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Impulsivity and aggressive behavior in Roman high and low avoidance rats: Baseline differences and adolescent social stress induced changes

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ABSTRACT

Adverse and stressful experiences during adolescence are often of a social nature. The social defeat model in rats is used as an animal model for bullying in humans. Usually large individual differences in response to social defeat are found. The personality type that is mostly affected and the underlying mechanisms are unknown. We used male rats of the Roman selection lines to test whether social defeat (between postnatal days 45 and 57) followed by social isolation has a different impact in animals with divergent levels of emotional reactivity and coping style. The level of offensive aggression, impulsivity and performance during frustrating non-reward (extinction) were used as measures for the adult coping style of animals. Impulsivity was measured by performance on an unpredictable operant conditioning schedule (variable interval-15, VI-15) for food reinforcement.

This study demonstrates that the adult, baseline level of impulsivity is higher in Roman high avoidance (RHA) rats. RHA rats showed a higher number of lever presses compared to Roman low avoidance (RLA) rats on a VI-15 schedule. The level of offensive aggression did not differ between the two lines. Surprisingly, a tendency towards more offensive aggression in RLA rats was found.

Social stress during adolescence disturbed the normal development of adult personality, mostly in RHA rats. RHA rats that were defeated during adolescence reduced the number of lever presses on the VI-15 schedule of reinforcement and were more persistent during a session of frustrating non-reward. However, we did not find an effect of social defeat on performance during extinction. A tendency towards increased attack latencies after social defeat in adolescence was found. The time spent on offensive aggression was unaffected by social defeat.

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1. Introduction

Adolescence is a period in life during which there is a steep increase in the incidence of psychopathologies such as depression [1], anxiety disorders [2] as well as substance abuse and addiction [3–6]. Among many developmental factors that contribute to this early onset of psychopathology, exposure to uncontrollable stress during adolescence may be particular relevant [7,8].

An important source of social stress in adolescents is being the victim of bullying and harassment. Bullying is associated with the development of severe symptoms of mental health problems, which are frequently long-lasting [9,10]. However, large individual differences in the consequences of bullying are found. Some victims do not suffer from any negative consequences after experiencing bullying, whereas others report severe negative emotions [11]. This is consistent

with the general notion that individual differences in sensitivity to stress and coping capacity are critical in the development of psychopathologies both in humans and in animals [12,13]. The mechanisms underlying those individual differences in susceptibility to the consequences of bullying are poorly understood.

In the current study, social defeat followed by social isolation was used as stressor in adolescent rats. This paradigm can be regarded as an animal model of bullying in humans [14]. Social defeat in adolescence has been shown to induce long-term behavioral changes, such as increased anxiety [15–19], a reduced behavioral response to amphetamine in adulthood [20], and an accelerated onset of adult-like agonistic behavior [21–23].

Similar to the consequences of bullying in humans, there are large individual differences in the response to social defeat in animals as well. Some animals appear to be more resistant to social stress than others. The emotional response to social stress might be a key factor in determining the long-term consequences of social defeat stress. Therefore, we used rats of the Roman selection lines to test whether social defeat has a different impact in animals with distinct levels of emotional reactivity and sensitivity to stressors [24].

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The proactive coping Roman high avoidance (RHA) rats have been selected for a high level of active avoidance in a two-way shuttle box task, whereas Roman low avoidance (RLA) rats show a more passive response in this task [25,26]. RLA rats show more pronounced emotional responses and increased activation of the hypothalamus–pituitary–adrenal (HPA) axis in response to stress compared to RHA rats [27,28]. On the other hand, RHA rats tend to be more impulsive [29,30] during operant behavioral conditioning tasks for food reinforcement [30].

The current experiment was aimed at testing the baseline differences in impulsivity and aggression in RHA and RLA rats and the adult consequences of social stress during adolescence on impulsivity and aggression. We hypothesized higher baseline levels of offensive aggressive behavior and impulsivity in RHA rats compared to RLA rats. Based on the increased anxiety levels after adolescent social stress observed by others [15,31], we expected a general decrease in impulsive and aggressive behavior in defeated rats of both strains. To test these hypotheses, we used a standard resident–intruder paradigm and an unpredictable (variable interval 15, VI-15) operant conditioning schedule for food reinforcement. Furthermore, extinction of lever-press behavior was used to determine performance during frustrating non-reward. We expected socially defeated animals to be less persistent during the extinction session compared to control animals.

2. Materials and methods

2.1. Animals

Breeding pairs of the Roman selection lines were obtained from a breeding colony at the Clinical Psychopharmacology Unit (APSI), University of Geneva, Switzerland. Roman High Avoidance rats and Roman Low Avoidance rats were bred under laboratory conditions in our own facilities. Rats were weaned at post natal day (pnd) 21 and housed in groups of four until the start of the experiment.

Animals were housed in temperature-controlled rooms ($21 \pm 2^\circ\text{C}$) under a 12 h light:dark cycle (lights off at 12 am). Water was available *ad libitum* throughout the experiment, food was restricted during operant conditioning tests, but was otherwise available *ad libitum*. Experiments were approved by the Groningen University Committee on Animal Experiments.

2.2. Experimental design

Rats of the Roman selection lines were defeated during adolescence (pnd 45–57). At an age of 4 months, animals were tested for the level of offensive aggression using a resident–intruder paradigm. After the resident–intruder paradigm, impulsive behavior was measured by an unpredictable operant conditioning schedule for food reinforcement and extinction of lever pressing behavior.

2.3. Adolescent social defeat

The resident–intruder paradigm was used for the social defeat. A similar procedure has been used in previous experiments in our laboratory [15]. Resident rats of the Wild-type Groningen (WTG) strain were housed with a tubally-ligated female in large observation cages ($80 \times 55 \times 50$ cm) to facilitate territorial aggression. Before the social conflict, females were removed from the cage of the residents. Residents were trained to rapidly and consistently attack naïve intruders and only those with attack latencies shorter than 2 min were used for the experiment. By using animals with a more or less similar readiness to attack, we tried to avoid variation in attack intensity.

Adolescent rats were subjected to social defeat at pnd 45 and 48 with direct physical contact for 10 min, thereafter animals were placed in a wire mesh cage ($31 \times 15 \times 15$ cm) for 50 min in the cage

of the resident. In this way, animals were protected from further attacks and injury, but remained in visual, auditory and olfactory contact with the resident. This period of psychosocial stress is known to be highly adverse [32]. On pnd 51, 54 and 57 animals were psychosocially stressed by placing them in the residents' cage for 15 min. Control animals were placed in a clean cage at corresponding days and times compared to defeat animals. Defeated animals were solitary housed after the first defeat for the rest of the experiment.

2.4. Resident–intruder test

The experimental animals were tested for aggressive behavior between pnd 120 and pnd 130. Animals were housed in large observation cages ($80 \times 55 \times 50$ cm) with an oviduct-ligated female of the corresponding (selection) line for one week to avoid social isolation and facilitate territorial behavior. After one week, the baseline level of aggressive behavior was tested in the resident–intruder test. Females were removed from the test cage prior to testing. During the first three tests an unfamiliar male conspecific (Wistar intruder) was introduced into the cage and the attack latency (time between introduction of the intruder and first attack) was scored. The intruder was removed after the first attack. If no attack occurred within 10 min the intruder was removed. During the fourth test the full range of behaviors was scored during 10 min. The frequency and duration of behavioral elements were scored. A total of 10 behavioral acts and postures were scored and grouped in 5 behavioral categories: 1) *Offense* (lateral threat, clinching, keep down, chasing, upright posture); 2) *Social exploration*; 3) *Non-social exploration* (ambulation, rearing); 4) *Inactivity*; 5) *Self-grooming*. The behavioral data of the last test and the four attack latencies were used to classify the offensive behavior of animals.

2.5. Operant conditioning

Skinner-box equipment (Med Associates Inc., St. Albans, VT) was installed in the home cage ($45 \times 30 \times 50$ cm) of animals with sawdust as bedding material. By testing animals in their home cage, we avoided handling and transport prior to testing and the behavior could be recorded undisturbed [33]. One retractable lever was located next to a food receptacle. Food receptacle entrances were detected with an infrared detector located inside the food receptacle. A food dispenser distributed 45 mg food pellets (Dustless Precision Pellets, Product# F0165; Bioserv, Frenchtown, NJ, USA). The training schedules and online data collection were controlled by a computer and an interface (MedPC, Med Associates Inc.) located outside the animal rooms. At the start of the operant conditioning phase, animals were housed in the operant conditioning cages.

Normal chow was removed one day prior to operant testing. Animals were tested daily and remained in the operant conditioning cages throughout the experiment.

At first, animals were trained to lever press using a fixed-ratio 1 (FR-1) schedule of reinforcement. During these sessions, each lever press resulted in the delivery of one food pellet into the food receptacle. After one week of FR-1 training, the schedule was changed to a variable-interval 15 (VI-15) schedule for one week. During this schedule, the first lever press resulted in a reward, after which a random refractory period started, lasting between 2 and 32 s, during which the animal could press the lever, but did not receive a reward. At the end of the VI-15 schedule an extinction session was done during which the tubing of the food delivery was disconnected from the cage, but all secondary cues were maintained. This session lasted for 1 h, at the same time as reinforced sessions took place.

The body weight of animals was gradually decreased to 90% of their free feeding body weight. Approximately 3 h after operant conditioning sessions additional chow was given.

2.6. Statistical analysis

Differences in groups of the Roman selection lines were determined using a two-way ANOVA. The selection line and experimental group were used as between subject factors. Student *t*-tests were used as post-hoc test. Distribution of lever presses over time was analyzed using a repeated measures ANOVA and Tukey post-hoc test. Group data are expressed as averages with standard error of the mean. A *p*-value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Offensive aggression

The results of the resident-intruder test are given in Table 1. There is a trend towards a significant increase in average attack latency in defeat animals ($F_{1,27} = 3.34$, $p = 0.08$) and interaction between strain and treatment ($F_{1,27} = 2.82$, $p = 0.11$). The total level of offensive aggression tended to be higher in RLA rats ($F_{1,27} = 3.74$, $p = 0.06$) compared to RHA rats, no interaction between strain and adolescent social defeat was found ($F_{1,27} = 0.09$, $p = 0.76$). RLA rats spent more time on social interaction ($F_{1,27} = 10.14$, $p = 0.004$), but less time on non-social exploration ($F_{1,27} = 6.04$, $p = 0.02$). A treatment and interaction effect was found in the time spent on grooming ($F_{1,27} = 5.63$, $p = 0.03$ and $F_{1,27} = 5.31$, $p = 0.03$ respectively), RHA control rats spent more time on grooming compared to the other groups. No effect was found on social exploration and immobility.

3.1.1. Operant behavior

During the fixed-ratio schedule of reinforcement, a difference in the number of lever presses was found between RLA and RHA rats ($F_{1,27} = 6.96$, $p = 0.01$). However, no significant interaction was found between strain and treatment ($F_{1,27} = 0.55$, $p = 0.47$).

RHA rats performed a significantly higher number of lever presses compared to RLA rats on a variable interval schedule of reinforcement ($F_{1,27} = 4.43$, $p = 0.05$). This difference is mainly caused by a difference in the number of lever presses in the control animals ($p = 0.03$). Furthermore, there is a trend towards a significant interaction effect between strain and treatment ($F_{1,27} = 3.16$, $p = 0.09$) (Fig. 1). The number of rewards on the VI-15 schedule did not differ between the two strains ($F_{1,27} = 0.45$, $p = 0.45$) and there was no treatment effect ($F_{1,27} = 2.10$, $p = 0.16$) on the number of obtained rewards.

During extinction, both control and defeated RHA rats performed significantly more lever presses compared to RLA rats ($F_{1,27} = 15.19$, $p = 0.001$). The distribution of lever presses over time is depicted in Fig. 2. There is a significant interaction effect of time, line and treatment ($F_{3,81} = 3.76$, $p = 0.01$), the post-hoc test revealed a significant difference between RLA control and RHA control at 15 min ($p = 0.01$). At 30 min and 45 min, there was a significant difference between RLA

Fig. 1. Performance on a VI-15 schedule in RLA ($n = 7-8$) and RHA ($n = 8$) rats. The data are expressed as the total number of presses $\pm$ SEM during the last one hour VI-15 session. RHA rats performed a significantly higher number of lever presses compared to RLA rats ($F_{1,27} = 4.43$, $p = 0.05$). Furthermore, there is a trend towards an interaction between strain and treatment ($F_{2,27} = 3.16$, $p = 0.09$).

defeated and RHA defeated animals ($p = 0.01$ and $p = 0.03$). There were no significant differences in the last interval of 15 min. The number of rewards and food receptacle visits during the different operant conditioning schedules are summarized in Table 2.

Fig. 2. A) The total number of lever presses during a one hour extinction session, *** indicates a significant difference between RHA and RLA animals, $p < 0.001$. Data are expressed as mean $\pm$ SEM. B) the number of lever presses distributed over time (in blocks of 15 min) during 1 h extinction of operant responding. Data are expressed as mean $\pm$ SEM. There is a significant interaction between strain, treatment and time ($F_{3,81} = 3.76$, $p = 0.01$) * $p < 0.05$.

Table 1

Behavior during resident-intruder test at pnd ~120 in rats of the Roman selection lines ($n = 7-8$ per group). Data are expressed as mean $\pm$ SEM. Attack latencies are in seconds, the other parameters are expressed as percentage of the total time of the test.

	RLA		RHA	
	Control	Defeat	Control	Defeat
Attack latency (s)	249 $\pm$ 58	257 $\pm$ 71	147 $\pm$ 41	357 $\pm$ 64
Offensive aggression	45 $\pm$ 12	43 $\pm$ 11	24 $\pm$ 5	27 $\pm$ 9
Social exploration	17 $\pm$ 6	25 $\pm$ 6	13 $\pm$ 2	18 $\pm$ 3
Non-social exploration	20 $\pm$ 4 ^a	16 $\pm$ 4 ^a	27 $\pm$ 3	30 $\pm$ 6
Inactivity	13 $\pm$ 5	12 $\pm$ 5	14 $\pm$ 3	14 $\pm$ 3
Grooming	5 $\pm$ 1	5 $\pm$ 2 ^b	22 $\pm$ 3 ^c	12 $\pm$ 3 ^b

^a Indicates a significant line differences $p < 0.05$.

^b Indicates a significant effect of defeat $p < 0.05$.

^c Indicates a significant interaction between line and defeat $p < 0.05$.

Table 2

Performance on the different schedules of reinforcement in rats of the Roman selection lines ($n = 7$ –8 per group). All schedules lasted for 1 h. The number of rewards obtained during the FR-1 schedule equals the number of lever presses on this schedule. Data are expressed as mean $\pm$ SEM. * indicates a significant line difference.

Schedule	Parameter	RLA		RHA	
		Control	Defeat	Control	Defeat
FR-1	Rewards	288 $\pm$ 16*	294 $\pm$ 15*	339 $\pm$ 12	322 $\pm$ 16
	Food receptacle visits	609 $\pm$ 81	485 $\pm$ 38	519 $\pm$ 48	550 $\pm$ 106
VI-15	Rewards	175 $\pm$ 4	176 $\pm$ 4	189 $\pm$ 4	171 $\pm$ 9
	Food receptacle visits	291 $\pm$ 40*	261 $\pm$ 41*	520 $\pm$ 87	356 $\pm$ 60
Extinction	Food receptacle visits	103 $\pm$ 38	61 $\pm$ 9	90 $\pm$ 11	64 $\pm$ 13

* $p < 0.05$.

4. Discussion

This study confirms the finding that RHA rats are more impulsive than RLA rats [29,30] and shows that social stress experienced during adolescence has long-lasting effects on adult behavior in RHA rats, but not in RLA rats. The baseline differences in impulsivity correspond with a study performed by Moreno and colleagues in which RHA rats have been shown to be more impulsive compared to RLA rats in the delay-discounting paradigm and the five-choice serial reaction time (5-CSRT) task [30]. There is a tendency to reduced lever pressing in defeated RHA rats compared to their respective control animals. This may be caused by increased levels of anxiety [19,31] and therefore increased inhibitory control induced by the social defeat in adolescence. In RLA rats, the level of impulsivity was not affected by social defeat.

During extinction, the level of responding was lower in all animals compared to reinforced sessions of the variable interval schedule. No difference was found between control and defeated animals neither in RHA nor in RLA rats. However, the distribution of lever presses over time during extinction was significantly affected. In the first time interval a pattern comparable to performance during the reinforced VI-15 schedule was visible, with RHA control animals pressing more compared to both RLA groups. Thereafter, the number of lever presses reduced in all groups. However, defeated RHA rats appeared to be more persistent and less flexible behaviorally than the other groups of animals, they showed more lever presses during the second and the third block of fifteen minutes.

The attack latency of animals can also be regarded as a measure of impulsivity or inhibitory control, since increased attack latencies indicate an inhibition of the tendency to start an aggressive encounter. RHA rats show a tendency to shorter attack latencies, whereas the attack latency of RHA rats is increased due to social defeat during adolescence. The attack latency of RLA rats was not affected by social defeat. Surprisingly, the level of offensive aggression is slightly higher in RLA rats compared to RHA rats.

Based on the two-tier model in which emotionality and coping style are used as two independent trait characteristics [24,34,35], we expected RLA rats to be less aggressive than RHA rats. In this model, RHA rats are proactive coping, low emotional animals, whereas RLA rats are reactive coping, high emotional animals. Driscoll and colleagues showed that RHA rats display higher levels of shock-induced aggression compared to RLA rats [36,37]. The inconsistency of our aggression results might be due to the fact that we measured offensive aggression, which in terms of motor patterns, adaptive function and neurobiology is different from shock-induced defensive-like aggressive behavior.

In previous studies in our laboratory, social defeat in rats of the Roman selection lines during adulthood did not induce major differences between the two lines in the long-term consequences (reduced

activity, reduced body temperature, reduced open field behavior) of the defeat [38]. This is in contrast with the results of the current study in which adolescent social defeat leads to a differential effect on adult behavior in RHA and RLA rats.

One of the confounding factors in the current experiment may be that the social defeat procedure included individual housing after social defeat. Social isolation appears to be an important factor in the long-term effects of defeat since social housing has been shown to reduce the impact of social defeat [39,40].

The results confirm the data obtained in rats of the wild-type Groningen strain, in which proactive coping rats are characterized by high levels of offensive aggression and high impulsivity levels, whereas low-aggressive animals show low levels of impulsive behavior. In this strain, social defeat during adolescence disturbed this relationship between aggression and impulsivity, which indicates that social stress during this period affects the normal development of personality characteristics (Coppens et al. in prep.).

The underlying neurobiological substrate mediating the long-term effects of social defeat on adult impulsive behavior most likely involves the prefrontal cortex. The relatively late development of this brain structure may be altered by social defeat during adolescence. It has been shown that the prefrontal cortex is undergoing major structural reorganization during adolescence [41–46]. For example, the density of prefrontal cortex derived axon terminals decreases significantly between adolescence and adulthood [45]. Also, dopamine D₁ and D₂ receptors are overproduced prior to puberty and pruned back to adult levels thereafter in the prefrontal cortex [43,47,48].

Therefore, social defeat might have an impact on these developmental changes and induce altered prefrontal cortex functioning. Indeed, levels of impulsivity [49,50] and aggression [51,52] are strongly related to prefrontal cortex functioning [53]. Moreover, stress has been shown to affect behavioral processes involving the prefrontal cortex [21–23,54]. Several studies show that RHA rats are most susceptible to stress induced changes in prefrontal cortex functioning. D'Angio and colleagues found that prefrontal cortex functioning is affected by stressful environmental stimuli in RHA rats, but not in the hyperemotional RLA rats. Extracellular DOPAC levels are increased after tail pinch, immobilization and forced locomotion in RHA rats [55].

Furthermore, fear-related behaviors are associated with increased dopamine output in the medial prefrontal cortex of RHA, but not RLA, rats [56]. These data support the general view that the RHA male is more susceptible to stressors, both during adolescence and adulthood. Whether the prefrontal cortex is causally involved in the consequences of social defeat during adolescence on adult coping style needs further research.

In summary, this study confirms that RHA rats are characterized by enhanced levels of impulsive-like behavior and that only in RHA rats adolescent social defeat stress induces long-lasting (i.e., decreasing) consequences on adult levels of impulsivity and aggressive behavior.

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