ACCSCIENCE PUBLISHING

Advanced Neurology

SHORT COMMUNICATION

Distinct phenotypes, shared etiology: Dissociation of absence epilepsy, audiogenic seizures, and anhedonia in a genetic rat model

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Abstract

Epilepsy is a heterogeneous neurological disorder, characterized by distinct seizure phenotypes. We examined the phenotypic expression of seizures in genetically predisposed rats, focusing onthe relationship between absence epilepsy (AE), audiogenic seizures (AGS), and anhedonia. Thirty rats were assessed longitudinally for AE at 6 and 10 months and for AGS susceptibility. Anhedonia was measured using 2% sucrose preference test. Statistical analysis revealed a striking mutual exclusivity between seizure types: only 1 male among 11 AE-positive rats developed AGS, whereas 10 of 19 AE-negative rats (all females) developed AGS. Seizure manifestations in these rats exhibited a binary pattern, with a shared genetic predisposition affecting either corticothalamic or brainstem neural circuits, resulting in either AE or AGS, respectively. No association was found between either seizure phenotypes and anhedonia, as sucrose preference remained uniformly high across all groups. Logistic regression identified male sex as a negative predictor of AGS risk and confirmed the suppressive effect of AE on AGS susceptibility, although the models were limited by small sample size and strong collinearity between sex and sucrose preference. These results demonstrate circuit-specific phenotypic divergence in genetic epilepsy, with important implications for understanding seizure network development and comorbidity profiles.

Keywords: WAG/Rij rats; Sex dimorphism; Phenotypic exclusivity; Spike-and-wave discharges

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Citation: Sitnikova E, Pupikina M. Distinct phenotypes, shared etiology: Dissociation of absence epilepsy, audiogenic seizures, and anhedonia in a genetic rat model. *Adv Neurol*. 2026;5(4):025010133. doi: 10.36922/AN025010133

Received: December 31, 2025

Revised: February 10, 2026

Accepted: February 28, 2026

Published online: April 15, 2026

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1. Introduction

Certain genetically predisposed rat strains provide a unique model for studying the complex relationships between different epilepsy syndromes and their psychiatric comorbidities. In these models, a shared genetic background can manifest as distinct neurological phenotypes, including non-convulsive absence epilepsy (AE) and reflex audiogenic seizures (AGS). AE is characterized by brief episodes of impaired consciousness associated with generalized spike-and-wave discharges (SWDs) on the electroencephalogram (EEG).[1-4] AGSs are brainstem-mediated convulsive episodes triggered by intense acoustic stimuli.[5-9] Notably, these AE and AGS may co-exist or

exhibit exclusive expression within the same genetic cohort[10], raising questions about common pathogenic pathways.

Furthermore, epilepsy is frequently associated with comorbid neuropsychiatric disorders, with anhedonia—a core symptom of depression characterized by the loss of pleasure—being a prominent concern.[11–13] The sucrose preference test is a validated, reliable measure of anhedonia-like behavior in rodents. We recently used this test in rats with a genetic predisposition to AE (Wistar Albino rats from Rijswijk, WAG/Rij rats[14,15]) and found no signs of anhedonia despite the presence of AE.[16,17] The relationship between anhedonia and specific epilepsy phenotypes remains poorly understood. Anhedonia in epilepsy may not always indicate depression, as it occurs in more than a third of patients without a depression diagnosis.[18] Understanding the relationship between anhedonia and specific epilepsy phenotypes is crucial for developing targeted interventions.

In this study, we used the WAG/Rij rat strain, which displays natural phenotypic variability. Some animals exhibited pronounced SWDs, representing a symptomatic phenotype, while others showed minimal or no epileptic activity at a given age, representing an asymptomatic phenotype. Comparing these subgroups serves as an internal control, allowing us to assess symptom correlations while minimizing genetic background as a confounding variable. The present study is a cohort (observational) study within a genetic model rather than an experimental design. Our primary aim isnot to compare affected versus healthy subjects, but to investigate correlations between spontaneously varying quantitative traits, such as AE and AGS, in genetically predisposed, drug-naïve animals. We employed an internal control strategy in a longitudinal study of 30 rats with a genetic predisposition to AE. The specific objectives were: (i) to examinethe relationship between the phenotypic expression of AE and the subsequent development of AGS; (ii) to explore whether these seizure types display mutually exclusive patterns or co-occur; and (iii) to assess the comorbidity of anhedonia (via sucrose preference) with either form of epilepsy. Phenotypic assessments were conducted at keytime points: AE at 6 and 10 months, sucrose preference at 6 months, and AGS at 11 months.

2. Materials and methods

2.1. Animals

The study cohort consisted of 30 rats (12 males and 18 females) from four litters born between February 18 and February 28, 2024. All animals shared a genetic background conferring susceptibility to AE, originating from WAG/Rij rats selectively bred for a non-epileptic AE phenotype. Rats were housed in a standard vivarium, with males and females separated into groups of three to four per cage. The study employed a longitudinal design, following the rats from 6 to 11 months of age.

The rats were maintained under controlled environmental conditions: a 12-h light/12-h dark cycle (lights on at 08:00), constant ventilation, and group housing by sex. Food and water were available *ad libitum* throughout the study. Rats remained housed with their original cage mates throughout the testing period. Experimental procedures complied with Directive 2010/63/EU of the European Parliament and of the Council regarding the protection of animals used for scientific purposes. The study protocol was approved by the institutional animal ethics committee (Protocol No. 4, December 13, 2022; updated on May 29, 2024). The study design is shown in Figure 1.

2.2. Absence epilepsy assessment

The experimental protocol for AE assessment was designed based on the methodology outlined by Pupikina and Sitnikova .[19] Prior to EEG recordings, the rats' heads were shaved to facilitate secure attachment of the EEG sensors. An intraperitoneal injection of xylazine solution (Xyla, containing 20 mg/mL of xylazine hydrochloride; Interchemie Werken De Adelaar, The Netherlands) was administered at a dosage of 2 mg/kg. Two EEG sensors were positioned on the frontal and parietal regions of the head. Recording sessions commenced 1–2 min following the xylazine injection and were continued for a duration of 7–10 min. Xylazine-induced SWDs served as reliable indicators of the epileptic phenotype within genetically predisposed rat strains.

Electroencephalogram signals were acquired using a wireless recording system (Physiobelt, Neurobotics, Russia) and visually inspected using Physiobelt software version 2.8.0 for Windows 10, as detailed in Ref.[19], to distinguish rats with AE from those without AE. Rats were classified as having AE if they exhibited several 8–10 Hz SWDs, each lasting more than 6 s. The detection of five or more SWDs within a 7–10 min recording period was considered indicative of AE; no distinction was made between mild and severe cases. Rats classified as epileptic (Epi+) at either the 6-month or 10-month observation points were designated as Absence Epi+.

Rats exhibiting minimal or no SWDs within the 8–10 Hz frequency range were categorized as non-epileptic. Rats recorded as non-epileptic at both observation points were

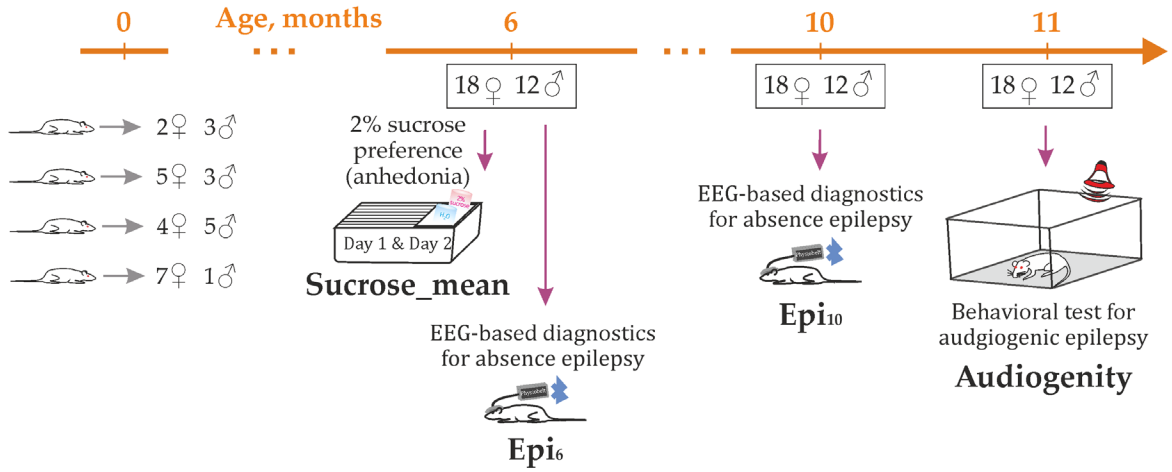


Figure 1. Schematic representation of the study design, including the rat cohort, ages, and experimental procedures. Absence epilepsy assessment was conducted at 6 and 10 months of age. Sucrose preference test (to assess anhedonia) was performed at 6 months of age. Finally, audiogenic seizure assessment was carried out at 11 months of age.
Abbreviation: EEG: Electroencephalogram.

designated as AE−. One rat (KN3x1) with incomplete data at the 10-month time point was classified based solely on its 6-month status.

2.3. Audiogenic seizure assessment

Audiogenic seizures were elicited by high-intensity, wide-frequency acoustic stimuli in a controlled experimental environment. The response in rats exhibited a highly stereotypical sequence, characterized by the following stages:

i. Latent period (0–10 s): Initial phase marked by brief behavioral arrest.
ii. Wild running phase: Characterized by explosive, violent, and disoriented locomotor activity, including galloping or leaping movements within the testing area.
iii. Clonic seizure phase: Not observed in this cohort.
iv. Tonic seizure phase: Not observed in this cohort.
v. Post-ictal depression phase: Not observed in this cohort.

The presence of a wild running phase was deemed a positive AGS response, and the rat was classified as AGS+. The absence of any convulsive response resulted in classification as AGS−. Two experimental protocols were employed:

(i) Classic protocol: Utilizing an electric bell as an acoustic stimulus, introduced to test AGS in the Krushinsky–Molodkina rat strain[6]. The protocol involved the presentation of sounds at intensities of 100–120 dB sound pressure level (SPL) within a soundproof chamber.

(ii) Key-ringing protocol: Utilizing a standard complex multipeak sound (key ringing) produced by a vibro device, with a frequency range of 13–85 kHz (peaking at 20–40 kHz) and a mean intensity of 50–60 dB, for a duration of 90 s. This protocol was introduced to test AGS in WAG/Rij and Wistar rats.[10,20]

The efficacy of both protocols was comparable. Rats exhibiting AGS in response to the key-ringing protocol were not subsequently subjected to the more stressful electric-bell test.

Rats were assessed for their susceptibility to AGS using the key-ringing method. The animals were placed in a transparent Plexiglas testing chamber measuring 60 cm × 60 cm × 60 cm. The acoustic stimulus, a standard complex multipeak sound, was generated by a vibro device (a custom-made mechanical key-ringing apparatus with 16 metallic keys) and presented for 90 s. A video recording of an AGS in a female rat, triggered by the key-ringing stimulus, is available at the following link: https://cloud.mail.ru/public/EJfn/VN7Bx1dxD.

The classic protocol is known to beassociated with a high level of stress.[21] The experiment was conducted within a soundproof/attenuating chamber to isolate the testing environment from external noise and contain the high-volume acoustic stimuli. An electric bell capable of producing sound levels ranging from 100 to 120 dB SPL was used as the acoustic stimulus. The experimental setup consisted of a transparent testing arena, a rectangular Plexiglas enclosure measuring 40 cm × 60 cm, positioned within the soundproof chamber. The duration of the electric bell acoustic stimulation was 60 s. The movements

and responses of the rats were recorded using video cameras (Logitech C920e, China) for detailed behavioral analysis and latency measurement. A video recording of an AGS, triggered by the electric bell (100–120 dB SPL), is available in the repository at the following link: https://cloud.mail.ru/public/HHSD/YRKgqJHJR.

2.4. Sucrose preference test (anhedonia)

At six months of age, a two-bottle choice test was conducted over two days to assess sucrose preference, a measure of anhedonia. Rats were singly housed and first habituated to two pre-weighed bottles (both containing water) for 24 h. This was followed by a 24-h test in whichone bottle contained a 2% sucrose solution and the other contained tap water. Bottle positions were switched after the first 24 h to control for side preference. Fluid intake was measured by weighing the bottles. Sucrose preference was calculated for each day as:

$$Sucrose\ preference = \frac{\text{Sucrose intake}(g)}{\text{Sucrose intake}(g)+\text{Water intake}(g)} \quad (1)$$

The final sucrose_mean variable was the average of the two daily preference scores. One missing value (rat KN0x2, Day 2) was imputed using the sex-specific mean of Day 2 values from the cohort.

2.5. Statistical analysis

Statistical analysis was performed using Statistic Calculators (https://statisticscalculators.com/). Group statistics wereperformed using *t*-test, two-way ANOVA for sucrose preference results, and two-sided Fisher's exact testfor the distribution of AE and AGS phenotypes in both sexes. Statistical significance was set at $\alpha = 0.05$.

Firth's penalized-likelihood logistic regression was used to model the multivariate relationship predicting AGSsusceptibility. This method reduces small-sample bias and addresses issues of complete or quasi-complete separation in the data. Two models were specified:

(i) Model 1: Audiogenity (1 = present, 0 = absent) ~ Sex (1 = male, 0 = female) + Epi_6 (1 = present at 6months, 0 = absent) + Sucrose_mean.
(ii) Model 2: Audiogenity ~ Sex + Epi_{10} (1 = present at 10months, 0 = absent) + Sucrose_mean.

Regression coefficients are reported as log-odds. Internal validation was performed using bootstrap resampling with 200 iterations. The events per variable (EPV) ratio was 4.0 (12 events for 3 predictors), which is below the recommended threshold of 10. This indicates that theresults should be interpreted with caution and are consideredhypothesis-generating. Pairwise Pearson correlation matrices were generated for the variables in each model to assess multicollinearity. Model fit and coefficient stability were evaluatedvia the bootstrap procedure.

3. Results

The cohort of 30 rats was stratified based on longitudinal AE and AGS status (Figure 1), as detailed in Table 1.

Table 1. Distribution of epileptic phenotypes in the genetically predisposed rat cohort ($N = 30$)

Epileptic phenotype	Female(*n*)	Male(*n*)	Total(*n*)
AE+AE+AGS+	0	1	1
AE+AE−AGS+	0	0	0
AE−AE+AGS+	0	1	1
AE+AE+AGS−	1	6	7
AE+AE−AGS−	0	0	0
AE−AE+AGS−	0	2	2
Total AE+(AGS with AE)	1 (0)	10 (1)	11 (1)
AE−AE−AGS−	7	2	9
AE−AE−AGS+	10	0	10
Total AE−(AGS without AE)	17 (10)	2 (0)	19 (10)

Notes: Indexes include absence epilepsy (AE) assessed at two ages (6 [the first AE] and 10 months [the second AE]) and audiogenic seizures (AGS).
Abbreviations: AE+: Absence epilepsy phenotype; AE−: No absence epilepsy; AGS+: Audiogenic seizures; AGS−: No audiogenic seizures.

3.1. Relationship between absence epilepsy and audiogenic seizures

Consolidating the AE phenotype at either 6 or 10 months (AE+AE+, AE−AE+, AE+AE− in Table 1) revealed a strong and statistically significant inverse relationship with AGS. Among the 11 AE+ rats, only one male (KN2y2; 3.3% of the cohort) exhibited AGS, suggesting that mixed phenotypes are extremely rare. In contrast, 10 females of the 19 AE− rats (52.6%) showed AGS.

The association between sex and the AE+ phenotype was highly significant ($p < 0.001$, Fisher's exact test), with the AE+ phenotype occurring predominantly in males ($n = 11$; 1 female and 10 males). The AE− phenotype occurred predominantly in females ($n = 19$; 17 females and 2 males). The AGS-only phenotype (without AE) was strongly female-biased. The proportion of female subjects with this phenotype (AE−AE−AGS+, $n = 10$; all females) was significantly higher than in other phenotypes ($p = 0.0024$, Fisher's exact test). These results provide strong evidence for sex-linked genetic mechanisms influencing epileptic processes in rats genetically predisposed to AE. Males aremore likely to develop AE, while females aremore likely to develop AGS.

3.2. Sucrose preference (anhedonia) analysis

The overall mean sucrose preference for the cohort was high (0.91 ± 0.12), indicating no global anhedonia. No significant differences in preference were found when comparing:

(i) AE: AE+ (0.90 ± 0.14; n = 11) vs. AE− (0.92 ± 0.11; n = 19); p = 0.63 (t-test).
(ii) AGS: AGS+ (0.91 ± 0.10; n = 12) vs. AGS− (0.91 ± 0.13; n = 18); p = 0.99 (t-test).

A two-way ANOVA comparing the four groups based on combined AE and AGS status also showed no significant effect on sucrose preference ($F(3,26) = 0.36$, $p = 0.79$). The two rats with notably low sucrose preference (KN1y6: 0.67; KN3x7: 0.35) both belonged to the AE−, AGS− phenotype group.

3.3. Multiple linear regression analysis

Two logistic regression models were developed to predict AGS susceptibility (Audiogenity = 1), using Epi_6 and Epi_{10} as predictor variables. The logistic regression equation for Model 1 (Predictor: Epi_6) is:

$$\text{logit}(P(\text{Audiogenity} = 1)) = 0.7101 - 0.2353 \times \text{Sex} - 0.1666 \times \text{Epi}_6 - 0.2400 \times \text{Sucrose_mean} \quad (2)$$

Interpretation of Model 1 coefficients:

(i) Sex: Males were less likely to have AGS (−0.2353) than females, potentially due to correlation, not causation.
(ii) Epi_6: AE at the age of 6 months appeared to be protective against AGS susceptibility, indicating a suppressive effect on audiogenic risk (−0.1666).
(iii) Sucrose_mean: A higher sucrose preference was weakly protective (−0.2400) against AGS susceptibility.

The correlation matrix (Table 2) revealed severalkey insights. Audiogenity showed a moderate negative correlation with sex (r = −0.3889), indicating thatmales were less likely to be AGS+. This inverse correlation suggests that males are less susceptible to AGS. The correlation between audiogenity and Epi_6 was weak and negative (r = −0.1181). The inverse correlation between audiogenity and sucrose_mean indicates that a higher sucrose preference is protective. The strongest correlation in the matrix was between sex and sucrose_mean (r = 0.6533), suggesting a significant association between male sex and higher sucrose preference in this cohort, which may confound the model.

Table 2. Pairwise correlations in Model 1

Parameter	Audiogenity = 1	Sex	Epi_6	Sucrose_ mean
Audiogenity = 1		−0.3889	−0.1181	−0.3860
Sex	−0.3889		0.1012	0.6533
Epi_6	−0.1181	0.1012		0.1145
Sucrose_mean	−0.3860	0.6533	0.1145	

The logistic regression equation for Model 2 (Predictor: Epi_{10}) is:

$$\text{logit}(P(\text{Audiogenity} = 1)) = 0.7250 - 0.3138 \times \text{Sex} - 0.1943 \times \text{Epi}_{10} - 0.0862 \times \text{Sucrose_mean} \quad (3)$$

This model showed that Epi_{10} suppressed AGS risk more than Epi_6, and the effects of sex and sucrose were attenuated. Interpretation of Model 2 coefficients:

(i) Sex: Males were less likely to have AGS (−0.3138), consistent with Model 1.
(ii) Epi_{10}: AE at the age of 10 months was protective against AGS susceptibility (−0.1943), similar to the effect of Epi_6 (−0.1666), but potentially stronger.
(iii) Sucrose_mean: A higher sucrose preference was not protective (−0.0862) against AGS susceptibility, and it was smaller and less significant compared to that in Model 1 (−0.2400).

Pairwise correlations in Model 2 revealed strong collinearity between sex and sucrose_mean (r = 0.7907) and independence between Epi_{10} and sucrose_mean (r = 0.0752). The correlation structure in Model 2 (Table 3) was similar to that in Model 1 (Table 2). Audiogenity maintained a moderate negative correlation with sex (r = −0.3889) and a weak negative correlation with Epi_{10} (r = −0.1181).

Table 3. Pairwise correlations in Model 2

Parameters	Audiogenity = 1	Sex	Epi_{10}	Sucrose_ mean
Audiogenity = 1		−0.3889	−0.1181	−0.3389
Sex	−0.3889		0.1012	0.7907
Epi_{10}	−0.1181	0.1012		0.0752
Sucrose_mean	−0.3389	0.7907	0.0752	

Both the Epi_6 and Epi_{10} models demonstrated a protective effect against audiogenic susceptibility. This finding is consistent with the results of Fisher's test, which confirm a trend toward exclusivity: a history of AE decreases the log-odds of susceptibility to AGS.

However, the weak correlation coefficients suggest that this predictive relationship is not strong in a multivariate context. Sex emerges as a more significant predictor, with a consistently negative coefficient, indicating that being male is associated with lower odds of AGS. The correlation with sucrose_mean was also negative but varied across models and was substantially confounded by its strong correlation with sex, making its independent contribution to predicting audiogenicity unclear. Given the low EPV (4.0), these multivariate findings should be interpreted with caution.

4. Discussion

Our study provides novel evidence for a striking phenotypic divergence in seizure expression within a genetically predisposed population. Themain finding is an almost complete mutual exclusivity between two distinct seizure types: non-convulsive AE (characterized by SWDs) and brainstem-mediated AGS. Seizure manifestation in our rats followed a binary pattern. Genetic predisposition appeared to activate one specific neural pathway while suppressing the alternative pathway.

We found that genetically predisposed rats exhibited a clear mutual exclusivity between AE and AGS, with mixed phenotypes occurring rarely (3.3%, $p = 0.0011$). This finding is consistent with the established neuroanatomy of these seizures. AE in models such as WAG/Rij rats is a corticothalamic disorder, initiated in the somatosensory cortex and sustained by resonant interactions with thalamic nuclei.[15,22] In contrast, genetically prone AGS, as observed in KM rats, primarily involves subcortical brainstem circuits, including the inferior colliculus, periaqueductal gray, and pontine reticular formation.[7,23] Our data suggest that a strong predisposition to hyperexcitability in one of these networks may developmentally suppress or outcompete the other. The single comorbid case is particularly noteworthy; it may represent a failure of this inhibitory developmental gating, or it could indicate a unique, more severe genotype that allows both networks to reach the seizure threshold. This observation aligns with clinical findings in which specific epilepsy syndromes rarely co-occur, highlighting the presence of underlying circuit-specific genetic architectures.

Sex dimorphism further shapes this divergence: males dominated the AE+ group (10/11), while females showed a strong AGS preponderance. This mirrors female-biased AGS susceptibility in Wistar audiogenic rats.[24] Wistar audiogenic rats, a genetically selected strain, exhibit female-biased susceptibility to AGS, with females showing a higher incidence of tonic convulsions and higher audiogenic response scores during initial testing compared to males. This sex dimorphism aligns with broader patterns in reflex epilepsy models, where females develop more severe AGS and audiogenic kindling faster than males, potentially influenced by estrous cycle stages. In WAG/Rij rat models, males exhibit higher SWD density.[25] Our multivariate regression reinforced these patterns, with Epi_6 and Epi_{10} negatively predicting AGS risk ($r = -0.12$ to -0.39), and male sex emerging as protective despite multicollinearity with sucrose preference ($r > 0.65$). Firth's logistic and bootstrap methods mitigated low EPV bias (EPV = 4), though larger cohorts are needed for stability.

Contrary to hypotheses linking epilepsy to anhedonia, sucrose preference showed no association with either phenotype, with uniformly high scores across groups. The two anhedonic outliers in seizure-free rats suggest alternative vulnerabilities, not epilepsy-driven hedonic deficits. This contrasts with a well-known reduced sucrose intake comorbid with AE in WAG/Rij rats.[11,13] Recently, however, in WAG/Rij rats, we did not observe anhedonia at the age of 6 and 12 months.[17] Overall, these findings highlight how genetic predisposition funnels into phenotype-specific hyperexcitability via developmental moderators such assex hormones and circuit plasticity. The Epi high/low grading, unused here, warrants future inclusion for severity insights. Small subgroups (e.g., male AGS) constrain interaction power, underscoring the needs for expanded cohorts to dissect epigenetic or neurochemical drivers.

The study has several limitations. The sample size, particularly within specific subgroups (e.g., males experiencing AGS), limits the statistical power to detect more complex interactions. Another significant methodological shortcoming is that sucrose preference, a fundamental test of anhedonia, was measured at only one time point: at 6 months. This cross-sectional design precludes evaluating how reward processing might change over time as seizures develop or progress. Consequently, it is impossible to establish whether alterations in sucrose preference precede, follow, or vary in relation to the onset of seizures. This static assessment may fail to capture crucial temporal dynamics, such as a gradual reduction in reward sensitivity or a temporary state of anhedonia following particular seizure episodes, which could offer a deeper understanding of the pathophysiological link between epilepsy and depressive-like behaviors.

5. Conclusion

We observed a strong and exclusive association between AE and AGS in genetically predisposed rats. The phenotypic expression of AE and AGS is nearly mutually exclusive, with mixed forms occurring only rarely (3.3%).

These findings provide experimental evidence for a binary seizure expression pattern, in which a shared genetic predisposition is most often expressed through a single, specific seizure network.

Neither AE nor susceptibility to AGS was associated with reduced sucrose preference. The genetic predisposition to seizures in this strain does not produce a concurrent hedonic deficit, distinguishing the mechanisms of epileptogenesis from those underlying this core depressive-like behavior.

Sex was identified as a key variable. Multivariate modeling indicated that male sex may serve as a negative predictor of AGS, potentially interacting with or confounding other behavioral measures, such as sucrose preference.

In general, our findings emphasize the complexity of genotype–phenotype relationships in epilepsy models and highlight the need for longitudinal, multi-phenotype assessments. The exclusive manifestation of seizure types suggests competing or divergent epileptogenic processes, providing a valuable model for investigating network-specific modifiers of seizure susceptibility. Future research with larger cohorts should focus on the neurobiological mechanisms underlying this exclusivity and further explore the influence of sex differences in phenotype determination.

Acknowledgments

None.

Funding

The article was prepared in full within the state assignment of the Ministry of Education and Science of the Russian Federation to the Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, for 2024–2026.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Evgenia Sitnikova
Formal analysis: Evgenia Sitnikova
Investigation: All authors
Methodology: Evgenia Sitnikova
Resources: Evgenia Sitnikova
Validation: Evgenia Sitnikova
Visualization: All authors
Writing—original draft: Evgenia Sitnikova
Writing—review & editing: Evgenia Sitnikova

Ethics approval and consent to participate

The ethics committee of the Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia, approved all phases of this study (Protocol no. 4, December 13, 2022; updated May 29, 2024).

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are available from the corresponding author, Evgenia Sitnikova, upon reasonable request. A video recording of an audiogenic seizure in a female rat, triggered by a key ring, is available at the following link: https://cloud.mail.ru/public/EJfn/VN7Bx1dxD. The file name is "Audiogenity_Keys_1female.mp4." A video recording of an audiogenic seizure triggered by an electric bell (100-120 dB SPL) is available in the repository at the following link: https://cloud.mail.ru/public/HHSD/YRKgqJHJR. The file name is "Audiogenity_Ring_3females.mp4."

References

1. Devinsky O, Elder C, Sivathamboo S, Scheffer IE, Koepp MJ. Idiopathic Generalized Epilepsy. *Neurology*. 2024;102(3).

   doi: 10.1212/WNL.0000000000208076

2. Hirsch E, French J, Scheffer IE, Bogacz A, Alsaadi T, Sperling MR, *et al*. ILAE definition of the Idiopathic Generalized Epilepsy Syndromes: Position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia*. 2022;63(6):1475-1499.

   doi: 10.1111/epi.17236

3. Crunelli V, Lőrincz ML, McCafferty C, *et al*. Clinical and experimental insight into pathophysiology, comorbidity and therapy of absence seizures. *Brain*. 2020;143(8):2341-2368.

   doi: 10.1093/brain/awaa072

4. Crunelli V, Leresche N. Childhood absence epilepsy: Genes, channels, neurons and networks. *Nat Rev Neurosci*. 2002;3(5):371-382.

   doi: 10.1038/nrn811

5. Mishra PK, Dailey JW, Reigel CE, Jobe PC. Audiogenic convulsions in moderate seizure genetically epilepsy-prone rats (GEPR-3s). *Epilepsy Res*. 1989;3(3):191-198.

   doi: 10.1016/0920-1211(89)90023-5

6. Poletaeva II, Surina NM, Kostina ZA, Perepelkina O V., Fedotova IB. The Krushinsky-Molodkina rat strain: The study of audiogenic epilepsy for 65 years. *Epilepsy Behav*. 2017;71.

doi: 10.1016/j.yebeh.2015.04.072

7. Ross KC, Coleman JR. Developmental and genetic audiogenic seizure models: Behavior and biological substrates. *Neurosci Biobehav Rev*. 2000;24(6).

   doi: 10.1016/S0149-7634(00)00029-4

8. Marescaux C, Vergnes M, Kiesmann M, Depaulis A, Micheletti G, Warter JM. Kindling of audiogenic seizures in Wistar rats: An EEG study. *Exp Neurol*. 1987;97(1).

   doi: 10.1016/0014-4886(87)90290-1

9. Romanova LG, Zorina ZA, Korochkin LI. A genetic, physiological, and biochemical investigation of audiogenic seizures in rats. *Behav Genet*. 1993;23(5).

   doi: 10.1007/BF01067984

10. Midzyanovskaya IS, Kuznetsova GD, Vinogradova L V., Shatskova AB, Coenen AML, van Luijtelaar G. Mixed forms of epilepsy in a subpopulation of WAG/Rij rats. *Epilepsy Behav*. 2004;5(5).

    doi: 10.1016/j.yebeh.2004.06.021

11. Sarkisova K, van Luijtelaar G. The WAG/Rij strain: A genetic animal model of absence epilepsy with comorbidity of depressiony. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2011;35(4):854-876.

    doi: 10.1016/j.pnpbp.2010.11.010

12. Sarkisova KY, Kuznetsova GD, Kulikov MA, Van Luijtelaar G. Spike–wave discharges are necessary for the expression of behavioral depression-like symptoms. *Epilepsia*. 2010;51(1):146-160.

    doi: 10.1111/j.1528-1167.2009.02260.x

13. Sarkisova KY, Midzianovskaia I., Kulikov M. Depressive-like behavioral alterations and c-fos expression in the dopaminergic brain regions in WAG/Rij rats with genetic absence epilepsy. *Behav Brain Res*. 2003;144(1-2):211-226.

    doi: 10.1016/S0166-4328(03)00090-1

14. van Luijtelaar G, van Oijen G. Establishing Drug Effects on Electrocorticographic Activity in a Genetic Absence Epilepsy Model: Advances and Pitfalls. *Front Pharmacol*. 2020;11:395.

    doi: 10.3389/fphar.2020.00395

15. Coenen AML, van Luijtelaar ELJM. Genetic animal models for absence epilepsy: a review of the WAG/Rij strain of rats. *Behav Genet*. 2003;33(6):635-655.

    doi: 10.1023/a:1026179013847

16. Sitnikova E, Pupikina M. Behavioral Phenotyping of WAG/Rij Rat Model of Absence Epilepsy: The Link to Anxiety and Sex Factors. *Biomedicines*. 2025;13(9):2075.

    doi: 10.3390/biomedicines13092075

17. Pupikina M, Sitnikova E. Reassessing anhedonia in Genetic Absence Epilepsy: Sucrose preference unaltered by spike-wave discharges in WAG/Rij rats. *Epilepsy Res*. 2025;218:107683.

    doi: 10.1016/j.eplepsyres.2025.107683

18. Roberts-West L, Vivekananda U, Baxendale S. Anhedonia in epilepsy. *Epilepsy Behav*. 2023;140:108966.

    doi: 10.1016/j.yebeh.2022.108966

19. Pupikina M, Sitnikova E. Non-invasive electroencephalography-based technique for rapid diagnostics of absence epilepsy in rats. *Adv Neurol*. 2024;3(4):4464.

    doi: 10.36922/an.4464

20. Sarkisova KY, Kulikov MA. Behavioral characteristics of WAG/Rij rats susceptible and non-susceptible to audiogenic seizures. *Behav Brain Res*. 2006;166(1):9-18.

    doi: 10.1016/j.bbr.2005.07.024

21. de Azevedo BA, Fontana P. Audiogenic seizures and the pineal gland. *Biol Psychiatry*. 1988;23(7):734-740.

    doi: 10.1016/0006-3223(88)90058-3

22. Meeren HKM, Van Cappellen van Walsum AM, Van Luijtelaar ELJM, Coenen AML. Auditory evoked potentials from auditory cortex, medial geniculate nucleus, and inferior colliculus during sleep–wake states and spike-wave discharges in the WAG/Rij rat. *Brain Res*. 2001;898(2):321-331.

    doi: 10.1016/S0006-8993(01)02209-0

23. Garcia-Cairasco N. A critical review on the participation of inferior colliculus in acoustic-motor and acoustic-limbic networks involved in the expression of acute and kindled audiogenic seizures. *Hear Res*. 2002;168(1-2).

    doi: 10.1016/S0378-5955(02)00371-4

24. Mishra PK, Dailey JW, Reigel CE, Tomsic ML, Jobe PC. Sex-specific distinctions in audiogenic convulsions exhibited by severe seizure genetically epilepsy-prone rats (GEPR-9S). *Epilepsy Res*. 1988;2(5):309-316.

    doi: 10.1016/0920-1211(88)90039-3

25. Lazarini-Lopes W, Campos-Rodriguez C, Palmer D, N'Gouemo P, Garcia-Cairasco N, Forcelli PA. Absence epilepsy in male and female WAG/Rij rats: A longitudinal EEG analysis of seizure expression. *Epilepsy Res*. 2021;176:106693.

    doi: 10.1016/j.eplepsyres.2021.106693