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Hyperactivity and Abnormal Exploratory Activity Developing in CD-1 Male Mice under Chronic Experience of Aggression and Social Defeats

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Abstract

Chronic social defeat stress induces diverse effects in mice of different strains and even in animals of the same strain. This paper aims to study the effect of repeated social defeats and, for contrast, repeated aggression in daily agonistic interactions on the behaviors of CD-1 male mice. The behavior of animals that have the same winning and losing track record during 3, 10, 21 days is studied in different tests. The level of aggressiveness, as estimated by the number and total time of attacks, decreases; nevertheless, direct and indirect forms of aggression demonstrated by the aggressive mice (winners) remain significantly high. The number of stereotypic behaviors (rotations and jumps) and total time of digging behaviors are significantly increased in the winners after 21 days compared to 3 and 10 days of intermale confrontations. Among the losers, chronic experience of social defeats is accompanied by the development of pronounced anxiety and a depression-like state estimated by the elevated plus-maze and the Porsolt test scores, respectively. Both groups of male mice with alternative social behaviors demonstrate abnormal locomotor and exploratory behaviors in the open-field test. This phenomenon may be viewed as hyperactivity developed under chronic agonistic interactions and specific for the outbred CD-1 mice. We believe that these animals may be potentially used for modeling the key symptoms of bipolar disorder.

Keywords

Chronic Social Defeats, Repeated Aggression, Hyperactivity, Depression, Anxiety, CD-1 Mice, Model of Bipolar Disorder

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1. Introduction

Chronic social defeat stress (CSDS) is an etiologic factor which is used for the production of depression-like states in mice [1]-[3]. However, CSDS induces different effects in mice of different strains and even in animals of the same strain [4]-[6]. For example, CSDS for 21 days is accompanied by the development of pronounced anxiety- and depression-like states in male mice of the C57BL/6J strain [2] [3] and anxiety without depressive state in defeated mice of the CBA/Lac strain [4], which is genetically predisposed to the development of cataleptic-like behavior [7]-[9]. In other studies [5] [10], some defeated mice of the C57BL/6J strain are shown to be less susceptible to CSDS: in 40% - 50% of the defeated males, no depression-like behaviors are observed. Thus, genetically defined characteristics or susceptibility to stress affecting psychoemotional states may be responsible for the development of specific behavioral symptoms under chronic agonistic interactions and may serve as a tool for modeling different psychoneurological pathologies.

Our first behavioral observations of outbred CD-1 mice allowed us to suggest that chronic agonistic interactions may lead to the development of psychopathologies other than in the above-mentioned inbred mice. CD-1 mice are widely used in research as a common outbred stock in general multipurpose models, safety and efficacy testing, aging, surgical and pseudopregnancy models [11] [12]. CD-1 mice are also susceptible to spontaneous amyloidosis [13], which is accompanied by disease status, intrastrain aggression, self-trauma and skin lesions [14]-[16]. CD-1 mice are often used in pharmacological studies [17] [18]. In behavioral studies, these mice have demonstrated the highest levels of intermale, interfemale and maternal aggression [12] [19]. Moreover, in most studies, using CSDS as a psychogenic factor for modeling depressive-like states in the C57BL/6J mice, CD-1 male mice larger than the defeaters are used as aggressors [3] [10] [20]. The authors note that, although aggressive behavior is demonstrated by many sexually experienced CD-1 mice, the degree, quantitative and qualitative characteristics of aggression vary greatly. Only about half of all screened CD-1 mice can be used in the experiments [10]. Interestingly, in interstrain comparisons, the CD-1 mice are the ones that demonstrate the lowest level of anxiety [19]. Considering these data and recognizing the importance of this mouse stock for numerous research areas, this paper describes the effects of repeated experience of aggression accompanied by victories in the winners or social defeats in the losers in daily agonistic interactions on the behavior of outbred CD-1 mice.

2. Materials and Methods

2.1. Animals

The CD-1 male mice maintained at the conventional Animal Facility of the Institute of Cytology and Genetics, SD RAS (Novosibirsk, Russia) were used. The animals were housed under standard conditions (12:12 hr light/dark regime, switch-on at 8.00 a.m.; food (pellets) and water available *ad libitum*). Experiments were performed on 10 - 12 week-old mice, 38 - 40 g of body weight.

2.2. Ethical Approval

All procedures were in accordance with the European Communities Council Directive of November 24, 1986 (86/609/EEC). The study was approved by Scientific Council N 9 of the Institute of Cytology and Genetics SD RAS of March, 24, 2010, N 613.

2.3. Generation of Aggressive and Submissive Behaviors in Male Mice

Prolonged negative and positive social experiences (defeats and victories) in male mice were induced by daily agonistic interactions [21] [22]. Pairs of weight-matched animals were each placed in a steel cage (14 × 28 × 10 cm) bisected by a perforated transparent partition, which allowed the animals to see, hear and smell each other but prevented physical contact. The animals were left undisturbed for two days to adapt to the new housing conditions and sensory contact before they were exposed to encounters. Every afternoon (14:00 - 17:00 p.m. local time), the cage lid was replaced by a transparent one, and 5 mins later (the period necessary for individual activation), the partition was removed for 10 minutes to encourage agonistic interactions. The superiority of one of the mice was firmly established within two or three encounters with the same opponent. The winning mouse would attack, bite and chase the losing mouse, which would display only defensive behavior (sideways posture,

upright posture, withdrawal, lying on the back or freezing). As a rule, aggressive confrontations between males were discontinued by lowering the partition if the sustained attacks had lasted 3 min or less to prevent damage to the losers. Each defeated mouse (losers, defeaters) was exposed to the same winner for three days; afterwards, each loser was placed, once a day after the fight, in an unfamiliar cage with an unfamiliar winner behind the partition. Each victorious mouse (winners, aggressors) remained in its original cage. This procedure was performed for 21 days and yielded an equal number of winners and losers. Three groups of animals were used: 1) Losers: groups of chronically defeated mice on the third (Los3), tenth (Los10) and twentieth first (Los21) days of agonistic interactions; 2) Winners: groups of chronically victorious mice demonstrating daily aggression on the third (Win3), tenth (Win10) and twentieth first (Win21) days of agonistic interactions; and 3) Controls: the mice without any consecutive experience of agonistic interactions. The detailed description of this behavioral method is presented elsewhere [22].

2.4. Behavioral Tests

2.4.1. Agonistic Interaction Test

After 5 mins of activation, partitions were removed and the behavior of animals in the agonistic interactions test was video-recorded for 10 mins during the encounter, and the data were documented. Regarding behavioral domains, the following components of agonistic behaviors were observed in the aggressive mice in relation to the losers and registered during the third (Win3), tenth (Win10) and twentieth first (Win21) days during the 10-min test: 1) Attack: latency of the first attack, attacking, biting and chasing; 2) Aggressive grooming: the winner mounting the loser's back, holding it down and spending much time licking and nibbling at the scruff of the loser's neck (during aggressive grooming, the loser appeared fully immobilized or sometimes stretched out its neck and then again froze under the winner); 3) Digging: digging up and scattering the sawdust on the loser's territory (kick-digs: pulling the sawdust forward with the forepaws; push-digs: pushing the sawdust backward with the hind paws); 4) Hostile behavior: the total time spent attacking, aggressively grooming and digging; 5) Self-grooming: body care activities (fur licking, head washing, and nose washing); 6) Threats: tail rattling, jumps and rotations (quick and sharp turns). The total time and/or number of events, as well as the fraction of animals demonstrating aggressive grooming and threats, were also measured.

The behavioral domain analysis in defeated mice included the following components of submissive behavior during the third (Los3), tenth (Los10) and twentieth first (Los21) days of agonistic interaction with the winners during the 10-min test: l) Active defense: sideways and upright postures when under the attacks of the winner; 2) Escape: fleeing from the winners; 3) Immobility or passive defense behavior: freezing, full submission (posture "on the back"), immobility evoked by the winners' attacks or aggressive grooming; 4) Rearing in search for a way out of the cage; 5) Approaches to the winners; 6) Waiting: sitting at the corner or at the cage's wall and observing the winner's movements. The total time or/and number of events were also measured. To eliminate the differences in a partner's behavior, the percentage of each posture's duration of the total time of defensive behavior in the losers or aggressive behavior in the winners were calculated. The Observer XT, Version 7.0 (Noldus Information Technology, Wageningen, Netherlands) were used for analysis.

2.4.2. Partition Test

The partition test [23] was used to estimate the mice's behavioral response to a conspecific. Mice were placed into the experimental cage, with a transparent perforated partition dividing the cage into equal parts. The number of approaches to the partition and the total time spent near it (moving near the partition, smelling and touching it with one or two paws, clutching and hanging, putting noses into the holes or gnawing the holes) were scored during 5 mins as indices of reacting to the partner in the neighboring compartment of the common cage. The time during which the males showed sideways posture or were "turning away" near the partition was not included in the total time recorded. Additionally, the total time and number of rearings were measured. On the testing day, behavioral responses of the winners and losers toward each other were recorded for 5 mins.

2.4.3. Elevated Plus-Maze Test

The elevated plus-maze test [24] was conducted using a plus-maze consisting of two open arms (25 × 5 cm) and two closed arms (25 × 5 × 15 cm). The two arms of each type were opposite to each other and extended from a central platform (5 × 5 cm). The floor and sidewalls of the maze were of gray opaque plexiglas material. The

maze was elevated to a height of 50 cm above the floor. Five minutes before exposure to the plus-maze, the standard cover of the mouse-containing cage was replaced by a transparent cover. The mouse was placed at the center of the plus-maze with its nose towards the closed arm. The following parameters of behavior were recorded during 5 mins: 1) Total entries; 2) Open-arm entries (four paws in open arm), closed-arm entries (four paws in closed arm), and central platform entries; 3) Time spent in open arms, closed arms, and central platform; 4) The number of passages (transition) from one closed arm to another; 5) The number of head dips (looking down toward the floor below the plus-maze); and 6) The number of peepings when the mouse was in closed arms (mouse extended its head from the closed arm and returned quickly back). Indices 1 and 4 were related to locomotor activity; indices 2 and 3, to anxiety level; and indices 5 and 6 to risk assessment behavior. The numbers of entries to the closed arms, open arms, and to the central platform were calculated as percentages of the total entries, and periods spent in the closed arms, open arms, and in the central platform were calculated as percentages of the total testing time. The plus-maze was placed in a dimly lit room and thoroughly cleaned between sessions.

2.4.4. Open-Field Test

The open-field test [1] was carried out in a 9 × 9 square blue-painted 100 × 100 cm plexiglas open field. It was illuminated by a 150 W electric lamp, 150 cm above the floor. Mice were placed carefully in the center of the field and the following behavioral parameters were recorded for 5 mins: 1) Latency of first movement from center (sec.); 2) Number of crossed squares; 3) Number and total time (sec.) of rearing; and 4) Number of self-groomings. Between the sessions, the open field was thoroughly washed with water and dried with napkins.

2.4.5. Porsolt Test

In the Porsolt test [25] each male was placed in a glass beaker (16.5 cm height, 11 cm inner diameter) containing 10 cm of water at $t = (25 \pm 1)^{\circ}C$ for a 5-min period. The total time of full immobility without any movements, total time of active avoidance (active behavior), as well as the time of drift (the time during which the mouse slowly moved around the beaker, moving one or two paws and supporting its body on the surface of the water) were recorded. Latency of first demonstration of full immobility during 5 sec. (without any movement) was also recorded. Between the sessions, the water was changed in the glass beaker.

2.5. Statistical Analysis

One-way ANOVA was used to reveal any significant influence of the factors “experience of aggression” (days) (Win3, Win10, Win21) or “experience of defeat” (days) (Los3, Los10, Los21) on the mice behavior in the agonistic interactions and partition tests. Additionally, one-way ANOVA was used to reveal any significant influence of the factor “groups” (control, Win21, Los21) on the different forms of mice behavior in the plus-maze and open-field tests. A post hoc pair wise comparison of the groups was made using the Bonferroni or LSD tests. For comparison of the behaviors (Win3 vs. Los3; Win10 vs. Los10; and Win21 vs. Los21 in the partition test, and the controls vs. Los21 in the Porsolt test), the *t*-test was used. The percentage of animals demonstrating aggressive groomings and threats in the agonistic interactions test was analyzed using the chi-square test. The Spearman correlational analysis was performed within every group of the winners in the agonistic interactions and partition tests. The behavioral structure was estimated in the 2nd, 10th and 21th tests as the percentage of the total time of the aggressive grooming, attacking, digging and self-grooming behavior for the winners, and as the percentage of the total time of active defense, waiting, escape and immobility in the losers. The data were reported as mean ± SEM ($n = 10$ - 14 per group).

3. Results

3.1. Agonistic Interactions Test

3.1.1. Winners

On day one, all male mice demonstrated agonistic behavior in 100% of cages: 8 pairs fought on par. On day two, 2 pairs fought on par, and on day three, 1 pair did. Three days later, the status of the winner and the loser became obvious. On the following days, throughout the entire experimental period, none of the males stopped fighting and no cases of inversion of the aggressive and submissive types of behavior on the opposite one were observed. Every day during the agonistic interactions tests the winners demonstrated strong aggression—described as those groups of chronically victorious mice that demonstrated daily aggression on the third (Win3),

tenth (Win10) and twenty first (Win21) days of agonistic interactions—were studied.

One-way ANOVA revealed the influence of the factor "experience" (days) on the number (F (2, 39) = 7.72; p < 0.001) and total time (F (2, 39) = 7.78; p < 0.001) of attacks, the total time of digging (F (2, 39) = 3.59; p < 0.037) and hostile behavior (F (2, 39) = 3.73; p < 0.033), the number of jumps (F (2, 39) = 4.80; p < 0.014) and rotations (F (2, 39) = 4.92; p < 0.012), and the sum of jumps and rotations (F (2, 39) = 5.21; p < 0.010). The post hoc Bonferroni test revealed significant differences (**Table 1**) in the following comparisons: Win3 vs. Win10 for the number (p < 0.005) and total time (p < 0.010) of attacks; Win3 vs. Win21 in the number (p < 0.004) and total time (p < 0.002) of attacks, and total time of digging behavior (p < 0.040); in the number of rotations (p < 0.025), jumps (p < 0.019) and sum of jumps and rotations (p < 0.016); and Win10 vs. Win21 for the number of rotations (p < 0.034) and sum of jumps and rotations (p < 0.039). Additionally, the Fisher LSD test revealed significant differences in the following comparisons: Win3 vs. Win10 and Win21 for the total time of hostile behavior (p < 0.026 and p < 0.022, respectively) and Win10 vs. Win21 for the number of jumps (p < 0.021). There were no differences in the latency of first attack between all groups of comparison because of large variability (**Table 1**).

In Win21, correlational analysis showed that the total time of attacks correlated positively with the total time of hostile behavior (R = 0.687; p < 0.007) and negatively with the sum of jumps and rotation (R = −0.566; p < 0.035) and latency of first attacks (R = −0.786; p < 0.001); additionally, the total time of hostile behavior correlated negatively with the latency of first attacks (R = −0.626; p < 0.002). As **Figure 1** shows, the prevailing behavior during agonistic interactions with the losers in all periods of confrontations was direct aggression (at-

Table 1. Behavior of aggressive male mice with 3 (Win3), 10 (Win10), 21 (Win21) days of agonistic interactions.

Behavioral parameters	Win3			Win10			Win21		
Latency of first attack, sec.	35.1	±	9.0	87.0	±	29.3	134.4	±	54.6
Attacks, N	26.1	±	2.9	13.5	±	2.6**	13.3	±	2.4**
Attacks, sec.	100.9	±	9.3	60.1	±	9.3**	53.1	±	9.2**
Diggings, N	7.1	±	1.1	8.8	±	1.9	13.9	±	2.9
Diggings, sec.	6.0	±	1.0	10.2	±	3.1	21.0	±	6.3*
Hostile behaviors, sec.	115.1	±	11.9	80.9	±	9.7*	80.1	±	9.2*
Jumps, N	1.6	±	0.9	3.1	±	1.0	10.6	±	3.6*+
Rotations, N	1.1	±	0.3	1.4	±	0.4	6.3	±	2.2*+
Jumps + rotations, N	2.8	±	1.1	4.5	±	1.4	16.9	±	5.6*+
Self-grooming, sec.	18.9	±	5.2	12.5	±	2.9	10.6	±	4.7
Aggressive grooming, %	1/14			4/14			3/14		
Threats, % males	10/14			7/14			9/14		
N animals	14			14			14		

Note: *p < 0.05; **p < 0.01 vs. Win3; +p < 0.05 vs. Win10.

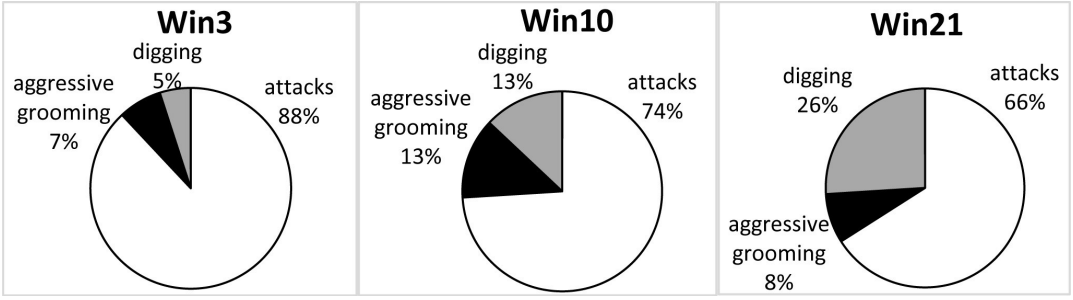

Figure 1. Structure of the behavior of Win3, Win10, and Win21 after the third, tenth and twentieth first days (respectively) of agonistic interactions expressed as the percentage of the total time of attacks, diggings and aggressive groomings. The structure of aggressive behavior in the winners did not change during all experimental periods. During most of the test time, winners demonstrated attacks or diggings.

tacks). Total time of digging behavior progressively increased from test to test of agonistic interactions.

3.1.2. Losers

A loser behavior became obvious after 3 days of agonistic interactions. Losers—described as those groups of chronically defeated mice on the third (Los3), tenth (Los10) and twenty first (Los21) days of agonistic interactions—were studied. In the first confrontations, the losers demonstrated mostly active defense and rearing in search for a way out of the cage. After a prolonged experience of defeats, the main behaviors were immobility and waiting. There were no differences between behaviors of Los10 and Los21.

One-way ANOVA revealed a significant influence of the factor "experience" (days) on the number (F (2, 38) = 30.60; $p < 0.0001$) and total time (F (2, 38) = 156.91; $p < 0.0001$) of active defense; on the number (F (2, 38) = 4.52; $p < 0.017$) and total time (F (2, 38) = 6.01; $p < 0.005$) of escape behavior, and on the number (F (2, 38) = 47.76; $p < 0.0001$) and total time (F (2, 38) = 23.89; $p < 0.0001$) of immobility behavior (**Table 2**). The post hoc Bonferroni test revealed significant differences in the following comparisons: Los3 vs. Los10 and Los21 for the number (for both comparisons $p < 0.0001$) and total time (for both comparisons $p < 0.0001$) of active defense and number and total time (for both comparisons $p < 0.0001$) of immobility behavior and Los3 vs. Los21 for the number ($p < 0.021$) and total time ($p < 0.004$) of escape behavior. Additionally, the Fisher LSD test revealed significant differences in Los3 vs. Los10 for the number of escape behavior ($p < 0.031$) and between Los10 vs. Los21 for immobility behavior ($p < 0.025$). There was no influence of the factor "experience" on the losers' approaches, rearing and waiting behaviors (**Table 2**). As **Figure 2** shows, the prevailing behavior during

Table 2. Behavior of the losers with 3 (Los3), 10 (Los10), 21 (Los21) days of agonistic interactions.

Behavioral parameters	Los3			Los10			Los21		
Active defense, N	18.8	±	2.3	5.6	±	1.1***	2.6	±	0.6 ***
Active defense, sec.	124.4	±	8.5	11.5	±	2.8***	4.9	±	1.5 ***
Escape, N	4.7	±	1.6	10.3	±	1.8*	11.9	±	2.0 *
Escape, sec.	11.0	±	3.1	20.4	±	3.0	30.5	±	5.5 **
Approach, N	5.7	±	1.3	6.8	±	1.7	3.5	±	1.0
Approach, sec.	20.2	±	6.3	28.8	±	9.0	10.5	±	3.3
Rearing, N	21.3	±	3.9	20.1	±	2.4	22.8	±	1.9
Rearing, sec.	60.9	±	13.3	45.4	±	7.1	46.1	±	4.1
Immobility, N	13.6	±	1.1	28.8	±	1.8***	33.8	±	1.6 ***+
Immobility, sec.	72.2	±	12.2	222.4	±	23.4***	214.5	±	14.1***
Waiting, N	5.3	±	0.8	7.1	±	1.6	9.8	±	1.6
Waiting, sec.	40.8	±	8.0	64.9	±	19.6	60.8	±	12.7
N animals	14			14			13		

Note: $^{*}p < 0.05$; $^{**}p < 0.01$, $^{***}p < 0.01$ vs. Los3; $+p < 0.05$ vs. Los10.

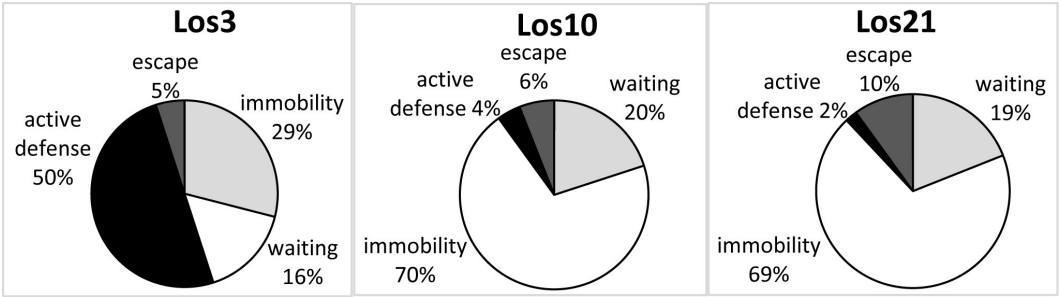

Figure 2. Structure of the behavior of Los3, Los10, and Los21 after the third, tenth and twentieth first days (respectively) expressed as the percentage of the total time of active defense, immobility, waiting and escape. In the first confrontations, the losers demonstrated active defense behavior; after 10 and 21 days of experience of defeats, the losers demonstrated immobility behavior.

agonistic interaction was active defense in Los3 and immobility in Los10 and Los20.

3.2. Partition Test

One-way ANOVA did not reveal a significant influence of the factor "groups" of the winners (control, Win3, Win10, and Win21) on all parameters of partition behavior, *i.e.* the number of approaches and total time spent near the partition as well as number of events and the total time of rearing behavior. Among the losers, one-way ANOVA revealed a significant influence of the factor "groups" (controls, Los3, Los10, and Los21) on the total time spent near the partition (F (3, 50) = 4.61; $p < 0.006$) and the number (F (3, 50) = 3.56; $p < 0.020$) and total time (F (3, 50) = 4.67; $p < 0.006$) of rearing behavior.

The post hoc Bonferroni test revealed differences (**Figure 3**) in the following comparisons: controls vs. Los3 ($p < 0.037$), Los10 ($p < 0.009$) and Los21 ($p < 0.027$) for the total time spent near the partition and controls vs. Los3 for the number ($p < 0.014$) and total time ($p < 0.003$) of rearing behavior. Additionally, the Fisher LSD test revealed significant differences when comparing the controls vs. Los10 ($p \leq 0.05$) and Los21 ($p < 0.016$) for the total time of rearing behavior. Student's t-test for independent samples revealed significant differences in the comparison of Win3 vs. Los3 ($t = 3.92$; $p < 0.001$), Win10 vs. Los10 ($t = 4.30$; $p < 0.001$), Win21 vs. Los21 ($t = 2.82$; $p < 0.009$) for total time spent near the partition.

In Win10 (but not in Win3 and Win21), the correlational analysis showed that the number of attacks correlated positively with the number ($R = 0.585$; $p < 0.028$) and total time ($R = 0.670$; $p < 0.009$) spent near the partition; total time of attacks correlated positively with the total time spent near the partition ($R = 0.620$; $p < 0.018$) and latency of first attacks correlated negatively with number of approaches to the partition ($R = -0.624$; $p < 0.017$).

3.3. Elevated Plus-Maze Test

Behavioral observations showed that mice from all groups (controls, Win21, Los21) were calm during the test. In the first minutes of the test, the losers spent much time in the center, quickly exiting and entering the closed arms and not daring to enter the open arms. Later, the mice began to explore the open arms. Soon after the beginning of the test, the controls started exploring both the closed and open arms. All groups reached the end of the open arms, although the losers preferred to stay in the closed arms and the center of the plus-maze.

One-way ANOVA revealed a significant influence of the factor "groups" (controls, Win21, Los21) on the number of closed-arm entries (F(2, 32) = 3.85; $p < 0.032$), open-arm entries (F(2, 32) = 4.70; $p < 0.016$), number of passages (F (2, 32) = 6.12; $p < 0.006$) and total entries (F(2, 32) = 8.50; $p < 0.001$). The post hoc Bonferroni test revealed (**Table 3**) an increased number of total entries in Win21 and Los21 in comparison with the controls ($p < 0.012$ and $p < 0.001$, respectively). In Los21, the number of closed-arm entries was significantly larger ($p < 0.035$) and the number of open-arm entries was significantly smaller ($p < 0.019$) in comparison with Win21. The

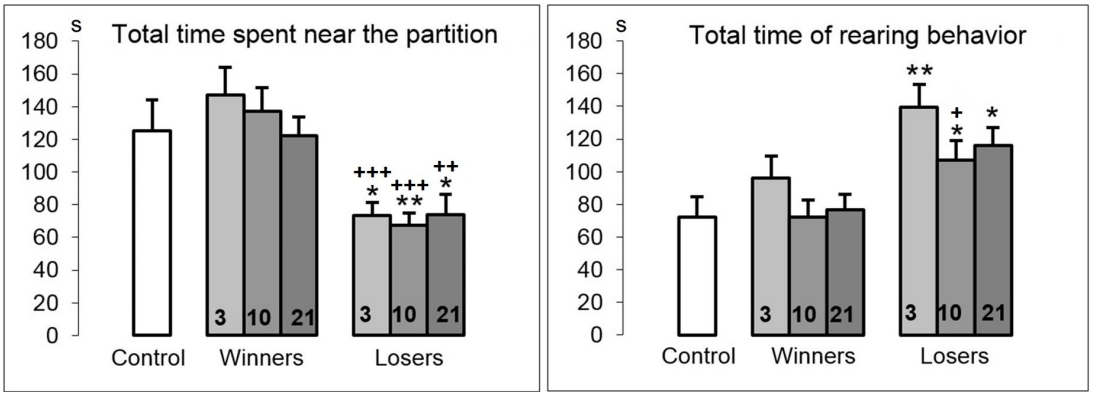

Figure 3. Total time spent near the partition as reaction to the partner in the neighboring compartment of the common cage and total time of rearing behavior of the winners and losers after 3, 10, 21 days of agonistic interactions. Total time spent near the partition decreased in the losers in comparison with the other experimental groups. Total time of rearing behavior was significantly higher in the losers in comparison with the controls. Results were indicated as follows: *$p < 0.05$; **$p < 0.01$ vs. the control; +$p < 0.05$; ++$p < 0.01$; +++$p < 0.001$ vs. winners of respective groups; $n = 14$ for each group.

Table 3. Behavior of the controls, Win21 and Los21 in the elevated plus-maze test.

Behavioral parameters	Control			Win21			Los21		
Closed arm entries, %	28.9	±	2.1	26.7	±	3.4	37.1	±	2.2+
Closed arm time, %	38.5	±	3.6	36.2	±	5.1	42.8	±	3.2
Central platform entries, %	49.1	±	0.5	49.4	±	0.5	49.7	±	0.4
Central platform time, %	32.7	±	1.6	36.9	±	2.6	40.2	±	2.5*
Open arm entries, %	21.9	±	2.1	23.9	±	3.2	13.2	±	2.04*+
Open arm time, %	28.8	±	3.8	26.9	±	4.0	16.9	±	3.3*
Total entries, N	26.0	±	1.3	36.5	±	2.9*	40.0	±	2.6***
Passages, N	2.9	±	0.5	3.5	±	1.0	6.8	±	0.8**+
Peepings, N	2.2	±	0.5	2.4	±	0.6	1.6	±	0.5
Head-dips, N	16.2	±	3.5	25.2	±	4.3	20.6	±	4.4
N mice	11			13			11		

Note: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ vs. control; $+p < 0.05$ vs. Win21.

number of passages was increased in Los21 compared to the controls and Win21 ($p < 0.009$ and $p < 0.022$, respectively). Additionally, the LSD test revealed differences between the controls and Los21 in open-arm entries ($p < 0.028$), open-arm time ($p < 0.037$) and central platform time ($p < 0.034$).

3.4. Open-Field Test

One-way ANOVA revealed a significant influence of the factor "groups" (controls, Win21, Los21) on the number of crossed squares (F (2, 37) = 13.78, $p < 0.0001$), number (F (2, 37) = 7.92, $p< 0.001$) and total time of rearing (F (2, 37) = 5.74, $p < 0.007$), and number of self-groomings (F (2, 37) = 3.27, $p < 0.049$). The post hoc Bonferroni test revealed significant differences (**Figure 4**) in the following comparisons: the controls vs. Los21 and Win21 (both $p < 0.0001$) for the number of crossed squares, the controls vs. Los21 ($p < 0.003$) and Win21 ($p < 0.005$) for the number of rearings, and controls and Los21 ($p < 0.044$) for the number of self-groomings. Thus, the number of crossed squares and number of rearings were increased and the number of self-groomings was decreased in the winners and losers in comparison with the controls. Behavioral observations showed that mice from all groups demonstrated rigid elevated tails in the open-field test. Tail position was approximately 30 - 45 relative to the body, and the angle of tail elevation was highest among the winners.

3.5. Porsolt Test

Student's t-test revealed significant differences in total time of immobility between the controls and Los21 (t = 2.26; $p < 0.034$); in Los21, this parameter was larger than in the controls (**Figure 5**). No differences in the latency of first full immobility, total time of active behavior and drift were found.

4. Discussion

On day one of this experiment, all CD-1 male mice displayed agonistic behavior in 100% of cages. Three days later, the status of the winners and losers became obvious. On the following days, there were no inversions of aggressive and submissive behaviors. Every day, the winners demonstrated aggression during all experimental periods. The scores estimating the aggressiveness in male mice—the total time and number of attacks and the total time of hostile behavior (the sum of the total time of attacks, diggings and aggressive grooming)—decreased in the CD-1 winners. On the one hand, the decrease in aggressiveness scores could be a consequence of changes in the behavior of the losers: the active defense and escape behaviors demonstrated by the losers in the first agonistic interactions stimulated the aggression in the attacking males. Thereafter, the behavior of the losers became passive and submissive (immobility, freezing and waiting), which inhibited aggression in the winners. As a result, the active forms of offensive aggression were partly replaced by aggressive grooming and indirect aggression, *i.e.* digging in the losers' territories. However, as our results show during agonistic interactions, the

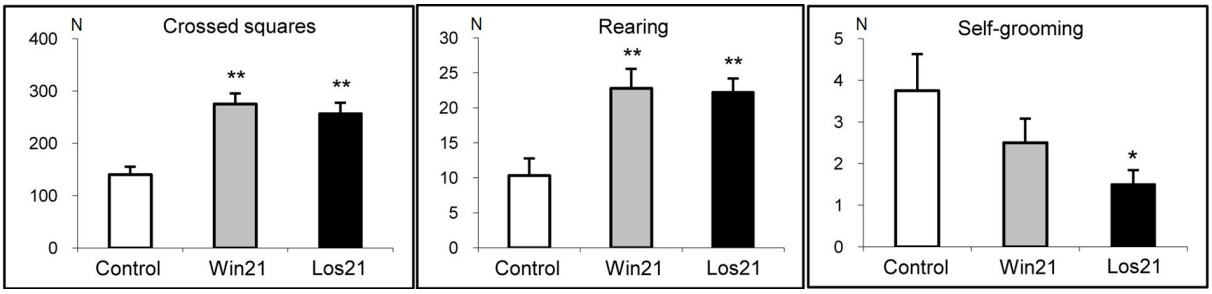

Figure 4. Behavior of Win21 and Los21 after 21 days of agonistic interactions in the open-field test. Winners and losers demonstrated hyperactivity and enhanced exploratory activity as estimated, respectively by enhanced number of crossed squares and number of rearings in comparison with the controls. $^{*}p < 0.05$; $^{**}p < 0.01$ vs. the control; $n = 12 - 14$.

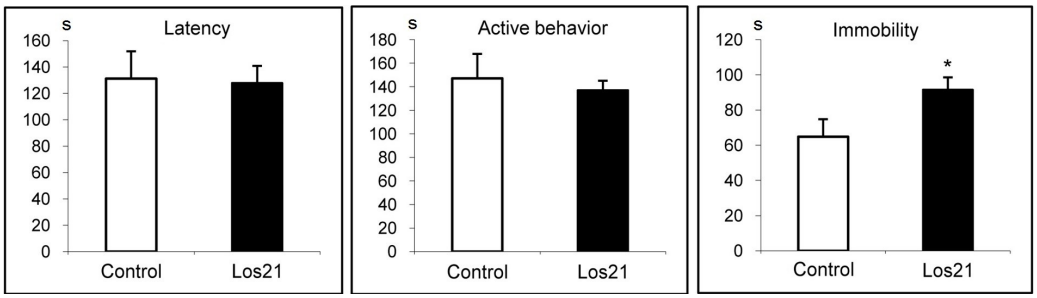

Figure 5. Behavior of Los21 after 21 days of agonistic interactions in the Porsolt test. Immobility time indicating a depression-like state increased in the losers. Results were indicated as follows: $^{*}p < 0.05$ vs. control, *t*-Student test; $n = 11 - 14$.

structure of the aggressive behavior in the winners did not change. Most of time during the test they demonstrated attacks or diggings. On the other hand, an increased number of jumps and rotations indicated the development of a locomotor abnormality manifested in repeated stereotypic behaviors, which could affect all the other forms of behavior. The significant negative correlation found between the total time of attacks and the sum of jumps and rotations in Win21 might support this assertion. Similarly with Win21, Win10 demonstrated strong aggression, but their number of jumps and rotations did not differ from those of the controls. Repeated stereotyped behaviors, which were rarely observed in the controls, could be attributed to the development of a psychopathology in the winners [26]. Overactive behaviors such as abnormal exploratory behavior and locomotor hyperactivity were displayed by the winners in the plus-maze and open-field tests. The number of crossed squares and rearing in the open-field test as well as the total number of entries in the elevated plus-maze test were significantly larger in the winners compared to the controls. Similar to earlier data on mice of other strains [23], there were significant correlations between the aggressiveness and partition test scores in the CD-1 winners. This means that the partition test could serve as a tool for measuring the expression of aggression motivation before agonistic interactions in male mice. Thus, in the winners, repeated experiences of aggression led to the development of severe aggressiveness, hyperactivity and abnormal exploratory activities and a high level of repeated locomotor patterns or stereotypes (jumps and rotations). Most of these changes manifested themselves under a prolonged (21 days) experience of aggression.

The expressed behavioral changes were observed in the losers with a repeated experience of social defeats. In the first confrontations, the losers demonstrated an active defense behavior and, after 10 and 21 days of defeat experience, an immobility behavior. In the plus-maze immediately after the start of the test, the losers spent much time in the central platform, quickly exiting and entering the closed arms, not daring to enter the open arms. Later the mice began to explore the open arms. Pronounced anxiety was found in the losers as estimated by the increased number of closed arm entries, decreased number of open arm entries and open arm time expressed in the percentages of total test time or number of entries. The controls explored both the closed and open arms. The total time spent near the partition as a reaction to a partner in the neighboring compartment in a common cage, which might be used as a measure of the level of communication, was significantly shorter in the losers compared to the winners and controls. Thus, both tests indicated an increased anxiety-like state in the defeated mice.

Surprisingly, the CD-1 losers displayed locomotor hyperactivity (*i.e.* an increased number of rearings and crossed squares in the open-field test, an increased number of passages and total entries in the plus-maze test and the number of rearings in the partition test) compared to the controls. A decrease in self-grooming behavior in the losers compared to the controls in the open-field test could be attributed to an increase in escape motivated behaviors (rearing) in stressful conditions and hyperactivity. The Porsolt test revealed an increased time of immobility in the losers compared to the controls, which could indicate the development of a depression-like state. Thus, CSDS seemed to lead to the development of pronounced anxiety, depression, and locomotor and exploratory hyperactivity in the losers. The analysis of behavioral changes in mice with alternative social behaviors indicated different mechanisms of hyperactivity development, which could be accompanied by pronounced anxiety and a depression-like state in the losers and by neurological symptoms (stereotypic behavior) without anxiety in the winners.

Previously, in a similar battery of tests, we studied the effects of chronic agonistic interactions on the behavior of mice from the C57BL/6J, CBA/Lac and DBA/2 strains [4] [26]-[28]. After three weeks of intermale confrontations, the level of aggressiveness was higher in the CD-1 mice compared to those from other strains. In the C57BL/6J and CBA/Lac winners (but not in the CD-1 winners), an increase in aggressive motivation was found as estimated by the partition test and the development of pronounced anxiety [27] [29], as estimated by the plus-maze test. DBA/2J winners demonstrated reduction of anxiety in the plus-maze test, whereas the CD-1 winners showed no changes in anxiety level. Earlier on, after E.B. Barratt's work with aggressive humans [30], we assumed that aggressiveness and anxiety in mice of different strains could be associated with orthogonal dependence.

Hyperactivity scores from the open-field test, estimated as the number of crossed squares, were similar in the DBA/2 and CD-1 winners; these strains also showed significantly higher scores than those of aggressive mice from other strains. After a prolonged experience of aggression, all winners demonstrated stereotyped locomotor patterns (jumps and rotations), which were almost never demonstrated by the losers and controls. However, in the DBA/2J winners, hyperkinesia manifested most frequently in the form of sudden involuntary head movements (jerks) [28].

In the C57BL/6J, CBA/Lac, and CD-1 losers, a prolonged exposure to CSDS led to increased immobility behavior in all tests, a decrease in communications in the partition test, and the development of pronounced anxiety as estimated by the plus-maze scores. The development of depressiveness in the Porsolt test was observed in the C57BL/6J and CD-1 losers but not in the CBA/Lac losers. Similarly to other strains, in the DBA/2J losers, exploratory behavior and locomotor activity in the open-field test did not change under repeated defeats, and no signs of depressiveness were detected in the Porsolt test [31]. Supposedly, the DBA/2J losers were less sensitive to CSDS than the mice of other strains. The CD-1 losers demonstrated a unique combination of hyperactivity—high exploratory and locomotor activities, pronounced anxiety and depressiveness.

Hyperactivity is a symptom of bipolar disorder, which is characterized by alternate episodes of depression and mania [32]. Mania periods are characterized primarily by overactive behavior [33] manifested as a variety of complex and multifaceted symptoms that challenge clear clinical distinctions. Such symptoms include overactivity, hypersexuality, irritability, and reduced need for sleep accompanied by cognitive deficits recently linked to functional outcomes [34]. In animal models for bipolar disorder [34]-[38], a mania-like state can be induced by psychostimulants such as amphetamine and methylphenidate, cardiac glycoside ouabain [39]-[45], sleep deprivation accompanied by hyperactivity, irritability, aggressiveness, hypersexuality, and stereotypes [46]-[48]. Additionally, genetically modified animals including mice with targeted mutations of the glutamate receptors, Clock gene, dopamine transporter, or transgenic mice were used for the modeling of the mania-like state [36], [49]-[54]. A comparative analysis of four mouse strains (Black Swiss, C57Bl/6, CBA/J and A/J) in a battery of tests showed a manic-like behavior in the Black Swiss strain [43]. The MNS mice derived via multiple rounds of selection from the outbred ICR mice proved to be an appropriate complex mania model adding sexual dimorphism, an altered diurnal activity profile, and seasonality to the set of interesting dispositional phenomena related to mania [55].

We believe that outbred CD-1 mice that demonstrated, under repeated experiences of aggression and defeat, several patterns of mania and depression simultaneously may be potentially used for modeling the key symptoms of bipolar disorder. The unique behavioral changes observed in the losers and winners might also be useful for pharmacological screening of novel drugs and for the study of molecular, cellular, and genetic mechanisms of hyperactivity. Moreover, when comparing the effects of repeated social experience of aggression and defeats

in mice of different strains, we can gain insights into the hereditary predisposition to behavioral disorders that occur in male mice exposed to long-term agonistic interactions.

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