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Hemispheric differences in the duration of focal onset seizures

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Objective: To assess hemispheric differences in the duration of focal onset seizures and its association with clinical and demographic factors.

Methods: A retrospective analysis was performed on adult patients with drug-resistant unifocal epilepsy, who underwent intracranial EEG recording between 01/2006 and 06/2016. Seizure duration was determined based on the subdural and/or stereo-EEG (sEEG) recordings. Hemispheric differences in seizure duration were statistically evaluated with regard to clinical and demographic data.

Results: In total, 69 patients and 654 focal onset seizures were included. The duration of seizures with left-hemispheric onset (n = 297) was by trend longer (91.88 ± 93.92 s) than of right-hemispheric seizures (n = 357; 71.03 ± 68.53 s; p = .193). Significant hemispheric differences in seizures duration were found in temporal lobe seizures (n = 225; p = .013), especially those with automotor manifestation (n = 156; p = .045). A prolonged duration was also found for left-hemispheric onset seizures with secondary generalized commencing during waking state (n = 225; p = .034), but not during sleep. A similar hemispheric difference in seizure duration was found in female patients (p = .040), but not in men.

Conclusions: Hemispheric differences in seizure duration were revealed with significantly longer durations in case of left-hemispheric seizure onset. The observed differences in seizure duration might result from brain asymmetry and add new aspects to the understanding of seizure propagation and termination.

KEYWORDS
focal epilepsy, intracranial EEG recording, lateralization, sEEG, seizure termination, semiology

1 | INTRODUCTION

Seizure duration is the result of seizure evolution and termination mechanisms. It is common sense that focal seizures spread through epileptic networks, whereby the thalamus holds a gate keeper function in secondary generalization of seizures.[1,2] The seizure end, on the other hand, is mainly determined by the depletion of (neuro-) metabolic substrates.[3,4] This is why most seizures end within 2–3 min without intervention.[5-7] However, differences in the duration of focal onset seizures were observed depending on the localization of the seizure onset zone, age, and seizure semiology,[5-9] suggesting individual modulators of seizure duration. Focal seizures, for example, are typically shorter in case of a frontal onset than seizures arising from the temporal lobe.[7,10] In contrast, focal to bilateral tonic–clonic seizures last longer in patients with frontal lobe epilepsy (FLE) than in patients with temporal lobe epilepsy (TLE) or idiopathic generalizing

epilepsy syndromes.[8] Generalized onset seizures usually terminate within 66 s, hence earlier than focal to bilateral tonic–clonic seizures, which terminate within 130 s.[5] Although brain asymmetry has been well described and interhemispheric differences in seizure manifestation suspected, no interhemispheric differences in seizure duration have been reported so far. Further, of the up to now available studies on seizure duration, only five examined the seizure duration using intracranial EEG (iEEG),[7,11-14] although iEEG allows a more precise seizure duration determination than surface recordings – if the electrodes are placed precisely and individualized in dependence of the suspected seizure onset zone.

This study thus aimed to systematically analyze hemispheric differences in the duration of focal onset seizures with regard to clinical and demographic parameters. To ensure high data quality, only patients with unifocal epilepsy syndromes, continuous video recording and iEEG evaluation, were included.

2 | METHODS

The study complies with the institutional review board-approved ethical guidelines. All subjects gave written informed consent to the scientific use of their clinically acquired data.

2.1 | Participants

A retrospective database search was conducted at the local Epilepsy Center in order to identify all adult patients with drug-resistant focal epilepsy syndromes who underwent iEEG recording (n = 136) between 01/2006 and 06/2016. The study was restricted to iEEG, because it offers the possibility of a more precise determination of seizure pattern onset and termination than surface EEG, at least in case of precisely and individualized placed iEEG electrodes. Only patients who experienced at least one seizure during the presurgical video-EEG evaluation were included in the study. Exclusion criteria encompassed an undetermined epileptogenic zone (n = 3), multifocal epilepsy (n = 44), seizure occurrence only during electrical intracranial stimulation (n = 8), unavailability of relevant clinical or electroencephalographic data (n = 8) as well as missing/declined study consent (n = 4), yielding a final cohort of 69 patients. The same patient cohort was analyzed in a previous study, where a detailed cohort description can be found.[7]

All patient data used in this study, such as age, age at disease onset, gender, epilepsy syndrome, hemispheric onset, etiology, and handedness, were extracted from the patient reports and anonymized after written informed consent to scientific use. The epilepsy syndromes were classified in an interdisciplinary patient management conference, based on EEG and video data, neuropsychological testing along with functional and structural imaging results. Semiologies were classified based on the current ILAE classification from 2017.[15] In the following, seizures of the category "focal to bilateral tonic–clonic" are described as "secondary generalized seizures" (n = 98). Focal onset seizures without generalization (n = 556) encompassed 366 motor seizures including 137 automotor seizures, as well as 190 non-motor seizures. The latter encompassed also subclinical seizures (n = 98) and isolated auras (n = 57).

The handedness of the patients was determined using the Edinburgh Handedness Inventory.[16] Functional tests like Wada or functional MRI were only performed in selected patients if clinically required, but electrical stimulation of the electrodes was conducted in all study patients. The same study cohort was part of a previous study on the impact of sociodemographic and clinical parameters on seizure duration.[7]

2.2 | Seizure duration

The seizure duration was determined based on iEEG recordings with subdural or depth electrodes. It was evaluated by at least two experienced epileptologists. The seizure duration (in seconds) resulted from subtraction of the time points of seizure pattern cessation and seizure pattern onset in iEEG. In case of an asynchronous seizure pattern ending, the latest detectable EEG seizure pattern was set as seizure pattern end. Status epilepticus or seizures with transition to periodic epileptiform discharges (PEDs) were excluded due to the undeterminable seizure duration. In case of secondary generalized seizures, the duration of the focal as well as the generalized phase were noted besides the duration of the whole seizure.

The signal from the EEG electrodes (AD-Tech Medical Instrument corporation, Racine, WI, USA) was recorded using XLTEK NeuroWorks software and a XLTEK EMU128FS amplifier (Natus Medical Incorporated, San Carlos, CA, USA) with a sampling rate of 1000 Hz and 12–16 bit A-D conversion. The iEEG electrodes were placed in an individualized manner in dependence of the localization of the suspected seizure onset zone.

2.3 | Statistical analysis

Mean and standard deviation were calculated for quantitative parameters. As we had to deal with multiple observations per patient, these were not generalizable to a broader population and can only be interpreted descriptively.

A univariate negative binomial model was used to analyze the association between the lateralization of the seizure and the seizure duration. A random intercept was included in the model to account for repeated measurements, that is, multiple seizures per patient. The interpretation was done for the duration ratio (DR), the exponential of the regression coefficient. A DR of 1 can be interpreted as equal seizure durations of left and right hemisphere, while values greater 1 indicate that the duration of left-hemispheric seizures was longer than right-hemispheric seizures and vice versa in the case of a DR < 1. Calculations were performed for the whole group as well as the following subgroups: epilepsy syndrome (TLE, FLE, POLE), semiology (with and without secondary generalization, subclinical

seizure, automotor seizure), vigilance state at seizure onset (awake, sleep), gender (female, male), and handedness (left, right). A *p*-value below .05 was considered significant.

3 | RESULTS

3.1 | Demographic and clinical characteristics

A total of 69 adult patients (33 men; 36 women) with drug-resistant unifocal epilepsy syndromes were included in the study. The mean age at the time of monitoring was 36.51 ± 12.08 years. On average, the patients had a disease duration of 20.30 ± 13.07 years. A comparable percentage of patients was diagnosed with TLE (*n* = 30; 43.48%) and FLE (*n* = 31; 44.93%), whereas only eight patients (11.59%) suffered from parieto-occipital lobe epilepsy (POLE). Right- and left-hemispheric epilepsy syndromes were almost equally represented with 36 (52.17%) patients with a right- and 33 (47.83%) patients with a left-hemispheric seizure focus. Handedness, distribution of gender, mean age, and disease duration did not significantly differ between right- and left-hemispheric epilepsy syndromes.

The average duration of all examined seizures was 80.50 ± 81.65 s (*n* = 654), whereby the duration of seizures with left-hemispheric onset (*n* = 297) was non-significantly, but by trend longer (91.88 ± 93.92 s) than the duration of right-hemispheric seizures (*n* = 357; 71.03 ± 68.53 s; DR =1.23, 95%-confidence interval (CI) [0.90; 1.70], *p* = .193). The DR of 1.23 indicates that according to the model, seizures with left-hemispheric onset were 1.23 times longer than right-hemispheric ones. The characteristics of all seizures are summarized in Table 1.

To identify the main drivers of the observed hemispheric differences, the analysis was repeated with regard to clinical and demographic parameters. The seizure durations and the respective statistical results are summarized in Table 2.

3.2 | Hemispheric differences with regard to the underlying epilepsy syndromes

A significantly longer seizure duration was revealed for left (*n* = 142; 121.62 ± 97.06 s) compared to right temporal lobe seizures (*n* = 83; 80.43 ± 48.38 s; DR: 1.53, 95% CI: [1.09; 2.13], *p* = .013; Figure 1A). No significant hemispheric difference was found in patients with FLE (left: *n* = 148; 64.74 ± 84.09 s; right: *n* = 195; 63.4 ± 74.34 s; DR: 0.97, 95% CI: [0.55; 1.73], *p* = .920) or POLE (left: *n* = 7; 62.14 ± 20.38 s; right: *n* = 79; 80 ± 70.06 s; DR: 0.71, 95% CI: [0.30; 1.71], *p* = .447). Also, for the FLE subgroup of orbitofrontal seizures no significant hemispheric difference was found, although this seizure type is known to quickly spread to the temporal lobe and to have long durations.

3.3 | Hemispheric differences in consideration of seizure semiology

Focal onset seizures without secondary generalization lasted by trend longer when they had a left- (*n* = 245; 89.76 ± 99.69 s) versus a right-hemispheric seizure onset (*n* = 311; 66.36 ± 67.08 s; DR: 1.27, 95% CI: [0.86; 1.85], *p* = .226). A significant difference was found for focal onset seizures with automatisms (left: *n* = 72; 94.71 ± 35.30 s; right: *n* = 84; 80.60 ± 45.16 s; DR: 1.29, 95% CI: [1.01; 1.65], *p* = .045; Figure 1B). Thereby, automotor seizures had the highest incidence in TLE (*n* = 111/194 focal seizures) compared to FLE (*n* = 28/292) and POLE (*n* = 17/70). No significant hemispheric difference, though, was found for the duration of subclinical

TABLE 1 Seizure characteristics

Variables	*n* (seizures)	Seizures with left-/right-hemispheric onset	Percentages (left-/right-hemispheric onset)
Focal onset seizures	654	297/357	45.4%/54.6%
Without secondary generalization	556	245/311	44.1%/55.9%
Motor seizures	366	148/218	40.4%/59.6%
Non-motor seizures	190	97/93	51.1%/48.9%
With secondary generalization	98	52/46	53.1%/46.9%
Localization of seizure onset zone			
Frontal lobe	343	148/195	43.2%/56.8%
Temporal lobe	225	142/83	63.1%/36.9%
Parietal/occipital lobe	86	7/79	8.1%/91.9%
Seizures in male/female patients			
Female patients	352	147/205	41.8%/58.2%
Male patients	302	150/152	49.7%/50.3%

TABLE 2 Seizure durations

	n (seizures)	Seizure duration (mean ± stdv [s])	Duration ration	95% CI [s]	*p*-value
All seizures	654		1.23	[0.90;1.70]	.193
Left hemispheric	297	91.88 ± 93.92			
Right hemispheric	357	71.03 ± 68.53			
Frontal lobe epilepsy	343		0.97	[0.55;1.73]	.920
Left hemispheric	148	64.74 ± 84.09			
Right hemispheric	195	63.40 ± 74.34			
Temporal lobe epilepsy	225		1.53	[1.09;2.13]	.013
Left hemispheric	142	121.62 ± 97.06			
Right hemispheric	83	80.43 ± 48.38			
Parieto-/occipital lobe epilepsy	86		0.71	[0.30;1.71]	.447
Left hemispheric	7	62.14 ± 20.38			
Right hemispheric	79	80.00 ± 70.06			
Focal onset seizure without generalization	556		1.27	[0.86;1.85]	.226
Left hemispheric	245	89.76 ± 99.69			
Right hemispheric	311	66.36 ± 67.08			
Focal onset seizure with secondary generalization	98		1.10	[0.81;1.49]	.554
Left hemispheric	52	101.83 ± 59.41			
Right hemispheric	46	102.66 ± 76.60			
Focal part of secondary generalized seizures	98		1.22	[0.72;2.04]	.460
Left hemispheric	52	40.40 ± 54.46			
Right hemispheric	46	44.22 ± 61.68			
Generalized part of secondary generalized seizures	98		0.99	[0.78;1.26]	.946
Left hemispheric	52	61.96 ± 23.95			
Right hemispheric	46	61.00 ± 27.37			
Focal onset seizure with automatisms	156		1.29	[1.01;1.65]	.045
Left hemispheric	72	94.71 ± 35.30			
Right hemispheric	84	80.60 ± 45.16			
Subclinical seizures	98		1.45	[0.80;2.63]	.227
Left hemispheric	46	98.07 ± 71.29			
Right hemispheric	52	66.83 ± 79.58			
Focal onset seizures during awake state	203		1.24	[0.82;1.86]	.304
Left hemispheric	79	116.59 ± 120.42			
Right hemispheric	124	67.07 ± 60.20			
Focal onset seizures during sleep	353		1.25	[0.81;1.92]	.311
Left hemispheric	166	76.99 ± 85.63			
Right hemispheric	187	65.88 ± 71.43			
Secondary generalized seizures during awake state	26		1.54	[1.03;2.31]	.034
Left hemispheric	7	165.86 ± 121.67			
Right hemispheric	19	101.21 ± 33.65			
Secondary generalized seizures during sleep	72		1.02	[0.72;1.46]	.893
Left hemispheric	45	91.87 ± 36.31			
Right hemispheric	27	103.67 ± 88.55			

(Continues)

TABLE 2 (Continued)

	n (seizures)	Seizure duration (mean ± stdv [s])	Duration ration	95% CI [s]	*p*-value
Seizures in female patients	352		1.54	[1.02;2.33]	.040
Left hemispheric	147	112.50 ± 107.16			
Right hemispheric	205	72.93 ± 66.29			
Seizures in male patients	302		1.00	[0.62;1.61]	.994
Left hemispheric	150	71.76 ± 73.77			
Right hemispheric	152	68.47 ± 71.58			

seizures (left: *n* = 46; 98.07 ± 71.29 s; right: *n* = 52; 66.83 ± 79.58 s; DR: 1.45, 95% CI: [0.80; 2.63], *p* = .227) and secondary generalized seizures (left: *n* = 52; 101.83 ± 59.41 s; right: *n* = 46; 102.65 ± 76.6 s; DR: 1.10, 95% CI: [0.81; 1.49], *p* = .554). Likewise, the duration of the focal (left: *n* = 52; 40.40 ± 54.46 s; right: *n* = 46; 44.22 ± 61.68 s; DR: 1.22, 95% CI: [0.72; 2.04], *p* = .460) and the generalized parts (left: *n* = 52; 61.96 ± 23.95 s; right: *n* = 46; 61 ± 27.37; DR: 0.99, 95% CI: [0.78; 1.26], *p* = .946) of secondary generalized seizures were not significantly different between seizures of left- and right-hemispheric onset.

3.4 | Hemispheric differences in consideration of vigilance state at seizure onset

Secondary generalized seizures commencing during awake state revealed a significant difference in seizure duration between seizures of left- and right-hemispheric onset (left: *n* = 7; 165.86 ± 121.67 s; right: *n* = 19; 101.21 ± 33.65 s; DR: 1.54, 95% CI: [1.03; 2.31], *p* = .034; Figure 2A). Though, no significant hemispheric difference was found for the duration of secondary generalized seizures commencing during sleep (left: *n* = 45; 91.87 ± 36.31 s; right: *n* = 27: 103.67 ± 88.55 s; DR: 1.02, 95% CI: [0.72; 1.46], *p* = .893) nor for focal seizures of either vigilance state (awake: left: *n* = 79; 116.59 ± 120.42 s; right: *n* = 124; 67.07 ± 60.20 s; DR: 1.24, 95% CI: [0.82; 1.86], *p* = .304; sleep: left: *n* = 166; 76.99 ± 85.63 s; right: *n* = 187; 65.88 ± 71.43 s; DR: 1.25, 95% CI: [0.81; 1.92], *p* = .311).

3.5 | Hemispheric differences in consideration of gender

Hemispheric differences in seizure duration were only found in female patients with a significantly longer duration of left-hemispheric seizures (left: *n* = 147; 112.50 ± 107.16 s; right: *n* = 205; 72.93 ± 66.29 s; DR: 1.54, 95% CI: [1.02; 2.33], *p* = .040; Figure 2B). In men, the seizure duration did not significantly differ between seizures of left- (*n* = 150; 71.76 ± 73.77 s) and right-hemispheric onset (*n* = 152; 68.47 ± 71.58 s; DR: 1.00, 95% CI: [0.62; 1.61], *p* = .994).

4 | DISCUSSION

This is the first study reporting hemispheric differences in the duration of focal onset seizures and evaluating its association with clinical and demographic factors. In detail, a significantly longer duration of left-hemispheric onset seizures was found in female patients, as well as TLE.

Up to now, it remains unclear whether prolonged epileptic activity or less efficient seizure inhibition mechanisms account for the longer left-hemispheric seizure durations. However, reports on a greater density of gray matter, transmitter and synapses on the dominant hemisphere[17-19] rather support the former notion. This is in line with our findings, as the vast majority of our patients were right-handed, thus left dominant.[20] In our study, the hemispheric differences in seizure duration were most pronounced in seizures with involvement of the temporal lobe, that is, automotor seizures. This finding suggests that the temporal lobe might potentially have a more pronounced hemispheric asymmetry in regard to seizure spread and termination than extratemporal brain regions. However, no significant hemispheric difference was found for the duration of orbitofrontal seizures, although they often quickly spread to the temporal lobe.[21,22] According to an imaging study,[23] the observed hemispheric difference might also partly be due to decreased connectivity in association with longer disease durations (left- vs. right-hemispheric TLE: 17.67 ± 14.71 vs. 22.00 ± 15.62 years; *p* = .401) and more severe epilepsy syndromes (percentage of secondary generalized seizures of temporal origin: left-hemispheric 16.9%; right-hemispheric 7.2%; *p* = .043) in patients with left compared to right-hemispheric TLE.

Hemispheric differences were further observed in the duration of secondary generalized seizures with onset during waking state, but not during sleep. Presumably, this is due to cortico-thalamo-cortical subnetworks that are temporally active during sleep. These may lead to an enhanced synchronization of the sleeping brain, levelling-up the hemispheric differences observed in the awake brain.[24] Interestingly, no hemispheric differences were previously found in the duration of 57 focal impaired awareness seizures (FIAS),[5] which are also associated with a prominent thalamic activation.[25] On the other hand, FIAS are most frequent in temporal lobe epilepsy which was associated with hemispheric differences in seizure duration in our study. However, detailed clinical and demographic information are not provided in the publication. Further, the analysis might have been underpowered with only 57 FIAS, versus 225 temporal lobe seizures in the current study.

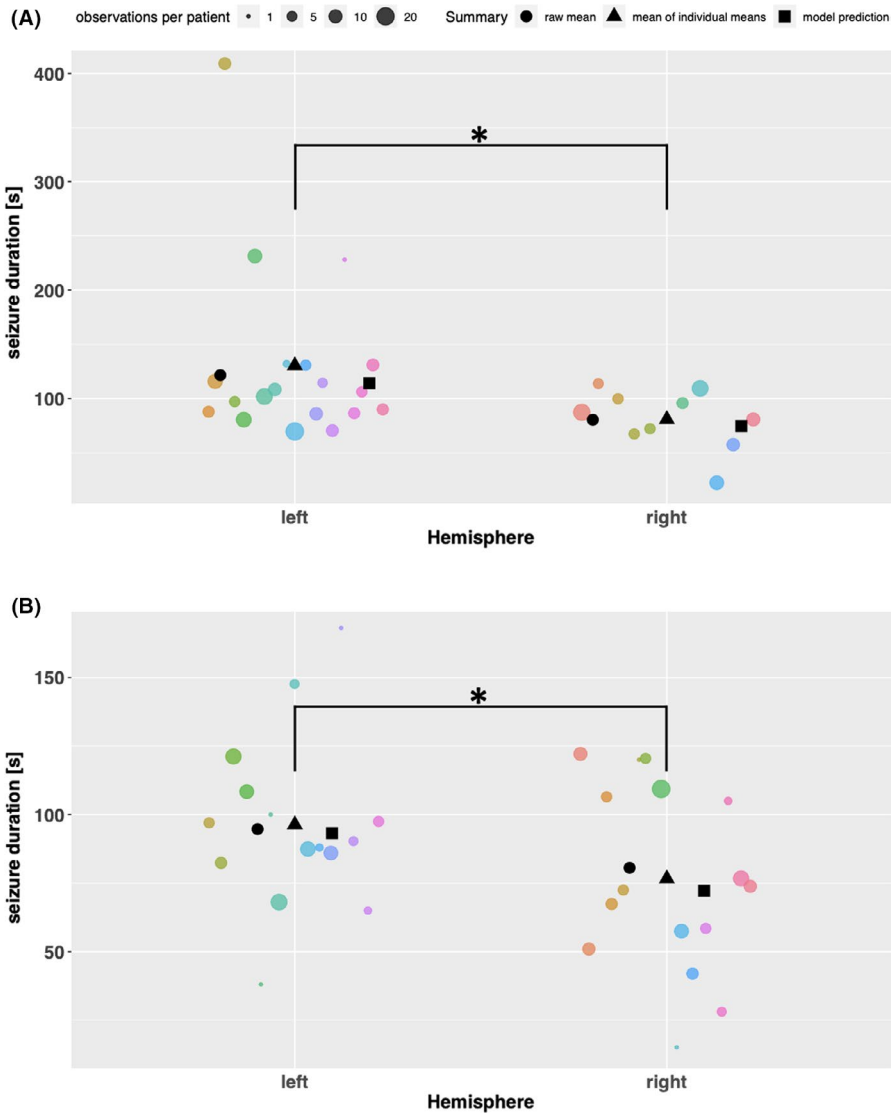

FIGURE 1 Hemispheric differences in seizure duration in temporal lobe epilepsy (A) and focal automotor seizures (B). In temporal lobe epilepsy, seizures with left-hemispheric (n = 142) onset had a significantly longer duration than seizures with right-hemispheric (n = 83) onset (p = .013). Similarly, left-hemispheric (n = 72) automotor seizures were significantly longer than those with right-hemispheric (n = 84) onset (p = .045). The seizure durations of individual patients are highlighted in different colors; the dot size represents the respective observation frequencies. Black symbols represent the raw mean (block dot), the mean of individual means (black triangle), as well as the model based predicted seizure durations

Gender analyses revealed hemispheric differences only in female patients with significantly longer seizure durations in case of a left- vs. right-hemispheric seizure onset. In contrast, no significant hemispheric difference was found in men. This finding is surprising, considering that men have a more accentuated brain asymmetry than women.[26,27] These gender differences in brain asymmetry are commonly attributed to the differences in sex hormone expression. Thereby, fetal testosterone expression is thought to promote functional lateralization and morphological brain asymmetry.[28,29] Hemispheric dominance, though, is a local rather than a global phenomenon[17] and not static, but, for example, modulated by the menstrual cycle.[30,31] Possibly, differences in mean age (men: 33.39 ± 10.59 years; women: 39.36 ± 12.79 years) and frequency of temporal lobe seizure origin (TLE: men: n = 11; women: n = 19) have biased our results. The sex differences in seizure duration in our study thus remain elusive but point out the need of systematic gender studies in epilepsy.

4.1 | Limitations

Limitations arise from the study's retrospective design, which potentially increases the error rate in data collection. The strict exclusion criteria further led to a rather selected cohort and limited number of patients. Especially, the subgroup analyses might thus have been underpowered. Further, patients with iEEG recording are a highly selected group of drug-resistant epilepsy patients. Although representative for the epilepsy patients evaluated in EMUs, it limits the transferability of our results to a broader patient group as pediatric

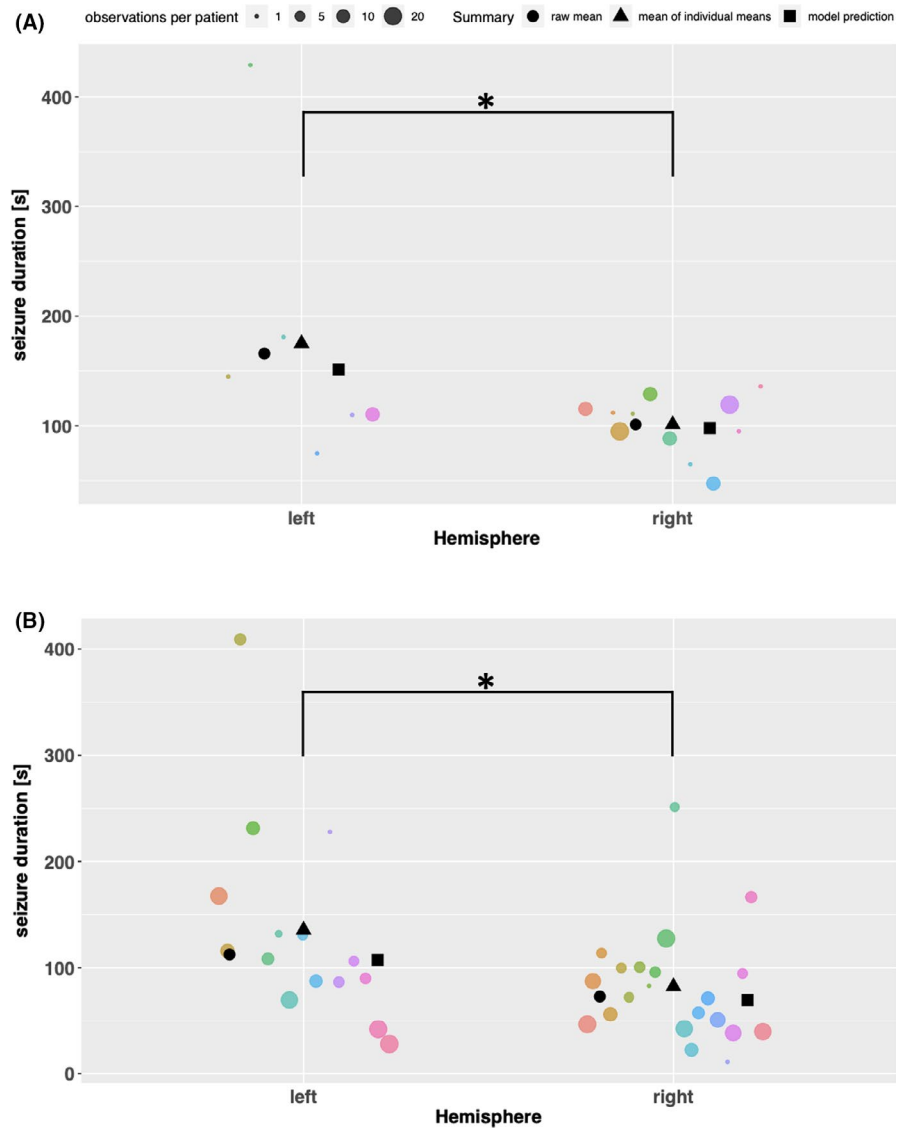

FIGURE 2 Hemispheric differences in seizure duration in secondary generalized seizures with onset during waking state (A) and focal onset seizures in female epilepsy patients (B). In the subgroup of secondary generalized seizures, a significant hemispheric difference in seizure duration was revealed for those commencing during waking state (left vs. right = 7 vs. 19; $p = .034$), but not for those with onset during sleep. In female patients, seizures with left-hemispheric ($n = 147$) onset revealed a significantly longer duration compared to those with right-hemispheric ($n = 205$) onset ($p = .040$). The seizure durations of individual patients are highlighted in different colors; the dot size represents the respective observation frequencies. Black symbols represent the raw mean (block dot), the mean of individual means (black triangle), as well as the model based predicted seizure durations

patients, drug-responsive patients, and patients with multifocal or generalized epilepsy syndromes have not been investigated. Also, hemispheric dominance was not explicitly assessed using fMRI or Wada testing, but electrical cortex stimulation was performed in all patients which provides a very high reliability for localizing eloquent cortex areas. In addition, the used standardized handedness questionnaires are sufficiently reliable and valid and offer an adequate probability to estimate hemispheric dominance.[32] Moreover, hormone levels and menstruation cycles were not assessed and should be evaluated in future studies in order to better understand gender differences in seizure duration. Further, follow-up studies are needed to evaluate the impact of seizure duration on postictal outcome parameters and to confirm the observed hemispheric difference in a larger scaled cohort.

5 | CONCLUSION

Left-hemispheric seizures, especially those of temporal origin and female patients, revealed a significantly longer duration than those of right-hemispheric onset. The presented results might shed light on the neuroanatomical mechanisms of seizure termination and provide valuable information for the assessment of seizure-related risks. Prospective studies are needed to further explore the observed

gender differences in focal epilepsy – a still underreported topic which might be of particular importance in focal epilepsies.

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CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

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.

DATA AVAILABILITY STATEMENT

All data used for analysis are presented in the manuscript. The discussion and conclusions only rely on the data presented.

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