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PTZ-induced seizures in mice require a revised Racine scale

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ABSTRACT

Seizure severity in experimental models of epilepsy is often evaluated by means of the Racine scale, in spite of the use of seizure induction methods that are different from those of the original paper by Racine in 1972. In such cases, the use of this scale is not always justified because some seizure behaviors are significantly different from those originally described or not present at all. Correspondingly, the pentylenetetrazole (PTZ) model, which is frequently used for antiepileptic drug research, lacked an adequate assessment tool to measure seizure severity. In 2009, an adapted intensity scale for PTZ-induced seizures was already designed for rats. Here, we evaluated electroencephalographic (EEG) and behavioral parameters after a single PTZ injection, to determine whether this scale is also suitable for use in mouse studies. We found that the scale designed for rats is quite robust and can thus be applied to score seizure severity in mice. Yet, certain convulsive behaviors and EEG characteristics were distinct between species. Therefore, a species-specific scale was designed, which included the concomitant EEG characteristic next to the behavioral expressions we observed, in order to establish a user-friendly scoring scale for PTZ-induced seizures in mice. To evaluate applicability, we utilized the scale in a seizure susceptibility study of a transgenic mouse model. We demonstrated that the maximum severity scores obtained with the newly revised Racine scale highly correlated with the administered dose. Hence, the revised scale differentiates well between different classes of seizure severity.

1. Introduction

The Racine scale is an often-used method of evaluating seizure severity in experimental models of epilepsy. Originally, this scale has been developed to describe the progression of limbic seizures with secondary generalization in the amygdala-kindling model [1,2]. In this particular case, kindling was achieved via repeated targeted electrical stimulation. However, many more seizure induction methods are currently implemented in epilepsy research. Apart from genetic modification, mainly two following methods can be distinguished: (1) acute seizure models that encompass the application of a single chemical (e.g., pentylenetetrazole (PTZ), strychnine), audiogenic, or electrical stimulus; and (2) chronic seizure models, in which either chemoconvulsants (e.g., kainic acid, pilocarpine) induce spontaneous recurrent seizures via structural damage after status epilepticus or repeated electrical stimulations trigger subtle, cumulative neuronal loss, and cellular alterations, better known as kindling [3,4].

Despite these different seizure induction methods, seizure intensity is often scored according to the same Racine scale, although the use of this scale is not always justifiable. Rats that were kindled in other limbic sites displayed responses that were different from those described according to Racine [5]. Moreover, different intensity classification systems have been established for audiogenic seizures, suggesting that the Racine scale is rather inappropriate for other experimental models that do not rely on kindling [6,7]. Correspondingly, the PTZ model, a frequently used model for antiepileptic drug assessment [8], lacked an adequate assessment tool to measure seizure severity. Therefore, in 2009, Lüttjohann et al. devised an adapted intensity scale for PTZ-induced seizures in rats, and sought to correlate electroencephalographic (EEG) parameters with behavioral expressions [9].

In current epilepsy research, mice are at least equally important as animal model as rats, especially given the fact that the transgenic approach for the generation of genetic seizure models is still more established in mice [10,11]. Because of our interest of applying the PTZ model to a transgenic mouse model, we sought to determine whether the Racine scale, redesigned by Lüttjohann et al. [9], was also applicable to mice, and in particular C57Bl/6J mice and their tau mutant littermates. According to our findings, this scale was quite robust, and grossly, all behavioral expressions could be demonstrated in mice. Yet, certain seizure behaviors (i.e., whisker trembling, tonic extension) were observed in mice, while they were absent in rats. Additionally, in this study, observed behaviors were correlated to species-specific EEG

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characteristics, thereby establishing a user-friendly severity assessment tool that is applicable for all acute PTZ-induced seizures in mice.

2. Materials and methods

2.1. Tau58/4 transgenic mice

Briefly, to create the Tau58/4 construct, a F115 TAU complementary deoxyribonucleic acid (cDNA) encoding the 135 AA human tau isoform (0N4R) containing the P301S mutation was cloned into the pTSC21K bacterial expression vector including the murine Thy1.2 gene [12] using the XhoI restriction site. Vector sequences were removed by NotI PvuI digestion. Injection and manipulation of mice were identical to described procedures [13]. Tau 58/4 mice were generated in a hybrid C57BL/6 × DBA2 background, and mice were backcrossed to C57BL/6J mice to create an isogenic line, as previously described [14]. Heterozygous (HET) Tau58/4 and wild-type (WT) littermates were created by crossing HET Tau58/4 males with purchased C57Bl/6J female mice. Only male mice were used in this study. All mice were group-housed in standard mouse cages under conventional laboratory conditions, and individually housed from the day of electrode implantation onward with constant room temperature (22 ± 2 °C), humidity level (55 ± 5%), and 12 h/12 h day/night cycle (lights on at 8 a.m.). Food and water were supplied ad libitum. Custom primers (Biolegio, The Netherlands) were used for genotyping by polymerase chain reaction (PCR) analysis performed on deoxyribonucleic acid (DNA) extracted from ear punches, collected from mice aged 4 weeks. All experiments were carried out in compliance with the European Community Council Directive (2010/63/EU) and were approved by the Animal Ethics Committee of the University of Antwerp (ECD approval n° 2014–82).

2.2. Video-EEG recording

By stereotactic surgery, four active screw EEG electrodes (E363/96/1.6, Plastics One Inc., Roanoke, U.S.A.) were implanted over the frontal and parietal cortices, while one ground and one reference electrode were placed over the cerebellum (*coordinates from reference point Bregma: right frontal cortex: anteroposterior (AP) +2.0 mm, mediolateral (ML) +2.0 mm; left frontal cortex: AP +2.0 mm, ML −2.0 mm; right parietal cortex: AP −2.0 mm, ML +2.0 mm; left parietal cortex: AP −2.0 mm, ML −2.0 mm; ground electrode: AP −4.90 mm, ML 0.0 mm; reference electrode: AP −6.70 mm, ML 0.0 mm*) [15]. All implanted electrodes were fixed to the skull with carboxylate cement (Durelon™, 3M ESPE S.A., Germany). The sockets were attached to an electrode pedestal (MS 363, Plastics One, Roanoke, U.S.A.), and the assembly was secured to the skull by carboxylate cement (Durelon™, 3M ESPE S.A., Germany). Postoperatively, animals were housed individually and carefully monitored for pain and distress. As a postoperative analgetic, 0.05 mg/kg buprenorphine (Vetergesic®, 0.3 mg/mL, Ecuphar, Oostkamp, Belgium) was subcutaneously administered every 12 h in a volume of 10 mL/kg for two days after surgery.

After a seven-day recovery period, video EEG commenced with 3 h of baseline EEG recording with a 40-channel EEG headbox (Large EEG headbox, Schwarzer Ahns, Germany). The first 2 h served as a habituation period for the animals to acclimatize to the experimental conditions. During the final hour, the actual baseline EEG was recorded and behavior was scored to ensure that the animals were free of epileptiform activity prior to seizure induction. After baseline recordings, acute seizures were induced by administration of a single dose of PTZ followed by behavioral and electrographic evaluation of seizure activity. The signal was sampled at a rate of 250 Hz and bandpass filtered between 0.5 and 30 Hz. Post-PTZ observations had a minimal duration of 1 h and were terminated when both behavior and EEG activity normalized for at least 15 min, with a maximum duration of 2 h. One day after the recordings took place, animals were sacrificed, and brains were extracted, frozen at −40 °C in 2-methylbutane on dry ice, and stored at −80 °C for further analyses.

2.3. Acute seizure induction with PTZ

For the induction of seizures, a single dose of PTZ (Sigma-Aldrich™, St. Louis, U.S.A.; purity ≥ 99%) was administered intraperitoneally according to randomly ascribed doses with different groups of animals being injected for each dose. In this experimental setup, five different doses of PTZ were studied (10, 20, 40, 60, and 80 mg/kg) within young adult (3-month-old) and aged (12–15-month-old) HET Tau58/4 and WT mice. In young adult Tau58/4 mice, the overexpression of mutated human tau does not yet result in the formation of neurofibrillary tangles (NFTs) and paired helical filaments (PHFs), while in the old age group, NFTs and PHFs are diffusely present in the brain. The injection volume was 10 mL/kg. At least 8 animals were used per dose group/genotype/age, except for the lowest and highest dose groups, in which fewer animals were used because of no response or premature death of the animals. All included animals are indicated in Table 1. Researchers were blinded to the dose, genotype, and age status of animals.

2.4. Seizure scoring analysis

For evaluation of seizures, animals were monitored both electrographically and behaviorally. The BrainRT™ software (OSG BVBA, Rumst, Belgium) was used for both registration and analysis of the different EEG traces. Automatic rhythm analysis was used to aid in the manual scoring of the epileptiform activity and characteristics, based on Lüttjohann et al. [9]. For analysis, a seizure was electrographically defined as high amplitude, rhythmic discharges representing a distinct EEG trace lasting for a minimum of 5 s. Epileptic events occurring within an interval of 5 s without the EEG returning to baseline are defined as belonging to the same event [16]. Based on this condition, all seizures were manually defined by indicating both start and stop positions of an observed electrographic seizure.

To assess the behavioral severity of the electrographically defined seizure, researchers performed observations by listing all perceived behaviors and their corresponding timepoint in real time (accurate to 1 s). Additionally, the experiment was recorded with a video camera (DCR-DVD105 DVD Handycam camcorder with 20× optical zoom, Sony). Via a video converter (Canopus ADVC55), the analog signal was digitally converted. In the BrainRT™ software, the video was synchronized with the recorded EEG. During EEG evaluation, the listed behaviors were consulted, and based on the described behavior within the time frame of the insult, EEG characteristics were correlated with behavioral expressions. In case of doubt, the video was consulted to reassess the observed seizure. Afterwards, these data were compared with the Racine score according to Lütthjohann et al., and an adapted scale was designed accordingly. When multiple different classes of severity occurred during one electrographically defined seizure, the most severe behavior represented the severity of that seizure. If an electrographic insult was not associated with any behavioral symptoms, a score of 1 was assigned, since the animal was probably in a state of behavioral arrest.

Table 1
Amount of animals included in the study and received doses per genotype and age.

PTZ dose (mg/kg)	Young (3 M)	Old (12–15 M)
10	11 mice (6 WT + 5 HET)	18 mice (9 WT + 9 HET)
20	16 mice (8 WT + 8 HET)	20 mice (11 WT + 9 HET)
40	17 mice (9 WT + 8 HET)	19 mice (10 WT + 9 HET)
60	17 mice (9 WT + 8 HET)	20 mice (11 WT + 9 HET)
80	16 mice (8 WT + 8 HET)	9 mice (4 WT + 5 HET)

HET, heterozygote Tau58/4; WT, wild-type Tau 58/4; PTZ, pentylenetetrazole; 3 M, three-month-old; 12–15 M, 12- to 15-month-old.

3. Results

We examined the applicability of Lüttjohann's revised Racine scale [9] in mice. By comparison of their reported findings in rats, we studied whether seizures manifested differently on EEG, as well as behaviorally in mice. Therefore, a detailed examination of EEG parameters and seizure severity-related behavioral parameters was performed after mice received a single dose of PTZ with different groups of animals being injected for different doses. All animals of both genotypes and both age groups (n = 163) were included into the analysis, to design a revised scale that is as uniformly as possible.

In this study, the following ten different behavioral categories were observed: (1) whisker trembling during behavioral arrest, (2) sudden behavioral arrest or motionless staring, (3) facial jerking expressed with the nose, (4) neck jerks, (5) clonic seizures while the animal falls into a sitting position, (6) clonic seizures while the animal was on its belly (without the loss of balance), (7) tonic–clonic seizures on its belly, (8) clonic seizures with the animal falling on its side, (8) tonic–clonic seizures with the animal falling on its side, (9) wild jumping, and (10) tonic extension (of either forelimbs alone or both fore- and hindlimbs) leading to death. The majority of these behaviors are visually displayed in Supplementary Video 1, in which a mouse is injected with a high dose of PTZ.

Each behavioral expression was then correlated to the EEG characteristic that occurred simultaneously (Fig. 1). Whisker trembling and behavioral arrest were accompanied by slowing of the EEG and intermittent spike–wave discharges, as was facial jerking. However, isolated facial jerking was only rarely observed, and was more often present when myoclonic jerks manifested. Myoclonic neck jerks were characterized by sharp spikes followed by spike–wave discharges and a slowing of the EEG. Clonic seizures with the animal falling into a sitting position had a distinct pattern on EEG, namely high frequency rhythmic waves with a small amplitude that were almost indistinguishable from an active wake EEG pattern. Severe (tonic-) clonic seizures were all characterized by high amplitude polyspikes and spike–wave discharges, although behavioral expressions ranged from clonic convulsions without loss of balance to wild jumping. Tonic extension and respiratory arrest coincided with an almost flat EEG trace. However, residual electrical activity was still present after amplification of the signal. This activity gradually decreased after the observer rated the animal as deceased. When the animal survived the tonic–clonic state, and did not go into respiratory arrest, a depression of the EEG was observed (Supplementary Fig. 1).

After administration of low doses of PTZ, some animals displayed whisker trembling during electrographically defined seizures. As described by Lüttjohann et al., the score '0' was assigned to this level of severity. In order to differentiate between animals that did not experience electrographically-defined seizures and animals that had whisker

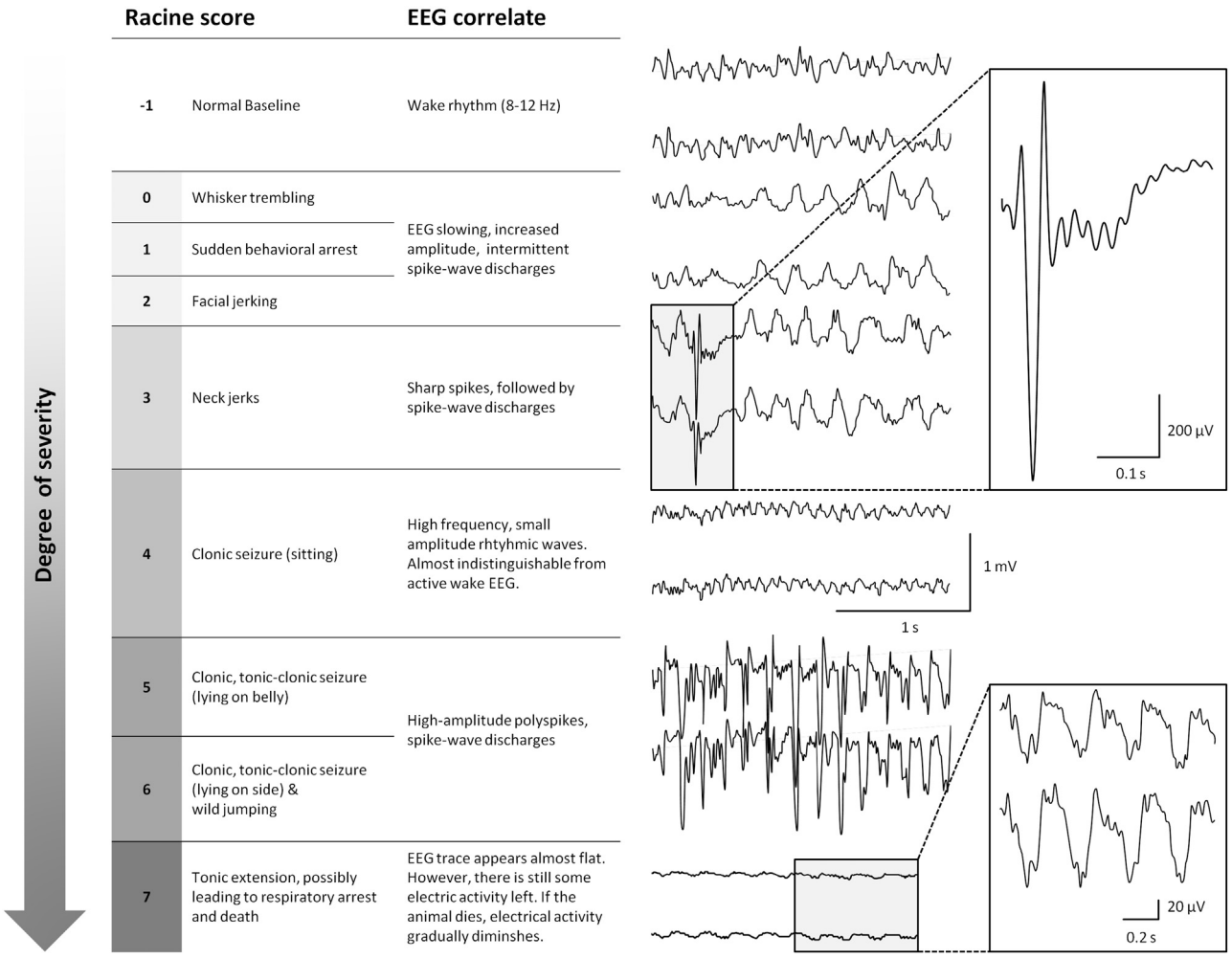

Fig. 1. Modified Racine scale for the behavioral scoring of seizure severity of PTZ-induced seizures in mice. This scale is applied for the occurrence of seizure-related behavioral changes in mice and the assessment of seizure severity. Each number represents a different degree of seizure severity. The higher the number, the more severe the seizure. Scores 0 to 2 represent partial/focal seizures, and stages 3 to 6 are generalized seizures. The maximum score of 7 represents tonic extension of the muscles, which, if prolonged, can lead to the death of an animal. For every degree of severity, the concomitant EEG correlate (in the right frontal and parietal lead) is displayed.

trembling during an epileptic episode, without deviating too far from the original scale, the nonconvulsive animals were assigned to severity level '− 1' in this study (Fig. 1).

Also, in this study, high (60 mg/kg and 80 mg/kg) single doses of PTZ evoked tonic extension of the limbs, followed by respiratory arrest. This behavioral phenotype was not reported by Lüttjohann et al., but given the relevance here, it was included into our scale. Only about 25% of all animals that died after PTZ injection (11/41) displayed tonic extension of the hindlimbs. In all other animals, the hindlimbs remained clonic (trampling, kicking) until death, while the forelimbs were tonically extended. Remarkably, in young three-month-old animals, tonic extension of the hindlimbs was observed much more frequently (9/14) than in 12- to 15-month-old mice (2/27). Young mice are less susceptible to PTZ-induced seizures compared with old mice at all dose groups, which possibly results in a different behavioral expression.

Low doses of PTZ (10–20 mg/kg) induced whisker trembling, behavioral arrest, and neck jerks (Fig. 2). Other behavioral expressions were not observed. High doses of PTZ (40–80 mg/kg) produced all seizure behaviors previously described, ranging from behavioral arrest to clonic and tonic seizures (Fig. 2). For every electrographically-defined seizure, only the most severe behavioral expression was taken into account. Since (tonic)-clonic seizures, while the animal is lying on its belly (but maintaining balance), were often immediately followed by more severe behaviors within the same electrographically-defined seizure, this behavior was undervalued in the analysis (Fig. 2). This is possibly also true for other behavioral categories (e.g., facial jerking was only observed in conjunction with neck jerks, every animal experienced wild jumping before dying of respiratory arrest).

Next, we assessed whether the revised scale (Fig. 1) is able to discriminate well between dose groups in our dataset. By taking into account the highest Racine score of each animal, the mean was plotted for each dose group (Fig. 2). To increase statistical power, all animals (Table 1) were included into the analysis. A gradual increase in maximum severity along increasing doses was observed. Independent samples *t*-tests revealed significant differences between all groups (all comparisons: $p < 0.001$). Moreover, there was a clear correlation between the maximum severity and the administered dose ($r = 0.908$, $p = 0.000$).

4. Discussion

In this study, we examined whether the revised Racine scale, as described by Lüttjohann et al. in 2009 [9], is also applicable to mice. We found that almost all previously described behavioral expressions in rats were also present in mice, indicating that previously mentioned revised scale has a high validity, even across species. Although it is justifiable to make use of this existing scale in mice, certain behavioral and EEG seizure characteristics were distinct between species. Therefore, we designed a mouse-specific and user-friendly scale by including the concomitant EEG correlate next to the behavioral expressions we observed in mice.

The study of Lüttjohann et al. observed that whisker trembling was only present in baseline conditions and disappeared upon administration of PTZ [9]. However, in this study, whisker trembling was regularly observed as a seizure behavior, especially at lower doses. In addition, at very high doses (60 and 80 mg/kg), tonic extension of the limbs was observed antecedent to respiratory arrest in around 25% of all cases. The majority (around 82%) of these animals were 3 months of age, suggesting that young mice are more prone to the display of tonic hindlimb extension during the occurrence of a lethal convulsion. Previously, we have demonstrated that old mice are more susceptible to PTZ-induced seizures. Possibly, the heightened sensitivity causes a more severe seizure manifestation, resulting in a different behavior expression profile.

Lüttjohann et al. have not mentioned tonic extension in their study. However, their administration schedule was very different from ours, since they started with an initial dose of 20 mg/kg PTZ intraperitoneally, and administered an additional dose of 10 mg/kg every 15 min.

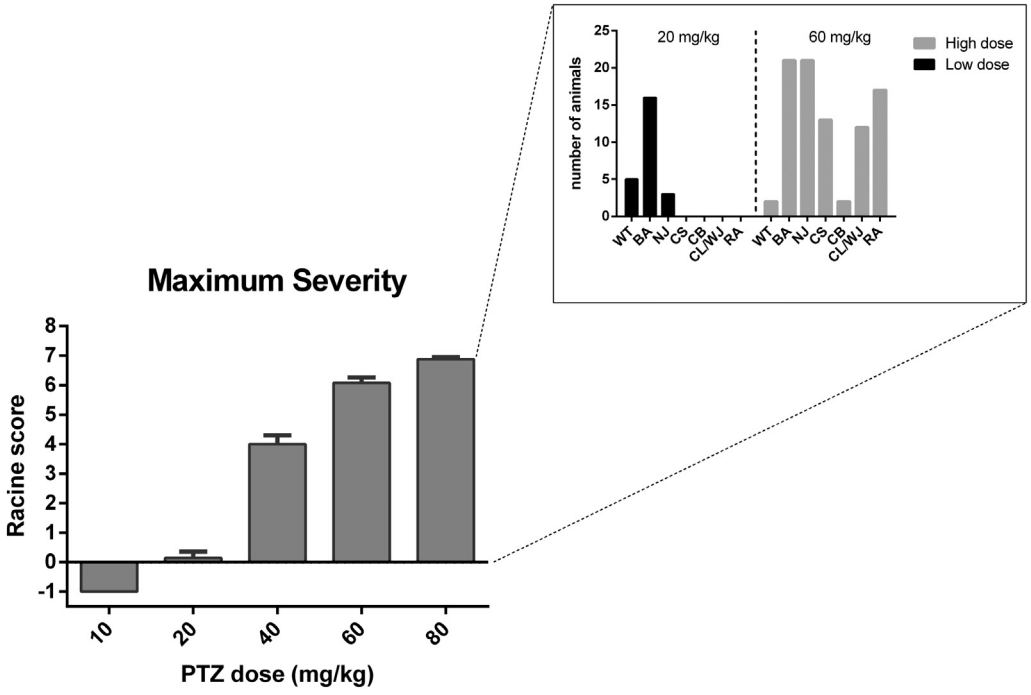

Fig. 2. Maximum seizure severity across all dose groups. A gradual increase in maximum severity for increasing doses was observed. Every dose group was significantly different from each other ($p < 0.001$). A clear correlation between Racine score and dose was present. The revised scale thereby answers quite well to the expected pattern of higher doses inducing more severe behavioral seizures. Data are represented as mean ± SEM. N = 163 (10 mg/kg: n = 29; 20 mg/kg: n = 36; 40 mg/kg: n = 36; 60 mg/kg: n = 37; 80 mg/kg: n = 25). Inset: behavioral expressions observed after low and high doses of PTZ. At low doses (e.g., 20 mg/kg), only nonmotor seizure behaviors were observed, including whisker trembling (WT), behavioral arrest (BA), and neck jerks (NJ). At high doses (e.g., 60 mg/kg), also motor seizures were present such as seated clonic seizure (CS), (tonic-) clonic seizures lying on the belly (CB), tonic–clonic seizures lying on the side (CL), wild jumping (WJ), and tonic extension with respiratory arrest (RA).

Additionally, if convulsive seizures lasted longer than 5 min, the researchers intervened to prevent lethality. It remains to be elucidated whether this is the true reason for not observing tonic extension or whether it is due to the single dose administration protocol. Devos et al., who performed single PTZ injections of 55 or 80 mg/kg in C57BL6/J mice, also included 'full tonic extension' into their severity score [17], which suggests that the inclusion of such behavior into a revised Racine scale is advised. Also, antiepileptic drug efficacy testing often relies on (high) single dose administration protocols, and thus encourages the inclusion of an extra Racine stage.

In this study, nonmotor seizures were always associated with slowing of the EEG, sometimes in the presence of spike–waves. Isolated sharp spikes highly correlated with severe behavioral twitches. Additionally, a rather distinct EEG pattern was observed when clonic 'sitting' seizures manifested. To our knowledge, such epidural EEG characteristics have not been previously described. Yet, they could be of potential interest for future epilepsy studies with epidural EEG electrode implants. Tonic–clonic seizures with high amplitude spikes, polyspikes, and sharp spike–wave discharges on the EEG resemble those described previously [9,18,19]. After (survival of) tonic–clonic convulsions, a depression/suppression of the EEG was observed, which has also been described in patients with epilepsy [20], stressing the prospect of a bench-to-bedside approach. By including the EEG correlate alongside the convulsive behaviors, we believe to have established a more user-friendly Racine scale that will allow (future) researchers to form a better understanding of what is observed on the EEG during convulsions in hope of improving the standardization between research groups. We should be aware that our study partly involved the use of a transgenic line and, although we do not expect this to have a major influence on seizure characterization, further follow-up in a pure isogenic C57Bl/6J line might be desirable.

To summarize, PTZ, administered as a single dose, reliably evokes seizures in mice. Low doses (up to 20 mg/kg) evoke nonmotor seizures, while high doses also produce motor seizures. We have demonstrated that the maximum severity scores obtained with the newly revised Racine scale for mice highly correlate with the administered dose, which indicates that the revised Racine scale is able to differentiate well between different classes of behavioral seizure severity.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.02.029.

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Conflicts of interests

The authors have no conflict of interest to declare.

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