Neurobiology of Stress 38 (2025) 100752

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

Cardiometabolic and anxiogenic consequences of chronic social defeat stress in male mice

Karen A. Scott [a,b], Sophia A. Eikenberry [c], Khalid Elsaafien [a,b], Caitlin Baumer-Harrison [c], Dominique N. Johnson [a,b], Jéssica Matheus Sá [a,b], Alessandro Bartolomucci [d], Colin Sumners [c], Eric G. Krause [a,b,*], Annette D. de Kloet [a,b,**]

[a] Neuroscience Institute, College of Arts and Sciences, Georgia State University, Atlanta, GA, 30303, USA
[b] Center for Neuroinflammation and Cardiometabolic Diseases, College of Arts and Sciences, Georgia State University, Atlanta, GA, 30303, USA
[c] Department of Physiology and Aging, College of Medicine, University of Florida, Gainesville, FL, 32611, USA
[d] Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN, 55455, USA

ARTICLE INFO

Handling Editor: Prof R Lawrence Reagan

Keywords:
Chronic social defeat
Hypertension
Autonomic nervous system
Baroreflex
Adrenal
Anxiety

ABSTRACT

Social adversity, such as that which occurs during subjugation to a lower social status, has profound psychological and cardiometabolic consequences that are conserved across species. Clinically, such adversity often arises from being of a lower socioeconomic status and may contribute to health disparities in cardiometabolic and affective disorders. To develop a better understanding of the cardiometabolic consequences of social adversity, we employ chronic social defeat stress (CSDS) in adult male mice. CSDS results in increases in body mass, that are accompanied by elevated lean and fluid mass, as well as several somatic indices of chronic stress. Moreover, mice exposed to CSDS exhibit increased anxiety-like behavior, spending more time in the closed arms of the elevated plus maze and less time in the center of an open field arena. Regarding cardiovascular parameters, initial social defeat sessions result in increases in blood pressure, activity, and temperature in comparison with control mice. Interestingly, while blood pressure returns to basal levels by the start of the light cycle for the first few days of defeat, 14 days of CSDS results in sustained elevations in blood pressure, lower activity and lower body temperature. Finally, the results of heart rate variability, spontaneous baroreflex sensitivity and adrenal transcriptome analyses were consistent with CSDS-induced autonomic dysfunction, effects that may contribute to the hypertension observed. Collectively, these data suggest that CSDS may be useful for modeling hypertension induced by chronic social stress, thereby enabling us to better understand the mechanisms that contribute to stress-induced cardiometabolic disease.

1. Introduction

Health disparities are perpetually afflicting our society such that disadvantaged societal groups are at an increased risk for cardiometabolic disease-associated morbidity and mortality relative to more privileged communities (Din-Dzietham et al., 2004; Grotto et al., 2008; Sims et al., 2012; Leng et al., 2015; de Mestral and Stringhini, 2017; Anstey et al., 2019; Chin-Hong et al., 2020; Forde et al., 2020; Snyder-Mackler et al., 2020; Neufcourt et al., 2021; Powell-Wiley et al., 2022). For example, those who are subjected to social adversities like discrimination (Din-Dzietham et al., 2004; Sims et al., 2012; Everson-Rose et al., 2015; Hill and Thayer, 2019; Forde et al., 2020; Teshale et al., 2023) or lower socioeconomic status (Grotto et al., 2008; Leng et al., 2015; de Mestral and Stringhini, 2017; Anstey et al., 2019; Neufcourt et al., 2021) are also at an increased risk for obesity, hypertension, and cardiovascular disease. Further exacerbating the impact, is the realization that the prevalence of these hardships and associated cardiometabolic impairments have increased over recent years, during the COVID-19 pandemic (Chin-Hong et al., 2020; Wadhera et al., 2021; Martin et al., 2024). While cardiometabolic pathology associated with social adversity is frequently attributed to external factors that are commonly coupled to stress, like poor diet and lack of health care, it is

* Corresponding author. Georgia Research Alliance Distinguished Investigator Center for Neuroinflammation and Cardiometabolic Disease Neuroscience Institute Georgia State University, USA.
** Corresponding author. Center for Neuroinflammation and Cardiometabolic Disease Neuroscience Institute Georgia State University, USA.
E-mail addresses: ekrause@gsu.edu (E.G. Krause), adekloet@gsu.edu (A.D. de Kloet).

https://doi.org/10.1016/j.ynstr.2025.100752
Received 22 April 2025; Received in revised form 18 July 2025; Accepted 12 August 2025
Available online 13 August 2025

important to emphasize that the psychosocial stress component, in and of itself, contributes to pathology (Costoli et al., 2004; Golden et al., 2011; Razzoli et al. 2014, 2015, 2018; Razzoli et al., 2014; Snyder-Mackler et al., 2020). Consistent with this, the cardiometabolic consequences of chronic social stress are conserved across social species and several animal models have been used to discern the associated pathophysiology (Snyder-Mackler et al., 2020).

Here, we employ an experimental paradigm in adult male mice, referred to as chronic social defeat stress (CSDS), to develop a better understanding of the cardiometabolic consequences of social adversity. This paradigm exploits the naturalistic behavior of mice where dominant and subordinate dyads live chronically in sensory contact and physically interact on a daily basis (Costoli et al., 2004; Golden et al., 2011; Razzoli et al. 2014, 2015). Social subordination induced in mice and other rodents by way of CSDS (or comparable paradigms) is associated with profound behavioral and immune consequences and, of particular relevance here, leads to altered adiposity and cardiovascular dysfunction (Sgoifo et al. 1999, 2005; Bartolomucci et al., 2003; Costoli et al., 2004; Sévoz-Couche et al., 2013; Razzoli et al., 2015; Brouillard et al., 2019; Morais-Silva et al., 2019). For example, rats exposed to social defeat stress exhibit autonomic disruptions that contribute to hypertension (Sgoifo et al., 1999; Sévoz-Couche et al., 2013; Brouillard et al., 2019; Morais-Silva et al., 2019). Then, in mice, *per se*, a protocol similar to the CSDS, namely Chronic Subordination Stress has been found to elevate blood pressure and heart rate, and reduce heart rate variability (Costoli et al., 2004; Razzoli et al., 2020; Grant et al., 2022); however, in-depth examinations of the cardiometabolic consequences of CSDS in mice are lacking, particularly, regarding the progression of hypertension and complementary autonomic disturbances.

Thus, the primary goal of the present studies is to evaluate the impact of CSDS in mice on the development and progression of cardiometabolic perturbations, with a particular emphasis being placed on understanding the pronounced and intensifying hypertension observed. Secondary goals involve the exploration of potential mechanism(s) that underlie the high blood pressure observed by evaluating indices of autonomic function and endocrine status, partially accomplished by way of analysis of telemetrically recorded cardiovascular parameters, as well as by conducting transcriptome analyses on the adrenal glands of mice exposed to CSDS and controls. Collectively, these studies provide a framework for future experiments that will examine the neural, endocrine and behavioral mechanism(s) underlying social adversity-induced precipitation of cardiometabolic diseases.

2. Materials and methods

2.1. Animals

All procedures were performed at the University of Florida (Gainesville, FL) or Georgia State University (GSU, Atlanta, GA) and were approved by their Institutional Animal Care and Use Committees. Experimental mice were C57BL/6J males (Jackson Laboratories) and were 8–10 weeks old at the initiation of the studies. Resident aggressor mice were CD-1 males and were obtained from Charles River. These mice were at least 10–12 weeks at the time of arrival and were retired from use before 24 months of age. All mice were maintained on a 12:12 h light/dark cycle (lights on between 06:00h and 18:00h) in temperature-controlled and humidity-controlled rooms with free access to food and water unless stated otherwise.

2.2. Chronic social defeat stress (CSDS)

To determine the impact of social stress on cardiovascular, metabolic and behavioral parameters, male C57BL6/J mice were divided into two groups: (1) those that were subjected to CSDS and (2) those that were designated as “Pair-housed controls”. Briefly, the CSDS paradigm used here is based on that which is described by Golden et al., (2011) and involves brief (≤10min) daily ‘defeat’ sessions, in which resident ‘aggressor’ (CD-1) mice are used to defeat the experimental C57BL/6J mice. In order to minimize circadian disruptions, the defeat sessions and daily maintenance of both controls and CSDS mice directly preceded the onset of the dark phase (i.e., 17:00–18:00). Immediately following submission, the defeated mouse was housed in the same cage as the aggressor, physically separated by a perforated divider that allows for continuous visual, auditory, and olfactory contact. Submission was defined as when the mouse was either pinned in a supine position, or sat upright or reclined, with head up in the air with neck and belly exposed (Frischknecht et al., 1982). Importantly, the C57BL/6J mouse was defeated and housed with a different CD-1 mouse each day, to reduce the likelihood of habituation, and this procedure continued for a period of ~14 days. A total of 35 control and 32 CSDS mice were used in these studies.

2.3. Surgery

A subset of mice (n = 14 [8 CSDS and 6 pair-housed control]) were used for cardiovascular experiments which required the implantation of radiotelemetry devices. The surgical procedure has been described previously (de Kloet et al., 2013; Mohammed et al., 2022; Baumer-Harrison et al., 2024). In brief, mice were anesthetized under isoflurane, administered analgesic (buprenorphine SR-LAB; 0.1 mg/kg), and body temperature was maintained on a heating pad throughout the surgery. Radiotelemetry transmitters (HD-X10; Data Sciences International, St. Paul, MN) were placed intraperitoneally and secured to the abdominal wall using 5-0 silk suture. The abdominal muscles were then closed with absorbable monofilament suture (size: 5-0). To implant the fluid-filled catheter, an incision was made on the midline of the ventral neck to expose the left carotid artery. The catheter was guided from the abdominal incision toward the neck incision, using a trocar. Subsequently, a segment (~1 cm) of the carotid artery was separated from the vagus nerve. Using two silk sutures (size: 5-0), the cranial end of the segment was permanently ligated, and the caudal end of the segment was temporarily occluded. Next, the carotid artery was punctured, and the catheter was inserted into the artery lumen and then secured using the silk suture. Finally, the skin was closed with non-absorbable monofilament suture (size: 5-0).

2.4. Recording and analysis of blood pressure, heart rate, activity, and core body temperature

During cardiovascular recordings, mice were housed in cages placed on PhysioTel® receivers (Data Sciences International, St. Paul, MN). To initiate data collection, devices were turned on by touching the animal with a magnet, immediately transmitting the signal. Data was continuously acquired using Ponemah Software (Data Sciences International, St. Paul, MN) for the duration of the experiment. Cardiovascular data were analyzed using Ponemah software. In order to evaluate heart rate, blood pressure, activity and core body temperature responses to CSDS throughout the 24-h course of the day, data were consolidated into hourly bins. These hourly bins were then averaged across three consecutive days to generate average daily baseline traces, as well as 24-h traces collected during Days 1–3 and Days 12–14 of the CSDS. Data were also evaluated throughout the entire time course of the study by determining the mean daily values for each of the parameters.

2.5. Analysis of heart rate variability

Ponemah Software was also used for Time Domain analysis of heart rate variability (HRV) as described (Thireau et al., 2008). Analysis was performed between 7 and 9 a.m. (for AM values) and 7 and 9 p.m. (for PM values). Average AM and PM values were obtained across multiple days (i.e., Days 1–3 of CSDS and Days 12–14 of CSDS).

2.6. Spontaneous baroreflex analysis

Spontaneous baroreflex analysis was performed using HemoLab Ver. 27.3 Software (http://haraldstauss.com/HaraldStaussScientific/hemolab/default.html) (Stauss, 2008). The software identifies sequences of four or more heartbeats where blood pressure and pulse intervals change in the same direction. These sequences are identified from raw pulsatile arterial blood pressure recordings extracted from the Ponemah files. For all sequences, a linear regression is calculated, and the average of the slopes of all linear regression lines are used as an index of baroreceptor-heart rate reflex sensitivity (Spontaneous Cardiac Baroreceptor Reflex Gain – sBRG) (Bertinieri et al., 1985; Di Rienzo et al., 1985). In addition, the ratio between the number of arterial blood pressure ramps followed by respective pulse interval reflex ramps, and the total number of arterial blood pressure ramps at a given period is calculated (Baroreflex Efficiency Index – BEI) (Bertinieri et al., 1985; Di Rienzo et al., 1985). Analysis was performed for all pair-housed controls and CSDS groups between 7 and 9 a.m. (for AM values) and 7 and 9 p.m. (for PM values). Average AM and PM values were obtained across multiple days (i.e., Days 1–3 of CSDS and Days 12–14 of CSDS).

2.7. Body weight and composition analysis

Throughout the course of the study, body weight was evaluated in subjects daily (between 17:00h and 18:00h). These measurements were obtained manually using a scale located in the animal housing room. In a subset of mice (n = 6/group), body composition was also analyzed at the end of the study. These measurements were obtained using a MiniSpec tdNMR (LF50, Bruker).

2.8. Behavioral assays

In subsets of CSDS and pair-housed control mice, anxiety-like behavior was assessed in Elevated Plus Maze (EPM) and Open Field Arena (OFA). These assays were performed during the light-phase (08:00 a.m.-12:00 p.m.) after Day 14 of CSDS. Briefly, the EPM test is 5 min and is performed in an arena that has two opposing open arms and two opposing closed arms. The arms are all raised 61 cm above the floor and are all 35 × 5 cm (l x w) with white floors. In addition, the walls of the closed arms are made of black polycarbonate and are 20 cm tall. To initiate the test, each mouse was placed in the center of the EPM, facing an open arm. Results, including the percentage of time spent in the closed arms and the distance traveled, were recorded and analyzed by Ethovision XT 13 (Noldus Information Technology, Netherlands). Finally, fecal boli were manually counted and recorded at the end of the test.

The OFA test is also a 5 min and is conducted in a 45 x 45 × 30 cm (l x w x h) square arena constructed of white plastic floor and walls. To initiate the test, the mouse was placed in the center of the open field arena and the mouse's movement is recorded. Similar to the EPM test, the results, including total distance traveled and entries into center (located in the center of arena with 50 % of total area) or edge were recorded and analyzed using Ethovision XT 13 software (Noldus Information Technology, Netherlands).

2.9. Humoral assays

Plasma was collected from subsets of mice (n = 20–21/group) at specific time points throughout the studies. Briefly, to measure basal plasma corticosterone levels, mice were brought from their housing room into the procedure room and blood was collected via tail snip into EDTA coated tubes within 3 min of removing the cage from the housing room. This procedure was performed (after 10 days of CSDS) at their predicted circadian nadir (0800h; AM basal) and peak (1700h; PM basal) of corticosterone secretion. Other plasma measurements (n = 5–6/group) were performed using samples that were collected at the time of euthanasia. Blood was centrifuged at 4 °C, 2500 x G, for 20 min. Plasma was aliquoted and stored at −80 °C until assays were run.

The following assays were used, and, in all cases, the manufacturer's instructions were followed: Plasma corticosterone was assessed by radioimmunoassay (MP Biomedicals, Orangeburg, NY, catalog #0712010). Plasma leptin, glucose and C-reactive protein assessed by ELISA (Crystal Chem, Elk Grove Village, IL, catalog #s 90030, 81692, and 90080, respectively).

2.10. Euthanasia and tissue collection

Mice were euthanized between 0800h and 1200h. Mice were deeply anesthetized using sodium pentobarbital (50 mg/kg i.p.) and blood was collected by way of cardiac puncture. Subsequently, mice were either (1) transcardially perfused with saline followed by 4 % paraformaldehyde to collect tissues for histology or (2) decapitated to collect tissues for weighing. Additionally, adrenals from a subset of mice (6 controls and 6 CSDS) were used for gene expression analysis via bulk RNA sequencing. These adrenals were rapidly weighed, then frozen on dry ice, and stored at −80 °C until further processing.

2.11. Adrenal RNA sequencing

RNA extraction and DNase treatment were performed on adrenals using RNeasy columns (Qiagen) according to the manufacturer's instructions. The remaining procedures were completed by the UF ICBR, as follows. RNA was checked for integrity using an Agilent Bioanalyzer and all samples that were evaluated had an RNA integrity number above 8.0 and were used for library construction with the NEBNext Poly(A) mRNA Magnetic Isolation Module (New England Biolabs, catalog #E7490). This was followed by RNA library construction with the NEBNext Ultra II Directional RNA Library Prep Kit (New England Biolabs, catalog #E7760) according to the manufacturer's user guide after which they were adjusted to equal molarity and sequenced on an Illumina NovaSeq (2 × 100bp) to achieve a minimum of 40M reads per sample. RNA-seq library preparation was performed at UF ICBR Gene Expression Core (https://biotech.ufl.edu/gene-expression-genotyping/, RRID:SCR_019145). Sequencing was performed at the ICBR NextGen Sequencing (https://biotech.ufl.edu/next-gen-dna/, RRID: SCR_019152).

2.12. Data analysis and statistics

Multiple statistical analyses were performed on the data collected here. In most cases, these analyses were performed using GraphPad, and results were considered statistically significant at $p < 0.05$. For blood pressure, heart rate, activity and core body temperature, binned data were analyzed using a two-way repeated measures ANOVA. Heart rate variability and baroreflex sensitivity were calculated as described above and then similarly analyzed using a two-way repeated measures ANOVA. When significant interactions were revealed, *post hoc* analyses (Šídák's multiple comparisons tests) were performed for the between and within subjects' comparisons as appropriate. Body composition, organ weights, humoral assays and behavioral tests were analyzed by way of unpaired t-tests.

Analysis of RNA sequencing data was performed by UF ICBR (RRID: SCR_01912) and first entailed the evaluation of differential gene expression between the CSDS and pair-housed control groups using the Ingenuity Knowledge Base (Genes only) and $p < 0.05$ and a fold change of 1.5 were selected as the cutoffs for expression changes. These results then underwent further ingenuity pathway analysis (IPA), and z-scores greater than or equal to 2 were taken to represent significant predictions of activation, while predictions of inhibition were made for z-scores less than or equal to −2.

3. Results

3.1. Chronic social defeat stress influences body weight, body composition, and other somatic indices of chronic stress in male mice

Chronic exposure to psychological stress has diverse effects on body weight, composition and other somatic indices of stress exposure and adaptation that often differ based on the nature of the stressor, as well as environmental and genetic factors (Dallman et al., 2003; Dallman, 2010; Dinsa et al., 2012; Razzoli et al., 2017; Kivimäki et al., 2023). Here, we initially sought to ascertain the somatic effects of chronic social defeat in adult male C57BL6/J mice using a CSDS paradigm (based on Golden et al. (2011)). As highlighted in Fig. 1, 14 days of CSDS significantly increases body weight over time (Fig. 1B; CSDS by time interaction; $F(14, 434) = 4.49$; $p < 0.0001$, two-way ANOVA). Analysis of body composition revealed increased lean [Fig. 1C; $t(10) = 2.43$; $p = 0.04$], decreased fat [Fig. 1D; $t(10) = 3.03$; $p = 0.01$] and elevated fluid mass [Fig. 1E; $t(10) = 6.60$; $p < 0.0001$] in CSDS mice relative to the pair-housed controls. Upon termination of the study, adipose tissue pads and other stress-sensitive tissues were dissected and weighed (Fig. 1F–J). In accordance with the body composition measurements, 14 days of CSDS resulted in reductions in the weights of all the white adipose tissue depots evaluated (Fig. 1F). On the other hand, brown adipose tissue mass was not altered (Fig. 1F). Furthermore, the CSDS paradigm induced thymic involution (Fig. 1G), while simultaneously causing enlargement of the spleen (Fig. 1H), adrenal glands (Fig. 1I) and heart (Fig. 1J–K), effects that are collectively consistent with immune dysfunction, chronic hypothalamic-pituitary-adrenal (HPA) axis activation, and cardiac hypertrophy.

Plasma samples from socially defeated and control subjects were used to evaluate the impact of CSDS on endocrine and other humoral endpoints (see Table 1). Notably, corticosterone levels were elevated in

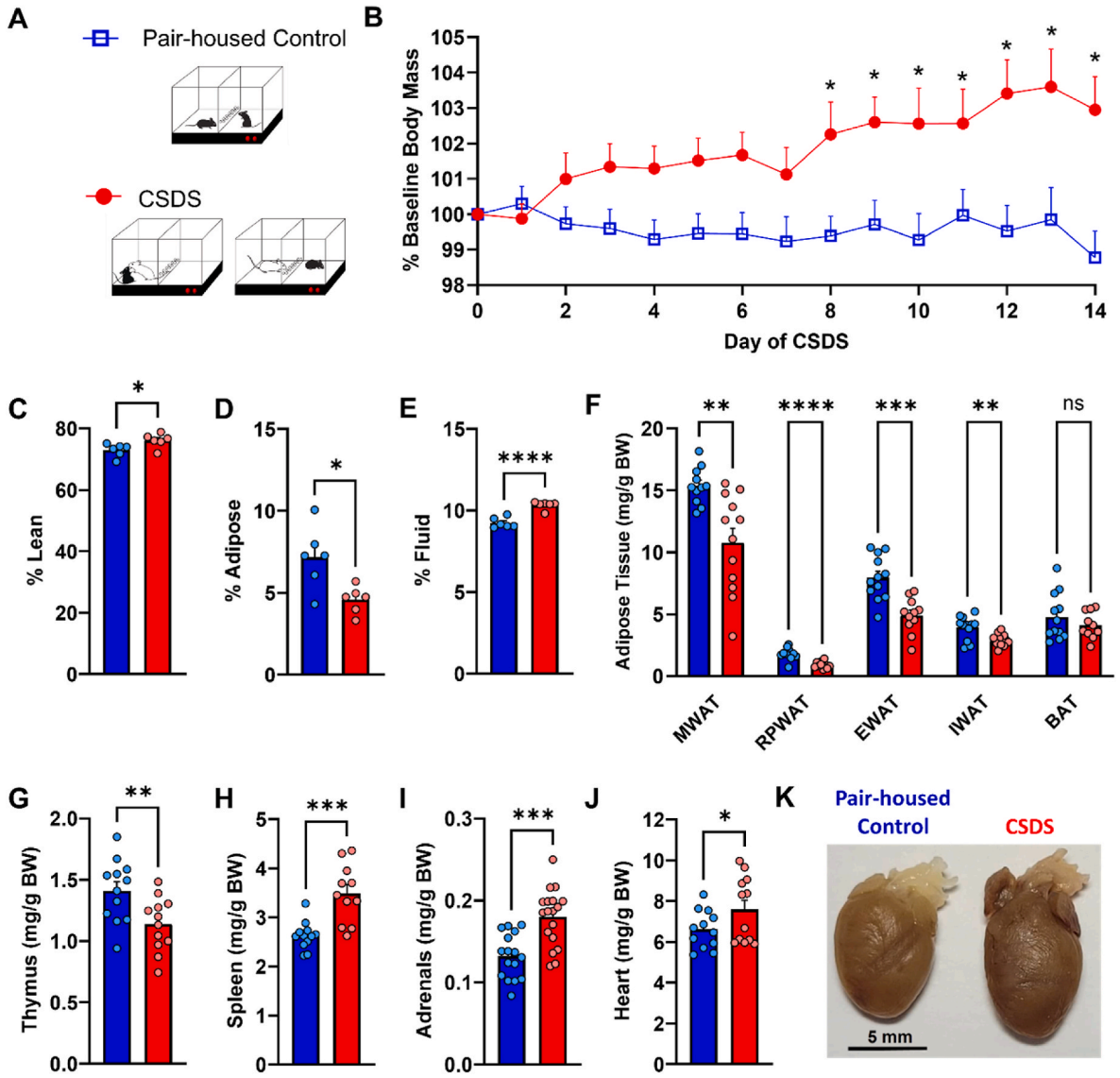

Fig. 1. Chronic social defeat stress influences body weight, body composition and other physiological indices of stress exposure. (**A**) Schematics depicting the pair-housed control and CSDS mice. (**B**) Trajectory of body weight changes during 14 days of CSDS or pair-housing conditions, expressed as percentage of baseline body weight; n = 15–18/group (2-way ANOVA; Šídák's *post hoc* multiple comparisons test, *, $p < 0.05$, relative to time = 0). (**C-E**) Body composition analysis performed via TD-NMR at the end of CSDS, highlighting percent (**C**) lean, (**D**) adipose and (**E**) fluid mass in CSDS mice and pair-housed controls; n = 6/group (un-paired *t*-test). (**F-J**) Individual organ weights assessed after 14 days of CSDS and plotted relative to body weight, highlighting differences in (**F**) mesenteric (MWAT), retroperitoneal (RPWAT), epididymal (EWAT), inguinal white adipose tissue (IWAT) and intrascapular brown adipose tissue (BAT), (**G**) Thymus, (**H**) Spleen, (**I**) Adrenals and (**J**) Heart; n = 11–16/group (un-paired t-tests). (**K**) Representative images of hearts collected from pair-housed control (left) and CSDS (right) mice. Bars represent SEM. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$.

Table 1
Chronic social defeat stress influences humoral parameters. n = 5–21/group; *, $p < 0.05$ (un-paired t-tests).

	CON	CSDS	Statistics
AM Corticosterone (ng/mL)	26.59 ± 3.03	43.06 ± 6.62	N = 20, 21; p = 0.0160
PM Corticosterone (ng/mL)	132.3 ± 13.8	102.8 ± 7.2	N = 21, 20; p = 0.0337
Glucose (mg/dL)	117.5 ± 7.16	105.4 ± 8.02	N = 6, 6; p = 0.1434
Leptin (ng/mL)	5.89 ± 0.689	3.12 ± 0.089	N = 6, 6; p = 0.0013
C-reactive Protein (ng/mL)	7.93 ± 0.272	10.1 ± 0.990	N = 5, 6; p = 0.0429

the AM (0800–0900h), but lowered in the PM (1700–1800), highlighting a potential disruption in the circadian rhythm of secretion. Additionally, while glucose levels (assessed in the AM only) were unaltered, leptin levels (assessed in the AM only) were reduced, results that are consistent with their reduced level of adiposity (Maffei et al., 1995). Last, the levels of acute-phase reactant C-reactive protein (CRP; assessed in the AM only) were elevated in CSDS mice relative to controls, results that are suggestive of a state of bodily inflammation and with previous studies that have revealed positive links among CRP levels, exposure to social stressors and cardiometabolic diseases (Johnson et al., 2013; Muscatell et al., 2020).

Overall, these findings highlight that chronic social stress using the CSDS model leads to an elevation in body mass that is the consequence of increases in lean and fluid mass, rather than adiposity. They further reveal that CSDS leads to bodily and humoral changes that are consistent with exposure to chronic stress and also with the observed reductions in adiposity.

3.2. Chronic social defeat stress induces anxiety-like behavior in male mice

Experience of social adversity is an established predictor of affective disorders, including generalized anxiety (Scott et al., 2014). To provide an index of anxiety-like behavior subsequent to CSDS, mice were again subjected to CSDS or pair-housed control conditions for 14 days. Afterwards, they underwent testing in either an EPM (Fig. 2A–D) or an OFA (Fig. 2E–F) test. As highlighted in Fig. 2A–D, CSDS mice spent significantly more time in the closed arms [t (16) = 2.89; p = 0.0106; Fig. 2B], deposited a higher quantity of fecal boli [p = 0.005; *Mann-Whitney U test;* Fig. 2C] and traveled a shorter distance [t (16) = 3.88; p = 0.0013; Fig. 2D] in the EPM than their pair-housed control counterparts. While CSDS mice did not exhibit a significant reduction in the time spent in the center of the OFA [t (10) = 1.89; p = 0.0874; Fig. 2F], they did enter the center fewer times [t (10) = 3.41; p = 0.0067; Fig. 2G] and exhibited decreased locomotion [t (10) = 4.96; p = 0.0006; Fig. 2H], which was similar to that observed with the EPM. Overall, these results suggest that CSDS induces anxiety-like behavior and reduces locomotor activity, findings that are consistent with previous reports (Bartolomucci et al., 2003; Araki et al., 2024; Harada et al., 2024).

3.3. Chronic social defeat stress in male mice causes robust and sustained increases in blood pressure that are exacerbated over time

Exposure to social adversity is also a predictor of hypertension and cardiovascular disease (Yan et al., 2003; Everson-Rose et al., 2015; Leng et al., 2015; Demakakos et al., 2018; Powell-Wiley et al., 2022). In order to determine the impact of CSDS on cardiovascular parameters, a subset of experimental subjects was implanted with telemetry devices that monitor systolic and diastolic blood pressure (SBP and DBP, respectively), mean arterial pressure (MAP), and heart rate (HR), as well as core body temperature and activity. Initial analyses involved assessing mean daily BP and HR for three days prior to the onset, and throughout the first 14 days, of CSDS (i.e., prior to behavioral assays Fig. 3A). In brief, two-way ANOVA revealed a significant Group by Day interaction for all cardiovascular parameters assessed [SBP, F (16, 192) = 3.25, p < 0.0001; DBP, F (16, 192) = 2.81, p < 0.0001; MAP, F (16, 192) = 3.03, p = 0.0002; HR, F (16, 192) = 5.090; p < 0.0001], with *post hoc* analyses revealing several specific time points at which these parameters were significantly elevated in the CSDS group relative to pair-housed controls.

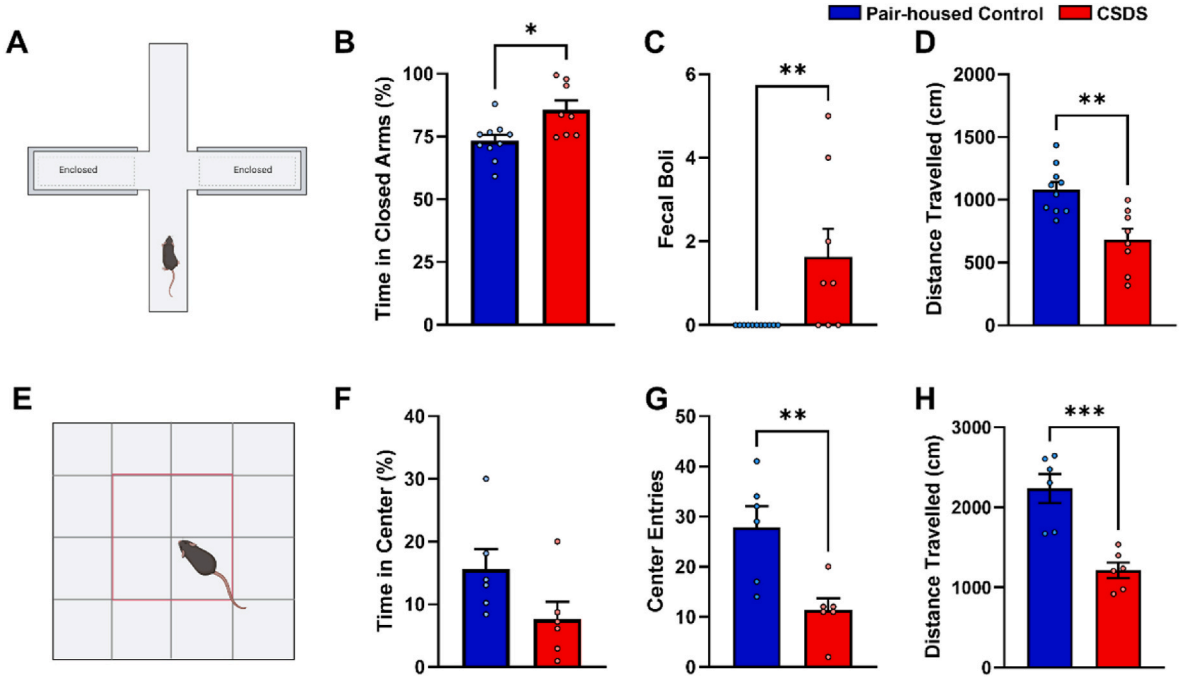

Fig. 2. Chronic social defeat stress increases anxiety-like behavior and reduces locomotor activity. (**A, E**) Schematics of Elevated Plus Maze (EPM) and Open Field Arena (OFA), respectively. Anxiety-like behavior and locomotor activity were assessed in the EPM (**A-D**) and OFA (**E-H**). EPM: n = 8 (CSDS), n = 10 (control); OFA: n = 6/group. Unpaired t-tests; bars represent SEM. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. Schematics made using Biorender.com.

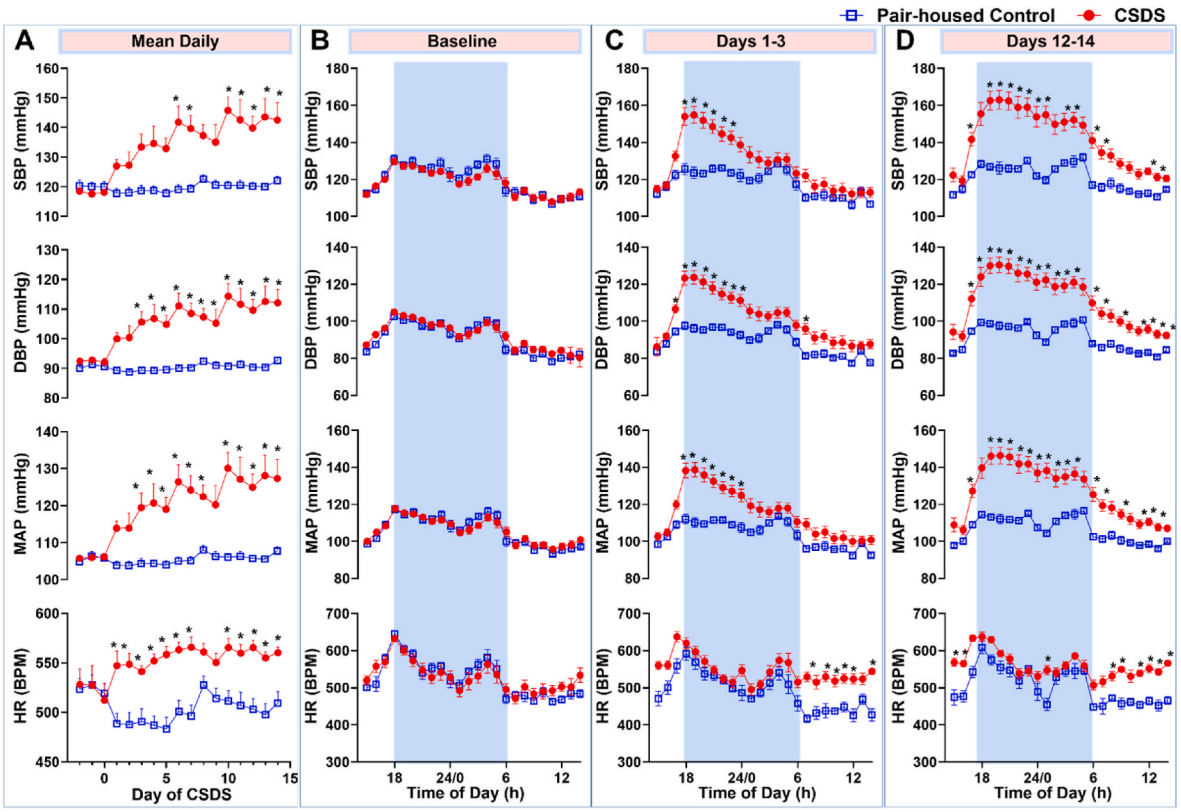

Fig. 3. Chronic social defeat stress elicits elevations in blood pressure and heart rate that are enhanced over time. (**A**) From top to bottom, mean daily systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and heart rate (HR) throughout the 14-day course of CSDS. (**B-D**) From top to bottom, mean hourly SBP, DBP MAP, and HR traces throughout the (**B**) baseline period, (**C**) Days 1–3, and (**D**) Days 12–14 of CSDS (n = 8) or pair-housing (n = 6). Bars represent + SEM. 2-way ANOVA; *, $p < 0.05$ (between-subjects, *post hoc*).

In addition, analysis of mean daily activity revealed a significant CSDS by 'Day of Defeat' interaction [F (16, 192) = 2.136; p = 0.008]; however, mean daily core body temperature was not significantly altered by CSDS (Supplemental Fig. 1A).

To determine the impact of the CSDS or pair-housed control conditions on cardiovascular parameters throughout the 24-h light-dark cycle, hourly bins of SBP, DBP, MAP and HR data were averaged across three different 3-day intervals (i.e., Baseline (Days -2-0), Days 1–3 and Days 12–14). Two-way repeated measures ANOVAs revealed a significant impact of 'Time of Day' on SBP, DBP, MAP or HR during the baseline recording period; however, there were no differences between the groups (Fig. 3B). On the other hand, on Days 1–3 and the Day 12–14, CSDS caused robust and sustained increases in SBP, DBP, MAP and HR that were considered statistically significant at several time points throughout the 24-h trace (Fig. 3C–D). That is, on Days 1–3, the ANOVA revealed a CSDS by 'Time of Day' interaction for SBP [F (23, 276) = 10.9; $p < 0.0001$], DBP [F (23, 276) = 7.22; $p < 0.0001$], MAP [F (23, 276) = 9.28; $p < 0.0001$] and HR [F (23, 276) = 3.38; $p < 0.0001$]. *Post hoc* analyses of BP during Day 1–3 indicated that the significant increases in these parameters occurred primarily during the dark-phase and lasted for approximately 6 h after the defeat session. Heart rates, on the other hand, were elevated at several time points during the light-phase. The ANOVA conducted on the data obtained during Days 12–14 similarly revealed CSDS by 'Time of Day' interactions for SBP [F (23, 276) = 8.68; $p < 0.0001$], DBP [F (23, 276) = 7.38; $p < 0.0001$], MAP [F (23, 276) = 7.90; $p < 0.0001$] and HR [F (23, 276) = 4.52; $p < 0.0001$]. In general, however, *post hoc* analyses of data collected during Days 12–14 indicated that BP was significantly elevated throughout the majority of the dark-phase and that these increases extended into the light-phase. Like what was observed during the Day 1–3, heart rates were higher in CSDS mice throughout the majority of the light-phase during Day 12–14.

Finally, telemetry was also used to monitor core body temperature and activity throughout the course of the study. Activity and core body temperature were then also analyzed in hourly bins to determine the impact of CSDS throughout the light-dark cycle during the baseline period, Days 1–3 and Days 12–14 of CSDS (Supp. Fig. 1B–C). During the baseline period (Supp. Fig. 1B), there were main effects of 'Time of Day', but no effects of CSDS on these parameters. During Days 1–3 (Supp. Fig. 1C), ANOVA revealed significant CSDS by 'Time of Day' interactions for activity [F (23, 276) = 2.11; p = 0.0027] and core body temperature [F (23, 276) = 2.25; p = 0.0012]; however, *post hoc* analyses did not reveal significant differences in individual timepoints for these parameters. During Days 12–14 (Supp. Fig. 1D), there were again CSDS by 'Time of Day' interactions for activity [F (23, 276) = 3.53; $p < 0.0001$] and core body temperature [F (23, 276) = 3.51; $p < 0.0001$]; however *post hoc* analyses did reveal individual time points of significant reductions in these parameters during the dark-phase (i.e., Activity 2300h; Temperature 1900h and 2300h).

Collectively, these telemetry data indicate that while CSDS causes minor reductions in activity and core body temperature, it causes robust and sustained elevations in BP and HR that are enhanced over time.

3.4. *Chronic social defeat stress promotes indices of autonomic dysfunction in male mice*

There are numerous mechanisms involved in blood pressure regulation (Dampney, 2016), and many of these same processes are impacted by chronic stress (Ulrich-Lai and Herman, 2009), thus potentially contributing to the cardiovascular perturbations that are observed during CSDS. Among the systems involved in blood pressure regulation is the autonomic nervous system, which, during stress, undergoes a

dramatic shift towards enhanced sympathetic and dampened parasympathetic outflow (Guyenet, 2006; Ulrich-Lai and Herman, 2009). These effects ultimately lead to increases in cardiac output and vascular resistance that elevate blood pressure. To begin evaluating the status of the autonomic control of the cardiovascular system in CSDS mice vs. pair-housed controls, telemetry data were analyzed to examine HRV in Time Domain using Ponemah software. The parameters assessed were NN-interval (the average time interval between successive heart beats, indicative of HR), SDNN (the standard deviation of all regular intervals, which reflects total autonomic variability), RMSSD (the square root of mean squared differences between adjacent regular intervals, which reflects short-term variations in HR) and pNN6 (the percentage of successive NN intervals that differ by more than 6 ms, which is correlated with parasympathetic activity (Thireau et al., 2008; Shaffer and Ginsberg, 2017).

As highlighted in Table 2, there were significant CSDS by 'Time of Day' interactions for all parameters during Days 1–3 of the experiment [Table 2; NN-interval, $F(1, 12) = 7.4$, $p = 0.02$; SDNN, $F(1, 12) = 5.7$, $p = 0.03$; RMSDD, $F(1, 12) = 14.2$, $p = 0.003$; pNN6, $F(1, 12) = 20.79$, $p = 0.02$], and also for NN-interval, RMSDD and pNN6 during Days 12–14 of the experiment [Table 2; NN-interval, $F(1, 12) = 5.1$, $p = 0.04$; RMSDD, $F(1, 12) = 17.1$, $p = 0.001$; pNN6, $F(1, 12) = 15.09$, $p = 0.0022$]. For SDNN (Day 12–14), there were significant main effects of Time of Day [$F(1, 12) = 28.80$, $p = 0.0002$] and CSDS condition [$F(1, 12) = 22.41$, $p = 0.0005$]. Intriguingly, while *post hoc* analyses revealed a significant impact of CSDS on all parameters during only the inactive phase (AM) for Days 1–3, significant decreases in the SDNN, RMSDD- and pNN6 (%) parameters were observed during both the AM and PM for Days 12–14. The implication is that CSDS results in autonomic dysfunction and that, while these effects are limited to the inactive phase early on in the paradigm (Days 1–3), they are prevalent during both the active and inactive phases after longer exposure to the CSDS (Days 12–14).

Table 2
Impact of CSDS on HRV as Assessed in the Time Domain. * indicates a significant main effect for CSDS, # indicates a significant main effect for time of day and $ indicates a significant interaction. The letters indicate between group differences determined by way of Šídák's multiple comparisons test (i.e., non-shared letters indicating a statistically significant difference between groups), $p < 0.05$. n = 8 CSDS and n = 6 controls.

	AM		PM	
	CON	**CSDS**	**CON**	**CSDS**
Days 1–3				
NN Interval (ms)# * $	142.4 ± 4.3 [a]	120.7 ± 3.2 [b]	105.5 ± 3.3 [c]	98.6 ± 2.0 [c]
SDNN (ms) $	10.0 ± 0.9 [a]	6.9 ± 0.8[b]	7.7 ± 0.4	7.8 ± 1.0
RMSSD (ms) $	8.2 ± 0.5 [a]	4.8 ± 0.6 [b]	5.1 ± 0.4 [b]	6.7 ± 1.0 [b]
pNN6 (%)# * $	30.1 ± 2.9 [a]	12.3 ± 2.7 [b]	13.2 ± 2.2 [b]	15.9 ± 3.3[b]
Days 12–14				
NN Interval (ms)# * $	137.9 ± 3.9 [a]	119.2 ± 2.7[b]	105.5 ± 3.3 [c]	98.6 ± 2.0 [c]
SDNN (ms)# *	9.8 ± 1.1	6.3 ± 0.3	7.0 ± 0.3	4.4 ± 0.4
RMSSD (ms)# * $	7.5 ± 0.6 [a]	4.2 ± 0.2 [b]	4.3 ± 0.3 [c]	3.0 ± 0.3 [d]
pNN6 (%)# * $	26.4 ± 2.7 [a]	9.7 ± 1.0 [b]	9.4 ± 1.7 [c]	3.7 ± 1.0[d]

3.5. Chronic social defeat stress attenuates spontaneous baroreflex sensitivity in male mice

The autonomic control of cardiovascular function relies heavily on the baroreflex, which involves the sensation of vascular stretch and consequent initiation of appropriate compensatory responses to maintain blood pressure within a set range (Guyenet, 2006). In order to provide an index of baroreflex function in CSDS and control mice, telemetry data underwent analyses of spontaneous baroreflex gain (sBRG) and baroreflex effectiveness index (BEI) using Hemolab software (Stauss, 2008). Briefly, sBRG compares spontaneous changes in arterial pressure to cardiac intervals, with lower values being indicative of an impairment in the baroreflex buffering of sudden changes in blood pressure by altering cardiac intervals. Similarly, BEI measures the time that the arterial baroreflex is actively engaged to control heart rate by comparing the number of systolic ramps to pulse intervals at a given period. In both cases, lower values for the parameters are indicative of reduced baroreflex sensitivity. As can be visualized in Fig. 4A, there were significant reductions in sBRG during the dark-phase (PM; treatment-effect, $F(1,13) = 19.72$, $p = 0.0007$) and BEI during the light-phase (AM; interaction-effect, $F(1,13) = 12.34$) early on (i.e., Days 1–3) in the CSDS paradigm. Later in the CSDS paradigm (i.e., Days 12–14; Fig. 4B), both sBRG and BEI were significantly reduced during the AM and PM periods (sBRG, treatment-effect, $F(1,13) = 18.72$, $p = 0.0008$; BEI, treatment-effect, $F(1,13) = 17.76$, $p = 0010$), data that collectively support a robust dampening in baroreflex sensitivity during CSDS.

3.6. Chronic social defeat stress alters the adrenal gland transcriptome in male mice

Another important component/effector of the autonomic nervous system, and of the HPA axis, is the adrenal gland. Hypertrophy and

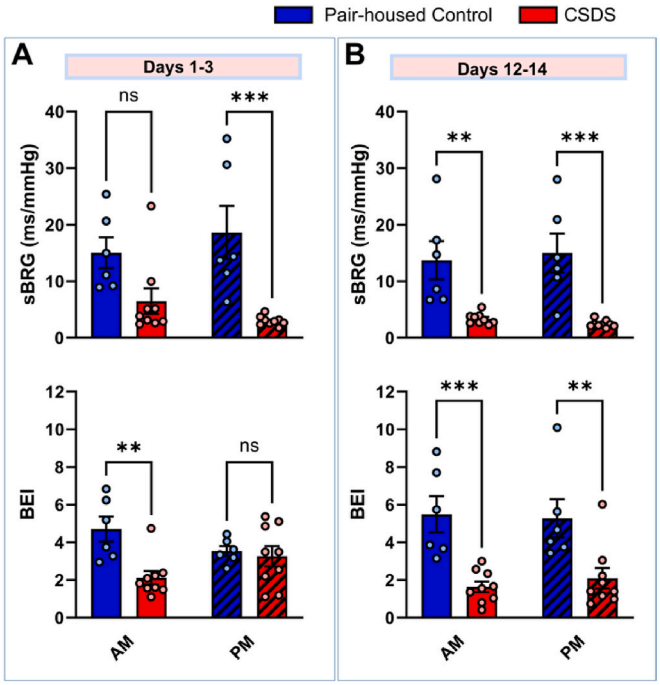

Fig. 4. Exposure to CSDS is associated with reduced baroreflex sensitivity. From top to bottom, spontaneous baroreflex gain (sBRG) and baroreflex effectiveness index (BEI) during (**A**) Days 1–3 and (**B**) Days 12–14. Note that AM values were obtained between 0700 and 0900 (i.e., during a 2-h window that started 1 h after lights ON), while PM values were obtained between 1900 and 2100 (i.e., during a 2-h window that started 1 h after lights OFF). 2-way ANOVA; *$p < 0.05$ (between-subjects, *post hoc*).

hyperplasia of the adrenal gland are frequent consequences of chronic stress exposure (Ulrich-Lai et al., 2006) and, as highlighted above (Fig. 1), CSDS mice have enlarged adrenals. Here, we sought to determine whether the transcriptome of the adrenals of mice subjected to CSDS was altered in a manner that is consistent with adrenal enlargement, with enhanced glucocorticoid synthesis, and with increased sympathetic activation, as indicated by raised catecholamine synthesis and secretion. To accomplish this, bulk RNA sequencing was conducted on the adrenals of CSDS mice and pair-housed controls, and the data was analyzed using the Ingenuity Knowledge Base (Genes only). The comparison made was CSDS genes vs. Control genes, and $P < 0.05$ was selected as the cutoff for expression changes. This criterion resulted in 2517 genes from a total of 15221 in the entire database showing significant changes (increase or decrease) in expression in the CSDS adrenals vs. control adrenals.

Ingenuity Analysis of Canonical Pathways (IPA) was performed on the genes that not only reached the $P < 0.05$ threshold but also displayed an at least 1.5-Fold Change (increase or decrease) in expression. These genes are displayed in the Volcano Plot, as shown in Fig. 5. From the IPA, Z-scores greater than or equal to 2 were taken to represent significant predictions of activation, while predictions of inhibition were made for Z-scores less than or equal to −2. The IPA revealed changes in gene expression in the CSDS group that were consistent with adrenal enlargement in these mice, and this was most apparent in the "Collagen Biosynthesis and Modifying Enzymes" pathway, which exhibited the highest -log(P-value) and positive Z-Score at 3.96 and 2.828427 respectively. Within this pathway, the expression of several collagen genes that are components of the adrenal cortex extracellular matrix (Otis et al., 2007; Kremer et al., 2024) was elevated, consistent with increased tissue growth. These genes included: Col1a1 (Collagen, type I, alpha 1), Col1a2 (Collagen, type 1, alpha 2), Col4a1 (Collagen, type IV, alpha 1) and Col5a3 (Collagen, type V, alpha 3). Respective Fold Changes in expression and Expr P-values for these genes are shown in Table 3.

The IPA Canonical Pathways associated with either enhanced glucocorticoid synthesis ("Cholesterol Biosynthesis") or with catecholamine synthesis and secretion ("Catecholamine Biosynthesis") did not exhibit Z-scores that were ≥2.0 or ≤ −2.0. Nonetheless, within the Cholesterol Biosynthesis pathway several genes exhibited increased expression, consistent with elevated steroid synthesis. These included two genes that are important for cholesterol biosynthesis: Dhcr7 (7-dehydrocholesterol reductase) and Dhcr24 (24-dehydrocholesterol reductase) (Table 3). Likewise, the expression levels of two genes that are critical for catecholamine synthesis within the adrenal medulla, Th (tyrosine hydroxylase) and Dbh (dopamine-b-hydroxylase), were significantly elevated (Table 3).

While the increased expression of the above genes in CSDS mice adrenals was consistent with the pathophysiological changes observed in these animals (adrenal enlargement, elevated plasma corticosterone, increased sympathetic activity – and consequent hypertension), the Ingenuity data also revealed very significant alterations in the expression levels of several other adrenal genes that are of interest in the CSDS model. To begin with, the largest change in expression of any gene in the CSDS mice was observed with Pdyn (Prodynorphin), which exhibited a 154.5-Fold increase [Expr P-value 1.23×10^{-14}] (Table 3). Prodynorphin is the precursor peptide for various dynorphins that exert actions via Kappa opioid receptors (KOR), and KOR agonists have been demonstrated to elicit anxiety, fear and depression in animal models (Chartoff and Mavrikaki, 2015). Furthermore, it has been demonstrated that deletion of the Pdyn gene in mice resulted in an anxiolytic phenotype that was reversed by administration of a KOR agonist (Wittmann et al., 2009). Therefore, the large increase in expression of Pdyn may contribute to the anxiety-like behavior observed in CSDS (Fig. 2).

Other changes in adrenal gene expression in CSDS mice might be regarded as more "protective" or compensatory mechanisms. To begin with, the expression of Nppb (natriuretic peptide type B) exhibited a highly significant 11.72-Fold increase (Table 3). There is evidence that BNP stimulates norepinephrine (NE) neuronal re-uptake and decreased NE release in the adrenal medulla (Vatta et al., 1997). Both actions are consistent with a blunting of the hormonal component of the sympathetic nervous system in the CSDS mice. Another gene whose adrenal expression was significantly increased in CSDS mice was the Oxtr (Oxytocin receptor), (Table 3). This is interesting as several studies have demonstrated that oxytocin can exert direct effects at the adrenal cortex to decrease glucocorticoid synthesis and secretion (Legros et al., 1988; Nussdorfer, 1996; Gimpl and Fahrenholz, 2001; Uvnas-Moberg et al., 2024); thus, the elevation of adrenal Oxtr expression in CSDS mice may reflect a compensatory mechanism for keeping elevated circulating corticosterone levels in check.

Table 3
Selected gene expression changes in the adrenal gland after CSDS.
Col1a1 (Collagen, type I, alpha 1); Col1a2 (Collagen, type 1, alpha 2); Col4a1 (Collagen, type IV, alpha 1); Col5a3 (Collagen, type V, alpha 3); Dhcr7 (7-dehydrocholesterol reductase); Dhcr24 (24-dehydrocholesterol reductase); Th (tyrosine hydroxylase); Dbh (dopamine-b-hydroxylase); Pdyn (Prodynorphin); Nppb (natriuretic peptide type B); Oxtr (Oxytocin receptor).

Process	Gene	Expr P-Value	Fold Change
Adrenal Enlargement	Col1a1	0.000462	1.958
	Col1a2	0.00444	1.51
	Col4a1	0.000233	1.6
	Col5a3	2.637×10^{-24}	2.82
Glucocorticoid Synthesis	Dhcr7	3.206×10^{-12}	1.54
	Dhcr24	4.479×10^{-6}	1.65
Catecholamine Synthesis	Th	5.8×10^{-5}	2.12
	Dbh	1.577×10^{-6}	1.78
Anxiety	Pdyn	1.23×10^{-14}	154.5
Compensatory Mechanisms	Nppb	0.00043	11.72
	Oxtr	3.7×10^{-18}	3.42

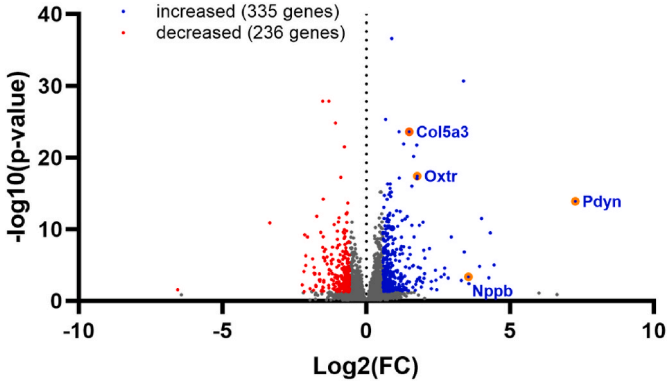

Fig. 5. Chronic social defeat stress (CSDS) alters the adrenal gland transcriptome. Volcano plot of gene expression alterations in the adrenal glands collected from CSDS mice relative to controls. (n = 6/group).

4. Discussion

The worldwide prevalence of hypertension, cardiovascular diseases, obesity, and mental illnesses continues to rise with the aging of the population (Chobanian et al., 2003; Virani et al., 2021; Martin et al.,

2024). Although there are numerous causative factors, social adversity is a contributor that, at least in part, accounts for disparities in the rates and associated treatment outcomes among individuals of differing ethnicities and socioeconomic classes (Din-Dzietham et al., 2004; Grotto et al., 2008; Sims et al., 2012; Leng et al., 2015; de Mestral and Stringhini, 2017; Razzoli et al. 2018, 2023; Anstey et al., 2019; Forde et al., 2020; Snyder-Mackler et al., 2020; Neufcourt et al., 2021; Lyons et al., 2025). The present studies use a CSDS paradigm in adult male wildtype C57BL6/J mice to model some of these societal problems, and to further elucidate their impact on cardiometabolic function. Key findings are that the stress of social subordination leads to severe hypertension that is associated with metabolic and behavioral abnormalities. These disruptions are accompanied by indices of autonomic imbalance, baroreflex dysfunction, fluid retention and endocrine disruptions. We further highlight alterations in the size and gene expression profile of the adrenal gland, as well as cardiac hypertrophy, splenomegaly and thymic involution. Intriguingly, many of these characteristics (e.g., enhanced autonomic outflow and fluid retention) are reminiscent of what occurs in hypertensive patients with low socioeconomic status (Lindhorst et al., 2007; Kim et al., 2018); the implication is that the CSDS paradigm is a clinically relevant model of social stress-induced hypertension.

The finding that cardiovascular responses to CSDS are heightened over time is novel and intriguing. While there are previous studies that have uncovered deleterious effects of social adversity on cardiometabolic parameters across species (Razzoli et al., 2020; Snyder-Mackler et al., 2020; Grant et al., 2022), this is the first CSDS study, to our knowledge, that provides detailed insight into the impact of earlier defeat sessions (i.e., Days 1–3) vs. later defeat sessions (i.e., Days 11–14) on blood pressure and heart rate over the entirety of the light-dark cycle. These findings highlight that, at least in terms of these cardiovascular perturbations, the subordinate subjects do not habituate to the CSDS that is imposed upon them.

The autonomic nervous system is an important mediator of hypertension and consequent cardiovascular dysfunction and plays an important role in regulating the body's responses to external and internal stressors. The present studies point to autonomic nervous system involvement in the observed hypertension in CSDS-exposed mice in two ways. First, HRV and indices of spontaneous baroreflex sensitivity are reduced. These findings are generally consistent with previous studies in rodents (Sgoifo et al., 1999; Costoli et al., 2004; Sévoz-Couche et al., 2013; Brouillard et al., 2019; Morais-Silva et al., 2019). An intriguing and novel finding here is that, like with the pressor responses to the CSDS, these alterations seem to be enhanced over time. The second set of results that infer autonomic nervous system involvement in the hypertension is the gene expression profile within the adrenal gland, which is suggestive of enhanced catecholamine synthesis within the adrenal medulla. Thus, the hypertension that arises during CSDS is likely the consequence of progressive autonomic perturbations; a finding that is highly relevant to human health, as hypertension during psychosocial stress is often also linked to comparable autonomic disturbances such as reduced baroreflex sensitivity (Lindhorst et al., 2007; Kim et al., 2018). Baroreflex sensitivity is impaired in otherwise healthy individuals reporting chronic psychosocial stress (Lucini et al., 2005), and is also associated with mood disorders and post-traumatic stress disorder (Davydov et al., 2007; Park et al., 2017). Interestingly, we found that cardiovascular responses to social defeat were similar across mice, whereas much of the literature using chronic social defeat identifies subsets of mice that are resilient. Such stratification is performed using a social interaction test (SIT), where the duration of time spent investigating a novel aggressor strain mouse is compared to time spent investigating an empty cup (Golden et al., 2011; Murra et al., 2022). We did not assess this in our mice, and perhaps we would have observed differences in the SIT despite similar cardiovascular responses. We did perform the open field test and did not observe a bimodal distribution in responses, and this fits with existing literature reporting no differences in open field behavior between resilient and susceptible mice (Murra et al., 2022).

The present studies also revealed that CSDS elevates body mass in mice, and an intriguing aspect of this elevated body mass is that it is a consequence of increases in lean and fluid mass, rather than adiposity. In fact, adipose tissue weights and, correspondingly, circulating leptin are reduced after CSDS. When considering the present results, in relation to the existing literature on stress and metabolism, it is important to recognize that chronic exposure to psychological stress has been reported to have diverse effects on body weight and composition that differ based on the nature of the stressor imposed, and on environmental and genetic factors (Dallman et al., 2003; Dallman, 2010; Dinsa et al., 2012; Razzoli and Bartolomucci, 2016). Even studies considering metabolic impacts of the specific subset of chronic stressors that arise from exposure to social adversity, *per se*, have produced mixed results (Dijkstra et al., 1992; Bartolomucci et al., 2004; Krishnan et al., 2007; Razzoli et al., 2009; Koch et al., 2016; Eudave et al., 2018). Here, CSDS augments body weight, at least in part by elevating fluid mass. Based on this finding, and the known interrelationship between fluid balance and hypertension, it is reasonable to speculate that the elevated fluid mass in CSDS mice may have a deleterious influence over blood pressure regulation and cardiovascular function, further contributing to pathology.

Mice subjected to CSDS also exhibit increased anxiety-like behavior and alterations in corticosterone levels, with elevations in this glucocorticoid occurring at the expected circadian nadir, and reductions occurring at the anticipated circadian peak of HPA axis activity. Regarding anxiety-like behavior, the increased levels observed in CSDS mice are generally consistent with previous studies (Krishnan et al., 2007; Venzala et al., 2012; Razzoli et al., 2014; Araki et al., 2024), and it is reasonable to speculate that perhaps one contributor to this behavior is the increased adrenal expression of prodynorphin, the product of the Pdyn gene (Table 1). Prodynorphin is known to exert anxiogenic behavior, through generation of dynorphin A metabolites. When generated systemically, certain of the smaller metabolites may traverse the blood brain barrier and exert anxiogenic activity via actions at KOR in the amygdala (Wittmann et al., 2009; Knoll et al., 2011; Sloan et al., 2012; Chartoff and Mavrikaki, 2015). The increases in circulating corticosterone levels were associated with adrenal hyperplasia and with increased expression of adrenal genes involved in Collagen Synthesis and Cholesterol Biosynthesis (Table 1). These findings are also not surprising, considering the known impact of social stress on the HPA axis (Krishnan et al., 2007). That is, the elevated nadir corticosterone level is in line with previous studies using similar social stress paradigms (Krishnan et al., 2007; Razzoli et al., 2014), as is the altered rhythmicity of the HPA axis that was observed (Sterlemann et al., 2008; Razzoli et al., 2014). It is also interesting to consider these corticosterone results in the light of other bodily measurements. For example, as mentioned above, we also observed reductions in adiposity and corresponding levels of leptin. As both adipose tissue and leptin levels have previously been found to modulate HPA axis stress responses (de Kloet et al., 2015; Douglass et al., 2023), it is possible that these metabolic alterations are further precipitating maladaptive effects of CSDS. In addition, CSDS mice also exhibit thymic involution and splenomegaly, which are similarly consistent with the body's adaptation to stress and are suggestive of impaired immune function response to CSDS (possibly due to elevated corticosterone).

Finally, an intriguing aspect of the adrenal transcriptome data is not only that the elevations in gene expression are consistent with the observed increases in sympathetic activity, circulating corticosterone and anxiety, but also that there are significant elevations in the expression of genes that may serve as endogenous regulators that attempt to offset or temper the deleterious actions of CSDS. Most notably, the significant elevations in Oxtr and Nppb might exert respective effects to suppress corticosterone production and the hormonal component of sympathetic nervous system activation in CSDS mice (Legros et al., 1988; Nussdorfer, 1996; Vatta et al., 1997; Gimpl

and Fahrenholz, 2001; Uvnas-Moberg et al., 2024). While these ideas are at present speculative, further investigation is warranted.

There are some limitations that should be acknowledged. First, sex as a biological variable is not addressed here. The rationale is that the paradigms that are used to instigate comparable social subordination stress in female mice differ profoundly from that which is used here. Consequently, direct comparisons are difficult to make between the sexes. Thus, we view the corresponding female study to be more appropriately included in a separate publication. Nonetheless, the completion of corresponding studies in female models of social subordination is immensely important, as social stress and cardiometabolic disease are just as important for women's health as for males. Second, while behavioral tests of anxiety are suggestive of enhanced anxiety-like behavior, they also revealed reductions in distance traveled in the EPM and OFA. Such reductions complicate the interpretation, as the tests rely on locomotor activity to effectively explore the arenas. Thus, while these data are consistent with several studies that also revealed increased anxiety-like behavior after CSDS exposure (Krishnan et al., 2007; Venzala et al., 2012; Razzoli et al., 2014; Araki et al., 2024), they also indicate that the socially subordinate mice are likely in a state of energy conservation. This is an intriguing finding in and of itself, which is further supported by telemetry data revealing that CSDS mice exhibit reduced activity and core body temperature over time. It is reasonable to predict that such a phenotype may ultimately exacerbate cardiovascular and metabolic disease progression.

Collectively, these studies support the use of CSDS in male mice as a model for social adversity-induced cardiometabolic and affective disorders. They further highlight autonomic imbalances, endocrine disruptions and fluid retention, that are likely contributors to the cardiometabolic disruptions. Overall, many of these characteristics are reminiscent of what occurs in hypertensive patients who are victims to comparable social adversities (e.g., of being of a lower social status) (Lindhorst et al., 2007; Kim et al., 2018). Thus, we propose that CSDS may serve as a clinically relevant model to uncover mechanisms underlying health disparities in cardiometabolic outcomes of individuals subjected to such social adversities.

CRediT authorship contribution statement

Karen A. Scott: Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Sophia A. Eikenberry:** Investigation. **Khalid Elsaafien:** Investigation, Funding acquisition, Formal analysis. **Caitlin Baumer-Harrison:** Investigation. **Dominique N. Johnson:** Investigation. **Jéssica Matheus Sá:** Writing – review & editing, Investigation. **Alessandro Bartolomucci:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Colin Sumners:** Writing – original draft, Funding acquisition, Conceptualization. **Eric G. Krause:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Annette D. de Kloet:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Funding

This work was supported by the National Institutes of Health [R01HL145028 (AdK and CS); R01AT013166 (AdK and EGK); R35HL150750 (EGK); K99HL175100 (KE); AG078520 and HL151740 (AB)] and the American Heart Association [AHA 23POST1020034 (KE)].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Annette de Kloet reports financial support was provided by National Institutes of Health. Eric Krause reports financial support was provided by National Institutes of Health. Khalid Elsaafien reports financial support was provided by American Heart Association Inc. Khalid Elsaafien reports financial support was provided by National Institutes of Health. Alessandro Bartolomucci reports financial support was provided by National Institutes of Health. Colin Sumners reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank Drs. Yanping Zhang and Alberto Riva of the UF Interdisciplinary Center for Biotechnology (ICBR), for assistance with the library preparation/RNA-sequencing studies (Dr. Yanping Zhang; RRID:SCR_019145) and their analysis (Dr. Alberto Riva, RRID: SCR_01912).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2025.100752.

Data availability

Data will be made available on request.

References

Anstey, D.E., Christian, J., Shimbo, D., 2019. Income inequality and hypertension control. J. Am. Heart Assoc. 8 (15), e013636.
Araki, R., Kita, A., Ago, Y., Yabe, T., 2024. Chronic social defeat stress induces anxiety-like behaviors via downregulation of serotonin transporter in the prefrontal serotonergic system in mice. Neurochem. Int. 174, 105682.
Bartolomucci, A., Palanza, P., Costoli, T., Savani, E., Laviola, G., Parmigiani, S., Sgoifo, A., 2003. Chronic psychosocial stress persistently alters autonomic function and physical activity in mice. Physiol. Behav. 80 (1), 57–67.
Bartolomucci, A., Pederzani, T., Sacerdote, P., Panerai, A.E., Parmigiani, S., Palanza, P., 2004. Behavioral and physiological characterization of Male mice under chronic psychosocial stress. Psychoneuroendocrinology 29 (7), 899–910.
Baumer-Harrison, C., Elsaafien, K., Johnson, D.N., Aponte, J.D.P., de Araujo, A., Patel, S., Bruce, E., Harden, S.W., Frazier, C.J., Scott, K.A., de Lartigue, G., Krause, E.G., de Kloet, A.D., 2024. Alleviating hypertension by selectively targeting angiotensin receptor expressing vagal sensory neurons. J. Neurosci. 44 (9), e115423202.
Bertinieri, G., di Rienzo, M., Cavallazzi, A., Ferrari, A.U., Pedotti, A., Mancia, G., 1985. A new approach to analysis of the arterial baroreflex. J. Hypertens. Suppl. 3 (3), S79–S81.
Brouillard, C., Carrive, P., Camus, F., Benoliel, J.J., Sevoz-Couche, C., 2019. Vulnerability to stress consequences induced by repeated social defeat in rats: contribution of the angiotensin II type 1 receptor in cardiovascular alterations associated to low brain derived neurotrophic factor. Eur. J. Pharmacol. 861, 172595.
Chartoff, E.H., Mavrikaki, M., 2015. Sex differences in kappa opioid receptor function and their potential impact on addiction. Front. Neurosci. 9, 466.
Chin-Hong, P., Alexander, K.M., Haynes, N., Albert, M.A., 2020. Pulling at the heart: COVID-19, race/ethnicity and ongoing disparities. Nat. Rev. Cardiol. 17 (9), 533–535.
Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo Jr., J.L., Jones, D.W., Materson, B.J., Oparil, S., Wright Jr., J.T., Roccella, E.J., National Heart, L., D. E. Blood Institute Joint National Committee on Prevention, P. Treatment of High Blood and C. National High Blood Pressure Education Program Coordinating, 2003. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289 (19), 2560–2572.
Costoli, T., Bartolomucci, A., Graiani, G., Stilli, D., Laviola, G., Sgoifo, A., 2004. Effects of chronic psychosocial stress on cardiac autonomic responsiveness and myocardial structure in mice. Am. J. Physiol. Heart Circ. Physiol. 286 (6), H2133–H2140.
Dallman, M.F., 2010. Stress-induced obesity and the emotional nervous system. Trends Endocrinol. Metabol. 21 (3), 159–165.
Dallman, M.F., Pecoraro, N., Akana, S.F., La Fleur, S.E., Gomez, F., Houshyar, H., Bell, M. E., Bhatnagar, S., Laugero, K.D., Manalo, S., 2003. Chronic stress and obesity: a new view of "comfort food. Proc. Natl. Acad. Sci. U. S. A. 100 (20), 11696–11701.
Dampney, R.A.L., 2016. Central neural control of the cardiovascular system: current perspectives. Adv. Physiol. Educ. 40 (3), 283–296.
Davydov, D.M., Shapiro, D., Cook, I.A., Goldstein, I., 2007. Baroreflex mechanisms in major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 31 (1), 164–177.

de Kloet, A.D., Krause, E.G., Solomon, M.B., Flak, J.N., Scott, K.A., Kim, D.H., Myers, B., Ulrich-Lai, Y.M., Woods, S.C., Seeley, R.J., Herman, J.P., 2015. Adipocyte glucocorticoid receptors mediate fat-to-brain signaling. Psychoneuroendocrinology 56, 110–119.
de Kloet, A.D., Pati, D., Wang, L., Hiller, H., Sumners, C., Frazier, C.J., Seeley, R.J., Herman, J.P., Woods, S.C., Krause, E.G., 2013. Angiotensin type 1a receptors in the paraventricular nucleus of the hypothalamus protect against diet-induced obesity. J. Neurosci. 33 (11), 4825–4833.
de Mestral, C., Stringhini, S., 2017. Socioeconomic status and cardiovascular disease: an update. Curr. Cardiol. Rep. 19 (11), 115.
Demakakos, P., Biddulph, J.P., de Oliveira, C., Tsakos, G., Marmot, M.G., 2018. Subjective social status and mortality: the English longitudinal study of ageing. Eur. J. Epidemiol. 33 (8), 729–739.
Di Rienzo, M., Bertinieri, G., Mancia, G., Pedotti, A., 1985. A new method for evaluating the baroreflex role by a joint pattern analysis of pulse interval and systolic blood pressure series. Med. Biol. Eng. Comput. 23, 313–314.
Dijkstra, H., Tilders, F.J., Hiehle, M.A., Smelik, P.G., 1992. Hormonal reactions to fighting in rat colonies: prolactin rises during defence, not during offence. Physiol. Behav. 51 (5), 961–968.
Din-Dzietham, R., Nembhard, W.N., Collins, R., Davis, S.K., 2004. Perceived stress following race-based discrimination at work is associated with hypertension in african-americans. The metro Atlanta heart disease study, 1999-2001. Soc. Sci. Med. 58 (3), 449–461.
Dinsa, G.D., Goryakin, Y., Fumagalli, E., Suhrcke, M., 2012. Obesity and socioeconomic status in developing countries: a systematic review. Obes. Rev. 13 (11), 1067–1079.
Douglass, A.M., Resch, J.M., Madara, J.C., Kucukdereli, H., Yizhar, O., Grama, A., Yamagata, M., Yang, Z., Lowell, B.B., 2023. Neural basis for fasting activation of the hypothalamic-pituitary-adrenal axis. Nature 620 (7972), 154–162.
Eudave, D.M., BeLow, M.N., Flandreau, E.I., 2018. Effects of high fat or high sucrose diet on behavioral-response to social defeat stress in mice. Neurobiol Stress 9, 1–8.
Everson-Rose, S.A., Lutsey, P.L., Roetker, N.S., Lewis, T.T., Kershaw, K.N., Alonso, A., Diez Roux, A.V., 2015. Perceived discrimination and incident cardiovascular events: the multi-ethnic study of atherosclerosis. Am. J. Epidemiol. 182 (3), 225–234.
Forde, A.T., Sims, M., Muntner, P., Lewis, T., Onwuka, A., Moore, K., Diez Roux, A.V., 2020. Discrimination and hypertension risk among African Americans in the Jackson heart study. Hypertension 76 (3), 715–723.
Frischknecht, H.R., Siegfried, B., Waser, P.G., 1982. Learning of submissive behavior in mice: a new model. Behav. Process. 7 (3), 235–245.
Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. 81 (2), 629–683.
Golden, S.A., Covington 3rd, H.E., Berton, O., Russo, S.J., 2011. A standardized protocol for repeated social defeat stress in mice. Nat. Protoc. 6 (8), 1183–1191.
Grant, M.K.O., Razzoli, M., Abdelgawad, I.Y., Mansk, R., Seelig, D., Bartolomucci, A., Zordoky, B.N., 2022. Juvenile exposure to doxorubicin alters the cardiovascular response to adult-onset psychosocial stress in mice. Stress 25 (1), 291–304.
Grotto, I., Huerta, M., Sharabi, Y., 2008. Hypertension and socioeconomic status. Curr. Opin. Cardiol. 23 (4), 335–339.
Guyenet, P.G., 2006. The sympathetic control of blood pressure. Nat. Rev. Neurosci. 7 (5), 335–346.
Harada, H., Mori, M., Murata, Y., Kohno, Y., Terada, K., Ohe, K., Enjoji, M., 2024. Divergent effects of chronic continuous and intermittent social defeat stress on emotional behaviors: impact on phosphorylated CREB and BDNF protein levels in the rat hippocampus. Neurosci. Lett. 835, 137851.
Hill, L.K., Thayer, J.F., 2019. The autonomic nervous system and hypertension: ethnic differences and psychosocial factors. Curr. Cardiol. Rep. 21 (3), 15.
Johnson, T.V., Abbasi, A., Master, V.A., 2013. Systematic review of the evidence of a relationship between chronic psychosocial stress and C-Reactive protein. Mol. Diagn. Ther. 17 (3), 147–164.
Kim, P., Evans, G.W., Chen, E., Miller, G., Seeman, T., 2018. In: Halfon, N., Forrest, C.B., Lerner, R.M., Faustman, E.M. (Eds.), How Socioeconomic Disadvantages Get Under the Skin and into the Brain to Influence Health Development Across the Lifespan. Handbook of Life Course Health Development. Springer International Publishing, Cham, pp. 463–497.
Kivimäki, M., Bartolomucci, A., Kawachi, I., 2023. The multiple roles of life stress in metabolic disorders. Nat. Rev. Endocrinol. 19 (1), 10–27.
Knoll, A.T., Muschamp, J.W., Daws, S.E., Ferguson, D., Dietz, D.M., Meloni, E.G., Carroll, F.I., Nestler, E.J., Konradi, C., Carlezon Jr., W.A., 2011. Kappa opioid receptor signaling in the basolateral amygdala regulates conditioned fear and anxiety in rats. Biol. Psychiatry 70 (5), 425–433.
Koch, C.E., Bartlang, M.S., Kiehn, J.T., Lucke, L., Naujokat, N., Helfrich-Forster, C., Reber, S.O., Oster, H., 2016. Time-of-day-dependent adaptation of the HPA axis to predictable social defeat stress. J. Endocrinol. 231 (3), 209–221.
Kremer, J.L., Santiago, V.F., Bongiovani Rodrigues, F., Auricino, T.B., Freitas, D.H.O., Palmisano, G., Lotfi, C.F.P., 2024. Extracellular matrix protein signatures of the outer and inner zones of the rat adrenal cortex. J. Proteome Res. 23 (8), 3418–3432.
Krishnan, V., Han, M.H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., Laplant, Q., Graham, A., Lutter, M., Lagace, D.C., Ghose, S., Reister, R., Tannous, P., Green, T.A., Neve, R.L., Chakravarty, S., Kumar, A., Eisch, A.J., Self, D.W., Lee, F.S., Tamminga, C.A., Cooper, D.C., Gershenfeld, H.K., Nestler, E.J., 2007. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131 (2), 391–404.
Legros, J.J., Chiodera, P., Geenen, V., 1988. Inhibitory action of exogenous oxytocin on plasma cortisol in normal human subjects: evidence of action at the adrenal level. Neuroendocrinology 48 (2), 204–206.
Leng, B., Jin, Y., Li, G., Chen, L., Jin, N., 2015. Socioeconomic status and hypertension: a meta-analysis. J. Hypertens. 33 (2), 221–229.
Lindhorst, J., Alexander, N., Blignaut, J., Rayner, B., 2007. Differences in hypertension between blacks and whites: an overview. Cardiovasc J Afr 18 (4), 241–247.
Lucini, D., Di Fede, G., Parati, G., Pagani, M., 2005. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. Hypertension 46 (5), 1201–1206.
Lyons, C.E., Pallais, J.P., McGonigle, S., Mansk, R.P., Collinge, C.W., Yousefzadeh, M.J., Baker, D.J., Schrank, P.R., Williams, J.W., Niedernhofer, L.J., van Deursen, J.M., Razzoli, M., Bartolomucci, A., 2025. Chronic social stress induces p16-mediated senescent cell accumulation in mice. Nat Aging 5 (1), 48–64.
Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., Kern, P.A., Friedman, J.M., 1995. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in Obese and weight-reduced subjects. Nat. Med. 1 (11), 1155–1161.
Martin, S.S., Aday, A.W., Almarzooq, Z.I., Anderson, C.A.M., Arora, P., Avery, C.L., Baker-Smith, C.M., Barone Gibbs, B., Beaton, A.Z., Boehme, A.K., Commodore-Mensah, Y., Currie, M.E., Elkind, M.S.V., Evenson, K.R., Generoso, G., Heard, D.G., Hiremath, S., Johansen, M.C., Kalani, R., Kazi, D.S., Ko, D., Liu, J., Magnani, J.W., Michos, E.D., Mussolino, M.E., Navaneethan, S.D., Parikh, N.I., Perman, S.M., Poudel, R., Rezk-Hanna, M., Roth, G.A., Shah, N.S., St-Onge, M.P., Thacker, E.L., Tsao, C.W., Urbut, S.M., Van Spall, H.G.C., Voeks, J.H., Wang, N.Y., Wong, N.D., Wong, S.S., Yaffe, K., Palaniappan, L.P., E. American Heart Association Council on, C. Prevention Statistics and S. Stroke Statistics, 2024. 2024 heart disease and stroke statistics: a report of US and global data from the American heart association. Circulation 149 (8), e347–e913.
Mohammed, M., Johnson, D.N., Wang, L.A., Harden, S.W., Sheng, W., Spector, E.A., Elsaafien, K., Bader, M., Steckelings, U.M., Scott, K.A., Frazier, C.J., Sumners, C., Krause, E.G., de Kloet, A.D., 2022. Targeting angiotensin type-2 receptors located on pressor neurons in the nucleus of the solitary tract to relieve hypertension in mice. Cardiovasc. Res. 118 (3), 883–896.
Morais-Silva, G., Costa-Ferreira, W., Gomes-de-Souza, L., Pavan, J.C., Crestani, C.C., Marin, M.T., 2019. Cardiovascular outcomes related to social defeat stress: new insights from resilient and susceptible rats. Neurobiol Stress 11, 100181.
Murra, D., Hilde, K.L., Fitzpatrick, A., Maras, P.M., Watson, S.J., Akil, H., 2022. Characterizing the behavioral and neuroendocrine features of susceptibility and resilience to social stress. Neurobiology of Stress 17, 100437.
Muscatell, K.A., Brosso, S.N., Humphreys, K.L., 2020. Socioeconomic status and inflammation: a meta-analysis. Mol. Psychiatr. 25 (9), 2189–2199.
Neufcourt, L., Zins, M., Berkman, L.F., Grimaud, O., 2021. Socioeconomic disparities and risk of hypertension among older Americans: the health and retirement study. J. Hypertens. 39 (12), 2497–2505.
Nussdorfer, G.G., 1996. Paracrine control of adrenal cortical function by medullary chromaffin cells. Pharmacol. Rev. 48 (4), 495–530.
Otis, M., Campbell, S., Payet, M.D., Gallo-Payet, N., 2007. Expression of extracellular matrix proteins and integrins in rat adrenal gland: importance for ACTH-Associated functions. J. Endocrinol. 193 (3), 331–347.
Park, J., Marvar, P.J., Liao, P., Kankam, M.L., Norrholm, S.D., Downey, R.M., McCullough, S.A., Le, N.A., Rothbaum, B.O., 2017. Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. J. Physiol. 595 (14), 4893–4908.
Powell-Wiley, T.M., Baumer, Y., Baah, F.O., Baez, A.S., Farmer, N., Mahlobo, C.T., Pita, M.A., Potharaju, K.A., Tamura, K., Wallen, G.R., 2022. Social determinants of cardiovascular disease. Circ. Res. 130 (5), 782–799.
Razzoli, M., Bartolomucci, A., 2016. The dichotomous effect of chronic stress on obesity. Trends Endocrinol. Metabol. 27 (7), 504–515.
Razzoli, M., Carboni, L., Arban, R., 2009. Alterations of behavioral and endocrinological reactivity induced by 3 brief social defeats in rats: relevance to human psychopathology. Psychoneuroendocrinology 34 (9), 1405–1416.
Razzoli, M., Karsten, C., Yoder, J.M., Bartolomucci, A., Engeland, W.C., 2014. Chronic subordination stress phase advances adrenal and anterior pituitary clock gene rhythms. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307 (2), R198–R205.
Razzoli, M., Lindsay, A., Law, M.L., Chamberlain, C.M., Southern, W.M., Berg, M., Osborn, J., Engeland, W.C., Metzger, J.M., Ervasti, J.M., Bartolomucci, A., 2020. Social stress is lethal in the mdx model of Duchenne muscular dystrophy. EBioMedicine 55, 102700.
Razzoli, M., Nyuyki-Dufe, K., Chen, B.H., Bartolomucci, A., 2023. Contextual modifiers of healthspan, lifespan, and epigenome in mice under chronic social stress. Proc. Natl. Acad. Sci. U. S. A. 120 (16), e2211755120.
Razzoli, M., Nyuyki-Dufe, K., Gurney, A., Erickson, C., McCallum, J., Spielman, N., Marzullo, M., Patricelli, J., Kurata, M., Pope, E.A., Touma, C., Palme, R., Largaespada, D.A., Allison, D.B., Bartolomucci, A., 2018. Social stress shortens lifespan in mice. Aging Cell 17 (4), e12778.
Razzoli, M., Pearson, C., Crow, S., Bartolomucci, A., 2017. Stress, overeating, and obesity: insights from human studies and preclinical models. Neurosci. Biobehav. Rev. 76 (Pt A), 154–162.
Razzoli, M., Sanghez, V., Bartolomucci, A., 2015. Chronic subordination stress induces hyperphagia and disrupts eating behavior in mice modeling binge-eating-like disorder. Front. Nutr. 1 (30).
Scott, K.M., Al-Hamzawi, A.O., Andrade, L.H., Borges, G., Caldas-de-Almeida, J.M., Fiestas, F., Gureje, O., Hu, C., Karam, E.G., Kawakami, N., 2014. Associations between subjective social status and DSM-IV mental disorders: results from the world mental health surveys. JAMA Psychiatry 71 (12), 1400–1408.
Sévoz-Couche, C., Brouillard, C., Camus, F., Laude, D., De Boer, S.F., Becker, C., Benoliel, J.J., 2013. Involvement of the dorsomedial hypothalamus and the nucleus tractus solitarii in chronic cardiovascular changes associated with anxiety in rats. J. Physiol. 591 (7), 1871–1887.

Sgoifo, A., Costoli, T., Meerlo, P., Buwalda, B., Pico'-Alfonso, M.A., De Boer, S., Musso, E., Koolhaas, J., 2005. Individual differences in cardiovascular response to social challenge. Neurosci. Biobehav. Rev. 29 (1), 59–66.
Sgoifo, A., Koolhaas, J.M., Musso, E., De Boer, S.F., 1999. Different sympathovagal modulation of heart rate during social and nonsocial stress episodes in wild-type rats. Physiol. Behav. 67 (5), 733–738.
Shaffer, F., Ginsberg, J.P., 2017. An overview of heart rate variability metrics and norms. Front. Public Health 5, 258.
Sims, M., Diez-Roux, A.V., Dudley, A., Gebreab, S., Wyatt, S.B., Bruce, M.A., James, S.A., Robinson, J.C., Williams, D.R., Taylor, H.A., 2012. Perceived discrimination and hypertension among African Americans in the Jackson heart study. Am. J. Publ. Health 102 (Suppl. 2), S258–S265.
Sloan, C.D., Audus, K.L., Aldrich, J.V., Lunte, S.M., 2012. The permeation of dynorphin A 1-6 across the blood brain barrier and its effect on bovine brain microvessel endothelial cell monolayer permeability. Peptides 38 (2), 414–417.
Snyder-Mackler, N., Burger, J.R., Gaydosh, L., Belsky, D.W., Noppert, G.A., Campos, F.A., Bartolomucci, A., Yang, Y.C., Aiello, A.E., O'Rand, A., Harris, K.M., Shively, C.A., Alberts, S.C., Tung, J., 2020. Social determinants of health and survival in humans and other animals. Science 368 (6493).
Stauss, H.M., 2008. Hemolab: a Data Acquisition and Data Analysis Software for Hemodynamic Studies.
Sterlemann, V., Ganea, K., Liebl, C., Harbich, D., Alam, S., Holsboer, F., Müller, M.B., Schmidt, M.V., 2008. Long-term behavioral and neuroendocrine alterations following chronic social stress in mice: implications for stress-related disorders. Horm. Behav. 53 (2), 386–394.
Teshale, A.B., Htun, H.L., Owen, A., Gasevic, D., Phyo, A.Z.Z., Fancourt, D., Ryan, J., Steptoe, A., Freak-Poli, R., 2023. The role of social determinants of health in cardiovascular diseases: an umbrella review. J. Am. Heart Assoc. 12 (13), e029765.
Thireau, J., Zhang, B.L., Poisson, D., Babuty, D., 2008. Heart rate variability in mice: a theoretical and practical guide. Exp. Physiol. 93 (1), 83–94.
Ulrich-Lai, Y.M., Figueiredo, H.F., Ostrander, M.M., Choi, D.C., Engeland, W.C., Herman, J.P., 2006. Chronic stress induces adrenal hyperplasia and hypertrophy in a subregion-specific manner. Am. J. Physiol. Endocrinol. Metab. 291 (5), E965–E973.
Ulrich-Lai, Y.M., Herman, J.P., 2009. Neural regulation of endocrine and autonomic stress responses. Nat. Rev. Neurosci. 10 (6), 397–409.
Uvnas-Moberg, K., Gross, M.M., Calleja-Agius, J., Turner, J.D., 2024. The yin and yang of the oxytocin and stress systems: opposites, yet interdependent and intertwined determinants of lifelong health trajectories. Front. Endocrinol. 15, 1272270.
Vatta, M.S., Presas, M.F., Bianciotti, L.G., Rodriguez-Fermepin, M., Ambros, R., Fernandez, B.E., 1997. B and C types natriuretic peptides modify norepinephrine uptake and release in the rat adrenal medulla. Peptides 18 (10), 1483–1489.
Venzala, E., Garcia-Garcia, A.L., Elizalde, N., Delagrange, P., Tordera, R.M., 2012. Chronic social defeat stress model: behavioral features, antidepressant action, and interaction with biological risk factors. Psychopharmacology (Berl) 224 (2), 313–325.
Virani, S.S., Alonso, A., Aparicio, H.J., Benjamin, E.J., Bittencourt, M.S., Callaway, C.W., Carson, A.P., Chamberlain, A.M., Cheng, S., Delling, F.N., Elkind, M.S.V., Evenson, K.R., Ferguson, J.F., Gupta, D.K., Khan, S.S., Kissela, B.M., Knutson, K.L., Lee, C.D., Lewis, T.T., Liu, J., Loop, M.S., Lutsey, P.L., Ma, J., Mackey, J., Martin, S. S., Matchar, D.B., Mussolino, M.E., Navaneethan, S.D., Perak, A.M., Roth, G.A., Samad, Z., Satou, G.M., Schroeder, E.B., Shah, S.H., Shay, C.M., Stokes, A., VanWagner, L.B., Wang, N.Y., Tsao, C.W., E. American Heart Association Council on, C. Prevention Statistics and S. Stroke Statistics, 2021. Heart disease and stroke Statistics-2021 update: a report from the American heart association. Circulation 143 (8), e254–e743.
Wadhera, R.K., Figueroa, J.F., Rodriguez, F., Liu, M., Tian, W., Kazi, D.S., Song, Y., Yeh, R.W., Joynt Maddox, K.E., 2021. Racial and ethnic disparities in heart and cerebrovascular disease deaths during the COVID-19 pandemic in the United States. Circulation 143 (24), 2346–2354.
Wittmann, W., Schunk, E., Rosskothen, I., Gaburro, S., Singewald, N., Herzog, H., Schwarzer, C., 2009. Prodynorphin-derived peptides are critical modulators of anxiety and regulate neurochemistry and corticosterone. Neuropsychopharmacology 34 (3), 775–785.
Yan, L.L., Liu, K., Matthews, K.A., Daviglus, M.L., Ferguson, T.F., Kiefe, C.I., 2003. Psychosocial factors and risk of hypertension: the coronary artery risk development in young adults (CARDIA) study. JAMA 290 (16), 2138–2148.