	55.9 (19)	11.8 (4)	32.3 (11)	5.9 (2)
INITIAL BRV DOSAGE					
≤100 mg	21	47.6 (10)	19.0 (4)	33.3 (7)	9.5 (2)
100–199 mg	14	57.1 (8)	0.0 (0)	42.9 (6)	7.1 (1)
>200 mg	5	60.0 (3)	0.0 (0)	40.0 (2)	0.2 (1)
LEV STATUS					
Direct switch from LEV to BRV	23	56.5 (13)	4.3 (1)	39.1 (9)	17.4 (4)
Start of BRV with previous exposure to LEV	13	61.5 (8)	7.7 (1)	30.8 (4)	0.0 (0)
Start of BRV without previous exposure to LEV	7	28.6 (2)	28.6 (2)	42.9 (3)	0.0 (0)
PREVIOUSLY FAILED AEDs (WITHOUT CURRENT)					
0–1	14	42.9 (6)	0.0 (0)	57.1 (8)	21.4 (3)
≥ 2	25	56.0 (14)	16.0 (4)	28.0 (7)	0.04 (1)
NUMBER OF AEDs AT START OF BRV					
0–1	3	66.6 (2)	0.0 (0)	33.3 (1)	33.3 (1)
2	8	62.5 (5)	0.0 (0)	37.5 (3)	25.0 (2)
≥3	28	46.4 (13)	14.3 (4)	39.3 (11)	3.6 (1)
SEIZURE SEMIOLOGY					
Focal onset seizures with or without preserved awareness	19	63.1 (12)	10.5 (2)	26.3 (5)	5.3 (1)
Focal to bilateral tonic-clonic seizures	26	42.3 (11)	15.4 (4)	42.3 (11)	7.7 (2)
Other generalized seizures	31	48.4 (15)	6.5 (2)	45.2 (14)	3.2 (1)

BRV, brivaracetam; LEV, levetiracetam; AEDs, antiepileptic drugs.

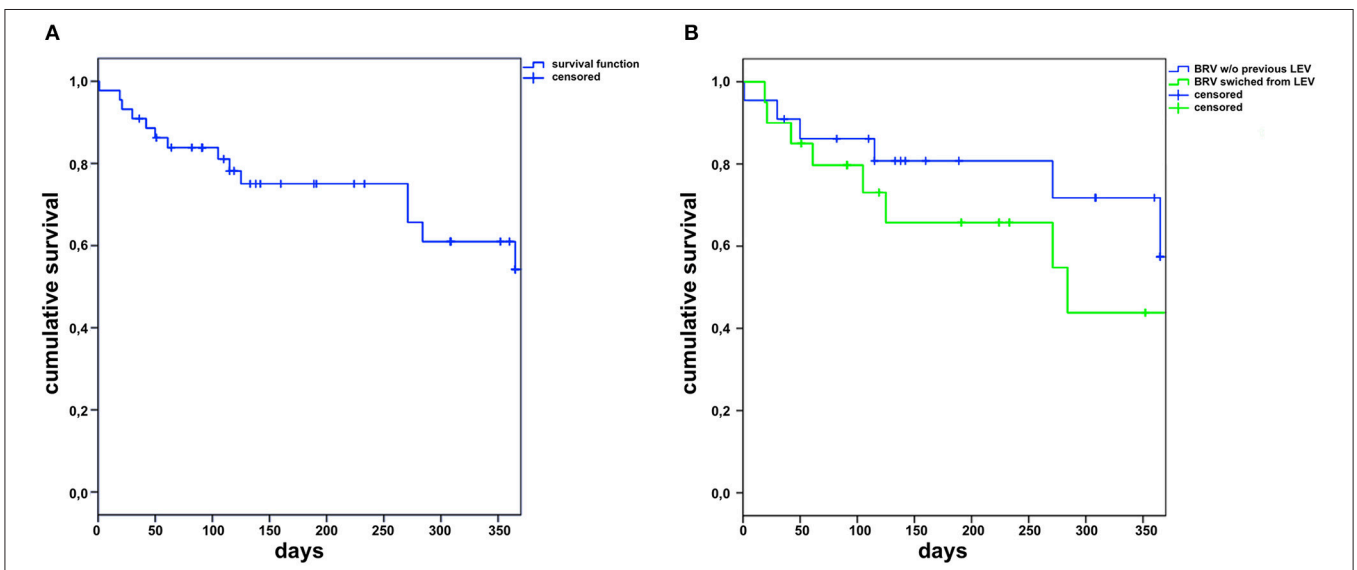

FIGURE 1 | Retention of brivaracetam (BRV) in the complete cohort **(A)** and in patients with (LEV) or without levetiracetam upon start of brivaracetam **(B)** (w/o, without).

and follow-ups of up to 24 months, are informative in this respect.

The cohort showed retention rates of 65% at 3 months, 52% at 6 months and 41% at 12 months which is in line with other BRV post-marketing studies (13, 20, 22, 23), and compare with results from other AEDs in frequent use as eslicarbazepine acetate (ESL), LCM, LTG, LEV, perampanel (PER), topiramate (TPM), VPA, and ZNS in patients with focal epilepsies (20, 24–29). Unfortunately, only limited information is available on efficacy and tolerability of AEDs in EE patients. This cohort showed a 50% responder rate of 36% at the 3-month follow-up with additional four patients (9%) being seizure-free. Of these four patients three had been already seizure free during baseline period. The corresponding figures were 43% and 5% at the 6 months follow-up and were 20% and 2% at more than 12 months follow up. These results are in line with other studies using different AEDs in EE (for the most part LGS and DS) including LEV (47%) (30), TPM (40-48%) (31, 32), felbamate (FBM, 50%) (33, 34), ZNS (53 %) (35), and PER (46%) (36) at 3-month follow-up. Other AEDs, and particularly rufinamide (RUF) and cannabidiol (CBD), have been thought promising for EE, and both rendered comparable results with 50% responder rates of 31–48% for RUF (37–39) and 44–50% for CBD (40, 41). Currently, especially the use of CBD as an antiepileptic drug is the subject of some controversy and there is a need for randomized controlled trials (RCT) to verify these findings (42, 43). It has been demonstrated that neurostimulation via an implanted vagal nerve stimulator has similar efficacy with 50% responder rates of 43% (44). Overall, responder rates in EE of ≥50% can be achieved in 30% to 45% of EE patients. While results appear to be similar for different AEDs, there may be differential effects regarding seizure types. PER, for example, may be especially effective for myoclonic or bilateral tonic-clonic seizures (45–47).

No significant difference in efficacy was seen between patients who switched to BRV from LEV and those who either started BRV with LEV treatment at some point in the past or those who had not been treated with LEV before. These findings contrast with other publications that reported lower responder rates with previous exposure to LEV. The difference may result from the small size of our cohort (3, 4), with the limited number of EE patients precluding statistical analysis of possible clinical response predictors. Notwithstanding that, male patients who had a smaller number of previously failed AEDs and a generalized seizure semiology (generalized tonic clonic, myoclonic, absence seizures) trended toward a better response with 50% responder rates exceeding 50%. Rapid titration of BRV (mean 10 days, median 5.5 days) to a mean daily dose of 153.1 mg (median 135 mg) with three patients on a daily dose of more than 200 mg makes under-dosing very unlikely in this study.

BRV was well tolerated in this often severely by BAEs affected subgroup, with only seven patients (16%) reporting TEAE and withdrawal of BRV from only four patients (9%). These findings compare with other post-marketing studies of BRV which showed TEAE in 37–38% (13, 20); the dominant BAEs were symptoms like irritability and aggression (16%). Taking into account of the possibility that this retrospective study may show reporting bias, a comparison with TEAE frequencies seen in trials of RUF (55–70%) (37, 38) and CBD (33–58%) (48, 49), it would seem that tolerance of BRV is good, but careful consideration should be given before using it in patients with a pre-existing intellectual disability (50). The most common reasons for discontinuing BRV were lack of efficacy (23%) and adverse drug events (11%) or both (5%).

Psychobehavioral TEAE were closely followed-up and were present in six patients (14%) while on BRV, leading to discontinuation of BRV in four patients (9%). Psychobehavioral TEAE while on LEV were reported in 14 patients (32%) at switch or in the past while exposed to LEV, details **Table 3.** Therefore, patients who experience psychobehavioral TEAE associated with LEV might be offered a switch to BRV.

As the study depends on interviews, underreporting of TEAE cannot be ruled out, representing a possible weakness in this study, but all visits and interviews were conducted by epilepsy specialists and documented immediately, minimizing the risk of such bias. Other major limitations of the study are the retrospective chart review and the relatively low number of patients that might lead to unreliable findings and large variability regarding seizure control. The retention rate is a

TABLE 3 | Characteristics of treatment-emergent adverse events (TEAEs) and their frequency ($n = 44$).

	TEAE under BRV		**TEAE only under LEV***	**TEAE under LEV and BRV**
	reported *n*(%)	leading to withdrawal *n*(%)	reported *n*(%)	reported *n*(%)
Overall	7 (15.9)	4 (9.1)	18 (40.9)	3 (6.8)
CNS related	1 (2.3)	1 (2.3)	5 (11.4)	1 (2.3)
Sedation/somnolence	1 (2.3)	1 (2.3)		
psychiatric	6 (13.6)	4 (9.1)	14 (31.8)	2 (4.5)
Irritability	4 (9.1)	2 (4.5)		
Aggression	3 (6.8)	2 (4.5)		
Other	1 (2.3)	0 (0.0)	2 (4.5)	1 (2.3)
Bruxism	1 (2.3)	0 (0.0)		

*BRV, brivaracetam; LEV, levetiracetam; *reported at switch or in the past while exposed to LEV.*

naturalistic functional endpoint encompassing efficacy, quality of life, tolerability, and safety, also no prospective baseline is required (51, 52). Measurement of retention might prove less prone to reporting bias as the prescription of medication is usually well documented.

CONCLUSIONS

BRV is effective and well-tolerated in patients with EE and the pattern of TEAEs compares with other AEDs in frequent use. Efficacy of BRV does not seem to depend on whether patients have previously been exposed to LEV or not. A direct switch from LEV to BRV is feasible for patients with EE. Taken in conjunction with other post-marketing studies on focal or idiopathic generalized epilepsies, it seems that BRV is a reasonable treatment option for patients with epileptic encephalopathies.

ETHICS STATEMENT

The study protocol is part of a retrosceptive analysis of efficacy anticonvulsants and was approved by the ethics commitee Frankfurt. Due to the retrosceptive nature of the study, written informed consent was not necessary.

AUTHOR CONTRIBUTIONS

LW, FR, SS-B, and AS generated the research idea, study design, and concept. LW, AB, FB, FH, II, KMK, SK, RK, GK, LL, GM, KM-S, FvP, PSR, BJS, IS, SS-B, and AS acquired the data. LW, SS-B, and AS analyzed the data and drafted the work. All authors made critical revisions for important intellectual content and interpreted the data. LW, SS-B, and AS wrote the manuscript. All authors approved the final manuscript.

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Initial Response to Antiepileptic Drugs in Patients with Newly Diagnosed Epilepsy As a Predictor of Long-term Outcome

*Lu Xia, Shuchun Ou and Songqing Pan**

Department of Neurology, Renmin Hospital of Wuhan University, Wuhan, China

Objective: To investigate the correlation between initial response to antiepileptic drugs (AEDs) and long-term outcomes after 3 years in patients with newly diagnosed epilepsy.

Methods: This prospective study included 204 patients with newly diagnosed epilepsy, who were followed-up for at least 36 months. The long-term seizure freedom at 36 months (36MSF) was evaluated in patients with seizure freedom 6 months (6MSF) or 12 months (12MSF) after initial treatment vs those with no seizure freedom after the initial 6 months (6MNSF) or 12 months (12MNSF). Univariate analysis and a multiple logistic regression model were used to analyze the association of potential confounding variables with the initial response to AEDs.

Results: The number of patients with 36MSF was significantly higher for patients that had 6MSF (94/131, 71.8%) than those that had 6MNSF [16/73, 21.9%; $\chi^2 = 46.862$, $p < 0.0001$, odd ratio (OR) = 9.051]. The number of patients with 36MSF was significantly higher in patients that had 12MSF (94/118 79.7%) than those that had 12MNSF (19/86, 22.1%; $\chi^2 = 66.720$, $p < 0.0001$, OR = 13.811). The numbers of patients that had 36MSF were not significantly different between patients that experienced 6MSF and 12MSF or between patients that had 6MNSF and 12MNSF. Abnormalities observed in magnetic resonance imaging or computed tomography and the number of seizures before treatment correlated with poor initial 6-month response to AEDs.

Significance: The initial 6-month response to AEDs is a valuable predictor of long-term response in patients with newly diagnosed epilepsy. The number of seizures before treatment and brain-imaging abnormalities are two prognostic predictors of initial 6-month seizure freedom.

Keywords: antiepileptic drugs, early response, long-term outcome, brain-imaging abnormalities, pretreatment seizure numbers

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***Correspondence:**
Songqing Pan
psq@medmail.com.cn

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INTRODUCTION

Epilepsy is one of the most common chronic brain diseases, affecting more than 50 million people worldwide (1). Although antiepileptic drugs (AEDs) can effectively control seizures in approximately 60–70% of patients with epilepsy, approximately 30% of patients with partial epilepsy and 25% of patients with generalized epilepsy have refractory seizures that are difficult to manage (2–4).

Therefore, early assessment of long-term therapeutic benefit is essential for clinical practice and patient counseling, or early referral for epilepsy surgery (5–7).

Previous studies have found that early response to AEDs is related to long-term seizure freedom (6, 8–10). Schmidt (11) reported that patients who are seizure-free for the initial 6 months have a 90% chance of being seizure-free at 12 months, whereas those who are not seizure-free at 6 months only have a 45% chance of being seizure-free at 12 months. This suggests that the response to AEDs in the initial 6 months is a good predictive indicator for the longer-term 12-month outcome. In a cohort of 107 patients with newly diagnosed epilepsy, Lindsten et al. (12) reported that all patients who were seizure-free 1 year after AED treatment achieved 5-year remission and only 34% of patients who had more than one seizure 1 year after diagnosis achieved 5-year remission. Accordingly, they suggested that seizure freedom 1 year after AED treatment was a good predictor of long-term remission. Although an association between the early response to AEDs over the initial 6 or 12 months with long-term outcomes in patients with newly diagnosed epilepsy has been reported, no observational studies have been performed that compare the prognostic value of the initial seizure freedom at 6 vs 12 months after AED treatment in the prediction of long-term seizure freedom.

In this study, we conducted a hospital-based study in patients with newly diagnosed epilepsy, who were followed-up for more than 3 years after AED treatment. The purpose of this study was to investigate if initial seizure freedom at 6 months can be used as an early predictor of long-term prognosis after 3 years, and to identify clinical variables that are associated with initial response to AEDs.

MATERIALS AND METHODS

Study Subjects

The study was approved by our institutional review board, and all subjects gave their informed consent. This prospective study included a total of 1,570 consecutive patients with newly diagnosed epilepsy, who visited the Epilepsy Outpatient Clinic at the Renmin Hospital of Wuhan University (Hubei, China) from June 1, 2009 to December 30, 2015. The inclusion criteria were as follows: patients with (1) newly diagnosed epilepsy; (2) a history of two or more clinically definite unprovoked seizures occurring at least 24 h apart, or evidence of a prior brain lesion resulting in seizure, or electroencephalography (EEG) epileptiform abnormalities and a significant brain-imaging structural abnormality, if they had only one seizure (13). The exclusion criteria were as follows: (1) patients with chronic epilepsy; (2) poor compliance; (3) patients lost to follow-up; (4) patients with a follow-up period of less than 3 years; (5) patients with onset interval of over 6 months; and (6) patients with progressive pathology, such as brain tumors, and epileptic encephalopathy. The diagnosis and evaluation were made by three experienced epileptic experts. Finally, 204 of 1,570 patients met the criteria and were included in the study.

The following information was recorded during the first visit: sex, age at seizure onset, pretreatment seizure numbers, pretreatment duration, epilepsy etiology, seizure type, EEG and magnetic resonance imaging (MRI) findings, family history of epilepsy, and history of febrile seizure. Epilepsy and seizure were classified according to the proposal of the International League Against Epilepsy (ILAE) (14–17). The seizure types were divided into generalized seizure and partial seizure. Epilepsy was classified as idiopathic and symptomatic seizure based on the etiology. The AEDs used in our Epilepsy center included valproate (VPA), carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM), levetiracetam (LEV), and clonazepam (CZP). According to ILAE and National Institute for Health and Care Excellence guidelines, the study was treated with CBZ, LTG, VPA, and LEV for adults with partial-onset seizures, OXC for children with partial-onset seizures, LTG and VPA for adults with generalized-onset tonic–clonic seizures, and VPA for children with generalized-onset tonic–clonic seizures as first-line options (18–20). Monotherapy with AEDs was used as the first-line treatment of choice. We start with low-dose at first and increase based on efficacy and tolerability but not exceed the limit dose (2,000 mg for VPA, 1,000 mg for CBZ, 1,500 mg for OXC, 250 mg for LTG, 300 mg for TPM, 2,000 mg for LEV, and 6 mg for CZP). If the first AED proved to be inefficient at enough dosage, an alternative AED was used as a substitute or added according to each patient's condition. A combination of three AEDs or more was avoided. AEDs were withdrawn and substituted immediately if serious side effects occurred. All patients were followed-up for more than 3 years through clinic visits or telephone calls. During the follow-up, the presence or absence of seizures and drug regimens were recorded.

Study Design

In this study, we evaluated the prognostic value of early therapeutic response to AEDs for the long-term outcome in patients with newly diagnosed epilepsy. Early and long-term responses to AEDs were defined as the absence of seizure for 6 and 36 months, respectively. The individual response evolution was defined as the change in response to AEDs at 6 and 36 months. We compared the response evolution in patients who were initially seizure-free at 6 months (6MSF) or at 12 months (12MSF) and had no seizure for 36 months with those who were not initially seizure-free at 6 months (6MNSF) or at 12 months (12MNSF) but had no seizure thereafter. Patients with seizures that occurred during the titration phase were excluded.

In addition, we also analyzed the influence of factors such as patient sex, age at seizure onset, pretreatment duration, seizure numbers before treatment, epilepsy etiology, seizure type, family history of epilepsy, history of febrile seizure, epileptiform discharges on EEG, and the presence of structural lesions on MRI or computed tomography (CT) in the initial 6-month response to AEDs.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., IL, USA) and GraphPad Prism 7.0 software. Chi-squared tests were used to compare differences in the long-term outcomes between patients with 6MSF vs 6MNSF, 12MSF vs 12MNSF. As the groups of 6MSF and 12MSF, 6MNSF and 12MNSF are not independent or mutually exclusive, when we longitudinally compare the

differences of long-term seizure remission between patients with 6MSF vs 12MSF and 6MNSF vs 12MNSF, customary statistical tests were unsuited. For comparing the differences, we assessed the proportions of long-term remission patients within 6MSF vs 12MSF and 6MNSF vs 12MNSF. Uncertainly of the estimates was controlled for by using modified Wald method 95% confidence intervals (CIs) form the binomial distribution (21). The rates and their CIs are presented as a forest plot. If the 95% CIs of the estimates were not overlapping, the seizure freedom rates were considered to be distinct between the categories (22). Each potential confounding variable was analyzed in patients with 6MSF vs 6MNSF with Chi-squared tests for Univariate analysis. Multiple logistic regression was used to analyze the prognostic predictors with significant difference on univariate analysis. Kaplan–Meier survival analysis was used to assess the time until the first seizure recurrence during maintenance treatment periods in different groups. A p value < 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

A total of 204 patients (80 females and 124 males) were included in this study. **Table 1** summarizes the detailed clinical characteristics of the 204 patients. The average age at onset of epilepsy was 17.0 years (range, 2–55 years). The mean follow-up duration was 4.8 years (range 3–6.5 years). Most patients (52.5%) had pretreatment over 6 months. Most patients (35.3%) started AED treatment after two unprovoked seizures, and only seven patients started AED treatment after the first unprovoked seizure. Epileptiform abnormalities on EEG were observed in 165 (80.9%) patients. Abnormal brain imagines were observed in 72 (35.3%) patients, including 14 patients with dysplasia, 18 patients with demyelination, 7 patients with hippocampal sclerosis, and 33 patients with posttraumatic damage.

TABLE 1 | Clinical characteristics of the 204 patients.

	N	%
Gender		
Women	80	39.2
Men	124	60.8
Age at seizure onset (years)		
≤16	115	56.4
>16	89	43.6
Number of seizures before treatment		
1–9 times	166	81.4
≥10 times	38	18.6
Pretreatment duration (months)		
<6	97	47.5
≥6	107	52.5
Seizure type		
Partial	157	77.0
Generalized	47	23.0
Epilepsy etiology		
Idiopathic	74	36.3
Symptomatic	130	63.7
MRI or CT record at entry		
Normal	132	64.7
Abnormal	72	35.3
EEG at entry		
Normal	39	19.1
Abnormal	165	80.9
Family history		
No	195	95.6
Yes	9	4.4
History of febrile seizure		
No	188	92.2
Yes	16	7.8

6MSF, patients who were seizure-free over the initial 6 months; 6MNSF, patients who were not seizure-free over the initial 6 months; EEG, electroencephalography; MRI, magnetic resonance imaging; CT, computed tomography.

The Response Evolution to AEDs

Of the 204 patients, 131 (64.2%) patients were seizure-free over the initial 6 months (6MSF) after AED initiation. Of the 131 patients with 6MSF, 94 (71.8%) were seizure-free for up to 36 months (36MSF) and 37 (28.2%) patients had at least one seizure over 7–36 months (36MNSF). By contrast, of the 73 (73/204, 35.8%) patients who were not seizure-free over the initial 6 months (6MNSF), only 16 (16/73, 21.9%) patients were seizure-free from 7–36 months and 57 (57/73, 78.1%) patients were not seizure-free during the whole study period. The number of patients with 36MSF was significantly higher in patients with 6MSF compared to those with 6MNSF [$\chi^2 = 46.862$, $p < 0.0001$, odd ratio (OR) = 9.051]. Similarly, the number of patients with 36MSF was significantly higher in patients with 12MSF than those with 12MNSF ($\chi^2 = 66.720$, $p < 0.0001$, OR = 13.811) (**Table 2**). However, **Table 3** presented the proportions of 36MSF patients with its 95% CI after initial 6MSF vs 12MSF and 6MNSF vs 12MNSF. **Figure 1** presented the rate of long-term seizure freedom with modified Wald method 95% CI for patients with 6MSF vs 12MSF (orange) and 6MNSF vs 12MNSF (blue) as forest plot. Overlapping of 95% CIs means that the accuracy of the long-term seizure freedom rate estimated did not significantly differ between patients with 6MSF and 12MSF, nor was there any significant difference between patients with 6MNSF and 12MNSF.

The Relationship between Clinical Variables and the Initial 6-Month Response to AEDs

Univariate analysis showed that the early 6-month response to AEDs was negatively correlated with the number of seizures before treatment ($p = 0.005$). Abnormalities on MRI or CT were significantly associated with poor initial 6-month response to AEDs ($p = 0.027$). Factors such as gender ($p = 0.313$), age at seizure onset ($p = 0.734$), pretreatment duration ($p = 0.210$), seizure type ($p = 0.328$), epilepsy etiology ($p = 0.875$), EEG result at diagnosis ($p = 0.723$), family history of epilepsy ($p = 0.579$), and history of febrile seizure ($p = 0.349$) were not significantly associated with the early 6 months response to AEDs (**Table 4**).

Multiple logistic regression was used to analyze the prognostic predictors with significant difference on univariate analysis. Therefore, we add the variables of the number of seizures before treatment and the brain-imaging results in the multivariate logistic regression analysis by backward way. In multivariate logistic regression analysis, the number of seizures before treatment and

TABLE 2 | The evolution of seizure freedom after the initial response in 204 patients with newly diagnosed epilepsy.

	N (%)	χ^2	*p*-Value	OR	95% CI
All patients (*N* = 204)					
Compare the evolution of seizure freedom between 6MSF (*N* = 131) vs 6MNSF (*N* = 73)					
Seizure-free at 6 and 36 months	94 (71.8)	46.862	$p < 0.0001$	9.051	4.620–17.730
Not seizure-free at 6 months but seizure-free at 36 months	16 (21.9)				
Compare the evolution of seizure freedom between 12MSF (*N* = 118) vs 12MNSF (*N* = 86)					
Seizure-free at 12 and 36 months	94 (79.7)	66.720	$p < 0.0001$	13.811	7.007–27.223
Not seizure-free at 12 months but seizure-free at 36 months	19 (22.1)				

6MSF, patients who were seizure-free over the initial 6 months; 6MNSF, patients who were not seizure-free over the initial 6 months; 12MSF, patients who were seizure-free over the initial 12 months; 12MNSF, patients who were not seizure-free over the initial 12 months; OR, odds ratio; CI, confidence interval.

TABLE 3 | Longitudinally compare the evolution of seizure freedom after early response of AEDs at 6 and 12 months in newly diagnosed epilepsy.

	N (%)	95% CI
Longitudinally compare the evolution of seizure freedom between 6MSF (*N* = 131) vs 12MSF (*N* = 118)		
Seizure-free at 6 and 36 months	94 (94/131, 71.8%)	63.5–78.8
Seizure-free at 12 and 36 months	94 (94/118, 79.7%)	71.5–86.0
Longitudinally compare the evolution of seizure freedom between 6MNSF (*N* = 73) vs 12MNSF (*N* = 86)		
Not seizure-free at 6 but seizure-free at 36 months	16 (16/73, 21.9%)	13.9–32.8
Not seizure-free at 12 but seizure-free at 36 months	19 (19/86, 22.1%)	14.6–32.0

6MSF, patients who were seizure-free over the initial 6 months; 6MNSF, patients who were not seizure-free over the initial 6 months; 12MSF, patients who were seizure-free over the initial 12 months; 12MNSF, patients who were not seizure-free over the initial 12 months; CI, confidence interval.

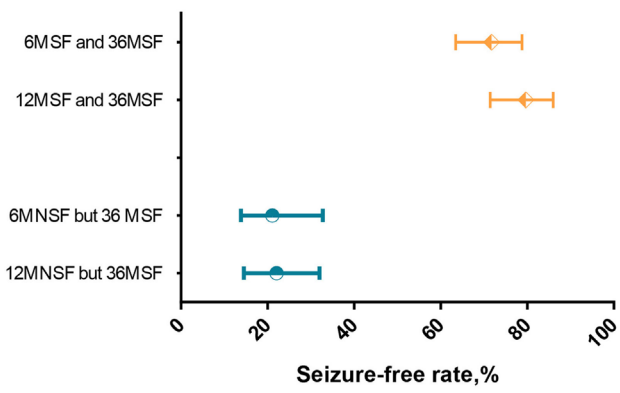

FIGURE 1 | Forest plot of long-term seizure freedom rates with modified Wald method 95% confidence interval (CI) for patients with 6MSF vs 12MSF (orange) and 6MNSF vs 12MNSF (blue). Overlapping CIs indicate no different long-term seizure freedom rates between 6MSF vs 12MSF and 6MNSF vs 12MNSF.

TABLE 4 | Patients with 6MSF (*N* = 131) vs 6MNSF (*N* = 73) as a prognostic factor.

	6MSF, *N* (%)	6MNSF, *N* (%)	*p*-Value	OR	95% CI
Gender					
Women	48 (36.6)	32 (43.8)	0.313	0.741	0.414–1.328
Men	83 (63.4)	41 (56.2)			
Age at seizure onset (years)					
≤16	75 (57.3)	40 (54.8)	0.734	1.105	0.621–1.966
>16	56 (42.7)	33 (45.2)			
Number of seizures before treatment					
1–9 times	114 (87.0)	52 (71.2)	0.005*	2.708	1.320–5.556
≥10 times	17 (13.0)	21 (28.8)			
Pretreatment duration (months)					
<6	58 (44.3)	39 (53.4)	0.210	0.693	0.390–1.231
≥6	73 (55.7)	34 (46.6)			
Seizure type					
Partial	98 (74.8)	59 (80.8)	0.328	0.705	0.349–1.424
Generalized	33 (25.2)	14 (19.2)			
Epilepsy etiology					
Idiopathic	47 (35.9)	27 (37.0)	0.875	0.953	0.526–1.727
Symptomatic	84 (64.1)	46 (63.0)			
MRI or CT record at entry					
Normal	92 (70.2)	40 (54.8)	0.027*	1.946	1.075–3.525
Abnormal	39 (29.8)	33 (45.2)			
EEG at entry					
Normal	26 (19.8)	13 (17.8)	0.723	1.143	0.547–2.389
Abnormal	105 (80.2)	60 (82.2)			
Family history					
No	126 (96.2)	69 (94.5)	0.579	1.461	0.380–5.619
Yes	5 (3.8)	4 (5.5)			
History of febrile seizure					
No	119 (90.8)	69 (94.5)	0.349	0.575	0.178–1.852
Yes	12 (9.2)	4 (5.5)			

6MSF, patients who were seizure-free over the initial 6 months; 6MNSF, patients who were not seizure-free over the initial 6 months; EEG, electroencephalography; MRI, magnetic resonance imaging; CT, computed tomography; OR, odds ratio; CI, confidence interval.

**p-Values obtained from chi-square tests with significant statistical differences.*

the brain-imaging results remained significantly different distributions in the 6MSF and 6MNSF groups. The OR of poor initial 6-month response to AEDs was 2.671 (95% CI 1.423–5.013) in patients with 10 or more seizures before treatment. The number of patients that reached 6 months seizure-free was significantly lower in patients that had 10 or more seizures before treatment than those that suffered only 1–9 seizures before treatment ($p = 0.002$). The OR of poor initial 6-month response to AEDs was 1.919 (95% CI 1.158–3.180) in patients presenting with brain-imaging (MRI or CT) abnormalities (**Table 5**).

In Kaplan–Meier survival analysis, first seizure recurrence during AED treatment was significantly earlier among patients that had 10 or more seizures before treatment compared with

TABLE 5 | Multivariate logistic regression analysis to explore the clinical variables of not being seizure-free at initial 6 months.

Clinical variables	OR	95% CI	*p*-Value
Abnormal MRI or CT result	1.919	1.158–3.180	0.011
≥10 seizures before treatment	2.671	1.423–5.013	0.002

MRI, magnetic resonance imaging; CT, computed tomography; OR, odds ratio; CI, confidence interval.

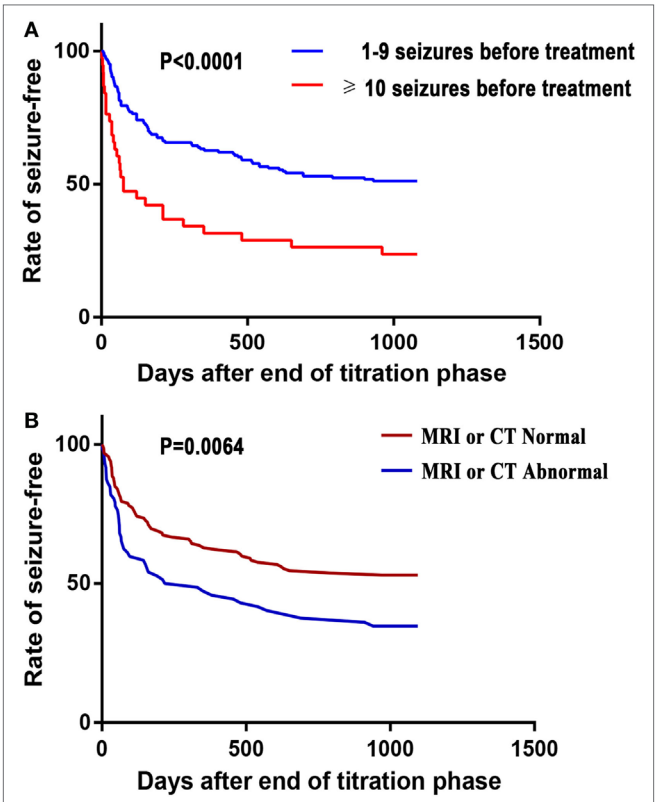

FIGURE 2 | Kaplan–Meier survival analysis of the time until the first seizure recurrence during antiepileptic drug treatment against the number of seizures before treatment **(A)** and brain-imaging results **(B)**.

those that had suffered 1–9 seizures before treatment ($p < 0.0001$; **Figure 2A**). The time until the first seizure was significantly different in patients with MRI or CT abnormalities than those without during AED treatment ($p < 0.0064$, **Figure 2B**).

DISCUSSION

In this study, the two main conclusions were as follows: (1) Response to AEDs over the initial 6 months serves as a good predictor of 36-month long-term outcome in patients with newly diagnosed epilepsy. It is not necessary to extend to 12 months for predicting the long-term outcome. Patients that responded poorly to the initial AED treatment are less likely to be seizure-free in the long run. (2) Patients with 10 or more seizures before treatment and with brain-imaging (MRI or CT) abnormalities were associated with poor initial 6-month response to AEDs.

In 2006 and 2013, the ILAE recommended that 12 months of remission, or three times the longest pretreatment inter-seizure interval, should be used as the minimum period to evaluate the long-term effectiveness of AEDs. Moreover, the recommended minimum period to assess the efficacy of AEDs is seizure freedom of 6 months (18, 20). In this study, we chose 36 months to evaluate the long-term effectiveness of AEDs, which, we believe, better reflects the long-term outcome of patients with newly diagnosed epilepsy compared with the 12 months used by most studies (11, 23, 24). It has been reported that 74.9% patients with newly diagnosed epilepsy were seizure-free over the first 6 months after starting AED treatment, and remained seizure-free for at least 12 months on unchanged treatment (23). Schmidt found that patients with seizure freedom over the initial 6 months had a 90% chance of being seizure-free at 12 months (11). In this study, we found that patients who were seizure-free over the initial 6 months had a 71.8% chance of being seizure-free at 36 months, whereas patients who were not seizure-free over the initial 6-month period had only a 21.9% chance of being seizure-free by 36 months. Furthermore, we found that the number of patients who were seizure-free at 36 months was not significantly different between patients who were seizure-free over the initial 6 or 12 months (71.8 vs 79.7%). Our findings support the theory that early response to AEDs over the initial 6 months is not only a powerful indicator of 12-month prognosis but is also an excellent predictor of the 3-year outcome for patients with newly diagnosed epilepsy. Notably, it is unnecessary to extend to 12 months for predicting the long-term outcome. In addition, since only 21.9% (16/73) of patients who failed to respond to AEDs were seizure-free after 36 months, early evaluation and identification of refractory epilepsy may be important for these patients to select nondrug therapies such as surgery, ketogenic diet and vagus-nerve stimulation.

Several studies have demonstrated that a high number of seizures before treatment is associated with poor response to AEDs (2, 25–28). Consistent with these studies, we found that 87.0% (114/131) of patients who suffered 1–9 seizures before AED treatment were seizure-free within the initial 6 months of treatment, while seizure freedom over the initial 6 months was 13.0% (17/131) for patients who experienced 10 or more seizures before treatment, respectively. 10 or more seizure occurrences were a significant predictor of poor response to early AEDs. This may be due to pathological conditions in the hippocampus, in which neuronal loss and mossy fiber sprouting are triggered by repeated seizures, leading to the formation of excitatory recurrent circuits (29). However, several studies have found that immediate AED treatment after the first unprovoked seizure appeared to reduce the risk of short-term recurrence, but did not improve the long-term prognoses (13, 30–32). Moreover, it has been reported that an increased number of seizures prior to AED treatment may be the result of pathophysiologic epilepsy changes, which may manifest as drug refractoriness, but do not cause drug refractoriness (2, 33, 34). The specific mechanisms that underpin drug refractoriness are still poorly understood, and warrant further study.

In this study, we found that brain-imaging abnormalities were associated with poor long-term outcomes in patients with

newly diagnosed epilepsy, which is consistent with previous studies (13, 35–37). According to the 2015 ILAE evidence-based guideline about the management of an unprovoked first seizure in adults, significant brain-imaging abnormalities (Level B) are associated with increased risk of seizure recurrence (13). Arthur et al. reported that MRI abnormalities were associated with increased risk of seizure recurrence only over the initial 9 months, but not over 18–27 months, in 150 children with normal physical and neurological examination results (37). In this study, we found that patients with brain-imaging abnormalities were less likely to reach 6-month seizure freedom. Furthermore, the first seizure recurrence was significantly earlier in patients that presented with brain-imaging abnormalities than those with normal MRI or CT records at entry. Therefore, examinations such as MRI or CT should be used as routine tests for newly diagnosed epilepsy. MRI and CT are not only used to assess the seizure outcome for patients with newly diagnosed epilepsy but also valuable for identifying other neurological disorders such as hippocampal sclerosis, focal cortical dysplasia, and brain tumors, which can be treated with surgery.

Several factors have been reported to be associated with a favorable outcome in patients with newly diagnosed epilepsy, including shorter duration of epilepsy, no epileptiform discharges, late age at seizure onset, and idiopathic epilepsy (8, 26, 29, 38–40). By contrast, our study found that only the number of seizures before treatment and brain-imaging abnormalities were associated with the early response to AEDs. Differences in population and design may be responsible for disparities among studies.

There are some limitations to the present study. First, as an observational study, our study is unable to illustrate the reason why early response to AEDs was significantly correlated with long-term outcome in patients with newly diagnosed epilepsy. Second, the sample size of our cohorts is relatively small. It is possible that some prognosis factors may be missed due to the small sample size. Further studies with a larger sample cohort are required.

To summarize, we found that the response to AEDs over the initial 6 months is a good predictor for evaluating long-term response in patients with newly diagnosed epilepsy. Our study suggests that patients with refractory epilepsy at the onset will also be refractory to AEDs with treatment. Our findings support the view that response to AEDs reflects inherent disease severity that is influenced by underlying pathology and genetics. Patients with more severe disease are more likely to have a higher number of seizures at the time of diagnosis. Patients with abnormal brain imaging have less probability of long-term remission. It is important to elucidate the pathogenesis of epilepsy, which may help to identify new treatments to cure the epilepsy itself, not just the seizures, and to devise alternative therapeutic strategies should AED treatment fail.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "Ethics Review Committee of Wuhan University Renmin Hospital" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the "Ethics Review Committee of Wuhan University Renmin Hospital."

AUTHOR CONTRIBUTIONS

LX: study design and draft the work; SO: picture editing and date analysis; SP: revising it critically for important intellectual content. All the authors read and approved the final manuscript.

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Alcohol Use and Alcohol-Related Seizures in Patients With Epilepsy

Michael Hamerle[1,2], Leyli Ghaeni[2], Alexander Kowski[2], Florian Weissinger[2] and Martin Holtkamp[2]*

[1] Department of Cardiology, University Hospital Regensburg, Regensburg, Germany, [2] Department of Neurology, Epilepsy-Center Berlin-Brandenburg, Charité—Universitätsmedizin Berlin, Berlin, Germany

Purpose: This study aimed to assess alcohol consumption and the occurrence of alcohol-related seizures in patients with epilepsy within the last 12 months.

Methods: In an epilepsy outpatient clinic, a standardized questionnaire was used to collect data retrospectively from consecutive adult epilepsy patients who had been suffering from the disease for at least 1 year. Logistic regression analyses were performed to identify independent predictors.

Results: A total of 310 patients with epilepsy were included. Of these, 204 subjects (65.8%) consumed alcohol within the last 12 months. Independent predictors for alcohol use were antiepileptic drug monotherapy (OR 1.901) and physicians' advice that a light alcohol intake is harmless (OR 4.102). Seizure worsening related to alcohol consumption was reported by 37 of the 204 patients (18.1%) who had used alcohol. All 37 subjects had consumed large quantities of alcohol prior to the occurrence of alcohol-related seizures regardless of their usual alcohol-drinking behavior. The amount of alcohol intake prior to alcohol-related seizures was at least 7 standard drinks, which is equivalent to 1.4 L of beer or 0.7 L of wine. In 95% of cases, alcohol-related seizures occurred within 12 h after cessation of alcohol intake. Independent predictors for alcohol-related seizures were generalized genetic epilepsy (OR 5.792) and chronic heavier alcohol use (OR 8.955).

Conclusions: Two-thirds of interviewed subjects had consumed alcohol within the last 12 months. This finding may be an underestimate due to patients' self-reporting and recall error. In all cases, the occurrence of alcohol related-seizures was associated with timely consumption of considerably large amounts of alcohol. Thus, a responsible alcohol intake seems to be safe for most patients with epilepsy. However, subjects with epilepsy and especially those with generalized genetic epilepsy should be made aware of an increased risk for seizures related to heavy alcohol consumption. Factors accompanying acute heavy alcohol intake such as altered sleep architecture, impaired adherence to antiepileptic medication, and metabolic disturbances may further facilitate the occurrence of seizures.

Keywords: alcohol-related seizures, alcohol-drinking behavior, epilepsy, generalized genetic epilepsy, alcohols

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****Correspondence:***
Michael Hamerle
michaelhamerle@hotmail.com

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INTRODUCTION

Alcohol consumption may trigger seizures in patients with epilepsy. Yet, there is currently little knowledge on the alcohol-drinking behavior of epilepsy patients. In the 1940s, William G. Lennox comprehensively analyzed alcohol consumption and the occurrence of alcohol-related seizures in 1,254 subjects with epilepsy (1). However, only about 30% of patients used alcohol, thus excluding

70% from any analysis of potential alcohol-related effects on the disease. The occurrence of alcohol-related seizures was reported by 21.1% of subjects who had used alcohol, and was more often stated by patients with symptomatic than with idiopathic or cryptogenic epilepsy (as classified at that time). Apart from this, there is little research on the occurrence of alcohol-related seizures in patients with epilepsy. A double-blinded, randomized, interventional study on 52 subjects with epilepsy demonstrated that a social alcohol intake over a 4-month-period did not increase seizure frequencies (2). In another interventional study on 14 patients with epilepsy and 10 healthy controls, acute moderate alcohol consumption initially suppressed epileptiform EEG-activity. Later however, when alcohol blood levels had declined, epileptiform EEG-activity was increased. Seizures occurred in some of those subjects and a rebound phenomenon was discussed (3).

Human and animal data have shown that acute alcohol intake has a biphasic effect on the central nervous system (CNS). Initially, the inhibitory gamma-aminobutyric acid (GABA)-ergic effect of alcohol exerts CNS depressant and anticonvulsant properties (4, 5). In the post-alcohol state, however, when alcohol blood levels decline, neuronal excitability is increased which may facilitate the occurrence of seizures in patients with epilepsy (6, 7).

The use of alcohol is very common in western societies (8). In Germany, 89% of all adults had consumed alcohol within the last 12 months (9). This makes it necessary for neurologists and other physicians to advise patients with epilepsy adequately on how to handle alcohol consumption with their chronic disease. The relationship between alcohol and epileptic seizures is complex. Research has mainly focused on the prevalence and pathophysiology of acute symptomatic seizures in the context of the alcohol withdrawal syndrome in alcohol-dependent subjects (10–12) and on the risk to develop epilepsy due to regular alcohol consumption (13, 14). However, there are only a few studies that have examined the patterns of alcohol drinking in subjects with a known history of epilepsy, and these are limited by outdated results or small sample sizes. In particular, data on seizure worsening associated with alcohol consumption in patients with epilepsy are very sparse. Therefore, we aimed (a) to systematically analyze the alcohol-drinking behavior of patients with epilepsy and (b) to identify independent predictors for alcohol use and the occurrence of alcohol-related seizures.

MATERIALS AND METHODS

Data Collection Using a Standardized Questionnaire, Interview Situations, and Interview Techniques

Between October 2008 and April 2010, consecutive patients treated at the Epilepsy Outpatient Clinic, Department of Neurology, Charité—Universitätsmedizin Berlin were informed about the study and invited to participate. The data collection on alcohol use was part of a research project systematically gathering information on nicotine, alcohol, and illicit drug use in epilepsy patients within the last 12 months. The data was collected by a standardized questionnaire (see Supplementary Material). We have published data on epilepsy and illicit drug use earlier (15). Only subjects ≥18 years who had suffered from epilepsy for at least 1 year were included. Epilepsy types and seizures were classified according to the International League Against Epilepsy (16). A single unprovoked seizure was defined as epilepsy if specific EEG alterations or causal brain lesions identified by magnetic resonance imaging (MRI) indicated an increased and enduring risk for further epileptic seizures (17). Subjects were excluded from participation if they had experienced status epilepticus or acute symptomatic seizures exclusively, if they had a history of psychogenic non-epileptic seizures, or if cognitive deficits, mental retardation or German language barrier impeded adequate understanding and reply to the questions. Patients with legal representatives were also not enrolled.

Prior to the interview, each participant was educated on the scientific background and purpose of the study. We placed great importance on a relaxed and informal interview atmosphere, and each subject was thoroughly informed that all moral aspects regarding nicotine, alcohol, and illicit drug use were irrelevant and that all data would be made anonymous and remain confidential. Thereby, we attempted to increase subjects' receptivity to the questions and avoid patients answering the questions in a more socially acceptable way. In several test-interviews, patients were intimidated when being asked about nicotine, alcohol, and illicit drug intake in front of their companions. Therefore, all interviews were held in a separate study room where only the interviewer and the patient were present. To ensure a standard and informal interview situation all patients were interviewed by the same person (MiHa) who was not one of the treating physicians at the Epilepsy Outpatient Clinic.

Alcohol consumption usually represents a taboo in the doctor-patient relationship and questions on the smoking status are answered more easily. Therefore, subjects were first queried about nicotine consumption and only later asked to give details on alcohol use. Toward the end of the interview, patients were questioned on illicit drugs. Study subjects passed through the domains of the questionnaire with an increasing social stigma degree.

In the opening question on alcohol use, subjects were asked: "Do you have any experience with alcohol consumption?" For this question, patients were able to respond in their own words and did not have to choose a predetermined response option. The interviewer carefully noted the given information on the quantity and frequency of alcohol consumption in the opening question. Subjects who had consumed alcohol within the last 12 months stated details on alcohol intake in the opening question and later by specifying the quantity and frequency of their individual alcohol consumption. Using that approach, the reliability of patients' responses on alcohol use could be evaluated regarding consistency. Data were excluded, if the patients' responses were inconsistent, if subjects were too hesitant to answer the questions, or if patients had refused to give details in only one of the interview's topics, that is nicotine, alcohol drinking and illicit drug use.

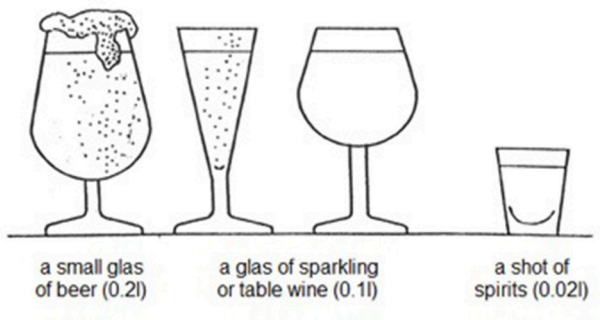

FIGURE 1 | Amounts of different alcoholic beverages that correspond to 1 standard drink as defined by the World Health Organization. This illustration has been shown to the participants of this study to guide them in estimating their individual average alcohol intake per drinking occasion.

To ensure a comparable evaluation, alcohol consumption was translated and expressed in standard drinks containing 10 g of pure alcohol (18). To assist subjects in measuring their individual average alcohol intake per drinking occasion, a chart illustrating different alcoholic beverages containing a single standard drink was shown to each study participant (**Figure 1**). Regarding the usual frequency of alcohol consumption within the last 12 months, subjects were able to choose one out of the following different categories: daily, almost daily, 1–2 times a week, 1–2 times a month or <1–2 times per month. According to that, patients who had consumed alcohol within the last 12 months were summarized in the following three alcohol drinking categories: Patients with alcohol intake of no more than 3–4 standard drinks daily, almost daily, 1–2 times per week or less than weekly were considered as light or occasional alcohol users. Moderate alcohol users were subjects who consumed more than occasional or light users but not more than 5–6 standard drinks daily, almost daily and not more than 9–10 standard drinks 1–2 times per week. Heavier alcohol use was considered as alcohol intake of more than 5–6 standard drinks daily, almost daily or more than 9–10 standard drinks 1–2 times per week. Alcohol abstinence was defined according to the World Health Organization (WHO) as a period of at least 12 months of non-consumption[1].

The Alcohol Use Disorder Identification Test (AUDIT) is a 10-item core questionnaire developed by the WHO to identify hazardous and harmful alcohol intake (18) (Supplementary Material: questions 32–41), and was applied in all subjects who had consumed alcohol within the last 12 months. Patients are able to score up to a total of 40 points in domains like harmful alcohol intake and dependency symptoms. We considered patients as AUDIT-positive with AUDIT scores ≥8. This cut-off has been found to provide an accurate measure of harmful alcohol drinking across age, gender, and cultures (19).

Apart from that, all interviewed subjects were asked what their trusted neurologist or physician had told them regarding alcohol consumption in the context of their epilepsy. Patients were able to choose one out of four response options: (a) alcohol should be avoided completely, (b) alcohol can be consumed without any restriction, (c) light alcohol intake is harmless, or (d) no advice given by the physician.

[1]*Lexicon of Alcohol and Drug Terms.* WHO. Available online at: http://www.who.int/substance_abuse/terminology/who_lexicon/en/

Alcohol-Related Seizures

In this study, an alcohol-related seizure was defined as a seizure in the context of epilepsy that occurred within short temporal relation to alcohol use (<24 h). Alcohol users were asked "Do you have experienced an alcohol-related seizure within the last 12 months?" If patients had experienced an alcohol-related seizure in the last 12 months, they were requested to recall details on the quantity of alcohol intake prior to the seizure and on the time between cessation of alcohol intake and seizure manifestation (<6 h/≥6–<12 h/≥12–<24 h). The quantity of alcohol intake again was calculated and expressed in standard drinks to ensure a comparable evaluation (**Figure 1**). If patients had experienced more than one seizure related to alcohol use within the last 12 months, they were asked to state details on the seizure occurrence they remembered the best.

Statistical Analysis

Continuous data are presented as mean ± standard deviation (*SD*) or median where appropriate. Logistic regression analyses were used to calculate odds ratios with 95% confidence intervals as estimates for variables independently predicting alcohol use and the occurrence of alcohol-related seizures within the last 12 months.

In the logistic regression models, clinical data on patients' sex, age at interview, duration of epilepsy, epilepsy type, antiepileptic drug therapy, seizure frequency, alcohol drinking behavior over the last 12 months, and physicians' advice on alcohol use were included as possible confounding variables. In the results section of logistic regression analyses, findings were only noted if 95% CIs of the confounding variable did not include 1; if the 95% CI included 1, the corresponding variable was not significant and therefore was not pointed out. Statistical analyses were calculated using IBM SPSS statistics 24.0.

RESULTS

Study Population

The study population consisted of 310 patients with epilepsy (**Table 1**). Of these, seven subjects had suffered from only one single unprovoked seizure: In four of these patients remote structural brain lesions were demonstrated by neuroimaging indicating focal epilepsy. In one patient, interictal EEG findings were consistent with generalized genetic epilepsy, and in two subjects, EEG showed regional spikes and sharp waves without MRI structural brain lesions indicating focal epilepsy of unknown origin.

Alcohol Consumption

Out of 310 interviewed subjects, 204 (65.8%) had used alcohol within the last 12 months, 158 (51%) within the last 30 days, and 108 (34.8%) within the last 7 days. Antiepileptic drug monotherapy (OR 1.901) and physicians' advice that a light alcohol intake is harmless (OR 4.102) were independent

TABLE 1 | Characteristics of the study population ($n = 310$).

Variable		No. (%)/mean ± *SD*[a]
Sex	Female	171 (55.2)
	Male	139 (44.8)
Age (in years)		44.7 ± 16.2
Duration of epilepsy (in years)		20.1 ± 16.8
Epilepsy type	Focal	213 (68.7)
	GGE[b]	67 (21.6)
	Unknown	30 (9.7)
AED[c]	Monotherapy	184 (59.4)
	Polytherapy	121 (39.0)
	No treatment	5 (1.6)
Seizure frequency	≥1/month	130 (41.9)
	<1/month	180 (58.1)
Alcohol use in the last 12 months	Alcohol abstinence	106 (34.2)
	Occasional or light use	147 (47.4)
	Moderate use	43 (13.9)
	Heavier use	14 (4.5)
Physicians' advice on the use of alcohol	Alcohol should be avoided completely	127 (41.0)
	No advice given	94 (30.3)
	Alcohol can be consumed without restriction	2 (0.6)
	Light alcohol intake is harmless	87 (28.1)

[a] *SD, standard deviation.*
[b] *GGE, generalized genetic epilepsy.*
[c] *AED, antiepileptic drug.*

predictors for alcohol use within the last 12 months (**Tables 2**, **3**). Out of the 204 patients who used alcohol, 147 (72%) were occasional or light alcohol users, 43 (21.1%) were moderate users and 14 subjects (6.9%) practiced heavier alcohol use. Nine subjects of the study population (2.9%) were AUDIT positive indicating hazardous and harmful alcohol use. All AUDIT positive subjects were heavier alcohol users.

Ninety-five patients (30.7%) were alcohol-experienced but had been abstinent in the last year. Eleven subjects 11 (3.5%) had never tried alcohol in their lifetime.

In alcohol-experienced subjects, who abstained from alcohol within the last 12 months ($n = 95$), epilepsy was reported to be the most common reason for no longer drinking alcohol ($n = 50$; 52.6%). Of those 50 patients, 49 subjects stated that they would consume alcohol if epilepsy had not been diagnosed and 16 patients stated that alcohol abstinence due to epilepsy is a challenge.

Alcohol-Related Seizures

Thirty-seven out of 204 alcohol users (18.1%) had experienced alcohol-related seizures within the last 12 months (**Table 4**). In 95% ($n = 35$) of cases, these seizures had occurred within 12 h after cessation of alcohol intake.

In multivariate analysis, subjects with heavier alcohol use in the last 12 months were more likely to experience alcohol-related seizures (OR 8.955), whereas occasional or light and moderate alcohol use was not associated with increased risk for alcohol-related seizures (**Tables 5**, **6**). However, most of the patients (78.4%) who reported alcohol-related seizures were occasional, light or moderate alcohol users who had changed their usual alcohol intake toward higher consumption on the drinking occasion prior to the seizures (**Table 4**). The amount of alcohol intake before the occurrence of alcohol-related seizures was very high in all of the cases with a mean of 13.3 ± 5.8 standard drinks (median 12.5, range 7–34), which is equivalent to 2.5 L of beer or 1.25 L of wine. The minimum was 7 standard drinks, equivalent to ∼1.4 L of beer or 0.7 L of wine.

Patients with generalized genetic epilepsy (OR 5.792) were more likely to experience alcohol-related seizures compared to patients with focal epilepsy (**Tables 5**, **6**). In patients with focal epilepsy, the mean amount of alcohol intake prior to alcohol-related seizures was 14.4 ± 6.5 (median 13, range 7.5–34) standard drinks, and in subjects with generalized genetic epilepsy 12.3 ± 5.9 (median 11.3, range 7–30). No significant difference was detected ($p = 0.366$).

In female patients, the mean amount of alcohol intake before alcohol-related seizures was 10.9 ± 3.1 standard drinks (median 11.3, range 7–15), and in male subjects, 15.4 ± 6.8 (median 15, range 7.5–34; $p = 0.02$).

Fifteen out of 95 (15.8%) alcohol-experienced but now abstinent subjects had experienced alcohol-related seizures in the past. In that group, the mean amount of alcohol intake prior to the seizures was 10.9 standard drinks. All of these patients stated that they had stopped alcohol consumption because of the experience of alcohol-related seizures.

DISCUSSION

In this study, we aimed to systematically analyze alcohol drinking and the occurrence of alcohol-related seizures in 310 epilepsy patients. Even though alcohol use may trigger seizures, 65% of interviewed subjects had consumed alcohol within the last 12 months and every third patient had consumed alcohol within the last 7 days. Our results are in line with previous population-based study findings from Canada reporting a 12-month prevalence of alcohol use in patients with epilepsy of 57.6% (20). In our study, most subjects were occasional or light alcohol users. Regarding chronic heavy alcohol consumption, our cohort of patients had used alcohol far more responsibly than the general adult German population. Only 2.9% of our interviewed study subjects were AUDIT positive indicating hazardous and harmful alcohol intake. By contrast, data from the general adult German population showed that a proportion of 19.7% is AUDIT positive (9).

In multivariate analysis, alcohol consumption within the last 12 months was independently related to AED monotherapy. It is highly likely that subjects with well-controlled epilepsies on

TABLE 2 | Possible confounding variables that were included in the logistic regression model regarding alcohol consumption within the last 12 months.

Variable		Alcohol use within the last 12 months ($n = 204$)	Alcohol-abstinence ($n = 106$)
		No. (%)/mean ± *SD*[a]	No. (%)/mean ± *SD*
Sex	Female	108 (52.9)	63 (59.4)
	Male	96 (47.1)	43(40.6)
Age (in years)		43.8 ± 15.9	46.3 ± 16.7
Duration of epilepsy (in years)		18.9 ± 15.8	22.5 ± 18.4
Epilepsy type	Focal	135 (66.2)	78 (73.6)
	GGE[b]	45 (22.1)	22 (20.8)
	Unknown	24 (11.7)	6 (5.6)
AED[c]	Monotherapy	130 (63.7)	54 (50.9)
	Polytherapy	69 (33.8)	52 (49.1)
	No treatment	5 (2.5)	0
Seizure frequency	≥1/month	76 (37.3)	54 (50.9)
	<1/month	128 (62.7)	52 (49.1)
Physicians' advice	Alcohol should be avoided completely	73 (35.8)	54 (51)
	No advice	56 (27.4)	38 (35.8)
	Alcohol can be consumed without restriction	2 (1)	0
	Light alcohol intake is harmless	73 (35.8)	14 (13.2)

[a] *SD, standard deviation.*
[b] *GGE, generalized genetic epilepsy.*
[c] *AED, antiepileptic drug treatment.*

TABLE 3 | Independent predictors for alcohol consumption within the last 12 months.

Variable		OR[a]	95% CI[b]	*P*-value
AED[c]	Polytherapy	1.0 (ref.)		
	Monotherapy	1.901	1.152–3.138	$p = 0.012$
	None	N/A[d]	N/A	N/A
Physicians' advice	Alcohol should be avoided completely	1.0 (ref.)		
	Alcohol can be consumed without restriction	N/A	N/A	N/A
	No advice	1.043	0.599–1.814	$p = 0.883$
	Light alcohol intake is harmless	4.102	2.078–8.097	$p < 0.0001$

[a] *OR, odds ratio.*
[b] *CI, confidence interval.*
[c] *AED, antiepileptic drug treatment.*
[d] *N/A, not available.*

monotherapy are more likely to consume alcoholic beverages than those with difficult-to-treat variants. Physicians' advice that "a light alcohol intake is harmless" was identified as an additional predictor for alcohol use. Patients with epilepsy may feel unsure about alcohol consumption on chronic medication and therefore may be willing to follow physicians' advices more often.

Thirty-seven out of 204 epilepsy patients who had consumed alcohol remembered that they had experienced an alcohol-related seizure within the last 12 months. These seizures occurred in the timely context of acute heavy alcohol consumption. The occurrence of seizures in short temporal relation to alcohol consumption may not prove that these seizures were necessarily causally related to alcohol use. The following arguments however support this hypothesis: Most subjects with alcohol-related seizures were occasional, light or moderate alcohol users but a noticeable change in their usual alcohol-drinking behavior toward higher consumption prior to the seizures could be documented. This taken together with the fact that almost all alcohol-related seizures (95%) had occurred within the first 12 h after cessation of alcohol intake support a causal relationship between alcohol use and temporally close seizure manifestation in these cases.

In the study population, generalized genetic epilepsy was an independent predictor for the occurrence of alcohol-related seizures. The mean alcohol intake prior to alcohol-related seizures was not higher in patients with generalized genetic epilepsy than in subjects with focal epilepsy. Lennox stated that alcohol-related seizures had occurred more often in patients with symptomatic than in cryptogenic or idiopathic epilepsies (1). The then applied syndromatic allocation, however, may not be in exact conformance with the present classifications (16, 17). Janz (21) later observed that alcohol-related seizures were more likely to occur in subjects with generalized genetic epilepsy

TABLE 4 | Clinical variables of patients with epilepsy who had experienced alcohol-related seizures within the last 12 months ($n = 37$).

Patient-ID	Alcohol intake prior to alcohol-related seizures (standard drinks)	Time between cessation of alcohol intake and seizure occurrence (range in hours)	Usual alcohol-drinking behavior within the last 12 months	Epilepsy type
#17	15	≥12–<24	Occasional or light use	Unknown
#25	8.75	<6	Occasional or light use	GGE [a]
#31	15	≥6–<12	Occasional or light use	Focal
#32	10	≥6–<12	Occasional or light use	Focal
#38	34	<6	Heavier use	Focal
#40	7	≥6–<12	Moderate use	GGE
#53	12	<6	Occasional or light use	Focal
#54	17.5	<6	Occasional or light use	Focal
#63	15	≥6–<12	Occasional or light use	GGE
#65	12.5	≥6–<12	Moderate use	GGE
#77	7.5	<6	Occasional or light use	GGE
#81	20	<6	Heavier use	GGE
#83	7.5	≥6–<12	Heavier use	GGE
#87	12	<6	Moderate use	GGE
#116	7.5	<6	Occasional or light use	Focal
#133	Not remembered	<6	Heavier use	Focal
#140	12.5	<6	Moderate use	GGE
#141	Not remembered	≥6–<12	Heavier use	Focal
#144	12.5	≥6–<12	Occasional or light use	Focal
#147	15	<6	Occasional or light use	Focal
#154	10	≥12–<24	Moderate use	Focal
#178	15	<6	Occasional or light use	Unknown
#185	15	<6	Heavier use	Unknown
#188	14.5	<6	Occasional or light use	Focal
#199	11.5	<6	Occasional or light use	Focal
#223	Not remembered	<6	Heavier use	GGE
#258	15	<6	Moderate use	GGE
#264	7.5	<6	Occasional or light use	GGE
#272	15	<6	Occasional or light use	Unknown
#274	30	<6	Occasional or light use	GGE
#276	10.5	≥6–<12	Occasional or light use	GGE
#278	12.5	<6	Occasional or light use	GGE
#280	13	≥6–<12	Occasional or light use	Focal
#282	7.5	≥6–<12	Occasional or light use	Unknown
#283	10	<6	Occasional or light use	GGE
#291	8.75	<6	Moderate use	GGE
#308	15	≥6–<12	Heavier use	Focal

[a] *GGE, generalized genetic epilepsy.*

than in those with focal epilepsy, which is consistent with our findings (21).

Acute alcohol consumption suppresses central nervous excitability by activating the inhibitory GABA-system (22). GABA is the major inhibitory neurotransmitter in the brain. Furthermore, alcohol inhibits glutamate activity, which is the major excitatory neurotransmitter of the CNS. Thus in subjects with epilepsy, alcohol intake initially reduces CNS epileptiform EEG-activity. Later however, when alcohol blood levels decline, epileptiform EEG-activity has been shown to be increased which is associated with a higher risk for seizures (4–6, 23). In an experimental study on mice with chronic epilepsy, seizure thresholds were measured after the administration of ethanol. Initially, anticonvulsant properties of ethanol were observed, but later a transient lowering of seizure thresholds and hyper-susceptibility to seizures were reported (7).

In patients with generalized genetic epilepsy, seizures commonly manifest within 30 min after awakening. A transcranial magnetic stimulation study on patients with genetic generalized epilepsy demonstrated that motor cortex excitability was significantly increased in the early morning (24). In subjects with generalized genetic epilepsy, this increased

TABLE 5 | Possible confounding variables that were included in the logistic regression model regarding the occurrence of alcohol-related seizures in patients with epilepsy within the last 12 months.

Variable		Alcohol-related seizure occurrence within the last 12 months ($n = 37$)	No alcohol-related seizures within the last 12 months ($n = 167$)
		No. (%)/mean ± *SD*[a]	No. (%)/mean ± *SD*
Sex	Female	17 (45.9)	91 (54.5)
	Male	20 (54.1)	76 (45.5)
Age (in years)		40.7 ± 14.7	44.5 ± 16.1
Duration of epilepsy (in years)		20.3 ± 15.1	18.6 ± 16
Epilepsy type	Focal	15 (40.6)	120 (71.9)
	GGE[b]	17 (45.9)	28 (16.8)
	Unknown	5 (13.5)	19 (11.3)
AED[c]	Monotherapy	22 (59.5)	108 (64.7)
	Polytherapy	14 (37.8)	55 (32.9)
	No treatment	1 (2.7)	4 (2.4)
Seizure frequency	≥1/month	13 (35.1)	63 (37.7)
	<1/month	24 (64.9)	104 (62.3)
Alcohol use within the last 12 months	Occasional or light use	22 (59.5)	125 (74.8)
	Moderate use	7 (18.9)	36 (21.6)
	Heavier use	8 (21.6)	6 (3.6)

[a] *SD, standard deviation.*
[b] *GGE, generalized genetic epilepsy.*
[c] *AED, antiepileptic drug.*

TABLE 6 | Independent predictors for the occurrence of alcohol-related seizures within the last 12 months in patients with epilepsy.

Variable		OR[a]	95% CI[b]	*P*-value
Epilepsy type	Focal	1.0 (ref.)		
	GGE[c]	5.792	2.427–13.823	$p < 0.0001$
	Unknown	2.185	0.664–7.189	$p = 0.198$
Alcohol use within the last 12 months	Occasional or light use	1.0 (ref.)		
	Moderate use	0.819	0.306–2.194	$p = 0.691$
	Heavier use	8.955	2.625–30.545	$p < 0.0001$

[a] *OR, odds ratio.*
[b] *CI, confidence interval.*
[c] *GGE, generalized genetic epilepsy.*

neuronal excitability in the early morning may be potentiated by the hyper-excitable post-alcohol state, and this effect may be responsible for the increased susceptibility to alcohol-related seizures compared to focal epilepsy.

Clinical Perspective

Most of our interviewed subjects (>80%) that consumed alcohol within the last 12 months did not experience alcohol-related seizures. Current data on the quantity of alcohol intake prior to the occurrence of alcohol-related seizures in patients with epilepsy highly suggest that these situations are related to the acute consumption of considerably large amounts of alcohol. Subjects who reported alcohol-related seizures had consumed at least 7 standard drinks before seizures occurred which is equivalent to 1.4 L of beer or 0.7 L of wine. Occasional or light and moderate alcohol-drinking behavior was not associated with alcohol-related seizure occurrences. In the general German population, 89% of all adults had used alcohol within the last 12 months, only 8% were alcohol-experienced but abstinent, and 3% had never used alcohol in their lifetime (9). In the present study, 30.7% of patients were alcohol-experienced but abstinent and 3.5% had never consumed alcohol in their lifetime. Therefore, the proportion of alcohol-experienced but abstinent subjects with epilepsy was almost four times higher than in the general population. Epilepsy was often stated to be the only reason for alcohol-abstinence, which felt challenging to many subjects. Alcohol abstinence may not be necessary as long as epilepsy patients practice a responsible alcohol intake. Subjects with generalized genetic epilepsy however should be made aware of their increased susceptibility to alcohol-related seizures.

Limitations

Our systematic data collection based on personal interviews allowed us to provide updated knowledge on the patterns of

alcohol drinking and the occurrence of alcohol-related seizures in a large cohort of 310 epilepsy patients.

Several limitations have to be discussed. First, our data on alcohol use depended on patients' self-reporting and may be affected by recall bias. It has been demonstrated that assessing alcohol consumption is biased by recall even when the recall period is only 1 week (25). In our study population, alcohol consumption is probably underestimated. However, this does not impact our main findings. Moreover, patients were seen at our institution at scheduled outpatient visits and did not attend the clinic after acute manifestations of alcohol-related seizures. Only a minority of patients documented details on alcohol-related seizures in seizure diaries. Our retrospective data collection on alcohol-related seizures also depended on subjects' recall capability, and may reflect bias due to recall errors. We addressed this by focusing only on alcohol-related seizures that had occurred within the last 12 months. Details were only recorded on those alcohol-related seizures that subjects were able to remember the best. As a consequence however, alcohol-related seizures may have also occurred after smaller amounts of alcohol intake or in other circumstances that were not taken into account in the present study.

Second, as patients were interviewed retrospectively on the occurrence of alcohol-related seizures, we were not able to provide data on AED drug levels after the acute manifestation of these seizures. We cannot exclude that subjects might have been more prone to seizure occurrences due to AED non-adherence. Furthermore, we cannot exclude hypoglycemic episodes caused by acute heavy alcohol consumption (26), which may have contributed to the manifestation of epileptic seizures (27).

Third, other studies have shown that alcohol consumption and especially the consumption of considerable large amounts of alcohol may reduce sleep quality by increasing light sleep and wake-up periods during the second half of the night time sleep period (28, 29). In addition to that, alcohol intake significantly suppresses REM sleep periods (30). Reduced sleep quality and consecutive sleep deprivation have long been discussed to facilitate the occurrence of seizures in patients with epilepsy (31), and especially in those with generalized genetic epilepsy (32–34). Altered sleep architecture due to acute alcohol consumption constitutes a non-negligible and important co-factor for seizure risk in patients with epilepsy. Due to the retrospective design of the present study, we were not able to assess sleep quality prior to alcohol-related seizure occurrences. Future prospective research, e.g., using polysomnography, will be needed to provide insight into the complex relationship between alcohol consumption, altered sleep architecture and timely manifestation of seizures.

Finally, the present study population was exclusively recruited at a tertiary care epilepsy center where usually patients with more severe variants of the disease are treated. This indicates a potential selection bias and our results may not be generalized to all epilepsy patients without restrictions.

ETHICS STATEMENT

The study was approved by the local Institutional Review Board (EA 1/146/08), and signed informed consent was obtained from all participants.

AUTHOR CONTRIBUTIONS

MiH: data collection, statistical, analysis, wrote manuscript. LG, AK, and FW helped recruiting patients, helped to improve manuscript. MaH: statistical analysis, wrote manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00401/full#supplementary-material

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Molecular Genetic Characterization of Patients With Focal Epilepsy Using a Customized Targeted Resequencing Gene Panel

Meng-Han Tsai[1], Chung-Kin Chan[2], Ying-Chao Chang[3], Chih-Hsiang Lin[1], Chia-Wei Liou[1], Wen-Neng Chang[1], Ching-Ching Ng[2], Kheng-Seang Lim[4] and Daw-Yang Hwang[5]**

[1] Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kaohsiung, Taiwan, [2] Genetics and Molecular Biology, Faculty of Science, Institute of Biological Sciences, University of Malaya, Kuala Lumpur, Malaysia, [3] Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [4] Division of Neurology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [5] Division of Nephrology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

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Edited by:
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***Correspondence:**
Meng-Han Tsai
menghan@cgmh.org.tw
Daw-Yang Hwang
910208@kmuh.org.tw

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Objective: Focal epilepsy is the most common subtype of epilepsies in which the influence of underlying genetic factors is emerging but remains largely uncharacterized. The purpose of this study is to determine the contribution of currently known disease-causing genes in a large cohort ($n = 593$) of common focal non-lesional epilepsy patients.

Methods: The customized focal epilepsy gene panel (21 genes) was based on multiplex polymerase chain reaction (PCR) and sequenced by Illumina MiSeq platform.

Results: Eleven variants (1.85%) were considered as pathogenic or likely pathogenic, including seven novel mutations. There were three *SCN1A* (p.Leu890Pro, p.Arg1636Ter, and p.Met1714Val), three *PRRT2* (two p.Arg217Profs*8 and p.Leu298Pro), two *CHRNA4* (p.Ser284Leu, p.Ile321Asn), one *DEPDC5* (p.Val516Ter), *one PCDH19* (p.Asp233Asn), and one *SLC2A1* (p.Ser414Ter) variants. Additionally, 16 other rare variants were classified as unknown significance due to inconsistent phenotype or lack of segregation data.

Conclusion: Currently known focal epilepsy genes only explained a very small subset of focal epilepsy patients. This indicates that the underlying genetic architecture of focal epilepsies is very heterogeneous and more novel genes are likely to be discovered. Our study highlights the usefulness, challenges and limitations of using the multi-gene panel as a diagnostic test in routine clinical practice in patients with focal epilepsy.

Keywords: focal epilepsy, multigene panel, targeted resequencing, NGS, multiplex PCR

INTRODUCTION

Focal epilepsy constitutes for about 60% of all epilepsies, which is the commonest phenotypic group of epilepsies (1). The etiology of more than half of the focal epilepsies remains uncertain despite high-quality neuroimaging studies (2–4). Some of these unsolved focal epilepsy patients may have a genetic etiology. Recently, patients with focal structural epilepsies were also found to

have a genetic cause, such as mTOR pathway genes mutations in focal cortical dysplasia (5, 6). Several disease-causing genes were identified in patients presented with focal seizures as part of their phenotypic spectrums through studies of large families (7–12). For examples, *LGI1* in familial lateral temporal epilepsies (13), *DEPDC5* in familial focal epilepsy with various foci (9, 10), *SCN1A* in genetic epilepsy with febrile seizure plus (GEFS+) (14, 15) and *CHRNA2, CHRNAB2, CHRNA4, KCNT1* in sleep related hypermotor epilepsies (16–19). A better understanding of the contribution of these genes in common focal epilepsies patients can be helpful in guiding appropriate tests and treatments in routine clinical care.

Recent advances in genomic medicine have significantly unveiled the influence of genetic factors in epilepsy. The targeted gene panel approach has been successfully used in specific syndromes and severe epilepsies, such as epileptic encephalopathies and familial epilepsies.(20–27) Hitherto, only two studies have addressed focal epilepsy specifically using targeted gene panel or whole exome sequencing (WES) with targeted gene analysis (28, 29). Here, we developed a more comprehensive focal epilepsy gene panel, with 21 genes, using multiplex polymerase chain reaction (PCR) based technique followed by massively parallel sequencing to study a large cohort of patients with focal epilepsies. We aim to better understand the contribution of currently known disease-causing genes to focal epilepsy and the utility of multi-gene panel in real-world clinical setting.

METHODS

Patients and Phenotyping

Patients with focal epilepsies were recruited for the Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Taiwan and the Neurology clinic, University of Malaya Medical Center, Malaysia. The clinical information, electroencephalography (EEG) and neuroimaging results were obtained from a direct interview or review of medical records. Most (506/593, 85.3%) of them underwent 3T or 1.5T brain MRI, the remaining 87 had brain CT scans. Patients who had focal structural epilepsy due to stroke, trauma, brain tumor, or focal cortical dysplasia were excluded. Patients with isolated generalized epilepsies were also excluded, but those who have both generalized and focal seizures were still included because some of the genes included in the panel were known to have both presentations. Positive family history was defined as the presence of epilepsy or seizures in the first or second-degree relatives. All of them were recruited regardless of family history and none had received prior genetic testing. All available family members were included for segregation analysis. This study was approved by the local human research ethics committees and written consents were obtained from all subjects. In minors and those with intellectual disabilities, consents were obtained from their legal guardian.

Focal Epilepsy Gene Panel

Venous blood was obtained and genomic DNA was extracted from peripheral blood leukocytes using QIAGEN DNA extraction kits (Qiagen, Germany), according to the manufacturer instructions (30). A customized focal epilepsy gene panel was used, including 21 genes: *SCN1A, SCN1B, SCN2A, SCN9A, DEPDC5, GRIN2A, GRIN2B, PRRT2, SLC2A1, PCDH19, KCNT1, KCNQ2, KCNQ3, KCNA2, CHRNA4, CHRNB2, CHRNA2, LGI1, GABRG2, HCN1, CHD2.* All coding exons and at least 10 base pair (bp) flanking sequences of the intron/exon boundaries were amplified using targeted specific primers, with a total 69,787 bp region. The amplicon sizes ranged from 204 to 432 bp with an average of 315 bp. Universal primer sequences, 5′-ACACTGACGACATGGTTCTACA-3′ and 5′-TACGGTAGCAGAGACTTGGTCT-3′ were added to the 5' end of all target-specific forward and reverse primers, respectively. Primers were pooled to generate six-plex primer pools per PCR with a final concentration of 1 uM. Libraries were prepared by using the Fluidigm Access 48.48 Array platform (Fluidigm, South San Francisco, California). Harvested amplicon pools underwent another PCR step to barcode the products according to the manufacturer's protocol. Barcoded PCR products were pooled and submitted to an Illumina MiSeq using 2 x 300 bp paired-end runs.

Bioinformatics Analysis

Raw read data was processed with FastQC, FastQ groomer, Trimmomatics to remove primer sequences, and then mapped to human reference genome (version GRCh37) with Burrows-Wheeler Aligner (BWA-MEM, version 0.7.15, http://bio-bwa.sourceforge.net/) (31, 32). The aligned BAM file was processed with SAM tool (http://www.htslib.org/) and Picard (http://picard.sourceforge.net/) to remove low quality mapped reads as well as duplicate reads. Indel realignment was performed using GATK tool as recommended by the Broad Institute GATK Best Practice (33, 34). Single nucleotide variants and small indels were called using FreeBayes (35). The read depth and coverage of each BAM files were calculated using BEDtools (36). Variants that did not adhere to the following criteria were excluded from further analysis: mapping quality<30, base quality<20, coverage<20, variants with strand bias and clustered variants. The variant calling was performed using the Galaxy platform (http://usegalaxy.org). Variants were annotated with wANNOVAR (http://wannovar.wglab.org). Only nonsense, nonsynonymous, splice-site and frameshift variants were further evaluated. Variants presented in the Thousand Genome Project (TGP, http://www.internationalgenome.org/), the Exome Variant Server (EVS, http://evs.gs.washington.edu/EVS/), more than 1 hit in the Board Institute Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org), and more than five hits in the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org) were excluded (37). Four prediction programs, including SIFT (v1.03) (38), PolyPhen-2 (v2.2.2 build r394) (39), MutationTaster 2 (40), and Combined Annotation Dependent Depletion (CADD v1.2)(41) were used to prioritize variants. The cutoff value of CADD was set at 20. Only variants predicted probably damaging by more than three *in silico* programs were further validated by Sanger sequencing.

Criteria for Pathogenicity of Filtered Variants

The confirmed rare variants were classified into pathogenic, likely pathogenic, and variants of unknown significance (VUS) modified from previous guidelines (42, 43). Variants presented in the disease databases (HGMD, http://www.hgmd.org/; ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/; LOVD, http://www.lovd.nl/) were classified as being known pathogenic. Null variants (including frameshift mutations, nonsense mutations, obligatory splicing sites mutations, and mutations affecting the initial codon) identified in known epilepsy genes, where loss of function is a known disease mechanism, were also considered to be pathogenic.

Ultra-rare missense variants (not present in TGP, EVS, $\leq$1 in ExAc and $\leq$5 in gnomAD) predicted to be deleterious or damaging by more than three of the four prediction programs were classified as likely pathogenic if their phenotypes correlate with the reported literature. If available, functional data and segregation analysis were taken into consideration. Variants that passed *in silico* prediction but the patient's phenotype was not previously associated with the gene were classified as VUS.

Statistical Analysis

Fisher exact test was used for comparison of categorical data. The statistical analysis was performed with R software, version 3.2.1 (44).

RESULTS

Patient Characteristics

Five hundred and ninety-three patients, including 298 (50.3%) Taiwanese and 295 (49.7%) Malaysian patients, were recruited and underwent customized focal epilepsy gene panel screening. Among them, 315 (53.1%) had temporal lobe epilepsies, 153 (25.8%) frontal lobe epilepsies, 26 (4.4%) occipital lobe epilepsies, 11 parietal lobe epilepsies (1.8%), 13 (2.2%) benign childhood epilepsy with centrotemporal spikes, and 20 (3.4%) had other syndromes with focal seizures, including 12 Dravet syndrome, 5 Lennox-Gastaut syndrome, 2 epilepsy aphasia spectrum disorders and one genetic epilepsy with febrile seizure plus (GEFS+). The localization was undefined in 55 (9.3%) patients. There were 99 (16.7%) patients had a positive family history and the remaining 494 (83.3%) were sporadic cases.

Customized Focal Gene Panel Study

Total 593 patients were screened with the focal epilepsy gene panel with a mean read depth of 142.4x, and 83.8% coverage of the target region for at least 20 reads.

A total of 27 variants were confirmed by Sanger sequencing in 25 individuals (4.2%), where two individuals had two different variants. Eleven variants (1.85%) were considered as pathogenic or likely pathogenic, including 4 reported and 7 novel mutations (**Table 1**); the remaining 16 variants were classified as VUS (Supplemental Table 1). Pathogenic and likely pathogenic variants were found in *SCN1A* (3 patients), *PRRT2* (3 patients), *CHRNA4* (2 patients), followed by one patient each in *DEPDC5, PCDH19,* and *SLC2A1* (**Table 1**). The pedigrees, clinical phenotypes, and characteristics of patients with pathogenic or likely pathogenic variants were summarized in **Figure 1**, **Table 2** and detailed in below. The clinical phenotypes, and characteristics of patients with variants of unknown significance were summarized in Supplemental Table 2. Pathogenic or likely pathogenic variants were found in 4 out of 99 focal epilepsy patients with a positive family history (4%) compared to 7 out of 494 sporadic focal epilepsy patients (1.4%, $p = 0.094$). We further divided our cohort into patients with specific syndromes and focal epilepsies with intellectual disabilities vs. "non-syndromic" focal epilepsies, the diagnostic rate was higher 12.8% (5/39) in syndromic/ID group than in "non-syndromic" group, which was 1.26% (7/554).

SCN1A

Three variant were found in *SCN1A*, including two patients with Dravet syndromes (p.Leu890Pro, p.Arg1636Ter) and one family with genetic epilepsy with febrile seizure plus (GEFS+) (p.Met1714Val, **Figure 1**). The missense mutation p.Leu890Pro is *de novo* and located in the pore-forming transmembrane S5 domain, while the inherited missense mutation in GEFS+ family (p.Met1714Val) is located in the pore-forming loop between S5 and S6 domain. Both are novel mutations and located in the hot-spot for disease-related missense mutations (45). The p.Met1714Val missense variant was also found in the affected son and proband's mother who had focal seizures in old age (**Figure 1**).

The patient with de novo p.Leu890Pro mutation had more than 10 seizures a month on Carbamazepine, Vigabatrin and Levetiracetam before the genetic diagnosis. His medication was changed to Topiramate, Levetiracetam and Clobazam in the following months after receiving the results and his seizure frequency drastically reduced to only 1-2 seizure a month.

PRRT2

Three variants were found in *PRRT2* gene, including two hotspot p.Arg217Profs*8 frameshift mutations that were inherited in the families with benign infantile epilepsies (**Figure 1**). The third missense variant p.Leu298Pro is novel and found in a patient with both focal epilepsy and paroxysmal kinesigenic dyskinesia. *In silico* programs predicted this missense mutation to be deleterious/damaging/disease causing. The available unaffected sister did not have the mutation, the affected brother had paroxysmal kinesigenic dyskinesia and epilepsy but was not available for testing. Functional study of this variant showed lack of membrane localization of the mutant protein, similar to the hotspot truncating mutation p.Arg217Profs*8 (Tsai et al., under review). Therefore, the variant is classified as pathogenic based on consistent phenotype and functional data.

CHRNA4

Two missense variants (p.Ser284Leu, p.Ile321Asn) were found in *CHRNA4*, both located in the transmembrane domain; the novel missense variant p.Ile321Asn

TABLE 1 | The pathogenic or likely pathogenic variants identified by customized focal epilepsy gene panel.

Case	Chr	Position	Ref	Alt	Genes (RefSeq access number)	Type	cDNA change	AA change	Protein Domain	gnomAD†	ExAC†	SIFT	PP2	MT	CADD	Phenotype	Inheritance	Significance
K91	2	166894563	A	G	SCN1A (NM_001165963.1)	Missense	c.T2669C	p.Leu890Pro	Transmembrane S5	np	np	D	P	D	26.5	Dravet syndrome	De Novo	Pathogenic
K39	2	166848645	T	C	SCN1A (NM_001165963.1)	Missense	c.A5140G	p.Met1714Val	Intramembrane, pore-forming	np	np	D	P	D	22.6	GEFS+	Inherited	Likely pathogenic
K903	2	166848879	G	A	SCN1A (NM_001165963.1)	Stopgain	c.C4906T	p.Arg1636Ter	Transmembrane	np	np	n/a	n/a	D	43	Dravet syndrome	De Novo	Pathogenic
K94	16	29825024	-	C	PRRT2 (NM_145239.2)	Frameshift	c.649dupC	p.Arg217Profs*8	Extracellular	np	np	n/a	n/a	n/a	n/a	Focal epilepsy	Inherited	Pathogenic
K400	16	29825024	-	C	PRRT2 (NM_145239.2)	Frameshift	c.649dupC	p.Arg217Profs*8	Extracellular	np	np	n/a	n/a	n/a	n/a	Infantile epilepsy and late focal epilepsy	Inherited	Pathogenic
K234	16	29825667	T	C	PRRT2 (NM_145239.2)	Missense	c.T893C	p.Leu298Pro	Cytoplasmic	np	np	D	D	D	26.1	Focal epilepsy and PKD	n/a	Pathogenic
K6042	20	61981912	G	A	CHRNA4 (NM_000744.6)	Missense	c.C851T	p.Ser284Leu	Transmembrane	np	np	D	D	A	32	Nocturnal focal epilepsy	n/a	Pathogenic
K5120	20	61981801	A	T	CHRNA4 (NM_000744.6)	Missense	c.T962A	p.Ile321Asn	Transmembrane	np	np	D	D	D	27.9	NFLE	n/a	Likely pathogenic
K5091	22	32211078	G	-	DEPDC5 (NM_001242896.1)	Stopgain	c.1546delG	p.Val516Ter	No information	np	np	n/a	n/a	n/a	n/a	Focal epilepsy	n/a	Pathogenic
K1014	X	99662899	C	T	PCDH19 (NM_00118488.0)	Missense	c.G697A	p.Asp233Asn	Extracellular, Calcium binding pocket	np	np	D	D	D	28.2	EFMR	De Novo	Pathogenic
K977	1	43393313	G	C	SLC2A1 (NM_006516)	Stopgain	c.C1241G	p.Ser414Ter	Transmembrane	np	np	D	n/a	D	42	Glut1 deficiency syndrome	De Novo	Pathogenic

Chr, Chromosome; AA, Amino Acid; gnomAD, Genome Aggregation Database; TPG, Thousand Genome Project; ExAc, Exome Aggregation Consortium; EVS, Exome Variant Server; PP2, PolyPhen2; MT, Mutation Taster; CADD, Combined Annotation Dependent Depletion ; n/a, not available; np, not present; NFLE, nocturnal frontal lobe epilepsy; GEFS+, genetic epilepsy and febrile seizure plus; FS, febrile seizures; EFMR, epilepsy and mental retardation limited to female; PKD, paroxysmal kinesigenic dyskinesia.

†*All variants were not present in the TGP or EVS databases.*

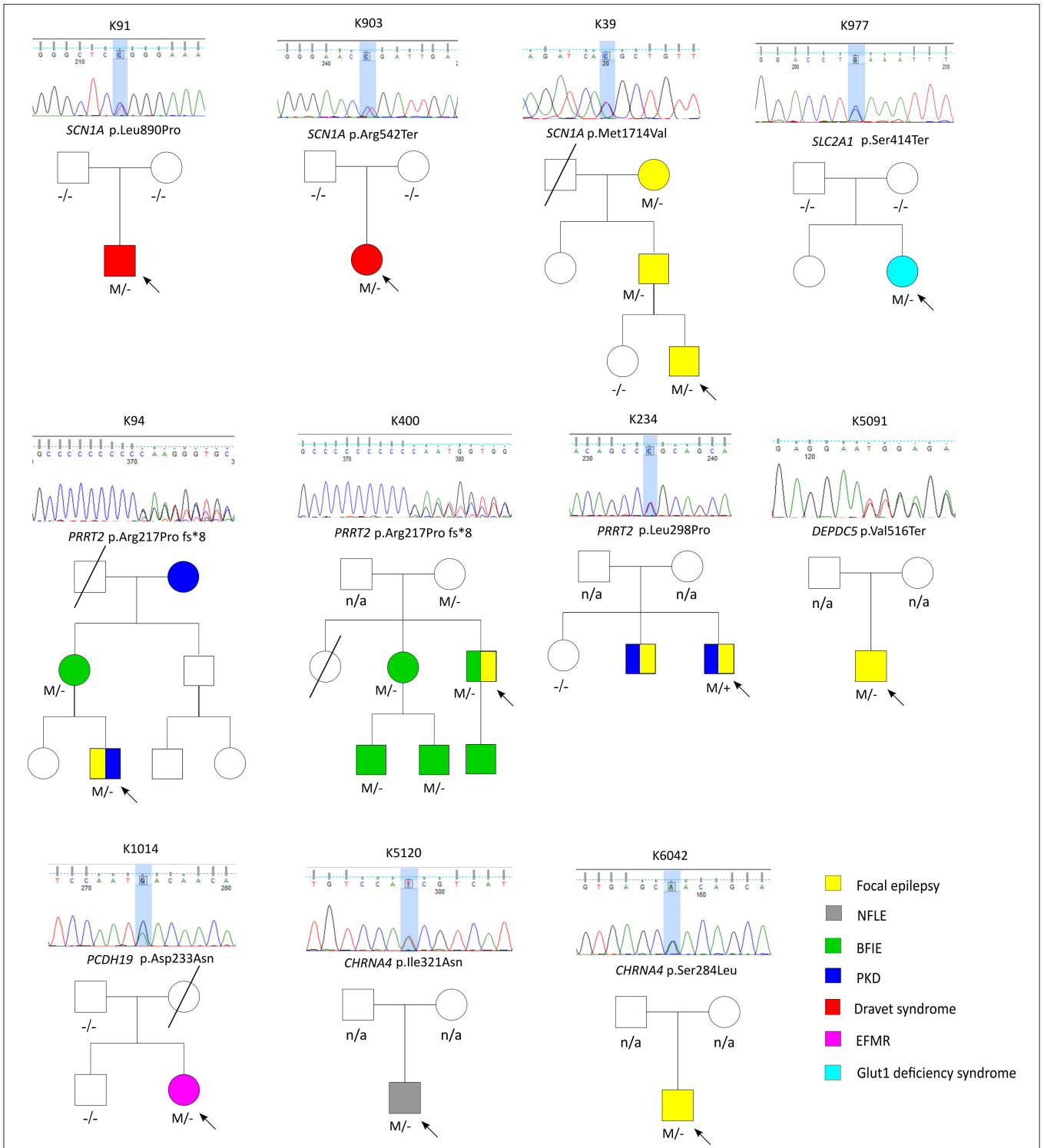

FIGURE 1 | The pedigrees of pathogenic and likely pathogenic variants identified by targeted multigene panel.

is predicted to be disease-causing by all *in silico* programs. Both patients had nocturnal frontal lobe epilepsy.

DEPDC5

The pathogenic nonsense mutation p.Val516Ter in *DEPDC5* is not presented in any control databases and is predicted to

TABLE 2 | The clinical phenotypes and characteristics of patients presented with pathogenic or likely pathogenic variants.

Case	Age/Gender	Gene	Diagnosis	Onset	Seizure type	EEG	Neuroimaging	Frequency	FH
K91	26/M	SCN1A	Dravet syndrome	8 months	Fever-related alternative hemi-clonic focal seizures, BTCS	Left temporal focal spikes	Normal	3–5/month	No
K39	55/M	SCN1A	GEFS+	3	Generalized seizures, occasionally focal seizures	Normal	Normal	1–2/year	Yes, his son has FS 3 months old and recurrent seizure at age of 15, both focal and generalized epilepsies, mother had elderly onset seizures after stroke
K903	19/F	SCN1A	Dravet syndrome	2 month for FS, 2.5 for afebrile seizure	Staring, BTCS, focal, and myoclonic jerks	Multifocal epileptiform discharges	Diffuse brain atrophy	1/week	No
K94	36/F	PRRT2	Focal epilepsy	7	Strange sensation –> BTCS	Normal	Normal	No seizure for years	Yes, son has infantile seizure 4 month
K400	31/M	PRRT2	BFIE, late focal epilepsy	4 months, recurrent at 18	BTCS	Right focal spike over central area	Right hippocampal and right anterior temporal arachnoid cyst	No seizure for years	Yes
K234	24/M	PRRT2	Focal epilepsy and PKD	21	Visual symptoms, ictal cry, BTCS	Focal left T-O sharp waves	Normal	No seizure for 2 years	Yes, brother has PKD
K6042	38/M	CHRNA4	Nocturnal focal epilepsy	7	Nocturnal BTCS	Right temporal sharp waves	Norma	Seizure free 1 year	No
K5120	44/M	CHRNA4	NFLE	16	Wandering at night with irrelevant verbal response	Right temporal theta activities	Normal	Seizure free 6 months	unknown
K5091	45/M	DEPDC5	Focal epilepsy	23	Dizziness then BTCS	Right hemisphere slow	Normal	1/year	No
K1014	33/F	PCDH19	EFMR	9 month	Staring episode, myoclonic, BTCS	Bilateral temporal epileptiform discharges	Normal	4–6 seizures/month	No
K977	8/F	SLC2A1	Glut1 deficiency syndrome	8 months	Focal seizure with impaired consciousness	Right frontal epileptiform discharges	Delayed myelination over periventricular area	1–2/year on ketogenic diet	No

FICS, focal impaired awareness seizures; BTCS, bilateral tonic-clonic seizures; EEG, electroencephalography; T, temporal; O, occipital; NFLE, nocturnal frontal lobe epilepsy; GEFS+, genetic epilepsy and febrile seizure plus; FS, febrile seizures; EFMR, epilepsy and mental retardation limited to female; FH, family history.

cause nonsense-mediated decay. Therefore, the mutation is likely to cause haploinsufficiency of the DEPDC5 protein, consistent with the currently known molecular mechanism. Clinically, the patient had focal epilepsy, consistent with the *DEPDC5* phenotypic spectrum.

PCDH19

The patient had febrile seizures at 9 months old and later developed fever sensitive seizure clusters and intellectual disability. The novel missense variant p.Asp233Asn is located in the extracellular domain; the amino acid forms part of the calcium binding pocket that is critical to the homophilic binding function of PCDH19. The variant is classified as de novo pathogenic because both unaffected parents did not carry the mutation.

SLC2A1

The patient had early onset focal seizures, intellectual disability, and low CSF glucose level, and clinically suspected GLUT1 deficiency syndrome. The novel nonsense variant p.Ser414Ter is located in the transmembrane domain and both unaffected parents did not have the mutation, thus the variant is classified as de novo pathogenic. The patient received ketogenic diet and responded partially to the therapy.

DISCUSSION

The real-world utility and experience of the multi-gene panel in focal epilepsies, the most common form of epilepsies, is very limited (28, 29). We screened a large cohort of focal epilepsy patients and found that 1.85% (11/594) can be attributed to a pathogenic or likely pathogenic variant. Our study highlights the usefulness but also challenges and limitations of using the multi-gene panel in focal epilepsies. The determination of the significance of identified genetic variants is complicated in real-world situation, which requires correct correlation between phenotypes and genotypes. It becomes more difficult when the phenotypes are not previously associated with the genes where variants are identified. It requires more studies to explore the boundaries of the phenotypic spectrum associated with each epilepsy gene. Some of the VUS may be reclassified as pathogenic or likely pathogenic when the phenotype-genotype relationship redefined. Moreover, we noted lack of segregation data is a common obstacle due to limited availability of the family members in routine clinical setting, which makes the determination of the pathogenicity of variants more difficult.

Previous studies using multi-gene panel in epilepsy with various genes (n = 35–327) have generated a diagnostic yield ranged from 10 to 48.5% (11, 21, 23–27, 32). Those studies selected patients with epileptic encephalopathy (21, 27), epileptic syndrome with suspected genetic etiology (12, 21, 32) or enriched for positive family history (21). The higher diagnostic yield was likely due to early onset epilepsies and severe/specific phenotypes such as epileptic encephalopathies (21), which are known to have a stronger genetic underpinning.

Our results are consistent with those reported by Hildebrand et. al., suggesting that currently known focal epilepsy genes only explain a small proportion (0.8–1.85%) of all focal epilepsy patients (29). After excluding patients with clinical suspected specific epilepsy syndromes, such as Dravet syndrome, GEFS+, EFMR and patients with intellectual disability, the diagnostic rate for "garden-variety" focal epilepsies was 1.26%. The reason for the slightly higher diagnostic rate in our study could be explained by the fact that most of our patients had not previously received genetic testing and 10 more genes were included in our panel (29). Interestingly, a recent study used WES based targeted gene analysis of 64 genes on 40 consecutive patients with focal epilepsies with suspected genetic etiology. (28) They reported a much higher positive rate at 12.5% (5/40), three variants were found when limiting to the 21 genes we studied (3/40, 7.5%). The higher yield rate could be explained by the presence of a positive family history of this study. In our study, patients with a positive family history also have a higher diagnostic rate (4% vs. 1.4%) although not statistically significant. Moreover, we did not include copy number variation (CNV), in-frame indels and splice-region variants that are not on the canonical site in this study, which may underestimate the diagnostic rate.

Taken together, our study found a multi-gene panel provides genetic diagnosis of a relatively small percentage of real-world patients with focal epilepsies. Our data indicate that the underlying genetic architecture of focal epilepsies is very heterogeneous and more genes await discovery. Supporting this, a recent study using WES reported positive findings in 38% of patients with focal epilepsy, including discovery of novel genes in 7% (46). The positive rate is expected to increase in the future when more causative genes are identified in focal epilepsy. Obtaining a correct genetic diagnosis is important as it may alter the clinical decision on epilepsy surgery, selection of antiepileptic drugs and reproductive counseling (28). In routine clinical care, careful selection of patients with specific phenotypes/syndromes or positive family histories, adopting a broader panel with more genes, or using WES or even whole genome sequencing are likely to further increase the diagnostic yield.

ETHIC APPROVAL AND CONSENTS TO PARTICIPATE

This study was approved by the local human research ethics committees (Chang Gung Medical Foundation Institutional Reviewer Board 104-2308B and University Malaya Medical Centre Medical Research Ethics Committee 944.3) and written consents were obtained from all subjects.

AUTHOR CONTRIBUTIONS

C-KC, Y-CC, C-HL, C-WL, W-NC, C-CN, and K-SL contributed to the acquisition and interpretation of the data and revising the manuscript for intellectual content. M-HT and D-YH contributed to the design and conceptualization of the

study; analysis and interpretation of the data; drafting, revising and final approval of the manuscript for intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00515/full#supplementary-material

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ORIGINAL RESEARCH
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Limitations of a Short Demographic Questionnaire for Bedside Estimation of Patients' Global Cognitive Functioning in Epilepsy Patients

Iris Gorny[1], Kristina Krause[1], Anita Albert[1], Sabrina Schneider[1], Leona Möller[1], Lena Habermehl[1], Adam Strzelczyk[1,2], Felix Rosenow[1,2], Anke Hermsen[1,2], Susanne Knake[1] and Katja Menzler[1]*

[1] Epilepsy Center Hessen, Philipps-University, Marburg, Germany, [2] Epilepsy Center Frankfurt Rhine-Main, Goethe University, Frankfurt, Germany

Objectives: The German socio-demographic estimation scale was developed by Jahn et al. (1) to quickly predict premorbid global cognitive functioning in patients. So far, it has been validated in healthy adults and has shown a good correlation with the full and verbal IQ of the Wechsler Adult Intelligence Scale (WAIS) in this group. However, there are no data regarding its use as a bedside test in epilepsy patients.

Methods: Forty native German speaking adult patients with refractory epilepsy were included. They completed a neuropsychological assessment, including a nine scale short form of the German version of the WAIS-III and the German socio-demographic estimation scale by Jahn et al. (1) during their presurgical diagnostic stay in our center. We calculated means, correlations, and the rate of concordance (range ±5 and ±7.5 IQ score points) between these two measures for the whole group, and a subsample of 19 patients with a global cognitive functioning level within 1 SD of the mean (IQ score range 85–115) and who had completed their formal education before epilepsy onset.

Results: The German demographic estimation scale by Jahn et al. (1) showed a significant mean overestimation of the global cognitive functioning level of eight points in the epilepsy patient sample compared with the short form WAIS-III score. The accuracy within a range of ±5 or ±7.5 IQ score points for each patient was similar to that of the healthy controls reported by Jahn et al. (1) in our subsample, but not in our whole sample.

Conclusion: Our results show that the socio-demographic scale by Jahn et al. (1) is not sufficiently reliable as an estimation tool of global cognitive functioning in epilepsy patients. It can be used to estimate global cognitive functioning in a subset of patients with a normal global cognitive functioning level who have completed their formal education before epilepsy onset, but it does not reliably predict global cognitive functioning in epilepsy patients in general, who often do not fulfill these criteria. It is therefore not a useful tool to be applied in the general neuropsychological presurgical evaluation of epilepsy patients.

Keywords: epilepsy, Wechsler Adult Intelligence Scale-III, short form, intelligence, cognitive function

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****Correspondence:***
Iris Gorny
gorny@med.uni-marburg.de

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INTRODUCTION

The precise assessment of individual cognitive resources and deficits is important for the comprehensive care of epilepsy patients, especially when epilepsy surgery is a feasible therapeutic approach. For the diagnosis and quantification of cognitive impairment in the individual, test results are compared not only to the specific test norms but also to the level of global cognitive functioning (2). The most commonly used measure of global cognitive functioning is the Wechsler Adult Intelligence Scale (WAIS) (3). However, especially in cognitively impaired patients, administration of the WAIS can be time-consuming, so various short forms have been developed. One common approach is to select a different number of subscales (from 2 to 10) of the WAIS (4, 5). The classifications have been shown to be quite robust and correlate highly with the WAIS, especially when seven or more scales are used (6). A different and even less time consuming approach is to estimate the level of global cognitive functioning by means of socio-demographic variables, such as educational attainment and occupational status (7). Studies with healthy controls showed good estimation rates for individuals whose global cognitive functioning level is within 1 SD of the mean (mean IQ range 85–115) (8). These scales may be useful to estimate premorbid cognitive functioning in patients (9, 10). However, these socio-demographic instruments are subject to cultural limitations and may only be applicable in the country in which they have been developed. In 2013, Jahn et al. published a first social formula for Germany, which showed robust results for healthy controls (1). However, the usefulness of this scale has not been investigated in patients with epilepsy.

MATERIALS AND METHODS

Participants

The study included forty adult patients with medically refractory epilepsy who completed a comprehensive neuropsychological assessment, including a nine scale short form of the German version of the WAIS-III (11) and the German socio-demographic estimation scale by Jahn et al. (1), during their routine presurgical diagnostic process.

As the socio-demographic estimation scale tends to represent the premorbid global cognitive functioning within the normal range and uses mainly educational items, we examined a subsample of 19 patients, who fulfilled the following two criteria: first, global cognitive functioning scores of the WAIS-III short form were within 1 SD of the distribution (IQ score = $85 \leq X \geq 115$) and, second, the onset of epilepsy occurred after completion of the patients' formal education (including academic and vocational training). Please see **Table 1** for demographic and seizure characteristics.

TABLE 1 | Demographic and epilepsy characteristics.

	Whole sample $n = 40$ Mean(SD)/%/[range]	Sub sample (IQ 85–115) $n = 19$ Mean(SD)/%/[range]
Age	35 (11.76) [17–65]	38.79 (10.87) [23–65]
Gender: female	47.5%	36.8%
Years of education	10.8 (1.7)	10.9 (1.6)
Duration of epilepsy (years)	10.37 (8.36)	6.47 (6.87)
Age at seizure onset	25.08 (13.98)	32.37 (11.21)
Type of epilepsy		
Temporal lobe epilepsy left/right	35%/30%	42.1%/31.6%
Frontal lobe epilepsy	15%	10.5%
Parieto-occipital	7.5%	–
Multifocal	2.5%	–
Generalized	5%	5.3%
Unknown	5%	10.5%
Seizure frequency per month	7.8 (18.75)	3.97 (7.21)
Seizure type		
Focal, not bilateral tonic–clonic	47.5%	36.8%
Focal to bilateral tonic–clonic	47.5%	57.9%
Generalized	5%	5.3%
Number of antiepileptic drug (AED)		
1	40%	52.6%
2	52.5%	47.4%
3	7.5%	–
AED (number of patients taking the AED)	Carbamazepin (6), lacosamid (9), lamotrigin (15), levetiracetam (17), oxcarbazepin (5), perampanel (1), topiramat (4), valproat (5), zonisamid (2)	Carbamazepin (3), lacosamid (3), lamotrigin (6), levetiracetam (9), oxcarbazepin (2), topiramat (1), valproat (3)

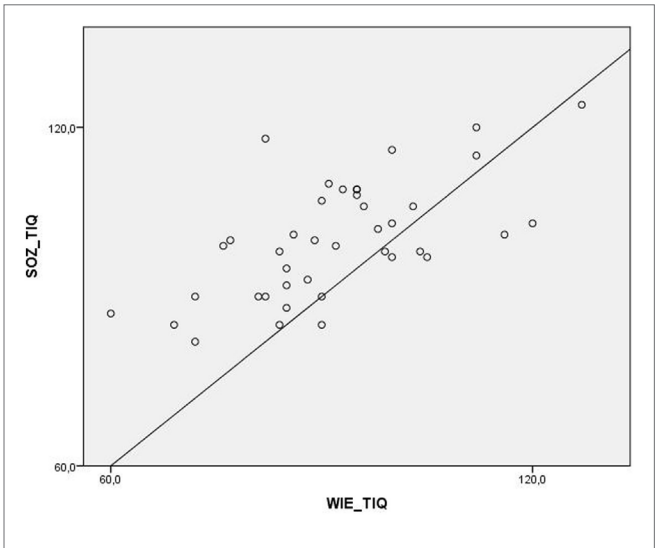

FIGURE 1 | Distribution of the total scores of the WAIS-IV and the socio-demographic estimation scale.

Measures

The measures evaluated for this study were the total IQ score of the eleven item socio-demographic estimation scale by Jahn et al. (1) (see also Supplementary Material: gender, birth order, highest level of secondary education, grade point average, highest vocational title, private Internet use, preferred newspapers/magazines, preferred type of literature, population of city of residence, duration of formal instruction in a musical instrument) and the

TABLE 2 | Means and classification accuracy of the WAIS-IV and the socio-demographic estimation scale.

	Wechsler Adult Intelligence Scale (WAIS)-III M (SD)	Social scale M (SD)	*P*	Mean difference	Within 5 points WAIS (%)	Within 7.5 points WAIS (%)
$n = 40$	92.0 (14.0)	100.13 (10.4)	<0.001	8.13	30	37.5
$n = 19$	96.21 (7.67)	101.79 (8.32)	<0.001	5.58	42.1	52.6

total score of the nine scale short form of the German version of the WAIS-III (vocabulary, similarities, arithmetic, digit span, picture completion, block design, matrix reasoning, digit symbol coding, symbol search).

Analysis

Statistical analyses were calculated using SPSS (IBM® SPSS® Statistics Version 23). The mean scores of the WAIS-III short form and the socio-demographic estimation scale were compared using dependent sample *t*-tests. Pearson correlations were determined and used as an overall measure of agreement between the two instruments. We also analyzed the relation between the difference of the two instruments and the epilepsy duration using Pearson correlations for the whole group and the subsample. Percent agreement was defined as the percentage of participants with ±5 and ±7.5 IQ score points between the WAIS-III short form and the estimation scale. The five-point criterion represented a stricter criterion and was used by, for example, Jahn et al. (1), and Spinks et al. (8), while the 7.5 criterion was applied by Jahn et al. as a more liberal criterion due to the reliability of the WAIS.

RESULTS

The mean socio-demographic estimation score was significantly higher than the mean WAIS-III short form score (**Figure 1**).

Both global cognitive functioning scores correlated significantly. The Pearson correlation was $r = 0.64$ ($p < 0.001$) in the whole group. The correlation was slightly lower, but still significant in the subsample ($r = 0.46$, $p < 0.05$).

There was a low correlation between the epilepsy duration ($r = 0.33$, $p < 0.05$) and the difference between the two measures in the whole sample and no significant correlation ($r = -0.20$, $p = 0.39$) in the subsample.

When applying the stricter criterion of an interval of ±5 IQ score points difference, agreement between the two measures was 30% in the whole sample and 42% in the subsample (IQ 85–115). When applying the more lenient criterion of a 7.5 IQ score point difference, agreement rose to 37.5% in the whole sample and 52.6% in the subsample (**Table 2**).

DISCUSSION

This study retrospectively assessed the usefulness of the socio-demographic estimation scale by Jahn et al. (1) for the estimation of global cognitive functioning as measured by a short form of the German version of the WAIS-III in the evaluation of epilepsy patients. While previous reports found no significant differences between the two scores in samples of healthy participants (1, 12), means of the demographic score significantly overestimated the WAIS-III scores in our epilepsy patient sample. The strength of the relationship between these two measures was moderate. These results are in line with the findings of previous studies in other patient populations (9). This overestimation might represent the difference between the premorbid level of global cognitive functioning as estimated by the socio-demographic estimation score and the current level at the time of assessment and might be due to the disorder itself or antiepileptic medication (13). However, classification accuracy in the subsample who had completed their formal education before epilepsy onset was similar to the 36.6% (±5 points) and 51.8% (±7.5 points) reported in healthy subjects (1). The shorter duration of epilepsy in these patients might contribute to this finding. This hypothesis is further supported by a weak correlation between epilepsy duration and discrepancy between the estimation scale and the WAIS-III in the whole group. The higher discrepancy between the two test results in patients with a longer duration of epilepsy might, however, also be influenced by the fact that patients with an early onset of epilepsy more often have severe epilepsy syndromes and an IQ below normal range. Accordingly, we did not find a significant correlation between epilepsy duration and discrepancy between the estimation scale and the WAIS-III in our subsample with an IQ within 1 SD of the mean. This finding and the lower estimation accuracy in the overall sample, which is in line with earlier studies (14), demonstrate the limitations of the estimation scale, which requires a minimum IQ score of 80 and is mainly based on the education level. The usefulness of the socio-demographic estimation scale is therefore limited in epilepsy patients in general due to the high proportion of patients who do not fulfill these criteria (15).

Future studies should ideally include a larger patient sample with different subsamples and make use of the full version of the WAIS instead of a nine scale short form. Since Jahn et al. (1) originally developed their scale in reference to WAIS-II, but provided proxy scores to the WAIS-III, future studies should reflect the recent developments and test revisions and thus employ the German version of the WAIS-IV.

CONCLUSION

The socio-demographic scale developed by Jahn et al. (1) overestimates global cognitive functioning in patients with epilepsy and only shows similar accuracy to results in healthy subjects in a subgroup of patients with normal global cognitive functioning up to 1 SD below the mean and who have finished their formal education before epilepsy onset. Therefore, the use of the estimation scale is limited in the population of epilepsy patients. Especially in the context of neuropsychological presurgical evaluations a detailed evaluation of the patient's level of global

cognitive functioning is highly recommended to ensure optimal presurgical evaluation results.

ETHICS STATEMENT

This retrospective study included clinically acquired data. Data were extracted from patient files of patients who had completed a complete pre-surgical neuropsychological evaluation. They were analyzed retrospectively in accordance with patient confidentiality guidelines.

AUTHOR CONTRIBUTIONS

IG: acquisition, analysis, interpretation of the data; drafting the work, final approval, and agreement to the work. KK: acquisition, interpretation of the data; revising the work, final approval, and agreement to the work. AA and SS: acquisition of the data; revising the work, final approval, and agreement to the work. LM, AS, and FR: conception of the work; revising the work, final approval, and agreement to the work. AH: conception of the work; acquisition of the data; revising the work, final approval, and agreement to the work. SK and KM: conception and design of the work; revising the work, final approval, and agreement to the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fneur.2018.00085/full#supplementary-material.

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Juvenile Myoclonic Epilepsy Shows Potential Structural White Matter Abnormalities: A TBSS Study

Martin Domin[1†], Sabine Bartels[2†], Julia Geithner[3], Zhong I. Wang[4], Uwe Runge[2], Matthias Grothe[2], Soenke Langner[5] and Felix von Podewils[2]*

[1] Functional Imaging Unit, Department of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany, [2] Department of Neurology, Epilepsy Center, University Medicine Greifswald, Greifswald, Germany, [3] Epilepsy Center Berlin-Brandenburg, Ev. Krankenhaus Königin Elisabeth Herzberge, Berlin, Germany, [4] Epilepsy Center, Neurological Institute, Cleveland Clinic Foundation, Cleveland, OH, United States, [5] Diagnostic and Interventional Neuroradiology, University Medicine Rostock, Rostock, Germany

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Fernando Cendes, Universidade Estadual de Campinas, Brazil

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***Correspondence:**
Matthias Grothe
matthias.grothe@uni-greifswald.de

† These authors have contributed equally to this work.

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Background: Several studies on patients with juvenile myoclonic epilepsy (JME) showed widespread white matter (WM) abnormalities in the brain. The aim of this study was to investigate potential structural abnormalities in JME patients (1) compared to healthy controls, (2) among JME subgroups with or without photoparoxysmal responses (PPR), and (3) in correlation with clinical variables.

Methods: A selection of 31 patients with JME (12 PPR positive) and 27 age and gender matched healthy controls (HC) were studied at a tertiary epilepsy center. Fractional anisotropy (FA) was calculated and intergroup differences analyzed using Tract Based Spatial Statistics (TBSS).

Results: Compared to HC the JME group showed reduced FA widespread and bilateral in the longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, anterior and posterior thalamic radiation, corona radiata, corpus callosum, cingulate gyrus and external capsule ($p < 0.01$). Subgroup analysis revealed no significant differences of WM alterations between PPR positive and negative patients and with clinical and epilepsy-related factors.

Conclusions: Widespread microstructural abnormalities among patients with JME have been identified.Prior findings of frontal and thalamofrontal microstructural abnormalities have been confirmed. Additionally, microstructural abnormalities were found in widespread extra-frontal regions that may help to validate pathophysiological concepts of JME.

Keywords: juvenile myoclonic epilepsy, photoparoxysmal responses, microstructural abnormalities, tract-based spatial statistics, network dysfunction

INTRODUCTION

Juvenile myoclonic epilepsy (JME, Janz syndrome) is a genetic generalized epilepsy (GGE) syndrome with a prevalence of 5–11% among all epilepsies (1, 2). The occurrence of bilateral myoclonic seizures (BMS) is mandatory for the diagnosis of JME, often combined with absence seizures (ABS) and/or generalized tonic-clonic seizures (GTCS) (1). The interictal

electroencephalography (EEG) characteristically shows generalized spikes and poly-spike waves ≥3 Hz (1, 3). About 30% of patients with JME show photoparoxysmal responses (PPR), defined as the occurrence of spikes, poly-spike-waves or repetitive spikes in the EEG in response to intermittent photic stimulation (PS) (4, 5).

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging (MRI) based structural imaging modality, that enables the depiction and quantification of white matter (WM) fiber tracts of the brain *in vivo*. Important DTI parameters are fractional anisotropy (FA) and mean diffusivity (MD) (6, 7). Compared to region-based approaches tract-based spatial statistics (TBSS) is a relatively new modality using whole brain DTI to generate a pseudo-anatomical "skeleton" of WM tracts on the basis of FA images (3, 8, 9).

Prior studies among patients with JME using DTI consistently found thalamocortical and cortico-cortical network abnormalities (2, 9–12). Furthermore, microstructural alterations in the genu of the internal capsule, the ascending reticular activating system (ARAS), and the ventromedial thalamus (VMT) were reported in the subgroup of PPR positive JME patients (2). A very recent TBSS study showed altered WM connectivity in the left corpus callosum (CC), thalamic radiation, superior longitudinal fasciculus (SLF), and corticospinal tract (CST), presuming an association with frontal cognitive and motor dysfunction in JME patients (13).

The aim of this study was to identify microstructural abnormalities in JME compared to healthy controls and between the subgroups of PPR positive (pPPR) and negative (nPPR) JME patients using TBSS. Furthermore, our aim was to determine potential associations between certain structural abnormalities and clinical features typical for JME.

MATERIALS AND METHODS

Patients

This study was approved by the local Institutional Review Board of the University Medicine Greifswald and conducted at a tertiary care epilepsy center (total population of the catchment area ≈500,000). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Thirty-one patients with JME and 28 healthy controls (HC) were prospectively recruited from the inpatient and outpatient clinic.

Abbreviations: ACR, anterior corona radiata; ARAS, ascending reticular activating system; ATR, anterior thalamic radiation; BMS, bilateral myoclonic seizures; CC, corpus callosum; CG, cingulate gyrus; CST, corticospinal tract; DTI, diffusion tensor imaging; EEG, electroencephalography; FA, fractional anisotropy; FMa, Forceps major; FMi, Forceps minor; GGE, genetic generalized epilepsy; GTCS, generalized tonic-clonic seizures; HC, healthy controls; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; JME, juvenile myoclonic epilepsy; MD, mean diffusivity; MRI, magnetic resonance imaging; nPPR, PPR negative; PCR, posterior corona radiata; pPPR, PPR positive; PPR, photoparoxysmal responses; PS, photic stimulation; PTR, posterior thalamic radiation; ROI, region of interest; SCR, superior corona radiata; SD, standard deviation; SLF, superior longitudinal fasciculus; SMA, supplementary motor area; TBSS, tract based spatial statistics; VMT, ventromedial thalamus; WM, white matter.

Inclusion criteria were as follows: (1) diagnosis of JME, (2) normal neurological examination and overall intelligence, (3) at least one abnormal routine EEG showing generalized spikes and/or poly-spike-waves. Cases with a history of epilepsy syndromes other than JME and severe brain trauma were excluded. Healthy controls had a normal clinical MRI and routine EEG examinations, no history of neurological disease and brain trauma, and no family history of epilepsy. Diagnosis of JME was made on the basis of the patients' medical history and EEG. Patients were considered as PPR positive (pPPR) if epileptiform discharges only occurred in response to intermittent PS; PPRs were classified according to classification scheme by Waltz et al.(14) Clinical data were collected by reviewing the medical records and during an interview.

Data Acquisition

MRI was conducted with a 3-Tesla MRI-Scanner (Verio, Siemens, Erlangen, Germany) using a 32-channel head coil. We applied a Siemens MDDW (Multi Directional Diffusion Weighting) sequence with the following parameter setup: voxel size isotropic 1.8 mm^3, matrix size 128 × 128 voxel, 80 slices, 1 acquisition and 64 directions. TR was 15,300 ms, TE: 107 ms and the total scan time was 17 min.

Preprocessing

The measured raw DICOM data was converted into NIFTI format using *dcm2nii*, which is part of the neuroimaging tool MRIcron. The tool *eddy_correct*, part of FSL, Smith et al. (15) was used to correct the diffusion-weighted data with respect to subject motion and deformations introduced by eddy current artifacts of the MRI scanner. Fractional anisotropy (FA) images were created by fitting a tensor model to the raw diffusion data using FSL DTI-FIT.

Tract-Based Spatial Statistics (TBSS)

Preparation for voxelwise statistical analysis of the FA data was carried out using the TBSS approach of FSL [Tract-Based Spatial Statistics, (8)]. We chose to replace the FLIRT/FNIRT registration of FSL with the tensor-based registration approach of DTI-TK (16), as Bach and colleagues (17) were showing this to be preferable over the default FSL approach. Here, the registration is based on the whole tensor matrix in each voxel, whereas the FSL mechanism utilizes the scalar FA values only. We followed the procedure and the manual provided by Zhang and colleagues (http://dti-tk.sourceforge.net/), where a first, crude group-wise template is created, which is iteratively refined by using affine and non-linear registrations, incorporating the tensor matrices instead of FA values. This process included the calculation of subject-specific non-linear transformations into a common template space (IIT; Illinois Institute of Technology) and a subsequent normalization of the individual FA images. These were then combined and thinned using a projection technique to create an average FA skeleton consisting of locally maximal FA values. Finally, each subject's aligned FA data was projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics.

Because of the spatial differences of the IIT template and the MNI-ICBM 152 nonlinear 6th generation, even if they are supposed to be in the same MNI template space, a non-linear registration between these two templates had to be calculated, as most atlases or regions-of-interest reside in the MNI-ICBM 152 space.

Statistics

FSL's tool for nonparametric permutation inference on neuroimaging data, *randomize* (18), was used to carry out the voxel-wise cross-subject statistics. This approach belongs to the permutation or randomization methods, which are used when the null distribution of the data is not known. This can be the case, if e.g., the noise of the data does not follow a simple distribution, as can be found in MRI data that contains noise following a Rician distribution. Voxel-wise statistics were corrected for multiple comparisons using the Family-wise-error approach (FWE) and, if necessary, contrast-specific p-values were corrected for the number of contrasts per test. Permutation-based testing included t-tests for group comparisons as well as for correlations with clinical data, which is permutationally equivalent to a partial correlation. We used 50,000 permutations (FSL default = 5,000) per test, as this number significantly reduces uncertainties of the p-values. Threshold-free cluster enhancement (TFCE) was used to enhance cluster-like structures without the need of preset clustering thresholds (TBSS-specific randomize parameter –T2).

At last, the FSL tool atlasquery automatically compared statistically significant voxels with common white matter atlases provided by Mori and colleagues (ICBM-DTI-81 white-matter labels atlas, JHU white-matter tractography atlas), which are part of the FSL software package (19).

RESULTS

Relevant clinical data of all patients and HC included in the study are given in **Table 1**. Thirty-one patients with JME (23 female) were enrolled (mean age 31.7 years; SD ± 10.95, range 18–62); mean age at epilepsy onset was 15.9 years (SD ± 6.4, range 2–36) and mean duration of epilepsy 15 years (SD ± 9.9, range 2–41). Twelve (38.7%) were pPPR [each classified as PPR type III or IV according to Waltz et al. (14)]. Seizure-free rate was 39% (n = 12), all of these patients were treated with AED (see **Table 1**).

JME vs. Healthy Controls

Several significant microstructural abnormalities among patients with JME compared to HC have been found (**Table 2**; Table S3 for cluster-related statistical information; **Figure 1**). Analysis of regional maxima revealed most significant FA reduction in the following bilateral regions: (1) superior and inferior longitudinal fasciculus (SLF/ILF), inferior fronto-occipital fasciculus (IFOF), anterior and posterior thalamic radiation (ATR/PTR), anterior, superior, and posterior corona radiata (ACR/SCR/PCR), body and splenium of corpus callosum (CC), cingulate gyrus (CG), hippocampus, corticospinal tract (CST), Forceps major (FMa) and minor (FMi), uncinate fasciculus and external capsule ($p < 0.01$). Considering a conservative threshold of $p < 0.01$ significant results were also found only on the right side in the anterior and posterior limb of internal capsule.

Photoparoxysmal Responses: pPPR vs. nPPR

Inter-group comparison between pPPR and nPPR JME revealed no significant FA differences. See Tables S4–S7 for raw uncorrected statistical results.

Correlation With Epilepsy Duration

No significant correlation was found between FA and duration of epilepsy (corrected for age and sex; **Table 1**). see Tables S8, S9 for raw uncorrected statistical results.

DISCUSSION

The aim of this study was to identify potential structural WM abnormalities in JME compared to HC and in between the two JME subgroups of pPPR and nPPR cases using TBSS. We additionally investigated clinical and epilepsy-related factors for an association with WM alterations. This TBSS analysis identified widespread FA reductions among patients with JME.

A very recent TBSS study among JME patients found microstructural abnormalities in the CC, thalamic radiation, SLF, and CST (13). This is consistent with both several of our findings in JME and prior findings among GGE patients in general (2, 9, 11) and underlines the reproducibility in identifying abnormal diffusion metrics in GGE patients using TBSS. Compared to HC our study reveals significant FA reductions in patients with JME bilateral in the previously described WM regions (SLF, thalamic radiation, CC, and CST), as well as the IFOF, FMa, FMi, CG, hippocampus, and—in addition to previously described regions—bilateral in the corona radiata.

TABLE 1 | Clinical data of all patients and controls included in the study.

	Patients	Controls
N =	31	28
Female (%)	23 (74%)	15 (54%)
Age: mean (range); SD	31.7 years (18–62); ± 10.9	27 years (19–34); ± 4.6
EO: mean (range); SD	15.9 years (2–36); ± 6.4	
ED: mean (range); SD	15 years (2–41); ± 9.9	
Seizure type: only BMS	4 (13%)	
+ GTCS	10 (32%)	
+ ABS	3 (10%)	
+ ABS + GTCS	12 (39%)	
unknown	2 (7%)	
PPR	12 (39%)	
SF [with/without AED]	12 (39%) [12/0]	
NSF [with/without AED]	19 (61%) [16/3]	

ABS, absence seizures; AED, antiepileptic drug; BMS, bilateral myoclonic seizures; ED, epilepsy duration; EO, epilepsy onset; GTCS, generalized tonic-clonic seizures; NSF, non seizure-free; PPR, photoparoxysmal response; SD, standard deviation; SF, seizure-free.

TABLE 2 | TBSS results–JME vs. healthy controls.

JHU_White-Matter_Tractography_Atlas	Average probability	Significance
Anterior thalamic radiation L	1.11	0.01
Anterior thalamic radiation R	0.87	0.01
Cingulum (cingulate gyrus) L	0.20	0.01
Cingulum (cingulate gyrus) R	0.13	0.01
Cingulum (hippocampus) L	0.02	0.01
Cingulum (hippocampus) R	0.01	0.01
Corticospinal tract L	0.78	0.01
Corticospinal tract R	0.96	0.01
Forceps major	0.38	0.01
Forceps minor	2.54	0.01
Inferior fronto-occipital fasciculus L	1.42	0.01
Inferior fronto-occipital fasciculus R	1.11	0.01
Inferior longitudinal fasciculus L	1.06	0.01
Inferior longitudinal fasciculus R	0.73	0.01
Superior longitudinal fasciculus (temporal part) L	0.98	0.01
Superior longitudinal fasciculus (temporal part) R	0.69	0.01
Superior longitudinal fasciculus L	2.35	0.01
Superior longitudinal fasciculus R	2.31	0.01
Uncinate fasciculus L	0.50	0.01
Uncinate fasciculus R	0.28	0.01
JHU_ICBM-DTI-81_White-Matter_Labels	**Overlap percentage**	**Significance**
Body of corpus callosum	4.29	0.01
Splenium of corpus callosum	0.08	0.01
Anterior limb of internal capsule R	0.11	0.01
Posterior limb of internal capsule R	0.02	0.01
Anterior corona radiata R	1.67	0.01
Anterior corona radiata L	2.03	0.01
Superior corona radiata R	3.33	0.01
Superior corona radiata L	0.21	0.01
Posterior corona radiata R	1.18	0.01
Posterior corona radiata L	0.31	0.01
Posterior thalamic radiation (include optic radiation) R	0.27	0.01
Posterior thalamic radiation (include optic radiation) L	0.01	0.01
External capsule R	0.06	0.01
External capsule L	0.03	0.01
Superior longitudinal fasciculus R	6.91	0.01
Superior longitudinal fasciculus L	5.66	0.01

L, left hemisphere; R, right hemisphere.

FA decrease reflects an impaired microstructural integrity likely reflecting reduced myelination of WM tracts, which was found to play a pivotal role in the pathophysiology of generalized epilepsies (2, 9, 11, 12). In addition to alterations of the thalamo-cortical network and the CC among JME patients, histopathological findings of "microdygenesis" predominantly in the frontal lobe, including the frontal CC, support the hypothesis of a parent pathophysiological role of thalamo-frontal as well as inter-frontal networks in generalized epilepsies and challenge the existing hypotheses of the thalamus as a key structure in generalized epilepsies.

In the past, the focus of region of interest (ROI) seed-based approaches was mainly on frontal areas and the thalamus (11, 20). More recent studies using whole brain approaches (TBSS) found network alterations also beyond the frontal lobes, including more posterior regions and particularly the precuneus (9, 21, 22), which is known to play a role as a part of the functional "default mode" network, in cognitive functions (23), and in generalized spike-wave discharges in GGE (22, 24, 25). Strong interconnections between the precuneus and both, parieto-occipital primary-visual and frontal areas are known (26, 27). Our TBSS findings indicate an involvement of large parts of the WM, predominantly comprising structures of the bilateral longitudinal fasciculus (SLF), the cortico-thalamic (corona radiata), and cortico-spinal (CST) connections, which are known to be linked with the precuneus. Conclusively, in addition to the previously described relation of widespread microstructural abnormalities and cognitive and personality characteristics in JME patients (28), our findings may lead to the hypothesis that the precuneus is part a widespread network and thereby involved in both cognitive characteristics and generalized spike-wave discharges in JME patients.

The CST contains motor fibers predominantly originating in the motor cortex targeting spinal alpha motor neurons, and the corona radiata (anterior/superior part) those between the thalamus and premotor cortex, including the supplementary motor area (SMA) (29). BMS and GTCS are predominantly characterized by motor symptoms. Therefore, it can be postulated that microstructural alterations of cortico-spinal and thalamo-frontal connections are an essential component of the propagation network of generalized seizures as previously suggested (2, 3, 9, 12, 13) and may even reflect an increased epileptogenicity with a lower threshold to generate generalized seizures, notably those with predominant motor symptoms. Taken together, an epileptogenic network involving cortico-cortical, thalamo-cortical, and cortico-spinal connections in patients with JME can be assumed. Different components of this network may be of special significance for certain clinical characteristics of JME, such as circadian rhythm of seizures (thalamus) and seizures with predominantly motor symptoms (frontal cortex, thalamo-frontal connections, CST, ACR/SCR, internal capsule). It can be hypothesized that the extent of microstructural abnormalities within this network may determine the clinical subtype of JME in the individual patient, however, this was not examined by our study protocol and should be a goal for future studies.

Photoparoxysmal Responses (PPR)

Photosensitive JME is considered to be a subtype of JME with a higher seizure risk (30). Additionally, increased FA has been shown in a cohort of pPPR JME patients in the ARAS and the VMT (2). Both ARAS and thalamus are known to be crucial in the circadian rhythm regulation (31), which may trigger the generation of seizures and may also be one

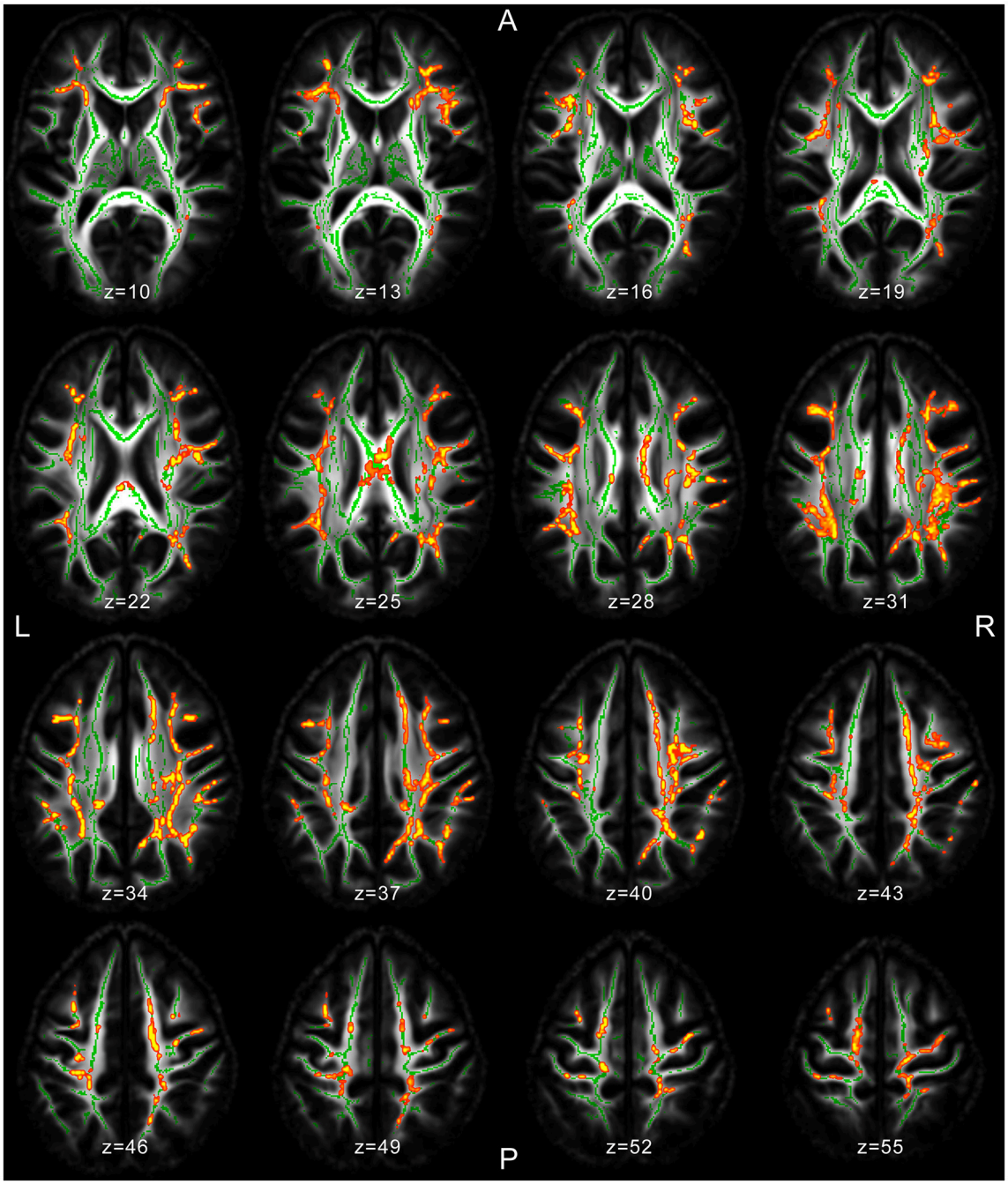

FIGURE 1 | MRI images of significant TBSS clusters in patients with JME compared to healthy controls superimposed to the skeleton (light green).

explanation for the association of seizures with awakening (2). Furthermore, networks involving retinal ganglion cells, ARAS, lateral geniculate nucleus, and the primary-visual cortex were shown to be essential in the epileptologenesis of JME and may also explain the association with awakening (2). Nevertheless, albeit microstructural WM abnormalities were found in the total JME group, our study revealed no significant differences between those who were pPPR and nPPR (see Tables S4–S7 for raw uncorrected statistical results).

Several limitations of our study need to be considered. Due to the relatively small group of 31 patients the possibility of Type-2 statistical errors should be considered. Nevertheless, the single-center approach ensures a consistent syndrome characterization of the included patients and increases the internal validity of

the data. Additionally, although JME is considered an easy-to-treat epilepsy syndrome, only 39% ($n = 12$) of our patients were seizure-free. Assuming favorable outcome as a reason for renunciation from our epilepsy center, a potential selection toward more intractable patients has to be considered.

Despite the above limitations, our results amend the knowledge on WM abnormalities in JME. Microstructural variations of JME patients support the hypothesis that JME is a network dysfunction involving both widespread cortical and subcortical (thalamus, thalamo-cortical connections) structures. Within this network the precuneus may play a pivotal role in the connection of cortico-cortical (fronto-occipital) and cortico-subcortical (thalamus) structures. Compared to whole brain approaches region-based approaches may not be sufficient to identify the spatial extent of microstructural WM abnormalities in JME. Taken together, our findings may help to generate hypotheses about structural and network connectivity and contribute to better understand the pathophysiology and epileptic networks in JME.

DISCLOSURE

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ETHICS STATEMENT

We confirm that we have read the Frontiers in Neurology position on ethics and procedures and confirm that this report is consistent with these guidelines.

AUTHOR CONTRIBUTIONS

MD, FvP, and UR generated the research idea, study design, and concept. SB, FvP, JG, and MG acquired and analyzed the data and drafted the work. MD and SL analyzed the data. All authors made critical revisions for important intellectual content and interpreted the data. MD, FvP, and SB wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00509/full#supplementary-material

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Structural Covariance Network of Cortical Gyrification in Benign Childhood Epilepsy with Centrotemporal Spikes

Lin Jiang[1,2†], Tijiang Zhang[3†], Fajin Lv[1], Shiguang Li[2], Heng Liu[3], Zhiwei Zhang[1] and Tianyou Luo[1]*

[1] Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2] Department of Radiology, The Third Affiliated Hospital of Zunyi Medical College, Zunyi, China, [3] Department of Radiology, Affiliated Hospital of Zunyi Medical College, Medical Imaging Center of Guizhou Province, Zunyi, China

Benign childhood epilepsy with centrotemporal spikes (BECTS) is associated with cognitive and language problems. According to recent studies, disruptions in brain structure and function in children with BECTS are beyond a Rolandic focus, suggesting atypical cortical development. However, previous studies utilizing surface-based metrics (e.g., cortical gyrification) and their structural covariance networks at high resolution in children with BECTS are limited. Twenty-six children with BECTS (15 males/11 females; 10.35 ± 2.91 years) and 26 demographically matched controls (15 males/11 females; 11.35 ± 2.51 years) were included in this study and subjected to high-resolution structural brain MRI scans. The gyrification index was calculated, and structural brain networks were reconstructed based on the covariance of the cortical folding. In the BECTS group, significantly increased gyrification was observed in the bilateral Sylvain fissures and the left pars triangularis, temporal, rostral middle frontal, lateral orbitofrontal, and supramarginal areas (cluster-corrected $p < 0.05$). Global brain network measures were not significantly different between the groups; however, the nodal alterations were most pronounced in the insular, frontal, temporal, and occipital lobes (FDR corrected, $p < 0.05$). In children with BECTS, brain hubs increased in number and tended to shift to sensorimotor and temporal areas. Furthermore, we observed significantly positive relationships between the gyrification index and age (vertex $p < 0.001$, cluster-level correction) as well as duration of epilepsy (vertex $p < 0.001$, cluster-level correction). Our results suggest that BECTS may be a condition that features abnormal over-folding of the Sylvian fissures and uncoordinated development of structural wiring, disrupted nodal profiles of centrality, and shifted hub distribution, which potentially represents a neuroanatomical hallmark of BECTS in the developing brain.

Keywords: Rolandic epilepsy, MRI, cortical development, connectome, hub

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***Correspondence:**
Tianyou Luo
ltychy@sina.com

†These authors have contributed equally to this work.

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INTRODUCTION

Benign childhood epilepsy with centrotemporal spikes (BECTS) is one of the most common types of epilepsy occurring between the age of 3–13 years, typically characterized by a total of 2–10 infrequent seizures, resolution by the age of 15–17 years (1), an excellent prognosis, and a "benign" nature. BECTS children frequently have language, cognitive, and somatosensory problems after reaching

adulthood (2). However, the neural basis for these problems is largely unclear.

Neuroimaging techniques have enabled improved characterization of the neural basis of BECTS. For example, morphometric studies revealed subtle anomalies in gray matter volume in the frontal, temporal, and left pars triangularis regions in BECTS children (3, 4). Diffusion-weighted studies have suggested the compromised microstructure of white matter in bilateral sensorimotor regions (5–7). Language task paradigms have also revealed atypical activation across different brain regions, particularly increased activation in the frontal, parietal and temporal areas (8–13). In addition, low-frequency fluctuations of spontaneous brain activity suggest abnormal local and global connections in BECTS patients (9, 14–24). Thus, children with BECTS present a wide distribution of alterations in the functional and structural organization within the brain.

Despite a number of existing neuroimaging studies, the etiology of BECTS remains elusive. BECTS is a unique age-dependent epilepsy with rare seizures, focal EEG abnormalities affecting the same well-delineated cortical region in most patients, and frequent mild to moderate cognitive dysfunctions. These problems, which are indicative of hemifacial seizures, as well as language and cognitive problems potentially stem from anomalous Sylvian fissure maturation. High-resolution structural imaging may facilitate exploration of the cortical landscape of BECTS. One recently validated algorithm, the local gyrification index, which detects subtle changes in the cortical landscape, permits the detection of atypical cortical folding in BECTS (25).

Recently, there have been increasing efforts to investigate the structural covariance of the coordinated cortical neuroanatomy (26–28). Such analysis will facilitate the qualification of anatomical relationships among cortical parcellations based on inter-areal covariation of different morphometric features, such as gray matter volume, cortical thickness, or even local gyrification. Although the biological significance of these association matrices remains vague, networks of gray matter covariance reflect patterns of coordinated structural maturation and disease propagation effects (28, 29). Based on associations between coordinated developmental changes in cortical networks and patterns of inter-areal covariations, children with BECTS likely exhibit differences in cortical folding (i.e., local gyrification) covariance, specifically reflecting the emergence of centrotemporal spikes during a critical period of brain development (i.e., from preschool to adolescence).

Therefore, in this study, we applied a graph theory analysis, the well-known connectome (30), of structural covariance based on the cortical gyrification index to characterize large-scale structural organization within the brain. This approach used graph theory to depict the human brain as a complex network comprising nodes (i.e., structural parcellations) and edges (i.e., structural covariance of the cortical gyrification) between the nodes. We investigated differences in cortical folding (i.e., local gyrification) and the covariance of the organization of networks of cortical folding patterns (i.e., local gyrification) between BECTS patients and their normally developing peer controls.

MATERIALS AND METHODS

Participants

We recruited 26 BECTS children (15 males/11 females; mean age ± SD: 10.35 ± 2.91 years) and 26 demographically matched healthy controls (15 males/11 females; mean age ± SD: 11.35 ± 2.51 years) (**Table 1**). The inclusion criteria for BECTS subjects were (a) BECTS with partial or secondarily generalized tonic–clonic seizures diagnosed by a board-certified pediatric neurologist based on International League Against Epilepsy criteria, excluding children with multiple seizure types; (b) EEG within the past year showing identifiable centrotemporal sharp waves/spikes and epileptiform activity activated by sleep; (c) 1–10 seizures within the past year; and (d) normal physical/neurological examinations. Exclusion criteria were (a) a history of serious medical or psychiatric disorder and (b) an imaging study suggesting a progressive structural central nervous system lesion. All subjects were right-handed. The mean duration of epilepsy from onset to time of scanning was 20.7 months (SD = 20, min = 4, and max = 84). At the time of inclusion in this study, EEG spike foci were left-sided in 14 patients, right-sided in five patients and bilateral in seven patients. This study was approved through the Medical Ethics Committee of the Affiliated Hospital of Zunyi Medical College, and written informed consent was obtained from all participants or their guardians after a complete description of the required measurements. Detailed demographic information and clinical measures are listed in **Table 1**.

Neurobehavioral Assessments

A comprehensive battery of standardized neuropsychological tests and MRI were performed on the same day for children with BECTS, including verbal and non-verbal intelligence, verbal–auditory memory, visual processing speed, visual–spatial attention, and cognitive flexibility and inhibition, to assess the cognitive abilities of each subject. The Wechsler Intelligence Scale for Children (WISC-IV) and its four subscales (31) were used.

MRI Acquisition

High-resolution structural MR images from all participants were collected using a GE 3.0-T (HDxt, GE Healthcare) scanner, stationed in the Department of the Radiology, the Affiliated Hospital of Zunyi Medical College, capturing T1-weighted 3D brain volume imaging (BRAVO)-sequence images (repetition time = 1,900 ms, echo times = 2.1 ms, inversion time = 900 ms,

TABLE 1 | Demographic details of the study cohorts.

Categories	BECTS (n = 26)	Controls (n = 26)	p Value
Sex (M/F)	15/11	15/11	>0.99
Age (years)	10.35 ± 2.91	11.35 ± 2.51	0.92
Education (years)	4.31 ± 2.77	5.65 ± 2.53	0.01
Handedness	26R	26R	>0.99
Duration (months)	Mean 38.81 (1–96)		–
IQ language	93.46 ± 14.73		–
IQ performance	85.77 ± 14.71		–
IQ over all	69.42 ± 9.52		–

flip angle = 9°, slice thickness = 1.00 mm, and matrix size = 256 × 256) yielding 160 axial slices with an in-plane resolution of 1.0 mm × 1.0 mm.

MRI Preprocessing

T1-weighted structural images were preprocessed using SPM12[1] and Computational Anatomy Toolbox (CAT)[2] based on MATLAB. Briefly, high-resolution structural images were first normalized to a customized child-sized brain template generated using the Template-O-Matic Toolbox[3] and subsequently segmented into gray matter, white matter, and cerebrospinal fluid. Using a projection-based thickness procedure, the cortical thickness was estimated, and central cortical surfaces for both hemispheres were created (32).

Calculation of Gyrification Parameters

The cortical thickness and central surfaces were employed as the basis to calculate gyrification index (33). We extracted the gyrification index based on absolute mean curvature, as described by Luders et al. (34). Briefly, cortical gyrification was established by calculating the mean curvature (35) across thousands of vertices on each individual central surface mesh model. The mean curvature maps (hereafter referred to as the gyrification index) were smoothed with a full width at a half maximum of 15 mm (36). The resulting smoothed cortical gyrification index was used for further statistical analyses and network construction.

Construction of a Structural Covariance Network

Graph analysis was performed using the Graph-Theoretical Analysis Toolbox (GAT) (37). We defined nodes using the Destrieux Atlas in FreeSurfer (38) with 148 cortical regions of interest (ROIs), and we defined edges by determining the inter-regional Pearson's correlation of cortical gyrification extracted from the individual gyrification surfaces in each group, with education included as covariates of nuisance.

We constructed a 148 × 148 association matrix M for each group with inter-regional Pearson's correlation coefficients (r_{ij}) between each pair of ROIs "i" and "j," then thresholded the r_{ij} into binary matrix A with values of 0 or 1, with thresholds setting across a range of network densities (D_{min}–D_{max}), where D_{min} (in this study, D_{min} = 0.11 and D_{max} = 0.45) means the lowest density that can make the networks fully connected (37). We computed both global and regional network measures across the density range of D_{min}–D_{max} (i.e., 0.11–0.45) at an interval 0.02. Then, by considering matrix A to be graph G, we defined the quantities N, K, D, i, j, and k as the total number of ROIs (i.e., 148), number of edges, percentage of surviving edges at a specific density threshold, and three randomly selected nodes, respectively. For a detailed description, see Ref. (37).

[1] www.fil.ion.ucl.ac.uk/spm.

[2] http://www.neuro.uni-jena.de/cat/.

[3] http://dbm.neuro.uni-jena.de/software/tom/.

Global Network Properties

We calculated global metrics including clustering, path length, small-worldness, and global efficiency. These measures are well characterized in the network analyses, and have been extensively described elsewhere (39, 40). Briefly, the small-worldness was defined as a combination of high clustering and short path length, i.e., the ratio of normalized clustering and normalized path length, defined as follows (41):

$$\text{Small-worldness } \sigma = \frac{C / C_{rand}}{L / L_{rand}},$$

where C denotes the clustering coefficient, L represents the characteristic path length, and C_{rand} and L_{rand} are the mean C and L of 20 random networks, and σ means the ratio of normalized clustering and normalized path length (i.e., small-worldness) (41). For the small-worldness index, we calculated the measures both at D_{min} (0.11) as well as across a range of densities (0.11–0.45) using the area under the curve (AUC). A network was considered small-world when the ratio σ at D_{min} was >1 (41).

Regional Network Properties and Hub Identification

We also computed regional centrality measures, including betweenness b_i, normalized degree k_i, and hubs' identification based on the b_i and k_i, then quantified the within- and between-group differences:

$$b_i = \sum_{m \neq i \neq n \in G} \frac{\sigma_{mn}(i)}{\sigma_{mn}},$$

$$k_i^B = \sum\nolimits_{j \in G} a_{ij} \text{ or}$$

$$k_i^W = \sum_{j \in G} W_{ij},$$

where b_i denotes the sum of the shortest paths that pass-through node i, k_i represents the number of edges between node i and other nodes, and b and k represent the mean betweenness and degree, respectively, of the entire network. Furthermore, b_i and k_i were used to identify the hubs of the network; nodes with regional values of at least 2 SDs greater than the mean value were recognized as hubs.

Statistics

For the cortical gyrification maps, we performed vertex-wise group inference on the smoothed cortical surfaces using general linear modeling implemented in CAT (40, 42), these including (1) vertex-wise gyrification differences between patients and controls, (2) correlations with neurobehavioral measures, and (3) correlations with chronological age (development). The results were corrected for multiple comparisons using a Monte Carlo simulation, with 10,000 iterations (family-wise error). For the topological measures, within- and between-group comparisons were done by using the GAT toolbox.

RESULTS

Table 1 shows the demographics for all subjects. There were no statistically significant differences between BECTS children and controls in relation to age ($p = 0.92$), gender ($p > 0.99$), and handedness ($p > 0.99$), although education showed significant differences between groups ($p = 0.01$) (**Table 1**).

Between-Group Analysis of Cortical Gyrification

The cortical gyrification analysis identified several clusters in bilateral cerebral cortices that were increased as the BECTS group compared with the controls (**Figure 1**; **Table 2**). These clusters included significantly increased gyrification in the bilateral Sylvain fissures, left pars triangularis, temporal, rostral middle frontal, lateral orbitofrontal, and supramarginal areas (**Figure 1**; **Table 2**). No significantly decreased clusters survived whole brain correction.

Within-Group Global Network Measures

The lowest network density that made the networks fully connected was at $D_{min} = 0.11$ in this study. To explore alterations in the network topology as a function of network density, we thresholded the constructed association matrices at the range of 0.11–0.45, with an interval of 0.02. Changes in the global measures as a function of network density are shown in **Figure 2**. The networks of both groups complied with a small-world organization, i.e., higher clustering than as well as short length path close to the random networks. That is, normalized clustering greater than 1 and a normalized path length close to 1. These metrics are thresholded both at the D_{min} (0.11), and across the predefined network densities interval (0.11–0.45).

Between-Group Differences in Global Network Measures

Differences across Network Densities

We examined the inter-group differences in the global metrics across the predefined network densities (0.11:0.02:0.45) (**Figure 2**). Both groups showed a small-world organization, i.e., a combination of higher clustering as well as short length path as mentioned earlier. Although the BECTS group showed a lower normalized clustering and a higher normalized path length, and a less optimal small-worldness, there were no significant inter-group differences ($p > 0.05$), suggesting a less optimized network architecture for children with BECTS.

AUC Analysis of Global Network Measures

In addition to contrasting the global measures at various densities, we compared their AUC (density range of 0.11:0.02:0.45) between the two groups. Similar to the case of different densities,

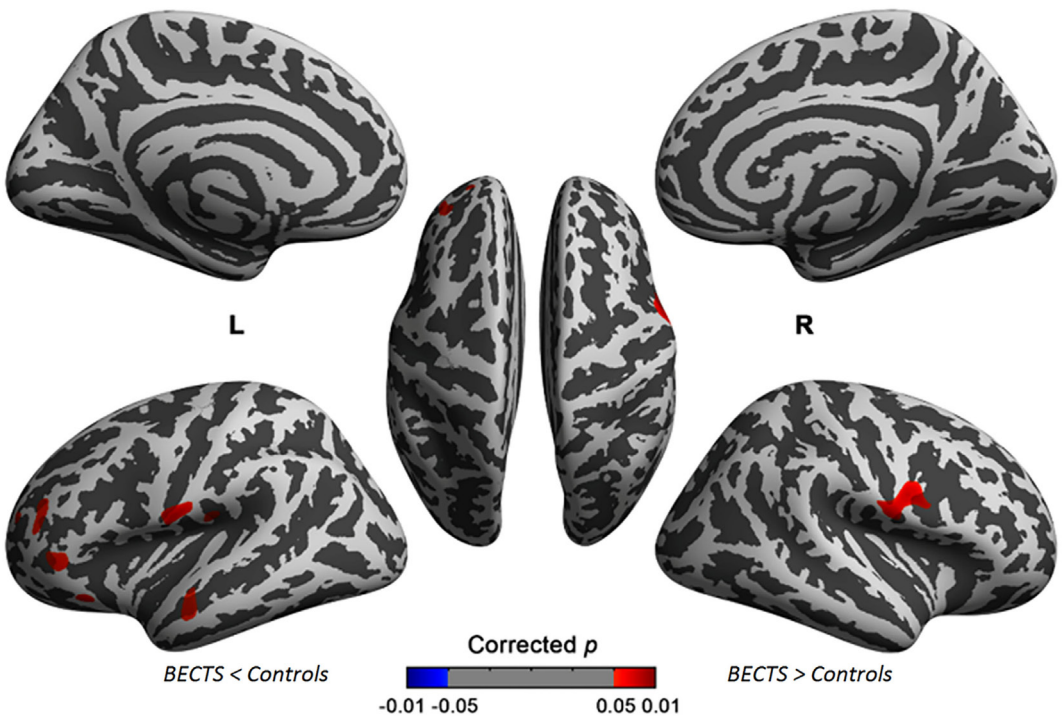

FIGURE 1 | Significant cortical gyrification clusters projected onto the inflated surfaces of the bilateral hemispheres. The significant clusters show increased gyrification in the BECTS group compared with their peer controls and surviving cluster correction ($p < 0.05$). Detailed information for these clusters is shown in **Table 2**.

the BECTS group did not exhibit a significantly different AUC for global network measures (p_gamma = 0.46, p_lambda = 0.20, p_sigma = 0.42, p_global efficiency = 0.23, p_mean local efficiency = 0.05, and p_mean node betweenness = 0.14) compared with the controls (**Figure 2**).

Between-Group Differences in Regional Network Measures

We also compared the regional metrics (at minimal network density range of 0.11) between the two groups (Figures S1A–C in Supplementary Material). Regions of normalized degree centrality, including the left middle occipital gyrus, left parahippocampal gyrus, and the inferior segment of the left circular sulcus of the insula, were significantly greater for the BECTS group, while the right middle frontal sulcus exhibited a significantly smaller degree centrality in the BECTS group (Figure S1A in Supplementary Material). Among regions of normalized nodal betweenness centrality, only the left triangular part of the inferior frontal gyrus and the inferior segment of the circular sulcus of the insula exhibited significantly greater betweenness in the BECTS group (Figure S1B in Supplementary Material). Among regions of normalized regional clustering, only the right transverse temporal sulcus exhibited significantly smaller clustering in the BECTS group (Figure S1C in Supplementary Material). All aforementioned regions survived following FDR correction ($p < 0.05$).

TABLE 2 | Results of group comparison of cortical gyrification between BECTS and controls groups.

Left patient > control			Right patient > control		
Surface area	**Vertex**	***p* Value**	**Surface area**	**Vertex**	***p* Value**
Sylvan fissure	539	0.00273*	Sylvan fissure	1,022	0.00273*
Par triangularis	263	0.00636*			
Temporal	254	0.00818*			
Rostralmiddle frontal	235	0.00818*			
Lateralorbito frontal	129	0.00636*			
Supramarginal	47	0.00909*			

*Based on Desikan-Killiany DK40 atlas.

AUC Analysis for Regional Measures

For the AUC of the regional network measure curves between the groups, the BECTS group showed increased normalized nodal clustering in the long insular gyrus and central sulcus of the left insula, similar to the identified differences across densities (**Figure 3**). The BECTS group also showed a greater normalized regional degree in several regions, including the right short insular gyri, left middle occipital gyrus, and left

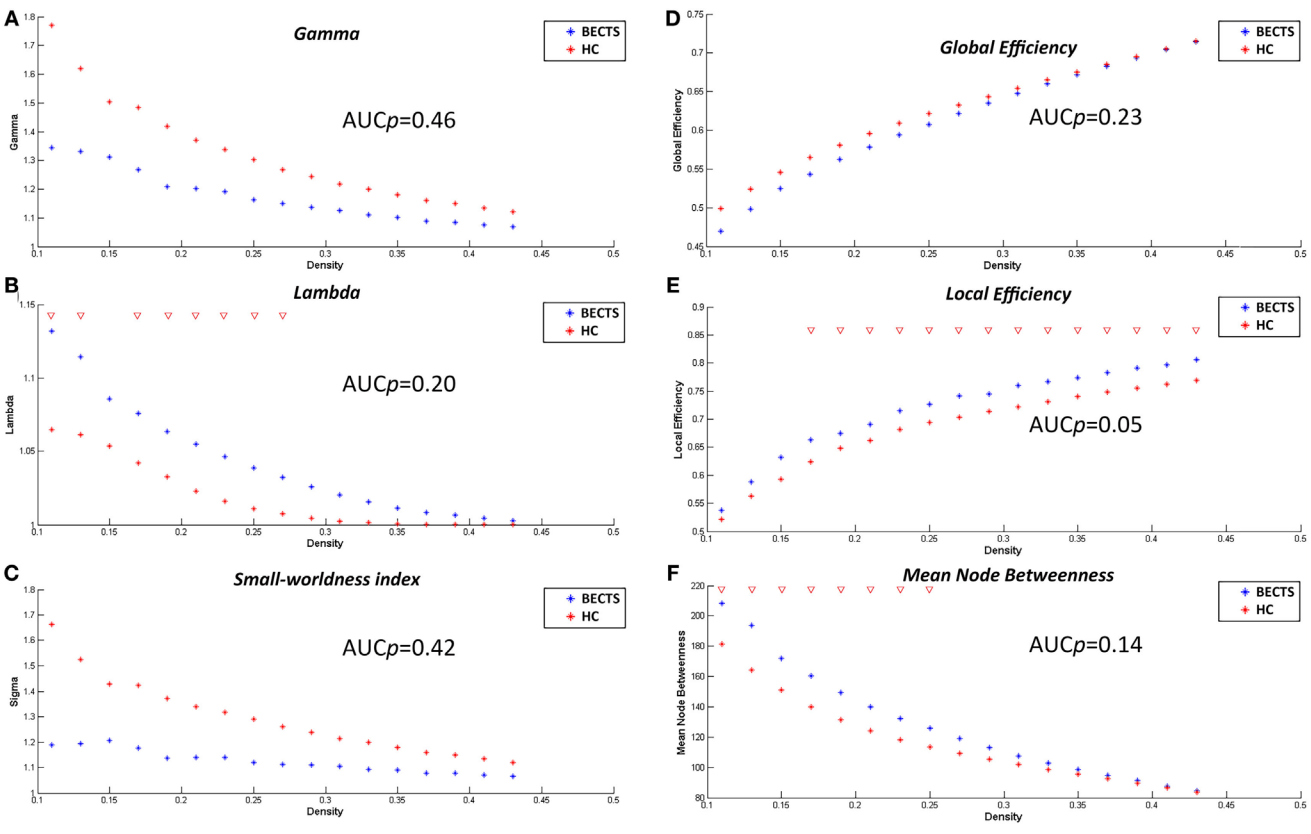

FIGURE 2 | Within-group global network measures, between-group differences in these measures across a range of network densities, and area under the curve (AUC) results. Normalized clustering **(A)**, normalized path length **(B)**, small-world index **(C)**, global efficiency **(D)**, local efficiency **(E)**, and mean node betweenness **(F)** of the BECTS and healthy control (HC) networks. The red inverted triangle indicates the difference between the two groups.

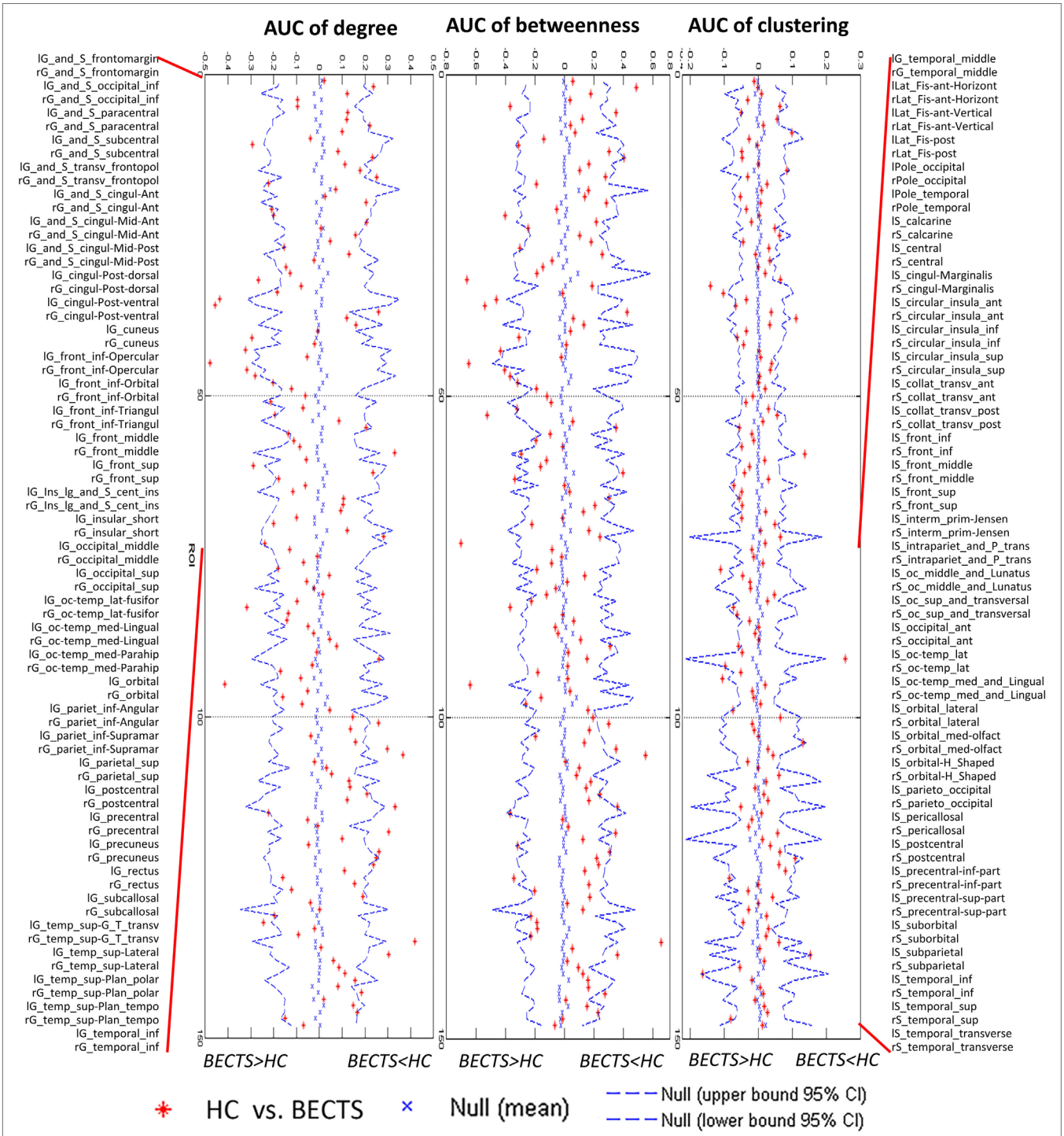

FIGURE 3 | Between-group differences of regional measures (normalized regional degree, betweenness, and clustering) across a range of network densities [i.e., area under the curve (AUC) results]. The red inverted triangle indicates the difference between the two groups. All regions survived following FDR correction ($p < 0.05$).

parahippocampal gyrus, and smaller degree centrality in the right middle frontal and left precentral sulcus (**Figure 3**). For normalized regional betweenness, the BECTS group showed greater betweenness centrality in the left inferior temporal gyrus and smaller betweenness centrality in the right middle frontal sulcus and inferior part of the left precentral sulcus (**Figure 3**). All aforementioned regions survived following FDR correction ($p < 0.05$).

Network Hubs

We used regional betweenness centrality as the basis for hub classification. A hub node was defined as the detected regional betweenness centrality 2 SDs higher than the mean network betweenness. Hubs were calculated based on the AUC of the nodal betweenness across a range of network densities (density range of 0.11:0.02:0.45) (**Figure 4**; Figure S2 and Table S1 in Supplementary Material for detailed results). The common hubs in both groups included the left superior frontal gyrus and left inferior segment of the circular sulcus of the insula. Network hubs specific for the BECTS group were identified in the right superior frontal gyrus, left parahippocampal gyrus, left precuneus, and left inferior temporal gyrus. Network hubs specific to controls were identified in the right fronto-marginal gyrus (of Wernicke) and sulcus, right straight gyrus, right middle frontal sulcus, and left inferior part of the precentral sulcus. The cores of the patient networks exhibited pattern changes characterized by a displacement of hubs to the left temporal and occipital lobes and a reduction in the right frontal lobe.

Random Failure and Targeted Attack Analysis

To analyze the vulnerability of the structural covariance networks to random as well as targeted attacks, we computed the mass of the largest persevering component in response to the successive removal of nodes randomly or targetedly. In all proportions of the deleted nodes, the resilience of the both structural networks to random failure was not significant different ($p > 0.05$) (left panel in **Figure 5**). Although the AUC of the resilience to random failure was increased in the BECTS group, this effect was not statistically significant (p value of AUC for target attack = 0.21, p value of AUC for random attack = 0.14). By contrast, the network of BECTS was less robust to targeted attack as compared with the control network, and this difference

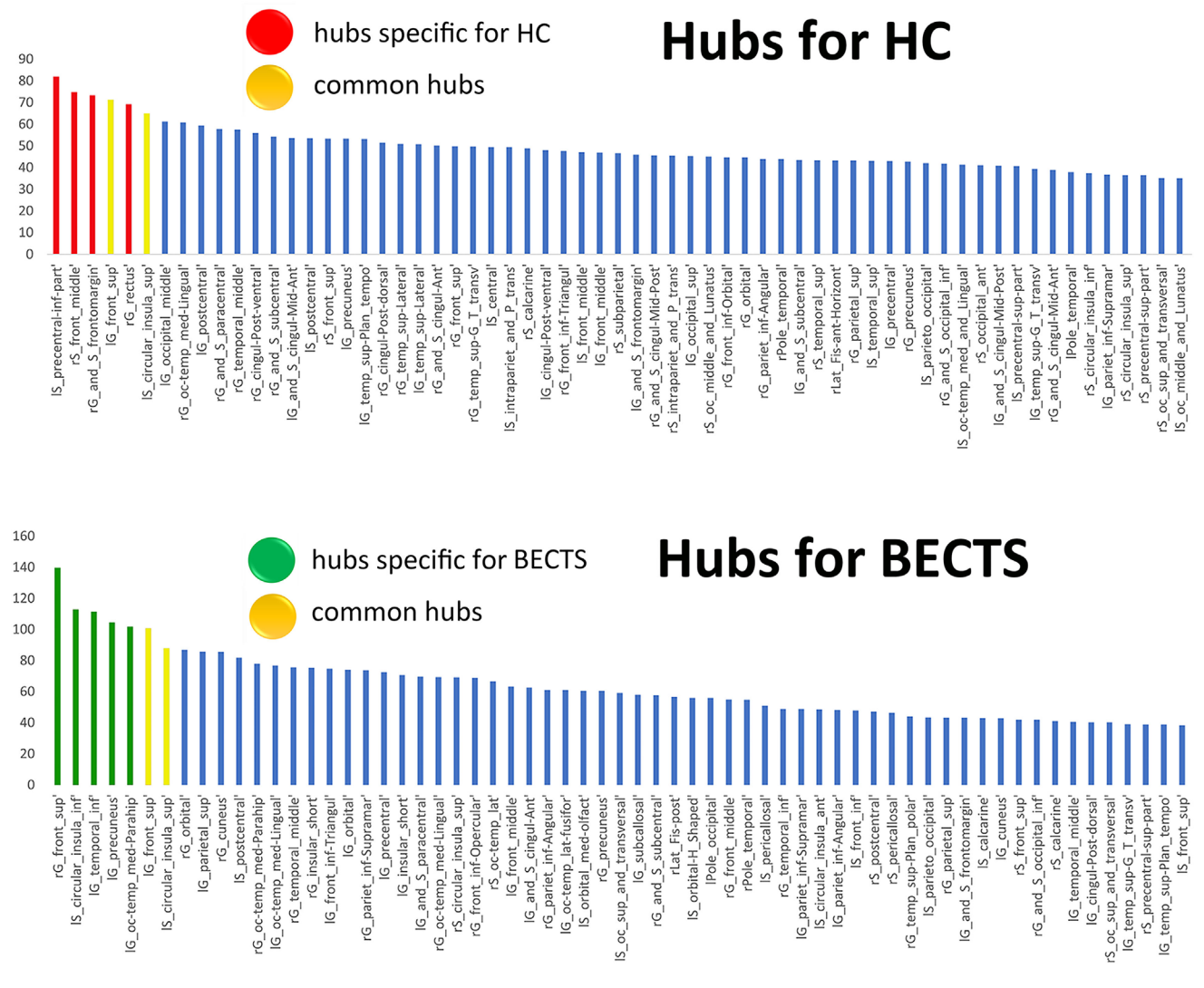

FIGURE 4 | Network hubs. The red color indicates hubs specific to healthy controls (HCs), the green color highlights hubs specific to children with BECTS, and the yellow color represents hubs that are common in both groups.

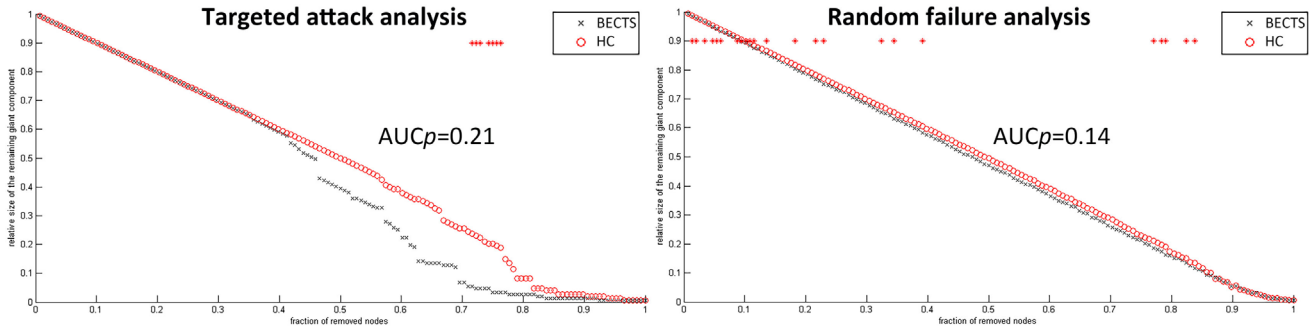

FIGURE 5 | Random and targeted attack analysis. Alterations in the size of the largest preserving component of the network are shown as a function of a fraction of randomly (left panel) and targetedly (right panel) removed nodes. In many proportions of the deleted nodes and the area under the curve (AUC) results, there was no significant difference between the two groups ($p > 0.05$) of the resilience of the networks to both targeted and random attacks. In general, network of BECTS showed less robust to the targeted attack as compared with the controls, but the statistical significance only appears at a few fractions of deleted nodes ($p < 0.05$, the red star indicates a significant difference across different network densities between the two groups).

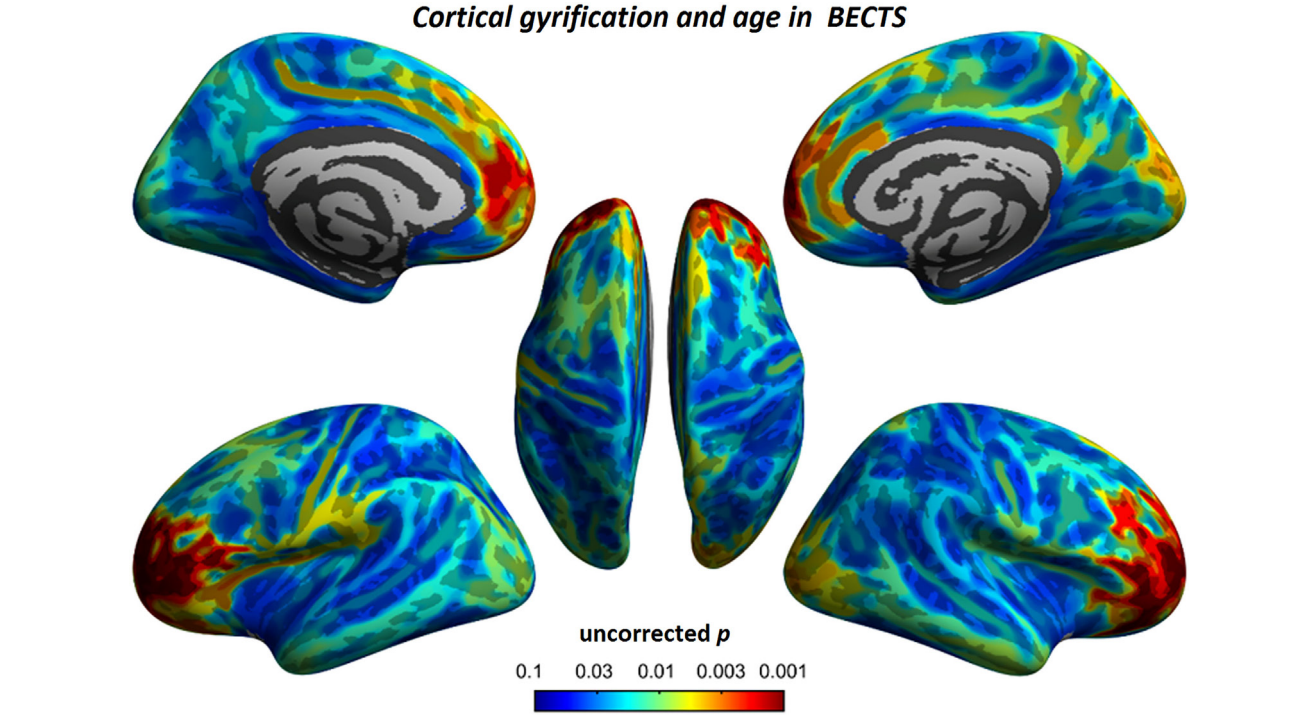

FIGURE 6 | Relationship between cortical gyrification and chronological age in children with BECTS. In children with BECTS, we did not observe significant age effects on the foci of Sylvian fissures, but we did detect frontal association cortices with significant positive relationships between cortical gyrification and age (vertex $p < 0.001$, cluster-level correction).

was significant for several fractions of attacked nodes ($p < 0.05$) (right panel in **Figure 5**). The same procedure was applied to analyze the response of the network to targeted attack by removing the nodes in a rank order of decreasing nodal betweenness centrality (right).

Correlation Analyses

To understand the relationship between age and altered cortical gyrification in children with BECTS, it is instructive to perform a regression analysis with chronological age in children with BECTS and their peer controls. Although we did not observe significant effects of age on the foci of the bilateral Sylvian fissures, we did detect other foci with significant positive relationships between the gyrification index and age (vertex $p < 0.001$, cluster-level correction), suggesting the uncoordinated development of patterns of transmodal areas (**Figures 6** and **7**). The Sylvian fissures are highly variable transmodal structures. To explore whether children with BECTS have developmental problems, we further conducted multiple regressions ruling out potential developmental problems. We also observed positive relationships

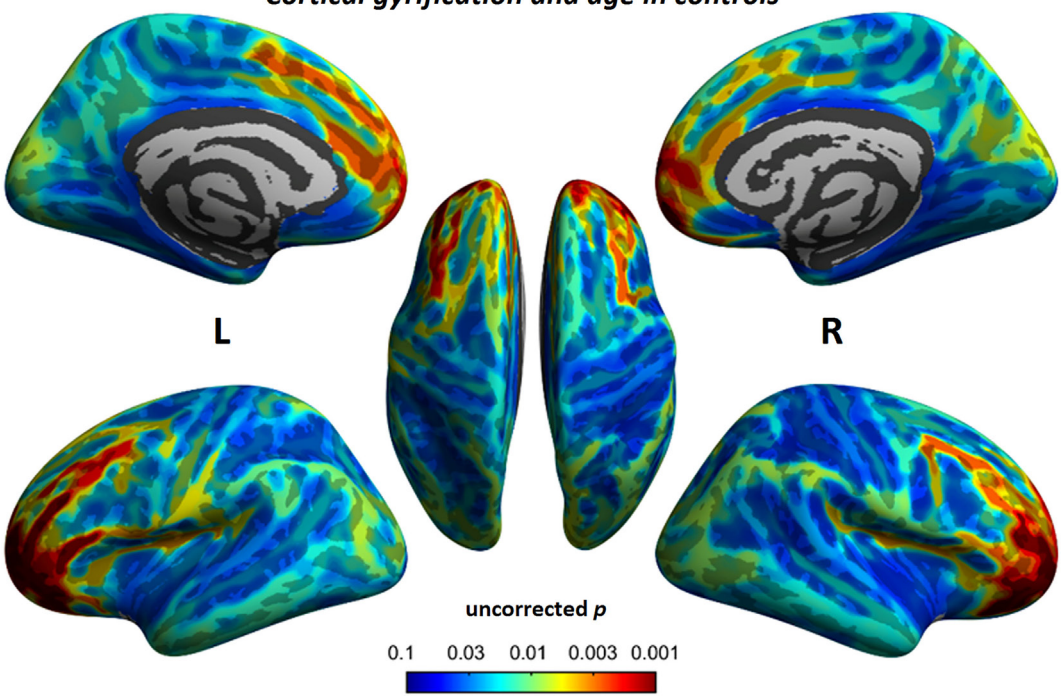

FIGURE 7 | Relationship between cortical gyrification and chronological age in typical developmental controls. Similar to children with BECTS, we also observed significant positive relationships between cortical gyrification and age (vertex $p < 0.001$, cluster-level correction).

between the gyrification index and duration of epilepsy (vertex $p < 0.001$, cluster-level correction) (**Figure 8**).

DISCUSSION

We investigated differences in cortical folding and its structural covariance networks between children with BECTS and their peer controls to confirm the effects of centrotemporal spikes on the developing brain. Specifically, children with BECTS exhibited (1) aberrant foci of cortical gyrification in BECTS, including bilateral Sylvain's fissures, left pars triangularis, temporal, rostral middle frontal, lateral orbitofrontal, and supramarginal areas, suggesting the preexistence of over-folding cortical sheets and subsequent atypical development of higher association cortices and (2) disrupted node properties in the structural network and a shift in the hub distribution. This study is the first to use a graph theory to investigate alterations in local gyrification covariance networks between BECTS adolescents and matched controls. Based on these findings, abnormal cortical folding and its nodal properties of structural wiring may underlie the neuroanatomical basis of BECTS.

The between-group results of cortical gyrification are generally in line with those of previous neuroimaging studies. The bilaterally increased gyrification in the Sylvian fissures was consistent with cortical thickness (14) and volumetric changes of gray matter (43), aberrant language recruitment using task paradigms (11), and altered functional connectivity and local intrinsic brain activity measured using resting-state fMRI in previous studies (10, 12, 15–19, 21–24, 44). For example, as shown in recent morphometric studies, children with BECTS have a thinner cortex in the frontal, temporal, and occipital regions and exhibit sparse (atypical) maturation of cortical thickness during development (14) as well as increased gray matter in the striatum and fronto–temporo–parietal cortex (striato–cortical circuit) (3, 43). In diffusion-weighted white matter integrity and anatomical connectivity analyses, BECTS patients demonstrated white matter impairment, particularly in the corpus callosum and forceps minor (5), the left superior longitudinal fasciculus, the retrolenticular region of the internal capsule, posterior thalamic radiation, and the sagittal stratum compared with controls (7). When considering a potential neurodevelopmental interpretation of these results, we observed a significant increase in the gyrification of Sylvian fissures. Anatomically, the Sylvian fissure comprises cytoarchitectonically discrete areas formed by the infolding or uneven growth of the outer cortex relative to inner structures of the frontal, parietal, and temporal opercula over the insula. Clinically, anomalous Sylvian fissure morphology was also observed in Williams syndrome (44, 45). This anatomical feature facilitates great morphological variation among hemispheres, both between and within brains. Altered cortical folding may result from neuronal or axonal injury. Alternatively, the folding abnormalities may share a common etiology, such as genetics, with BECTS. Apart from the Sylvian fissures, we also observed increased gyrification in the transmodal cortices, including the left pars triangularis, temporal, rostral middle frontal, lateral orbitofrontal, and supramarginal areas. The etiology of BECTS

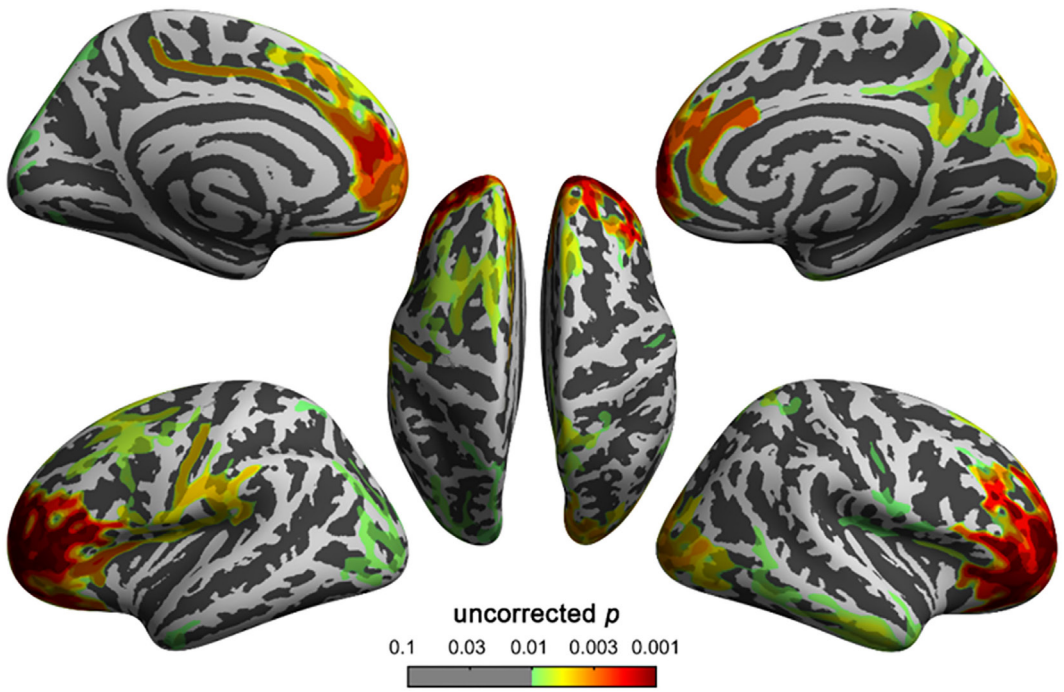

FIGURE 8 | Correlation between cortical gyrification and duration (months) of epilepsy in children with BECTS. We observed a positive correlation between cortical gyrification in children with BECTS and the duration of epilepsy in the frontal cortices (vertex $p < 0.001$, cluster-level correction).

consists of centrotemporal spikes that lead to language, cognitive, and developmental dysfunction *via* perturbation of the underlying connectivity. Neuroimaging and lesion behavior studies have correlated Sylvian fissures with language development and linguistic behaviors. The orbitofrontal region plays a role in behavior and emotion, the pars triangularis area of language and executive functions, and the temporal–parietal regions in multidomain information processing. The increased cortical folding in these regions may provide biological insights associated with subsequent outcomes.

Beyond the comparison of local gyrification profiles, we must consider the network architecture of the gyrification of the brain anatomical covariance. Globally, BECTS patients showed an insignificantly different but less optimal connectome compared with the controls. These connections with decreased normalized local clustering, increased normalized path length, and reduced small-worldness, suggesting a deviation from optimal tradeoff between segregation and integration (28, 30, 41). Using various morphological measures to construct the covariance network, previous studies have stably demonstrated small-world architecture in structural brain networks during normal development in healthy subjects (46). This network organization enables efficient information processing by providing an optimal balance between segregation and integration. Despite the lack of significant intergroup differences, these measures were lower than previously reported.

We identified between-group differences in regional network measures across several brain systems, consistent with the between-group comparison in this study and previous findings. Several regions in the left occipital, left temporal, and left insular surfaces exhibited increased centrality (clustering, betweenness, and degree centrality), while other regions in the right middle frontal sulcus and left precentral sulcus showed reduced centrality in the BECTS network compared with the controls. As elements of brain networks, individual nodes have unique centralities crucial for defining functional specialization (30). Numerous neuropsychological studies have demonstrated subtle long-term language and neurocognitive deficits, specifically in cognitive functions subserved by the prefrontal, temporal, and sensorimotor cortices, in BECTS individuals (24). Some regions with increased centrality in the BECTS network are consistent with the between-group comparison of local gyrification in this study and have previously been demonstrated to have compromised gray matter volume, blood flow or neuronal integrity in individuals with BECTS (1–15). These studies may explain the enhanced centrality in the responding areas for fine motor and multidimensional sensory processing (especially the left side) and the reduced centrality in the prefrontal regions (particularly the right side) in the BECTS group, suggesting disrupted anatomical interactions among the frontal, insular, and temporal regions and the remaining areas of the brain.

The regions identified as hubs in both groups were involved in working memory, language, attention, and interoceptive functions. By contrast, the regions with increased centrality in BECTS were involved in memory, visuospatial processing, and self-awareness. For example, the anterior insula contains an

interoceptive representation that provides the basis for all subjective feelings from the body (16). The anterior insula is often activated in conjunction with the anterior cingulate cortex, and these two structures function together as limbic sensory and motor cortices that engender salient feelings and motivations, respectively (17). In addition, we determined that the shared hubs between the two groups were limited to the left superior frontal gyrus and left inferior segment of the circular sulcus of the insula. We identified an association between increased hub number with a shift to non-hub regions during normal development in the BECTS group. This finding may correlate with the variability across individuals.

For random and targeted attack analysis, there was no statistical significance on the AUC between the two groups, suggesting a similar resilience of both networks in response to random failure and targeted attack. However, BECTS network showed less resilient in response to targeted attack, and the overall between-group difference was significant at several fractions of removing nodes. This observation is consistent with the results of the regional measures, suggesting the BECTS network has fewer central hubs than the controls because hubs in the structural connectome are energy demanding and vulnerable to major diseases (47).

BECTS occurs during a critical period of brain development and has been associated with subsequent language and cognitive issues. One study examined abnormalities in structural and functional connectivity and their convergence in this cohort. Previous studies showed significantly decreased structural/functional connectivity coupling in these children compared with their peer controls, with prominent impairment in centrotemporal network convergence (9). Over the past decade, there has been increasing interest in investigating the intrinsic brain architecture in BECTS using resting-state fMRI (48). This intrinsic architecture represents the topographies of functionally connected areas across the brain (also known as resting-state networks, or intrinsic connectivity networks) (48). Evidence for the impact of Rolandic spikes on the intrinsic architecture has revealed significant disruptions, both locally and globally. For example, Tang et al. (49) examined the regional homogeneity of resting blood-oxygen-level-dependent signals and observed increased regional homogeneity (local connectivity) in the central, premotor, and prefrontal regions and decreased local connectivity in bilateral orbitofrontal cortices and temporal poles in children with BECTS (49). Additional studies (21, 22) also investigated the regional homogeneity changes in BECTS children who were and were not receiving antiepileptic drug medications, showing that antiepileptic drug medications inhibit regional homogeneity in the epileptogenic focus. Other studies utilizing functional connectivity reported decreased default mode functionality (12) in children with BECTS, and this decreased functionality coupled with the frontoparietal network (15) to decrease inter-hemispheric functional connectivity between the bilateral frontal cortices and cerebellum (16), disrupt topological organization with reduced local segregation in sensorimotor areas, and decrease nodal centralities predominantly around the Rolandic fissure and other linguistics and attention control areas (19). More recently, a study using real-time EEG-fMRI successfully identified disruptions among the intrinsic networks subserving language, behavior, and cognition functions during interictal Rolandic spikes (or centrotemporal spikes) in children with BECTS (18). Such findings suggest Rolandic spikes disturb intrinsic activity, and these patterns may be reconfigured using antiepileptic medications.

There are several limitations to this study. First, although neurobehavioral assessments in normally developing controls were absent, we propose that these individuals had better profiles. Second, because of the limited sample size, we did not subdivide the patient cohort into different subgroups based on epileptogenic foci.

CONCLUSION

This study is the first to apply a graph theory to investigate changes in local gyrification correlation networks between children with BECTS and matched controls. The results suggest BECTS may be a condition that features the abnormal over-folding of the Sylvian fissures and the uncoordinated development of structural wiring, disrupted nodal profiles of centrality, and shifted hub distribution that may represent a neuroanatomical hallmark of BECTS in the developing brain.

ETHICS STATEMENT

This study was approved through the Medical Ethics Committee of the Affiliated Hospital of Zunyi Medical College, and written informed consent was obtained from all participants or their guardians after a complete description of the required measurements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fneur.2018.00010/full#supplementary-material.

FIGURE S1 | Between-group differences of regional measures of normalized regional degree **(A)**, betweenness **(B)**, and clustering **(C)**, and across a range of network densities [i.e., area under the curve (AUC) results] with corresponding measures in **(D–F)**. The red inverted triangle indicates the difference between the two groups. All regions survived following FDR correction ($p < 0.05$).

FIGURE S2 | Network hubs. The red color indicates hubs specific to healthy controls (HCs), the green color highlights hubs specific to children with Benign childhood epilepsy with centrotemporal spikes (BECTS), and the yellow color represents hubs that are common in both groups.

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Digital Care in Epilepsy: A Conceptual Framework for Technological Therapies

Rupert Page[1], Rohit Shankar[2,3], Brendan N. McLean[4], Jane Hanna[5] and Craig Newman[6]*

[1] Dorset Epilepsy Service, Poole Hospital NHS Foundation Trust, Poole, United Kingdom, [2] Cornwall Partnership NHS Foundation Trust, Truro, United Kingdom, [3] Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, United Kingdom, [4] Royal Cornwall Hospital, Truro, United Kingdom, [5] SUDEP Action, Wantage, United Kingdom, [6] Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom

Epilepsy is associated with a significant increase in morbidity and mortality. The likelihood is significantly greater for those patients with specific risk factors. Identifying those at greatest risk of injury and providing expert management from the earliest opportunity is made more challenging by the circumstances in which many such patients present. Despite increasing recognition of the importance of earlier identification of those at risk, there is little or no improvement in outcomes over more than 30 years. Despite ever increasing sophistication of drug development and delivery, there has been no meaningful improvement in 1-year seizure freedom rates over this time. However, in the last few years, there has been an increase in patient-triggered interventions based on automated monitoring of indicators and risk factors facilitated by technological advances. The opportunities such approaches provide will only be realized if accompanied by current working practice changes. Replacing traditional follow-up appointments at arbitrary intervals with dynamic interventions, remotely and at the point and place of need provides a better chance of a substantial reduction in seizures for people with epilepsy. Properly implemented, electronic platforms can offer new opportunities to provide expert advice and management from first presentation thus improving outcomes. This perspective paper provides and proposes an informed critical opinion built on current evidence base of an outline techno-therapeutic approach to harnesses these technologies. This conceptual framework is generic, rather than tied to a specific product or solution, and the same generalized approach could be beneficially applied to other long-term conditions.

Keywords: epilepsy technology, automated epilepsy risk monitoring, electronic health platforms, mobile apps, Epilepsy Self-Monitor, self-empowerment, co-production of health records

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****Correspondence:***
Rohit Shankar
rohit.shankar@nhs.net

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INTRODUCTION

Clinical Challenges

Epileptic seizures are a manifestation of bulk electrochemical discharges within the brain and symptomatic of a wide range of different possible neurological and other physical disorders. Consequently, for presentations with paroxysmal neurological symptoms, particularly involving alteration of consciousness, epilepsy is a diagnostic consideration. The potential manifestations of these discharges

Abbreviations: DNA, did not attend; EHR, electronic health record; EpSMon, Epilepsy Self-Monitor; PwE, people with epilepsy; SUDEP, sudden unexpected death in epilepsy; UX, user experience.

are protean and can be diagnostically difficult even for epilepsy specialists. The core of accurate diagnosis of the disorder is based on history. Contemporaneous witness accounts are crucial, but the availability and accurate recall of the latter decays significantly over time. In time-pressured environments such as primary care and the emergency settings where the first presentation occurs, diagnostic accuracy may be little better than chance (1–3). Studies from the UK and elsewhere in Europe have consistently revealed that people with epilepsy (PwE) experience significant difficulties in accessing specialists in an emergency setting (4).

Epilepsy has been recognized since antiquity, but the first broadly effective treatment was identified less than 200 years ago. Over 20 chemicals with anticonvulsant properties have made been used widely, with more than half of these available in the last 20 years (**Figure 1**). Despite their increasing pharmacological specificity, these agents have not led to a significant increase in the proportion of patients who are seizure free (5). Delays in referral for epilepsy surgery or other specialized approaches for those with drug-refractory epilepsy are a common finding (6, 7).

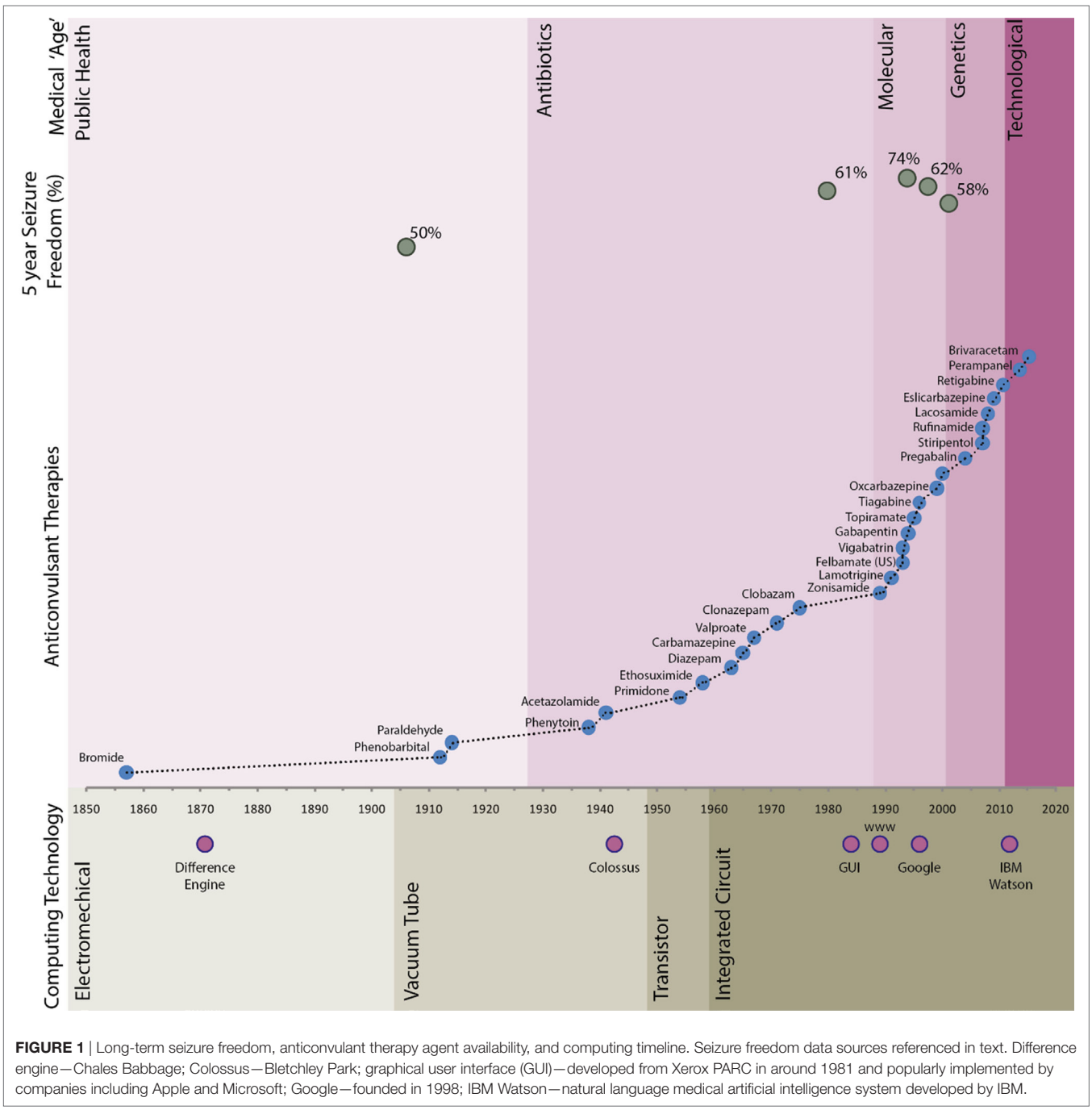

FIGURE 1 | Long-term seizure freedom, anticonvulant therapy agent availability, and computing timeline. Seizure freedom data sources referenced in text. Difference engine—Chales Babbage; Colossus—Bletchley Park; graphical user interface (GUI)—developed from Xerox PARC in around 1981 and popularly implemented by companies including Apple and Microsoft; Google—founded in 1998; IBM Watson—natural language medical artificial intelligence system developed by IBM.

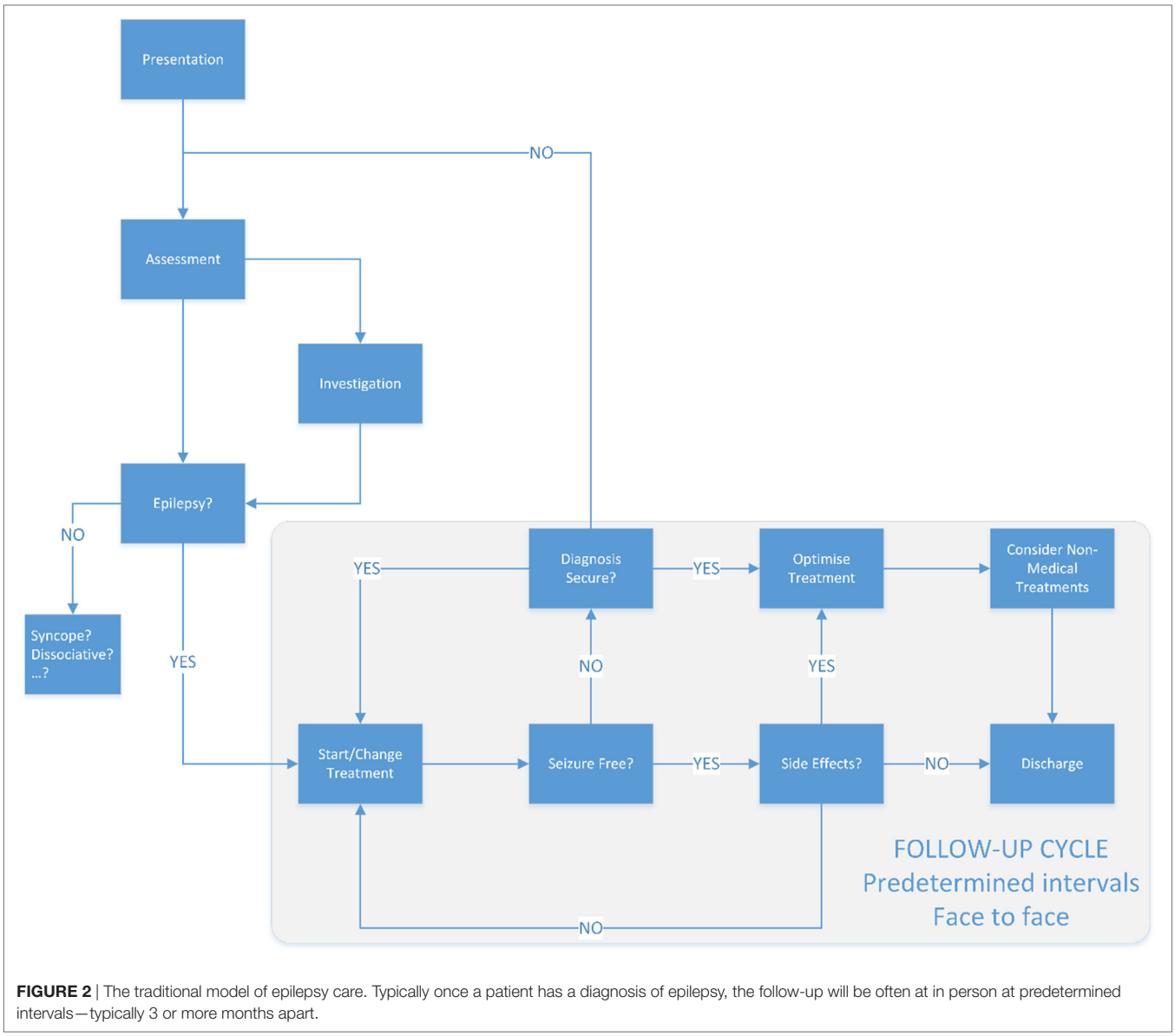

FIGURE 2 | The traditional model of epilepsy care. Typically once a patient has a diagnosis of epilepsy, the follow-up will be often at in person at predetermined intervals—typically 3 or more months apart.

Much of how outpatient-based neurological care is delivered today would be familiar to John Hughlings Jackson (1835–1911) (**Figure 2**). Over the last 30 years, technology has made rapid advances. The confluence of developments in material and computer science has contributed to a plethora of devices and applications that now seem mundane. Medicine in general has been slow to adapt to these changes, generally developing modish and superficial applications that ape aspects of existing clinical care provision (8, 9). For epilepsy, the focus has primarily been on real-time seizure detection, electronic versions of paper forms or diaries (10). Implantable or wearable stimulators are currently the limit of therapeutic technological intervention. These approaches, while laudable in aim, often fail to integrate into clinical care pathways resulting in increased workload for already busy clinicians and do not deliver on their promise. Comprehensive reviews of these technologies are available (11).

The challenges of recruiting, training, and retaining specialist clinical staff to support patients with long-term conditions such as epilepsy is difficult and likely to become more so (12). Around 70% of the cost for any Acute Trust in the UK is staff, thus leveraging the existing workforce to support patients in the community is essential to maintain service provision.

Technical Challenges

Changing existing working practices is difficult, even when the reasons to do so are clear (13). Medicine is not immune to this problem. Attempts to introduce electronic health records (EHRs) have been bedeviled by difficulties (14–16). An increasing body of evidence has shown that poorly thought out, and implemented systems and clinical user interfaces have led to time being lost entering data into the EHR, potentially with a detrimental effect on the interaction between patient and clinician (17, 18). Patient

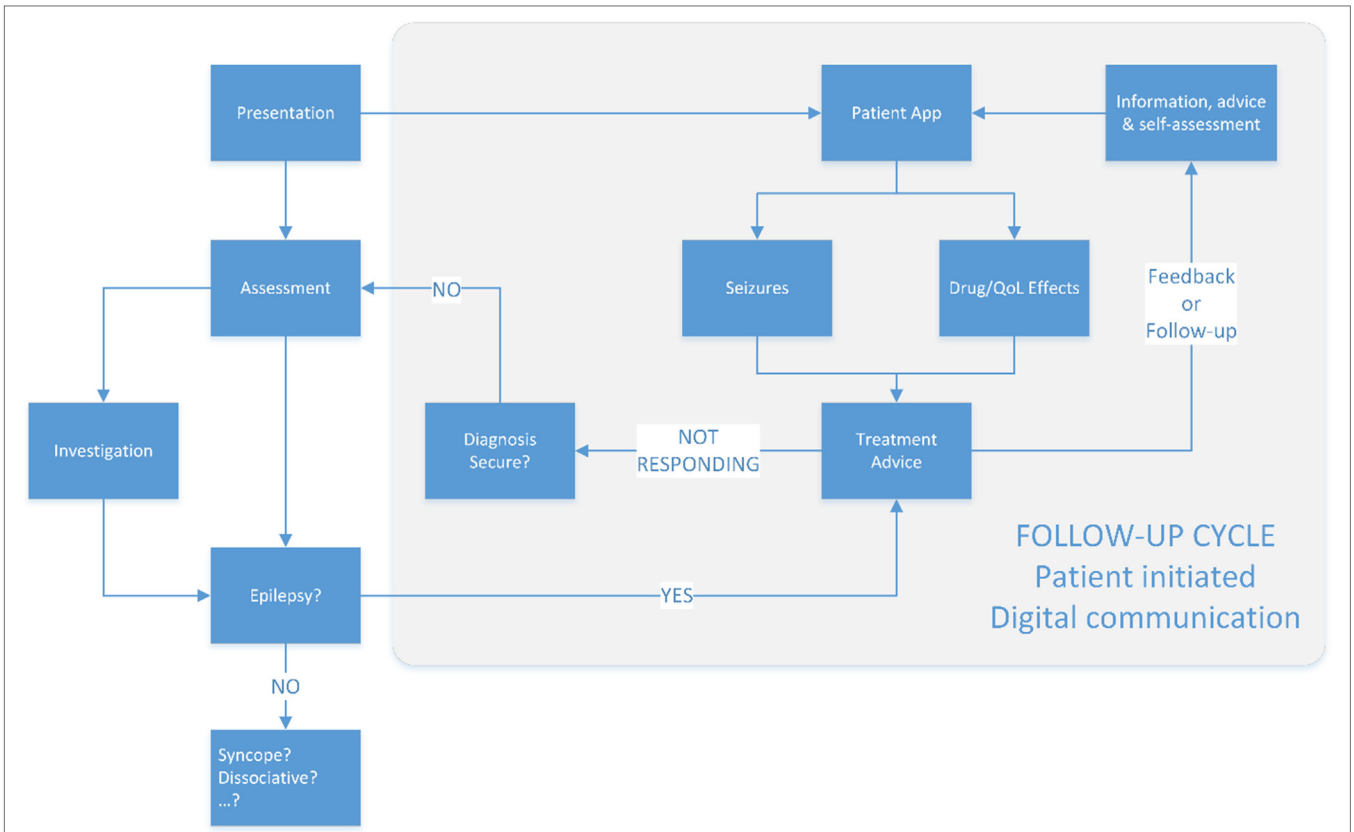

FIGURE 3 | The proposed new model of epilepsy care. Follow-up is patient triggered, supported by design to ensure that alerts to the clinical team are notified in proportion to their severity on an evidenced based approach.

contributed data, such as seizure or symptom diaries, are often in paper format. If it is in electronic form, it usually cannot be easily integrated into the clinical record.

While clinicians may not be able to change their EHR, patients are free to change between different applications and technology according to their needs and personal preferences. Surveys from the US suggests that over 20% of mobile smartphone apps are used only once in 6 months (19). By comparison, the neurology outpatient clinic "did not attend" rate is typically around 7% (20). If patients are to be safely engaged and retained in clinical follow-up using a technological solution, then this must be easy to use and of value to them. From a technical perspective, it needs to meet national security requirements for data both at rest and in transit. In addition, the patient contributed data must be able to be correctly registered against clinical EHRs from different vendors when the patient changes their care provider, as well as being able to share this with different teams within the care economy.

Patient Challenges

Technology has had a pervasive influence on the modern world, from the Internet to autonomous vehicles. There is an increasing acceptance of "electronic first" approaches to communication and interaction in the consumer sphere, although it is only lately being accepted in the medical realm. The widespread availability of smartphone technology and focused user experience (UX) design has undoubtedly made for a more seamless experience for people of all ages. Despite the widespread availability of technology, there remains a significant minority who prefer to avoid technological solutions. The size of this latter group is likely to diminish over time due to increasing familiarity and demographics. The provision of Wi-Fi or broadband connectivity, particularly in remote or rural areas is often poor. In some areas of the UK, a cellular signal remains unavailable. An electronic rather than paper-based system also poses many challenges to the traditional dynamics of a patient–clinician communication, not least the loss of eye-contact that frequently results. Unless managed sensitively, this can adversely impair the ability of the practitioner to obtain clinical information critical to diagnosis and management.

Opportunities

A patient co-authored record has the potential to reduce clinical data entry requirements while increasing the relevance of that record (**Figure 3**). Paired with instant communication and alert thresholding, patients with long-term conditions such as epilepsy can be safely managed on a patient-triggered follow-up basis. The real-time nature of the communication with specialists can reduce the risk of preventable harms to patients, including sudden unexpected death in epilepsy (SUDEP) (21, 22).

The addition of dynamic and informed patient consent to this coauthored record opens the possibility of real-world

post-marketing surveillance studies at a fraction of the cost of traditional pharmaceutical trials (23).

CONCEPT

To take advantage of the opportunities technology may offer, it is necessary to reconsider the traditional approach to managing patients presenting with possible epilepsy. Current best practice in the UK recommends patients presenting with a possible first seizure to be referred to a specialist and to be seen "as soon as possible" (24). Any investigations required including imaging are expected to be undertaken "soon" after they are requested. A pathway to take advantage of the new technology begins at the first presentation with a possible seizure and uses commonly available platforms to facilitate rapid assessment, risk stratification, and communication.

The conceptual framework offered is intended to be generic in outline, rather than focused on a specific device or platform. It describes a hypothetical technology-enabled "scaffold" on which a more modern and timely epilepsy service might be built. The current rate of technological development means that present offerings may rapidly be overtaken by other approaches. The aim of this paper therefore is to suggest a standardized approach that can be employed across a shifting framework of devices and platforms, to the consistent benefit of PwE. Where relevant, it uses the direct experience of the authors to evidence the benefits that may be derived.

At First Presentation

A majority of first seizure presentations in the UK will be seen or referred to hospital. Following clinical assessment, patients with possible first seizure can be offered a suite of downloadable resources for seizures and epilepsy that reflect both national best practice and local guidelines with signposting. These resources should include an electronic symptom/seizure diary application, which is registered to the local EHR for the Epilepsy Team. The data collected at the time of presentation should include information which can be used to stratify patients for seizure/SUDEP risk, based on published evidence and validated tools (22, 25). This information should be included in the electronic referral, which is notified to the First Seizure Clinic and Epilepsy Team. Outpatient investigation and appointment details are sent to the patient electronically *via* the smartphone diary application. Relevant information recorded in the patient smartphone application is communicated to the care team, using the updated risk stratification. This information may include manually recorded possible seizures, witness accounts, and video as well as data from wearable devices. Investigations, advice, and management are adjusted based on the up-to-date information, with the timing of first clinical review adjusted according to the live recurrence risk.

Work done by the Epilepsy Self-Monitor (EpSMon) collaboration has shown that patients can be engaged with a smartphone application on a regular basis and that they can use it to help reduce their risk of injury and death through uncontrolled epileptic seizures.

Clinical Notification and Messaging

Clinically relevant updates entered *via* registered patient smartphone application(s) need to be notified to the Epilepsy Team. These updates require automatic grading using evidence-based markers of seizure severity morbidity. Risk stratifying the alerts handling in the clinical application, combined with the agreed clinical goals of treatment, prevents alert notification fatigue for the Epilepsy Team and focuses attention on the "at need" population. Lower risk updates are summated on a weekly, monthly, or 3-monthly basis agreed with the patient and care team, with an established escalation process for unexpected worsening. These lower risk updates are commented on by the Epilepsy Team, and this feedback is passed to the patient or care team through the system. The ongoing real-time feedback loop is required to maintain patient engagement and update treatment plans to optimize care.

The Epilepsy Care Alliance has demonstrated a smartphone application can be used to leverage limited clinical resources to provide real-time advice to patients with epilepsy. In doing so, the rate of hospital admission for patients known to have epilepsy has fallen by over 30% (Page, unpublished data).

Coauthored Record

Where appropriate, wearable devices may be used to help supplement patient provided data. This may be in terms of improving seizure recording, for instance, in terms of nocturnal seizures, or by logging lifestyle data around activities such as exercise and sleep. Patients need to be able to confirm or deny putative seizures recorded by a wearable device as these currently will not reliably record all seizures and are prone to false positives. A daily summary of the relevant life-logging data provided should be registered against the clinical record, where appropriate patient consent is obtained.

Semiautomated clinical assessment of the data obtained would permit meaningful personal insights into aspects such as possible seizure triggers and medication side effects. Such approaches may facilitate statistically valid correlations in individuals if there is a sufficiently large data set obtained. Patients would need to assess their seizure severity and risk of SUDEP using a clinically validated approach, such as EpSMon (10, 26). This provides them with details of modifiable and non-modifiable risks. The assessment should be updated at regular intervals to provide an insight into risks that they can modify.

Ongoing Care

Engaging patients with a technological approach to any long-term condition requires awareness of behavioral trends for the population to minimize drop-out of "at need" patient groups. This may include techniques such as online training videos and refresher modules. It requires a process for reaching out to patients who may become disengaged from the electronic process or find it too cognitively taxing to commit to. In addition, an ability to update the "techno-therapy" to both take advantage of new developments in medical, computing, and material science, as well as a constantly shifting series of operating systems and physical platforms is essential to maintain clinical utility and patient usability.

For epilepsy, successful implementation of the techno-therapeutic approach described should allow patients to be assessed once in a traditional face-to-face clinic with subsequent "follow-up appointments" being completed using asynchronous text or data-based approaches or using technologies such as Skype, apart

from a small subset who may need face-to-face review. With the development of augmented/blended reality approaches even this requirement may shrink.

The transition from traditional follow-up to a patient-triggered follow-up process will require some reconfiguration of clinical services. This would be expected to include more time focused on surveillance of patient contributed data using automation, data analysis tools, and structured notifications, with relatively less time spent in face-to-face review.

Evidence Base

The EpSMon (22) is a digital self-assessment smartphone app which comprehensive review of technological devices for epilepsy has been published elsewhere (11, 27). This conceptual framework has been influenced by the clinical experience of the authors in developing approaches to help advance technology-enabled care. A summary of this is outlined below.

The EpSMon (28) is a digital self-assessment smartphone app, which provides PwE access to a patient facing version of the clinical epilepsy risk checklist (22). Users are prompted to assess their risk status relative to the current evidence on risk of SUDEP with resultant education and suggestions to seek appropriate levels of clinical contact when appropriate. EpSMon has been downloaded by 4,000 users. Recognition that EpSMon would likely best fit within existing NHS care has been supported by slower than expected take-up, technology peer review (11, 27) (NIHR) and commissioning of the project into NHS England's innovation accelerator program (29). Additional learning prompts expansion of the technology to include a website version (for increased accessibility), increased epilepsy management features (medication reminder and seizure log), and increased interoperability with patient flagging or data management systems.

The Epilepsy Care Alliance has developed an electronic system for managing PwE, using patient smartphone application and wearable technology deployed to a small pilot group of PwE. This is combined with team-based messaging that notifies of any patients admitted to Poole Hospital known to the Dorset Epilepsy Service. This has been running since September 2016 and is being actively updated. There was a 30% reduction in admissions to Poole hospital for PwE known to the epilepsy service. In addition, in those patients who were using the electronic app, there was a reduction in the median interval to medication adjustment of over 3 weeks compared with before introduction of the technology. The impact on quality of life and seizure freedom attainment rates in this group are currently the subject of ongoing analysis.

DISCUSSION

Technological "solutions" for patients typically focus on a specific disease or condition. There is frequently a varying degree of clinical certainty as to the diagnosis. This uncertainty is typically most pronounced at the initial presentation, due to a combination of missing/misleading information and lack of specialist input. This is particularly true for epilepsy, a condition with is characterized by both altered awareness of the patient and the unpredictability of seizures. To ensure that patients are not placed at avoidable risk due to clinical uncertainty at the outset, "prescribing" an application suited for presentations of altered awareness including high risk conditions such as epilepsy is prudent. The use of open application programming interfaces enables data that are already entered to be moved to other disease-specific applications as diagnostic certainty increases. Such an open standard for data facilitates easier sharing of information between different applications. It would also help foster an ecosystem of patient applications, which can evolve to keep pace with the needs of patients.

From a public health perspective, it is often difficult to determine the real-world frequency of disorders and their eventual outcomes. Case selection is fraught with bias depending on the source of the study. Long-term follow-up can be challenging and is often resource and cost prohibitive. Most long-term conditions, including many causes of epilepsy, are believed to persist for the remainder of life after diagnosis. The "gold-standard" for epilepsy is typically 1-year seizure freedom, with the risk of seizure recurrence thought to progressively drop in subsequent years. Most patients would not be followed-up beyond 2 or 3 years of seizure freedom. Data on late seizure recurrence and life-long seizure freedom as well as long-term impact of many anticonvulsant medications are lacking. Changing the way in which the health-care system interacts with people with long-term conditions from their first presentation through the rest of their life, based on their needs, provides an opportunity to assess the true impact of lifestyle, disease, and clinical interventions on quality of life. One would expect that this would provide new evidence and insights that may radically change future care and advice.

The transition to a "digital first" architecture for clinicians and patients requires technological transparency. This is the means of data collection facilitates the clinical assessment rather than dominating it. Providing a smartphone-based application for the patient contributed part of the record is an approach that fits the consumer trend of technology uptake and use, while reducing costs to the health-care economy. In view of the rapidly evolving nature of computing, machine learning, and materials science, opportunities for improvements in health care are likely to increase faster through such approaches than advances in traditional medical research and drug development. The shifting population demographic and focus on UX would be expected to progressively reduce the "digitally disenfranchised." The current orthodox method of long-term care provision will undoubtedly change over the coming years. While these changes need to be inclusive and sustainable and clinically led they must be alert to the possibilities that technological development can enable.

ETHICS STATEMENT

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. No ethical approval was needed.

AUTHOR CONTRIBUTIONS

RP and RS wrote the initial draft. It was edited and developed further by BM, JH, and CN. All the authors have contributed to the development, concept, writing, editing, and delivery of the paper.

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REVIEW
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Automatic Computer-Based Detection of Epileptic Seizures

Christoph Baumgartner[1,2,3]*, *Johannes P. Koren*[1,2] *and Michaela Rothmayer*[1]

[1] *Department of Neurology, General Hospital Hietzing with Neurological Center Rosenhügel, Vienna, Austria,* [2] *Karl Landsteiner Institute for Clinical Epilepsy Research and Cognitive Neurology, Vienna, Austria,* [3] *Medical Faculty, Sigmund Freud University, Vienna, Austria*

Automatic computer-based seizure detection and warning devices are important for objective seizure documentation, for SUDEP prevention, to avoid seizure related injuries and social embarrassments as a consequence of seizures, and to develop on demand epilepsy therapies. Automatic seizure detection systems can be based on direct analysis of epileptiform discharges on scalp-EEG or intracranial EEG, on the detection of motor manifestations of epileptic seizures using surface electromyography (sEMG), accelerometry (ACM), video detection systems and mattress sensors and finally on the assessment of changes of physiologic parameters accompanying epileptic seizures measured by electrocardiography (ECG), respiratory monitors, pulse oximetry, surface temperature sensors, and electrodermal activity. Here we review automatic seizure detection based on scalp-EEG, ECG, and sEMG. Different seizure types affect preferentially different measurement parameters. While EEG changes accompany all types of seizures, sEMG and ACM are suitable mainly for detection of seizures with major motor manifestations. Therefore, seizure detection can be optimized by multimodal systems combining several measurement parameters. While most systems provide sensitivities over 70%, specificity expressed as false alarm rates still needs to be improved. Patients' acceptance and comfort of a specific device are of critical importance for its long-term application in a meaningful clinical way.

Keywords: seizure, detection, scalp-EEG, ECG, sEMG, SUDEP

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***Correspondence:**
Christoph Baumgartner
christoph.baumgartner@wienkav.at

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INTRODUCTION

In general, automatic seizure detection must be distinguished from automatic seizure prediction. While seizure detection methods aim to detect ongoing seizures as soon as possible after seizure onset, seizure prediction models try to identify upcoming seizures well before seizure onset. In the present review we will focus on automatic seizure detection, while the reader is referred to excellent reviews on the current status of seizure prediction (1–4).

Automatic computer-based seizure detection currently is one of the major research questions in clinical epileptology for the following reasons:

1. Documentation of seizure frequency, seizure severity and seizure type by patients and their relatives represents the most important outcome parameter for epilepsy treatment both in everyday clinical practice and for the assessment of the efficacy of medical and non-medical treatment interventions in clinical trials. However, seizure documentation by patients and their relatives has been shown to be highly unreliable. In a study using video-EEG monitoring as the gold standard for seizure documentation, 55.5% of all seizures, 73.2% of complex partial seizures, 26.2% of simple partial seizures, 41.7% der secondary generalized tonic-clonic seizures, 85.8% of seizures arising out of sleep and 32.0% of seizures arising out of wakefulness remained unnoticed or were not documented by patients (5). In a study using a long-term, implanted seizure advisory system in patients with drug-resistant focal epilepsy for several months, a very low agreement between seizures noticed in patients' seizure diaries and those objectively documented on invasive EEG was found. Most patients significantly underestimated their seizure frequency. Because the relationship between patient and EEG documented seizures was highly variable from month to month, the application of a hypothetical correction factor seems not feasible (6). Therefore, objective and automatic documentation of seizure frequency, seizure severity, and seizure type is urgently needed in everyday clinical epileptology, but also in clinical epilepsy research to objectively assess the efficacy of therapeutic interventions in clinical trials (7).
2. Persons with active epilepsy face a standardized mortality ration of 2–3 (8, 9). Patients with severe severely drug-refractory epilepsy even suffer from a sevenfold increase in mortality rate over 3 years (10). The most frequent causes of death include cerebrovascular diseases, pneumonia, and neoplasia (8). Sudden unexpected death in epilepsy (SUDEP) represents the most frequent epilepsy associated cause of death and is most probably mediated through seizure associated cardiac, pulmonary or other autonomic dysfunctions (11). Automatic monitoring of EEG, cardiac, respiratory, and other autonomic changes during seizures therefore could be useful to elucidate the pathomechanisms underlying SUDEP (12). Generalized tonic-clonic seizures occurring out of sleep are a significant risk factor for SUDEP with supervision during night currently representing the only preventive measure (11, 13, 14). Automatic detection of nocturnal generalized tonic-clonic seizures could alert relatives, friends or caregivers leading to check on the patient, and provide sufficient stimulation to prevent respiratory arrest (15).
3. Automatic seizure detection systems could be used as seizure alarm devices for patients without reliable auras alleviating the unpredictability of seizures and their potential social embarrassments. Automatic seizure detection systems and warning devices could also help to prevent seizure associated injuries (10). This would significantly reduce the fear of seizures and thus improve the quality of life for persons with epilepsy (16). However, warning devices based on seizure detection would be clinically useful only in patients with subclinical seizures detected by the system or in order to alert significant others about an ongoing seizure enabling them to set protective measures. On the contrary, a warning device would be useless for patients if seizures have already started and lead to impairment of consciousness. Therefore, warning devices ideally should be based on seizure prediction rather than on seizure detection.
4. Automatic seizure detection systems could open the way to on-demand therapies, such as acute administration of anticonvulsants or acute electrical stimulation in selected brain areas, in order to stop ongoing seizures (7, 17–21).
5. During video-EEG-monitoring (VEM) in the epilepsy monitoring unit (EMU), applications for automatic seizure detection systems include enhancement of patient safety, more efficient data analysis, automatic documentation of seizures, and computer-based neurological and neuropsychological testing during and after seizures.

   Patient safety in order to avoid seizure related injuries, to recognize seizure induced cardiac arrhythmias and finally to prevent SUDEP has become a central issue during VEM (22–25). While optimum patient safety can be ensured only by continuous observation through trained personnel (25, 26), several surveys showed that only 56–80% of EMUs can provide continuous personal patient surveillance (23–25, 27). Automatic on-line seizure detection and warning systems could provide a significantly less personnel intensive alternative to personal patient surveillance in the EMU. However, only 15–19% of EMUs actually use on-line seizure detection and warning systems (24, 27).

   Automatic seizure detection could optimize data review in the EMU and thus could facilitate a more efficient personnel assignment (28–30). Although agreement on EEG seizure identification between human electroencephalographers is high with an average any-overlap sensitivity of 92% and false positives per hour rate of 0.117 applying any-overlap comparisons (i.e., whether there was any detection overlap between experts during a period annotated as a seizure), high seizure rates as well as short and long seizure durations with ambiguous offsets can make analysis rather complicated resulting in suboptimal agreements even between EEG experts (31). Therefore, automatic seizure detection systems could improve seizure documentation during VEM.

   The exact analysis of clinical seizure semiology is essential for correct seizure classification as well as for the localization of the seizure onset zone and pathways of seizure spread (32, 33). Proper assessment of many essential features of seizure semiology require systematic interactive testing for various cognitive, behavioral, sensory, and motor functions during and after seizures (32, 33). However, immediate ictal testing frequently is not possible due to personnel limitations (34). Recently, a seizure detection system triggering automatically a series of video-recorded behavioral tasks presented in the patient's room [Automatic Responsiveness Testing in Epilepsy (ARTiE)] has been introduced which could optimize assessment of these functions during seizures (34).
6. Finally, automatic seizure detection has become increasingly important for the detection of non-convulsive seizures and non-convulsive status epilepticus in critical care patients (35).

PERFORMANCE MEASURES OF AUTOMATIC SEIZURE DETECTION AND ALARM ALGORITHMS

Visual annotation of seizures by EEG experts remains the gold standard for performance evaluation of seizure detection and seizure alarm algorithms. In general, agreement on seizure annotation between EEG experts is high. However, discrepancies can occur in case of high seizure rates as well as in case of seizures with short and long durations. These caveats have to be considered during assessment of computer-based seizure detection algorithms (31). Preferably, agreement on seizure annotations should be obtained by several blinded EEG experts (29, 36).

Seizure detection and alarm algorithms usually are evaluated and compared concerning the following performance measures (1, 37):

True positives (TP) meaning that the algorithm detected a seizure identified by the human expert;
False negatives (FN) meaning that the algorithm missed a seizure identified by the human expert;
False positives (FP) meaning the algorithm erroneously detected a seizure which was not confirmed by the human expert;
Sensitivity defined as the ratio TP/(TP + FN);
Specificity defined as the number of false positive alarms per hour referred to as false positive alarm rate (FAR).
Alarm algorithms need to provide both on-line calculation and short detection delays.
Detection delay is defined as the time interval between the time of seizure onset identified by the human expert and the time when the computer algorithm sets the alarm. Detection delays in the range of a few seconds are required for alarm devices (38, 39).

MEASUREMENT PARAMETERS FOR AUTOMATIC SEIZURE DETECTION

Ictal EEG changes which can be measured on scalp-EEG and intracranial EEG represent the electrophysiological correlates of epileptic seizures. Therefore, analysis of ictal EEG represents the most direct biomarker for automatic epileptic seizure detection. While specificity of intracranial EEG is considerably higher than that of scalp-EEG, drawbacks of intracranial EEG based seizure detection include the sampling problem due to limited coverage of the cerebral cortex and a less well defined specificity as compared to scalp-EEG. Motor manifestations representing a prominent feature of many seizures can be assessed with surface electromyography (sEMG), accelerometry (ACM), video detection systems, and mattress sensors. Most epileptic seizures are accompanied by changes in physiologic parameters like heart and respiration rate, oxygen saturation, skin temperature, and sweat secretion. These parameters can be measured by electrocardiography (ECG), respiratory monitors, pulse oximetry, surface temperature sensors, and electrodermal activity (EDA) (**Table 1**).

We focused our review on automatic seizure detection based on scalp electroencephalography (scalp-EEG), electrocardiography (ECG) and surface electromyography (sEMG) because these modalities have been studied most extensively in the literature. For seizure detection based on other modalities the reader is referred to some recent excellent reviews (12, 16, 40).

AUTOMATIC SEIZURE DETECTION BASED ON SCALP ELECTROENCEPHALOGRAPHY (SCALP-EEG)

Ideally scalp-EEG based seizure detection algorithms should detect a broad range of seizures in patients with different epilepsy syndromes and seizure-onset zones with high sensitivity and specificity. Algorithms should facilitate fast and robust analysis of large amounts of EEG data. All EEG data acquired during VEM should be analyzed, including artifacts, all neurophysiological states as well as non-ictal physiological and pathological EEG patterns (37).

While scalp-EEG based seizure detection algorithms can use either single or multiple scalp-EEG channels, most algorithms applied in a clinical setting use multiple EEG channels. In multiple channel systems, the montage can significantly influence for performance of the algorithm (41). For computational reasons and for patient comfort (especially in an outpatient setting) a proper selection and reduction of electrode numbers is important (42–44). While using all 21 channels of the International 10-20-system provided a sensitivity of 84%, reduction to only 8 frontal and temporal electrodes yielded an average sensitivity of 79%, a restriction to only 7 temporal, parietal, and occipital electrodes an average sensitivity of 68% (43). After data acquisition, artifact rejection needs to be applied. Detection of EEG seizure patterns is based on characteristic changes with respect to frequency, amplitude and/or rhythmicity

TABLE 1 | Measurement parameters for automatic seizure detection.

Electrophysiological correlates of epileptic seizures
Scalp-EEG
Intracranial EEG
Measurement of motor manifestations
Surface electromyography (semg)
Accelerometry (ACM)
Video detection systems
Mattress sensors
Measurement of physiologic parameters
Heart rate → electrocardiography (ECG)
Respiration rate → respiratory monitors
Oxygen saturation → pulse oximetry
Skin temperature → surface temperature sensors
Sweat secretion → electrodermal activity (EDA)

using different linear and non-linear time-frequency signal analyses techniques (37, 45, 46).

In general non-patient specific and patient specific algorithms can be distinguished. Non-patient specific algorithms can be applied without a priori knowledge about the patient's individual electrographic seizure patterns. Therefore these algorithms are easy to use with identical parameter settings for all patients which is important for the application in a busy clinical environment. Patient specific algorithms, on the other hand, try to improve the performance by parameter adjustments for each individual patient (47–49). However, such patient specific detection algorithms need specific training and interactive, sometimes complex individualized parameter adjustments.

Table 2 provides a selection of non-patient specific algorithms tested in a clinical setting (28–30, 37–39, 41, 46, 50–58).

Due to the large amount of EEG data, patients and seizures analyzed we summarize here the studies published by the Erlangen group (37, 41) and the Vienna group (30, 56, 57).

Hopfengärtner et al. (37, 41) analyzed 25,278 h of EEG in 159 patients [117 temporal-lobe epilepsies (TLE); 35 extra-temporal lobe epilepsies (ETLE); 7 others] containing 794 seizures. They applied an adaptive thresholding technique and calculated the integrated power in the frequency band from 2.5 to 12 Hz for a seizure detection montage including basal temporal electrodes referenced against the average of Fz-Cz-Pz. With this approach they could obtain a sensitivity of 87.3% and a FAR of 0.22/h. Performance for TLE patients (18,996 h of EEG including 589 seizures; sensitivity 89.9%, FAR 0.19/h) was better as compared to ETLE patients (5,192 h of EEG including 172 seizures; sensitivity 77.4%, FAR 0.25/h).

Fürbass et al. (30) performed a prospective multi-center study in 3 epilepsy centers. The algorithm was developed on additional 25,567 h of EEG from 310 patients (including 124 patients with 1,113 seizures and an additional 186 patients without seizures) (30, 56, 57). While for the prospective data set a mean sensitivity of 81% and a FAR 0.29/h could be obtained, in the development dataset mean sensitivity was 75% and FAR was 0.3/h. In the prospective data set, 16 seizures unnoticed during routine visual analysis (3% of all seizures) were detected by the algorithm. Sensitivity was better for TLE (83%) than for ETLE (64%).

Table 3 summarizes some clinically applied patient specific algorithms (47–49, 58–61). Of course performance is higher for patient-specific as compared to non-patient specific algorithms. Nevertheless it should be mentioned the amount of EEG, patients and seizures reported in the literatures is drastically higher for non-patient specific algorithms indicating their easier use in clinical setting.

In conclusion, non-patient specific scalp-EEG based seizure detection algorithms provide sensitivities between 73 and 96% (62). Difficult to detect are EEG seizure patterns with short duration, with low amplitude, with circumscribed highly focal activity, with high frequency, with unusual non-rhythmic morphology and those obscured by artifact. These features frequently apply to seizures of extratemporal origin which therefore are more difficult to detect than seizures of temporal lobe origin (30, 37, 58). Specificity (FAR) of non-patient specific scalp-EEG based seizure detection algorithms varies between 0.11 and 5.38/h. Low FARs are essential for the acceptance of an algorithm in a clinical setting, especially if the algorithm is applied as an alarm device. Here high FAR would result in unnecessary concerns and anxiety of patients as well as frequent unnecessary responses and actions by caregivers. FAR can be caused by physiological and pathological brain activity including sleep patterns, rhythmic non-epileptiform activities

TABLE 2 | Non-patient specific, scalp-EEG based seizure detection algorithms tested in clinical settings.

References	EEG sample (hours)	Patients	Seizures	Sensitivity (%)	Specificity FAR (per hour)	Detection delay (seconds)
Gotman (50)	4362	44	179	73.2	0.84	n.a.
Pauri et al. (28)	461	12	253	81.4	5.38	n.a.
Gabor et al. (51)+	528	22	62	90.3	0.71	n.a.
Gabor (52)*	4554	65	181	92.8	1.35	n.a.
Wilson et al. (53)	1049	426	672	76.0	0.11	n.a.
Saab and Gotman (38)	360	16	69	76.0	0.34	10.0
Kuhlmann et al. (54)	525	21	88	81.0	0.60	16.9
Meier et al. (38)	1403	57	91	> 96.0	<0.5	2.0
Schad et al. (55)	423	6	26	59	0.15	n.a.
Kelly et al. (29)	1200	55	146	79.5	0.08	n.a.
Zandi et al. (46)	236	26	79	91.0	0.33	7.0
Hopfengärtner et al. (41)	3248	19	148	90.9	0.29	19
Hopfengärtner et al. (37)	25278	159	794	87.3	0.22	n.a.
Hartmann et al. (56)	4300	48	186	83.0	0.3	n.a.
Fürbass et al. (57)	22000	275	623	73.0	0.30	n.a.
Fürbass et al. (30)*	15684	205	526	81.0	0.29	n.a
Fürbass et al. (30)+	25567	310	113	75.0	0.30	n.a.

*FAR, false positive alarms per hour; +development data set; *prospective data set.*

TABLE 3 | Patient specific, scalp-EEG based seizure detection algorithms tested in clinical settings.

References	EEG sample (hours)	Patients	Seizures	Sensitivity (%)	Specificity FAR (per hour)	Detection delay (seconds)
Qu and Gotman (47)	1071	10	n.a.	n.a.	1.40	n.a.
Qu and Gotman (59)	29.7	12	35	100	0.03	9.5
Qu and Gotman (60)	n.a.	12	47	100	0.02	9.35
Shoeb et al. (61)	60	36	139	94	0.25	8.0
Khamis et al. (48)	1624	10	83	91.6	0.27	n.a.
Minasyan et al. (49)	625	25	86	100	0.02	4.0

FAR, false positive alarms per hour.

like frontal intermittent rhythmic delta activity (FIRDA) or temporal intermittent rhythmic delta activity (TIRDA) or by various especially rhythmic artifacts (including chewing, tooth brushing, repetitive movements, eye movements etc.) (30, 37, 58). Algorithms need to be developed and tested on large amount of EEG data containing also prolonged time periods of interictal EEG across all stages of the sleep-waking cycle and including all kinds of artifacts and non-ictal physiological and pathological EEG patterns in order to obtain stable and reproducible results in a clinical setting (30, 37, 58).

While patient specific algorithms can further enhance sensitivity and selectivity, drawbacks of these approaches include sometimes complex parameter adjustments and the necessity of training for individual patients (47–49).

If a detection algorithm is used as an alarm system, on-line calculation with short detection delays represents a prerequisite. Detection delays reported in the literature vary between 2 and 19 s (39).

Draw-backs of scalp-EEG based seizure detection systems include the complexity of the EEG signal, attenuation of the EEG signal by skull and scalp and the fact that large parts of the cerebral cortex including mesial frontal, basal frontal, and mesial temporal areas are not accessible to the scalp-EEG. The most significant limitation remains the application of scalp-EEG based seizure detection systems in an outpatient setting because it is not acceptable for patients to wear EEG electrode arrays for prolonged time periods in everyday life (58). Recently developed subcutaneous EEG electrodes may offer a practical solution for this problem (63). Chronically implanted intracranial electrodes represent another option for long-term outpatient EEG recordings which have been successfully applied for seizure prediction (6) and seizure detection with responsive brain stimulation (17–21). However, despite their invasive nature these devices suffers from high rates of false positive detections limiting the clinical usefulness for seizure detection in a clinical setting (64). The reader is referred to an recent excellent paper on the problems and future aspects of seizure detection based on invasive EEG recordings (64).

AUTOMATIC SEIZURE DETECTION BASED ON ELECTROCARDIOGRAPHY (ECG)

ECG represents a simple and easy to record signal for automatic seizure detection. Many seizures are accompanied by a pronounced ictal sinus tachycardia (65). Ictal sinus tachycardia is caused primarily by direct activation of the central autonomic network through epileptic discharges and to a much lesser extent the mere consequence of motor manifestations during epileptic seizures (66). Cortical areas of the central autonomic network include the amygdala, the anterior insula, the anterior cingulate cortex, the ventromedial prefrontal cortex, and the posterior orbitofrontal cortex. Subcortical areas of the central autonomic network are represented in the hypothalamus, the periaqueductal gray matter, the parabrachial Köller-Fuse region, the nucleus of the tractus solitarius, the nucleus ambiguous and the ventrolateral medulla oblongata (67).

Compared to the EEG, the ECG signal is highly robust and less prone to artifacts. Long-term ECG recordings can be easily obtained in an ambulatory setting using ambulatory ECG, smart watches and minimally invasive implantable loop recorders for prolonged time periods. Contrary to long term scalp EEG recordings these systems impose no burdens or restrictions to the patient and are well tolerated by patients. Compared to long-term intracranial EEG recordings, implantable loop recorders are far less invasive, carry only negligible risks for the patients, are widely available commercially and considerably less costly than implantable EEG recording devices. Finally, the ECG signal is simpler to process and to analyze than the EEG signal.

Definition of ictal sinus tachycardia is rather heterogeneous in the literature (65). The most frequent definition refers to a heart rate >100 beats per minute (bpm) corresponding to the threshold for a maximum normal heart rate for patients older than 15 years. Other definitions include a heart rate >120 bpm, a heart rate >10 bpm above baseline heart rate, age-adjusted thresholds and not further specified significant changes in heart rate relative to baseline (65).

In general, a lower threshold will result in a higher sensitivity, but lower specificity corresponding to a higher FAR, whereas a higher threshold will be associated with a lower sensitivity, but a higher specificity corresponding to a lower FAR.

Concerning algorithms for detection of ictal sinus tachycardia, so-called threshold and curve fitting algorithms can be distinguished. Threshold algorithms set an alarm when the average heart frequency in an analyzing time window exceeds the average heart frequency in a baseline time window by a predefined threshold parameter of 2.5–25 bpm. The duration of the analyzing time window can be varied for instance from 5 to 15 s, while the duration of the baseline time window is kept constant at 20 s (68). The most recent version of the

vagal nerve stimulator incorporates a so-called cardiac based seizure detection algorithm (CBSDA) which compares the most recent heart rate to a background heart rate established over approximately the previous 5 min of R–R intervals. Whenever heart rate (during a presumed seizure) exceeds baseline heart by 20–70% (the actual value can be programmed in 10% increments) for at least 1 s an automatic on-demand stimulation is triggered in a closed loop fashion (69). Curve fitting algorithms on the contrary calculate changes in heart frequency based on predefined algorithms resulting in an increased specificity and shortened detection latency (68, 70, 71).

According to a recent review article incorporating 34 articles ictal sinus tachycardia can be observed in 82% of patients (65). While some studies reported consistent ictal heart rate changes within a given patient (72, 73), others observed intraindividual variability of ictal heart rate changes (68, 71, 74–76). The absolute increase in heart rate averaged 34.23 bpm per seizure and 33.51 bpm per patient (weighted average across several studies) (65). Concerning seizure types, ictal sinus tachycardia was observed in 12% of subclinical seizures, in 71% of focal onset seizures, in 64% of generalized seizures and in 76% of mixed seizure types (weighted average across several studies) (65). Concerning seizure onset zone, ictal sinus tachycardia was more consistent and prevalent in seizures of temporal origin as compared to those of extratemporal origin (65). While the effect of seizure onset lateralization was inconsistent (65), some studies suggest a more pronounced increase in heart rate during seizures arising from the non-dominant hemisphere (70, 71, 77–79). Secondarily generalized tonic-clonic seizures result in a higher ictal heart rate as compared to complex partial seizures (80). Finally, an elevated heart rate was observed already prior to seizure onset in those focal seizures evolving to secondarily generalized seizures as compared to those focal seizures which remained localized (81).

In a study with intracranial electrodes, the temporal relationship between the onset of ictal tachycardia, seizure onset on intracranial EEG, seizure onset on scalp-EEG and clinical seizure onset was investigated (82). Ictal tachycardia occurred after seizure onset on intracranial EEG in all seizures with mean latencies of 21.6–23.7 s. On the contrary, ictal tachycardia preceded scalp-EEG onset in 9/13 patients and in 48/78 seizures with mean latencies of 7.8–14.0 s. Furthermore, ictal tachycardia occurred before the first clinical sign in 10/13 patients and in 56/78 seizures with mean latencies of 6.5–9.5 s. Ictal tachycardia was observed earlier in seizures arising from the hippocampal formation than in those of extrahippocampal onset. Finally, ictal tachycardia occurred earlier in seizures originating from the right temporal lobe as compared to those originating from the left temporal lobe. The authors concluded that ictal tachycardia is an ictal rather than a preictal phenomenon and that ictal tachycardia may be an appropriate noninvasive marker for closed-loop interventions (82).

Concerning specificty, heart rate increases during epileptic seizures occur faster and are more pronounced as compared to those associated with physical exercise or nocturnal arousals (83, 84). In the VNS study, a mean sensitivity of 80% with a FAR of 0.5–7.2/h and a detection latency of 6–35 s could be achieved using the cardiac based seizure detection algorithm (CBSDA) (69).

Analysis of heart rate variability represents a very promising approach for ECG based seizure detection. Especially the so-called modified cardiac sympathetic index (CSI100) seems to be suitable to detect the abnormal increase in sympathetic tone during epileptic seizures (85). Thus, the CSI100 based algorithm showed an excellent performance for seizure detection: All seizures were detected in 13/17 patients with a mean detection latency of 16 s (range: 6 s before and 50 s after EEG or clinical seizure onset). Furthermore, the CSI100 based algorithm could differentiate very well between ictal ECG changes and physiologic, exercise-induced ECG changes, while a simple analysis of the heart rate failed to do so (85).

AUTOMATIC SEIZURE DETECTION BASED ON SURFACE ELECTROMYOGRAPHY (SEMG)

Quantitative analysis of surface electromyography (sEMG) represents a valuable tool for the detection of seizures with prominent motor manifestations (16).

The deltoid muscle, the anterior tibialis muscle (86–89) as well as the brachial biceps and triceps muscles (90, 91) have been used as recording sites for sEMG based seizure detection.

For the detection of generalized tonic-clonic seizures sEMG from the deltoid muscle yielded higher sensitivity, but lower specificity than sEMG from the anterior tibialis muscle [deltoid muscle: sensitivity 100%, false positive alarm rate 1 per 24 h, detection latency 13.7 s (86); anterior tibialis muscle: sensitivity 57%, false positive alarm rate 1 per 12 days, detection latency 25 s (87)]. For the detection of tonic seizures with sEMG applied to the deltoid muscle a sensitivity of 53–63% with a false positive alarm rate of 0.08 bis 7.90/h could be obtained (89).

Continuous sEMG recordings for 1,399 h from the brachial biceps and triceps muscle were performed in 33 patients with 196 epileptic seizures (21 generalized tonic-clonic seizures, 96 myoclonic, 28 tonic, 12 absence, and 42 focal seizures with or without loss of awareness) and 4 nonepileptic spells. The algorithm detected 20 of 21 generalized tonic-clonic seizures corresponding to a sensitivity of 95% with an average detection latency of 20 s. While only one false positive alarm was observed in the postictal phase after a generalized tonic-clonic seizure, no false positive alarms were triggered by other seizure types (90).

In a prospective multicenter phase III trial in 199 patients investigated in 11 epilepsy monitoring units, sEMG from the brachial biceps muscle detected 35 out of 46 of generalized tonic-clonic seizures corresponding to a sensitivity of 76% with a false positive alarm rate of 2.52/24 h. If the device was correctly placed over the midline of the biceps muscle, 29/29 of generalized tonic-clonic seizures could be detected (sensitivity 100%, mean false positive alarm rate 1.44/24 h, mean detection latency 7.70 s). While mild to moderate adverse events (mostly skin irritation caused by the electrode patch that resolved without treatment) occurred in 28% of participants leading to study withdrawal in 9%, no serious adverse events were reported (91).

In a prospective study in 71 patients from 3 centers sEMG recordings from brachial biceps muscle (mean recording time per patient 53.19 h, total recording time 3735.5 h), a sensitivity of 93.8% (30 out of 32 generalized tonic-clonic seizures) with a median detection latency of 9 s (range: −4 to 48 s) and a false alarm rate was 0.67/24 h could be obtained. No adverse events were observed (92).

Quantitative sEMG analysis provides direct information about the electric activity in the motor cortex and therefore is useful to elucidate the pathomechanisms of convulsive seizures (93). Thus sEMG can differentiate between generalized tonic-clonic seizures and maximal voluntary muscle contraction (93). sEMG correctly classified 24/25 (96%) of generalized tonic-clonic seizures and 18/19 (95%) of psychogenic non-epileptic seizures corresponding to an overall diagnostic accuracy of 95% (94). Furthermore, the tonic phase of generalized tonic-clonic seizures showed different quantitative features as compared to tonic seizures. Furthermore, due to its high temporal resolution sEMG facilitates a detailed characterization of the temporal evolution of generalized tonic-clonic seizures suggesting that the same inhibitory mechanisms involved in the prevention of buildup of seizure activity, contribute to seizure termination. Thus, quantitative sEMG can be viewed as a neurophysiologic biomarker for detection of generalized tonic-clonic seizures and for the automated differentiation between convulsive and non-convulsive epileptic seizures (93).

CONCLUSION

Automatic computer-based seizure detection and warning devices are important for objective seizure documentation, for SUDEP prevention, to avoid seizure related injuries and social embarrassments as a consequence of seizures, and to develop on demand epilepsy therapies. Automatic seizure detection systems can be based on direct analysis of epileptiform discharges on scalp-EEG or intracranial EEG, on detection of motor manifestations of epileptic seizures using surface electromyography (sEMG), accelerometry (ACM), video detection systems, and mattress sensors and finally on the assessment of changes of physiologic parameters accompanying epileptic seizures measured by electrocardiography (ECG), respiratory monitors, pulse oximetry, surface temperature sensors, and electrodermal activity (EDA). Different seizure types affect preferentially different measurement parameters. While EEG changes accompany all types of seizures, sEMG and ACM are suitable primarily for the detection of seizures with major motor manifestations. Therefore, multimodal systems combining several different measurement parameters certainly represent the future of automatic seizure detection (16, 58). While most systems provide sensitivities over 70%, specificity expressed as false alarm rates still needs to be improved. Patients' acceptance and comfort of a specific device are of critical importance for its long-term application in meaningful clinical way.

AUTHOR CONTRIBUTIONS

CB conceived, designed and wrote the manuscript, prepared the tables and reviewed the final version. JK revised the manuscript, prepared the tables and proofread the final version. MR revised the manuscript, prepared the tables and proofread the final version of the paper.

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Automated Long-Term EEG Review: Fast and Precise Analysis in Critical Care Patients

Johannes P. Koren[1,2], Johannes Herta[3], Franz Fürbass[4], Susanne Pirker[1,2], Veronika Reiner-Deitemyer[2], Franz Riederer[1,2], Julia Flechsenhar[2,5], Manfred Hartmann[4], Tilmann Kluge[4] and Christoph Baumgartner[1,2,6]*

[1] Karl Landsteiner Institute for Clinical Epilepsy Research and Cognitive Neurology, Vienna, Austria, [2] Department of Neurology, General Hospital Hietzing With Neurological Center Rosenhügel, Vienna, Austria, [3] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria, [4] Center for Health and Bioresources, AIT Austrian Institute of Technology GmbH, Vienna, Austria, [5] Epilepsie-Zentrum Berlin-Brandenburg, Ev. Krankenhaus Königin Elisabeth Herzberge, Berlin, Germany, [6] Medical Faculty, Sigmund Freud University, Vienna, Austria

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Vincent Alvarez, Hôpital du Valais, Switzerland

***Correspondence:**
Johannes P. Koren
johannes-peter.koren@wienkav.at

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Background: Ongoing or recurrent seizure activity without prominent motor features is a common burden in neurological critical care patients and people with epilepsy during ICU stays. Continuous EEG (CEEG) is the gold standard for detecting ongoing ictal EEG patterns and monitoring functional brain activity. However CEEG review is very demanding and time consuming. The purpose of the present multirater, EEG expert reviewer study, is to test and assess the clinical feasibility of an automatic EEG pattern detection method (Neurotrend).

Methods: Four board certified EEG reviewers used Neurotrend to annotate 76 CEEG datasets à 6 h (in total 456 h of EEG) for rhythmic and periodic EEG patterns (RPP), unequivocal ictal EEG patterns and burst suppression. All reviewers had a predefined time limit of 5 min (± 2 min) per CEEG dataset and were compared to a predefined gold standard (conventional EEG review with unlimited time). Subanalysis of specific features of RPP was conducted as well. We used Gwet's AC_1 and AC_2 coefficients to calculate interrater agreement (IRA) and multirater agreement (MRA). Also, we determined individual performance measures for unequivocal ictal EEG patterns and burst suppression. Bonferroni-Holmes correction for multiple testing was applied to all statistical tests.

Results: Mean review time was 3.3 min (± 1.9 min) per CEEG dataset. We found substantial IRA for unequivocal ictal EEG patterns (0.61–0.79; mean sensitivity 86.8%; mean specificity 82.2%, $p < 0.001$) and burst suppression (0.68–0.71; mean sensitivity 96.7%; mean specificity 76.9% $p < 0.001$). Two reviewers showed substantial IRA for RPP (0.68–0.72), whereas the other two showed moderate agreement (0.45–0.54), compared to the gold standard ($p < 0.001$). MRA showed almost perfect agreement for burst suppression (0.86) and moderate agreement for RPP (0.54) and unequivocal ictal EEG patterns (0.57).

Conclusions: We demonstrated the clinical feasibility of an automatic critical care EEG pattern detection method on two levels: (1) reasonable high agreement compared to the gold standard, (2) reasonable short review times compared to previously reported EEG review times with conventional EEG analysis.

Keywords: neurotrend, intensive care unit, continuous EEG, non-convulsive seizures, status epilepticus, standardized critical care EEG terminology

INTRODUCTION

Nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) are a common burden for neurological critical care patients. People with epilepsy or epileptic encephalopathy often develop ongoing NCSE after status epilepticus (SE) with prominent motor activity (convulsive SE) (1–4). Functional outcome and prognosis may be worse in patients with ongoing NCSE due to increased metabolic demand and thus causing secondary brain damage (5–8). Recent studies show mortality of up to 40% in super-refractory SE and increased costs and length of stay associated with refractory course (9). Continuous EEG (CEEG) in neurological intensive care units is currently considered the gold standard for detecting NCS and NCSE as well as monitoring sedoanalgesia and induced burst suppression patterns in patients with refractory or super-refractory SE (10). However, CEEG is very labor-intensive and time consuming in terms of visual real time analysis in daily practice (11). Automatic analysis tools are a promising approach to solve this shortcoming of CEEG. Previous publications focused mostly on quantitative EEG analysis and showed seizure identification sensitivities of 43–94% (11–17).

Our study group developed an automated analysis software called NeuroTrend (NT) and previously described the mathematical and technical details of the software (18). In short, NT consists of several mathematical algorithms which detect rhythmic and periodic EEG patterns (RPP, i.e., periodic discharges, rhythmic delta activity and spike-and-wave complexes) according to the ACNS standardized critical care EEG terminology (SCCET) as well as faster rhythmic activity in the theta and alpha range. The core idea of NT is to give a smooth overview of up to 100 h of CEEG in a graphical user interface (GUI), visualizing automatic analysis results in a horizontal fashion. Raw EEG data of each detection result can be easily assessed and reviewed on a separate computer monitor. In this way EEG reviewers can focus on pre-analyzed episodes of interest.

Abbreviations: ACNS, American Clinical Neurophysiology Society; CEEG, continuous electroencephalography; CCEEG, critical care continuous electroencephalography; CSA, compressed spectral array; EEG, electroencephalography; FN, false negative; FP, false positive; GUI, graphical user interface; ICU, intensive care unit; IRA, interrater agreement; MRA, multirater agreement; NCS, nonconvulsive seizures; NCSE, nonconvulsive status epilepticus; NT, NeuroTrend; PD, periodic discharges; QEEG, quantitative electroencephalography; RDA, rhythmic delta activity; RPP, rhythmic and periodic EEG patterns; SCCET, Standardized Critical Care EEG Terminology; SE, status epilepticus; SW, spike-and-wave complexes; TN, true negative; TP, true positive.

NT showed high sensitivity for the detection of RPP in a previous study (19). Results of this study were critically reviewed and the software was further improved in terms of specificity. In a second study, NT was evaluated as bedside monitoring in intensive care nurses (non-EEG-expert reviewers). Herta et al. showed that multirater agreement (MRA) and interrater agreement (IRA) were almost perfect for spike-and-wave complexes, rhythmic delta activity, and burst suppression. Electrographic seizure patterns and periodic discharges showed substantial agreement (20).

The current study focuses on the clinical feasibility of NT as CEEG review tool. Specifically we hypothesized, that NT is a time saving method which detect relevant findings in CEEG with high accuracy. Therefore we conducted a multirater study with four board certified EEG reviewers (expert EEG reviewers) annotating CEEG datasets using NT with predefined time limits (5 min ± 2 min) and compared theses annotations with a predefined gold standard.

METHODS

We recruited four experienced, board certified EEG reviewers (SP, VR, FR, and JF) from our department to review 80 continuous EEG (CEEG) datasets of 20 critical care patients, each lasting 6 h, with an automatic EEG analysis software (Encevis, NeuroTrend, AIT Austrian Institute of Technology GmbH, Vienna, Austria; http://www.encevis.com). The NT setup for the current study consisted of an EEG viewer (computer monitor #1, 1920 × 1080 pixels) and the separate trending tool GUI (computer monitor #2, 1280 × 1024 pixels). **Figures 1**, **2** give an overview of the NT GUI. All reviewers had more than 5 years of EEG reading experience and were blinded to patient selection, quantity of negative controls and conclusions of other reviewers.

Setup and Training

All four reviewers had moderate experience with critical care EEG recordings (i.e., all four reviewers read critical care EEGs on a weekly basis) and none with the automatic EEG analysis software (Encevis, NeuroTrend). We therefore trained all reviewers prior to our study with a modified version of the Critical Care EEG Monitoring Research Consortium's Training Module, (ACNS SCEET Training Module, http://www.acns.org/practice/guidelines) (21), refreshed the knowledge about state-of-the-art nonconvulsive seizure (NCS) criteria (Salzburg Consensus Criteria) (22) and gave an introduction to NT and its GUI. The initial training phase lasted 1 h. Subsequently, 10 training datasets of continuous critical care

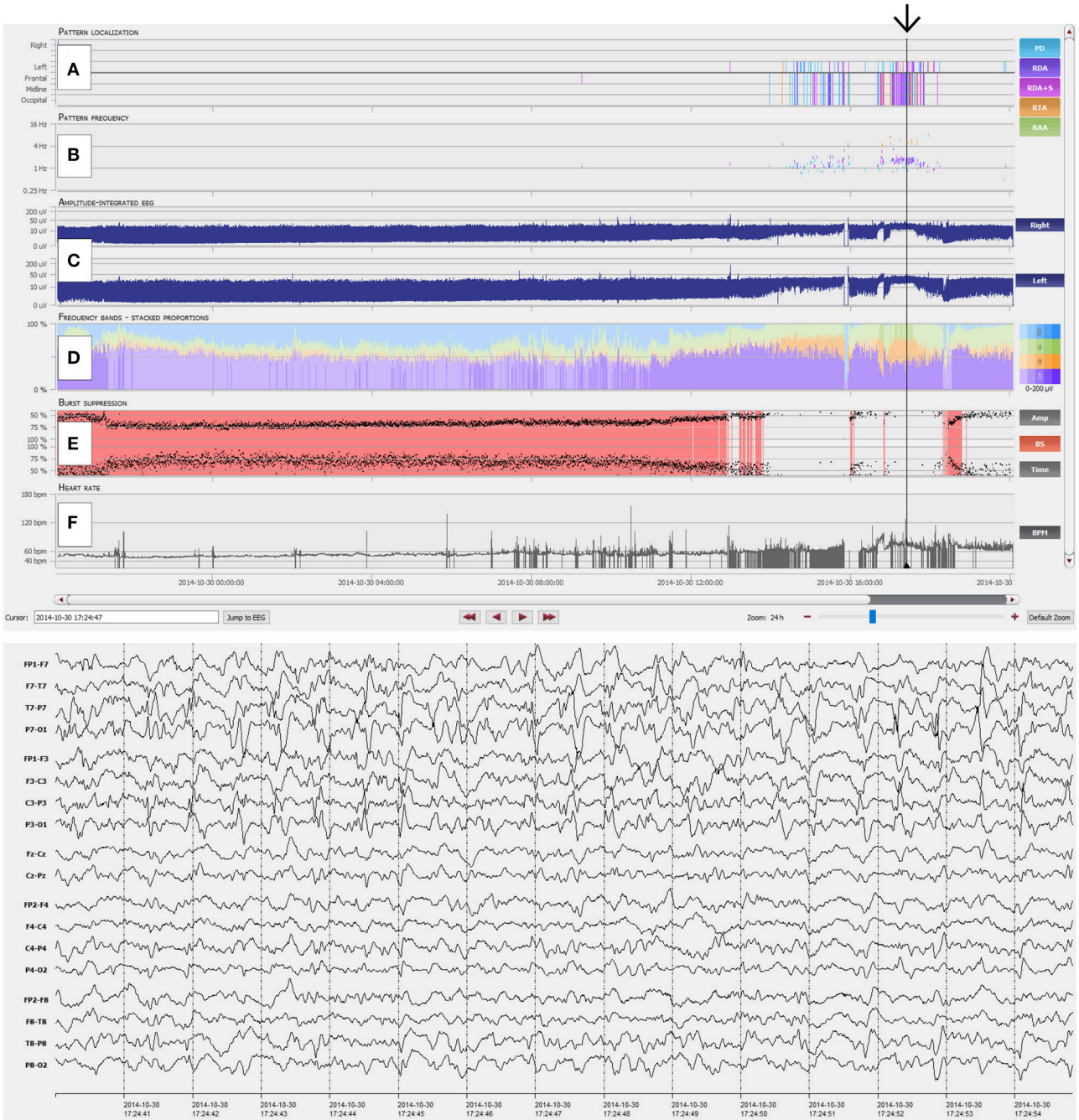

FIGURE 1 | Overview of the NeuroTrend graphical user interface (GUI). **(A)** Automatic, color coded pattern detection (light blue: PD, periodic discharges; violet: RDA, rhythmic delta activity; pink: RDA+S, rhythmic delta activity plus superimposed spikes; orange: RTA, rhythmic theta activity; light green: RAA, rhythmic alpha activity); **(B)** Related frequencies of detected EEG patterns (the same color code as in A is used); **(C)** Amplitude integrated EEG for left and right hemisphere; **(D)** Frequency bands (beta-alpha-theta-delta) in a color coded (blue: beta; green: alpha; orange: theta; violet: delta), stacked proportion view (stronger colors signal higher amplitudes); **(E)** Burst suppression detection (continuous red markers signal presence of burst suppression); **(F)** Heart rate frequency plot. The black arrow highlights an EEG example of 1.5-2 c/s left hemispheric periodic discharges with superimposed rhythmic activity, which can be easily detected with the Neurotrend GUI.

EEGs (CCEEG) were provided to all four reviewers. This second phase of training lasted also 1 h. Training slides were provided for self-study but could not be used during review.

EEG Data

Twenty CCEEG datasets out of 98 consecutive monitored, neurological critical care patients were randomly selected using Microsoft Excel's random number generation function. No

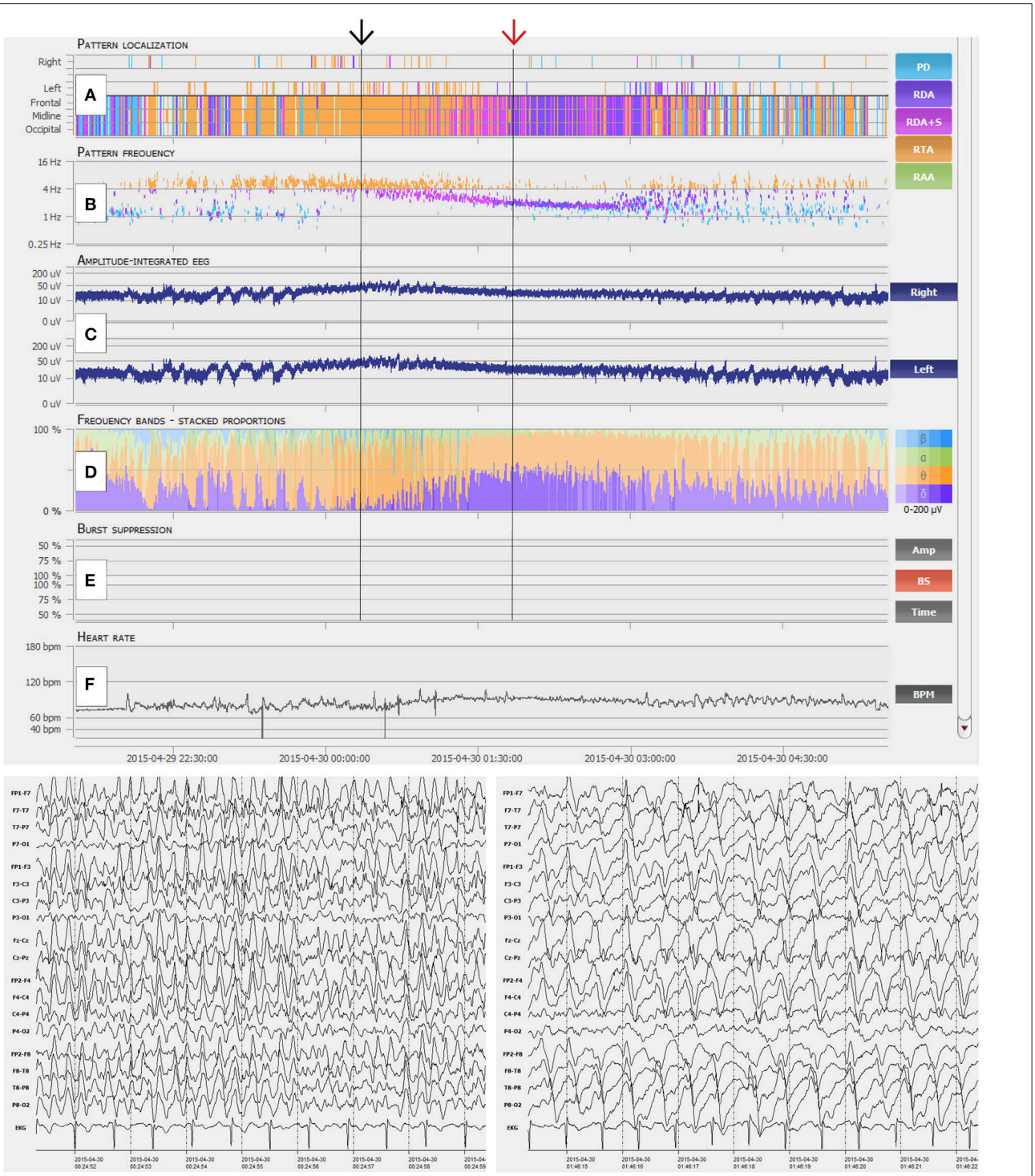

FIGURE 2 | Interpretation of NeuroTrend. **(A)** Recurrent seizures are detected as generalized rhythmic theta activity (RTA, orange plots) between 22:30 and 00:00. Then ongoing seizure activity is displayed by ongoing detection of RTA until 01:30. Around 01:00 detection of generalized rhythmic delta activity (RDA, pink and violet plots) overlap with RTA and further increases until 03:00. **(B)** Related pattern frequency detection reveal clear cut seizures above 3 c/s between 22:30 and 01:30 (black arrow). Overlapping RDA show a steady decrease from 3.5 to 2 c/s (red arrow). **(C)** Amplitude integrated EEG shows increment and decrement over both hemispheres at the beginning of each seizure from 22:30 to 23:30. Then a steady increase over both hemispheres can be seen during ongoing seizure activity from 00:00 until 01:00. **(D)** Frequency bands show a dominance of theta activity during seizure activity and the overlap of theta and delta activity around 01:30. **(E)** No burst suppression was detected. **(F)** Heart rate does not really show a concordance to seizure activity. In synopsis, this example represent typical spatiotemporal evolution of electrographic seizure activity, which can be easily detected with the graphical user interface of Neurotrend.

patient could be drawn twice. We tried to provide a reflection of the actual incidences of rhythmic and periodic EEG patterns seen in critical care EEG recordings in our monitored patients. Therefore, the selection process was as follows:

1) Six patients without any rhythmic or periodic EEG pattern were selected as negative controls
2) All patients with RPP and/or electrographic seizures were separated in to four pools according to their dominant EEG pattern (i.e., PD, RDA, SW, electrographic seizures). Because 14 patients had to be selected, we calculated the relative proportion within the RPP/electrographic seizure group for each pattern. We calculated a relative incidence of 51% for PD and therefore selected 7 patients with PD for the present study. Accordingly, we selected 4 patients with RDA (relative incidence of 27%), 2 patients with electrographic seizures (relative incidence of 13%) and 1 patient with SW (relative incidence of 9%).

All CEEGs were recorded with a Micromed EEG recording system (SystemPLUS Evolution 1.04.95, Micromed S.p.A., Veneto, Italy) using 21 electrodes placed according to the International 10-20 system with a sampling rate of 256 Hz. Patients with less than 19 surface electrodes due to operational wounds, less than 24 h CEEG duration, technical insufficient EEG data and training datasets were excluded from the selection process.

The first 24 h of each CEEG dataset of every patient was cut into four equal parts, each part lasting 6 h. Thus, 80 CEEG datasets à 6 h were obtained. These datasets were randomized and then used for the review process.

Clinical Data

All reviewers obtained a short written overview of the original medical history for each patient included in the study. Medication, original EEG reports, medical procedures after CEEG and clinical diagnosis were withheld.

Review Process

All four reviewers analyzed 80 randomized CEEG datasets with NT. In order to answer our hypothesis, we set a 5 min time limit for each dataset (i.e., 6 h of CEEG). This time limit could be extended to a maximum of 7 min. The exact review duration for each dataset was recorded.

Reviewers had to use predefined annotation sheets (Supplementary Material 1) and annotate each CEEG dataset separately. We used following items according to the ACNS SCEET (21): (1) Presence of rhythmic or periodic EEG patterns (yes/no) (2) if yes, what does the annotated pattern represent (Status epilepticus/electrographic seizure/no ictal activity) (3) Localization (Main Term 1; generalized/lateralized/bilateral independent) (4) Morphology (Main Term 2; electrographic seizure pattern/spike-and-wave complexes/rhythmic delta activity/periodic discharges) (5) Prevalence (>90%/50–89%/10–49%/1–9%) (6) Frequency (>3Hz/1-3Hz/<1Hz), (7) Trend (evolution/fluctuation/stationary) (8) Presence of burst-suppression (yes/no) and (9) EEG background activity (slowing, yes/no; localization, focal/generalized; duration, intermittent/continuous).

Gold Standard

Two independent clinical neurophysiologists (JK and JH) with substantial CCEEG reading experience reviewed all CEEG datasets prior to this study. Our general CCEEG review strategy was described elsewhere (23). In short all CEEGs were classified according to the ACNS SCCET (21) and NCS criteria proposed by Leitinger et al. (Salzburg Consensus Criteria) (22). If discrepancies in the classification of certain EEG patterns occurred between the two reviewers, a third board-certified electroencephalographer (CB) with substantial CCEEG reading experience was involved. The third reviewer was involved in approximately 30% of all CEEG datasets, mainly to clarify the morphology (Main Term 2) of rhythmic and periodic EEG patterns. Using this method, we obtained consensus agreements for all CEEG datasets. We considered this visual EEG review consensus agreement as gold standard for the present study.

Statistical Analysis

Differences of review times between reviewers were calculated per patient and per EEG dataset with the Kruskal-Wallis test, because the recorded review times did not show a normal distribution. Chi-square test was used for categorical and ordinal data.

For IRA we used Gwet's multirater agreement coefficients AC_1 (for categorical data) and AC_2 (for ordinal data) (24). Gwet's AC_1 and AC_2 solve some shortcomings of established kappa coefficients, i.e., reliable performance if several raters show high or low agreement or if the true prevalence of classes being rated is nonuniform (25–27). We calculated IRA of each reviewer and our defined gold standard for the following annotation items:

1) Presence of RPP defined as follows:
   a. No pathologic EEG patterns according to ACNS SCCET Main Term #2 and NCS criteria (equals "rhythmic and periodic EEG patterns not present" in the annotation sheet)
   b. Interictal EEG patterns according to ACNS SCEET Main Term #2 but not fulfilling NCS criteria (equals "rhythmic and periodic EEG patterns present" and one of the following items "spike-and-wave complexes (SW)," "rhythmic delta activity (RDA)" or "periodic discharges (PD)" and "no ictal activity" in the annotation sheet)
   c. Ictal EEG patterns fulfilling NCS criteria (equals "rhythmic and periodic EEG patterns present" and "Status epilepticus" or "electrographic seizure" in the annotation sheet)
2) Presence of unequivocal ictal EEG patterns (yes/no) defined as ictal EEG patterns fulfilling NCS criteria (equals "rhythmic and periodic EEG patterns present" and "Status epilepticus" or "electrographic seizure" in the annotation sheet)
3) Presence of burst-suppression (yes/no) according to ACNS SCEET Background EEG defined as "burst-suppression present" in the annotation sheet.

We calculated unweighted MRA between all four reviewers for following annotations items:

1) Presence of RPP as defined in the IRA section

2) Presence of unequivocal ictal EEG patterns as defined in the IRA section
3) Presence of burst-suppression as defined in the IRA section

We performed a subanalysis of RPP according to ACNS SCCET Main Terms and Modifiers. Annotations without RPP were excluded in the following manner: if two or less out of four reviewers did not annotate RPP in a specific EEG dataset, then this dataset was excluded from further analysis. We used custom weighted analysis (further details are provided in the Supplementary Material 2) and calculated MRA of the remaining EEG datasets for the following items:

a. Localization (Main Term #1) defined as localization of RPP (equals "rhythmic and periodic EEG patterns present" and one of the following items "generalized", "lateralized" or "bilateral independent" in the annotation sheet).
b. Morphology (Main Term #2) defined as morphology of RPP (equals "rhythmic and periodic EEG patterns present" and one of the following items "SW," "RDA," or "PD" in the annotation sheet)
c. Prevalence (Modifier #1) defined as prevalence of RPP (equals "rhythmic and periodic EEG patterns present" and one of the following items ">90%," "50–89%," "10–49%," or "1–9%" in the annotation sheet)
d. Frequency (Modifier #3) defined as frequency of RPP (equals "rhythmic and periodic EEG patterns present" and one of the following items ">3 Hz," "1–3 Hz" or "<1 Hz" in the annotation sheet)
e. Trend (Modifier #9) defined as trend of RPP (equals "rhythmic and periodic EEG patterns present" and one of the following items "evolution," "fluctuation," or "stationary" in the annotation sheet)

Following categories were used to quantify IRA and MRA: slight agreement 0.01–0.20; fair agreement 0.20–0.40; moderate agreement 0.40–0.60; substantial agreement 0.60–0.80; and almost perfect agreement 0.80–1 (25, 28). Confidence intervals of 95% were calculated as well.

Performance analysis of individual reviewers compared to the gold standard was conducted as follows for unequivocal ictal EEG patterns and burst suppression: CEEG datasets with positive reviewer annotation for ictal EEG patterns/burst suppression and positive gold standard annotation for ictal EEG patterns/burst suppression were counted as true positive (TP). If the gold standard showed no annotation in CEEG datasets with reviewer annotations for ictal EEG patterns/burst suppression, than they were counted as false positive (FP). CEEG datasets without reviewer annotation for ictal EEG patterns/burst suppression and without gold standard annotation for ictal EEG patterns/burst suppression were counted as true negative (TN). If the gold standard showed an annotation for ictal EEG patterns/burst suppression in CEEG datasets without a reviewer annotation, than they were counted as false negative (FN). We then calculated sensitivity (TP/[TP+FN]) and specificity (TN/[TN+FP]).

Statistical analysis was performed using the commercially available statistical software SPSS (IBM SPSS Statistics Version 21), Microsoft Office Excel 2010 and 2013, quantpsy.org (interactive online statistical calculation tool) and AgreeStat 2015.6 (http://agreestat.com). Bonferroni-Holmes correction for multiple testing was applied to all statistical tests. Significance levels for all statistical tests were set at $p < 0.05$ after Bonferroni-Holmes correction.

RESULTS

Four CEEG datasets were excluded from the study because of technical issues and low data quality. Therefore, the remaining 76 datasets, 6 h of CEEG each, were annotated by all four reviewers (in total 456 h of EEG). Mean review time was 12 min (± 5.3 min) per patient and 3.3 min (± 1.9 min) per CEEG dataset. There was a statistical significant difference of individual review times per patient and per CEEG dataset between reviewers (**Table 1**).

IRA of RPP showed substantial agreement for Reviewer #1 (Gwet's AC_1 0.72) and #3 (0.68) compared to the gold standard. Reviewer #2 (0.45) and #4 (0.54) showed moderate agreement (**Table 2**; $p < 0.001$ for all reviewers).

IRA of unequivocal ictal EEG patterns showed substantial agreement for all four reviewers compared to the gold standard. Sensitivity of individual reviewers ranged from 68.4 to 97.4% (mean 86.8%) and specificity from 68.4% to 92.1% (mean 82.2%) (**Table 3**; $p < 0.001$ for all reviewers).

TABLE 1 | Mean review times of four independent EEG reviewers, who analyzed 76 continuous EEG segments of 20 critical care patients à 6 h.

	REV-1	REV-2	REV-3	REV-4	*P*-Value*
Review time in minutes per patient (mean ± standard deviation)	9.1 (± 6.0)	10.2 (± 5.1)	15.2 (± 4.6)	13.6 (± 5.6)	0.007
Review time in minutes per 6 h of continuous EEG (mean ± standard deviation)	2.5 (± 1.8)	2.8 (± 2.1)	4.0 (± 2.3)	3.8 (± 1.4)	<0.001

*All four EEG reviewers used an automatic detection software (Encevis NeuroTrend) and had a predefined time limit of 5 min per EEG segment. All EEG segments were randomized and reviewed independently. *p-Values of Kruskal-Wallis test after Bonferroni-Holmes correction for multiple testing; REV, reviewer.*

TABLE 2 | Interrater agreement on the incidence of rhythmic and periodic EEG patterns in 76 continuous EEG segments of 20 critical care patients à 6 h.

	Rhythmic and periodic EEG patterns			
	Gwet's AC_1	95% C.I.	*P*-Value*	Agreement
REV-1	0.72	0.59–0.86	<0.001	Substantial
REV-2	0.45	0.28–0.62	<0.001	Moderate
REV-3	0.68	0.54–0.82	<0.001	Substantial
REV-4	0.54	0.38–0.71	<0.001	Moderate

*Four board certified EEG reviewers used an automatic detection software (Encevis NeuroTrend) and had a predefined time limit of 5 min per EEG segment vs. gold standard (visual EEG analysis of three experienced EEG reviewers having unlimited time). All EEG segments were randomized and reviewed independently. *p-Values of Chi-Square test after Bonferroni–Holmes correction for multiple testing; REV, reviewer.*

IRA of burst-suppression showed substantial agreement for all four reviewers compared to the gold standard. Sensitivity of individual reviewers ranged from 93.3 to 100% (mean 96.7%) and specificity from 73.9 to 79.6% (mean 76.9%) (**Table 4**; $p < 0.001$ for all reviewers). **Figures 3**, **4** show examples of NeuroTrend detections.

Unweighted MRA between reviewers showed moderate agreement regarding RPP (Gwet's AC_1 0.54; $p = 0.07$) and unequivocal ictal EEG patterns (0.57; $p = 0.04$). Almost perfect agreement was achieved for burst-suppression (0.86; $p = 0.93$; **Table 5**). It should be noted, that a high, non-significant difference in unweighted MRA analysis for binary items, emphasizes a very high agreement between all four reviewers.

We included 45 CEEG datasets à 6 h of 15 critical care patients in our subanalysis of specific features of RPP (Main Terms and Modifiers according to the ACNS SCEET). Custom weighted MRA showed substantial agreement between reviewers for localization of RPP (Gwet's AC_2 0.65; $p = 0.02$), frequency of RPP (0.72; $p < 0.001$) and trend of RPP (0.74; p = 0.09). Moderate agreement was achieved for morphology of RPP (0.53; $p < 0.001$) and prevalence of RPP (0.56; $p = 0.02$; **Table 6**).

TABLE 3 | Sensitivity, specificity and interrater agreement on the incidence of unequivocal ictal EEG patterns in 76 continuous EEG segments of 20 critical care patients à 6 h.

	Ictal EEG patterns					
	Gwet's AC_1	95% C.I.	Sensitivity	Specificity	*P*-Value*	Agreement
REV-1	0.71	0.55–0.87	92.1%	78.9%	<0.001	Substantial
REV-2	0.61	0.43–0.79	68.4%	92.1%	<0.001	Substantial
REV-3	0.79	0.65–0.93	89.5%	89.5%	<0.001	Substantial
REV-4	0.66	0.49–0.84	97.4%	68.4%	<0.001	Substantial

*Four board certified EEG reviewers used an automatic detection software (Encevis NeuroTrend) and had a predefined time limit of 5 min per EEG segment vs. gold standard (visual EEG analysis of three experienced EEG reviewers having unlimited time). All EEG segments were randomized and reviewed independently. *p-Values of Chi-Square test after Bonferroni-Holmes correction for multiple testing; REV, reviewer.*

TABLE 4 | Sensitivity, specificity, and interrater agreement on the incidence of burst suppression in 76 continuous EEG segments of 20 critical care patients à 6 h.

	Burst suppression					
	Gwet's AC_1	95% C.I.	Sensitivity	Specificity	*P*-Value*	Agreement
REV-1	0.69	0.52–0.85	93.3%	78.3%	<0.001	Substantial
REV-2	0.68	0.53–0.85	100%	73.9%	<0.001	Substantial
REV-3	0.71	0.56–0.87	96.7%	79.6%	<0.001	Substantial
REV-4	0.69	0.53–0.85	96.7%	76.1%	<0.001	Substantial

*Four board certified EEG reviewers used an automatic detection software (Encevis NeuroTrend) and had a predefined time limit of 5 min per EEG segment vs. gold standard (visual EEG analysis of three experienced EEG reviewers having unlimited time). All EEG segments were randomized and reviewed independently. *p-Values of Chi-Square test after Bonferroni–Holmes correction for multiple testing; REV, reviewer.*

DISCUSSION

We conducted a multirater study to evaluate an automatic EEG pattern detection method (Encevis, NeuroTrend) for critical care CEEG in comparison to gold standard visual EEG analysis. Time limits were set to demonstrate the added value of NT.

Review Times

In general, very short review times (2.5–4 min per 6 h of CEEG; 9 to 15 min per 24 h of CEEG) were observed during our study, although there were statistical significant differences between individual reviewers. In comparison to a recent publication, which determined review times of various combinations of quantitative EEG (QEEG) and raw EEG analysis (QEEG only, 6 min; QEEG and raw EEG analysis, 14.5 min; raw EEG only, 19 min), our recorded review times were reasonable short (13). Another paper reported average review times of 8 min per 24 h of CEEG with compressed spectral array (CSA) guided review and 38 min with conventional visual EEG review. If seizures were present, prolonged review times were observed: 10 min for CSA and 44 min for conventional review (11). Other publications on automatic CEEG analysis did not report review times, although this a main point of interest (14, 16, 17).

Rhythmic and Periodic EEG Patterns and Ictal Activity

Two reviewers showed substantial agreement for RPP in the IRA analysis. The other two reviewers had moderate agreement for RPP compared to the gold standard. Because RPP were a three point item (no pathologic EEG patterns according to ACNS SCEET Main Term #2 present; rhythmic or periodic EEG patterns according to ACNS SCEET Main Term #2 present; ictal EEG patterns according to current NCS criteria), unweighted agreement coefficient analysis was expected to be lower than in binary items. Also unweighted MRA showed only moderate agreement for RPP, meaning that the reviewers moderately matched in their annotations among each other. In the custom-weighted subanalysis of specific RPP (i.e., periodic discharges, rhythmic delta activity and spike-wave complexes) substantial MRA was found for localization, frequency and trend. Morphology and prevalence showed moderate agreement, reflecting the difficult assessment of these patterns. Due to our study design we could not report sensitivity and specificity of RPP detection. A previous publication reported high overall sensitivities of periodic epileptiform discharges (100%) and rhythmic delta activity (97.1%) with CSA guided review (11). Specificity and MRA was not assessed by the authors. To the best of our knowledge, other publications about automated critical care CEEG analysis did not assess RPP. We believe, that due to our strict time limits, the detailed assessment of difficult rhythmic and periodic EEG patterns was limited. However, we wanted to demonstrate that a straight-forward analysis of several hours of critical care CEEG is possible and feasible in a few minutes with our proposed automatic detection software.

We observed substantial IRA for unequivocal ictal EEG patterns with sensitivities ranging from 68 to 97% (mean 87%)

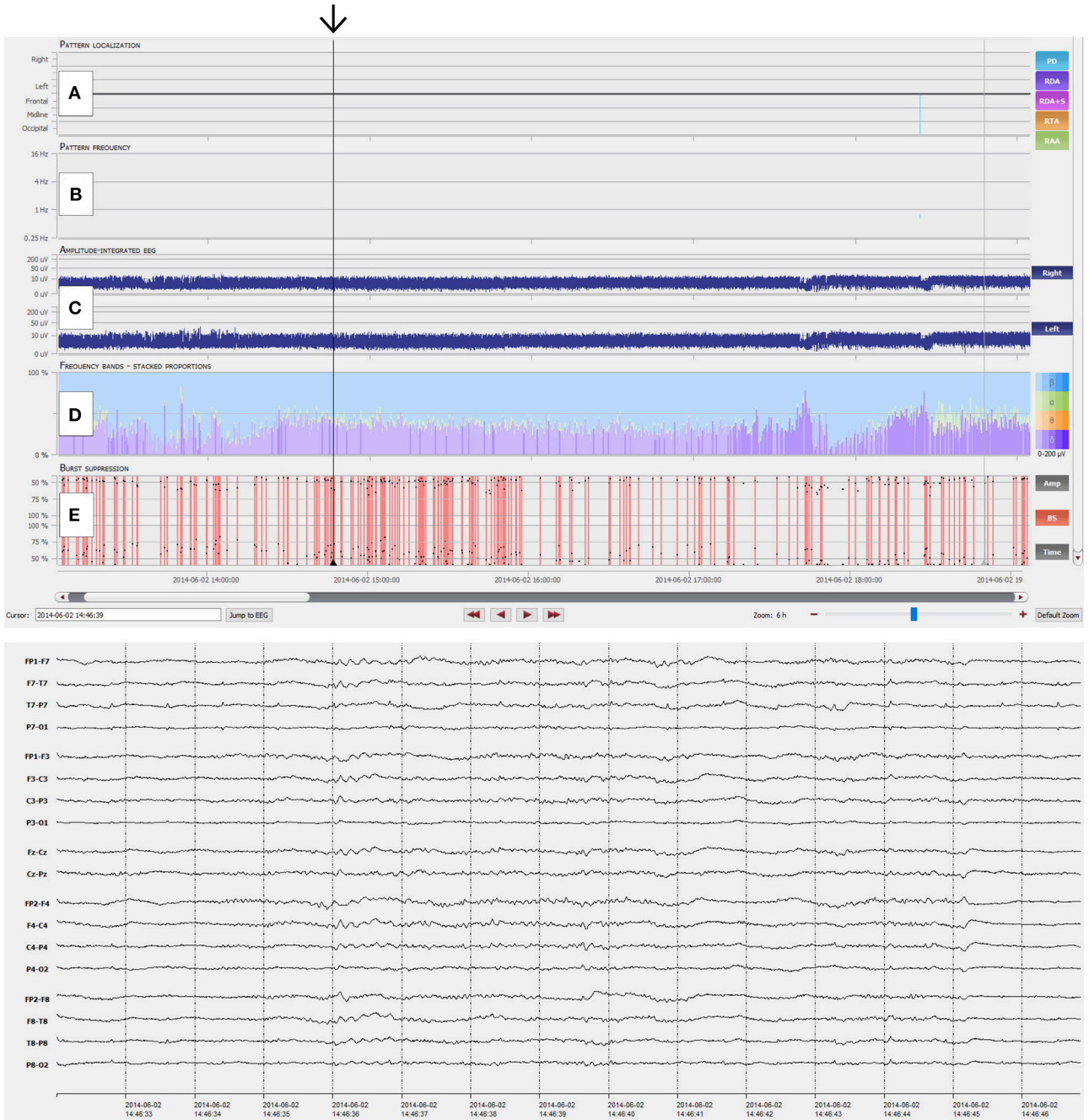

FIGURE 3 | NeuroTrend example of a 49-year-old man with left temporal gliosis and sepsis. Six hours of continuous EEG (CEEG) are depicted with the Neurotrend GUI. Suppressed EEG due to sedoanalgesia can be clearly identified (black arrow). **(A)** No rhythmic or periodic EEG pattern was detected. **(B)** No pattern frequencies are displayed. **(C)** Amplitude integrated EEG shows a stable amplitude of 5–10 μV over both hemispheres. **(D)** Frequency bands show a low amplitude beta activity with underlying, low amplitude delta activity. **(E)** Burst suppression detection shows several periods with burst suppression. GUI, graphical user interface.

and specificities from 68 to 92% (mean 82%), while MRA showed moderate agreement for ictal patterns. Our findings are in good agreement with previous studies, which used different QEEG techniques: overall sensitivities of seizure identification of 67–93%, specificities of 61–91% and false positive detection rates of 0.05–1 per hour were reported (11, 13–17). Low-amplitude, slow-frequency seizures which sometimes arise from RPP, seem to be harder to detect with automatic CEEG analysis, especially if RPP are continuously present (13). In our experience, automated, separate pattern detection results are very helpful in

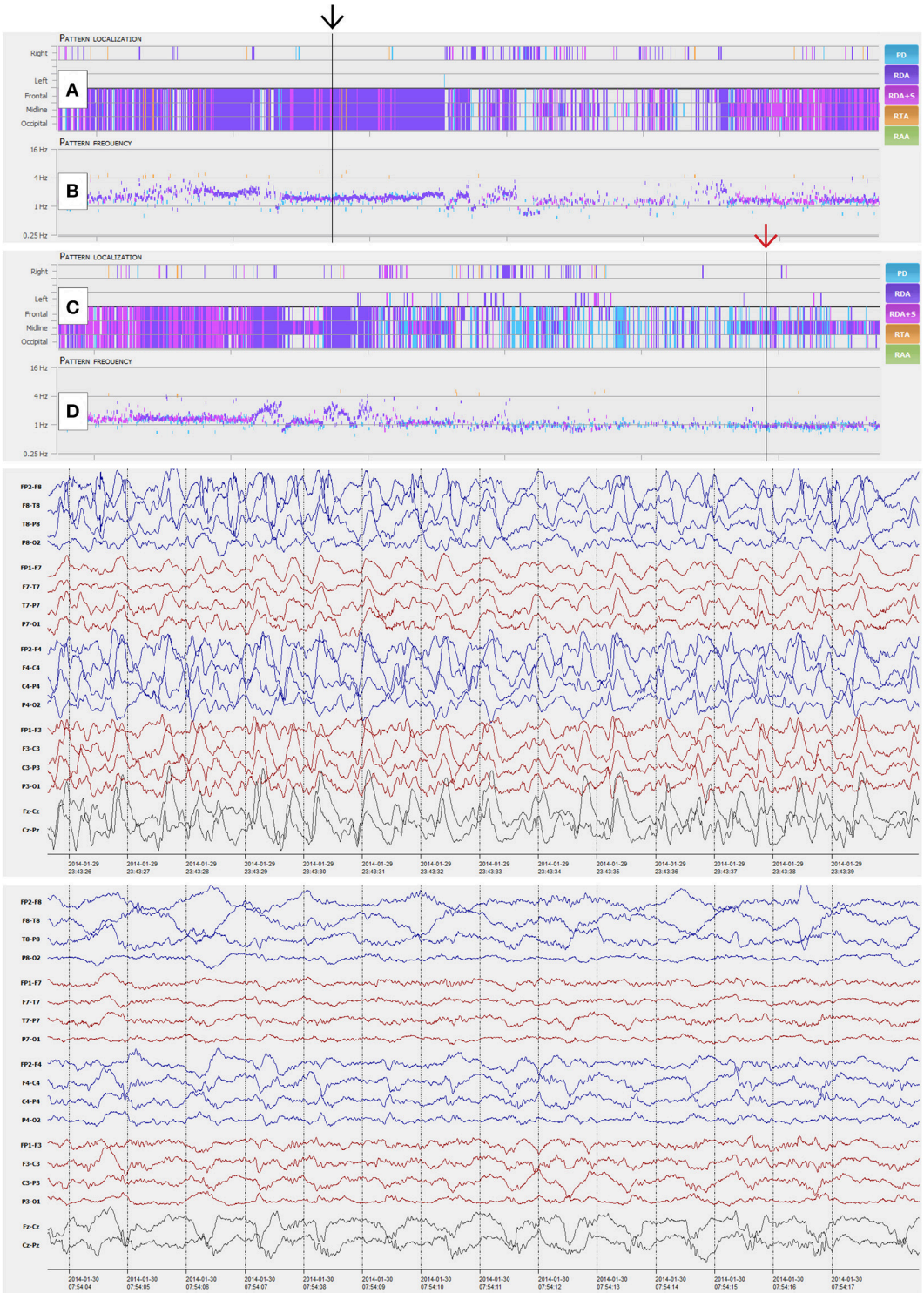

FIGURE 4 | NeuroTrend examples of a 41-year-old woman with morphine abuse and sepsis. Six hours of continuous EEG (CEEG) are depicted with a compressed Neurotrend GUI in the top section (Amplitude integrated EEG, frequency bands, burst suppression detection, and heart rate frequency plot are hidden in this example). **(A**,**B)** display a stable detection of 1.5 c/s generalized rhythmic delta activity (GRDA, black arrow). The following 6 h of CEEG in the section below, show an overlap with a more periodic EEG pattern around 1 c/s after 3 h of recording (**C**,**D**, red arrow). GUI, graphical user interface.

such demanding cases, but more review time may be needed, compared to clear cut high-frequency seizures.

We observed substantial IRA for burst suppression patterns with sensitivities ranging from 93 to 100% (mean 97%) and specificities from 74 to 80% (mean 77%). Kappa values of IRA were almost identical in a previous study conducted by our group, whereas sensitivity was lower and specificity slightly higher (29). Furthermore, MRA showed almost perfect agreement for burst suppression in the present study. This possibly reflects the good presentation of burst suppression patterns in the GUI of NT. In a recent survey, clinical neurophysiologists used automatic critical care CEEG analysis tools in 59% for burst suppression monitoring and in 29% for monitoring the depth of sedation (30). This findings emphasizes the need for a good performance of automatic burst suppression detection during critical care CEEG monitoring.

Study Design

We conducted an EEG-expert reader study to specifically evaluate the combined review approach of the NeuroTrend GUI with predefined time limits. NeuroTrend was developed and designed to use with two monitors with one screen for the automatic EEG pattern detection GUI and one screen for cross checking raw EEG (conventional review). This design intends to substantially reduce the workload of CEEG review by pre-filtering and categorizing relevant and important EEG information. Therefore, a study design was needed, which allowed independent EEG readers to annotate critical care continuous EEG with this specific review approach. To avoid possible reviewer bias, we did not conduct a second review and annotation round with conventional EEG analysis by the same four reviewers. This second review would not have been independent, because our review setup already included both automatic EEG pattern detection and conventional EEG review. Therefore, we compared individual annotations of the four included reviewers for each CEEG dataset with our defined gold standard (IRA) and among each other (MRA).

TABLE 5 | Unweighted multirater agreement (MRA) on the incidence of rhythmic and periodic EEG patterns, unequivocal ictal EEG patterns, and burst-suppression in 76 continuous EEG segments of 20 critical care patients à 6 h.

	Unweighted MRA			
	Gwet's AC_1	95% C.I.	*P*-Value*	Agreement
Rhythmic and periodic EEG patterns	0.54	0.43–0.65	0.07	Moderate
Ictal EEG patterns	0.57	0.44–0.69	0.04	Moderate
Burst-suppression	0.86	0.77–0.94	0.93	Almost perfect

*Four board certified EEG reviewers used an automatic detection software (Encevis NeuroTrend) and had a predefined time limit of 5 min per EEG segment. All EEG segments were randomized and reviewed independently. *p-Values of Chi-Square test after Bonferroni-Holmes correction for multiple testing.*

TABLE 6 | Custom weighted multirater agreement (MRA) on the incidence of specific features of rhythmic and periodic EEG patterns in 45 continuous EEG segments of 15 critical care patients à 6 h.

	Custom weighted MRA–subanalysis of specific EEG features			
	Gwet's AC_2	95% C.I.	*P*-Value*	Agreement
Localization (Main Term 1)	0.65	0.52–0.79	0.02	Substantial
Morphology (Main Term 2)	0.53	0.41–0.65	< 0.001	Moderate
Prevalence	0.56	0.43–0.69	0.02	Moderate
Frequency	0.72	0.60–0.85	< 0.001	Substantial
Trend	0.74	0.64–0.85	0.09	Substantial

*All four board certified EEG reviewers used an automatic detection software (Encevis NeuroTrend) and had a predefined time limit of 5 min per EEG segment. EEG segments were randomized and reviewed independently. *p-Values of Chi-Square test after Bonferroni-Holmes correction for multiple testing.*

Limitations

Our study has several limitations: First, training for our reviewers consisted of several steps but lasted just 2 h. Because all four reviewers were not familiar with the ACNS SCEET, which is currently not intended for regular clinical use, the learning curve may have been prolonged and might have affected annotations at the beginning of each reviewer. Longer training may provide higher agreement between reviewers and conventional EEG review (gold standard), especially for difficult, fluctuating rhythmic and periodic EEG patterns (17). Second, the predefined time limit for each CEEG dataset might have pushed the reviewers to hasty decisions. Based on CEEG review results, often critical decisions have to be made in intensive care patients and people with epilepsy on the ICU. Therefore it is not reasonable to limit CEEG review time in everyday clinical practice. However, if automatic CEEG pattern or seizure detection methods are scientifically tested without time limits, an added value is hard to prove. Third, compared to a previous publication on IRA of RPP using ACNS SCEET, our results showed lower agreement, sensitivity and specificity (25). The authors used snippets of EEGs (10 s to 1 min) to demonstrate the feasibility and reproducibility of SCCET Main terms and Modifiers. However, we focused on a straight-forward analysis of long term critical care EEG recordings with very short review times using an automatic EEG pattern detection method. Therefore, our results are reasonable from a clinical point of view.

CONCLUSIONS

We provided evidence for the clinical feasibility of our proposed automatic EEG analysis software. It is a rapid and reasonable high sensitive review tool, but currently cannot replace raw EEG analysis and electrophysiological decision making in critical care patients due to the partly moderate specificity and interrater agreement. We observed very short review times, yet still reasonable high agreement for rhythmic and periodic EEG patterns, unequivocal ictal EEG patterns and burst suppression.

ETHICS STATEMENT

The study protocol was approved by the institutional ethics commission (Ethikkomission Medizinische Universität Wien, Ethikkommission der Stadt Wien). Informed consent was given by all reviewers, that volunteered for the study. Patients included in the study were mainly not able to give consent during continuous EEG recordings. Therefore, the ethics commission requested that all patients that were not able to give consent and their relatives receive a written patient information and/or were informed about the study and the possibility to withdraw their personal data in the future.

STATISTICAL TESTING

JK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

AUTHOR CONTRIBUTIONS

JK: study idea, study setup, study execution, statistical analysis, writing the manuscript, editing the manuscript; JH, FF, MH, TK, and CB: study idea, editing the manuscript; SP, VR-D, FR, and JF: study execution, editing the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00454/full#supplementary-material

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