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Cardiovascular outcomes related to social defeat stress: New insights from resilient and susceptible rats

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ABSTRACT

Stress exposure is an important risk factor for psychiatric and cardiovascular disorders. Two phenotypes related to coping with stress can be observed in rodents that experience chronic social defeat stress (SDS): susceptible, showing social avoidance and behavioral changes related to depression, and resilient, showing none of these alterations. Moreover, a strong correlation exists between depression and the development of or mortality due to cardiovascular diseases. Nevertheless, little is known about cardiovascular alterations related to SDS exposure in those phenotypes or their correlation with depressive-like behaviors. Using a chronic SDS protocol followed by the social interaction test, we identified Wistar rats as resilient or susceptible to SDS. Susceptible animals showed increased depressive-like behaviors with resting tachycardia and decreased heart rate variability (HRV) due to increased sympathetic tone in the heart and a less effective baroreflex. In contrast, resilient rats were protected from these alterations by increased vagal tone, resulting in greater HRV values. To our knowledge, our study is the first to indicate that harmful cardiovascular outcomes are related to depressive-like behaviors in susceptible rats and to suggest a mechanism by which resilient rats are protected from these changes. Also, our results suggest that enhanced HRV and vagal tone may be an important trait in resilient individuals.

1. Introduction

The impact of stress-related disorders on public health systems is such that the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes, as a separate topic, diseases related to trauma and stressor exposure, depression being one of the most impactful (American Psychiatric Association, 2013). Globally, depression is the fifth leading cause of years lived with disability (YLDs) (Vos et al., 2017). Depression is also strongly correlated with the development of and mortality due to cardiovascular diseases (Penninx, 2016). Meta-analyses evaluating the impact of depression on the later development of cardiovascular diseases show that depressed patients have an increased risk for developing coronary heart diseases (Nicholson et al., 2006; Wu and Kling, 2016).

Animal models of stress exposure also support this correlation. Chronic exposure to diverse stress protocols induces a variety of depressive-like symptoms, such as anhedonia and behavioral despair, in addition to neuroendocrine, sleep, and weight disturbances (Deussing, 2006; Jaggi et al., 2011). Among the animal models of stress, the exposure of rodents to social defeat stress (SDS) stands out due to its ethological relevance and similarity to psychosocial stress experienced by humans. It consists of exposing the animal to an intense, unpredictable, and inescapable confrontation with an aggressive conspecific (Hammels et al., 2015). After chronic exposure to SDS, animals show behavioral and physiological alterations related to anxiety and depression, such as decreased body weight gain, anxiogenic responses in the elevated plus maze (EPM), novelty suppression of feeding, anhedonia, increased immobility time in the forced swim test (FST) (Venzala et al., 2012), social avoidance (Berton et al., 2006; Jaisinghani and Rosenkranz, 2015), autonomic imbalance, resting tachycardia, and electrophysiological alterations in the heart (Sévoz-Couche et al., 2013; Sgoifo et al., 2014).

Heart rate variability (HRV) is a natural and physiological phenomenon that reflects the complex and reciprocal interactions along the brain-heart axis. It is easy to obtain and has important implications regarding the development and prognosis of cardiovascular diseases (Mccraty and Shaffer, 2015). HRV analysis aids in the identification of patients at risk of death by cardiovascular diseases and the evaluation of autonomic control of the heart (Cygankiewicz and Zareba, 2013; Kleiger et al., 2005). Evidence obtained in humans and animal subjects has indicated that decreased HRV is associated with many psychiatric disorders, including depression (Carnevali et al., 2018; Minassian et al., 2015; Sgoifo et al., 2015).

Despite the importance of stress exposure to the development of

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psychiatric and cardiovascular disorders, not every exposed individual develops diseases (Cohen et al., 2007). In this sense, individual differences in the response of the organism to adverse events may be related to an individual's ability to adapt to adversity, i.e., resilience or susceptibility to stress. Resilience can be interpreted as an individual's ability to maintain health in the face of adversity, whereas susceptibility consists of the opposite, individuals that show maladaptive responses facing problems and challenges (Wood and Bhatnagar, 2015).

The use of the social interaction test (SIT) to classify socially defeated mice into susceptible and resilient phenotypes has helped to clarify the behavioral and neurobiological bases of stress resilience (Krishnan et al., 2007). Accordingly, after chronic exposure to SDS, susceptible mice show social avoidance and behavioral alterations related to depression, whereas resilient mice do not (Golden et al., 2011; Pfau and Russo, 2015). Until now, no study has used SIT to identify rats that are susceptible and resilient to SDS and correlate the stress-susceptibility phenotype with depressive-like behavior development. Also, an investigation of distinct stress-induced cardiovascular outcomes in susceptible and resilient rats is lacking in the literature and can offer new insights about the impact of stress on cardiovascular disorders.

Here, we use the SIT to identify rats that are resilient and susceptible to SDS and evaluate behavioral alterations related to depression and cardiovascular parameters in both phenotypes.

2. Material and methods

2.1. Experimental subjects

Fifty-seven male Wistar rats (230–260 g) were used as experimental subjects. Animals were obtained from the animal breeding facility of Sao Paulo State University (UNESP) (Botucatu-SP, Brazil) and were transferred to our animal facility at least 7 days before the beginning of experiments. They were kept in a room with controlled temperature (23 °C ± 2), on a 12 h reverse light-dark cycle (lights on 10 pm), in groups of four per cage (32 × 40 × 16 cm). Water and food were offered *ad libitum* during the entire experiment. All stress exposures and behavioral tests were performed during the dark phase of the cycle, and animals were tested randomly throughout this period (1 p.m. to 6 pm). Cardiovascular recordings were performed during the light phase of the cycle, and animals were tested randomly throughout this period (11 p.m. to 4 am).

Six male Long Evans rats (weighing more than 400 g during aggressive encounters) were used as aggressors in the chronic SDS protocol. They were kept in a different animal facility, each one in a cage (32 × 40 × 16 cm), forming a stable colony with a fertile female Long Evans rat. The room was maintained under the same conditions described above. One week before their use as aggressors in the study, the residents were screened to ensure similar levels of aggressiveness using non-experimental Wistar rats as intruders. Residents that were not able to provoke at least one event of submissive posture (at least 4 s of supine posture) from two different animals in a 5-min test on 2 consecutive days were not used in the experiments. One hour before each aggressive encounter, females and pups were removed from the resident's home cage and kept undisturbed in the animal facility with water and food offered *ad libitum*. Aggressors were transferred to the defeat room at least 1 h prior to aggressive encounters.

All procedures involving animal use were approved by the university ethics committee for animal care and use (CEUA/FCF/CAr 01/2017), and all experiments were conducted according to the principles of the Brazilian National Council for Animal Experiments Control (CONCEA), based on the NIH Guidelines for the Care and Use of Laboratory Animals.

2.2. Experimental procedure

After SDS and identification of coping phenotypes, animals were divided into two groups: the first (n = 26) was submitted to evaluation of behavioral alterations related to anxiety and depression and the second (n = 31) to the evaluation of cardiovascular alterations. The experimental timeline is depicted in Fig. 1.

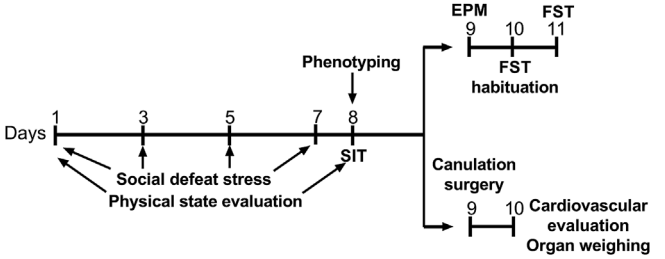

Fig. 1. Graphical representation of the experimental procedure. Social defeat stress was performed every other day (days 1, 3, 5 and 7) for 7 days, totalizing 4 aggressive encounters. Stress coping phenotypes were identified by the SIT 24 h later. After the phenotyping, animals were used to evaluate the behavioral alterations related to anxiety and depression or were cannulated to the recording of cardiovascular parameters. SIT, social interaction test; EPM, elevated plus maze; FST, forced swim test.

2.2.1. Social defeat stress

Our intruder-resident protocol of chronic SDS was based on a previously described method (Boyson et al., 2011), with some modifications. Briefly, it consists of exposing the animals to be stressed (intruders) to the home-cage of an aggressive conspecific (residents).

For 7 days, the intruders were exposed to an aggressive encounter in the resident's home-cage to be defeated. Each aggressive encounter occurred in a specific room and lasted for 25 min, divided into three phases: in the first, called the incitation phase, the intruders were protected by a protective metal grid cage for 5 min to stimulate aggressiveness in the resident. Subsequently, in the defeat phase, the intruders were removed from the protective cage and placed in confrontation with the aggressive Long Evans for 10 min. The intruders were then placed again in the resident's home cage, secured by the protective cage for 10 min (post-defeat phase). At the end of the aggressive encounter, the intruders were replaced in their home cages until the next defeat (48 h later). Therefore, each intruder rat was exposed to four stress sessions. Each intruder was exposed to a different aggressor in each aggressive encounter, which was randomly performed during the dark phase of the light-dark cycle.

The experimental subjects (stressed and control animals) were weighed before each aggressive encounter. Control animals were handled (cage changes, weighing, and coat state evaluation) during the occurrence of the social defeat sessions.

2.2.2. Physical state evaluation

Coat state deterioration was used as an index of the animal's motivational state for self-centered activities and depressive-like behavior (Nollet et al., 2013).

Before the first aggressive encounter (initial coat state score) and SIT (final coat state score), control and stressed animals were evaluated regarding the state of their coats, using a scale from 3 to 0, wherein 3 represents healthy and well-cared-for fur, while 0 represents unhealthy and dirty fur, with hair loss and piloerection. Intermediate states were scored as variations of 0.5 points. The coat state deterioration score was expressed as the difference between the initial and final coat state scores.

2.2.3. Social interaction test

Twenty-four hours after SDS, intruder rats were identified as resilient or susceptible by their interaction ratio (IR) in the SIT based on a procedure described previously for mice (Golden et al., 2011), with modifications.

The social interaction arena (Supplementary Fig. S1) is a black-floored acrylic box (80 cm length x 80 cm width x 25 cm height) with a transparent acrylic enclosure (20 cm length x 15 cm width x 24 cm height) centered on one of the walls (custom-made, Master One, Ribeirão Preto-SP, Brazil). The arena is divided virtually into an interaction zone (15 cm width around the enclosure) and an avoidance zone (15 cm length x 15 cm area projecting from both corner joints opposing the target enclosure).

Experimental subjects were exposed to the arena for 5 min divided into two phases: in the first one, the no-target phase, animals explored the arena freely for 2.5 min with the target enclosure empty. At the end of this phase, the experimental subjects were removed from the arena for 30 s, and the empty target enclosure was changed to one containing a new and non-aggressive male Long Evans rat. Subsequently, the animals were replaced in the arena for 2.5 min. The time spent in the interaction and avoidance zones during the no-target and target phases was evaluated using a camera connected to a microcomputer with behavioral analysis software ANY-maze (Stoelting Co., Wood Dale-IL, USA).

Intruders were identified as resilient or susceptible based on *k-means* cluster analysis of the IR, using a two-subgroup classification. Animals classified in the cluster with the lower mean were identified as susceptible, while those in the higher mean cluster were identified as resilient. The IR was calculated as the time spent in the interaction zone during the target phase/time spent in the interaction zone during the no-target phase.

2.2.4. Elevated plus maze

Anxiety-like behavior was evaluated in the EPM 24 h after the SIT. The protocol is based on rodents' natural aversion to open and high places, mimicked by the open arms of the EPM (Pellow and File, 1986).

The EPM is a plus-shaped wooden apparatus, elevated 50 cm above floor level with two open arms (50 cm length x 10 cm width x 0.25 cm height) and two opaque closed arms (50 cm length x 10 cm width x 40 cm height) connected by a common central platform (10 cm length x 10 cm width).

Rats were placed on the central platform of the EPM facing an open arm, and their behavior was video-recorded by a camera fixed to the roof for 5 min for analysis of the number of entries (arm entry = four paws in the arm) into the closed arms, percentage of entries into the open arms (number of entries in the open arms/total x 100), and percentage of time spent in the open arms [(time spent in open arms/total) x 100]. Behavioral analyses were performed using the software X-Plo-Rat 2005 (developed by the research team of Dr. Morato, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, USP, Brazil).

2.2.5. Forced swim test

Depressive-like behavior was evaluated by the FST 48 h after the SIT. The method is based on behavioral despair, that is, the immobility that rodents eventually show when exposed to an inescapable, threatening situation. In the FST, an increase in immobility time is correlated with an increased negative mood (depressive-like behavior) (Porsolt et al., 1978).

Rats were placed in an acrylic tank (30 cm diameter) filled with water (40 cm height) at 25 ± 1 °C in two phases: habituation and test. During the habituation phase, experimental subjects were placed in the water tank for 15 min. Twenty-four hours later, animals were placed again in the tank and video recorded for 5 min for the evaluation of time spent immobile (lack of movements except those necessary to float), swimming (active horizontal movements aimed at escape from the tank), climbing (active vertical movements against the tank walls aimed at escape from the tank), and latency to the first immobility event. After each exposure to the water tank, animals were towel-dried and kept in a dry cage for 15 min, after which they were replaced in their home cage. Behavioral analyses were performed using the software X-Plo-Rat 2005.

2.2.6. Femoral artery and vein cannulation

Twenty-four hours after SIT, animals were anesthetized with tribromoethanol (250 mg/kg, 1 mL/kg, i.p.) and catheters (a 4-cm segment of PE-10 heat-bound to a 13 cm segment of PE-50; Clay Adams, Parsippany-NJ, USA) were implanted into the femoral artery for pulsatile arterial pressure (PAP) recording and blood sampling and into the femoral vein for drug infusion. Both catheters were tunneled under the skin and exteriorized near the neck at the animal's dorsum. The animals were kept in individual cages and in the recording room for the rest of the experiment. As prophylaxis, animals received the non-steroidal anti-inflammatory flunixin meglumine (2.5 mg/kg, 0.1 mL/100 g, s.c., Chemitec Agro-Veterinária Ltd., São Paulo-SP, Brazil) for postoperative analgesia and a poly-antibiotic formulation containing streptomycin and penicillin (560 mg/kg, 0.2 mL, i.m., Zoetis Ltd., Campinas-SP, Brazil) to prevent infection.

2.2.7. Measurement of cardiovascular parameters at rest

Twenty-four hours after surgery, animals were connected to a pressure transducer (DPT100, Utah Medical Products Inc., Midvale-UT, USA) by the femoral artery cannula. PAP was recorded for 60 min using an amplifier (Bridge Amp ML221, ADInstruments, Dunedin-OTA, NZ) connected to a digital acquisition board (PowerLab 4/30 ML866, ADInstruments) and LabChart PRO software (ADInstruments, Dunedin). The mean (MAP), systolic (SAP), and diastolic (DAP) arterial pressures, as well as the heart rate (HR) were derived from the PAP.

2.2.8. Power spectral analysis of pulse interval and systolic arterial pressure

Heart rate (HRV) and blood pressure (BPV) variabilities were evaluated by power spectral analysis of the pulse interval (PI) and SAP using Cardioseries v2.6.2 software (developed by Daniel P.M. Dias, Departamento de Fisiologia, Faculdade de Medicina de Ribeirão Preto, USP, Ribeirão Preto-SP, Brazil) (Duarte et al., 2015). Stationary temporal series of PI were extracted from the registry of 60 min of PAP. HRV and BPV were calculated from the total variance of these series in the time domain. Frequency domain analysis was also calculated from the power of oscillatory components in the frequency bands of low frequency (LF, 0.20–0.75 Hz) and high frequency (HF, 0.75–3.0 Hz) using the Fast Fourier Transform (FFT).

2.2.9. Assessment of baroreflex sensitivity and effectiveness

Baroreflex sensitivity and effectiveness were evaluated by spontaneous baroreflex analysis through the sequence analysis method and by the classical pharmacological approach (Costa-Ferreira et al., 2016; Parati et al., 2000).

The sequence method evaluated baroreflex functioning over physiological fluctuations of the SAP without pharmacological manipulation. For this, stationary temporal series of PI were extracted from the registry of 60 min of PI and SAP and analyzed beat-to-beat to identify the sequences in which an SAP increase was accompanied by PI prolongation (up sequences) or an SAP decrease was accompanied by PI shortening (down sequences). A sequence was considered as a baroreflex sequence only when the Pearson correlation coefficient between SAP and PI was greater than 0.8. Spontaneous baroreflex sensitivity was assessed based on the slope (ms/mmHg) of the linear regression between SAP and PI. Spontaneous baroreflex effectiveness was evaluated by the baroreflex effectiveness index (BEI), calculated as the ratio between baroreflex sequences and the total number of consecutive SAP increases.

The classical pharmacological approach evaluates baroreflex functioning during acute blood pressure changes evoked by vasoactive agents. In this sense, baroreflex activity was assessed via the pharmacological approach by intravenous infusion of the α1-adrenoceptor agonist phenylephrine (70 μg/mL at 0.4 mL/min.kg) and the nitric oxide donor sodium nitroprusside (SNP) (100 μg/mL at 0.80 mL/min.kg), using an infusion pump (KD Scientific, Holliston-MA, USA), at the end of 60 min of recording of resting cardiovascular parameters.

Vasoactive drugs were infused on a randomized schedule, and the second infusion was not performed until the cardiovascular parameters returned to control values (an approximately 5-min interval). The infusions lasted for 20–30 s, resulting in the administration of a total dose of 9–14 μg/kg of phenylephrine and 26–40 μg/kg of SNP. Sigmoid curves were constructed using MAP variations versus the reflex HR responses. Five parameters were evaluated using the sigmoid curves: (1) lower HR plateau (P1, Δbpm) (i.e., the maximum reflex bradycardia); (2) upper HR plateau (P2, Δbpm) (i.e., the maximum reflex tachycardia); (3) HR range (bpm) (i.e., the difference between the upper and lower plateau levels); (4) median blood pressure (BP50, ΔmmHg) (i.e., MAP at 50% of the HR range) and (5) average gain (G, bpm/mmHg) (i.e., the average slope of the curves between +1 and −1 standard derivations from the BP50). Reflex HR responses during blood pressure increases and decreases were analyzed separately using linear regression analysis. Their slopes were compared to evaluate changes in baroreflex gain.

2.2.10. Plasma corticosterone measurement

During the first hour of the light phase of the cycle, 30 min before the measurement of resting cardiovascular parameters, a blood sample (200 μL) was collected from the femoral artery for the determination of basal plasma corticosterone. Samples were collected in heparinized plastic tubes [5 μl of heparin (5000 UI/ml)] (Hepamax-S®, Blausiegel, Cotia, SP, Brazil), centrifuged at 2000 g for 10 min at 4 °C, and plasma was stored at −80 °C until quantification. Plasma corticosterone levels were estimated using a commercial corticosterone enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Item No. 501320, Cayman Chemical, Ann Harbor-MI, USA). Plasma samples were diluted (1:250) in ELISA buffer provided by the kit prior to quantification.

2.2.11. Organ weight measurements

At the end of baroreflex evaluation, the animals were euthanized by urethane overdose (2.5 g/kg, 1 mL/100 g, i.p.) and decapitated. The adrenals, kidneys, spleen, heart, and thymus were removed, trimmed of fat and conjunctive tissues, and weighed. Organ weight was expressed as absolute weight (g) and as relative weight (g/kg body weight).

2.3. Statistics

Statistical analyses were performed using Statistica 7.1 software (StatSoft, Inc., Tulsa, OK-USA), and graphs were made using GraphPad Prism 7 software (GraphPad Software Inc., La Jolla-CA, USA). Values were expressed as mean +SEM.

Stress-coping phenotypes were identified by *k-means* cluster analyses of the IR of intruder animals. Data were classified into two clusters, maximizing between-cluster distance and minimizing within-cluster distance.

Data were analyzed by one-way analysis of variance (ANOVA) considering the factor phenotype (control x resilient x susceptible) or by repeated-measures ANOVA, considering the factor phenotype (control x resilient x susceptible) as the independent factor and session (no target x target) or time (initial x final) as the repeated measurement. In cases where ANOVA showed significant differences ($p \leq 0.05$), The Newman-Keuls *post hoc* test was performed.

The correlation between immobility time and IR was assessed using Pearson's correlation analysis. Separate correlation analyses were performed for control and stressed groups.

3. Results

Our results confirmed the large difference in social interaction among animals exposed to SDS. The *k-means* cluster analyses separated stress-exposed animals in two groups, demonstrating the social avoidance expected by susceptible rats to SDS. One-way ANOVA of the IR

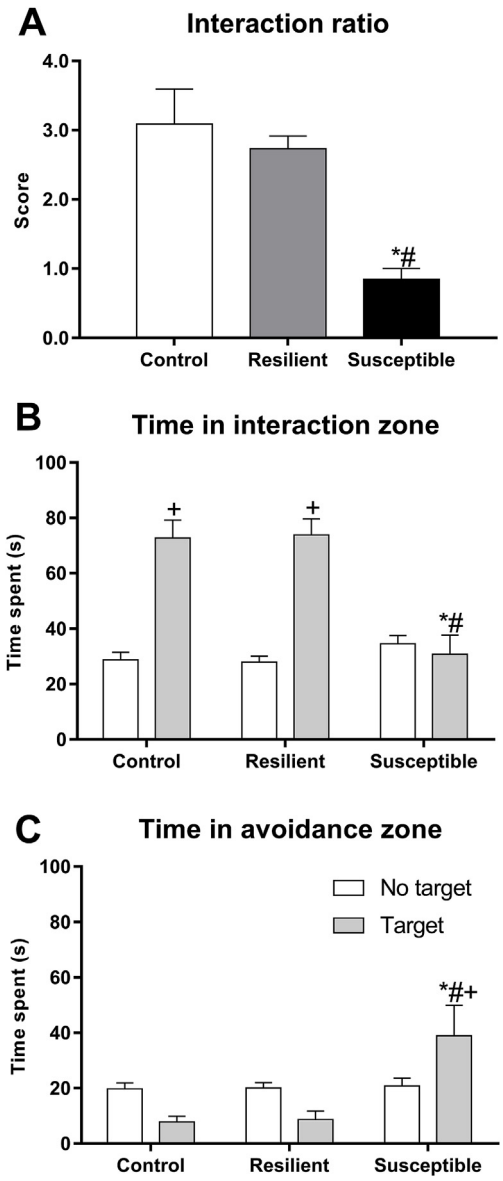

Fig. 2. Interaction ratio and time spent in interaction and avoidance zones of the social interaction apparatus in resilient and susceptible phenotypes to social defeat stress. Social interaction test was performed 24 h after the last social defeat episode. Bars represent means +SEM (n = 18–20 animals per group). A, interaction ratio. B, time spent in the interaction zone. C, time spent in the avoidance zone. *, $p < 0.05$ relative to control group; #, $p < 0.05$ relative to resilient group; +, $p < 0.05$ relative to time spent in the no-target phase of the same group.

(Fig. 2A) showed a significant effect of phenotype ($F_{2,54} = 13.43$, $p < 0.001$). The Newman-Keuls *post hoc* test indicates a lower IR in the susceptible group compared with the control and resilient ($p < 0.001$) groups but no differences between the resilient and control groups ($p = 0.43$). A graphical representation of the distribution of IR values is available as supplementary material (Supplementary Fig. 2).

Regarding the time spent in the interaction zone (Fig. 2B), repeated-measures ANOVA showed a significant effect of phenotype ($F_{2,54} = 13.43$, $p < 0.01$), session ($F_{1,54} = 71.91$, $p < 0.001$), and the phenotype and session interaction ($F_{2,54} = 22.38$, $p < 0.001$). The *post hoc* analysis revealed that control ($p < 0.001$) and resilient ($p < 0.001$) animals spent more time in the interaction zone when the target was present compared with the no-target session, while susceptible animals spent the same amount of time when the target was

Table 1
Body weight and body weight gain of resilient and susceptible phenotypes to social defeat stress in experiment 1.

		Control	Resilient	Susceptible
Body weight (g)	Initial	251 ± 7	249 ± 7	258 ± 8
	Final	284 ± 6	271 ± 7	276 ± 7
Body weight gain (g)		33 ± 3	**22 ± 4***	**18 ± 4***

Numbers represent means ± SEM (n = 18–20 animals per group). *, $p < 0.05$ relative to control group.

present ($p > 0.05$). Susceptible animals spent less time in the interaction zone when the target was present compared with the control ($p < 0.001$) and resilient groups ($p < 0.001$).

There was a main effect of phenotype ($F_{2,54} = 5.93$, $p < 0.01$) and of the interaction between phenotype and session ($F_{2,54} = 7.55$, $p < 0.01$) for the time spent in the avoidance zone (Fig. 2C). The Newman-Keuls *post hoc* test revealed an increase in time spent in the avoidance zone when the target was present in susceptible animals compared with the no-target session ($p < 0.01$) and compared with the control ($p < 0.01$) and resilient ($p < 0.01$) groups.

Body weight gain (Table 1) was affected in socially defeated animals, as resilient and susceptible groups gained less weight during SDS exposure. One-way ANOVA showed a significant effect of the phenotype factor ($F_{2,54} = 4.33$, $p < 0.05$). Body weight gain was lower in resilient ($p < 0.05$) and susceptible ($p < 0.05$) animals than in control animals. There were no significant differences among the groups in the initial or final body weights of the animals ($p > 0.05$).

After SDS exposure and phenotype identification in the SIT, our results indicate a decrease in anxiety levels in resilient animals tested in the EPM. One-way ANOVA failed to show significant differences regarding the number of entries into the closed arms ($p > 0.05$) (Fig. 3A) or the percentage of entries into the open arms ($p > 0.05$) (Fig. 3B). On the other hand, there was a significant effect of phenotype ($F_{2,23} = 3.77$, $p < 0.05$) on the percentage of time spent in the open arms of the apparatus (Fig. 3B). The resilient group spent more time in the open arms of the EPM than the control ($p < 0.05$) and susceptible ($p = 0.05$) groups.

Susceptible animals showed increased depressive-like behaviors in the FST. One-way ANOVA of the immobility time (Fig. 4A) showed a significant effect of phenotype ($F_{2,23} = 4.68$, $p < 0.05$). The Newman-Keuls *post hoc* test revealed an increased immobility duration in susceptible animals when compared with control ($p < 0.05$) and resilient animals ($p < 0.05$). The latency to being immobile for the first time (Fig. 4B) was also affected by the phenotype. One-way ANOVA showed a significant effect of phenotype ($F_{2,23} = 5.34$, $p < 0.01$), and the Newman-Keuls test revealed a decrease in immobility latency in susceptible animals relative to control ($p < 0.01$) and resilient ($p = 0.05$) ones. There were no significant alterations in the time spent swimming (Fig. 4C), despite a trend toward a significant effect of phenotype ($F_{2,23} = 2.77$, $p = 0.08$). One-way ANOVA showed a significant effect of phenotype ($F_{2,23} = 4.69$, $p < 0.05$) on climbing behavior (Fig. 4D). Newman-Keuls *post hoc* test revealed a decrease in time spent climbing in susceptible animals compared with the control ($p = 0.05$) and resilient ($p < 0.05$) groups.

Pearson's correlation analysis revealed a negative correlation between time spent immobile and IR in stressed animals (Supplementary Fig. 3A) ($r = -0.4722$, $p < 0.05$). On the other hand, there was no correlation between these variables in non-stressed (control) animals (Supplementary Fig. 3B) ($r = 0.0736$, $p > 0.05$).

Coat state deterioration (Fig. 5) was altered only in susceptible animals after SDS, which showed increased deterioration. One-way ANOVA showed significant differences for the phenotype factor ($F_{2,28} = 5.07$, $p < 0.05$). Susceptible animals had higher coat state deterioration scores than control ($p < 0.05$) and resilient animals

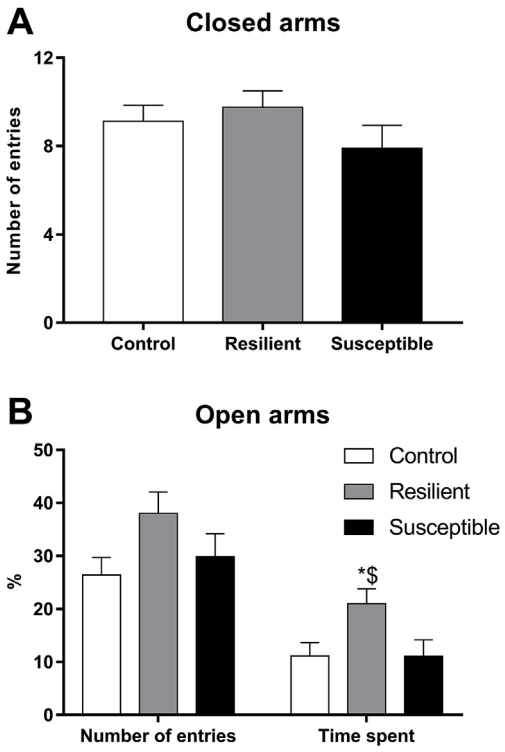

Fig. 3. Anxiety-like behaviors of resilient and susceptible phenotypes to social defeat stress in elevated plus maze. The test was performed 48 h after the last social defeat episode. Bars represent means +SEM (n = 8–10 animals per group). A, number of entries in the closed arms of the apparatus. B, percentage of number of entries and time spent in the open arms of the apparatus. *, $p < 0.05$ relative to control group; $, $p < 0.05$ relative to susceptible group.

($p < 0.05$).

Regarding basal HR values (Fig. 6A), one-way ANOVA showed a significant effect of the phenotype factor ($F_{2,19} = 8.20$, $p < 0.01$). Susceptible animals showed resting tachycardia compared with control ($p < 0.01$) and resilient rats ($p < 0.01$). There were no significant phenotype-related alterations in MAP, SAP, or DAP (Fig. 6) ($p > 0.05$).

A significant effect of the phenotype factor ($F_{2,19} = 19.04$, $p < 0.001$) was found for the total variance of PI (indicative of HRV) (Fig. 7A). The Newman-Keuls *post hoc* test revealed a decrease in HRV in susceptible animals compared with control ($p < 0.05$) and resilient animals ($p < 0.001$). There was also an increase in HRV in resilient animals relative to controls ($p < 0.01$). On the other hand, there were no significant alterations in the total variance of SP (indicative of blood pressure variance) ($p > 0.05$) (Supplementary Fig. 4A).

Power spectral analysis revealed an increase in the power of oscillatory components in low-frequency bands in susceptible animals and an increase in RMSSD and the power of oscillatory components in high-frequency bands in resilient animals. One-way ANOVA of the RMSSD (Fig. 7B) showed a significant effect of phenotype ($F_{2,19} = 4.88$, $p < 0.05$). The resilient group showed increased RMSSD when compared with the control ($p = 0.05$) and susceptible groups ($p < 0.01$). Similarly, one-way ANOVA showed a significant effect of the phenotype ($F_{2,19} = 4.67$, $p < 0.05$) on the HF power spectrum (Fig. 7D), whereas the Newman-Keuls test revealed an increase in resilient animals relative to control ($p < 0.05$) and susceptible animals ($p < 0.05$). There was a significant effect of the phenotype ($F_{2,19} = 3.65$, $p < 0.05$) on the LF power spectrum (Fig. 7C). The Newman-Keuls test revealed a significant increase in susceptible animals relative to controls ($p < 0.05$) and a small trend in resilient animals relative to controls ($p = 0.09$). There were no significant alterations in sympathovagal balance ($p > 0.05$) (Fig. 7E) nor in the LF power spectrum to the vessels (Supplementary Fig. 4B).

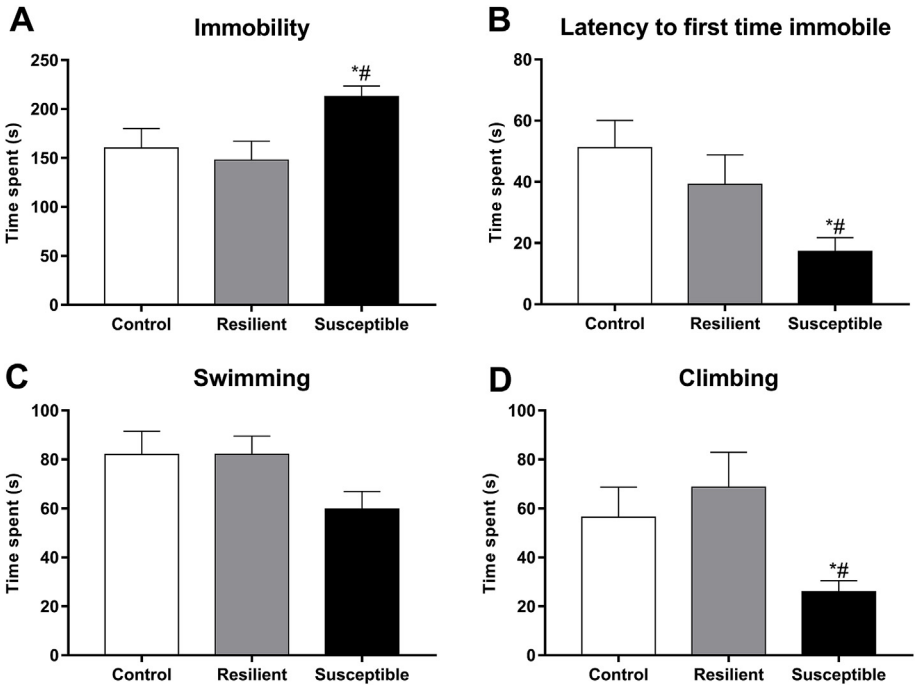

Fig. 4. Depressive-like behaviors of resilient and susceptible phenotypes to social defeat stress in the forced swim test. The test was performed 96 h after the last social defeat episode. Bars represent means + SEM (n = 8–10 animals per group). A, time spent immobile. B, latency to exhibit first immobility episode. C, time spent in active horizontal movements. D, time spent in active vertical movements towards the walls of the apparatus. *, $p < 0.05$ relative to control group; #, $p < 0.05$ relative to resilient group.

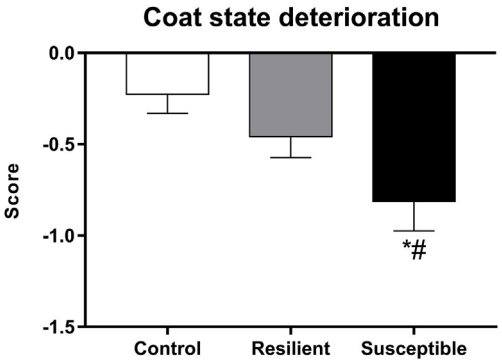

Fig. 5. Coat state deterioration in resilient and susceptible phenotypes to social defeat stress. Fur quality was evaluated right before each aggressive encounter and social interaction test. Bars represent means + SEM (n = 8–12 animals per group). *, $p < 0.05$ relative to control group; #, $p < 0.05$ relative to resilient group.

Spontaneous baroreflex gain and effectiveness differed between phenotypes. Regarding spontaneous baroreflex gain (Fig. 8A), one-way ANOVA showed a significant effect of the phenotype factor on the slope of all baroreflex sequences ($F_{2,19} = 3.95$, $p < 0.05$), the slope of up baroreflex sequences ($F_{2,19} = 5.55$, $p < 0.05$), and that of down baroreflex sequences ($F_{2,19} = 6.93$, $p < 0.05$). The slope of all sequences was increased in susceptible animals relative to controls ($p < 0.05$), whereas the slope of up and down sequences was greater in the susceptible group relative to the control ($p < 0.05$) and resilient groups ($p < 0.05$). Baroreflex effectiveness was decreased in susceptible animals (Fig. 8B). One-way ANOVA showed a significant effect of phenotype ($F_{2,19} = 4.09$, $p < 0.05$). The Newman-Keuls *post hoc* test revealed a lower BEI in susceptible animals than in control ($p < 0.05$) and resilient animals ($p < 0.05$).

There were no significant alterations in the baroreflex according to non-linear (Fig. 9A) or linear regression (Fig. 9B) in the classical pharmacological approach. One-way ANOVA showed no significant differences in P1, P2, HR range, BP50, or gain ($p > 0.05$) (Supplementary Table 1).

There was a significant effect of phenotype ($F_{2,19} = 4.52$, $p < 0.05$) on resting plasma corticosterone levels (Table 2). Resilient animals showed higher values of resting corticosterone than control ($p = 0.05$) and susceptible animals ($p < 0.05$).

Stressed animals showed increased adrenal gland weight (Table 2). One-way ANOVA of absolute adrenal weight showed a significant effect of phenotype ($F_{2,19} = 3.47$, $p = 0.05$). *Post hoc* analysis showed a trend toward increased absolute weight in resilient and susceptible animals relative to controls ($p = 0.06$ and $p = 0.08$, respectively). One-way ANOVA of relative adrenal weight showed a significant effect of the phenotype ($F_{2,19} = 5.30$, $p < 0.05$). The Newman-Keuls *post hoc* test revealed an increase in the relative adrenal weights of resilient ($p < 0.05$) and susceptible rats ($p < 0.05$) in comparison to control group.

Relative heart weight was affected in susceptible animals (Table 2). One-way ANOVA showed no alteration in absolute heart weight ($p > 0.05$). On the other hand, relative weight was affected by the phenotype ($F_{2,19} = 4.04$, $p < 0.05$). Susceptible rats had increased relative heart weights when compared with control ($p < 0.05$) and resilient rats ($p < 0.05$).

Thymus weight was decreased in stressed animals (Table 2). One-way ANOVA of absolute thymus weight showed a significant effect of phenotype ($F_{2,19} = 9.18$, $p < 0.01$). Resilient and susceptible rats had decreased absolute thymus weight relative to controls ($p < 0.01$). There was a trend toward a significant effect of the phenotype ($F_{2,19} = 3.07$, $p = 0.06$) on relative thymus weight. The Newman-Keuls test revealed a trend toward decreased relative thymus weight in resilient animals compared with controls ($p = 0.07$).

There were no significant alterations in absolute or relative spleen or kidney weight ($p > 0.05$) (Table 2).

4. Discussion

Rats susceptible to SDS showed increased immobility in the FST and coat state deterioration, indicating a depressive-like state in these animals. This phenotype was also associated with increased basal HR, reduced HRV, and lower baroreflex effectiveness, probably due to an autonomic imbalance toward an increase in the sympathetic contribution. Resilient rats were protected from these alterations, which was possibly related to the increased vagal tone to the heart and greater

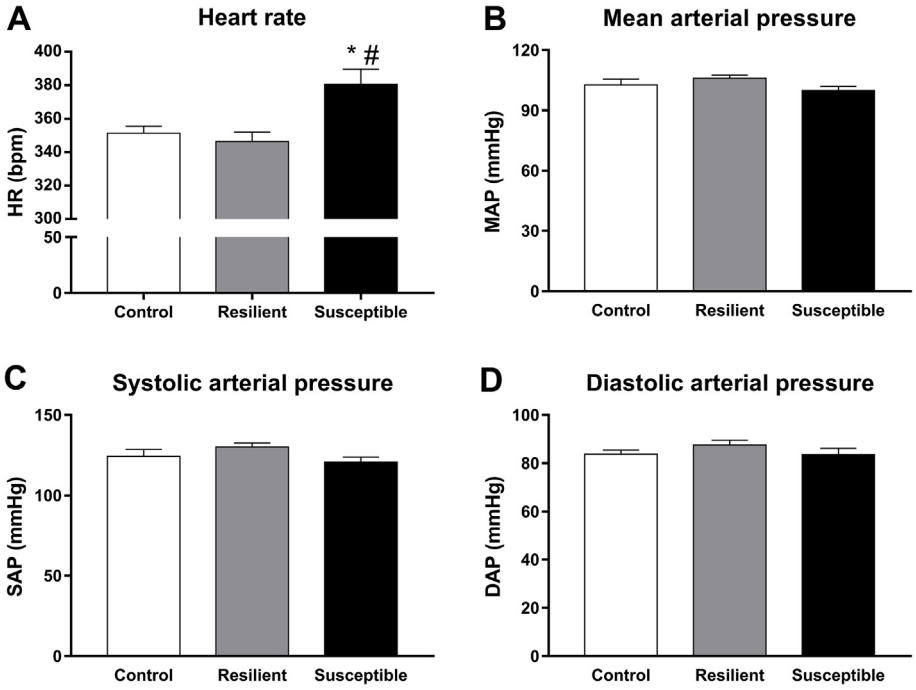

Fig. 6. Heart rate and blood pressure during rest in resilient and susceptible phenotypes to social defeat stress. Animals were cannulated 48 h after the last social defeat episode and cardiovascular parameters were recorded 24 h later. Bars represent means +SEM (n = 6–8 animals per group). A, heart rate (HR). B, mean arterial pressure (MAP). C, systolic arterial pressure (SAP). D, diastolic arterial pressure (DAP). *, $p < 0.05$ relative to control group; #, $p < 0.05$ relative to resilient group.

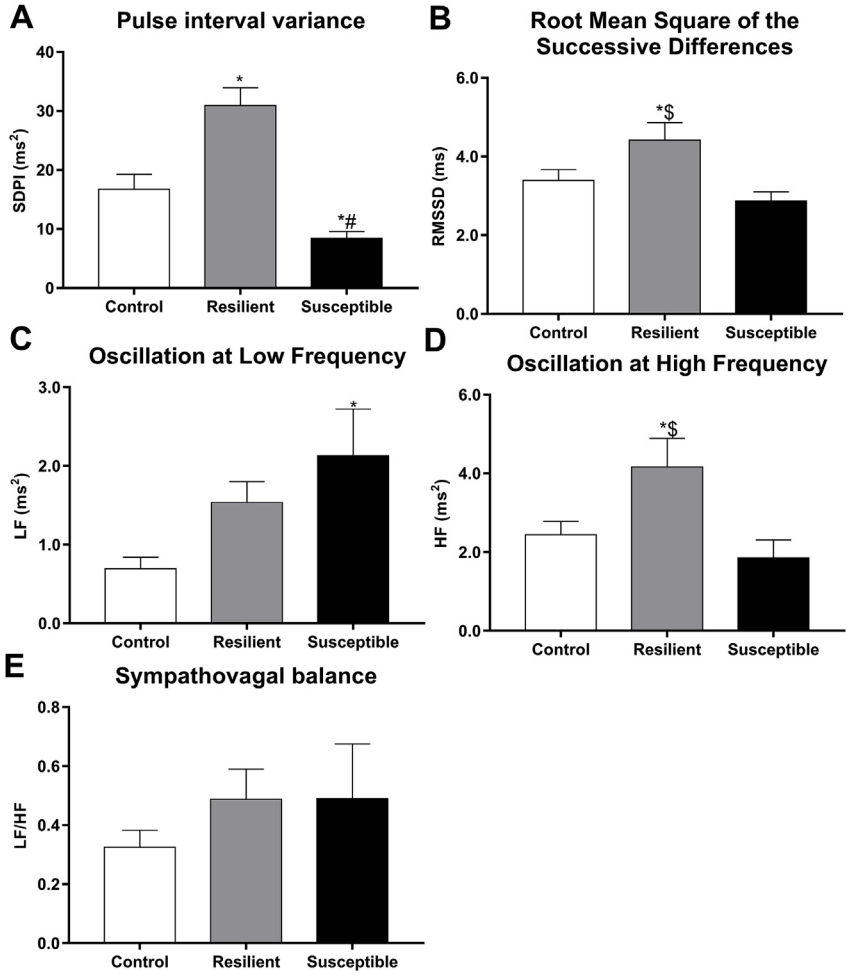

Fig. 7. Power spectral analyzes of pulse interval in time and frequency domains in resilient and susceptible phenotypes to social defeat stress. Stationary periods of pulse interval were extracted from the registry of resting pulsatile arterial pressure held 72 h after the last social defeat episode. Bars represent means +SEM (n = 6–8 animals per group). A, total variance of pulse interval in the time domain. B, Root Mean Square of the Successive Differences (RMSSD). C, power of oscillatory components in the frequency bands of low frequency (LF, 0.20–0.75 Hz). D, power of oscillatory components in the frequency bands of high frequency (HF, 0.75–3.0 Hz). E, sympathovagal balance calculated using LF/HF ratio. SDPI, standard deviation of pulse interval; LF, low frequency; HF, high frequency. *, $p < 0.05$ relative to control group; #, $p < 0.05$ relative to resilient group; $, $p < 0.05$ relative to susceptible group.

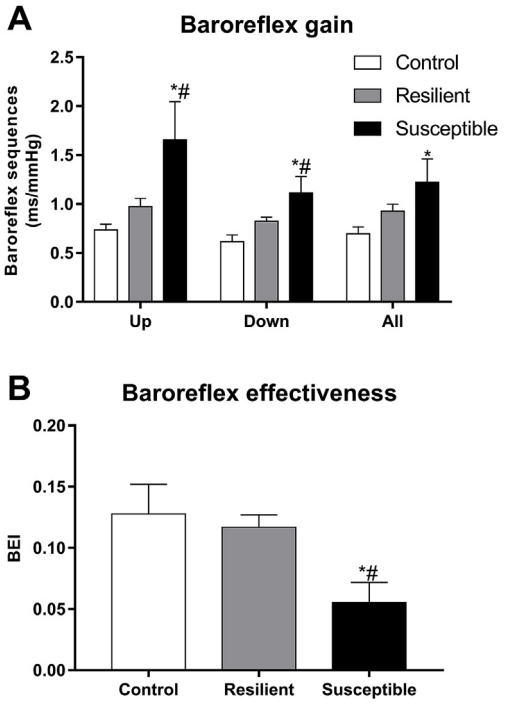

Fig. 8. Spontaneous baroreflex gain and effectiveness in resilient and susceptible phenotypes to social defeat stress. Stationary periods of pulse interval and systolic arterial pressure were extracted from the registry of resting pulsatile arterial pressure held 72 h after the last social defeat episode. Bars represent means +SEM (n = 6–8 animals per group). A, baroreflex gain of up, down and all baroreflex sequences. B, baroreflex effectiveness index (BEI). *, $p < 0.05$ relative to control group; #, $p < 0.05$ relative to resilient group.

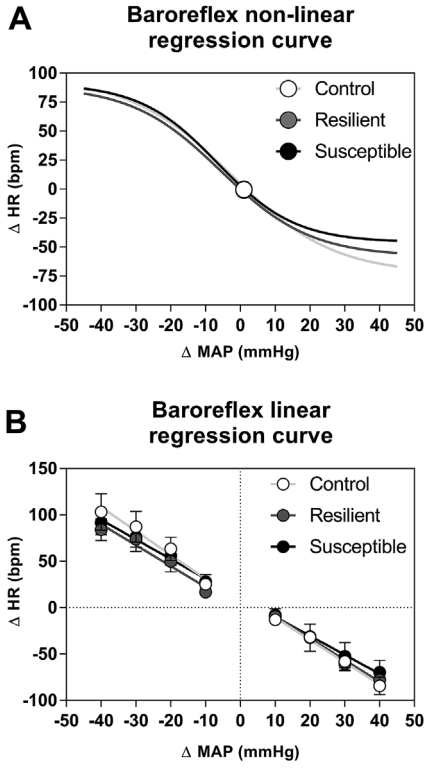

Fig. 9. Baroreflex activity during an acute pressure stimulus in resilient and susceptible phenotypes to social defeat stress. Drugs were infused right after the 60 min of resting of recording resting cardiovascular parameters. Points and lines represent means ± SEM (n = 6–8 animals per group). ΔHR, heart rate variation; ΔMAP, mean arterial pressure variation.

HRV found in our study. These results are summarized below (Table 3).

Correlational analysis between IR and immobility during FST in stressed animals revealed a negative correlation, where SDS-exposed animals that presented the lowest values of IR showed the largest values of immobility in FST performed later. These data also reinforce the use of social avoidance, at least in rodents, as a hallmark of a depressive-like state. As stated above, it is already used for mice (Golden et al., 2011), while reports using rats are limited (Pfau and Russo, 2015). Based on our results, this procedure seems reliable for identifying rats that are resilient and susceptible to SDS, increasing the potential use of rats as animal models to study resilience to stress, in addition to mice. We separated the groups based on social interaction performed 1 day after SDS, but it is possible that this group difference is long lasting. One recent report (Riga et al., 2017) showed that rats exposed to SDS can be separated into two populations according to social interaction, and this difference persists for up to 6 months.

Expanding the repertory of behavioral alterations related to depression that appear only in susceptible individuals, we found an increase in coat state deterioration. This index is similar to the diminished individual care and personal hygiene found in depressed patients at clinics (Alonso et al., 2004; American Psychiatric Association, 2013). Increased coat state deterioration was identified after rodent exposure to chronic stress protocols and was reversible only through chronic antidepressant treatment (Ibarguen-Vargas et al., 2008; Law et al., 2016; Smolinsky et al., 2009). Rodent strains that are more susceptible to stress-induced depressive-like behaviors also show greater coat state deterioration than resilient lineages (Voorn et al., 2004; Yalcin et al., 2008), as do mice susceptible to chronic variable stress (Nasca et al., 2014). This result, together with immobility during FST, supports our classification of rats as susceptible or resilient to SDS, demonstrating that only susceptible animals develop a depressive-like state.

In contrast to previous findings in mice (Golden et al., 2011; Krishnan et al., 2007), resilient rats showed decreased anxiety-like behaviors when evaluated in the EPM. Inconsistent data are available in the literature regarding the effects of chronic social defeat on anxiety-like behaviors in rodents. This effect is variable and depends on the exposure time to stressors, animal strain, behavioral apparatus used to evaluate anxiety, and ambient characteristics during the test (Blanchard et al., 2001; Hammels et al., 2015). Nevertheless, mice selected as susceptible to chronic social instability based on the corticosterone response show increased anxiety-like behaviors in the EPM (Schmidt et al., 2010). Up to now, the reason for such discrepancies has been unclear. Our first hypothesis is that the anxiolytic response to stress is part of a coping mechanism in resilient rats. It could develop during SDS sessions and act as a protective factor against the negative consequences of stress during future stress episodes. Another hypothesis is that resilient rats are less anxious than susceptible rats prior to SDS exposure, and this lesser anxiety makes the rat less prone to adverse consequences of stress. At least in mice, this hypothesis does not appear to be supported. Unpublished data from our laboratory showed that mice classified as susceptible or resilient according to their IR do not present differences in anxiety-like behaviors in the EPM before repeated SDS. However, additional experiments are needed to elucidate the importance of such characteristics in rats.

Reinforcing the strong relationship between cardiovascular diseases and depressive-like behaviors, in susceptible rats we found cardiovascular alterations that are, in general, related to a poor prognosis for the development of cardiovascular diseases. Autonomic imbalance toward an increased sympathetic contribution, resting tachycardia, lower HRV, and baroreflex impairment has been associated with the development of arrhythmias, myocardial infarction, and arterial hypertension (Sgoifo et al., 2015, 2014). Those alterations are similar to that found in rats exposed to a wide range of stressors during adolescence, an age at which individuals are more susceptible to the effects of stress (Crestani, 2017). Surprisingly, but not unexpectedly, resilient rats are protected from those harmful alterations.

Table 2
Corticosterone during rest, absolute and relative wet weight of adrenals, kidneys, spleen, heart, and thymus of resilient and susceptible phenotypes to social defeat stress.

		Control	Resilient	Susceptible
Corticosterone (ug/dL)		2.25 ± 0.73	**8.51 ± 2.54**$^{*\$}$	2.26 ± 0.95
Adrenals	Absolute (g)	0.061 ± 0.007	0.083 ± 0.007	0.078 ± 0.004
	Relative (g/kg)	0.21 ± 0.02	**0.33 ± 0.03***	**0.31 ± 0.02***
Kidneys	Absolute (g)	2.17 ± 0.05	2.10 ± 0.07	2.08 ± 0.11
	Relative (g/kg)	7.77 ± 0.21	8.20 ± 0.29	8.32 ± 0.46
Spleen	Absolute (g)	1.12 ± 0.10	1.12 ± 0.10	1.23 ± 0.12
	Relative (g/kg)	4.01 ± 0.34	4.35 ± 0.39	4.96 ± 0.52
Heart	Absolute (g)	0.92 ± 0.03	0.87 ± 0.04	0.90 ± 0.05
	Relative (g/kg)	3.28 ± 0.07	3.33 ± 0.05	**3.60 ± 0.12**$^{*\#}$
Thymus	Absolute (g)	0.35 ± 0.02	**0.23 ± 0.01***	**0.26 ± 0.03***
	Relative (g/kg)	1.20 ± 0.10	0.91 ± 0.07	1.02 ± 0.10

Numbers represent means ± SEM (n = 6–8 animals per group). *, $p < 0.05$ relative to control group. #, $p < 0.05$ relative to resilient group. $, $p < 0.05$ relative to susceptible group.

Table 3
Summary of behavioral and cardiovascular alterations in resilient and susceptible phenotypes to social defeat stress.

		Resilient	Susceptible
Social avoidance		=	↑
Coat state		=	↓
Open arms time on EPM		↑	=
Immobility on FST		=	↑
Body weight gain		↓	↓
Corticosterone during rest		↑	=
Resting heart rate		=	↑
Resting blood pressure		=	=
Resting heart rate variability		↑	↓
Vagal tonus		↑	=
Sympathetic contribution to autonomic balance		=	↑
Vascular sympathetic tonus		=	=
Baroreflex sensitivity	Spontaneous	=	↑
	Pharmacologic	=	=
Baroreflex effectiveness		=	↓
Organ weight	Adrenals	↑	↑
	Kidneys	=	=
	Spleen	=	=
	Heart	=	↑
	Thymus	↓	↓

↓, ↑, = indicates a decrease, an increase or no alteration relative to the control group, respectively.

Resting tachycardia is consistently described in rodents after stress exposure, especially were social isolation (Grippo et al., 2011, 2010, 2007) and chronic variable stress are involved (Duarte et al., 2015; Grippo et al., 2003, 2002). However, few works have shown this alteration in socially defeated rodents (Crestani, 2016; Sévoz-Couche et al., 2013). A possible explanation is that previous studies carried out a joint analysis of resilient and susceptible animals, which could mask the elevation in HR after stress exposure.

Increase in basal HR values have been reported as a risk factor for the development of cardiovascular diseases (Tadic et al., 2018). Individuals with higher HR present an increased risk to the development of arterial hypertension (Kim et al., 1999; Palatini et al., 2006), heart failure (Aune et al., 2017; Khan et al., 2015; Woodward et al., 2014), myocardial infarction (Aune et al., 2017; Fox et al., 2013; Wang et al., 2017; Zhang et al., 2016), and death after ischemic stroke (Nolte et al., 2016; Qiu et al., 2016). A recent meta-analysis showed that an increase of 10 BPM in resting HR enhances by 15% the risk of cardiovascular diseases and by 17% the mortality rate from other causes (Aune et al., 2017). In war veterans, who are at high risk for the development of stress-related disorders, greater HR values are associated with an increased risk of cardiovascular diseases and mortality (Pittaras et al., 2013). Lower levels of basal HR and higher HRV values are related to a lower incidence of depression in humans (Jandackova et al., 2016). Preclinical studies also show this relationship. Mice exposed to chronic variable psychological stress showed resting tachycardia and reduced endothelial function, which increased ischemic damage in a model of stroke (cerebral artery occlusion) (Custodis et al., 2011). In non-human primates treated with an atherogenic diet (Beere et al., 1984; Kaplan et al., 1987) and in rabbits with surgically induced atherosclerosis (van Hoof et al., 2017), HR reduction retarded the formation of atherosclerotic plaques.

Together with resting tachycardia, susceptible animals showed a decrease in HRV, while resilient rats had increased HRV. The literature shows that chronic stress exposure decreases HRV though alterations in the balance of sympathetic and parasympathetic tonus to the heart (Lombardi, 1996). This could be induced by enhanced sympathetic tone (Grippo et al., 2008, 2003; Vieira et al., 2017), decreased vagal tone (Wood et al., 2012), or a concomitant increase in sympathetic tone and decrease in vagal tone (Sévoz-Couche et al., 2013), depending on the stress length and protocol.

Autonomic imbalance toward an increase in the sympathetic contribution may explain the resting tachycardia and lower HRV. Other studies have shown that submissive rats in SDS exhibit decreased HRV and a shift in sympathovagal balance towards an increase in sympathetic tone (Wood et al., 2012). These animals also show increased depressive-like behaviors after SDS exposure, showing a susceptible phenotype (Wood et al., 2010). Therefore, susceptibility to SDS is related to a propensity for pathologic increases in sympathetic nervous system control of the heart.

Increased vagal tone to the heart might be interpreted as an adaptive response that protects resilient animals from cardiovascular and behavioral changes. To our knowledge, our study is the first to provide a potential mechanism wherewith resilient animals are protected from harmful cardiovascular and behavioral alterations related to stress exposure. Studies in humans showed that more self-compassionate individuals have both greater vagal tone to the heart and HRV (Svendsen et al., 2016). The self-compassion trait seems to be related to how individuals cope with stress, wherein more self-compassionate individuals cope better with adversity (Luo et al., 2018). Similarly, individuals with greater basal values of HRV are less likely to show symptoms of depression (Jandackova et al., 2016) and report suffering less from psychosocial stress (Lischke et al., 2018). On the other hand, lower baseline levels of HRV are associated with the inability to accept and regulate negative emotions (Visted et al., 2017; Williams et al., 2015) and to post-traumatic stress syndrome development after deployment in active marine members (Minassian et al., 2015, 2014). Thereby, self-compassion and HRV in humans seems to be related to stress resilience. Although it is not possible to access self-compassion in rats, the greater values of HRV found in resilient animals in our study corroborates data obtained from studies with human beings. Moreover, decreased anxiety-like behaviors in resilient rats could be a trait of

stress resilience.

Based on the works cited above, as well as our results, HRV seems to be a natural trait to determine how an individual copes with stress. Greater values of HRV and vagal tone to the heart probably precede SDS exposure and are likely inherent in resilient individuals, which could be part of the mechanism involved in resilience or a consequence of the status of neural pathways in those subjects. More studies are necessary to address whether these parameters are naturally higher in resilient individuals and if HRV could be a predictor of stress resilience. At least for humans, there is a growing body of evidence pointing to high HRV as a marker of stress resilience (Carnevali et al., 2018).

It can be argued that sympathovagal balance should be altered in resilient or susceptible animals since they showed altered vagal tone and an autonomic imbalance toward an increase in the sympathetic contribution. In resilient animals, there is a small trend toward an increased HF power spectrum. This could counterbalance the greater LF power spectrum, maintaining normal values of sympathovagal balance. More studies are necessary, using other techniques such as pharmacological blockade of autonomic branches to the heart, to confirm if this trend is biologically relevant. In susceptible animals, it is possible that the increase in the LF power spectrum was not sufficient to alter autonomic balance, since vagal tone to the heart is naturally higher (Task Force, 1996) and could mask the increase in sympathetic tone.

The decrease in BEI should be responsible for the autonomic imbalance in susceptible rats. Others have found altered baroreflex activity in rodents exposed to chronic variable stress (Almeida et al., 2015) and SDS (Sévoz-Couche et al., 2013). A less effective baroreflex decreases the inhibitory control of this reflex in the medullary neurons responsible for sympathetic system activation, which are tonically activated, increasing the sympathetic tone to the heart and vessels (Barman and Yates, 2017; Grassi et al., 2006). In our study the increase in sympathetic tone occurred exclusively to the heart, not affecting autonomic control of the vessels. An interesting result obtained here was the increased spontaneous baroreflex sensitivity, besides the decrease in effectiveness. It seems that SDS elicited functional alterations in both afferent and efferent arcs of the baroreflex. Although peripheral information seems to reach the central nervous system in an improved way in susceptible mice, autonomic responses are blunted, resulting in decreased baroreflex effectiveness.

Scientific literature concerning changes in heart weight is controversial. Although some studies have shown increased heart weight in stress-exposed animals as an indicator of heart hypertrophy (Carnevali et al., 2015; Costa-Ferreira et al., 2016; Vieira et al., 2017), others have found decreased heart weight associated with collagen deposition (Costoli et al., 2004) or no alteration (Almeida et al., 2015; Cruz et al., 2016). We found increased relative heart weight specifically in rats susceptible to SDS. In contrast to our study, Krishnan et al. (2007) found that only resilient mice show increased heart weight after SDS exposure. Cardiac hypertrophy also does not occur in female rats exposed to chronic variable stress, despite the female sex being more prone to the development of cardiovascular diseases and depression (Issler and Nestler, 2018; Vieira et al., 2017).

If we consider the increased heart weight in susceptible animals as a sign of cardiac hypertrophy, it should be related to increased sympathetic tone to the heart. The pathogenesis of cardiac hypertrophy involves diverse factors, including increased sympathetic activity (Samak et al., 2016; Yamazaki and Yazaki, 2000), and molecular alterations in cardiac hypertrophy are considered as the first step in the development of heart failure (Ritter and Neyses, 2003). On the other hand, it is also an important and reversible adaptive response during pregnancy and to exercise in athletes. Thus, the increased heart weight observed in our study should be interpreted with caution. Despite suggesting a dysfunction when analyzed together with other alterations found in the susceptible phenotype, only a histological analysis could confirm our hypothesis, especially considering the discrepancies found in the literature. The findings reported here could be a result of decreased body weight gain in these animals, for example.

Contrary to popular belief, SDS exposure is not inoffensive to resilient individuals, since some physiological alterations were found in both phenotypes. This study and others (Hammels et al., 2015) found decreased body weight gain, adrenal gland hypertrophy, and increased thymic involution in both susceptible and resilient rodents. These alterations seem to be related to hypothalamic-pituitary-adrenal (HPA) axis activation and circulating glucocorticoids (Harvey and Sutcliffe, 2010; Reul et al., 2015; Tarcic et al., 1998; Ulrich-Lai et al., 2006). These results also confirm that the differences found between resilient and susceptible rats are not related to the robustness of the stress faced by each phenotype, since both groups showed physiological alterations related to a general response to an adverse event.

Our study found increased basal corticosterone blood levels specifically in resilient animals 3 days after the end of SDS. This results seems to contradict the outcomes of human studies, since increased morning corticosterone is a common finding in patients suffering from depression (Bhagwagar et al., 2005; Holsboer, 2000; Vreeburg et al., 2009). Similarly to humans, increased basal plasma corticosterone was reported in rats presenting vulnerability to SDS (Wood et al., 2010). On the other hand, patients who had recovered from depression showed increased morning salivary cortisol levels (Bhagwagar et al., 2003), while depressive patients under selective serotonin reuptake inhibitor (SSRI) treatment showed elevated evening cortisol (Manthey et al., 2011). Resilient mice present increased basal corticosterone 39 days after the last defeat (Krishnan et al., 2007), whereas animals that were less prone to stress-induced depressive-like behaviors had higher levels of morning corticosterone after SDS exposure (Bowens et al., 2012). Thus, it is unclear to us the biological significance of such discrepancies, which could be related to differences in used species, time after the onset of disease or stress exposure, and medication history.

5. Conclusions

In summary, resilient animals are protected from behavioral and cardiovascular outcomes related to SDS exposure and present changes that can be interpreted as adaptive responses, such as increased HRV and vagal tone to the heart. On the other hand, susceptible animals show increased depressive-like behaviors and harmful cardiovascular outcomes, along with an autonomic imbalance toward an increase in the sympathetic contribution and baroreflex impairment.

To our knowledge, our study is the first to indicate maladaptive cardiovascular alterations and a correlation with increased depressive-like behaviors in rats susceptible to SDS, along with a possible mechanism by which resilient rats are protected from these changes. Our results suggest the importance of studying strategies that improve HRV and vagal tone, since they could be useful in the prevention or treatment of cardiovascular diseases related to stress and depression.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://

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