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Research Article

# The resident-intruder model: a platform for in-depth study of novel molecules with antidepressant activity

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## Abstract

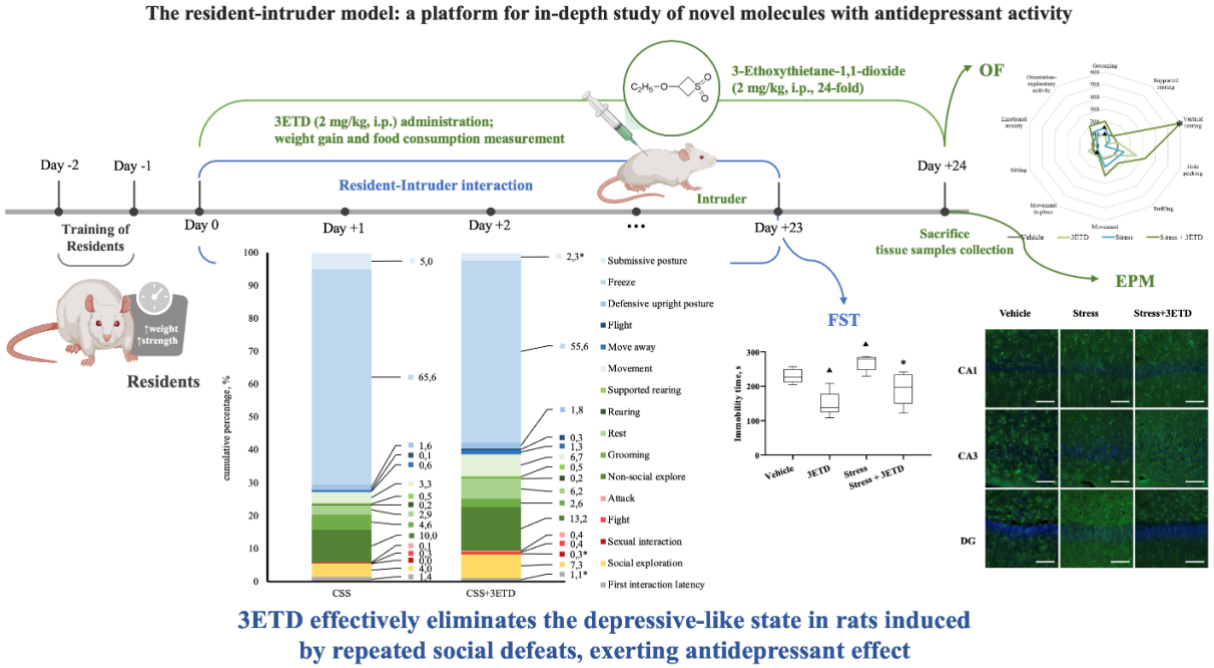
**Introduction:** The aim of the study was to investigate the features of the resident-intruder paradigm as a basic translational method for in-depth evaluation of antidepressant activity of new compounds using the example of 3-ethoxythietane-1,1-dioxide (3ETD), which has antidepressant activity.

**Materials and Methods:** A depressive-like state in white non-inbred rats (intruders) was modeled by long-term (24-day) exposure to chronic social stress (CSS) during interaction with residents. Intruders were divided into 4 experimental groups (n=6). Intruders of the CSS and CSS+3ETD groups interacted with residents daily for 10 min from Day 0 to Day +23, 30 min after intraperitoneal administration of 3ETD (2 mg/kg, 3ETD, CSS+3ETD groups) or saline (Vehicle and CSS groups). At the end of the experiment, the behavior of intruders of all groups was studied in the forced swimming test (FST, Day +23), open field test, and elevated plus maze test (Day +24). Intruders' body weight and food consumption were measured daily. After euthanasia (Day +24), the weight coefficients of internal organs were calculated and the level of apoptosis markers/regulators in the rat hippocampus was determined immunohistochemically.

**Results and Discussion:** CSS induced a state similar to asthenic depression in intruders: it increased immobility time in FST, the duration of passive behaviors (including submissive), while the duration of active behaviors (defensive, exploratory, social) decreased. 3ETD eliminated these manifestations, exerting an antidepressant effect: it reduced the despair behavior in FST, enhanced motor activity, social and exploratory behavior of intruders, stimulated active defense and reduced passive defense during contact with residents, as well as reduced apoptosis in the hippocampus of intruders, exhibiting neuroprotective properties.

**Conclusion:** The resident-intruder model allows modeling in rats a condition similar to the human asthenic depression and demonstrating the antidepressant effect of novel molecules, as was shown on the 3ETD example when administered at a dose of 2 mg/kg/day intraperitoneally.

# Graphical Abstract





# Keywords

antidepressant activity, resident-intruder, animal outbred strain, thietane


# Introduction

Effective treatment of depressive disorders is a pressing healthcare issue both in the Russian Federation and globally, as evidenced by their high prevalence (332 million people worldwide, 6.8 million people in the Russian Federation) and burden (56.3 million Disability-Adjusted Life Years (DALYs) worldwide, 2.9 million DALYs in the Russian Federation, according to the Institute for Health Metrics and Evaluation 2021), as well as the growing demand for antidepressants (the global antidepressant market totaled $18.7 billion in 2024, Global Market Insights Inc.).

Unfortunately, many promising molecules that have demonstrated significant antidepressant properties in preclinical studies have failed to show activity in clinical trials. The reason may be that the models used to reproduce depressive-like states in animals and to study the antidepressant activity of new compounds lack validity (Belzung 2014). To date, there is no universal model of depression that can reliably reproduce in animals the behavioral, metabolic, biochemical, and genetic changes similar to depression that could be reversed by antidepressants. At the same time, the most valid (i.e. possessing constructive, face and predictive validity) are considered to be models based on social stress – loss of control over the social environment (social defeat, social isolation and others), which ensures the proximity of the mechanisms underlying depressive state development in humans and animals, animal reproduction of the main symptoms of depression and demonstration of the treatment efficacy (Czéh et al. 2016). In particular, the chronic social defeat stress model (chronic social stress – CSS) is characterized by very strong construct, face and predictive validity, and allows inducing core symptoms of major depressive disorder and posttraumatic stress disorder in rodents (Petković and Chaudhury 2022), which is a valuable advantage at the stage of preclinical studies of new molecules.

There are various modifications of this method, differing in the purposes of application (research/induction of aggressive/defensive/depressive-like behavior), model objects (rats, mice, etc.), objects of study (residents/intruders), frequency and duration of social contacts (Czéh et al. 2016). The protocol for the present study was based on the resident-intruder paradigm described by Koolhaas et al. (2013) and adapted for an in-depth study of the antidepressant effect of 3-ethoxythietane-1,1-dioxide (3ETD) – a novel compound discovered at Bashkir State Medical University (BSMU), which showed pronounced antidepressant activity and an atypical mechanism of action (acting on 5HT1A-, 5HT12A/2C-, α2- receptors) (Nikitina and Gaisina

2022) when administered intraperitoneally (i.p.) to non-inbred male mice. The antidepressant properties of 3ETD were confirmed in a reserpine depression model in rats (Nikitina et al. 2025); however, this study demonstrated insufficient construct validity of the method (no changes in the level of brain-derived neurotrophic factor), as well as its low informativeness in terms of characterizing the antidepressant effect and determining the potential clinical niche of the drug candidate (anxious/asthenic depression), which served as the background for the present study.

# Materials and Methods

### Experimental animals

The experiment was conducted on male (250-400 g) and female (200-250 g) white non-inbred rats in accordance with *The Rules of Good Laboratory Practice of the Eurasian Economic Union in the Field of Drugs* (Decision No. 81 of the Council of the Eurasian Economic Commission dated November 3, 2016 "On Approval of Rules of Good Laboratory Practice of the Eurasian Economic Union in the Sphere of Circulation of Medicines") and *The European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes* (ETS No. 123, 1986). The rats were kept under 12-h light regime (08:00-20:00) at 20-22°C, 40-60% relative humidity and free access to water and food (compound feed for laboratory animals, GOST R 50258-92, GROUP-SPETSKOM LLC, Russia). The experiment was approved by the Expert Council on Biomedical Ethics in Theoretical Disciplines of Bashkir State Medical University (BSMU, minutes No. 9, 2020).

### Drugs and treatment

3-Ethoxythietane-1,1-dioxide (3ETD, 2 mg/kg) was synthesized at the Department of Pharmaceutical, Analytical and Toxicological Chemistry of BSMU. The compound was dissolved in saline with Tween-80 (Panreac Quimica S.A.U., Spain), and injected i.p. (0.4 mL per 200 g body weight) to intruders of Group 2 and Group 4 thirty min prior to a "resident-intruder" confrontation. Intruders of Group 1 and Group 3 received saline i.p.

### Experimental design

The design of the experiment was based on the resident-intruder paradigm (Koolhaas et al. 2013). Large male rats weighing 350-400 g were defined as "residents" and housed in individual 90x50x60 cm cages one week prior to "resident-intruder" interactions (Day -6). From Day -6 to Day 0 the residents were kept with females, and on Days -2 and -1 they were trained in dominant behavior by interacting with non-experimental male rats (250-300 g) twice a day.

Male rats defined as "intruders" (250-300 g) were divided into the following experimental groups: 1) Vehicle; 2) 3ETD; 3) CSS; 4) CSS+3ETD.

Intact rats (Groups 1 and 2) had no physical, visual, olfactory or auditory contact with residents throughout the experiment. Stressed intruders (Groups 3 and 4) interacted with residents daily for 10 min (excluding repeated contact between residents and intruders). After the confrontation, the intruder kept in the resident's cage for 24 h, were separated from the resident by a transparent perforated partition until being moved to the next resident's cage.

Throughout the experiment, the body weight gain of the intruders and their food intake were recorded.

At the end of the experiment (Day +24), the animals were euthanized, the brains were removed for further histological and immunohistochemical (IHC) analysis, as well as internal organs (liver, spleen, thymus, adrenal glands) for subsequent determination of their weight coefficients.

The experimental design is summarized in Figure 1.


**Figure 1.** Design of the "resident-intruder" model. ***Note:*** FST – forced swimming test, OP – open field test, EPM – elevated plus maze test, i.p. – intraperitoneally.

### Resident-intruder interaction analysis

Interactions between residents and intruders were conducted daily from Day 0 to Day +23 during

the dark phase from 20:00 to 20:10 (10 min). Thirty min after saline / 3ETD administration, stressed intruders were placed in resident cages, partitions were removed and animal behavior was recorded on a video camera (Panasonic V760). Using the RealTimer software (RPC OpenScience Ltd, Russia), the duration of behavioral patterns of intruders was recorded in s and the behavior types were calculated (Table 1), as well as the cumulative percentage of each indicator in the structure of intruder behavior using the formula:

$$Cumulative\ percentage\ = \frac{Sum\ of\ shares\ of\ pattern\ (behavior\ type) on\ each\ experimental\ day\ \times 100}{24}$$

**Table 1.** The indicators analyzed during resident-intruder confrontations

| Individual patterns | "Social interaction" behavior type | "Social inactivity" behavior type | "Defense" behavior type |
|---|---|---|---|
| first interaction latency | attack | non-social explore | submissive posture |
| social exploration | fight | movement | freeze |
| submission latency | sexual interaction | rearing | defensive upright posture |
| | | supported rearing | move away |
| | | grooming | flight |
| | | rest | |

***Note:*** the behavior types were calculated as a sum of the patterns listed in the corresponding column of the table.

### Behavioral tests

The development of a depressive-like state in intruders and the antidepressant effect of the compound were assessed in the forced swimming test (FST) according to R. Porsolt (1979) on Day +23; additionally, on Day +24, the open field (OF) and elevated plus maze (EPM) tests were performed (Sestakova et al. 2013).

### Histological and immunohistochemical analysis of rat hippocampus

The histological analysis was performed using the equipment of the Centre for Molecular and Cell Technologies of the Saint-Petersburg State University Research Park.

To assess the ability of 3ETD to correct stress-induced changes, IHC detection of glial fibrillary acidic protein (GFAP) as a marker of astrocytic glia in the intruders' hippocampus was performed. On Day +24, the brains were extracted from three animals from each group and fixed by immersion in 10% neutral formalin pH 7.4. Using a cryostat microtome (Leica CM – 3050S, Germany), frontal 30 μm-thick sections were made. The sliced sections were mounted on silane-coated glass slides.

IHC staining was performed on glass slides by indirect immunofluorescence labeling using primary rabbit polyclonal antibodies against GFAP (Dako, USA, 1:200) and secondary goat antibodies against rabbit IgG conjugated with a fluorochrome (Alexa Fluor 568, Molecular Probes, Thermo Fisher Scientific, USA, 1:250). Unmasking antigen epitopes was performed by boiling in citrate buffer pH 6.0 in a microwave histoprocessor (Milestone KOS). To block non-specific antibody binding, the sections were incubated at room temperature with a solution of the following composition: 0.3% Triton X-100; 10% normal goat serum (NGS, Sigma G9023) in phosphate buffer pH 7.4. Incubation of sections with primary antibodies was performed overnight in a humid chamber at 4°C, followed by incubation with secondary antibodies in a humid chamber for 2 hours at 37°C. Cell nuclei were stained with DAPI (4,6-diamidino-2-phenylindole). The sections were mounted in glycerol.

The structures of the hippocampal formation and hippocampal cytoarchitectonic fields were defined according to the rat brain atlas (Paxinos and Watson 2006). The areas CA1, CA3 and the dentate gyrus (DG) of the dorsal hippocampus were examined under a fluorescent microscope Leica DM 6000 with a camera DFC65FX. Morphometric analysis was performed on digital images of the sections using an open-source FIJI software (http://fiji.sc/Fiji). The number of IHC(+)-cells in 36 fields of view (100*200 μm frame) in 3 brain sections of each animal was counted.

### Statistical analysis

For statistical analysis, the Statistica 13.3 software package (StatSoft, USA) was used. Descriptive statistics included Shapiro-Wilk test, median (Me) and interquartile range, comparative statistics – nonparametric tests of Kraskell-Wallis, Mann-Whitney / Friedman,

Wilcoxon (multiple and pairwise comparison of independent / dependent samples) (Oliveira 2020). The results were defined as statistically significant at $p<0.05$.

# Results

### Behavioral changes in intruders treated with 3ETD in the forced swimming, open field, and elevated plus maze tests

As a result of 24-fold social defeat experience, intruders of the CSS group developed despair behavior, manifested by increased immobility time (IT) in FST (by 23%, p=0.016, Day +23, Figure 2A) and grooming in OF (by 50%, p=0.039, Day +24 day, Figure 2B) compared to the vehicle group.

3ETD counteracted CSS by reducing IT FST to the vehicle level (by 30%, p=0.011, Figure 2A) and also increased the number of rearings in OF (6-fold, p=0.043) compared to the CSS group (Figure 2B).

No significant changes in the EPM test were detected.

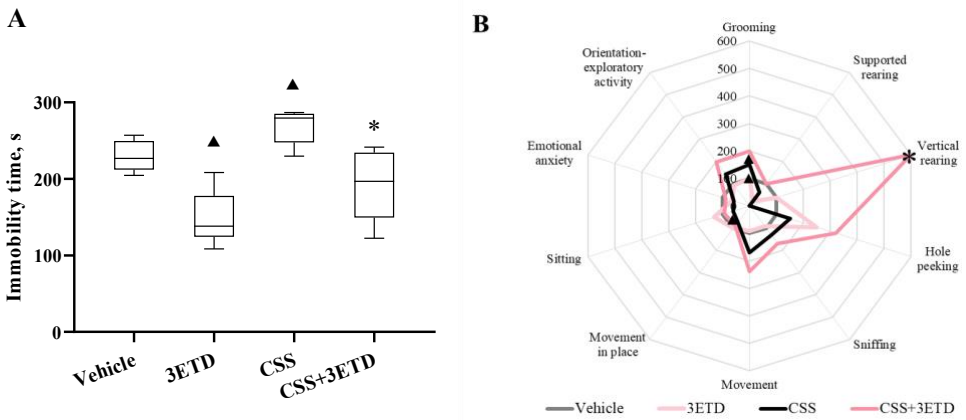



**Figure 2**. Behavioral changes in intruders treated with 3-ethoxythietane-1,1-dioxide (3ETD) in the forced swimming test **(A)** and open field test **(B)**. ***Note:*** CSS – chronic social stress; **A** shows group medians, interquartile range, minimum and maximum; **B** shows group medians expressed as percentages relative to the vehicle; * $p<0.05$ (Mann-Whitney test, pairwise comparison with the CSS group), ▲ $p<0.05$ (Mann-Whitney test, pairwise comparison with the vehicle).

### Behavioral changes in intruders treated with 3ETD during interactions with residents

The behavior of intruders during confrontations with residents changed significantly throughout the experiment.

In dynamics, CSS caused a decrease in the duration of "social interaction" (by 58-100% on Days +8, +18, +19 and +22), "social inactivity" (by 38-71% on Days +1, +2, +3, +6, +7, +14, +19), "social exploration" (by 44-96% on Days +2, +3, +6, +13, +14, +15, +16, +17, +18, +20, +22, +23), "submission latency" (by 13% on Day +7, by 41% on Day +13), as well as an increase in "defense" (by 15-45% on Days +1, +2, +3, +7, +13, +14, +16, +17, +18) due to passive defensive forms ("freeze" and "submissive posture") compared with Day 0 ($p<0.05$, Wilcoxon test, Figure 3).

3ETD counteracted intruder behavior changes caused by CSS. When analyzing the structure of intruder behavior, it was found that 3ETD decreased the cumulative percentage of "submissive posture" (2.2 times, p=0.018) and "first interaction latency" (1.3 times, p=0.045), and also increased the cumulative percentage of "social interaction" (2.8 times, p=0.045) by increasing the cumulative percentage of the pattern "sexual interaction" (35.6 times, p=0.017) compared to the CSS group (Figure 4).

Pairwise comparisons between two groups at each time point of the experiment revealed that 3ETD significantly increased the duration of "social exploration" by 6-27 times (on Days +2, +3, +4, +6, +16), "social interaction" by 5-26 times (on Days +3, +4, +6, +7, +22) due to the patterns "attack" (on Days +4, +5), "fight" (on Days +3, +22), "sexual interaction" (on Day +4), and the duration of "social inactivity" by 2-5 times (on Days +2, +6, +14) due to the patterns "movement" (on Days +1, +2, +4, +4, +5, +6, +7), "non-social explore" (on Days +6, +14), "rearing" (on Day+7) and "supported rearing" (on Days +6, +7).

The duration of defensive behavior under the influence of 3ETD decreased by 1.3-2 times (on Days +2, +4, +6, +14) due to passive defensive forms "submissive posture" (on Days +21, +22) and "freeze" (on Days +4, +6), while active defensive forms "flight" (on Days +7, +11, +19) and "move away" (on Days +6, +16, +17) increased ($p<0.05$, Mann-Whitney test, comparison with the CSS group, Figure 3).

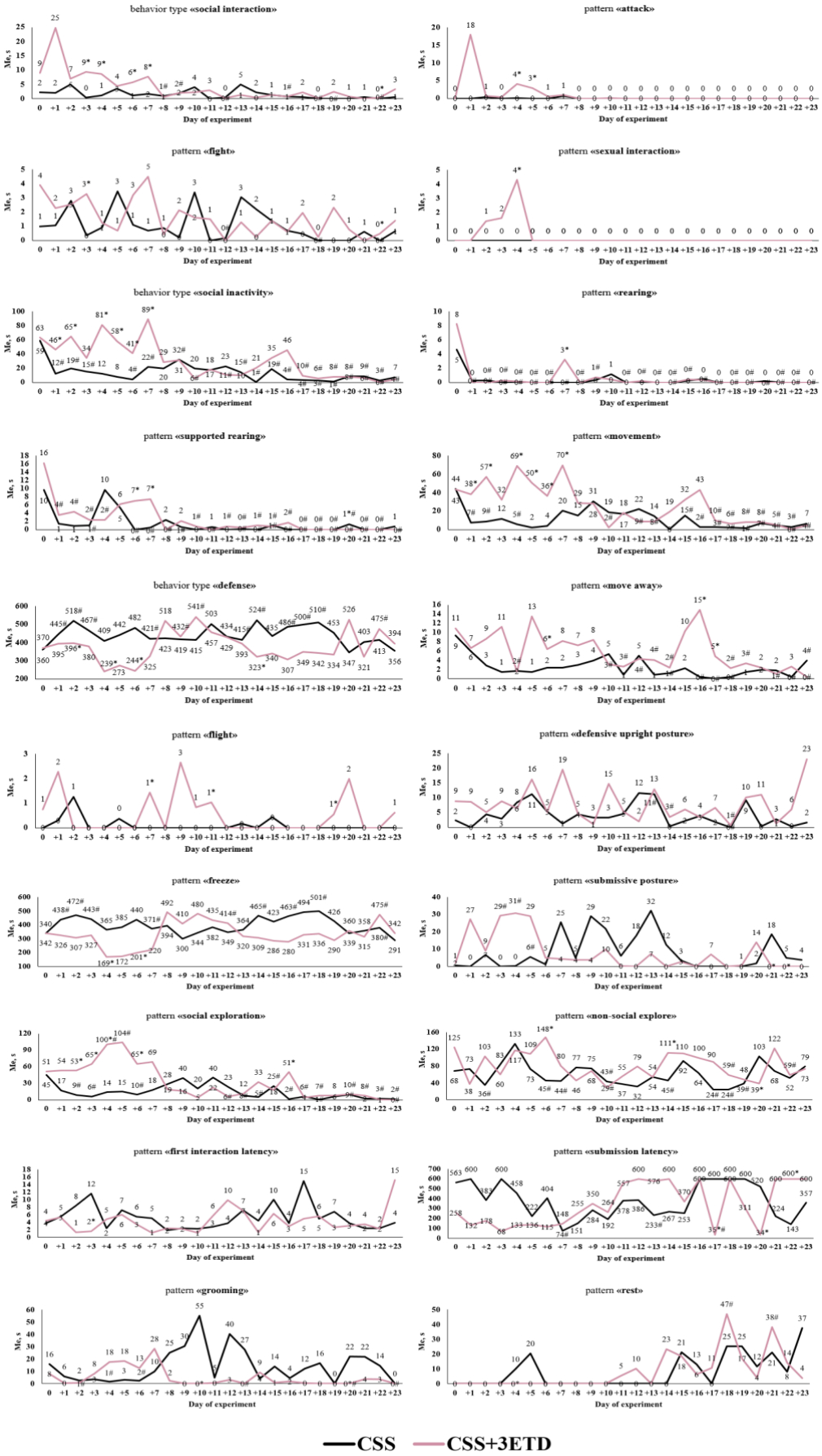



**Figure 3**. Behavioral changes in intruders treated with 3-ethoxythietane-1,1-dioxide (3ETD) during confrontations with residents. ***Note:*** CSS – chronic social stress; graphs show group medians; * p<0.05 (Mann-Whitney test, pairwise comparison with the CSS group), # p<0.05 (Wilcoxon test, pairwise comparison with Day 0).

**Effect of 3ETD on weight gain, internal organ mass and food consumption of intruders**

Neither CSS nor 3ETD affected intruder body weight, internal organ mass ratios, or food intake.

**Immunohistochemical changes in the hippocampus of intruders treated with 3ETD**

Histological analysis showed that astrocytes were concentrated predominantly in the marginal and radial layers of the CA1 and CA2 fields of the dorsal hippocampus adjacent to the pyramidal layer.

CSS significantly increased the number of GFAP(+) cells compared to the vehicle group in all hippocampal areas studied: by 60% in CA1, by 28.6% in CA3, and by 33.3% in DG ($p<0.001$).

3ETD reduced the CSS-induced increase in astrocyte number by 12.5% in CA1 and DG, by 33.3% in CA3 ($p<0.001$) compared to the CSS group, and in CA3 it was reduced to the vehicle level ($p=0.886$) (Figure 5).

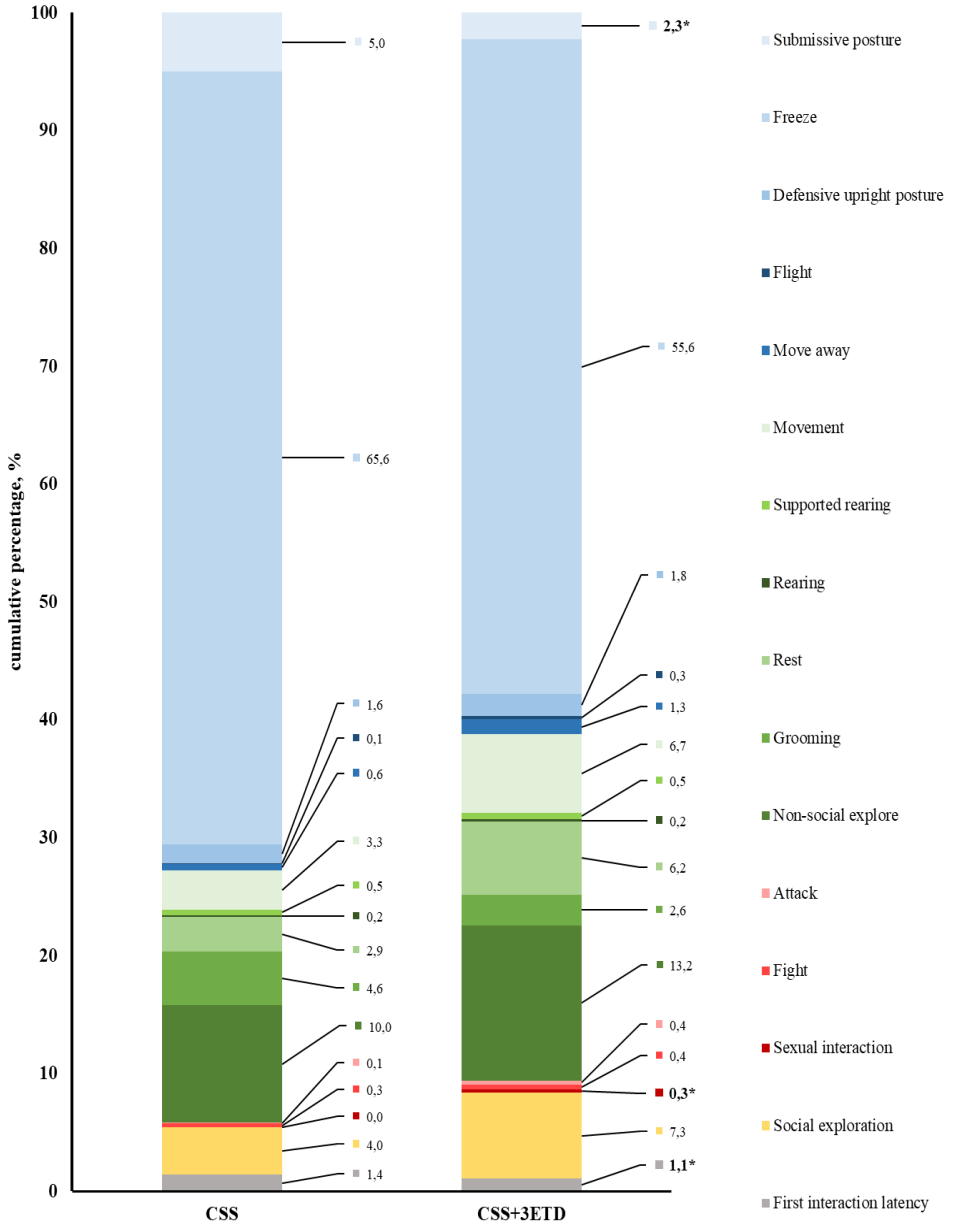



**Figure 4**. Changes in the behavioral structure of intruders treated with 3-ethoxythietane-1,1-dioxide (3ETD) during confrontations with residents. ***Note:*** CSS – chronic social stress; graphs show cumulative percentages of behavioral patterns (%), calculated using the formula: *cumulative percentage = sum of shares of pattern / behavior type on each experimental day * 100 / 24*; the "social interaction" behavior type is indicated in shades of red, the "social inactivity" behavior type is indicated in shades of green, and the "defense" behavior type is indicated in shades of blue; * $p<0.05$ (Mann-Whitney test, pairwise comparison with the CSS group).

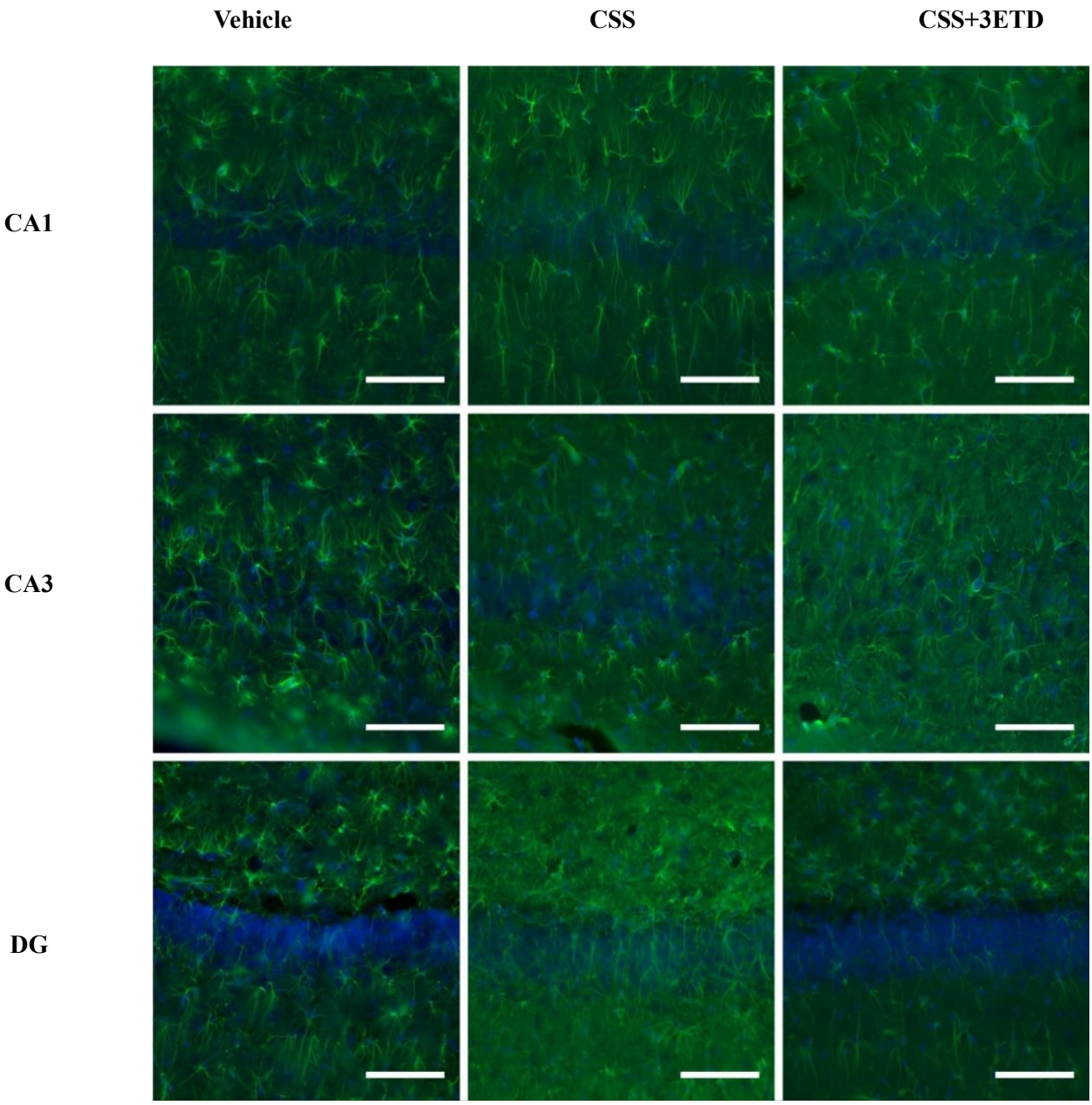



**Figure 5.** Immunolocalization of GFAP in the hippocampal regions CA1, CA3 and dentate gyrus of intruders treated with 3-ethoxythietane-1,1-dioxide (3ETD). ***Note:*** CSS – chronic social stress, DG – dentate gyrus. Immunohistochemical staining with anti-GFAP antibodies (astrocytes, green fluorescence), DAPI staining (cell nuclei, blue fluorescence). Scale bar 100 μm.

# Discussion

A key stage in the preclinical evaluation of antidepressant activity of novel molecules is the study of their effect in animal depression models that reproduce the etiology and pathogenesis (construct validity), symptoms (face validity) and treatment effect (predictive validity) as closely as possible to humans. Models based on social stress (loss of control over the social environment) meet these requirements. Loss of social status is associated with a greater risk of developing depression in humans (Czéh et al. 2016), similarly, animals exposed to social defeat exhibit decreased exploratory behavior, anhedonia, increased immobility (Petković and Chaudhury 2022) and submissive behavior (Koolhaas et al. 2013). The possibility of extrapolating the identified effects to humans suggests a potential clinical niche for a future drug, which is particularly valuable at the preclinical research stage.

To model a depressive-like state in rats, we used the resident-intruder paradigm (Koolhaas et al. 2013), based on exposing intruders to chronic social defeat when interacting with residents. The duration of the experiment (24 days) was determined based on the results of our previous studies (Nikitina et al. 2021) and published data from other researchers (Bakshaliyeva 2010; Lu

et al. 2021), indicating that the development of a distinct depressive-like state requires at least 20-fold confrontation – a shorter duration of the experiment does not lead to a significant change in the behavior of intruders. The present study demonstrates the use of the resident-intruder paradigm for an in-depth assessment of the antidepressant effect of 3ETD, which exhibits pronounced antidepressant properties in screening behavioral tests in mice (Nikitina and Gaisina 2022), as well as in a reserpine-induced depression model in rats (Nikitina et al. 2025).

The intruders were subjected to CSS (interaction with residents) daily from Day 0 to Day +23; to assess the development of a depressive-like state FST was used (Day +23). The interpretation of behavioral changes in intruders during confrontations with residents was based on Koolhaas et al. (2013), Shabanov and Lebedev (2007), and Bakhshaliyeva (2010).

CSS caused significant changes in the behavior of intruders, similar to asthenic depression in humans: the intruders demonstrated despair behavior (increased immobility in FST, Day +23) and increased passive forms of defense ("submissive posture" – the main criterion for the depressive-like state development (Koolhaas et al. 2013), and "freeze"), as well as a decrease in active behaviors – social ("social exploration", "fight", "social interaction"), exploratory ("inactivity", "non-social explore"), motor activity ("rearing", "supported rearing", "movement"), active forms of defense ("move away") compared to the initial level of Day 0. CSS did not alter significantly rat body weight, feed intake, and internal organ weight coefficients.

Depressive-like symptoms developed in intruders were effectively treated with 3ETD. Thus, 3ETD eliminated CSS-induced despair behavior in FST (reduced IT to the level of intact animals), improved intruders' social behavior (increased "social exploration" and "social interaction", decreased "first interaction latency" and "grooming" – an indicator of social inactivity (Shabanov and Lebedev 2007)) and individual behavior (duration and cumulative percentage of "non-social explore", duration of "movement", "rearing" and "supported rearing") during interaction with residents. The defensive behavior in the CSS+3ETD group was lower than in the CSS group, which was associated with a decrease in the duration of passive defensive patterns ("freeze" and "submissive posture"), which had a leading share in both groups. 3ETD had no effect on intruder body weight, feed intake, and internal organ weight coefficients compared to those in both CSS and vehicle groups.

It is known that stress causes morphofunctional changes in the limbic system, in particular, a decrease in the volume of the hippocampus (Smirnov et al. 2013), one of the most sensitive structures to stress factors (Tyurenkov et al. 2019), has been noted. Studies have shown that the main cause of hippocampal volume reduction is pathologic changes in pyramidal layer neurons accompanied by reactivation of astrocytes (Yao et al. 2021). Astrogliosis is one of the most important indicators of degenerative changes in the brain and is manifested by an increase in the number of astrocytes, their hypertrophy, and increased synthesis of a number of proteins, such as vimentin, nestin, and glial fibrillary acidic protein (GFAP) (Kolomeets and Uranova 2014). Therefore, we analyzed the distribution of the astrocytic marker GFAP in CA1, CA3 and DG of the hippocampus as a marker of astrogliosis and apoptosis using IHC staining. It was found that CSS increased the number of GFAP(+) cells in all hippocampal regions studied, while 3ETD reduced this effect, which can be interpreted as a manifestation of a neuroprotective action.

# Conclusion

Chronic social defeats over 24 days lead to the development in intruders of a condition similar to asthenic depression in humans, manifested by decreased social, exploratory, motor and active defensive behavior and increased passive behaviors during interaction with residents, as well as increased immobility in FST and astrogliosis in rat hippocampus. The antidepressant effect of 3ETD (2 mg/kg), eliminating CSS-induced symptoms, and its influence on the intraspecific behavior of animals were demonstrated – a reduction of immobility time in FST and the share of passive behaviors during confrontations with residents, an increase in exploratory, social and motor activity and the share of active defensive behavior. 3ETD also exerted neuroprotective properties, reducing the level of CSS-induced changes in the rat hippocampus.

The results of the study indicate that the CSS method can be considered as a basic translational model for in-depth characterization of the antidepressant effect of new molecules at the preclinical research stage.

# Additional Information

**Conflict of interest**

The authors declare the absence of a conflict of interests.

### Ethics statement

The experiment was approved by the Expert Council on Biomedical Ethics in Theoretical Disciplines of Bashkir State Medical University (BSMU, minutes No. 9, 2020).

### Data availability

Data corroborating the results of this study may be acquired by the corresponding author upon reasonable request.

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