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Original Research

Passive Behavioral Patterns in Symptomatic WAG/Rij Rats: Dissociation From Absence Epilepsy and Sex-Dependent Link Between Early Fear Coping and Post-Stress Freezing

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Abstract

Background: Acute stress exposure can lead to delayed behavioral changes, which are widely regarded as core endophenotypes of post-traumatic stress disorder (PTSD). Identifying pre-existing behavioral traits that predict later maladaptive responses is crucial. We investigated whether early fear-related passive coping behavior during an active avoidance task predicts subsequent freezing reactions in a safe, stimulus-free environment. This context-inappropriate fear pattern may model individual vulnerability to PTSD-like symptoms. We used Wistar Albino rats from Rijswijk (WAG/Rij rats), which are genetically predisposed to develop absence epilepsy. This condition is non-convulsive and characterized by sudden, brief periods of behavioral arrest known as absences. Absence-like seizures in WAG/Rij rats are accompanied by spike-and-wave discharge (SWDs) on electroencephalogram (EEG) and behavioral arrest. We also examined the relationship between the severity of absence epilepsy and passive behavioral patterns in WAG/Rij rats at symptomatic ages (10–12 months), as well as sex-related differences. **Methods:** We used an automated fear-conditioning paradigm to identify individual differences in baseline stress vulnerability that predict delayed, context-independent freezing behavior. Rats were tested in an active avoidance paradigm to assess fear-induced passive behavior under threat at the age of 9 months, and the percentage of passive behavioral responses was scored. Rats were then tested in a safe environment using the StartFear system, and the percentage of freezing was measured monthly at the ages of 10, 11, and 12 months. Finally, the rats underwent EEG examination, and SWDs were scored during 12-hour dark-phase recordings. **Results:** In the safe environment, 10- to 12-month-old WAG/Rij rats exhibited low levels of freezing (9.5%–13.9% of the total time). No significant sex differences were observed in freezing behavior within the safe environment. However, in the unsafe, fear-inducing active avoidance task, males displayed significantly higher levels of passive behavior than females. Female rats showed strong correlations between passive responses in the fear-inducing situation and freezing in the safe environment, whereas males did not. Results from EEG examinations indicated that males exhibited a higher number of SWDs than females. Neither the percentage of freezing in the safe environment nor the percentage of passive responses in the active avoidance task correlated with the severity of absence epilepsy, as assessed by the number and duration of SWDs. WAG/Rij rats tested after avoidance training exhibited low freezing in the StartFear paradigm and a sex-dependent increase in passive responses following conditioning; these findings are consistent with altered tonic inhibitory regulation but require naïve controls and EEG-behavior coupling to establish causality. **Conclusions:** Four primary conclusions emerge from this study: (1) symptomatic WAG/Rij rats exhibit low levels of freezing in a safe environment; (2) sex differences exist in unsafe contexts, but not safe ones; (3) there is a sex-dependent association between early passive behavior and later freezing; (4) there is no relationship between the severity of absence epilepsy and passive behavioral patterns. Therefore, thalamocortical disturbances associated with SWDs do not correlate with fear-related freezing or passive coping behaviors, suggesting a distinction between seizure-related immobility and non-seizure passive behaviors. There is also a sex-specific link between early passive coping and later context-inappropriate freezing, warranting further study in models of anxiety and PTSD.

Keywords: age factors; behavior, animal; disease models, animal; WAG/Rij rats; electroencephalography; epilepsy, absence; freezing reaction; sex characteristics

1. Introduction

Post-traumatic stress disorder (PTSD) is clinically significant trauma- and stressor-related disorder that can arise after exposure to extremely threatening or horrific events, such as actual or threatened death, serious injury, sexual violence, disasters, accidents, or military combat [1,2,3,4]. The World Health Organization estimates that a substantial proportion of the global population will experience a potentially traumatic event in their lifetime, with a significant fraction developing PTSD [5,6]. Its core features include re-experiencing (flashbacks), avoidance, hyperarousal, and critically, delayed behavioral alterations that emerge or persist long after the acute stressor has ended. Understanding why only some individuals succumb to these changes while others remain resilient is a central question in mental health research. Given the ethical and practical limitations

of studying the neurobiological underpinnings of trauma responses in humans—especially the prospective identification of pre-existing vulnerability traits—experimental studies in animals have become indispensable. Prospective human research is relatively scarce because it requires large longitudinal cohorts exposed to unpredictable traumatic events, while retrospective designs are vulnerable to recall bias and cannot reliably establish whether a factor preceded trauma. Animal models, by contrast, permit controlled pre-trauma behavioral and neurobiological profiling, experimental manipulation of candidate vulnerability factors, and longitudinal assessment of susceptibility versus resilience [7,8]. Over the past decades, animal models of PTSD have matured considerably, moving from simple acute stress paradigms to sophisticated approaches that capture the longitudinal, delayed, and individual-specific nature of the disorder. These models are not merely maturing; they are becoming increasingly refined to evaluate individual phenotypic traits that predispose subjects to delayed behavioral alterations following acute stress exposure. One of the most critical contributions of animal experimental studies is the identification of pre-existing (i.e., pre-trauma) phenotypic traits that predict later maladaptive responses. This is nearly impossible to capture prospectively in humans without massive, costly longitudinal cohorts. In rodents, baseline measures of fear conditioning, active avoidance, or exploratory behavior can be obtained before any stressor is applied. Animals that display high levels of passive coping (e.g., freezing) under threat may later exhibit context-inappropriate freezing in a safe environment, mimicking the hypervigilance and overgeneralization of fear seen in PTSD patients. By linking such pre-existing traits to delayed outcomes, animal studies provide evidence for a genuine vulnerability endophenotype, not merely a reaction to the trauma.

One of the key advantages of animal models is their ability to dissociate trauma-related behavioral changes—such as context-inappropriate freezing—from comorbid neurological conditions that might confound interpretation in human studies. A compelling example comes from research on absence epilepsy, a non-convulsive form of epilepsy characterized by abrupt, brief disruptions in awareness known as “absences” or “staring spells” [9,10,11]. These episodes are reliably detected via electroencephalography (EEG) as high-amplitude spike-and-wave discharges (SWDs) [12,13,14,15]. SWDs could be observed in several generalized epilepsies, including childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy [11,16,17]. Spontaneous SWDs occur during absence-like seizures in genetic rat models of absence epilepsy, such as Wistar Albino rats from Rijswijk (WAG/Rij rats) and Genetic Absence Epilepsy Rats from Strasbourg (GAERS) rats [18,19,20,21,22], as well as in Sprague Dawley, Long Evans and Wistar rats [23,24,25,26]. SWDs in rat models predominantly occur during periods of relaxed behavioral states and are characterized by an abrupt cessation of all behaviors. This distinctive behavioral pattern, often referred to as the “absence state” or “behavioral arrest”, is marked by a sudden and transient loss of consciousness and responsiveness to external stimuli [25,27,28,29,30].

At first glance, the behavioral arrest observed during an absence seizure may resemble fear-induced freezing, a passive coping response commonly studied in PTSD research. However, the underlying mechanisms are fundamentally distinct. Seizure-related immobility in absence epilepsy arises from thalamocortical network disturbances that transiently disrupt motor control [31,32,33,34,35,36,37,38]. In contrast, fear-induced freezing is an adaptive survival strategy—an active, threat-assessment behavior that precedes fight-or-flight decisions. Critically, rats with absence epilepsy (i.e., GAERS and WAG/Rij rats) are known to exhibit neurobehavioral comorbidities, including anxiety and depressive-like behaviors [39,40,41,42,43], which may independently predispose them to passive coping strategies. Both seizure burden and these comorbidities in WAG/Rij rats are known to increase with age [20,44,45,46], raising the question of whether the primary epileptic phenotype itself is associated with a heightened predisposition to passive behavior, potentially reflecting shared neurobiological substrates.

The regulation of freezing behavior and the pathogenesis of absence epilepsy share a common neural substrate: thalamic tonic GABA-A inhibition [47,48,49,50,51]. This form of inhibition, sustained by persistent activation of extrasynaptic GABA-A receptors through ambient GABA, acts as a powerful gating mechanism in the thalamus. In the mediodorsal (MD) thalamic nucleus, tonic GABA-A activity suppresses fear extinction, thereby promoting freezing behavior, a key adaptive defense response [52,53]. Supporting this, blocking GABA-A receptors with gabazine removes this tonic brake and reduces freezing, whereas selectively enhancing extrasynaptic GABA-A currents with THIP increases tonic inhibition and intensifies freezing [48]. However, the same tonic inhibitory mechanism becomes maladaptive in absence epilepsy. In Genetic Absence Epilepsy Rats from Strasbourg (GAERS), thalamocortical neurons exhibit an aberrantly increased extrasynaptic GABA-A receptor-dependent tonic current [51]. This pathological enhancement, linked to compromised GABA uptake by the transporter GAT-1 and to larger, faster GABA-A currents in the reticular thalamic nucleus, critically drives the generation of absence seizures. Thus, a shared thalamic GABA-A tonic mechanism governs both adaptive freezing and its pathological derangement in absence epilepsy, where the same molecular machinery—extrasynaptic GABA-A receptors and ambient GABA—becomes dysregulated to produce seizure activity instead of controlled defensive behavior.

Table 1. Theoretical framework for passive behavioral responses.

Component	Operational description	Test conditions	Interpretation	Relation to SWDs
Passive behavior	Absence of avoidance response or movement in an active avoidance task	Presence of aversive stimuli (e.g., electric foot shock)	State-dependent maladaptive response, characterized by freezing under threat	Not directly measured; evaluated retrospectively using SWD scores
Freezing (StartFear)	Complete lack of movement in a safe environment, automatically scored	Absence of stimuli in a safe environment	Trait-like baseline inhibition or generalized anxiety	Not measured in real time; evaluated retrospectively using SWD scores
SWD-related immobility (not analyzed)	Brief behavioral arrest coincident with SWDs on EEG	(Not examined in this study)	Ictal motor phenomenon during seizures, distinct from emotional freezing	Direct temporal relation (not examined)

SWD, spike-and-wave discharge; EEG, electroencephalogram.

We examined two types of passive behavior independent of SWDs, as EEG was not recorded simultaneously with behavioral tests: passive behavior in the active avoidance task (an unsafe environment — an aversive context involving electric foot shock) and spontaneous freezing in the StartFear system (a neutral, safe environment). Both behaviors reflect fear-related immobility but occur in different contexts and may involve distinct neurobehavioral processes. We did not examine SWD-related ictal immobility or attempt to correlate SWD events with freezing. Our focus was exclusively on spontaneous, non-seizure related passive behavior and its relationship to baseline absence epilepsy severity, as measured by the total SWD number and duration, rather than on seizure-induced immobility. Table 1 highlights this distinction, which is essential for interpreting our findings. Any freezing or passive behavior measured here should be interpreted as behaviorally driven immobility.

Freezing is an intricate behavioral response involving multiple brain regions and neural pathways, including the basolateral and central amygdalar nuclei, ventrolateral periaqueductal grey, hypothalamus (as part of the hypothalamus–pituitary–adrenal axis), ventromedial prefrontal cortex, anterior cingulate cortex, cerebellum and periaqueductal grey [54]. Given the established anxiety- and depressive-like comorbidities in absence epilepsy, we tested whether the severity of the epileptic phenotype predicts heightened passive behavioral strategies across contexts in symptomatic WAG/Rij rats (9–12 months of age).

The present study was designed to evaluate individual phenotypic traits predisposing subjects to delayed behavioral alterations following acute stress exposure. These behavioral shifts are widely interpreted as core endophenotypes of PTSD [55,56,57,58,59]. Although numerous animal models of PTSD have been developed, most have historically overlooked baseline individual variability in stress vulnerability. In humans, the lifetime prevalence of PTSD among those exposed to traumatic events is approximately 5.6%, with significant variation across countries, income groups, and WHO regions [5]. To address this translational gap and model individual susceptibility to stress, we employed a Pavlovian fear conditioning paradigm followed by assessment of context-independent generalized freezing behavior in a novel, safe environment. Here we used an automated freezing measurement using the StartFear system to identify vulnerable and resilient individuals based on their initial response to stress [60]. We tested two hypotheses: (1) freezing in a novel, neutral environment increases with age in the symptomatic WAG/Rij rats; and (2) severe epileptic activity (quantified by SWD burden) is associated with stronger passive behavioral patterns across different contexts. To test these hypotheses and assess the consistency of behavioral inhibition as a potential trait, we measured the level of passive responses in two conditions presented in a fixed order. First, we used an aversive environment with an active avoidance paradigm to assess passive coping under an inescapable threat. Second, we used a neutral, non-aversive environment with the StartFear system to assess behavioral freezing in the safe context. The fixed order was chosen to avoid potential long-term effects of intense aversive conditioning on subsequent tests and invasive EEG procedures.

Finally, promoting policies such as “Sex as a Biological Variable” ensure that research reflects the complex interplay of sex and biology [61,62]. Female rodents are increasingly included in preclinical research, providing needed diversity. This inclusion is critical because male and female rats exhibit different behavioral responses in fear-conditioned tasks (see references in [63]). Female rats are known to acquire shuttle box avoidance more rapidly than males (see references in [63]) and often display brief, high-velocity movement termed “darting” in response to fearful experience, whereas males predominantly freeze [64,65]. In fear conditioning experiments, males freeze more frequently than females [55,66,67]. However, little is known about sex differences in passive behavioral patterns in symptomatic WAG/Rij rats. The present study aims

to fill a gap in knowledge about sex differences in passive behavioral patterns among symptomatic WAG/Rij rats.

2. Materials and Methods

2.1 Animals

This study was performed in 32 adult WAG/Rij rats of both sexes (21 females and 11 males). All rats were littermates born to 4 mothers with absence epilepsy confirmed by EEG examination. Rats were bred and housed in a vivarium of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences. The rats were kept under standard conditions with a 12 h:12 h light-dark cycle (light on at 8 a.m.), with constant ventilation and airing. Before surgery, rats were housed in small same-sex groups (3–4 subjects per cage) and provided with unlimited access to food and water. Animals were maintained in accordance with institutional animal welfare guidelines after completion of the experiments, as the rats were retained for other research purposes.

First, we tested passive behaviors in a fear-inducing active avoidance task in rats at 9 months of age (Fig. 1A). In this experiment, rats were trained to avoid a potentially harmful and noxious stimulus (an electric shock). As a result, they displayed a significant level of fear [67,68,69,70]. At 10, 11, and 12 months of age, rats were repeatedly tested in a safe environment using the StartFear system (PanLab). In the final test, neither electric shocks nor external stimuli were applied, and freezing and passive behaviors were assessed.

2.2 Fear-Induced Passive Behavior

This test was conducted using the two-alternative choice paradigm, in which an electric shock served as the unconditioned stimulus. This classical active avoidance test paradigm involved training rats to shuttle between compartments when presented with a warning signal (a tone). The test does not provide a permanently safe place for the rat, as the rat may receive a shock if it remains in a location where it has previously been shocked. The two-way shuttle box consisted of two compartments, each measuring 30 × 26 × 30 cm, separated by an opaque wall with a passage in the middle. The grid floor was made of 3 mm stainless steel bars spaced 1 cm apart. An electric foot shock (0.5 mA, 5 Hz) was used as the unconditioned stimulus, while a pure tone at 70 dB served as the conditioned stimulus. Both stimuli were delivered automatically using customary computer software. A Logitech HD Pro C920 video camera (China) was mounted above the shuttle box to monitor the experiment. The entire experiment was controlled by a computer system located in an adjacent room.

Habituation. To acclimatize, the rats were placed into small cages and moved into the experimental room for 10 minutes before the experiment began. Each rat was placed in the shuttle box for three minutes for habituation to the experimental surroundings.

Test. Rats were first presented with the conditioned stimulus (tone) for 20 s. The experiment consisted of 50 experimental trials and included foot-shocks delivered in either compartment 4.5 s after the tone, while the opposite compartment was always designated as “safe” (Fig. 1A). The rat was able to avoid a foot-shock by passing to the opposite “safe” compartment. The time between the onset of the tone stimulus and the rat’s movement to the opposite compartment was recorded. The maximal duration of electric stimulation was 40 s. The interval between trials was chosen at random between 20 s and 50 s. After the end of the training session, the shuttle box was cleaned with a 50% ethanol solution to remove olfactory cues.

Three types of behavior were defined (Fig. 1B): (1) avoidance, in which the rat avoided the electrical foot shock, (2) escape, in which the rat moved to the safe chamber after receiving the electrical foot shock and (3) passive behavior, in which the rat remained in the same chamber and endured the electrical foot shock. To prevent excessive electrical stimulation, the test was terminated if no avoidance responses occurred during 20 trials (n = 6 rats, including 5 males and 1 female; see Fig. 1B, bottom track for example). The percentage of passive responses was computed. To characterize the rats’ passive coping strategies in an inescapable conflict, here we calculated the proportion of trials in which the rat failed to perform the active avoidance or escape response, resulting in enduring the foot-shock.

2.3 Freezing in a Neutral, Non-Aversive Environment

Rats were placed in the test chamber of the StartFear system, also known as the Startle and Fear Combined System (PanLab, Barcelona, Spain). The chamber contained a grid floor equipped with a sensitive weight transducer system (Fig. 1). This system recorded the signal produced by the animals’ movements. The signal was transmitted through the load cell unit to the PC and analyzed using FREEZING Software (version 1.3, Harvard Apparatus, Holliston, MA, USA). Each rat was tested for 3 minutes, which was determined to be the optimal duration for observing freezing behavior in rats [71]. The program classified behavior as either motionless or active by analyzing pressure dynamics on the platform in standard intervals of 0.5 seconds. A threshold of 3 conventional units (1.5 seconds) of motionless was used to determine freezing behavior, as defined in our earlier study [71]. Minor movements, such as teeth grinding or whisker twitching were not recorded.

During the experiment, each rat spent three minutes exploring the chamber without any sound or shock. The percentage of time spent freezing was then calculated and analyzed. The test was repeated three times for each rat at different ages: 10 months (9.9 ± 0.3), 11 months (11.3 ± 0.2), and 12 months (12.3 ± 0.2).

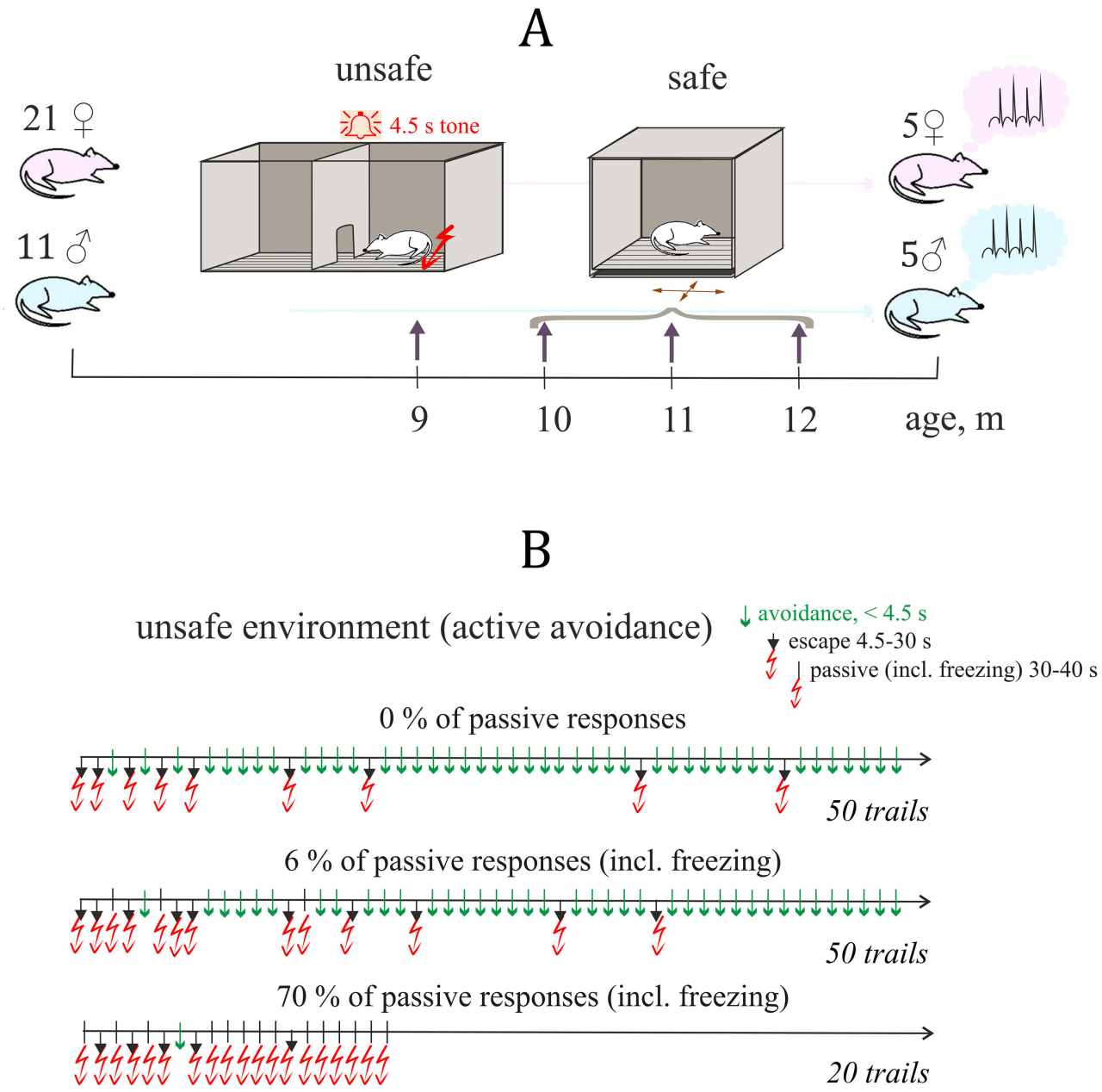

Fig. 1. Experimental design overview. (A) Rats were initially tested in a fear-inducing environment using classical two-chamber active avoidance tests at 9 months of age. Subsequently, the rats were repeatedly tested in a safe environment with the StartFear system for 3 minutes at 10, 11 and 12 months of age to assess freezing behavior. At the end of the behavioral experiments, 10 rats (5 females and 5 males) were randomly selected for electroencephalographic (EEG) examination during free behavior and were implanted with chronic electrodes. Spontaneous spike-wave discharges in EEG, which are the hallmarks of absence epilepsy, were schematically depicted on the right. (B) Behavioral testing in the unsafe situation (active avoidance tests) included 50 trials in which the conditioned stimulus (a tone) was followed by the unconditioned stimulus (an electrical foot shock) with a 4.5-s delay. The test was terminated after 20 trials if no avoidance responses were observed, in order to prevent excessive electrical stimulation.

2.4 EEG Examination

After completing behavioral experiments, 10 rats (5 females and 5 males) were randomly selected to examine the severity of absence epilepsy using chronically implanted EEG electrodes.

Epidural electrodes were permanently implanted to record brain activity during free behavior. The surgery was performed under the administration of isoflurane anesthesia, a powerful and widely used general anesthetic. The rodent's head was securely fixed in the Kopf stereotaxic apparatus. Three active epidural screw electrodes were im-

planted over the left and right frontal cortex (AP ±2; L 2.5) and the occipital cortex (AP 6; L 3). A reference screw electrode was placed on the right cerebellum. The coordinates are given in millimeters relative to the bregma. After the surgery, the rats were housed individually and given unlimited access to food and water. They were allowed a minimum of 10 days to recover.

EEG was recorded in a quiet room with a 12:12 light-dark cycle (lights on at 8 a.m.). Each rat was placed in standard Plexiglas cages (25 cm × 60 cm × 60 cm), allowed to move freely and had free access to food and water. The connectors on the rat's head were connected to a multi-channel amplifier (PowerLab 8/35, ADInstruments, Sydney, Australia) through a swivel connector. EEG signals were filtered from 0.5 to 200 Hz, digitized at 400 samples per second per channel, and saved to a hard disk.

SWDs appeared spontaneously in the EEG as a sequence of generalized high-voltage 8–9 Hz spikes interrupted by waves [20,22,29,72,73]. In Fig. 2A, the three-channel cortical EEG recording shows typical SWDs occurring abruptly against a normal background.

Here, we used a wavelet-based algorithm to identify SWDs in EEGs, as described in our earlier studies [74,75]. Briefly, the EEG signal was processed using the continuous wavelet transform with the complex Morlet wavelet as the basic function. Wavelet power was measured in two frequency bands: 8–10 Hz and 17–20 Hz (Fig. 2B). For each frequency band, we selected thresholds for wavelet power, and SWDs were detected when the wavelet power in both bands exceeded these threshold values. To enhance the selectivity of this method, we set the minimum duration of seizure activity at 2 seconds. Using this algorithm, SWDs were identified during a 12-hour interval of the dark phase (from 8 p.m. to 8 a.m.). The number of SWDs and duration of SWDs were scored.

Data were statistically analyzed using the Mann-Whitney U test, Friedman Analysis of Variance (ANOVA) with Kendall's coefficient of concordance, and Pearson correlation analysis.

3. Results

We first analyzed the level of passive behavior during the fear-induced active avoidance task at 9 months of age, followed by an assessment of freezing behavior in the safe environment of the StartFear system at 10, 11, and 12 months (experimental timeline, Fig. 1A). Subsequently, to determine the severity of absence epilepsy and its potential relationship with behavioral measures, electroencephalographic recordings were performed between 12 and 13 months of age in a randomly selected subset of 10 rats (5 males, 5 females). SWDs, which are the electrophysiological hallmarks of absence epilepsy, were detected using a semi-automated algorithm and manually verified for scoring (Fig. 2A,B). The factor of sex significantly affected the number of SWDs during the 12-hour dark phase (Mann-Whitney U test, $p = 0.012$, Fig. 2C), with males exhibiting a higher number of SWDs than females. In contrast, no significant sex difference was observed in the mean duration of individual SWDs ($p = 0.40$, Fig. 2C). This pattern of sex-dependent differences in SWD frequency, but not duration, is consistent with previous findings reported by Lazarini-Lopes et al. [46] in WAG/Rij rats and our recent findings [76].

3.1 Unsafe (Fear-Induced) Environment

This experiment was conducted using the classical active avoidance test. In this paradigm, rats attempted to proactively prevent the onset of an unpleasant stimulus, such as a scrambled foot-shock. Three behavioral reactions were observed: avoidance, escape and passive behavior (Section 2.2). Passive behavior was recorded when the rat endured the electrical foot shock without moving to the safe compartment for 30–40 seconds. This behavior exhibited characteristics of passivity, including a lack of movement and distress vocalization as previously documented in our studies [67,77]. To assess the rat's passive behavioral patterns, we calculated the proportion of passive responses relative to the total number of trials. The percentage of passive responses in females was significantly lower than in males (Mann-Whitney U test, $p = 0.00025$, Fig. 3A).

3.2 Safe Environment

The rats' movements were recorded, and the proportion of time they remained immobile was analyzed (% of freezing shown in Fig. 3B). The total number of rats was 32; however, due to incomplete observations, the available sample sizes per age were as follows: 10 months, n = 27; 11 months, n = 27; and 12 months, n = 26. A subset of animals with complete data at all three time points (n = 19) was used for the primary repeated-measures analysis. A one-way repeated-measures ANOVA was conducted on the complete cases to examine age-related differences in percent freezing. Sphericity was assumed because Mauchly's test could not be performed reliably due to low statistical power. The analysis revealed no significant main effect of age, $F(2, 36) = 0.13$, $p = 0.878$, partial $\eta^2 = 0.007$, indicating that the percentage of freezing did not change significantly across 10, 11, and 12 months. Pairwise comparisons were conducted using paired-samples *t*-tests with Bonferroni correction for multiple comparisons. The mean difference between 10 and 11 months was 1.42% (95% confidence interval [CI] [−4.66, 7.50]), which was not significant, $t(18) = 0.49$, $p = 0.629$, Cohen's $d = 0.113$. Similarly, the difference between 10 and 12 months was 0.95% (95% CI [−4.92, 6.81]), $t(18) = 0.34$, $p = 0.738$, $d = 0.078$, and the difference between 11 and 12 months was −0.47% (95% CI [−6.43, 5.48]), $t(18) = -0.17$, $p = 0.869$, $d = -0.038$. All confidence intervals contained zero, and none of the pairwise differences reached statistical significance after correction.

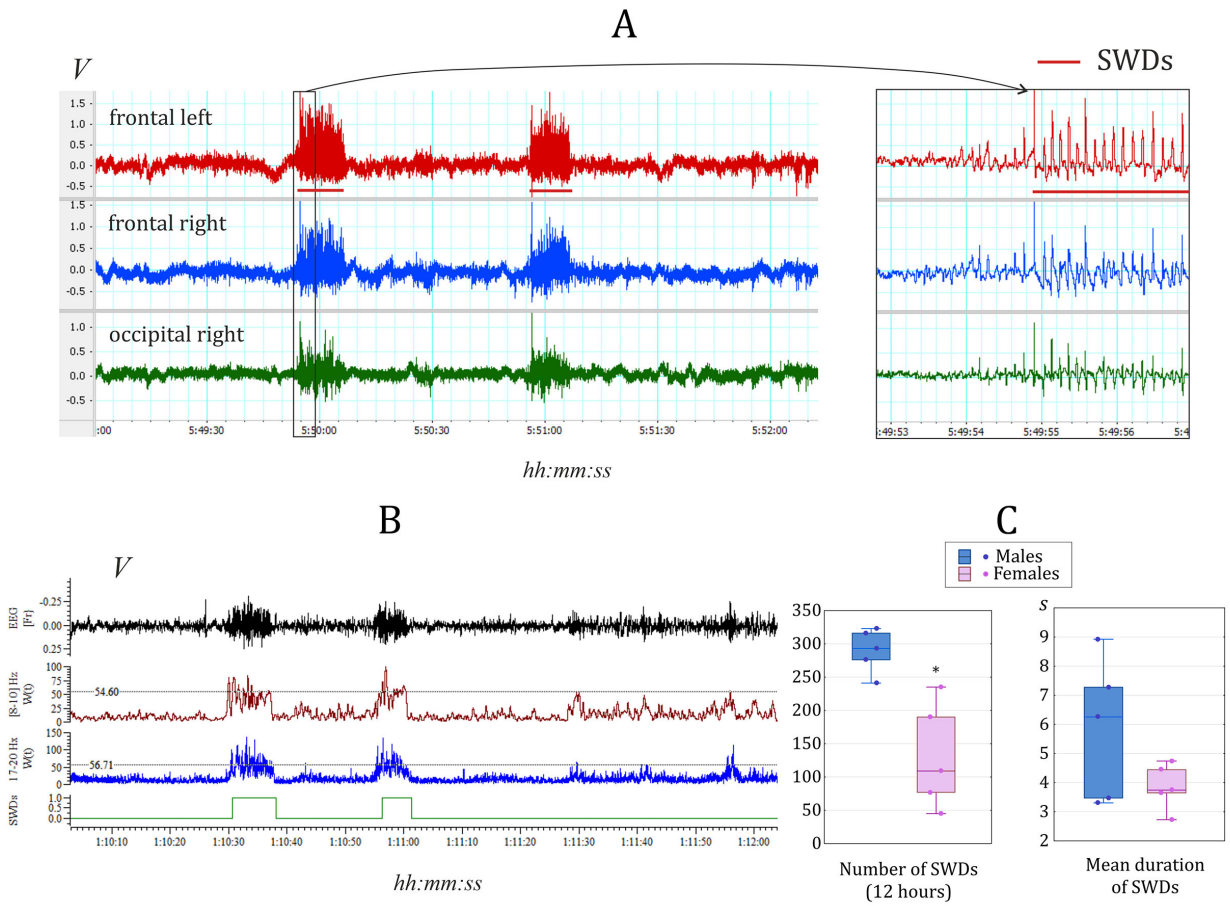

Fig. 2. Spontaneous spike-and-wave discharges (SWDs) as hallmarks of absence epilepsy in Wistar Albino rats from Rijswijk (WAG/Rij rats). (A) Representative electroencephalogram recorded from an awake, freely moving 12.5-month-old WAG/Rij rat using chronically implanted epidural cortical electrodes. SWDs consist of high-amplitude (approximately 8–9 Hz) spike-and-wave complexes; an expanded view is shown in the right inset. (B) Schematic of a wavelet-based detection algorithm for SWDs, illustrating the distribution of wavelet power across two frequency bands: 8–10 Hz (fundamental) and 17–20 Hz (first harmonic). (C) Quantification of the number and mean duration of SWDs over a 12-h recording period. Data are presented as medians with 25th to 75th percentiles (boxes); whiskers indicate the range. Asterisk (*) denotes a statistically significant difference between males and females ($p < 0.05$; Mann-Whitney test).

Because the data contained outliers and showed non-normal distributions, a Friedman test was conducted for robustness. For the entire sample (n = 19), no significant effect of age was found ($\chi^2(2) = 2.95$, $p = 0.229$). The Kendall's coefficient of concordance (W = 0.078) and the average rank correlation (r = 0.383) revealed a very weak association, indicating that freezing behavior did not change consistently across the three time points. Subgroup analyses found no age effect in males ($\chi^2(2) = 0.50$, $p = 0.779$) or females ($\chi^2(2) = 4.03$, $p = 0.133$).

To examine whether fear-related passive responses during an active avoidance task predict subsequent freezing reactions later in life—specifically in a safe, stimulus-free environment—we computed correlations between the percentage of passive responses in the active avoidance task (measured at 9 months of age) and the average percentage of freezing in the StartFear system (measured across 10–12 months of age), separately for each sex.

Fig. 3C shows the relationship between early passive responses and subsequent freezing behavior. A significant positive correlation was found only in females (n = 14, r = 0.83, $p < 0.005$, Fig. 3C). No significant correlation was observed in males (n = 9, r = 0.19, $p = 0.63$, Fig. 3C).

Among male subjects tested at 9 months, seven exhibited a high proportion of passive responses (>60%) during the active avoidance task. Of these seven males, four displayed minimal freezing (<8%) during subsequent testing (Fig. 3C). This pattern of high passive responses and low freezing suggests fear extinction. The remaining three males, along with one female subject, showed high freezing levels (>30%, Fig. 3C). These four subjects with high passive responses and significant freezing may be considered at risk for traumatic exposure and PTSD-like symptoms.

In general, male subjects exhibited notable inter-individual differences in the expression of passive responses across the two environments. Fear-induced passive

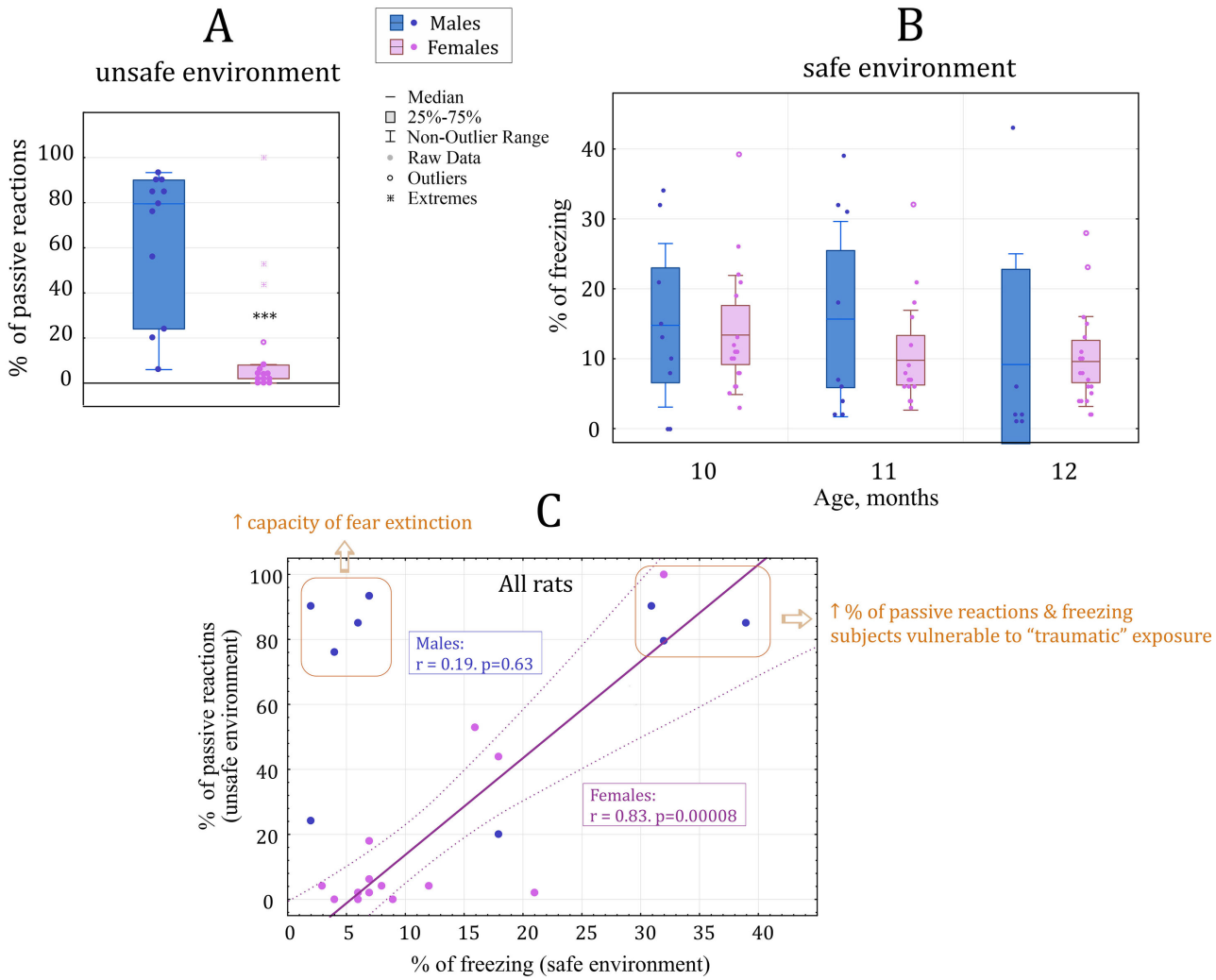

Fig. 3. Sex differences in passive behavior during the active avoidance test (unsafe environment) and freezing behavior in the StartFear test (safe environment). (A) Percentage of passive behavioral responses observed in the active avoidance test (unsafe environment). *** — statistically significant difference between males and females ($p < 0.0005$; Mann-Whitney test). (B) Percentage of freezing behavior recorded in the StartFear cage (safe environment), measured at three consecutive age points. (C) Pearson correlations between the percentages of passive behavioral responses in unsafe conditions (active avoidance scenario) and in safe conditions (StartFear cage). Correlation coefficients were calculated separately for each sex (14 females and 9 males).

reactions during the active avoidance test at 9 months predicted increased freezing responses in a safe context later in life only in females, not in males. This sex-specific association suggests that females may generalize or retain fear-related behavioral strategies across different environmental contexts (unsafe vs. safe), whereas males do not demonstrate such cross-situational fear consistency.

3.3 Passive Behavior and Absence Seizures

Exploratory correlation analyses were conducted to assess the relationship between behavioral measures and electroencephalographic parameters of absence epilepsy in a subset of animals (n = 10, including 5 males and 5 females) following the completion of behavioral testing. SWD parameters included the total number of SWDs during the 12-hour dark-phase recording (Fig. 4A) and the mean duration of individual SWDs (Fig. 4B). Pearson correlation coefficients were calculated for the number of SWDs (Fig. 4A) and the mean SWD duration (Fig. 4B). No significant correlations were found between any SWD parameter and any behavioral measure. Specifically, the percentage of passive responses in the active avoidance task did not correlate significantly with the number of SWDs ($r = 0.30$, $p = 0.41$; Fig. 4A) or with the mean duration of SWDs ($r = 0.47$, $p = 0.17$; Fig. 4B). Similarly, the percentage of freezing in the safe environment showed no significant association with the number of SWDs ($r = –0.33$, $p = 0.35$; Fig. 4A) or with the mean SWD duration ($r = 0.21$, $p = 0.57$; Fig. 4B).

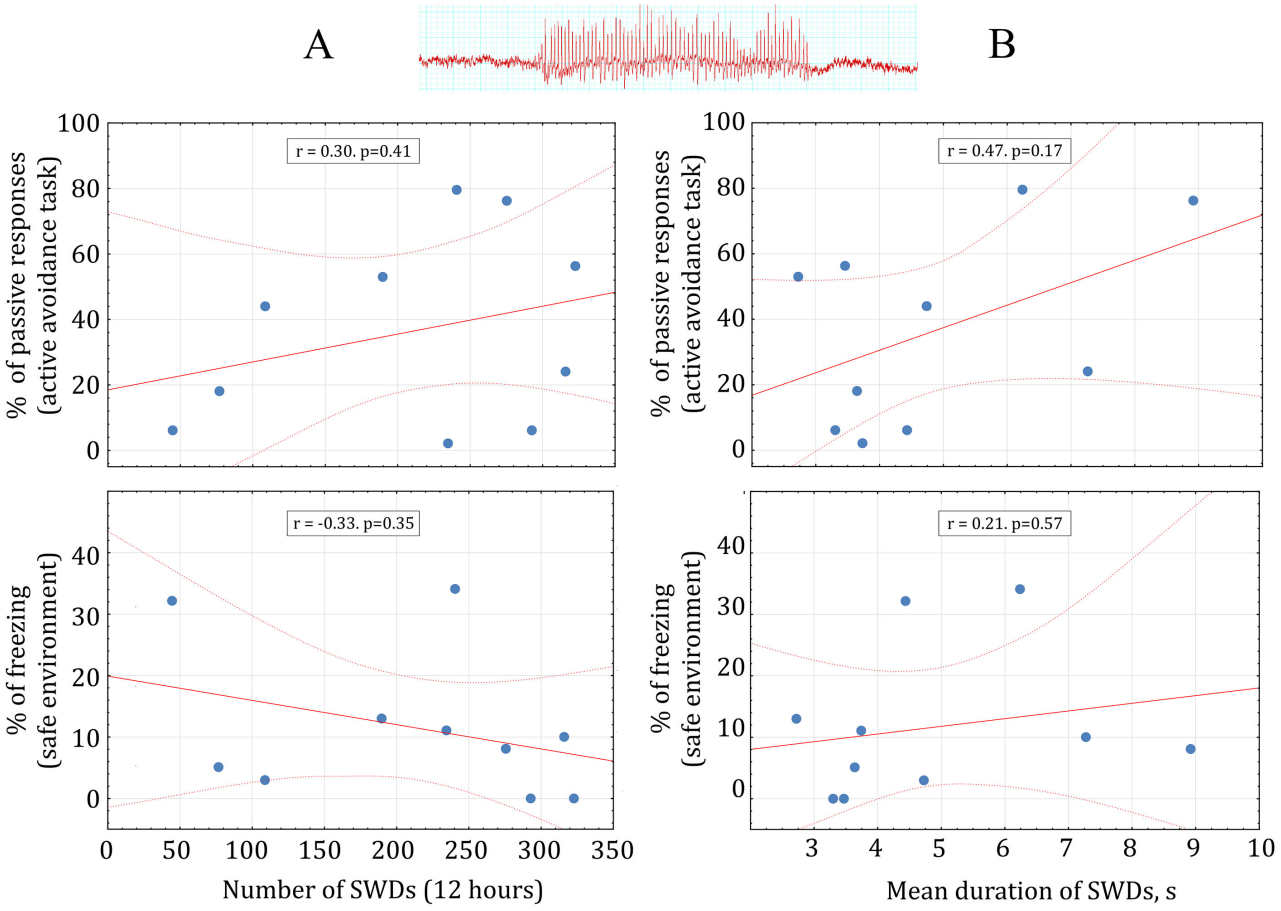

Fig. 4. The correlations between epileptic spike-and-wave discharge (SWD) parameters and the results of behavioral assessments (n = 10). (A) The number of SWDs; (B) Mean duration of SWDs. Pearson correlation coefficients are provided. Red solid lines show correlations, and dashed lines represent 95% confidence intervals.

Taken together, these exploratory findings indicate that, within the examined sample of symptomatic 10- to 12-month-old WAG/Rij rats, the severity of absence epilepsy—as measured by both SWD number and duration—is not significantly associated with passive behavioral expression in either an unsafe (fear-inducing) or a safe context. The absence of statistically significant correlations suggests that seizure-related immobility and fear-induced passive coping are distinct phenotypes in this model. However, the limited sample size (n = 10) warrants cautious interpretation and replication in larger cohorts.

4. Discussion

This study is the first to explore how severe absence epilepsy relates to passive behavior in genetically predisposed rats. We observed passive behaviors in symptomatic WAG/Rij rats in both unsafe and safe environments.

Our findings yielded four primary conclusions. First, in an unsafe, fear-inducing situation, 9-month-old WAG/Rij male rats were more passive than female subjects. Second, there was no significant sex difference in freezing in a safe environment in 10–12-month-old WAG/Rij rats (both sexes demonstrated low freezing). Third, a high percentage of passive behavioral responses during an active avoidance task predicted later context-inappropriate freezing in a safe environment only in females, whereas males showed divergent outcomes, highlighting a sex-dependent link relevant to PTSD models. Fourth, neither the percentage of passive responses in a fear-inducing situation nor the percentage of freezing reactions in a safe environment correlated with the number of SWDs or duration, suggesting absence epilepsy severity was unrelated to these passive behavioral reactions.

It is well known that a novel or stressful environment is not favorable for SWD occurrence [78,79,80]. Exposure to a new environment is considered a mild stressor for rodents. In 2005, Midzyanovskaya et al. [81] concluded that rats with non-convulsive epilepsy showed behavioral excitement coupled with fear reactions to novelty during a mild stress challenge, but adopted a passive strategy under more stressful conditions. Here, we induced minimal stress in rats by placing them in the StartFear cage and found that freezing time varied between 9.5% and 13.9% of total time. In contrast, Russo and Parsons [55] reported near-zero percent freezing in Sprague Dawley rats placed into condition-

ing chambers. This discrepancy may be explained by strain differences (WAG/Rij vs. Sprague Dawley rats) and age differences (2 vs. 10–12 months old). The overall freezing level in WAG/Rij rats may be higher than in healthy strains, suggesting altered emotionality in the epileptic strain. This interpretation is consistent with the findings of Karson et al. [45], who reported "*WAG/Rij rats exhibited worse emotional and spatial memory performances in passive avoidance and Morris water maze tests compared to their age-matched Wistar controls at 13 months but not at 5 months of age*".

4.1 Sex Differences in Passive Behavior and Their Dissociation From Absence Epilepsy Severity in Symptomatic WAG/Rij Rats

Our study was performed on WAG/Rij rats at the symptomatic age of 9–12 months. All subjects randomly selected for EEG examination exhibited spontaneous SWDs. Over a 12-hour period, male rats showed more frequent SWDs than females. This finding is consistent with the longitudinal EEG analysis by Lazarini-Lopes et al. [46], who reported that both the mean duration of SWDs and the total time spent in SWDs were lower in females than in males at 6, 7, 8, and 9 months of age. Moreover, our recent non-invasive examination of thirty WAG/Rij rats at 6 and 10 months of age confirmed that absence seizures are more pronounced in males than in females [76].

Despite these sex differences in seizure expression, our data indicate that the severity of absence epilepsy was not associated with passive behavioral patterns in either safe or unsafe environments. The well-established disturbances in thalamocortical networks underlying absence epilepsy [31,33,34,35,37,82] do not appear to correlate with freezing or fear-related passive behavioral responses. This conclusion is supported by behavioral studies on operant conditioning in WAG/Rij rats, which have shown that consciousness is maintained during SWDs, permitting voluntary control [30,83,84]. Taylor et al. [84] specifically demonstrated that "*SWD and associated immobility in rats may not reflect the obvious cognitive/behavioral interruption classically associated with absence seizures*". In this study, 73% of checks during reward periods were performed within 6 seconds after SWDs ended [84]. Nevertheless, these findings remain open to interpretation. The exact nature of rats' awareness during SWDs and their ability to control such discharges is not yet fully understood. Future studies could resolve some ambiguities by modifying task rules, for example, by altering the required duration of rewarded SWDs. Additionally, it is important to control for changes in the arousal system, as arousal levels may be suppressed in rats with absence epilepsy [30,78,85].

A substantial body of literature indicates that female rats exhibit lower levels of passive behavior than males under fear-inducing conditions (see references in [86]). Previously, we found that approximately 26% of male rats at 8–9 months of age, but none of the females, were passive and unable to perform the task [67]. In the present study, we observed that only female rats showed a remarkable relationship between passive responses in fear-inducing and safe environments. Specifically, strong correlations between the percentage of freezing in the safe environment and the percentage of passive responses in the unsafe environment were found exclusively in the female group. Male rats, in contrast, exhibited more passive reactions in the fear-inducing situation, and these reactions dissociated from their freezing behavior in the safe environment.

4.2 Passive Coping as a Sex-Specific Predictor of Later Freezing: Insights for PTSD

In our rats, passive behavior during an active avoidance task (e.g., passive coping) predicted later freezing in a safe context only in females, showing a positive correlation. Males showed no associations: high passive responders in a fear-inducing situation further split into low- and high-freezing groups in a safe environment. These results could be relevant for PTSD models, where persistent fear and overreaction to safe environments occur. Our data suggest the link between early passive coping and later inappropriate freezing depends on sex.

In females, passive avoidance at nine months strongly predicts later freezing in safe environments, resembling a PTSD-like pattern. Early passive coping signals a risk for fear overgeneralization. This aligns with clinical findings that women are twice as likely as men to develop PTSD and often exhibit stronger fear responses [87,88,89]. Female rats may have difficulty distinguishing threat from safety, possibly due to hormonal effects, such as estrogen's influence on the amygdala and hippocampus. Therefore, passive coping in females may indicate vulnerability to chronic, generalized fear.

Among males showing a high percentage of passive responses in the avoidance task, some exhibited minimal freezing (resilience-like) later in life, while others showed high freezing (PTSD-like). This suggests that in males, unlike females, passive coping behavior under fear-related conditions alone is insufficient to predict long-term increased freezing in safe conditions. We suggest the following two factors might determine whether a male rat develops resilient or vulnerable trajectories: individual differences in fear extinction capacity, peritraumatic stress hormone levels. These results call into question the notion that passive coping invariably leads to negative consequences. While this is true for females, it does not apply to males. In the context of PTSD, this suggests the need for sex-specific models. When screening for PTSD in rodents using fear-induced avoidance tasks, the method is more effective for females. Males, however, require a broader assessment that includes passive avoidance, extinction learning, or stress reactivity. Interventions aimed at reducing fear generalization, such as cognitive-behavioral therapy or extinction

training, may benefit women who exhibit high levels of passive coping. Men with similar behavior may require tailored approaches based on their subgroup's freezing response.

4.3 Interpretive Considerations for Fixed Task Order

A critical methodological feature of the current study is the fixed order of behavioral tests: active avoidance in an unsafe environment at 9 months of age, followed by repeated StartFear assessments in a safe, stimulus-free environment at 10, 11, and 12 months. While this design was chosen to first establish a stable baseline of passive behaviors under explicit threat before examining spontaneous freezing in a non-aversive context, it introduces a potential interpretational confound that warrants careful discussion.

While we cannot fully eliminate this confound, several aspects of our design and data reduce its impact. First, StartFear testing was conducted at 10, 11, and 12 months. If avoidance training only temporarily suppressed freezing, the amount of freezing would increase over time. Instead, freezing remained low and stable in both sexes, suggesting a persistent trait or a long-lasting change. The one-month gap between training and the first StartFear session is longer than the typical fear extinction retention period in rats, although stress sensitization can last longer.

Active avoidance training pairs a conditioned stimulus, such as a light or tone, with an unavoidable foot shock, forcing the animal to learn a movement to avoid it. This training causes lasting changes, including an increased stress response, stronger fear of contextual cues, altered brain plasticity in the hippocampus and amygdala, and changes in activity and risk assessment [57,90,91]. These effects can last for weeks to months, especially in rodent models of stress and anxiety [70,91,92]. When tested later in a new, safe environment (StartFear cage), the animals' freezing behavior reflects past aversive experiences rather than a naive reaction. This issue is common in longitudinal studies and must be considered when comparing behaviors across different contexts.

4.3.1 The Influence on Conclusion 1 "Low Freezing in a Safe Environment"

Our initial conclusion—that 10–12-month-old WAG/Rij rats showed low levels of freezing when placed in a safe environment—may have been influenced by prior avoidance training. Repeated shocks and successful avoidance learning might have caused habituation of fear responses or extinction of threat expectancy. Alternatively, the rats may have learned that the shock-paired context was dangerous, while the StartFear context was safe, leading to rapid habituation. Another possibility is that avoidance training increased stress reactivity, causing hyperarousal without freezing, such as more active exploration or vigilant scanning. Therefore, low freezing might reflect a change in behavior rather than low fear. Without a control group of shock-naive rats, we cannot assess these effects. Our observation of low freezing is valid but needs replication in shock-naive animals to confirm it as a stable trait.

4.3.2 The Influence on Conclusion 2 "Sex Differences in Freezing Across Contexts"

Our second conclusion was that (a) no significant sex difference appeared in freezing in the safe environment, but (b) in the unsafe, fear-inducing active avoidance task, males showed more passive reactions than females. This key finding may reflect sex-dependent carryover effects due to the fixed test order, not true trait differences.

First, observations in a safe environment. Females and males may differ in how they generalize, extinguish, or habituate to aversive memories formed during avoidance training. For example, female rodents often exhibit faster extinction of conditioned fear and lower contextual fear retention compared to males [64,65,86,93,94]. If females in our study habituated or extinguished shock memories faster, they might show lower freezing in StartFear testing (one month later), while males might still show residual suppression. Alternatively, females may habituate more to novel environments after stress, resulting in lower freezing regardless of prior experience. Both scenarios would lead to no net sex difference in the safe environment. Therefore, we cannot confidently conclude that there is no inherent sex difference in freezing behavior in a safe environment.

Second, the observed male-biased passive reactions in the unsafe avoidance task may be due to this task was administered first. Both sexes were naive to shock before testing. Importantly, our comparison between the unsafe task at 9 months and the safe environment at 10–12 months is not affected by task order. The sex difference in the avoidance task comes from the initial session, so it is not influenced by previous interventions.

Interpreting this sex difference as evidence of a stable, context-dependent passive coping style is supported by the avoidance task, which measures reactions to immediate, predictable threat and differs from spontaneous freezing in a safe environment. However, because our study lacked a counterbalanced design, we cannot rule out the possibility that avoidance training affected later freezing differently in males and females. For example, if males exhibited stronger fear conditioning during avoidance (as indicated by higher freezing), they might suppress freezing in the safe environment due to proactive interference or stress-induced dysregulation, whereas females might show fewer changes. This would exaggerate the dissociation.

4.3.3 The Influence on Conclusion 3 "No Correlation Between SWDs and Freezing"

Our third conclusion—that absence epilepsy (number and duration of SWDs) did not correlate with the passive behavior in a safe environment—is less affected by order

effects as long as the correlations were calculated within each sex and only within the StartFear dataset. However, prior avoidance training could have changed freezing behavior variability, reducing our ability to detect a true correlation. If training made freezing levels more uniform, it could cause a false null result. This is unlikely since SWDs are genetically predetermined [18,22,44,95]. Consequently, prior shock probably did not mask or amplify any correlation with SWD severity. Nevertheless, testing shock-naive animals would better confirm the lack of a relationship.

A testable hypothesis is that male WAG/Rij rats retain stronger contextual fear memory after active avoidance, leading to more reduced freezing in a safe environment. In contrast, females show faster extinction or better context discrimination, keeping freezing near baseline. This suggests that if naive animals were tested only in the safe environment, females would show low freezing, while males would show higher freezing without prior avoidance training. The lack of sex differences in safe-environment freezing might reflect reduced male freezing due to avoidance training. Testing this hypothesis requires a 2 × 2 experimental design (order: avoidance first vs. StartFear first; sex). Until then strong claims about no sex differences in safe-environment freezing are premature.

4.4 A Common Neural Substrate for Passive/Freezing Behavior and Absence Epilepsy

The present findings from the WAG/Rij rat model offer a nuanced perspective on the proposed conceptual framework linking thalamic tonic GABA-A inhibition to both absence epilepsy [47,48,49,50,51] and passive coping behaviors [52,53]. The concept predicts that stronger thalamic tonic GABA-A inhibition should both increase passive/freezing behavior and help trigger seizures. In male WAG/Rij rats, we found this pattern: males showed more passive behavior and higher SWD frequency than females. This suggests the same thalamocortical network—especially the mediodorsal thalamus and reticular thalamic nucleus—is more excitable in males due to tonic inhibition, leading to both passivity and seizures. The lack of a direct link between SWD and freezing in the StartFear tests means tonic GABA-A likely acts as a permissive factor, not a direct, dose-dependent cause of both behaviors.

The absence of significant correlations between SWD severity and either measure of passive behavior (fear-induced or context-free freezing) indicates that seizure-related immobility and fear-induced passive coping are dissociable phenotypes in the WAG/Rij rat model. Several explanations are possible. First, increase tonic GABA-A inhibition may be localized, as differential expression of extrasynaptic GABA-A receptor subunits (e.g., $\alpha4\beta\delta$ vs. $\alpha5\beta\gamma2$) across thalamic subnuclei could produce distinct functional outcomes. The mediodorsal thalamus is involved in fear extinction and freezing, whereas absence seizures involve broader thalamocortical circuitry, including the ventrobasal complex and reticular thalamic nucleus [20,21,23,24,31,32,33,34,35,36,37]. Second, the temporal dynamics differ: absence seizures manifest as paroxysmal 5–9 Hz SWDs lasting seconds, while tonic GABA-A inhibition produces sustained, ambient-level modulation. The behavioral measures we collected (average freezing across sessions) may not capture the phobic or context-conditioned components most sensitive to tonic inhibition. Third, this concept is based on experimental data from GAERS [51], but the WAG/Rij model may differ from GAERS in the precise molecular pathology. While GAERS shows GAT-1 dysfunction and enhanced tonic currents, WAG/Rij rats—though both are absence models—may exhibit compensatory mechanisms or alternative pathogenic pathways that decouple seizure generation from behavioral suppression.

Our findings support the conceptual overlap in shared neural circuitry and molecular mechanisms, but caution against assuming a direct phenotypic correlation. WAG/Rij rats exhibit both increased passive coping (primarily in males) and absence epilepsy, indicating overactive thalamic tonic inhibition. However, since these traits are not directly linked, additional factors such as developmental processes, network alterations, or influences outside the thalamus likely determine whether increased tonic inhibition leads to behavioral changes, seizures, or both.

In summary, the WAG/Rij model provides partial support for the tonic GABA-A hypothesis. Seizure susceptibility and passive coping frequently co-occur, suggesting a shared underlying mechanism. However, their lack of direct correlation indicates a more modular system. Future research should specifically target thalamic extrasynaptic GABA-A receptors in WAG/Rij rats to determine whether modulating these receptors affects both SWDs and freezing behavior. This approach would provide stronger evidence for a shared mechanism than correlational studies alone.

4.5 Limitations

All StartFear measurements were obtained after avoidance/shock training; therefore, reported low freezing should be interpreted as post conditioning behavior rather than a naïve baseline trait. Since all animals experienced the avoidance task before StartFear testing, the design cannot fully separate inherent traits from experience-dependent effects. Future work including naïve WAG/Rij cohorts, EEG screened controls, counterbalanced test order, and EEG during StartFear is necessary to determine whether reduced freezing reflects an intrinsic tonic inhibition phenotype or a consequence of prior aversive experience.

Several methodological constraints affect the interpretation of these findings. First, the fixed order of behavioral tests—shock-based avoidance at 9 months followed by safe-environment StartFear tests at 10 and 12 months—may cause confounds. Prior exposure to shock-based avoidance can alter baseline freezing, stress reactivity, arousal state, and exploratory behavior for extended periods, and these

effects may differ by sex. Consequently, low freezing in the safe environment may reflect altered responses from earlier aversive learning, not a natural trait of WAG/Rij rats. The lack of sex differences and context dissociation might result from sex-based carryover effects like fear generalization or extinction. Without counterbalanced order or shock-naive controls, we cannot confirm if these patterns show stable behaviors or order effects.

Second, the small sample size for EEG recordings represents a critical limitation. EEG recording is an invasive procedure requiring 1–2 h of surgery and a 2-week recovery period. We lacked the technical capacity to assess the severity of absence epilepsy in all rats included in behavioral tests. As a result, correlation analyses between SWD parameters and behavioral freezing were performed on only five animals per sex. This limited statistical power renders our negative findings (i.e., no correlation between SWD burden and passive behavior) inconclusive. Larger cohorts are necessary to determine whether a true relationship exists or whether the null result reflects insufficient power. Furthermore, we did not perform video monitoring during long-term EEG recordings. Therefore, we cannot rule out that sex differences in spontaneous locomotor or resting activity during the recording period may have contributed to the observed sex difference in SWD number. Developing a non-invasive EEG system to assess absence epilepsy severity would benefit future studies.

Third, the absence of a non-epileptic control strain (e.g., Wistar rats) limits understanding if the observed behaviors are specific to the epileptic WAG/Rij rats or general in rats without epilepsy. Without such a control, we cannot determine if low freezing in the safe environment, sex differences in active avoidance, or the lack of correlation between SWDs and behavior are unique to the WAG/Rij strain or common across strains. This is especially important for interpreting sex differences, as fear-related differences between sexes exist in non-epileptic strains.

Fourth, we did not measure minor movements, such as teeth grinding during freezing in the safe environment. Rats grind their teeth (brux-like activity) when stressed, anxious, or in pain [96]. This brux-like activity is linked to emotional stress and can be reduced by anti-anxiety drugs [96]. Increased teeth grinding may show stress even without visible freezing. Since we did not closely monitor the facial area during StartFear testing, we cannot confirm if stress-related orofacial behaviors occurred. Detailed video analysis of facial behavior during freezing should be explored in future research.

The identified limitations highlight the exploratory nature of this study, which should be considered primarily as a hypothesis-generating endeavor. To establish robust conclusions regarding the relationship between absence epilepsy severity, sex, and passive behavior patterns, it is imperative to conduct replication studies using larger, counterbalanced experimental designs.

5. Conclusions

Our study reveals that passive behavioral patterns in WAG/Rij rats are not directly related to the severity of absence epilepsy, exhibit significant sex differences, and highlight a female-specific link between early fear coping responses and later freezing. In the fear-inducing active avoidance task, male WAG/Rij rats displayed significantly higher levels of passive behavior compared to females. Conversely, in a safe environment, no sex differences in freezing were observed; low levels (9.5–13.9%) persisted across ages 10 to 12 months without substantial age-related changes.

We identified a sex-specific predictive relationship in which early fear-induced passive responses at nine months significantly correlated with subsequent freezing in a safe environment only in females ($r = 0.83, p < 0.005$). This suggests a sex-dependent consistency in passive coping across contexts. In contrast, males did not show such a correlation; several exhibited minimal freezing later, indicating potential fear extinction.

The lack of correlation between the number and duration of SWDs and passive responses indicates that these are neurobiologically distinct in WAG/Rij rats. This dissociation suggests that passive responses in the active avoidance task are not simply manifestations of seizure-related pathology. A subset of animals (three males and one female) exhibiting high passive responses in an unsafe context and high freezing in a safe context may be at increased risk for trauma-related maladaptive responses, potentially modeling core PTSD-like endophenotypes. These findings suggest that certain individuals may be vulnerable to PTSD-like behaviors based on their early fear-coping responses.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

ES—data curation, formal analysis, visualization, writing—original draft; ES and AK—conceptualization, funding acquisition, project administration, supervision, writing—review & editing; ES and AV—methodology; AV and MP—investigation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Experiments in rats were carried out in accordance with EU Directive 2010/63/EU for animal experiments, the National Institutes of Health Guide for the Care and Use of Laboratory Animals and ARRIVE 2.0 (see **Supplementary**

Material). The study protocol was approved by the Ethics Committee of the Institute of the Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences (protocol No. 4 approved on 26 October 2021 for EEG investigation and protocol No. 4 approved on 13 December 2022 for behavioral examination).

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN52427.

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