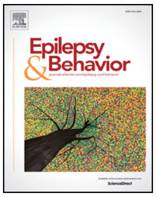
Epilepsy & Behavior 95 (2019) 26–33

Contents lists available at ScienceDirect

Epilepsy & Behavior

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



High seizure load during sensitive periods of development leads to broad shifts in ultrasonic vocalization behavior in neonatal male and female C57BL/6J mice

Suzanne O. Nolan [a], Samantha L. Hodges [b], Siena M. Condon [d], Ilyasah D.A. Muhammed [a], Lindsay A. Tomac [a], Matthew S. Binder [a], Conner D. Reynolds [e], Joaquin N. Lugo [a,b,c,*]

[a] Department of Psychology and Neuroscience, Baylor University, Waco, TX 76798, USA
[b] Institute of Biomedical Studies, Baylor University, Waco, TX 76798, USA
[c] Department of Biology, Baylor University, Waco, TX 76798, USA
[d] University Scholars Program, Baylor University, Waco, TX 76798, USA
[e] Texas College of Osteopathic Medicine, University of North Texas Health Science Center, Fort Worth, TX 76107, USA

ARTICLE INFO

Article history:
Received 8 February 2019
Revised 20 March 2019
Accepted 20 March 2019
Available online 22 April 2019

Keywords:
Critical period
Autism
Flurothyl
Developmental disorder
Spectrogram

ABSTRACT

There is increasing evidence that seizures during early development can impact ultrasonic vocalizations (USVs) emitted from neonatal mice. However, most of the effects of early-life seizures have been reported using chemoconvulsants that produce continuous seizures (status epilepticus). In the present study, we evaluated the impact of different seizure frequency loads during early-life vocalization development in C57BL/6J male and female mice. For the high seizure load (HSL) paradigm, we administered 3 flurothyl seizures to mice on postnatal day (PD) 7 through PD11, and recorded USVs on PD12. We found that the induction of seizures across PD7–11 resulted in increased average duration ($P < 0.05$) and cumulative duration ($P < 0.05$) of USVs across both sexes. Call-type analyses indicated several call-type changes, including reduced production of complex call-types from males' HSL condition. For the low seizure load (LSL) paradigm, we induced 3 flurothyl seizures only on PD10 and recorded USVs on PD12. We found no change in any spectral or temporal features of USVs. However, call-type production analyses indicated that both male and female animals from the LSL paradigm also produced changes in call-types. This study provides evidence that the magnitude of communication impairment following seizures is significantly impacted by seizure frequency load early in development.

1. Introduction

Epilepsy is a neurological disorder that impacts an estimated 50 million individuals worldwide [1], with particularly high incidence in the pediatric population [2]. Children with epilepsy experience an increased risk of psychiatric and behavioral comorbidities [3] and cognitive deficits [4,5]. It is estimated that half of all individuals with epilepsy have some form of cognitive or psychiatric condition [6,7]. The magnitude of these cognitive impairments can be related to any number of variables. For example, results from large cohort studies indicate that lifetime seizure load is related to the magnitude of deficits in working memory and executive functioning performance [8,9]. Similarly, the timing of the seizure onset is a potent predictor of the magnitude of cognitive dysfunction, as earlier onset of seizures during childhood is significantly related to more severe cognitive impairments later in life [8,10]. This early childhood vulnerability is potentially due to developmental processes occurring during this sensitive period, as synaptic plasticity mechanisms implicated in learning and memory are occurring at a high rate [11].

Similar to cognitive impairments, children who experience a seizure in the first year of life also have a higher risk for autism than the general population [12]. Data from animal models support the notion that experiencing high seizure load (HSL) during this sensitive period may produce lasting disruptions in the development of sociability, suggesting a role for recurrent seizures in the etiology of autistic-like phenotypes [13]. However, less is known about the relationship between seizure load during sensitive periods of brain development and another aspect of autistic-like behavior, communication. Clinical data indicate the presence of seizure-induced communication impairments, as childhood epilepsy has been shown to result in an increased likelihood of developing speech disorders [14].

Previous studies in both mouse and rat models have reinforced the relationship between seizures and communication deficits. A single instance of status epilepticus (SE) can affect qualitative and quantitative aspects of neonatal ultrasonic vocalization (USV) behavior [15–18].

---

* Corresponding author at: Baylor University, Department of Psychology and Neuroscience, One Bear Place # 97334, Waco, TX 76798, USA.
E-mail address: joaquin_lugo@baylor.edu (J.N. Lugo).

https://doi.org/10.1016/j.yebeh.2019.03.037
1525-5050/

Our lab has reported male-specific suppression in the quantity and total duration of 50-kHz calls on postnatal day 12 in 129SvEvTac mice following exposure to kainic-acid (KA)-induced SE on postnatal day 10 [16]. Using the same KA seizure paradigm and a broader spectrum vocalization recording system, total USV quantity and duration were found to be suppressed on PD12 following SE on PD10 in C57BL/6J mice, as well as changes in call-type production patterns [15]. These findings suggest that a single episode of SE on PD10 is sufficient to produce changes in communicative behavior during development.

While the previous findings have sufficiently detailed the impact of one episode of SE on vocalization behavior during a sensitive period of development, it is unclear if the magnitude of these communication alterations may be related to the seizure frequency load, similar to the evidence for seizure-induced cognitive impairments. To address this question, we conducted two separate experiments. In the first experiment, we exposed male and female C57BL/6J pups to three seizures per day, each day across PD7 – PD11 using the chemoconvulsant flurothyl, designated as the HSL paradigm. One day following exposure to the seizure paradigm, USVs were collected on PD12 using the Avisoft recording system. Quantitative and spectrographic analyses were conducted to detect changes in aspects of this behavior following exposure to seizures. In the second experiment, we exposed mice to three flurothyl seizures on PD10, designated as the "low seizure load" (LSL) paradigm, and recorded and analyzed PD12 USVs in the same manner. We hypothesized that the magnitude of seizure load would be related to the magnitude of changes in aspects of USVs.

2. Materials and methods

2.1. Animals

Male and female C57BL/6J pups were bred at Baylor University for this experiment. All pups were housed in individual cages with parents and littermates. The light cycle was kept at 12-hr light/dark, and the colony room was kept at an ambient temperature of 22 °C. Animals had *ad libitum* access to food and water. All procedures performed were in accordance with Baylor University Institutional Animal Care and Use Committee, as well as the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. All testing was conducted during the light cycle, specifically between 8 am and 5 pm.

2.2. Flurothyl seizure induction

Prior to the first seizure on PD7, animals were randomly assigned to receive either seizures or control procedures, and toes were clipped to maintain animal identity throughout the experiment. After toes were clipped, animals were placed back into the home cage for 30 min before the first seizure. For the first seizure on PD7, pups were isolated from the home cage and placed in a clear plexiglass inhalation chamber (29 cm × 16 cm × 15 cm), inside a laboratory fume hood (Kewaunee ® Scientific Corp., NC, USA). Flurothyl (bis-2,2,2-trifluroethyl ether) (Sigma-Aldrich, St. Louis, MO, USA) was pumped into the chamber at a rate of 50 μL/min, using a syringe pump (Model: 11 Plus, Harvard Apparatus). Following seizure induction, animals were placed in separate containers with a same-treatment counterpart and monitored. These containers were filled with clean bedding and warmed with a heating pad to ambient nesting temperature (~35 °C). Following the first and last seizures each day, the animals received a subcutaneous injection at the nape of the neck of 1.0 mL of 0.9% saline solution, to reduce the effects of dehydration. Control procedures included placing the animals in an identical induction chamber outside the fume hood for an identical amount of time and similar injections of saline to prevent dehydration. To test the impact of seizure load on our outcome measures, we had two seizure paradigms. The HSL paradigm was administered as follows: each seizure animal received 3 seizures per day from PD7—PD11, with 2 h between each seizure episode, for a total of 15 seizures per animal. The LSL paradigm was administered as follows: each seizure animal received 3 seizures on PD10, with 2 h between each episode.

2.3. Ultrasonic vocalization recording

To assess changes in USV behavior following seizures, we examined USVs on PD12 using the isolation-induced USV paradigm previously described [15,16]. All vocalizations were recorded in the afternoon (between 1 and 5 pm), approximately 24 h after the last seizure for the HSL paradigm and 48 h later for the LSL paradigm. Briefly, all pups were weighed and transferred to a holding cage with fresh bedding, warmed by an electronic heating pad to ambient nesting temperature (~35 °C). The USVs were recorded using a condenser microphone (CM16/CMPA, Avisoft Bioacoustics, Germany) connected to an ultrasound-recording interface (UltraSoundGate 116Hb, Avisoft Bioacoustics), which allowed assessment of all USVs on a continuous spectrum from 0 to 125 kHz. Each pup was individually placed into another housing pan, within an acrylic sound-attenuating chamber (40 cm × 40 cm × 30 cm) where USVs were recorded for 2 min. Following recording, the pups were placed back into the holding cage with their littermates. This procedure was repeated until each pup in the litter was tested. An experimenter remained in the room during all recordings. At the conclusion of testing, pups were returned to the home cage.

2.4. Ultrasonic vocalization analyses

Following the conclusion of all testing, all files were downloaded and Avisoft SASLab Pro software (Avisoft Bioacoustics, Germany) was used to convert all USV files (.wav) into spectrograms using a fast Fourier transformation procedure. The following parameters for our lab have been set to maintain consistency between experiments: FFT length = 1024, time window overlap = 75% (100% Frame, Hamming window), time resolution = 1 ms. Sampling frequency was set at 22050. Additionally, call-types were manually identified by an experimenter blinded to treatment identity, using a previously described classification scheme [15]. For the HSL paradigm, all animals vocalized during the recording period, and none were excluded from analysis ($n_{\text{male control}} = 7$, $n_{\text{female control}} = 12$, $n_{\text{male seizure}} = 8$, $n_{\text{female seizure}} = 10$). For the LSL paradigm, 3 subjects did not vocalize (2 female control and 1 female seizure) and were excluded from subsequent analysis, leaving the final sample sizes as follows: $n_{\text{male control}} = 8$, $n_{\text{female control}} = 8$, $n_{\text{male seizure}} = 10$, $n_{\text{female seizure}} = 10$.

2.5. Statistical analysis

All data were analyzed using IBM SPSS Statistics 23 (Aramonk, NY). Results were evaluated using a two-way (Treatment [control, seizure] × Sex [male, female]) analysis of variance (ANOVA) for each time point examined (seizures on PD7–PD11 and seizures only on PD10). Figures were created using GraphPad Prism Software 7.0 (San Diego, CA). Any significant interactions were followed by creating a unique group identifier (Group) for each of the treatment combinations (i.e., male seizure) and examined using Fisher's least significant difference (LSD) posthoc, at the level of $P < 0.05$.

3. Results

3.1. High seizure load early in development results in increased cumulative and average call duration as well as changes to the call-type production distribution

A two-way ANOVA was conducted that examined the effect of treatment and sex on the aforementioned parameters for USVs recording during the testing window. There was no interaction of treatment and sex, $F(1, 33) = 3.56$, $P = 0.07$, nor a treatment effect on the number of vocalizations produced, $F(1, 33) = 1.42$, $P = 0.24$ (Fig. 1a). Results for the average duration of calling behavior indicated that the average length of the vocalizations produced was significantly increased in pups that received the seizures, $F(1, 33) = 4.58$, $P < 0.05$, though this variable did not significantly interact with sex, $F(1, 33) = 0.24$, $P = 0.63$ (Fig. 1b). The cumulative duration of vocalizations was also increased in animals that experienced seizures, $F(1, 33) = 6.00$, $P < 0.05$, and this was not dependent on the sex of the subject, $F(1, 33) = 2.45$, $P = 0.13$ (Fig. 1c). Fundamental frequency, or pitch, was not significantly affected by treatment, $F(1, 33) = 0.11$, $P = 0.75$, even across the sexes, $F(1, 33) = 3.53$, $P = 0.07$ (Fig. 1d). Results also indicated that seizures increased the average peak amplitude of the vocalizations, $F(1, 33) = 6.63$, $P < 0.05$, regardless of the sex, $F(1, 33) = 1.66$, $P = 0.21$ (Fig. 1e). Average peak frequency was not affected by the treatment, $F(1, 33) = 2.81$, $P = 0.10$, regardless of sex, $F(1, 33) = 3.04$, $P = 0.09$ (Fig. 1f).

3.2. High seizure load early in development results in changes in call-type production patterns

Using previously defined schemas, aspects of calling behavior were examined, and USVs were categorized by call-type [19]. A chi-square analysis revealed that the distribution of call-types produced between pups that experienced seizures and controls were significantly

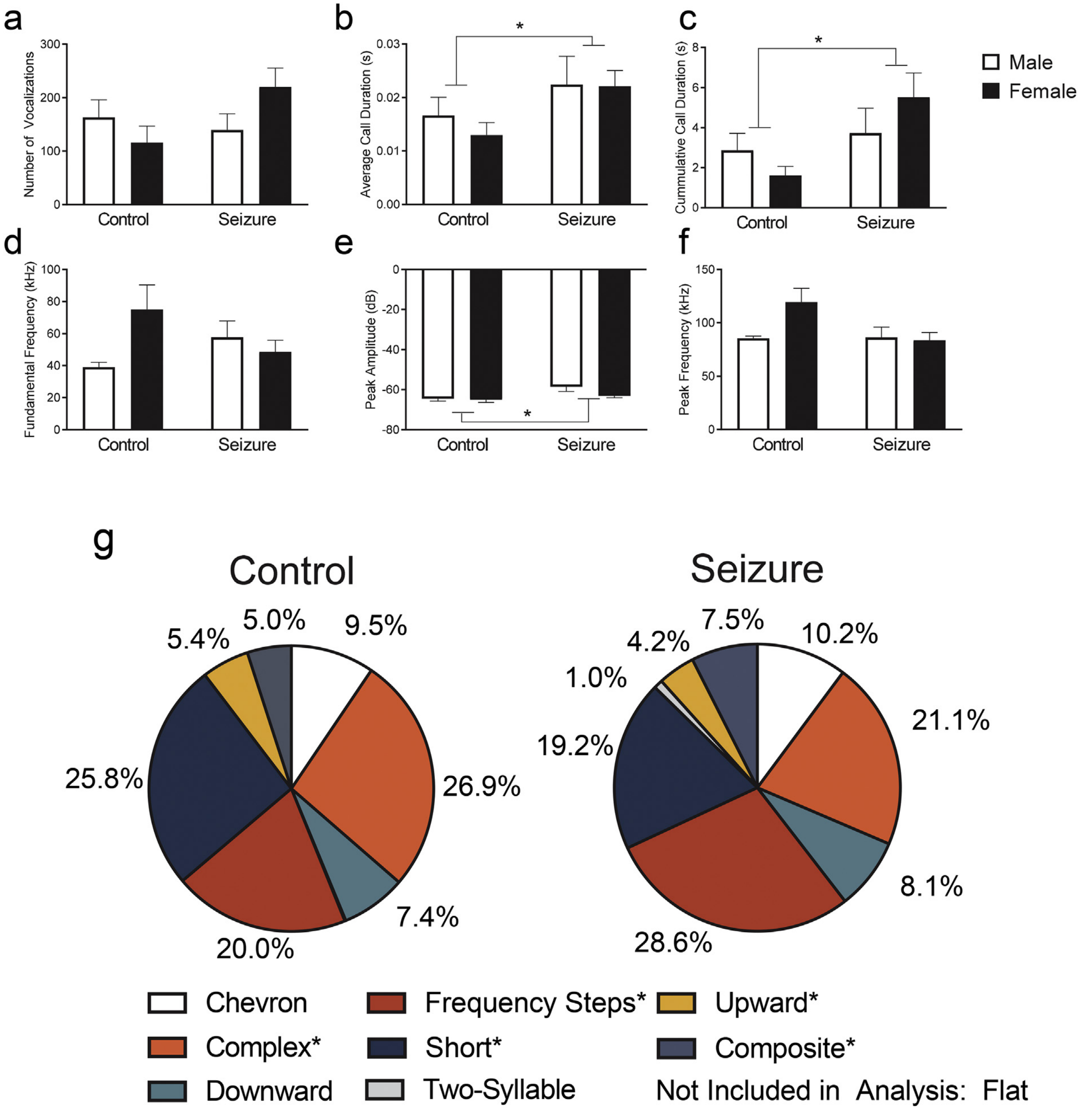


Fig. 1. Changes in quantitative aspects of vocalization behavior following exposure to high seizure load. A. No changes were found in the number of vocalizations produced between the two groups. B. The average call duration was significantly increased in animals that experienced high seizure load. C. The total time spent vocalizing was also significantly increased in animals that experienced high seizure load. D. No changes were found in average fundamental frequency across the groups. E. Average peak amplitude was significantly increased in animals that experienced seizures. F. No changes were noted in the average peak frequency across all calls produced between the two groups. G. Across the sexes, pups that experienced high seizure load on PD7–PD11 produced a significantly different call profile compared with controls. Specifically, they produced fewer upward, complex, and short call-types as well as more frequency step, two-syllable, and composite call-types * = $P < 0.05$. The bar graphs represent the mean, and the error bars represent the standard error of the mean.

different, χ^2 (7) = 121.64, $P < 0.001$. Subsequent Z-tests for column proportions indicated that production of several specific call-types differed from each other at the level of $P < 0.05$. Animals that received seizures produced proportionally fewer upward, complex, and short call-types while producing proportionally more frequency step, two-syllable, and composite call-types (Fig. 1g). Flat-type calls were not included in the analysis as they were not produced by any subjects.

Moreover, when these analyses were split by sex, differences appeared. Call-type production was significantly different between males who received seizures and controls, χ^2 (7) = 109.8, $P < 0.001$. Subsequent Z-tests for column proportions indicated production of several specific call-type differed from each other at the level of $P < 0.05$. Specifically, male pups that received the seizures produced fewer complex calls, more frequency step, and two-syllable call-types compared with male control pups (Fig. 2a). Female pups that received seizures also produced a significantly different call-type production profile compared with female control pups, χ^2 (7) = 97.4, $P < 0.001$. Subsequent Z-tests for column proportions indicated that several proportions significantly differed at the level of $P < 0.05$. Specifically, female pups that received seizures produced fewer upward and short, as well as more frequency step, two-syllable, and composite call-types compared female control pups (Fig. 2b).

3.3. Low seizure load elicits no changes in quantitative aspects of ultrasonic vocalization behavior on PD12

Results from the two-way ANOVA indicated that no changes in the following variables were noted after experiencing three seizures: number of vocalizations, $F(1, 32) = 1.93$, $P = 0.17$ (Fig. 3a), average duration, $F(1, 32) = 0.33$, $P = 0.57$ (Fig. 3b), cumulative duration, $F(1, 32) = 1.32$, $P = 0.26$ (Fig. 3c), average fundamental frequency, $F(1, 32) = 0.004$, $P = 0.95$ (Fig. 3d), average peak amplitude, $F(1, 32) = 0.11$, $P = 0.74$ (Fig. 3e), and average peak frequency, $F(1, 32) = 0.14$, $P = 0.71$ (Fig. 3f). Moreover, sex did not interact with treatment on any variable of interest: number of vocalizations, $F(1, 32) = 0.01$, $P = 0.92$, average duration, $F(1, 32) = 0.01$, $P = 0.91$, cumulative duration, $F(1, 32) = 0.007$, $P = 0.93$, average fundamental frequency, $F(1, 32) = 0.001$, $P = 0.98$, average peak amplitude, $F(1, 32) = 0.09$, $P = 0.77$, and average peak frequency, $F(1, 32) = 2.37$, $P = 0.13$.

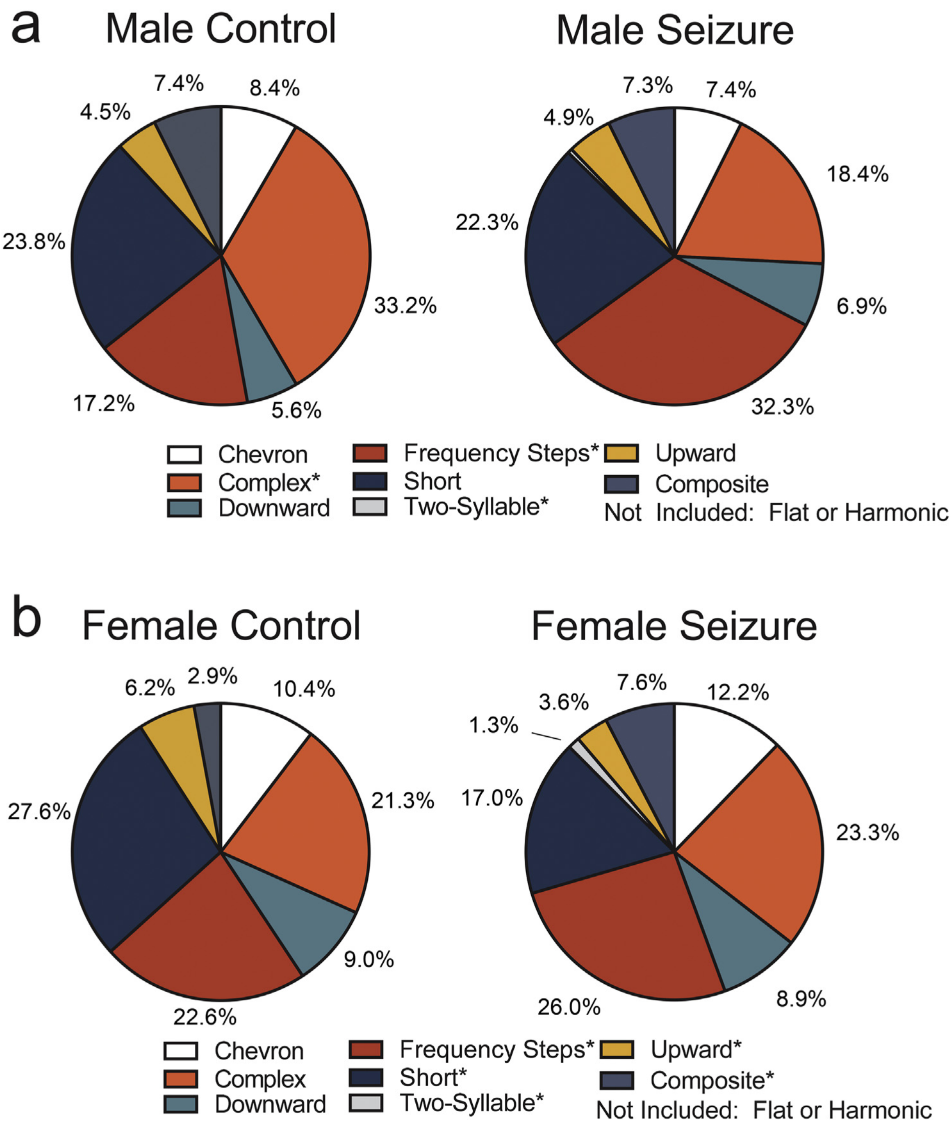


Fig. 2. Changes in qualitative aspects of vocalization behavior following exposure to high seizure load. A. Male pups that experienced high seizure load produced fewer complex, and more two-syllable and frequency step call-types compared with males that did not experience multiple seizures. B. Female pups that experienced seizures produced fewer upward and short call-types as well as more frequency step, two-syllable, and composite call-types compared with female pups who did not experience seizures. * = $P < 0.05$.

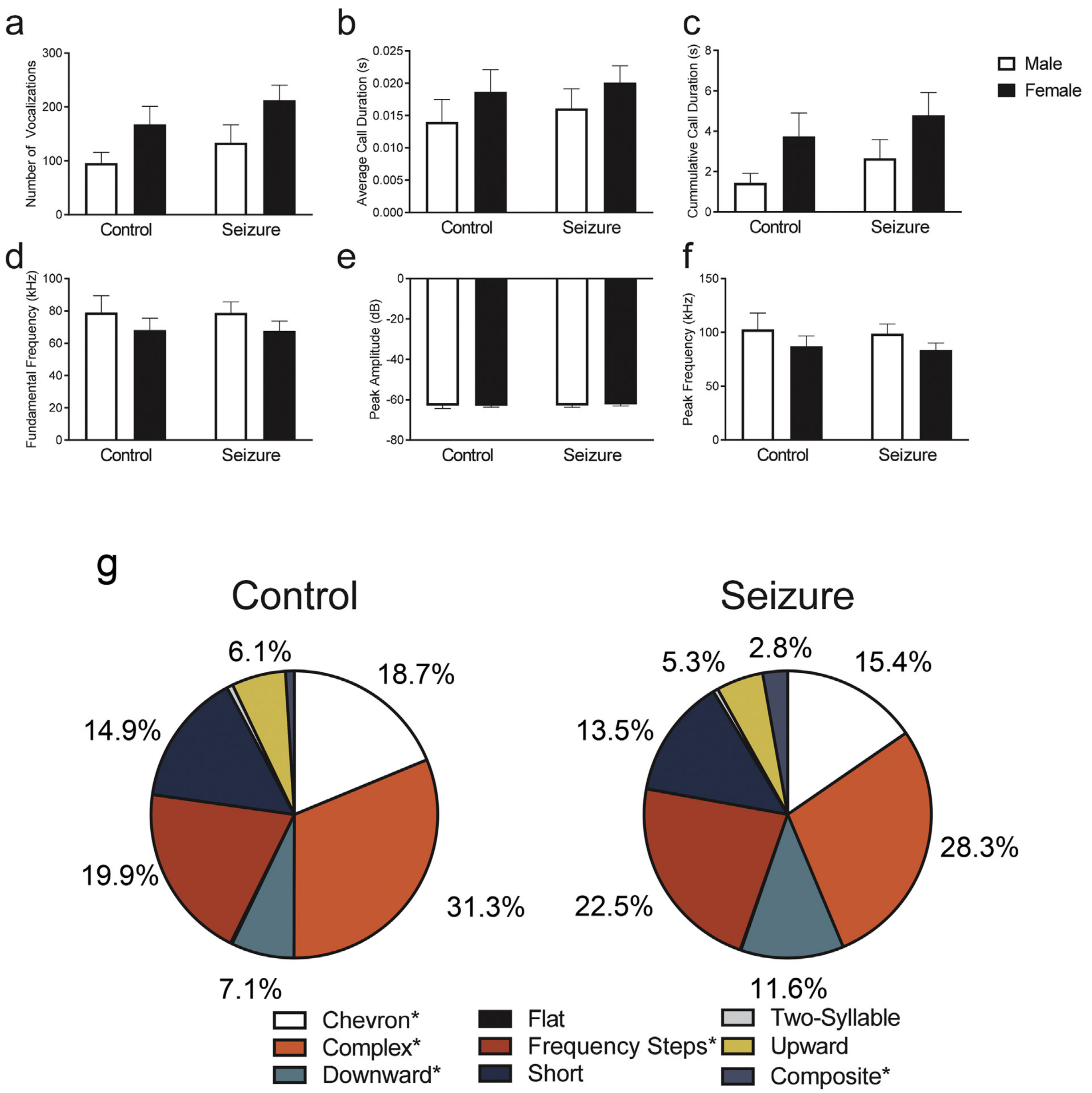


Fig. 3. No changes to quantitative aspects of calling behavior on PD12 after low seizure load. A. No changes were detected in the number of vocalizations produced. B. No changes were noted in the average duration of calling behavior. C. No changes were noted in the cumulative duration of calling behavior during the testing window. D. No changes were noted in the average fundamental frequency of all calls made between groups. E. No changes were noted in the average amplitude of calls produced between groups. F. No changes were noted in the average peak frequency of calls produced between groups. G. Across the sexes, pups that received low seizure load on PD10 alone produced a significantly different call profile compared with the controls. Specifically, they produced proportionally fewer chevron and complex call-types as well as more composite, downward, and frequency step call-types. The bar graphs represent the mean, and the error bars represent the standard error of the mean.

3.4. Low seizure load early in development alters call-type production patterns

Using previously defined schemas, aspects of calling behavior were examined, and USVs were categorized by call-type. Chi-square analysis revealed that call-type production proportions differed between the seizure and control groups, χ^2 (8) = 66.83, $P < 0.001$. *Z*-tests for column proportions indicated that several call-type proportions were significantly different between groups at the level of $P < 0.05$. Namely, both male and female animals that received three seizures on PD10 produced proportionally fewer chevron and complex call-types and proportionally more composite, downward, and frequency step call-type than male and female control pups (Fig. 3g).

Moreover, when these analyses were split by sex, results were different from the effect of treatment across the two sexes. Call-type production was significantly different between males who received seizures, χ^2 (7) = 97.0, $P < 0.001$. Subsequent *Z*-tests for column proportions indicated that several proportions significantly differed at the level of $P < 0.05$. Specifically, male pups that received the seizures produced more composite, downward, and frequency step call-type as well as fewer short call-types compared to male control pups (Fig. 4a). Female pups that received seizures also produced a significantly different call-type production profile compared with female control pups, χ^2 (8) = 73.6, $P < 0.001$. Subsequent *Z*-tests for column proportions indicated that several proportions significantly differed at the level of $P < 0.05$. Specifically, female pups that received seizures

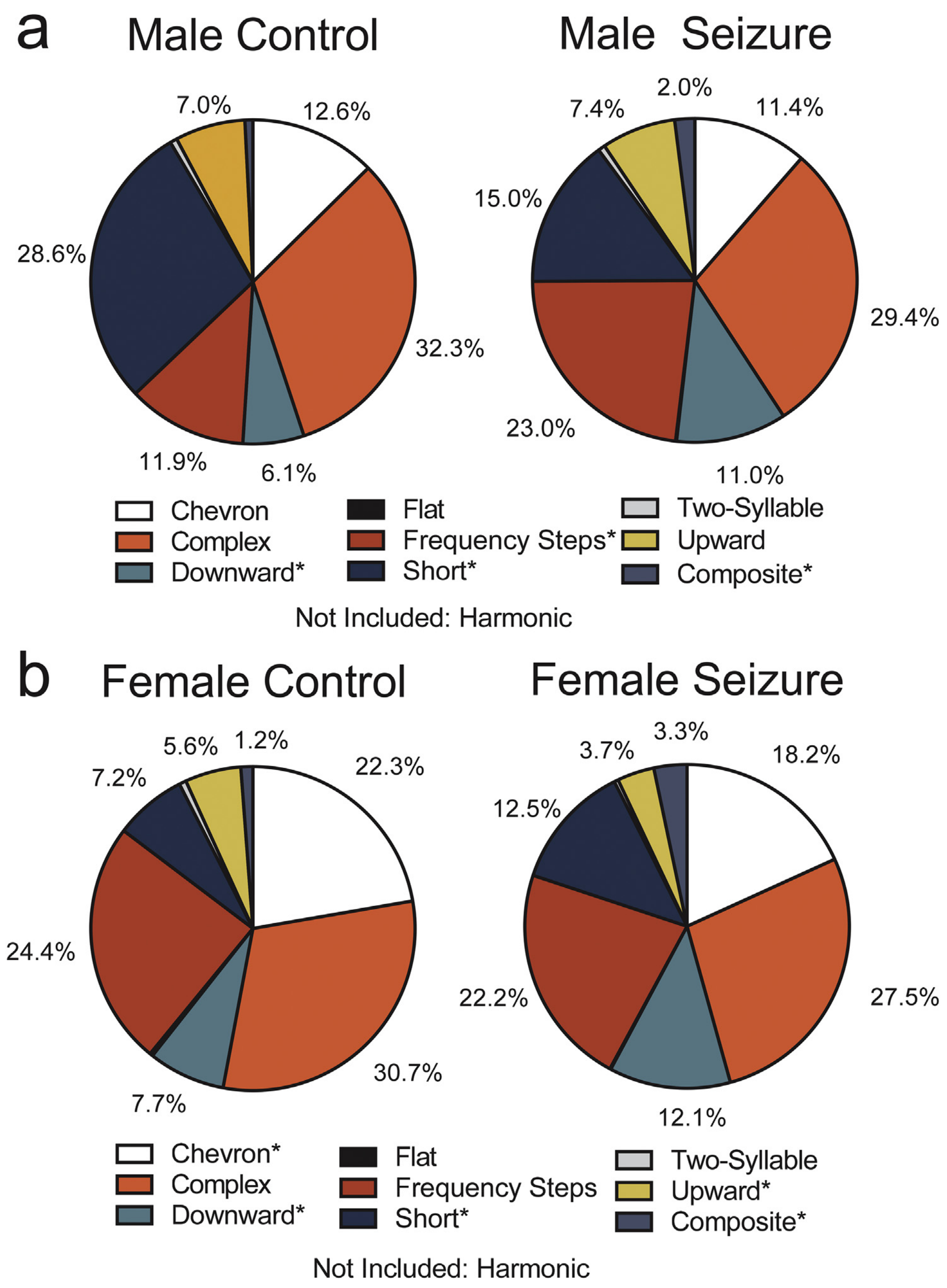


Fig. 4. Changes in qualitative aspects of vocalization behavior following exposure to low seizure load. A. Male pups that experienced low seizure load produced more composite, downward, and frequency step call-types as well as fewer short call-types on PD12, compared with male pups that experienced no seizures. B. Female pups that received low seizure load produced fewer chevron and upward, as well as more composite and short call-types compared with females that did not receive seizures.

produced fewer chevron and upward, as well as more composite and short call types than female control pups (Fig. 4b).

4. Discussion

Childhood epilepsy can lead to persistent communication impairments [14]. Previous rodent studies have supported this relationship, demonstrating that experiencing early life seizures results in impairments in communicative behavior in rodent models. The present study hypothesized that comparable to the relationship of cognitive impairments and seizure load, a HSL during a developmentally sensitive window results in a greater magnitude of autistic-like communication impairments. The findings of the present study strongly demonstrate that experiencing a HSL (15 seizures over 5 days), but not a LSL (3 seizures in one day), during early development increases both average call duration, cumulative call duration, and peak amplitude over the testing window on PD12. Moreover, exposure to both HSL and LSL changes the distribution of call-types produced, specifically reducing the proportion of complex call-types produced in male subjects.

In the current study, call duration was increased in the group with HSL compared to controls. These findings spanned both average and cumulative duration, unrelated to the number of calls produced. An increase in call duration more strongly elicits maternal approach [20]. Increased call duration has been reported across many mouse models of the autism spectrum disorder (ASD), including the inbred BTBR T+tf/J (BTBR) strain [19], the tuberous sclerosis complex 2 (*TSC2)* knockout [21], and the Fragile X mental retardation (*Fmr1)* knockout [22]. One future study could be to determine whether the increase in call duration from the group with seizures functions to increase retrieval of the pup. The disruption in USVs due to the HSL may be an early indicator of autistic-like behavioral deficits. We previously found that the 15 seizures induced from PD7–11 result in social behavior deficits during adulthood [13]. Therefore, it appears that one of the consequences of the HSL during early development may be autistic-like behavioral deficits across the lifetime of the mice.

Our results are different from previous studies that described a pattern of decreased call frequency in both rat and mouse pups [15,16,18]. In the Lopez-Meraz et al., 2014 study, they found a suppression in the number of USVs in PD14 rats [18]. A similar suppression of USVs was reported in the other two studies, which were conducted in mice [15,16]. One key difference between these studies and the current study is that they used the chemoconvulsant pilocarpine or kainic acid to induce status epilepticus on a single day. Differences between these studies and the current study could be due to the type of seizure induction, the number of seizures induced on a single day, or the day the seizures were induced. Kainic acid and pilocarpine result in acute neuronal injury across various regions of the brain [23,24]. However, exposure to recurrent flurothyl seizures, used to mimic recurrent generalized tonic–clonic seizures, does not show the same acute damage [25]. Thus, it is possible that the different types of seizure induction could be impacting the developing brain in different ways.

Early life seizures are known to cause widespread damage and persistent neurological dysfunction. The sex of the animal is considered a major mediator of this seizure-induced injury, as the trajectory of brain development differs between the two sexes, particularly early in life, rendering males more vulnerable to damage. This male-specific vulnerability extends to some behavioral consequences after early life seizures, such as social play impairments and cognitive impairments [26,27]. Similar to previous studies, the current study found exposure to a HSL during this sensitive period reduced the proportion of complex call-types produced in male subjects, but not in female subjects [15]. In conjunction with previous literature, this suggests that males are particularly vulnerable to call-type changes. Overall, our findings add more evidence to the observation that sex differences may exist in the response to seizure activity during this sensitive period.

We initially hypothesized that we would find an interaction of sex and treatment in most features of USVs. However, most of our findings did not detect that sex mediated seizure-induced changes in the number of calls or their duration. Previous work from our lab has demonstrated significant, male-specific suppression in the quantity and total duration of 50-kHz calls following status epilepticus [16]. This discrepancy could be attributed to a multitude of methodological factors, including the recording system used. For example, the previous study in our lab used the Ultravox recording system. We recently demonstrated that the Ultravox system is less sensitive than the Avisoft system used in the current study [28]. A subsequent study in our lab used the more sensitive Avisoft recording software and found suppression of total USV quantity and duration on PD12 following KA-induced status epilepticus on PD10 in male C57BL/6J mice [15].

The present study hypothesized that the impact of a HSL during this critical window would be related to a greater impact on vocalization production, similar to previous studies showing that lifetime seizure frequency is related to a greater risk of cognitive impairment in later life [8,9]. Cognitive impairments are a fundamental concern following seizures and are considered one of the largest comorbidities in epilepsy [29,30]. Another common comorbidity for individuals with epilepsy is ASD, but this relationship is less clear [12]. The USVs are not typically considered an expression of cognitive behavior, but rather their disruption indicates changes in autistic-like social communication [14]. Thus, the findings of the present study support that similar to the relationship of lifetime seizure load and cognitive dysfunction, higher seizure load is related to increased communication dysfunction in the present rodent model.

In the current study, we found qualitative and quantitative changes to the USVs following multiple generalized seizures early in development. This study also provides support for future studies determining the meaning of the different call-types. These call-types are defined based on duration, spectrographic shape, and frequency changes, and their proportions vary significantly based on environmental context, background strain, and sex of the mouse [19,31]. While previously published studies have also utilized other call-type categorization schemas, we selected this one for the present study because of its application in the ASD rodent field. Previous studies in ASD mouse models have similarly found reduced complex call-types during the early postnatal period [19,32,33]. While the distribution of call-type percentages can be modulated by background strain alone, decreased complex calls in ASD models appears consistent across background strains, specifically C57BL6/J, BTBR, and FVB.129, suggesting that this finding occurs at levels above chance. Moreover, in another monogenic model of ASD, representative sequences from the mutant pups, containing fewer complex calls, were less likely to elicit maternal approach [33]. Combined with the findings in the ASD literature, we believe that this supports that this suppression of complex call production is an indicator of an ASD-like communication deficit. Altogether, these findings suggest a need for subsequent studies to elucidate the value communicated by the different call-types.

5. Conclusions

Individuals with epilepsy can suffer from a number of behavioral comorbidities, including communication deficits. The results of the present study corroborate and extend previous findings, demonstrating that experiencing a HSL, but not LSL, early in development elicits significant changes in vocalization behavior, including increased average call duration and decreased complex call production. Moreover, these results support the conclusion that sex differences may exist in response to developmental insults such as seizures.

Acknowledgments

The authors would also like to thank other members of the Lugo lab for their contributions to the lab. This work was supported by the National Institutes of Health (NIH) [Grant Number: NS088776].

Author contributions

JNL, SN, and SH were involved in project design. SN, SH, SC, IM, LT, and MB collected the data. IM, LT, SC, and SN analyzed the data. SN wrote the manuscript. All authors revised the article critically and approved the final version for submission.

Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.03.037.

References

[1] Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy — a review. Epilepsy Res 2009;85:31–45.
[2] Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129:256–64.
[3] Baca CB, Vickrey BG, Caplan R, Vassar SD, Berg AT. Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. Pediatrics 2011; 128(6):e1532–43.
[4] Strauss E, Loring D, Chelune G, Hunter M, Hermann B, Perrine K, et al. Predicting cognitive impairment in epilepsy: findings from the Bozeman epilepsy consortium. J Clin Exp Neuropsychol 1995;17:909–17.
[5] Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. Lancet Neurol 2004;3:663–72.

[6] Wiebe S, Hesdorffer DC. Epilepsy: being ill in more ways than one. Epilepsy Curr 2007;7:145–8.

[7] Karouni M, Arulthas S, Larsson PG, Rytter E, Johannessen SI, Landmark CJ. Psychiatric comorbidity in patients with epilepsy: a population-based study. Eur J Clin Pharmacol 2010;66:1151–60.

[8] Black LC, Schefft BK, Howe SR, Szaflarski JP, H-s Yeh, Privitera MD. The effect of seizures on working memory and executive functioning performance. Epilepsy Behav 2010;17:412–9.

[9] Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. Progress in Brain Research. Elsevier; 2002. p. 429–38.

[10] Berg AT, Zelko FA, Levy SR, Testa FM. Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes a prospective cohort study. Neurology 2012;79:1384–94.

[11] Greer PL, Greenberg ME. From synapse to nucleus: calcium-dependent gene transcription in the control of synapse development and function. Neuron 2008;59: 846–60.

[12] Saemundsen E, Ludvigsson P, Hilmarsdottir I, Rafnsson V. Autism spectrum disorders in children with seizures in the first year of life - a population-based study. Epilepsia 2007;48:1724–30.

[13] Lugo JN, Swann JW, Anderson AE. Early-life seizures result in deficits in social behavior and learning. Exp Neurol 2014;256:74–80.

[14] Sillanpaa M. Epilepsy in children: prevalence, disability, and handicap. Epilepsia 1992;33:444–9.

[15] Reynolds CD, Nolan SO, Huebschman JL, Hodges SL, Lugo JN. Early-life status epilepticus acutely impacts select quantitative and qualitative features of neonatal vocalization behavior: spectrographic and temporal characterizations in C57BL/6 mice. Epilepsy Behav 2017;72:58–62.

[16] Reynolds CD, Smith G, Jefferson T, Lugo JN. The effect of early life status epilepticus on ultrasonic vocalizations in mice. Epilepsia 2016;57:1377–85.

[17] Keller A, Saucier D, Sheerin A, Yager J. Febrile convulsions affect ultrasonic vocalizations in the rat pup. Epilepsy Behav 2004;5:649–54.

[18] Lopez-Meraz ML, Medel-Matus JS, Morgado-Valle C, Beltran-Parrazal L, Perez-Estudillo C, Manzo J. Effect of lithium-pilocarpine-induced status epilepticus on ultrasonic vocalizations in the infant rat pup. Epilepsy Behav 2014;31:263–6.

[19] Scattoni ML, Gandhy SU, Ricceri L, Crawley JN. Unusual repertoire of vocalizations in the BTBR T+tf/J mouse model of autism. PLoS One 2008;3:e3067.

[20] Smith JC. Responses of adult mice to models of infant calls. J Comp Physiol Psychol 1976;90:1105.

[21] Young DM, Schenk AK, Yang S-B, Jan YN, Jan LY. Altered ultrasonic vocalizations in a tuberous sclerosis mouse model of autism. Proc Natl Acad Sci U S A 2010;107: 11074–9.

[22] Reynolds CD, Nolan SO, Jefferson T, Lugo JN. Sex-specific and genotype-specific differences in vocalization development in FMR1 knockout mice. Neuroreport 2016; 27:1331–5.

[23] Kubova H, Druga R, Lukasiuk K, Suchomelova L, Haugvicova R, Jirmanova I, et al. Status epilepticus causes necrotic damage in the mediodorsal nucleus of the thalamus in immature rats. J Neurosci 2001;21:3593–9.

[24] Sankar R, Shin DH, Liu H, Mazarati A, Pereira de Vasconcelos A, Wasterlain CG. Patterns of status epilepticus-induced neuronal injury during development and long-term consequences. J Neurosci 1998;18:8382–93.

[25] Holmes GL, Gairsa JL, Chevassus-Au-Louis N, Ben-Ari Y. Consequences of neonatal seizures in the rat: morphological and behavioral effects. Ann Neurol 1998;44: 845–57.

[26] Akman O, Moshe SL, Galanopoulou AS. Sex-specific consequences of early life seizures. Neurobiol Dis 2014;72(Pt B):153–66.

[27] Castelhano AS, Scorza FA, Teixeira MC, Arida RM, Cavalheiro EA, Cysneiros RM. Social play impairment following status epilepticus during early development. J Neural Transm (Vienna) 2010;117:1155–60.

[28] Binder MS, Hernandez-Zegada CJ, Potter CT, Nolan SO, Lugo JN. A comparison of the Avisoft (5.2) and Ultravox (2.0) recording systems: implications for early-life communication and vocalization research. J Neurosci Methods 2018;309:6–12.

[29] Chauviere L, Rafrafi N, Thinus-Blanc C, Bartolomei F, Esclapez M, Bernard C. Early deficits in spatial memory and theta rhythm in experimental temporal lobe epilepsy. J Neurosci 2009;29:5402–10.

[30] Hermann B, Meador KJ, Gaillard WD, Cramer JA. Cognition across the lifespan: antiepileptic drugs, epilepsy, or both? Behavior;Epilepsy Behav 2010;17:1–5.

[31] Brudzynski SM. Handbook of ultrasonic vocalization : Window into the mammalian brain. Elsevier Science & Technology; 2018.

[32] Hiramoto T, Kang G, Suzuki G, Satoh Y, Kucherlapati R, Watanabe Y, et al. Tbx1: identification of a 22q11.2 gene as a risk factor for autism spectrum disorder in a mouse model. Hum Mol Genet 2011;20:4775–85.

[33] Takahashi T, Okabe S, Broin PÓ, Nishi A, Ye K, Beckert MV, et al. Structure and function of neonatal social communication in a genetic mouse model of autism. Mol Psychiatry 2016;21:1208–14.