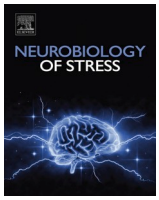
Neurobiology of Stress 33 (2024) 100689

Contents lists available at ScienceDirect

Neurobiology of Stress

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



Behavioral coping with chronic defeat stress in mice: A systematic review of current protocols

Alina Díez-Solinska [a], Zurine De Miguel [b,c], Garikoitz Azkona [a], Oscar Vegas [a,d,*]

[a] Department of Basic Psychological Processes and Their Development, University of the Basque Country UPV/EHU, 20018, Donostia-San Sebastian, Spain
[b] Department of Psychology, California State University, Monterey Bay, CA, USA
[c] Department of Health Sciences, Public University of Navarre UPNA, 31006, Pamplona, Spain
[d] Biogipuzkoa Health Research Institute, 20014, Donostia-San Sebastian, Spain

ARTICLE INFO

Handling Editor: Prof R Lawrence Reagan

Keywords:
Chronic
Social stress
Defeat
Coping
Behavior
Mice
HPA
SAM
Corticosterone
Coping strategy
Neuroendocrine system

ABSTRACT

Social stress is the most significant source of chronic stress in humans and is commonly associated with health impairment. Individual differences in the behavioral coping responses to stress have been proposed to mediate the negative effects of stress on physical, behavioral and mental health. Animal models, particularly mice, offer valuable insights into the physiological and neurobiological correlates of behavioral coping strategies in response to chronic social stress. Here we aim to identify differences and similarities among stress protocols in mice, with particular attention to how neuroendocrine and/or behavioral responses vary according to different coping strategies, while highlighting the need for standardized approaches in future research. A systematic review was undertaken following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement). A total of 213 references were identified by electronic search, and after the screening, 18 articles were found to meet all the established criteria. We analyzed differences in the stress protocol, the characterization and classification of coping strategies and the physiological and behavioral differences according to coping. The results show that differences in behavioural expression under chronic social stress (coping) may also be associated with physiological differences and differential susceptibility to disease. However, this review also underlines the importance of a cautious interpretation of the results obtained. The lack of consistency in the nomenclature and procedures associated with the study of coping strategies for social stress, as well as the absence of a uniform classification, highlight the importance of using a common language when approaching the study of coping strategies. Thereby, this review encourages the development of a more defined method and criteria for assessing coping strategies, based on both behavioral and biological indicators.

1. Introduction

Stress is commonly associated with health impairment (Kendler et al., 2003; Slavich and Irwin, 2014), with social stressors being among the most significant sources of stress in humans (Albus et al., 2005; DeVries et al., 2007; Kemeny and Schedlowski, 2007; Scott et al., 2012). Interestingly, not every individual exposed to stress experiences adversed effects, and it has been suggested that individual differences in coping behaviors may influence how stress impacts health (Del Giudice et al., 2011; Sapolsky, 1994; Wood, 2014).

Behavioral coping strategies are not isolated; they are accompanied by unique physiological and neurobiological responses (Benus et al., 1991; Koolhaas et al., 1999; Marchetti and Drent, 2000; Øverli et al., 2007), which in turn can play an important role in impacting the underlying biology, increasing the risk and vulnerability to health impairment. Different coping styles are associated with varying stress-related illnesses. For instance, individuals with proactive strategies are more prone to suffer cardiovascular diseases (e.g., hypertension), gastrointestinal issues (e.g., gastric ulcers), and behavioral disorders (e.g., substance abuse), while those displaying passive strategies have a higher risk of infectious diseases, increased tumor progression, and anxiety-like behaviors (Cabib et al., 2021; De Miguel et al., 2011; Del Giudice et al., 2011; Sapolsky, 1994; Vegas et al., 2006; Wood, 2014). Therefore, investigating the relationship between behavioral and physiological responses to stress is important to understanding stress resilience and vulnerability to diseases associated with stress-induced health impairments. For example, social stress can activate the

* Corresponding author. Department of Basic Psychological Processes and their Development, University of the Basque Country, Avda. Tolosa 70, Donostia, 20018, Spain.
E-mail address: o.vegas@ehu.eus (O. Vegas).

https://doi.org/10.1016/j.ynstr.2024.100689
Received 10 September 2024; Received in revised form 18 October 2024; Accepted 6 November 2024
Available online 8 November 2024

Acronyms

ACTH	Adrenocorticotropic Hormone
AMYG	Amygdala
CORT	Corticosterone
CRH	Corticotropin-Releasing Hormone
CPP	Conditioned Place Preference
CSC	Chronic Subordinate Colony Housing
CSDS	Chronic Social Defeat Stress
DA	Dopamine
DBH	Dopamine-Beta-Hydroxylase
E	Epinephrine
EPM	Elevated Plus Maze
FST	Forced Swimming Test
GR	Glucocorticoid Receptor
HPA	Hypothalamic-Pituitary-Adrenal
HPC	Hippocampus
HPT	Hot Plate Tests
HT	Hypothalamus
IL	Interleukin
LC	Locus Coeruleus
L/D	Light/Dark (L/D) Box
MR	Mineralocorticoid Receptor
MWM	Morris Water Maze
NE	Norepinephrine
NORT	Novel Object Recognition Test
OFT	Open Field Test
PFC	Prefrontal Cortex
SAM	Sympathetic-Adrenal-Medullary
SCM	Sensorial Contact Model
SD	Social Defeat
SDR	Social Disruption Stress
SIT	Social Interaction Test
SPT	Sucrose Preference Test
TNF	Tumor Necrosis Factor
VTA	Ventral Tegmental Area

sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes, resulting in stress behavioral responses, and physiological changes. During chronic stress, the repetitive activation of SAM and HPA axes, as well as particular stress associated behaviors, have been associated with an increased risk for health impairment and vulnerabilities.

The activation of these axes begins with the perception of the stimulus as a threat, and the activation of brain cortical (prefrontal cortex; PFC) and subcortical regions, such as the amygdala (AMYG), and the hippocampus (HPC). These areas reach the hypothalamus (HT), the brainstem and the spinal cord, enabling the physiological (e.g. CORT release, increased blood pressure and heart rate) and behavioral (e.g. fight or flight response, anxiety-like behavior, decision making) stress responses. Thus, during stressful events, a rapid physiological adaptation is mediated by epinephrine (E) and norepinephrine (NE) secreted from the adrenal medulla and NE from sympathetic nerves. Alongside NE, corticotropin-releasing hormone (CRH) is released from the HT and induces the secretion of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH in turn, triggers the systemic release of glucocorticoids (CORT) from the adrenal gland (for a review see Godoy et al., 2018; Irwin and Cole, 2011). Norepinephrine and glucocorticoid release induced by chronic exposure to stressors (lasting from hours to days), leads to an increase in heart rate, elevated blood pressure, immune system alterations and metabolic dysregulation. Furthermore, these physiological responses have been shown to exacerbate brain damage (O'Connor et al., 2021; Yaribeygi et al., 2017) and increase vulnerability to developing cardiovascular, inflammatory, metabolic and psychiatric diseases (Belmaker and Agam, 2008; Chandola et al., 2006; Sapolsky, 2000; Schmidt et al., 2008).

While chronic stress is linked to an increased risk of health problems, some individuals are more resilient while others are more susceptible to its negative effects. These differences in resiliency and susceptibility, may be explained by individual differences in behavioral and physiological response to stressors (Lazarus and Folkman, 1984; Schneiderman et al., 2005). Animal models, particularly mice, offer valuable insights into the physiological and neurobiological correlates of behavioral coping strategies in response to chronic social stress. The social defeat stress paradigm in male mice is commonly used to induce chronic social stress. This model allows for the study of distinct behavioral and physiological responses among dominant and submissive mice, providing valuable insights into stress coping mechanisms and a better understanding of the potential impact of stress on mental and overall health. Despite the existence of a growing body of literature focusing on analyzing behavioral and physiological coping strategies in mice using chronic social stress as a model, there is currently no review available that consolidates and compares various protocols and approaches to gain a clearer understanding of behavioral coping strategies and their association with physiological responses and impact on health.

Through a meticulous review of studies analyzing behavioral coping strategies in mice under chronic social stress, we aim to identify differences and similarities among stress protocols, as well as neuroendocrine and/or behavioral responses as a function of coping strategy. The results from this analysis can help to better inform the experimental design of studies aimed to investigate the mechanisms underlying the negative impact of chronic social stress on health, which ultimately will help to develop more effective therapeutic interventions for stress-related disorders.

2. Material and methods

This systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement) flowsheet (Moher et al., 2009).

2.1. Search strategy

The search was carried out on December 1, 2023 and was accomplished by two authors (AD-S and GA) who independently examined the full texts of potentially relevant studies and applied the eligibility criteria to select, by consensus, those studies to be included. The systematic search was conducted in Web of Science, Scopus, and PubMed. As the main aim of the study was to examine the coping strategy of male and female mice under chronic social stress, the following search terms were used in the above-mentioned databases: ("coping strategy" OR coping) AND ("social stress" OR "psychosocial stress") AND (mice OR mouse). The filters included were document type (article), and language (English). We also used Web of Science filters to exclude human research. We comprehensively searched for published full-text studies.

2.2. Study inclusion and exclusion criteria

Included studies were those carried out in mice submitted to chronic social stress (during at least 6 days) that describe mice's behavior while coping with the stressful condition. Physiological features characterizing those mice were also collected although there was not an inclusion criterion by itself (studies including coping characterization but not biological measures were included).

Excluded studies comprised all those publications that were not

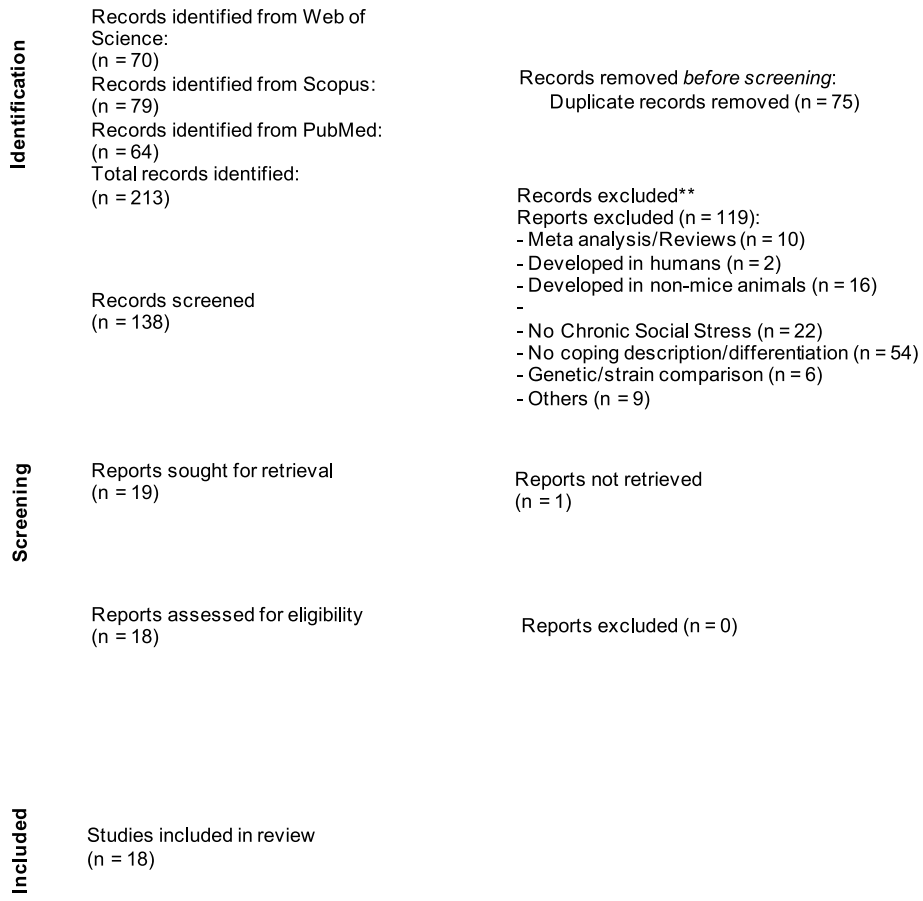


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of the process for the 18 selected studies in the systematic review.

written in English, were non-peer-reviewed (e.g., book chapters or meeting abstracts) and were not original research articles (e.g., reviews or meta-analyses). Human studies as well as studies performed in non-mice animals were also excluded. In addition, studies describing mice's behaviors but not specifying particular coping styles and studies that applied acute or non-social stress were likewise left out. Finally, the studies that compared subjects regarding their strain (e.g., C57BL/6 or BALB/c) or their artificially selected characteristics (e.g., LAL and SAL mice) were also excluded.

Thus, this review was focused on coping characterization, the following stress procedures, and the physiological and behavior differences according to mice coping strategy.

2.3. Statistical analysis

Frequency (%) statistics were used to describe the sample, sometimes about the total number of articles selected (18), others about the total number of protocols described (20).

3. Results

3.1. Study selection

We systematically searched for references related to coping strategies in mice upon chronic social stress. A total of 213 references were identified by electronic search; 138 full-text studies were evaluated by the eligibility criteria after removing the duplicate records (n = 75) and 118 were excluded based on criteria explained in section 2.2. Finally, 18 met all the established criteria (Fig. 1). It should be noted that one of these studies implemented three different protocols: one in males and two in females (Leclair et al., 2021), resulting in 20 reviewed protocols.

3.2. Differences in the chronic social stress procedure

To analyse the differences in various chronic social stress procedures (Table 1), we considered the number of days that the stress procedure lasted (6–21 days), the exposure time to social defeat (5min-2hours/daily), housing conditions, and mice's strain, age and sex, as represented in Fig. 2.

3.2.1. Variation in the chronic social defeat stress duration

The procedures reviewed reported different durations of chronic social defeat stress with some lasting a minimum of 6 days and others a maximum of 21 days (Fig. 3a). The most frequently used duration is a 10-day protocol (10/18, 55.5%) (Ballestin et al., 2021; Friedman et al., 2014, 2016; Laine et al., 2018; Murra et al., 2022; Reguilón et al., 2022; Rosado et al., 2023; Ródenas-González et al., 2021; Savignac et al., 2011), with one of the studies implementing 3 different experimental procedures (Leclair et al., 2021). The next most used procedure is a 21-day duration protocol (3/18, 16.7%) (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013, 2016). Individual publications (1/18, 5.5% per duration) have also reported 6 (Savignac et al., 2011), 7 (Avitsur et al., 2003), 15 (Bartolomucci et al., 2003), 18 (Goñi-Balentziaga et al., 2020) and 19-day (Foertsch et al., 2017) duration stress protocols.

3.2.2. Variation in the duration of social defeat encounters

Social encounters are the time when mice are repeatedly exposed to dominant territorial mice that exhibit bouts of socially aggressive behaviors and maintain dominance (Golden et al., 2011) (Fig. 3b). Direct social encounters last from 5 min (11/20, 55%) (Ballestin et al., 2021;

Table 1
Chronic Social Stress procedures characteristics across selected studies.

Behavioral Coping	Stress model	Procedure	Mouse Strain	Age (weeks)	Sex	Reference
Active vs. Passive	SCM based on the RIP (Kudryavtseva et al., 1991)	21 Days: 5 min confrontation/day followed by 24 h sensory contact	OF-1	8	Male	Gómez-Lázaro et al. (2012)
	SCM based on the RIP (Kudryavtseva et al., 1991)	21 Days: 5 min confrontation/day followed by 24 h sensory contact On day 24: another social defeat	OF-1	7	Male	Pérez-Tejada et al. (2013)
	SCM based on the RIP (Kudryavtseva et al., 1991)	21 Days: 5 min confrontation/day followed by 24 h sensory contact	OF-1	8	Male	Pérez-Tejada et al. (2016)
	SD (Tornatzky and Miczek, 1993)	10 Days: 5 min confrontation (on PND 54, 57, 60 and 63) preceded and followed by 10-min sensory contact	C57BL/6	8	Male	(Ballestin et al., 2021)
	Modified CSDS (Golden et al., 2011)	10 Days: 10 min confrontation/day followed by 24 h sensory contact	C57BL/6	8	Male	Rosado et al. (2023)
Active Aggressive vs. Active non-Aggressive vs. Passive Reactive	SCM based on the RIP (Kudryavtseva et al., 1991) with modifications (Vegas et al., 2006)	18 Days: 5 min confrontation/day followed by 24 h sensory contact. On days 1 and 9, after confrontation, mice were subjected to another 5 min of sensory contact	OF-1	8	Male	Goñi-Balentziaga et al. (2020)
Pro-active vs. Re-active	CSC (Langgartner et al., 2015)	19 Days housed together with a dominant mouse	C57BL/6N	5–6	Male	Foertsch et al. (2017)
Dominant vs. Submissive	P-F (Avitsur et al., 2002)	7 Days: 30 min confrontation/day. 6 nightly PF (3 nightly cycles-one night left-3 nightly cycles) (differences regarding rearing conditions: Group Housed (GH) and Isolated Housed (IH)).	C57BL/6	7–10	Male	Avitsur et al. (2003)
	Modified CPS (Bartolomucci et al., 2001)	15 Days: 5–15 min confrontation/day (regarding the first attack) followed by 24 h sensory contact	Swiss CD-1	12	Male	Bartolomucci et al. (2003)
	Modified SDR (Avitsur et al., 2001)	6 Days: 2 h confrontation/day with no sensory contact (the intruder is trained to be the aggressive)	BALB/c	12–13	Male	Savignac et al. (2011)
Resilient vs. Susceptible	CSDS (Golden et al., 2011)	10 Days: 5 min confrontation/day followed by 24 h sensory contact	C57BL/6J	8–11	Male	Murra et al. (2022)
	SD (Tornatzky and Miczek, 1993)	10 Days: 5 min confrontation (on PND 27, 30, 33 and 36) preceded and followed by 10-min sensory contact	C57BL/6J	4	Male	Reguilón et al. (2022)
	SD-L (Beitia et al., 2005; Krishnan et al., 2007; Kudryavtseva et al., 1991)	10 Days: 10 min confrontation/day followed by 24 h sensory contact	BALB/c, C57BL/6	10–11	Male	Savignac et al. (2011)
	SD (Cao et al., 2010; Chaudhury et al., 2013; Golden et al., 2011; Krishnan et al., 2007)	10 Days: 10 min confrontation/day followed by 24 h sensory contact	TH-GFP, TH-Cre C57BL/6	8	Male	Friedman et al. (2014)
	CSDS (Chaudhury et al., 2013; Friedman et al., 2014; Golden et al., 2011; Krishnan et al., 2007)	10 Days: 10 min confrontation/day followed by 24 h sensory contact	C57BL/6J, TH-BAC-Cre on a C57BL/6J background	8	Male	Friedman et al. (2016)
	CSDS (Golden et al., 2011; Laine et al., 2017)	10 Days: 10 min confrontation/day followed by 24 h sensory contact	D2, 129, BALB/c, C57BL/6	7	Male	Laine et al. (2018)
	CSDS (Ferrer-Pérez et al., 2019; Montagud-Romero et al., 2016; Rodríguez-Arias et al., 2017)	10 Days: 5 min confrontation (on PND 47, 50, 53 and 56) preceded and followed by 10 min sensory contact	C57/BL/6	7–8	Male	Ródenas-González et al. (2021)
Dominant vs. Submissive Active vs. Passive Resilient vs. Susceptible	Male CSDS (Golden et al., 2011) Female CSDS (Takahashi et al., 2017) Interfemale CSDS (Newman et al., 2019)	Males: 10 Days: 10 min confrontation/day followed by 24 h sensory contact (male aggressors) Females: 10 Days: 5 min confrontation/day with no sensory contact after encounters (DREADD males as aggressors) Interfemale: 10 Days: 5 min confrontation/day followed by 24 h sensory contact (female Swiss Webster as aggressors)	C57BL/6 J	Males CSDS: 13 Females CSDS: 13 Interfemale CSDS: 13	Male and female	LeClair et al. (2021)

Abbreviations: CPS: Chronic Psychosocial Stress. CSC: Chronic subordinate colony housing. CSDS: Chronic Social Defeat Stress. CSS: Chronic Social Stress. DREADD: male transgenic Esr1-Cre aggressor mice, expressing AAV-Gq-DREADD in the ventromedial hypothalamus. SCM: Sensorial Contact Model. SD: Social Defeat. SD-L: Social Defeat Long. SDR: Social Disruption Stress. P-F: Pair-Fighting model. RIP: resident-intruder paradigm.

Goñi-Balentziaga et al., 2020; Gómez-Lázaro et al., 2012; Leclair et al., 2021; Murra et al., 2022; Pérez-Tejada et al., 2013, 2016; Reguilón et al., 2022; Ródenas-González et al., 2021) to 2 h (1/20, 5%) (Savignac et al., 2011). Some studies allowed the social encounters to last 10 (6/20, 30%) (Friedman et al., 2014, 2016; Laine et al., 2018; Leclair et al., 2021; Rosado et al., 2023; Savignac et al., 2011) or 30 min (1/20, 5%) (Avitsur et al., 2003). Remarkably, one of the studies (1/20, 5%) varied the duration between 5 and 15 min concerning the moment of the first attack of the aggressor (Bartolomucci et al., 2003), and another study maintained a constant colony housing for 19 days (1/20, 5%) (Foertsch et al., 2017).

3.2.3. *Variation in the agonistic encounter paradigm*

Three different protocols were used to confront mice, the resident-intruder paradigm, the Social Disruption Paradigm (SDR) and the chronic subordinate colony housing (CSC) (Fig. 3c). Except for three

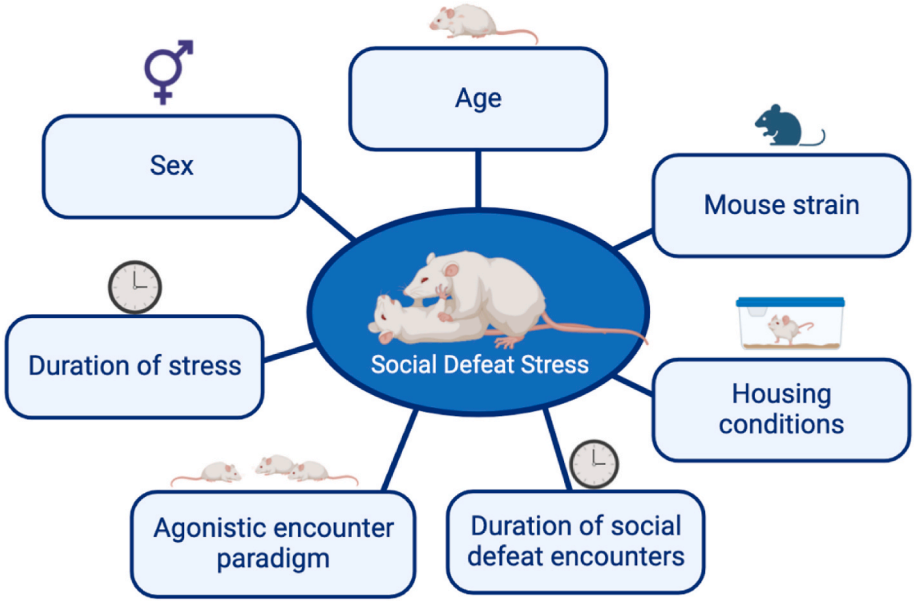


Fig. 2. Procedure elements altered across chronic social defeat protocols.

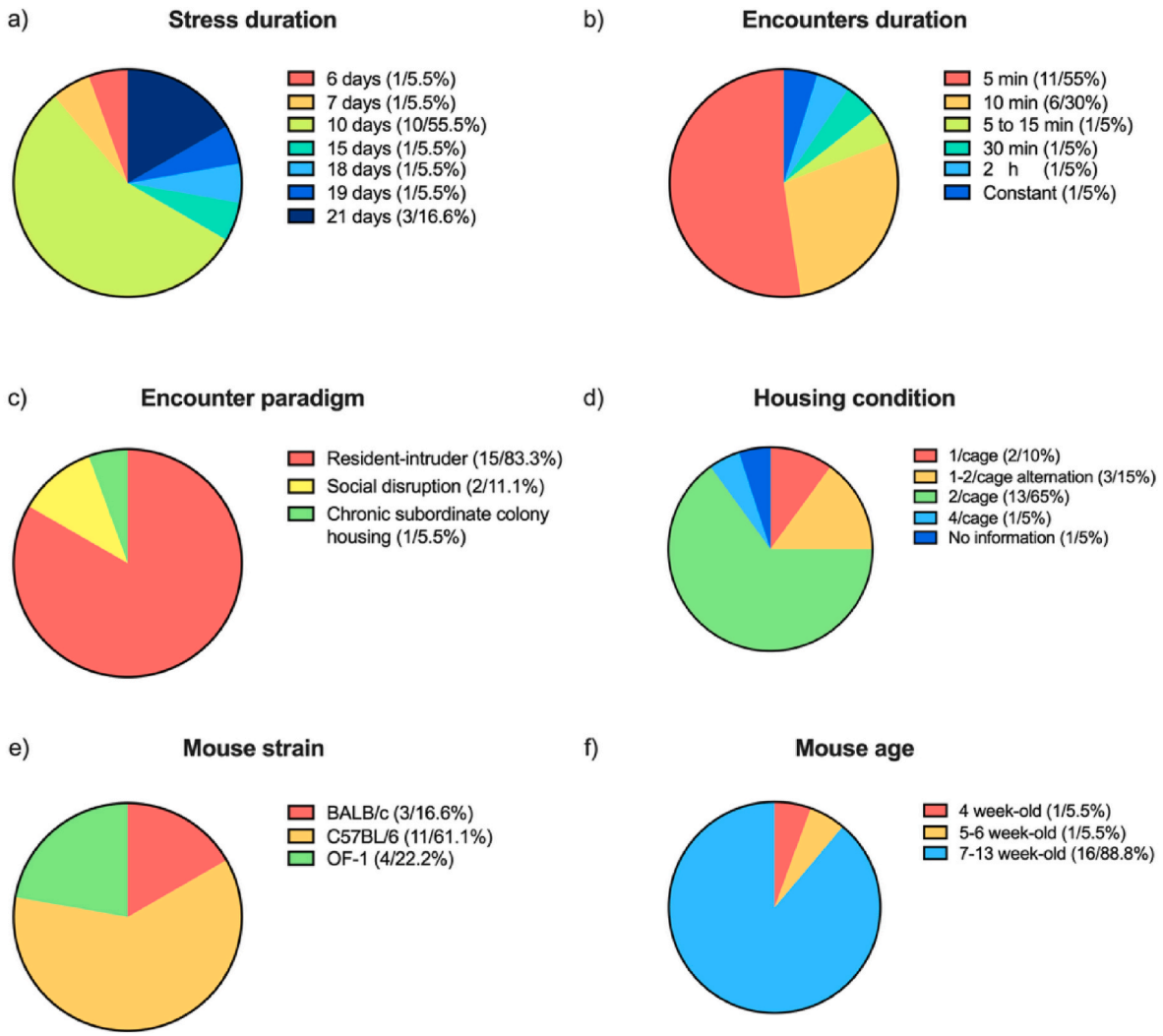


Fig. 3. Relative frequency of a) stress duration, b) encounter duration, c) encounter paradigms, d) housing conditions, e) mouse strains and f) mouse ages across reviewed protocols.

Table 2
Behavioral coping differentiation approaches across selected studies.

Behavioral Coping	Behavioral Test	When	Behavioral characteristics (Analyzed -observed behaviors)	Reference
Active (A) vs. Passive (P)	VR defeats	During (day 18) and after (day 21) stress procedure	Coping behaviors assessed: avoidance-flee, defense-submission, digging/self-grooming, exploration at distance, immobility, non-social exploration and social exploration (Brain et al., 1989) ↑A: exploration (especially non-social) ↓P: immobility, avoidance-flee, ↓ digging and self-grooming, ↓ social and non-social exploration	Gómez-Lázaro et al. (2012)
		During stress procedure (day 21)	Coping behaviors assessed: avoidance-flee, defense-submission, digging/self-grooming, exploration at distance, immobility, non-social exploration and social exploration (Brain et al., 1989) ↑A: exploration (especially non-social) ↑P: immobility ↓ social and non-social exploration, self-grooming and digging	Pérez-Tejada et al. (2013)
			Coping behaviors assessed: avoidance-flee, defense-submission, digging/self-grooming, exploration at distance, immobility, non-social exploration and social exploration (Brain et al., 1989) ↑A: exploration ↓P: social and non-social exploration, self-grooming and digging, ↑ flee, immobility and submission	Pérez-Tejada et al. (2016)
	VR defeats	During stress procedure (All encounters: days 1, 4, 7 and 10)	Coping behaviors assessed: avoidance-flee and defensive-submissive (Rodríguez-Arias et al., 1998). ↑ P: avoidance/flee and defensive/submissive behaviors	(Ballestin et al., 2021)
	VR defeats	During stress procedure (days 1 and 10)	Coping behaviors assessed: running to the opposing end of the cage, biting, boxing, lunging at the aggressor, immobility and submissive behavior A: running to the opposing end of the cage after attack, biting, boxing or lunging at the aggressor (A Score = (nº of A behaviors (Escape + Fighting) – nº of P behaviors)/nº Attacks). P: immobility or submissive behavior in response to attack	Rosado et al. (2023)
Active Aggressive (AA) vs. Active non-Aggressive (ANA) vs. Passive Reactive (PR)	VR defeats	During stress procedure (days 1 and 9)	Coping behaviors assessed: attack, threat, non-social exploration, social investigation, exploration from a distance, digging, body care, avoidance, flee, defense/submission, sexual behavior and immobility (Brain et al., 1989) and immobility and exploration during NPI AA: proactive strategy, attack and threat behaviors, non-social exploration, immobility ↓PR: reactive strategy, less attacks and threats, non-social exploration, immobility ↑ ANA: intermediate group, minimal attack and threat, activity than PR, and defense and flight behaviors All: changed behavior over time (↓ non-social exploration, ↑ immobility)	Goñi-Balentziaga et al. (2020)
Pro-active vs. Re-active	VR defeats	During (1h. in the morning and evening on days 1, 8 and 15)	Coping behaviors assessed: pro-active behaviors (attacking, mounting, chasing); re-active behaviors (flight, avoiding, submissive upright posture, scouting) and received offensive (attacks, mounts and chase received) (Reber and Neumann, 2008; Reber et al., 2016) Pro-active: attacking, mounting and chasing Re-active: flight, avoiding, submissive upright posture and scouting. Risk of being attacked and wounding	Foertsch et al. (2017)
Defeated Dominant (Dom) vs. Submissive (Sub) mice	VR defeats	During stress procedure (first 15 min of days 1 and 7)	Intruder (In) (aggressor) and Resident (Res) (defeated) status assessed: In: aggressive behaviors (chasing, mounting and biting) = Dom Res: no aggressive behaviors = Sub ResSub could display A (avoid being attacked, flee and jump) or P (ventral body surface directed towards the aggressor) behaviors P: ↑ displayed by Group-Housed (GH) than Individual-Housed (IH) during attacks A: ↑displayed by IH than GH during attacks ↑ GH and IH: jumping from 1st to last P-F.	Avitsur et al. (2003) *the defeated mice are the residents
	VR defeats	During stress procedure (N/S days)	Intruder (In) (defeated) and Resident (Res) (aggressor) status assessed: (In and Res) Dom: ↑ chasing and biting (In and Res) Sub: ↑ upright posture, flight and squeaking vocalization ResDom and InDom: = 1st attack and total attacking time	Bartolomucci et al. (2003) *Only Intruders are reported as they only measure autonomic function on them

(*continued on next page*)

Table 2 (*continued*)

Behavioral Coping	Behavioral Test	When	Behavioral characteristics (Analyzed -observed behaviors)	Reference
			InSub: ↓ activity in dark phase InDom: ↑ activity in dark phase InDom and InSub: = activity in light phase InDom: after the 1st interaction they showed attack behavior InSub: no further attacks after 1st interaction	
	VR defeats	During stress procedure (days 1 and 6)	Resident (defeated) Status: active/passive, aggressive/defending, fur score and wounds to divide into Dom and Sub. Dom: active and aggressive behaviors (tail rattling, chasing, fight attacks) Sub: ↑ passive and avoidant behaviors (escaping, defensive response, upright posture, immobility) Both: ↓ Dom. behaviors over time (from day 1–6) and Sub. behaviors and non-social exploration Sub and Dom:↑ minor wounds than non-stressed (day 6) Sub: ↑ Fur score than non-stressed (day 6)	(Savignac et al., 2011) *the defeated mice are the residents
Resilient (R) vs. Susceptible (S)	SIT	After stress procedure (day 11)	R: ≥1 (SIT ratio score) S: <1 (SIT ratio score)	Savignac et al. (2011)
	SIT	After stress procedure (day 11)	R: ≥1 (SIT ratio score) S: <1 (SIT ratio score)	Friedman et al. (2014)
	SIT	After stress procedure (day 11)	R: ≥1 (SIT ratio score) S: <1 (SIT ratio score)	Friedman et al. (2016)
	SIT	After stress procedure (day 11)	R: ≥1 SD (SIT ratio score) S: <1 SD (SIT ratio score) B6 are more R 129, BALB, DS are more S	Laine et al. (2018)
Dominant vs. Submissive Active vs. Passive Resilient vs. Susceptible	Dom vs. Sub through hierarchy testing (tube test, warm spot test). Hierarchy stability through hierarchy manipulation in dyads. A vs. P by VR defeats (Days 1 and 10) R vs. S through SIT	Dom vs. Sub before stress procedure A vs. P during stress procedure R vs. S after stress procedure	Dom: >3 (DS score) Sub: ≤ −3 (DS score) Intermediates: −3 < DS score <3 Dom and Sub ranks were validated with warm spot test: Dom: ↑ time in the warm corner than Sub A: running to the opposing end of the cage after attack, biting, boxing or lunging at the aggressor (A Score = (nº of A behaviors (Escape + Fighting) – nº of P behaviors)/nº Attacks). P: immobility in response to attack R: >1 (SIT ratio score) S: <1 (SIT ratio score)	LeClair et al. (2021)
Active vs. Passive Resilient vs. Susceptible	A vs P by VR defeats R vs. S through SIT	A vs. P during stress procedure (days 1 and 10) R vs. S before and after stress procedure	Coping behaviors assessed for P: freezing (upright freeze, forward freeze and crouch back); and for A: escape and fight A: escape related to S; fighting (day 1) related to R P: not related to R nor S R: >1 (SIT ratio score score) S: ≤1 (SIT ratio score)	Murra et al. (2022)
	A vs. P by VR defeats R vs. S through CPP	A vs. P during stress procedure (days 1 and 10) After stress procedure (day 31)	Coping behaviors assessed: flight, submission and attack A: ↓ flight and ↓ submission. Attacks. Related to R P: ↑ flight and ↑ submission. No attacks. Related to S R vs. S through C score (↑ time in the drug compartment) R: ↓ C score (not response to the rewarding effects of cocaine) S: ↑ C score (response to the rewarding effects of cocaine)	Ródenas-González et al. (2021)
	A vs. P by VR defeats R vs. S through SIT	A vs P during stress procedure (days 1, 4, 7 and 10) After stress procedure (day 11)	Coping behaviors assessed for A and P: defensive/submissive (upright submissive position, limp forepaws, upwardly angled head and retracted ears) and avoidance/flee A: ↑ latency to display the defeat posture, fight-back or active escape P: ↑ immobile and submissive behaviors R: >1 (SIT ratio score) S: <1 (SIT ratio score) R and S: = coping behaviors. Both defensive and flee and ↓ latencies to show these behaviors in the 4th defeat	Reguilón et al. (2022)

Abbreviations: C score: Conditioning score. DS score: David's score for the Tube Test results. NPI: Non-physical interaction. P-F: Pair-Fighting. SD: Standard Deviation. SIT: social interaction test. VR: Videorecording.

articles (15/18, 83.3%), all included in this review utilized the resident-intruder paradigm. The resident-intruder paradigm involves placing an intruder mouse in the cage of another mouse, referred to as the resident mouse. This arrangement creates a natural agonistic encounter, allowing aggressive behaviors to emerge. Typically, intruder mice display defensive and coping behaviors, while residents exhibit offensive behaviors towards the intruder (Kemble et al., 1993; Koolhaas et al., 1999). Two studies (2/18, 11.1%) used the SDR for which they selected aggressive mice based on a pre-experimental screening of aggressive behaviors. They used them as aggressive intruders, with the resident ones being stressed (Avitsur et al., 2003; Savignac et al., 2011). Finally, Foertsch et al. (2017) (1/18, 5.6%) used the CSC stress in which the

experimental mice were housed with a dominant mouse for 19 days.

3.2.4. Variations in housing conditions

Housing conditions refer to the conditions describing how animals are housed in between social defeat encounters (Fig. 3d). These include the number of animals housed in the cage (group size), and whether animals are exposed to only sensory input from the aggressor(s) (called sensory contact between residents and intruders). Following social defeat encounters, the majority of researchers (13/20, 65%) housed both residents and intruders (n = 2/cage) in sensory contact within the residents' cage until the next day's social defeat encounter (Bartolomucci et al., 2003; Friedman et al., 2014, 2016; Goñi-Balentziaga et al., 2020; Gómez-Lázaro et al., 2012; Laine et al., 2018; Leclair et al., 2021; Murra et al., 2022; Pérez-Tejada et al., 2013, 2016; Rosado et al., 2023; Savignac et al., 2011). Constant sensory contact was ensured by employing a perforated Plexiglas wall, enabling mice to perceive the presence of another mouse while preventing physical interaction. In three studies (3/20, 15%), sensory contact was limited to 10 min before and after the social defeat encounters (n = 2/cage), with mice being isolated (n = 1/cage) during the remaining time (Ballestin et al., 2021; Reguilón et al., 2022; Ródenas-González et al., 2021). Two studies (2/20, 10%) separated residents and intruders once the social defeat encounter concluded (n = 1/cage) (Leclair et al., 2021; Savignac et al., 2011), while one (1/20, 5%) kept animals together (n = 4/cage) throughout the entire experimental procedure (Foertsch et al., 2017). Notably, one study (1/20, 5%) did not provide information on housing conditions between social defeats (Avitsur et al., 2003).

3.2.5. Variations in mouse strain

Mouse strain refers to the specific lineage of mice used to be defeated during social defeat encounters (Fig. 3e). Mouse strains used in laboratories can be categorized into inbred and outbred based on their genetic variability. The majority of the studies included in this review used inbred mouse strains, which are characterized by being more genetically similar. The most frequently used inbred mouse strain is the C57BL/6 (11/18, 61.1%) (Avitsur et al., 2003; Ballestin et al., 2021; Foertsch et al., 2017; Friedman et al., 2016; Laine et al., 2018; Leclair et al., 2021; Murra et al., 2022; Reguilón et al., 2022; Rosado et al., 2023; Ródenas-González et al., 2021; Savignac et al., 2011), followed by BALB/c (3/18, 16.7%) (Laine et al., 2018; Savignac et al., 2011; Savignac et al., 2011), and genetically modified mice with a C57BL/6 genetic background (2/18, 11%) (Friedman et al., 2014, 2016). Interestingly, one study that used both C57BL/6 and BALB/c also used the 129 and D2 mouse strains (Laine et al., 2018). The remaining studies utilized outbred mice, such as OF-1 (4/18, 22.2%) (Goñi-Balentziaga et al., 2020; Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013, 2016), and Swiss CD-1 (1/18, 5.5%) (Bartolomucci et al., 2003).

3.2.6. Variations in mouse age

The age of the mice at the start of the stress procedures ranged from 4 week-old (i.e. adolescence) (1/18, 5.6%) (Reguilón et al., 2022), 5-6 week-old (i.e. juvenile) (1/18, 5.6%) (Foertsch et al., 2017), to 7-13 week-old (i.e. adulthood) (16/18, 88.8%) (Avitsur et al., 2003; Ballestin et al., 2021; Bartolomucci et al., 2003; Friedman et al., 2014, 2016; Goñi-Balentziaga et al., 2020; Gómez-Lázaro et al., 2012; Laine et al., 2018; Leclair et al., 2021; Murra et al., 2022; Pérez-Tejada et al., 2013, 2016; Rosado et al., 2023; Ródenas-González et al., 2021; Savignac et al., 2011; Savignac et al., 2011) (Fig. 3f).

3.2.7. Variations in mouse sex

In terms of the sex of the mice employed, all the reviewed studies used male mice in their stress procedures (18/18, 100%). Only the study conducted by LeClair et al. (2021), which involved three different stress procedures and employed female mice for two of the procedures.

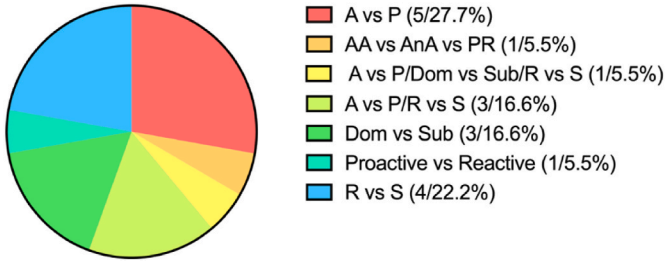


Fig. 4. Relative frequency of different classifications of behavioral coping strategies across reviewed studies. A: Active. AA: Active Aggressive. ANA: Active Non-Aggressive. Dom: Dominant. P: Passive. PR: Passive Reactive. R: Resilient. Sub: Submissive. S: Susceptible.

3.3. Behavioral coping strategies

We examined different types of behavioral coping classifications reported by the 18 studies included in the review (Table 2, Fig. 4). All studies used video recordings of animals and subsequently evaluated the behaviors displayed by mice. The scores for behaviors were then analyzed using statistical methods to further categorize animals into groups. Behavioral videotaping and evaluation have been reported at different times during social stress. Behaviors are considered to be analyzed during stress if the recording starts at the beginning of social stress and terminates at the end of the social stress. Behavioral analysis is considered before or after if the recording occurs before the social stress or after, respectively.

3.3.1. Studies classifying active versus passive coping strategies to social defeat stress

Individuals commonly use active and passive behavioral coping strategies to reduce internal or external demands induced by stressful experiences (Bandler and Shipley, 1994; Folkman and Lazarus, 1980; Obrist, 1981). An active coping strategy refers to behaviors used by individuals to directly engage with the stressor (Carver, 1997), while a passive coping strategy is used to avoid the stressor. In mice coping with social defeat stress, active strategies involve defensive and fighting behaviors and passive strategies involve freezing, immobility, and submission (Leclair et al., 2021).

It is important to note that both strategies have been associated with distinctive benefits and costs depending on the environmental conditions (de Kloet and Molendijk, 2016; Dingemanse and Wolf, 2010; Gandhi et al., 2017). However, with chronic social defeat stress, a passive coping strategy has been often proposed as a model of dysfunctional and maladaptive stress coping (Cabib et al., 2021; Wood and Bhatnagar, 2015). It has been linked to negative health consequences, such as altered immune response and HPA reactivity (Chida et al., 2008), as well as a higher risk of diseases such as cancer (Vegas et al., 2006).

Seven studies (7/18, 38.9%) classified mice into passive or active based on their behavior. Animals within the active group exhibited increased aggressive behaviors, increased exploration compared to animals within the passive group, which showed more submissive behaviors, less social and non-social exploration, less self-grooming and digging and more immobility (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013, 2016; Rosado et al., 2023). Avitsur et al. (2003) classify mice into active escape or passive submissive, and Goñi-Balentziaga et al. (2020) reported three types of behavioral strategies, active aggressive, active non-aggressive and passive reactive, based on the number of attacks, the mobility, the time in exploration and their strategy during the social stress (e. g. flight, fight).

While coping categorization was determined by observing mice behaviors during social defeat episodes, studies differ on the time point at which the evaluation was done during the social stress. For example, Ballestin et al. (2021) conducted behavioral evaluations on days 1, 4, 7, and 10 of a 10-day stress procedure, and Pérez-Tejada et al. (2016)

Table 3
Behavioral outcomes after coping with chronic social stress regarding coping strategies.

Behavioral Coping	Behavioral Tests	When	Behavioral characteristics	Reference
Active (A) vs. Passive (P)	FST	After CSDS	Both: ↓ climbing than non-stressed	Gómez-Lázaro et al. (2012)
			P: ↑ immobility	Pérez-Tejada et al. (2013)
			Both = ↑ swimming latency than non-stressed	
	NPT	After CSDS	Both = ↑ latency to ingest palatable food than non-stressed	Pérez-Tejada et al. (2013)
	SIT, CPP and SA	After CSDS	SIT: divides into Resilient (R) and Susceptible (S) S: ↑ cocaine intake (CPP and SA) than R P: These strategies are more used by S A: promotes resilience A: ↓ cocaine seeking behaviour induced by stress	(Ballestin et al., 2021)
	Modified MWM, SI, TST, OFT, SST	Before and after CSDS	Before: Modified MWM (working memory) High flexibility (HF): 1SD < value < +1SD Low flexibility (LF): value outside SD After: SI, TST, OFT, SST (Emotional behavior) HF and LF: similar coping (A vs P) on Day 1. LF: No changes in coping between day 1 and 10. HF: Decreased A coping between day 1 and 10. HF that changed for P on day 10 had ↑ SI ratio than HF that sustained A	Rosado et al. (2023)
Active Aggressive (AA) vs. Active non-Aggressive (ANA) vs. Passive Reactive (PR)	FST, OFT, SAT and SPT	After CSDS	FST: PR: ↑ immobile than ANA and AA, ↓ swimming than ANA, AA and non-stressed OFT: PR: ↑ immobile and ↓ distance traveled than AA and non-stressed No differences in SPT nor SAT relative to coping	Goñi-Balentziaga et al. (2020)
	EPM	After CSDS	S (B6): ↓ time in open zones than Controls	Laine et al. (2018)
			R: ↑ time in closed arms and ↓ entries into open arms (+ anxious behavior) than the control group	Reguilón et al. (2022)
			Both: anxiety-like behavior	
	CPP	After CSDS	S: increased preference for the cocaine-associated compartment	Ródenas-González et al. (2021)
			R: Preference for cocaine dose → ↑ time spent in the drug-paired compartment = C score than control mice	Reguilón et al. (2022)
	FST	After CSDS	No differences	Friedman et al. (2014)
			R, S and Controls (B6): = inmobility time	Laine et al. (2018)
			S: ↑ immobile than R mice	Murra et al. (2022)
	OESA	After CSDS	R: ↑ ethanol intake compared to control and S mice in FR1, to control mice in FR3 and BP values than control mice	Reguilón et al. (2022)
	OFT	After CSDS	R (B6): ↓ distance traveled than Controls	Laine et al. (2018)
			S (D2): ↓ distance traveled than Controls	
			Both: ↓ time in the centre than Controls (anxiety-like)	Murra et al. (2022)
	SAT (=SIT)	After CSDS	R and S (B6): ↓ locomotor activity than Controls	Laine et al. (2018)
			S (D2): ↓ locomotor activity than Controls	
	SPT	Before and after CSDS	S: ↓ Sucrose Preference	Friedman et al. (2014)
	SIT	After CSDS	BALB/c (S): ↑ SA ↓ IR ↑ Distance C57BL/6 (R): ↓ Behavioral impairments Both: Defeated and Sub. Behaviors	Savignac et al. (2011)
	Von Frey Test	After CSDS	S: needed a lower filament force to elicit a mechanical response than Controls (↑ nociception sensitivity) and a trend to lower pain threshold than R R: similar filament force threshold to Controls	Murra et al. (2022)
Dominant vs. Submissive Active vs. Passive Resilient vs. Susceptible	SIT	After CSDS	Male CSDS: Well established hierarchies Dom: more R Sub: more S Day 1: Dom and Sub: Similar A and P behaviors Day 10: Dom: ↑ A behaviors than Sub A: more R Female CSDS: Dom: more R Day 1: Dom and Sub: Similar A and P behaviors Interfemale CSDS: Dom: more R Sub: more S Dom and Sub: Similar A and P behaviors	LeClair et al. (2021)

Abbreviations: CPP: Conditioned Place Preference. CSDS: Chronic Social Defeat Stress. EPM: Elevated Plus Maze. FST: forced swimming test. HPT: Hot Plate Tests. L/D: Light/dark (L/D) box. MWM: Morris Water Maze. NORT: Novel Object Recognition Test. NPT: Novel Palatable Test. OESA: Oral Ethanol Self-Administration. OFT: Open Field Test. SAT: Social Avoidance Test. SIT: Social Interaction Test. SPT: Sucrose Preference Test. SST: Sucrose Splash Test.

conducted the behavioral evaluation at a single time point during the final episode of social defeat. Two studies assessed behavior on days 18 and 21, reporting maintenance of the adopted coping strategy with increased behavioral differences between passive and active mice in terms of immobility and social and nonsocial exploration on day 21 (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013). In contrast, Rosado et al. (2023) assessed behavior on the first and last day of the 10 days of stress, and Goñi-Balentziaga et al. (2020) assessed the behavior on the first and middle day (day 9) of the social stress. In this study, it was observed that all stressed animals changed their behavior as a function of time.

3.3.2. Studies classifying proactive versus reactive coping strategies to social defeat stress

The classification of coping strategies as proactive and reactive, emphasizes the role of environmental stimuli (and their potential influence on behavior) and the timing in which coping strategies are engaged (anticipating stressors or responding once they occur) (Benus et al., 1990; Koolhaas et al., 1999; Oh et al., 2018).

Proactive coping strategies refer to those strategies where individuals anticipate the occurrence of a stressor (Koolhaas et al., 1999; Oh et al., 2018). Individuals employing proactive coping tend to exhibit lower flexibility, more rigid routine-like behaviors and increased impulsivity (Coppens et al., 2012). They also display offensive behaviors towards male conspecific rivals, take more risks, and often exhibit a greater preference for seeking novel stimuli (David et al., 2004; Groothuis and Carere, 2005; Steimer and Driscoll, 2005). In contrast, reactive coping occurs as a response to a stressor (Koolhaas et al., 1999; Oh et al., 2018). These individuals are flexible in their behavior and rely on environmental stimuli rather than following routines (Coppens et al., 2010). In this review, only one study (1/18, 5.5%) used this classification (Foertsch et al., 2017). In this study social encounters were recorded during stress procedures (on days 1, 8 and 15 of the 19-day procedure), and animals were categorized based on the exhibited behaviors. Foertsch et al. (2017) classified mice into the proactive (animals that displayed increased attacking, chasing and mounting behaviors) and the reactive (animals that exhibited increased flight behavior, avoiding, submissive upright posture and scouting responses) calculating an overall Dominance Index. This index was determined by the difference between the number of proactive behaviors and the number of reactive behaviors observed on the video-recorded encounters. Their findings indicate a positive correlation between adopting a reactive coping strategy and the likelihood of experiencing attacks and injuries from the resident animal.

3.3.3. Classification of dominant versus submissive roles during social defeat stress

Dominant and submissive behavioral roles are categories that define the position a mouse holds within its social group hierarchy. During mouse interactions, distinct behavioral patterns emerge, eventually establishing their rank in the social order. Mice exhibiting aggressive behaviors, such as attacking, biting, or chasing, are typically identified as dominant, whereas those engaging in evasive actions, such as running away, jumping, or freezing are associated with a submissive phenotype.

Three studies (3/18, 16.7%) utilized this classification. Social encounters were recorded during stress procedures, and animals were categorized based on the exhibited behaviors. Bartolomucci et al. (2003a,b), classified mice as Dominant or Submissive, regardless of their condition as residents or intruders within the social stress paradigm. Savignac et al. (2011a,b) focused exclusively on defeated animals, categorizing them as well into Dominant and Submissive groups. Avitsur et al. (2003) animals were classified as intruders dominants or submissive residents.

Interestingly, these studies used different behaviors to categorize mice into dominant and submissive phenotypes. To determine dominance, some of these behaviors included, but were not limited to, increased chasing, biting, tail rattling, fight attacks, upright posture, flight behavior, reduced squeaking vocalization, escaping defensive response, and immobility. However, not all behaviors were analyzed in these three studies; each study focused on a subset of these behaviors.

3.3.4. Studies classifying resilient vs susceptible individuals to social stress

As mentioned before, coping strategies are usually defined as the behaviors displayed by an individual to deal with a stressful situation. Nevertheless, certain studies approach behavioral coping by examining the social behaviors exhibited by animals post-chronic stress exposure. This is accomplished by assessing mice's behavioral outcomes in the social interaction test (SIT) wherein animals are categorized as either "resilient" (displaying social interaction) or "susceptible" (exhibiting social avoidance). This classification is typically determined using the social interaction (SI) ratio formula (100 x (interaction time, target present)/(interaction time, target absent)), where animals scoring above 100 are categorized as resilient and those scoring below 100 as susceptible (Golden et al., 2011). It should be noted that some studies (Murra et al., 2022; Reguilón et al., 2022; Wood and Bhatnagar, 2015) have examined the health consequences associated with displaying different behavioral coping strategy, suggesting distinct outcomes depending on the coping style adopted (Koolhaas et al., 1999). For instance, passive coping strategies have been related to susceptibility to stress-related pathophysiology such as depression (Wood, 2014; Wood and Bhatnagar, 2015) while active coping strategies have been related to resiliency to some diseases such as hypertension (Southwick et al., 2005).

Four studies (4/18, 22.2%) divided mice into resilient and susceptible using the aforementioned SI ratio, obtained the day after the 10-day stress procedure (Savignac et al., 2011; Friedman et al., 2014, 2016; Laine et al., 2018). Interestingly, three studies (3/18, 16.7%) used the active vs. passive classification and then correlated their categorization with the resilient and susceptible phenotypes (Murra et al., 2022; Ródenas-González et al., 2021; Reguilón et al., 2022). All of them analyzed active and passive coping behaviors during the CSDS by videorecording (VR) during the first (day 1) and the last (day 10) social encounters, and Reguilón et al. (2022) VR also social encounters from days 4 and 7. Coping behaviors assessed included freezing (upright freeze, forward freeze and crouch back), escape/avoidance/flee, fight/attack and defensive/submissive (upright submissive position, limp forepaws, upwardly angled head and retracted ears) behaviors. These studies also examined the resilient and susceptible phenotypes, although each of them did it differently. To do so, Murra et al. (2022) implemented the SIT before and after CSDS, Reguilón et al. (2022) did it only after (day 11); and Ródenas-González et al. (2021) used the Conditioned Place Preference (CPP) after the CSDS (day 31).

3.4. Behavioral correlates of coping characterization

Chronic stress can trigger the appearance of anxiety-like and depressive-like behaviors such as social withdrawal or anhedonia (Belzung and Lemoine, 2011). These and other symptoms have been studied through different behavior tests such as the social withdrawal test, the Elevated Plus Maze (EPM), the Sucrose Preference Test (SPT), the Forced Swimming Test (FST) or the Tail Suspension Test (TST) (Tran and Gellner, 2023). Furthermore, chronic stress can also lead to cognitive impairments in mice (Keeler and Robbins, 2011; Yu et al., 2011) that have been examined through behavior tests such as the Morris Water Maze (MWM) test or the Novel Object Recognition Test (NORT) (Tran and Gellner, 2023). In this review, we examined the different types of behavioral parameters reported by the 18 studies included (Table 3).

Thirteen articles (13/18, 72.2%) assessed behavior or cognitive changes regarding coping strategies by performing one or more behavioral tests. These tests have been carried out mainly after the stress procedure, although two studies (2/18, 11.1%) have also performed

Table 4
Physiological responses to chronic social stress regarding coping strategies: neuroendocrine, autonomic and neuroimmune response.

Behavioral Coping	HPA axis	SAM axis	Immune System	Others (?)	Reference
Active (A) vs. Passive (P)	P: ↑ CORT plasma levels and ↑ GR in HT than non-stressed and A: ↓ MR/GR ratio than non-stressed in HT	–	P: ↑ IL-6 and TNF-α in spleen than non-stressed and A A: ↑ IL-6 and TNF-α in spleen than non-stressed	P: ↑ 5-HT_{1A} receptor mRNA levels than non-stressed in HPC	Gómez-Lázaro et al. (2012)
	P: ↑ CORT plasma levels than non-stressed and A A: ↑ CORT plasma levels than non-stressed P: ↑ CRH than A in HT and ↑ CRH than non-stressed in AMYG Both: ↑CRH and CRH-R1 than non-stressed	P: ↓NE plasma levels than non-stressed ↓ E plasma levels than A A: ↑TH and DBH in adrenal glands than non-stressed and P	–	–	Pérez-Tejada et al. (2013)
	–	A: ↓ receptor α2a mRNA expression than P on day 23 in PFC P: ↓ receptors α2a and α1b mRNA expression than A on day 24 in PFC	P: ↑ IL-6 than A in HT and AMYG ↑ IL-1B than non-stressed in HT ↑ IL-1B than A and non-stressed in HPC A: ↓ TNF-a and iNOS than non-stressed in PFC	–	Pérez-Tejada et al. (2016)
	R (A) and S (P): ↑ CORT than non-stressed	–	S: ↑ IL-6 in ST and HC than non-stressed Both: ↓ CX3CL1 in ST and HC than non-stressed	–	(Ballestin et al., 2021)
Active Aggressive (AA) vs. Active non-Aggressive (ANA) vs. Passive Reactive (PR)	ANA: ↑ CORT plasma levels than AA after 1st interaction	–	All: ↑ spleen weight than non-stressed	Stressed:↑tumor foci than non-stressed mice PR: ↑tumor foci than ANA, AA and non-stressed mice ANA: ↑tumor foci than non-stressed mice AA and non-stressed: = tumor foci	Goñi-Balentziaga et al. (2020)
Pro-active vs. Re-active	Re: attacks and bites received correlate with splenic CORT resistance and with basal and LPS-induced splenocyte viability. CORT resistance is dependent on bite wounds and the presence of CD11b + cells. Splenic immune activation and CORT resistance following social stress are dependent on wounding, which is associated with a reactive coping	–	–	–	Foertsch et al. (2017)
Dominant (Dom) vs. Submissive (Sub)	–	Both: strong autonomic activation during interactions InD: autonomic activation (marked hypertermia and marked ↑HR) with no habituation InS: autonomic activation (slight hypertermia and slight ↑HR) with moderate habituation (although persistent autonomic activation)	–	–	Bartolomucci et al. (2003)
	Sub: ↑ CORT plasma levels than Controls (trend, non-significant)	–	Both: ↑ TNF-a, IL-10 and IL-12p70 plasma levels than non-stressed Both: ↑ IL-1B, IL-6 and CXCL than non-stressed (although more acute increase in Sub.) Sub: ↑ CXCL1 than Dom	Both: mild inflammatory cell infiltration, ↓ globet cells and ↑ muscle thickness of the colon Both: body weight	Savignac et al. (2011)
	Exp 1: IH and GH: CORT resistance in splenocytes	–	Exp 1: IH and GH: ↑ splenomegaly	–	Avitsur et al. (2003)
Resilient (R) vs. Susceptible (S)	Before CSDS: R, S and non-stressed: = CORT After CSDS: R: ↑CORT plasma levels than non-stressed S: ↓body weight than R and non-stressed	–	–	–	Murra et al. (2022)

(*continued on next page*)

Table 4 (*continued*)

Behavioral Coping	HPA axis	SAM axis	Immune System	Others (?)	Reference
	–	–	Both: ↑ CX3CL1 in PFC than non-stressed S: ↑ IL-6 in ST than non-stressed	–	Reguilón et al. (2022)
	BALB/c (S) ↑ CORT plasma levels, ↓ thymus weight, ↓ heart weight and ↑ spleen weight than C57BL/6 (R)	–	–	–	Savignac et al. (2011)
	–	–	–	S: hyperactivity of VTA DA neurons	Friedman et al. (2014)
	–	–	–	S: Upregulation of KCNQ channels normalizes the hyperactivity of VTA DA neurons (potentiates resilience and is a potential target for depression treatment)	Friedman et al. (2016)
	–	–	–	R (D2): thinner myelin mPFC axons than Controls and S S (C57BL/6): thinner myelin vHPC axons than R and Controls and thicker in the BNST compared to R and Controls R (C57BL/6): thicker myelin axons on mPFC than Controls S (BALB/c): gained less weight than Controls Both (C57BL/6): = lost weight	Laine et al. (2018)
	–	–	Both: = IL-6	–	Ródenas-González et al. (2021)

Abbreviations: 5-HT: serotonin. AMYG: amygdala. CRH: Corticotropin-releasing hormone. CORT: corticosterone. DBH: dopamine-beta-hydroxylase. E: epinephrine. GR: glucocorticoid receptor. HPC: hippocampus. HT: hypothalamus. IL: interleukin. LC: locus coeruleus. MR: mineralocorticoid receptor. NE: norepinephrine. PFC: prefrontal cortex. SAM axis: TH: tyrosine hydroxylase. TNF: Tumor necrosis factor. vHPC: ventral hippocampus. VTA: ventral tegmental area.

some behavioral tests before the stress procedure to assess the behavioral differences not only among animals using different coping mechanisms but also to evaluate behavioral or cognitive differences before and after stress (Friedman et al., 2014; Rosado et al., 2023).

Mice using a passive (Pérez-Tejada et al., 2013) or a passive-reactive (Goñi-Balentziaga et al., 2020) coping strategy showed higher immobility rates in both the FST and the OFT (Goñi-Balentziaga et al., 2020), as well as a higher cocaine intake in the CPP and SA tests (Ballestin et al., 2021). Interestingly, in the study by Rosado et al. (2023), mice characterized as High-Flexible, as determined through the modified MWM before the CSDS, exhibited a transition in their coping strategy from active to passive during the CSDS. Remarkably, when comparing resilient and susceptible mice, two studies found no differences in the immobility time in the FST (Friedman et al., 2014; Laine et al., 2018). In contrast, resilient and susceptible mice from distinct strains (D2 and B6) exhibited heightened immobility in two behavioral tests, the OFT and the Social Avoidance Test (SAT), when compared to control mice (Laine et al., 2018). Additionally, Laine et al. (2018) revealed that susceptible B6 mice spent less time in the open arms of the EPM, indicating an increase in anxiety-like behaviors compared to control mice. In this sense, Savignac et al. (2011) also demonstrated that BALB/c susceptible exhibited social avoidance during the SIT, despite covering a greater distance. Their findings led to the conclusion of fewer behavioral impairments in resilient mice. Finally, Friedman et al. (2014) performed the SPT before and after the CSDS and observed that susceptible mice presented anhedonia, which suggested depressive-like behavior in these mice. Regarding dominant and submissive mice, mice submitted to CSDS showed well-established hierarchies being dominants more resilient and submissive more susceptible. At the beginning of the stress procedure, both displayed active and passive coping strategies similarly, but, in the end, dominant ones displayed more active coping behaviors, which was related to a more resilient phenotype (Leclair et al., 2021). Similarly, LeClair et al. (2021) also studied female mice submitted to CSDS by either a male or a female aggressor. Their protocols revealed that both dominant and submissive mice exhibited active and passive coping behaviors to a comparable extent, with dominant female mice being more resilient than their submissive counterparts. In a separate study conducted by Reguilón et al. (2022), where resilient and susceptible mice again did not exhibit differences in displaying active or passive coping behaviors, resilient mice demonstrated a preference for cocaine in the CPP test, increased ethanol intake in the Oral Ethanol Self-Administration (OESA) test, and heightened anxiety-like behavior in the EPM compared to control mice. Nevertheless, according to Murra et al. (2022), both resilient and susceptible mice showed anxiety-like behavior as they spent less time in the centre of the OFT compared to control mice. In this study, they also revealed that susceptible mice presented higher immobility rates in the FST and a lower pain threshold in the Von Frey test.

3.5. *Physiological responses to chronic social stress regarding coping strategies*

We examined different types of physiological parameters reported by the 18 studies included in the review (Table 4).

3.5.1. *Neuroendocrine behavioral coping correlates*

Eight studies reported measurements associated with the activity of the HPA axis (9/18, 50%). Mice displaying active and passive strategies, after CSDS, have higher CORT plasma concentration than non-stressed mice (Ballestin et al., 2021; Pérez-Tejada et al., 2013). However, subjects displaying passive coping also showed higher CORT plasma concentration compared to active subjects after the last social defeat encounter (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013). Nevertheless, the results observed by Goñi-Balentziaga et al. (2020) diverge from the aforementioned. Although they found that after the first social interaction (day 1), active-non-aggressive mice showed higher CORT concentration than active-aggressive animals, no differences were observed at the middle (day 9) or the end (day 18) of CSDS. Additionally, Avitsur et al. (2003) found that resident mice, which were exposed to stress and consequently considered submissive, exhibited

CORT resistance in splenocytes, by reducing the ability of these cells to respond to CORT. However, neither mice housing conditions (Individually-Housed - IH or Grouped-Housed - GH mice) nor their individual behavioral differences (active-escape or passive-submissive) had any effect on this aspect. Similarly, Foertsch et al. (2017) demonstrated that glucocorticoid resistance following social stress were shown to be influenced by the presence of bite wounds which, in turn, was associated with reactive coping. Concerning dominant and submissive coping styles, submissive mice showed higher, but not significant, CORT concentration than non-stressed mice 2 h after stress exposure, and, additionally, no significant differences were found in plasma CORT concentration between these coping strategies (Savignac et al., 2011). However, differences were observed between resilient (or unsusceptible) and susceptible (or vulnerable) individuals. Plasma CORT levels following chronic stress exposure varied across studies, with higher levels typically found in susceptible (Savignac et al., 2011) or resilient (Murra et al., 2022) groups compared to the non-stressed control mice. Passive mice showed higher glucocorticoid receptor (GR) gene expression in the HT compared to the non-stressed mice (Gómez-Lázaro et al., 2012). Besides, passive mice presented higher CRH gene expression in the same area compared to active mice (Pérez-Tejada et al., 2013).

Three studies (3/18, 16.67%) explored the relationship between observed individual differences in behavior and SAM system activity (Bartolomucci et al., 2003; Pérez-Tejada et al., 2013, 2016). Passive mice presented lower plasma E levels and lower α1b receptor gene expression in PFC than active mice, as well as lower NE levels compared to non-stressed mice. Active mice showed higher TH and DBH mRNA expression levels in the adrenal glands compared to non-stressed and passive mice (Pérez-Tejada et al., 2013, 2016). α2a receptor mRNA expression varied depending on the period elapsing the stress and the sampling. The α2a receptor mRNA expression in the PFC was found to be lower in active mice when the sampling was carried out on day 23, whereas it was lower in passive mice when the sampling was taken on day 24, after one more defeat exposure (Pérez-Tejada et al., 2016). Only one study using the dominant/submissive classification included SAM system measurements in their work. This study revealed that stressed animals had a strong autonomic activation during social defeats, although dominants' physiological response (body temperature and heart rate) was more pronounced and they did not present habituation over time (Bartolomucci et al., 2003).

3.5.2. Neuroimmune behavioral coping correlates

Exposure to chronic stress has been shown to have complex effects on the immune system. The dysregulation or suppression of both innate and acquired immunity responses has been largely studied and discussed. For instance, the increase of glucocorticoids or catecholamines levels as a result of stress exposure has been related to several immune system impairments (Murison, 2016). One of the most studied effects of stress exposure has been the alteration of cytokines number, balance, distribution or function (Butts and Sternberg, 2008; Chrousos, 2009; Glaser and Kiecolt-Glaser, 2005). Nevertheless, the effects of stress vary among studies and they depend on the characteristics of the stress such as the intensity (low/intense), the duration (acute/chronic), and the typology (social/physical) of the stress procedure, as well as on the measurement techniques utilized (Dhabhar, 2014).

Eight (8/18, 44.4%) of the included studies in this review observed different immune and inflammatory response, regarding the individual behavioral differences. For instance, mice displaying Passive coping presented higher cytokine levels, such as interleukin −6 (IL-6), tumor necrosis factor-α (TNF-α) or interleukin - 1β (IL-1β), as well as inducible nitric oxide synthase (iNOS) enzyme compared to Active and non-stressed mice within different brain structures (i.e. hippocampus (HPC), hypothalamus (HT), prefrontal cortex (PFC), striatum (ST)) or in the spleen (Ballestin et al., 2021; Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2016). However, Ródenas-González et al. (2021) did not find differences in IL-6 levels in the striatum. Additionally, the spleen, involved in numerous immunological functions, increased its weight and was higher in stressed mice regardless of their coping style (Avitsur et al., 2003; Goñi-Balentziaga et al., 2020). In addition, Avitsur et al. (2003) also observed more cluster of differentiation 11b (CD11b) expression on splenic monocytes in stressed mice. Furthermore, differences in cytokine levels and spleen size and function were also found when classifying mice into dominant and submissive. Regarding cytokines and according to Savignac et al. (2011), both groups showed higher cytokines plasma levels (TNF-α, interleukin-10 (IL-10) and interleukin-12p70 (IL-12p70)) than non-stressed subjects, although the difference in some of them (IL-1β, and IL-6) was more pronounced in Submissive mice. Finally, considering Resilient and Susceptible phenotypes, Susceptible mice showed higher chemokine (C-X3-C motif) ligand 1(CX3CL1) levels at the PFC and chemokine (C-X-C motif) ligand 1 (CXCL1) and chemokine (C-C motif) ligand 2 (CCL2) levels (Reguilón et al., 2022).

3.5.3. Other physiological behavioral coping correlates

Observed individual differences in behavior have been associated with differences in other biological parameters. Six of the studies (6/18, 33.3%) explored additional biological parameters not related to the HPA axis, SAM system or immune system. For instance, regarding mice displaying a passive or active coping style, one study revealed an increase of the 5-H_{1A} receptor mRNA levels in the HPC in mice with a passive coping style, which revealed a serotonin deficit in these subjects (Gómez-Lázaro et al., 2012), and interestingly, passive-reactive mice were also the ones to show more tumor foci in the lung after CSDS (Goñi-Balentziaga et al., 2020). About dominant and submissive coping strategies, a study revealed no observable differences in terms of weight and colon damage between mice exhibiting either of these strategies. However, both coping strategy groups exhibited decreased body weight and mild microscopic damage in the colon, likely attributed to gut epithelial barrier dysfunction induced by elevated levels of some cytokines, as mentioned in the 'Immune system' section (Savignac et al., 2011). Concerning the resilient and susceptible classification, susceptible mice presented higher myelin-related gene expression and weight alterations when compared to resilient mice (Laine et al., 2018). Furthermore, susceptible mice exhibited increased activity in the ventral tegmental area's (VTA) dopamine (DA) neurons (Friedman et al., 2014). In this sense, Friedman et al. (2016) also examined the impact of KCNQ channels on VTA DA neuron activity, revealing their role in promoting resilience. The stabilization of activity through these channels resulted in the reversal of the susceptible phenotype.

4. Discussion

The study of behavior and physiology during chronic social stress is a useful approach to better understanding the impact of stress on health and the underlying mechanisms. Moreover, a large body of work supports the idea that different coping styles mediate individual vulnerability to stress-related diseases. Thus, investigating individual differences in coping with environmental demands is essential for understanding variations in health among both human and nonhuman animals. This literature review focuses on the different experimental approaches used to study coping strategies in mice exposed to Social Defeat Stress as well as their behavioral and physiological correlates. The studies included in this review revealed variations in several aspects of the experimental approaches: the experimental subjects used (1), the chronic social stress procedures (2), the coping style concept interpretation (3), and behavioral (4) and biological (5) outcomes following chronic social stress.

4.1. Experimental subjects

Understanding the background characteristics of experimental subjects, such as their strain, sex and, age is crucial when investigating

coping strategies. In particular, the use of highly inbred strains in studies offers advantages such as reducing the number of animals per experiment and facilitating result replication. However, although genetic standardization provides consistency within inbred strains (i.e. C57BL/6), its lack of variability may limit its effectiveness in exploring individual differences in coping strategies and emotional reactivity. Alternative studies use inter-inbred strains, (i.e. C57BL/6 *vs* BALB/c), highlighting the importance of genetic background in behavioral studies (Ducottet and Belzung, 2004; Võikar et al., 2001). Outbred mice (i.e. OF-1) more accurately represent the genetic diversity found in humans. This is essential for studying how different genetic backgrounds can affect behavior traits, disease susceptibility, progression and response to treatment (Azkona and Sanchez-Pernaute, 2022).

Moreover, research consistently shows that male and female mice exhibit distinct behavioral differences, which are influenced by a combination of genetic, hormonal, and environmental factors, as well as neurobiological differences in brain structure (Viveros et al., 2012). While we included males and females in our search criteria, only one of the articles used female mice. This could be attributed, among other reasons, to the predominance of social defeat as a model of chronic stress in males. Transferring this model to female mice is challenging due to the well-documented sexual dimorphism in behavior, as noted by Kelley (1988). Thus, male mice tend to be more territorial and aggressive than females, while females are more social and protective (Brain and Parmigiani, 1990; Cox and Rissman, 2011). It is, therefore, crucial to expand research methodologies that incorporate female mice in the study of coping strategies to social stress, to also be able to draw conclusions that are representative of both sexes. For instance, in this context, vicarious social defeat stress model has been applied in adult male and female rodents, yielding promising outcomes. This model involves a mouse witnessing a physical defeat of a conspecific. Interestingly, Warren et al. (2020) observed that subjects submitted to this paradigm exhibited a similar behavioral phenotype to mice that have experimented themselves the social defeat stress. Thereby, witness stress emerges as an effective alternative to the chronic social defeat stress model for studying stress responses in both male and female subjects.

Another fundamental characteristic of the experimental subjects is their age. Although most of the mice in the selected papers were adults ($\geq$8 weeks), we included one paper with adolescent mice (4 weeks old) and one with juvenile mice (5–6 weeks old). Research on C57BL/6J mice has shown that age-related changes in behavior are significant, with older mice (16–48 weeks), exhibiting decreased locomotor activity, motor function, and social behavior, as well as increased anxiety-like behavior (Shoji, 2016). It is important to consider the rapid development and aging process of mice, with every month of a mouse's life being approximately equivalent to 2.5 human years (Dutta and Sengupta, 2016), which highlights the need for careful consideration of age when designing behavioral tests and interpreting results.

4.2. Chronic social stress procedures

The neurobiology of stress and social behavior in rodents is closely linked, with social interactions serving as both stressors and buffers (Beery and Kaufer, 2015). The procedures employed to model social chronic stress differed on chronicity (i.e., stress days), time and frequency (i.e., stress hours/day), paradigm (i.e., resident-intruder, social disruption or subordinate colony-housing), and housing conditions (i.e., sensory-contact, isolation or group-housed). The coping strategies may be conditioned to some degree by these procedural differences. Prevot et al. (2021) showed that chronic stress in mice led to the emergence of anxiety-like behaviors within 7 days, and anhedonia-like behaviors after 35 days, with longer exposure resulting in more pronounced molecular alterations. In this sense, regardless of the model used, the time point selected for behavioral analysis to evaluate coping strategies can also be relevant. As this and other studies have shown, some coping behaviors might be observed with chronic but not acute social stress (Prevot et al., 2021; Zamudio et al., 2009), which suggests that the behaviors that characterize an active vs. passive could also be different depending on the length of the stress model applied. At the same time, chronic social stress has also been shown to be influenced by various social and individual-personal factors. In this sense, not only the social stress paradigm but also housing conditions which include differences in the frequency and duration of social interactions, the establishment of social hierarchies or the presence of aggressive behaviors, can determine the coping strategies displayed in the face of social stress. For example, it has been observed that environmental enrichment and optimization of group size can reduce aggressive behavior (Van Loo et al., 2003), and that mice housed individually, and not in groups, show altered immune-endocrine responses to stress (Bartolomucci et al., 2003; Ortega-Saez et al., 2023; Palermo-Neto et al., 2008), and lower anxiety profile, with reduced neophobic responses and greater exploration of a new environment (Bartolomucci et al., 2003).

4.3. Different behavioral coping strategies for chronic social stress

Numerous studies have shown that when confronted with social stressors, the behavioral strategies displayed by various species, including humans, can be categorized into at least two fundamental dimensions (Benus et al., 1991; Koolhaas et al., 1999; Marchetti and Drent, 2000; Øverli et al., 2007). These differences observed in the behavioral response to adverse situations have been commonly defined as behavioral stress coping strategies or coping styles.

The papers included in this review were selected because the studies described behavioral phenotypes in mice in response to chronic social stress. While the selected papers have in common the use of mice and a model of social defeat stress, they differed in the strategy used to identify social stress coping strategies, probably due to a different conceptualization of this construct. Some authors use behavioral analysis to classify groups of mice during social stress to determine the social status: dominant *vs.* submissive/subordinate; others use behavioral analysis after social stress to determine its effects on different biological systems and health: resilient vs. susceptible; and other authors use the behavioral analysis to classified groups based on the behavioral strategy used to cope with the stressor: active/proactive *vs* passive/reactive.

This widespread use of the concept of "coping style" calls for a common definition. Traditionally, the most commonly used definition states that coping style is "a coherent set of behavioral and physiological responses to stress that is consistent over time and is characteristic of a given group of individuals" (Koolhaas et al., 1999). However, the assessment of both dimensions, behavioral and physiological, in the same study is not commonly found in the selected behavioral studies (see Table 2), and certain state eventual behavioural characteristics are often confused with trait stable behavioural characteristics. For example, the dominant/submissive or resilient/susceptible conditions, despite their close association with coping strategies, cannot be considered stable trait characteristics. Indeed, consensus regarding the stability of active and passive coping strategies also remains unclear. It has been suggested that highly flexible animals that change from one to the other strategy may indicate a behavioral adaptation to specific circumstances (Rosado et al., 2023). Additionally, the level of aggressiveness, which can determine the dominant or subordinate status, has proven to be one of the fundamental dimensions to establish the different coping strategies for social defeat stress (Díez-Solinska et al., 2024; Koolhaas et al., 1999), however, the eventual status during agonistic social interactions alone offers little information to build the behavioral profile of an individual.

Similarly, the concepts of coping and resilience are commonly misconceived as interchangeable, despite their distinct differences (Van der Hallen et al., 2020). Stress coping strategies are commonly presented in the scientific literature as a moderating factor of the negative health effects associated with social stress in numerous species (Korte et al., 2005; Vegas et al., 2006), including humans (Perez-Tejada et al., 2019).

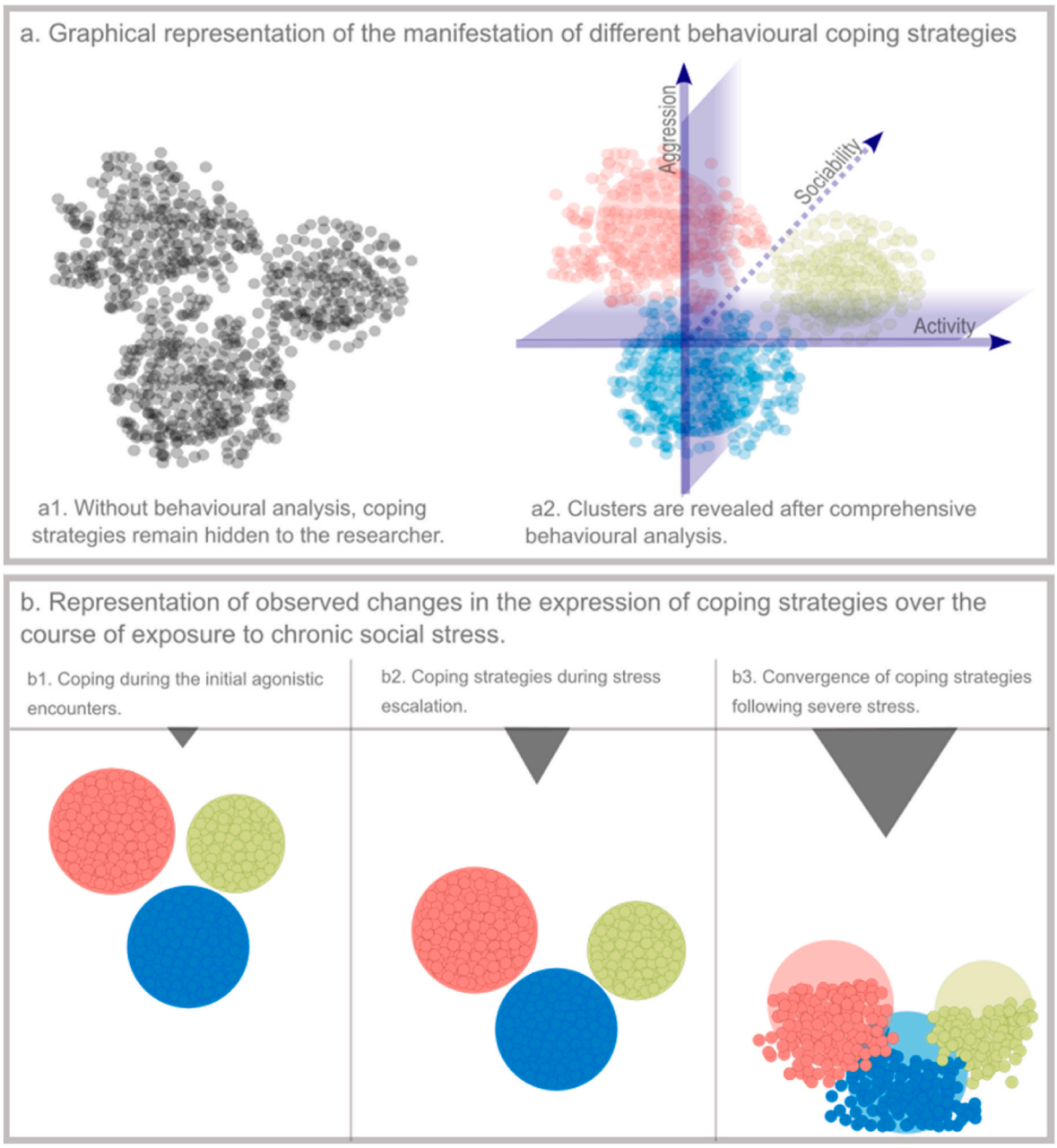


Fig. 5. Graphical simulations of behavioural clusters representing different social stress coping strategies. (a). Hidden clusters (a1), are shown after comprehensive behavioural analysis (a2); this example is presented with 3 variables that have been proved to be effective revealing social stress coping strategies: *activity, aggression* and *sociability*. (b). Although different environmental factors, including social stress, may modify coping strategies, these subjects tend to stay in their cluster of belonging (b2), as long as the intensity of this external force does not reach a certain threshold, at which point the clusters merge, and previous behavioural differences disappear because there is no longer behavioural variability (b3).

Specifically, active coping strategies are commonly associated with positive physical and psychological outcomes, and thus with resilience to stress (Southwick et al., 2005). However, although both constructs, coping style and resilience, are related, they belong to different levels of analysis. When coping style and resilience are interpreted separately, the observations reveal that each coping strategy - whether active/-proactive or passive/reactive - exhibits a unique susceptibility to various infectious diseases (Koolhaas et al., 1999; Sgoifo et al., 2014). For instance, whereas passive coping has been commonly associated with mood disorders such as anxiety and depression (Berton et al., 2012; Buwalda et al., 2005), active coping has been associated with antisocial behavior disorders (de Boer et al., 2009) and substance abuse (Moal, 2016). Thus, while an active or passive strategy may be adaptive (resilient) or non-adaptive (vulnerable) depending on environmental demands, resilience or vulnerability are concepts that do not represent pre-existing individual differences (Sih et al., 2004; Wood and Bhatnagar, 2015). In this regard, Murra et al. (2022) noted that the degree of social interaction in the SIT before stress does not predict social responses in this test after stress, nor does it predict the classification as resilient vs. susceptible.

The unique stable behavioral traits identified in male mice exposed to chronic social defeat stress are; i) the active fight-flight response, which describes proactive subjects, showing high levels of aggression and territorial control (Cannon, 1915); and ii) the passive conservation-withdrawal response (Engel and Schmale, 1972), describing reactive subjects, showing low aggression and high levels of

immobility.

The papers included in this review also differ in the strategy used to classify mice according to their behavior. As noted above, most of the studies collected used the SIT protocol described by Golden et al. (2011), applied after social stress. Although coping strategies are considered individual trait characteristics maintained over time (Koolhaas et al., 2007; Saccheri and Hanski, 2006), the detection of coping strategies can be limited when subjects are exposed to extreme social stressors over an extended period. The different strategies become more difficult to observe behaviorally because the behavioral repertoire is reduced. In this regard, Murra et al. (2022) note that the behavior observed in the first social interaction before stress was critical in determining the final behavior phenotype. Therefore, we would consider it more appropriate to classify the behavioral strategies when the behavioral repertory is diverse and easier to observe, normally at the beginning of the exposure to chronic social stress. In order to illustrate the main conclusions drawn from these experimental studies on chronic social stress coping strategies, Fig. 5 is presented. If behavioral coping strategies are not carefully observed and assessed, they may remain hidden and seem indistinguishable across groups (Fig. 5a1). Once behavioral characterization can be addressed, distinct coping strategies can emerge, allowing for a clearer division of subjects (Fig. 5a2). It should be noted that these strategies may shift as stress intensifies, with subjects within the same group tending to adopt similar behavioral changes (Fig. 5b1, 5b2). When stress becomes more intense due to its chronicity or severity, the differences between groups may disappear, as the severity of the stress could lead to more homogeneous responses across individuals (Fig. 5b3).

4.4. Neuroendocrine and autonomic response in subjects with different coping strategies for social stress

The negative effects of chronic social stress on physical and mental health (i.e. cancer progression and depressive-like behaviors) have usually been attributed to alterations of the physiological stress response, including changes to the neuroendocrine response and/or a brain neurochemical imbalance.

In all the papers reviewed, the induction of social stress was carried out by applying a protocol involving social defeat, and all the papers that analyzed corticosterone levels observed a significant increase in this peripheral biomarker of HPA axis activation following social stress, demonstrating the efficacy of this model to induce the physiological stress response. Corticosterone plasmatic concentration has been shown to increase with CSDS protocol at 10 days (Hodes et al., 2014; Jochems et al., 2015; Murra et al., 2022; Savignac et al., 2011), 18 days (Goñi-Balentziaga et al., 2020) and 21 of CSDS (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013), while a non-significant 3-fold increase in CORT was found with 6 days of SDR (Savignac et al., 2011). These data suggest that 10 days of social defeat is sufficient to induce HPA axis activation.

Interestingly, differences in corticosterone concentration have been observed among mice displaying distinct coping strategies; higher corticosterone levels are generally observed in subordinate vs dominant mice, and in passive or susceptible animals compared to non-stressed mice (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013; Savignac et al., 2011), and active mice (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013; Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013). Additionally, GRs are highly expressed in the hypothalamus of subjects exhibiting passive behaviors (Gómez-Lázaro et al., 2012; Pérez-Tejada et al., 2013) and there is evidence of increased glucocorticoid resistance in the spleens of mice more susceptible to stress (Avitsur et al., 2003). In contrast to these results Murra et al. (2022) observed higher corticosterone levels in resilient subjects, suggesting that more socially interactive mice had higher corticosterone responses to the social stress challenge (Murra et al., 2022). The differential expression and activation of GRs and MRs, as well as the balance between these receptors, may be crucial in distinguishing a resilient from a susceptible phenotype. Specifically, GR activation has been linked to susceptibility by facilitating a shift from active to passive coping styles, while MRs activation has been usually associated to a resilient phenotype. Furthermore, resilience appears to also be related to a rapid and efficient MR activation followed by a GR termination to restore homeostasis (de Kloet and Joëls, 2024). These findings collectively suggest that glucocorticoids' role in the negative effects of social stress is complex and may be influenced by individual and environmental factors.

Along with the activation of the HPA axis, it is also known that repeated social defeat stress activates the SNS. Bartolomucci et al. (2003) highlight the strong and persistent autonomic activation occurring even after daily aggressive interactions with the same opponent for 15 days (Bartolomucci et al., 2003). Both subordinates and dominants showed tachycardia and hyperthermia, while only the subordinates showed a significant reduction in activity compared to the dominants. In this sense, these authors point out that dominants seem to develop hyperactivation of the autonomic nervous system. Pérez-Tejada et al. (2013) observed lower plasma NE levels in passive subjects compared to controls, lower levels of adrenal dopamine β-hydroxylase, tyrosine hydroxylase and plasma E compared to the active subjects (Pérez-Tejada et al., 2013), and lower expression of alpha2A-adrenoceptor gene expression in the prefrontal cortices (Pérez-Tejada et al., 2016). Subjects displaying a passive behavioral strategy also show a deficit in serotonin concentration and an increased activity in dopaminergic neurons within the midbrain, specifically within dopaminergic neurons of the VTA (Friedman et al., 2016). Interestingly, it has been found that pharmacological activation of adrenergic receptors on midbrain DA neurons induces pro-resilient effects, whereas antagonizing these receptors blocks this effect in susceptible mice (Zhang et al., 2019). These results support the idea that behavioral coping strategies are accompanied by a distinct activation of the neuroendocrine and autonomic nervous systems during social defeat stress, which might play a relevant role in the increased risk for physical and mental susceptibility associated with social stress (Pereira et al., 2017).

4.5. Immune changes in subjects with different coping strategies for social stress

It is well known that stress-induced changes in the autonomic nervous system and the HPA axis can affect immune function (Moynihan et al., 1994; Murison, 2016). One of the most studied effects of chronic social stress exposure on immune function is the modulation of peripheral and central cytokines (Bartolomucci et al., 2003; Glaser and Kiecolt-Glaser, 2005). All the studies included in this review that analyzed some aspect of the immune system observed a deleterious effect of social stress and 62.5% of the articles also found statistically significant differences in the immune system endpoints depending on the coping strategy. Animals displaying a passive social stress coping strategy generally showed increased levels of cytokines (IL-6, TNF-α, IL1-β, etc.) both in the peripheral (spleen, plasma) and central system (hypothalamus, hippocampus, amygdala, prefrontal cortex, striatum), supporting the idea that the increased susceptibility associated with the passive strategy could be mediated by the immune system. Only a few studies in this review analyzed and reported neurochemical differences depending on the coping strategy employed, more research addressing immune endpoints is necessary to further understand the role of the immune system in mediating the negative effects of the social stress response on mental health, as pointed out by the inflammatory hypothesis of depression (Slavich and Irwin, 2014).

4.6. Physical and mental health in subjects with different coping strategies for social stress

Although, overall health and proper function of the immune system are intertwined, only two papers in this review address this relationship

Box 1
Guide for the study of coping strategies under chronic social stress

- **The definition of Coping Style.** Adopt as a common definition of coping style, the one most widely used in the experimental field, proposed by Koolhass et al., in 1999: "*a coherent set of behavior and physiological responses to stress that is consistent over time and is characteristic of a given group of individuals*" (Koolhaas et al., 1999).
- **Behavioral Phenotyping of coping strategies:**
  a) Adopt a common set of behavioral characteristics observed in the face of social stress, including dimensions that have been shown to be fundamental in establishing coping styles, such as: *activity (active-passive), emotionality (proactive-reactive), aggressiveness (aggressive-non-aggressive)* (Fig. 5a).
  b) Analyse coping strategies at the beginning of the exposure to chronic social stress, in order to access the individual's entire behavior repertoire (Fig. 5b), as this has shown the strongest relationship with the behavioral and biological variables analyzed in the long term.
- **Endophenotyping of coping strategies.** Include biological variables in the study of coping strategies, which may help not only to classify and characterize clusters, but also to identify the mechanisms that may underlie the differential susceptibility to the adverse stress effects.

in the context of coping strategies to stress. Goñi-Balentziaga et al. (2020) showed that mice with a passive-reactive coping strategy developed the highest number of tumor foci in the lungs (Goñi-Balentziaga et al., 2020), and Savignac et al. (2011a,b) revealed increased tissue damage in the colon with exposure to chronic stress, but no differences were observed as a function of dominant vs. submissive clusters (Savignac et al., 2011).

Similarly, although many papers apply different behavioral tests after the chronic social stress, few address the risk increase for cognitive or mental diseases (i.e. depression). In this review, we found that following the CSDS, traditional readings of anxiety and depression-like behaviors (such as the open field and the forced swim test), are not clearly reflected in coping strategies (Murra et al., 2022). However, authors such as Ballestin et al. (2021) and Reguilón et al. (2022) identify animals classified as resilient according to their SIT scores, as resistant to the depressive-like behaviors produced by social defeat. Animals that are resilient to depressive-like behaviors are also resilient to the reinforcing effects of cocaine and alcohol consumption during adulthood (Ballestin et al., 2021) but exhibit the most anxious and addictive behaviors when social stress is applied during adolescence (Reguilón et al., 2022). These results support the hypothesis that there exists a special sensitivity to social stressors in periods of greater development of the nervous system, including adolescence (Charmandari et al., 2005), and point to possible differences in the coping strategies observed, depending on the developmental period in which the social stress occurs, as noted above (see section 4.1).

Some of the papers included in this review support the hypothesis that inflammatory processes play a relevant role in the pathophysiology of mental illnesses like depressive disorder (Soskin et al., 2012). The results of this review, which show an increase in the expression of central inflammatory cytokines after CSDS (see section 4.5), which aligns with the inflammatory hypothesis of depression, especially in those subjects classified as passive (Pérez-Tejada et al., 2016) or susceptible (Ballestin et al., 2021; Reguilón et al., 2022; Ballestin et al., 2021; Reguilón et al., 2022). However, these findings should be interpreted with caution, as the increased cytokine levels does not necessarily imply a causal link with depressive behaviors. In summary, understanding individual differences in coping with social stress can provide valuable insights into the wide variability of negative effects of stress on overall health.

5. Conclusion and future directions

While the results of this review allow us to speculate that certain social stress coping strategies are more prone to physiological dysregulations and health risks, it also shows us the importance of a cautious interpretation of the results obtained. The lack of consistency in the nomenclature and procedures associated with the study of coping strategies for social stress, as well as the absence of a uniform classification, highlight the importance of using a common language when approaching the study of coping strategies. Thereby, this review encourages the development of a more defined method and criteria for assessing coping strategies, based on both behavioral and biological indicators. To support this effort, we have compiled a summary of the most commonly used practices that can be considered as a guide for the study of the coping strategies (see Box 1).

Funding

This study was supported by a Basque University predoctoral grant (PIF22/192), a Basque Government IT757-13 Project Grant, and a Spanish Ministry of Economy and Competitiveness Project Grant RTI2018–098264-B-I00 (MCIU/AEI/FEDER, UE)

CRediT authorship contribution statement

Alina Díez-Solinska: Writing – original draft, Formal analysis, Data curation. **Zurine De Miguel:** Writing – original draft, Supervision, Data curation. **Garikoitz Azkona:** Writing – original draft, Formal analysis, Data curation. **Oscar Vegas:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

Albus, C., De Backer, G., Bages, N., Deter, H.C., Herrmann-Lingen, C., Oldenburg, B., Orth-Gomer, K., 2005. [Psychosocial factors in coronary heart disease – scientific evidence and recommendations for clinical practice]. Gesundheitswesen 67 (1), 1–8. https://doi.org/10.1055/s-2004-813907.

Avitsur, R., Stark, J.L., Sheridan, J.F., 2001. Social stress induces glucocorticoid resistance in subordinate animals. Horm. Behav. 39 (4), 247–257. https://doi.org/10.1006/hbeh.2001.1653.

Avitsur, R., Stark, J.L., Dhabhar, F.S., Sheridan, J.F., 2002. Social stress alters splenocyte phenotype and function. J. Neuroimmunol. 132 (1–2), 66–71. https://doi.org/10.1016/s0165-5728(02)00310-7.

Avitsur, R., Stark, J.L., Dhabhar, F.S., Kramer, K.A., Sheridan, J.F., 2003. Social experience alters the response to social stress in mice. Brain Behav. Immun. 17 (6), 426–437. https://doi.org/10.1016/S0889-1591(03)00034-5.

Azkona, G., Sanchez-Pernaute, R., 2022. Mice in translational neuroscience: what R we doing? Prog. Neurobiol. 217, 102330. https://doi.org/10.1016/j.pneurobio.2022.102330.
Ballestin, R., Alegre-Zurano, L., Ferrer-Perez, C., Cantacorps, L., Miarro, J., Valverde, O., Rodriguez-Arias, M., 2021. Neuroinflammatory and behavioral susceptibility profile of mice exposed to social stress towards cocaine effects. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 105. https://doi.org/10.1016/j.pnpbp.2020.110123.
Bandler, R., Shipley, M.T., 1994. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? Trends Neurosci. 17 (9), 379–389. https://doi.org/10.1016/0166-2236(94)90047-7.
Bartolomucci, A., Palanza, P., Gaspani, L., Limiroli, E., Panerai, A.E., Ceresini, G., Parmigiani, S., 2001. Social status in mice: behavioral, endocrine and immune changes are context dependent. Physiol. Behav. 73 (3), 401–410. https://doi.org/10.1016/s0031-9384(01)00453-x.
Bartolomucci, A., Palanza, P., Parmigiani, S., Pederzani, T., Merlot, E., Neveu, P.J., Dantzer, R., 2003a. Chronic psychosocial stress down-regulates central cytokines mRNA. Brain Res. Bull. 62, 173–178. https://doi.org/10.1016/j.brainresbull.2003.09.009.
Bartolomucci, A., Palanza, P., Sacerdote, P., Ceresini, G., Chirieleison, A., Panerai, A.E., Parmigiani, S., 2003b. Individual housing induces altered immuno-endocrine responses to psychological stress in male mice. Psychoneuroendocrinology 28 (4), 540–558. https://doi.org/10.1016/s0306-4530(02)00039-2.
Beery, A.K., Kaufer, D., 2015. Stress, social behavior, and resilience: insights from rodents. Neurobiol. Stress 1, 116–127. https://doi.org/10.1016/j.ynstr.2014.10.004.
Beitia, G., Garmendia, L., Azpiroz, A., Vegas, O., Brain, P.F., Arregi, A., 2005. Time-dependent behavioral, neurochemical, and immune consequences of repeated experiences of social defeat stress in male mice and the ameliorative effects of fluoxetine. Brain Behav. Immun. 19 (6), 530–539. https://doi.org/10.1016/j.bbi.2004.11.002.
Belmaker, R.H., Agam, G., 2008. Major depressive disorder. N. Engl. J. Med. 358 (1), 55–68. https://doi.org/10.1056/NEJMra073096.
Belzung, C., Lemoine, M., 2011. Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. Biol. Mood Anxiety Disord. 1 (1), 9. https://doi.org/10.1186/2045-5380-1-9.
Benus, R.F., Bohus, B., Koolhaas, J.M., van Oortmerssen, G.A., 1990. Behavioural strategies of aggressive and non-aggressive male mice in response to inescapable shock, 21 (2), 127–141.
Benus, R.F., Bohus, B., Koolhaas, J.M., van Oortmerssen, G.A., 1991. Behavioural differences between artificially selected aggressive and non-aggressive mice: response to apomorphine. Behav. Brain Res. 43 (2), 203–208. https://doi.org/10.1016/s0166-4328(05)80072-5.
Berton, O., Hahn, C.G., Thase, M.E., 2012. Are we getting closer to valid translational models for major depression? Science 338 (6103), 75–79. https://doi.org/10.1126/science.1222940.
Brain, P.F., Parmigiani, S., 1990. Variation in aggressiveness in house mouse populations. Biol. J. Linn. Soc. 41 (1–3), 257–269. https://doi.org/10.1111/j.1095-8312.1990.tb00834.x.
Brain, P.F., McAllister, K.H., Walmsley, S.V., 1989. Drug effects on social behaviour: methods in ethopharmacology. In: Boulton, A.A., Baker, G.B., Greenshaw, A.J. (Eds.), Neuromethods Volume 13 Psychopharmacology. The Humana Press Inc, pp. 689–739.
Butts, C.L., Sternberg, E.M., 2008. Neuroendocrine factors alter host defense by modulating immune function. Cell. Immunol. 252 (1–2), 7–15. https://doi.org/10.1016/j.cellimm.2007.09.009.
Buwalda, B., Kole, M.H., Veenema, A.H., Huininga, M., de Boer, S.F., Korte, S.M., Koolhaas, J.M., 2005. Long-term effects of social stress on brain and behavior: a focus on hippocampal functioning. Neurosci. Biobehav. Rev. 29 (1), 83–97. https://doi.org/10.1016/j.neubiorev.2004.05.005.
Cabib, S., Campus, P., Latagliata, E.C., Orsini, C., Tarmati, V., 2021. Repetitive and inflexible active coping and addiction-like neuroplasticity in stressed mice of a helplessness-resistant inbred strain. Behav. Sci. 11 (12). https://doi.org/10.3390/bs11120174.
Cannon, W.B., 1915. Bodily Changes in Pain, Hunger, Fear and Rage: an Account of Recent Researches into the Function of Emotional Excitement. D Appleton & Company. https://doi.org/10.1037/10013-000, 10.1037/10013-000.
Cao, J.L., Covington, H.E., Friedman, A.K., Wilkinson, M.B., Walsh, J.J., Cooper, D.C., Han, M.H., 2010. Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. J. Neurosci. 30 (49), 16453–16458. https://doi.org/10.1523/JNEUROSCI.3177-10.2010.
Carver, C.S., 1997. You want to measure coping but your protocol's too long: consider the brief COPE. Int. J. Behav. Med. 4 (1), 92–100. https://doi.org/10.1207/s15327558ijbm0401_6.
Chandola, T., Brunner, E., Marmot, M., 2006. Chronic stress at work and the metabolic syndrome: prospective study. BMJ 332 (7540), 521–525. https://doi.org/10.1136/bmj.38693.435301.80.
Charmandari, E., Tsigos, C., Chrousos, G., 2005. Endocrinology of the stress response. Annu. Rev. Physiol. 67, 259–284. https://doi.org/10.1146/annurev.physiol.67.040403.120816.
Chaudhury, D., Walsh, J.J., Friedman, A.K., Juarez, B., Ku, S.M., Koo, J.W., Han, M.H., 2013. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature 493 (7433), 532–536. https://doi.org/10.1038/nature11713.
Chida, Y., Hamer, M., Wardle, J., Steptoe, A., 2008. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat. Clin. Pract. Oncol. 5 (8), 466–475. https://doi.org/10.1038/ncponc1134.
Chrousos, G.P., 2009. Stress and disorders of the stress system. Nat. Rev. Endocrinol. 5 (7), 374–381. https://doi.org/10.1038/nrendo.2009.106.
Coppens, C.M., De Boer, S.F., Koolhaas, J.M., 2010. Coping styles and behavioural flexibility: towards underlying mechanisms. Phil. Trans. Biol. Sci. 365 (1560), 4021–4028. https://doi.org/10.1098/rstb.2010.0217.
Coppens, C.M., De Boer, S.F., Steimer, T., Koolhaas, J.M., 2012. Impulsivity and aggressive behavior in Roman high and low avoidance rats: baseline differences and adolescent social stress induced changes. Physiol. Behav. 105 (5), 1156–1160. https://doi.org/10.1016/j.physbeh.2011.12.013.
Cox, K.H., Rissman, E.F., 2011. Sex differences in juvenile mouse social behavior are influenced by sex chromosomes and social context. Gene Brain Behav. 10 (4), 465–472. https://doi.org/10.1111/j.1601-183X.2011.00688.x.
David, J.T., Cervantes, M.C., Trosky, K.A., Salinas, J.A., Delville, Y., 2004. A neural network underlying individual differences in emotion and aggression in male golden hamsters. Neuroscience 126 (3), 567–578. https://doi.org/10.1016/j.neuroscience.2004.04.031.
de Boer, S.F., Caramaschi, D., Natarajan, D., Koolhaas, J.M., 2009. The vicious cycle towards violence: focus on the negative feedback mechanisms of brain serotonin neurotransmission. Front. Behav. Neurosci. 3, 52. https://doi.org/10.3389/neuro.08.052.2009.
de Kloet, E.R., Joëls, M., 2024. The cortisol switch between vulnerability and resilience. Mol. Psychiatr. 29 (1), 20–34. https://doi.org/10.1038/s41380-022-01934-8.
de Kloet, E.R., Molendijk, M.L., 2016. Coping with the forced swim stressor: towards understanding an adaptive mechanism. Neural Plast. 2016, 6503162. https://doi.org/10.1155/2016/6503162.
De Miguel, Z., Vegas, O., Garmendia, L., Arregi, A., Beitia, G., Azpiroz, A., 2011. Behavioral coping strategies in response to social stress are associated with distinct neuroendocrine, monoaminergic and immune response profiles in mice. Behav. Brain Res. 225 (2), 554–561. https://doi.org/10.1016/j.bbr.2011.08.011.
Del Giudice, M., Ellis, B.J., Shirtcliff, E.A., 2011. The adaptive calibration model of stress responsivity. Neurosci. Biobehav. Rev. 35 (7), 1562–1592. https://doi.org/10.1016/j.neubiorev.2010.11.007.
DeVries, A.C., Craft, T.K., Glasper, E.R., Neigh, G.N., Alexander, J.K., 2007. 2006 Curt P. Richter award winner: social influences on stress responses and health. Psychoneuroendocrinology 32 (6), 587–603. https://doi.org/10.1016/j.psyneuen.2007.04.007.
Dhabhar, F.S., 2014. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol. Res. 58 (2–3), 193–210. https://doi.org/10.1007/s12026-014-8517-0.
Díez-Solinska, A., Goñi-Balentziaga, O., Beitia-Oyarzabal, G., Muñoz-Culla, M., Vegas, O., Azkona, G., 2024. Chronic defeat stress induces monoamine level dysregulation in the prefrontal cortex but not in the hippocampus of OF1 male mice. Behav. Brain Res. 467, 115023. https://doi.org/10.1016/j.bbr.2024.115023.
Dingemanse, N.J., Wolf, M., 2010. Recent models for adaptive personality differences: a review. Philos. Trans. R. Soc. Lond. B Biol. Sci. 365 (1560), 3947–3958. https://doi.org/10.1098/rstb.2010.0221.
Ducottet, C., Belzung, C., 2004. Behaviour in the elevated plus-maze predicts coping after subchronic mild stress in mice. Physiol. Behav. 81 (3), 417–426. https://doi.org/10.1016/j.physbeh.2004.01.013.
Dutta, S., Sengupta, P., 2016. Men and mice: relating their ages. Life Sci. 152, 244–248. https://doi.org/10.1016/j.lfs.2015.10.025.
Engel, G.L., Schmale, A.H., 1972. Conservation-withdrawal: a primary regulatory process for organismic homeostasis. Ciba Found. Symp. 8, 57–75. https://doi.org/10.1002/9780470719916.ch5.
Ferrer-Pérez, C., Castro-Zavala, A., Luján, M., Filarowska, J., Ballestín, R., Miñarro, J., Rodríguez-Arias, M., 2019. Oxytocin prevents the increase of cocaine-related responses produced by social defeat. Neuropharmacology 146, 50–64. https://doi.org/10.1016/j.neuropharm.2018.11.011.
Foertsch, S., Fchsl, A.M., Faller, S.D., Hlzer, H., Langgartner, D., Messmann, J., Reber, S. O., 2017. Splenic glucocorticoid resistance following psychosocial stress requires physical injury. Sci. Rep. 7, 1–12. https://doi.org/10.1038/s41598-017-15897-2.
Folkman, S., Lazarus, R.S., 1980. An analysis of coping in a middle-aged community sample. J. Health Soc. Behav. 21 (3), 219–239. https://doi.org/10.2307/2136617.
Friedman, A.K., Walsh, J.J., Juarez, B., Ku, S.M., Chaudhury, D., Wang, J., Han, M.H., 2014. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science 344 (6181), 313–319. https://doi.org/10.1126/science.1249240.
Friedman, A.K., Juarez, B., Ku, S.M., Zhang, H., Calizo, R.C., Walsh, J.J., Han, M.H., 2016. KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. Nat. Commun. 7, 1–7. https://doi.org/10.1038/ncomms11671.
Gandhi, W., Morrison, I., Schweinhardt, P., 2017. How accurate appraisal of behavioral costs and benefits guides adaptive pain coping. Front. Psychiatr. 8, 103. https://doi.org/10.3389/fpsyt.2017.00103.
Glaser, R., Kiecolt-Glaser, J.K., 2005. Stress-induced immune dysfunction: implications for health. Nat. Rev. Immunol. 5 (3), 243–251. https://doi.org/10.1038/nri1571.
Godoy, L.D., Rossignoli, M.T., Delfino-Pereira, P., Garcia-Cairasco, N., de Lima Umeoka, E.H., 2018. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. Front. Behav. Neurosci. 12, 127. https://doi.org/10.3389/fnbeh.2018.00127.
Golden, S.A., Covington, H.E., Berton, O., Russo, S.J., 2011. A standardized protocol for repeated social defeat stress in mice. Nat. Protoc. 6 (8), 1183–1191. https://doi.org/10.1038/nprot.2011.361.

Gómez-Lázaro, E., Garmendia, L., Beitia, G., Perez-Tejada, J., Azpiroz, A., Arregi, A., 2012. Effects of a putative antidepressant with a rapid onset of action in defeated mice with different coping strategies. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 38 (2), 317–327. https://doi.org/10.1016/j.pnpbp.2012.04.019.

Goñi-Balentziaga, O., Garmendia, L., Labaka, A., Lebeña, A., Beitia, G., Gómez-Lázaro, E., Vegas, O., 2020. Behavioral coping strategies predict tumor development and behavioral impairment after chronic social stress in mice. Physiol. Behav. 214, 112747. https://doi.org/10.1016/j.physbeh.2019.112747.

Groothuis, T.G.G., Carere, C., 2005. Avian personalities: characterization and epigenesis. Neurosci. Biobehav. Rev. 29 (1), 137–150. https://doi.org/10.1016/j.neubiorev.2004.06.010.

Hodes, G.E., Pfau, M.L., Leboeuf, M., Golden, S.A., Christoffel, D.J., Bregman, D., Russo, S.J., 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc. Natl. Acad. Sci. U.S.A. 111 (45), 16136–16141. https://doi.org/10.1073/pnas.1415191111.

Irwin, M.R., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11 (9), 625–632. https://doi.org/10.1038/nri3042.

Jochems, J., Teegarden, S.L., Chen, Y., Boulden, J., Challis, C., Ben-dor, G.A., Berton, O., 2015. Enhancement of stress resilience through Hdac6-mediated regultation of glucocorticoid receptor chaperone dynamics. Biol. Psychiatr. 77 (4), 345–355. https://doi.org/10.1016/j.biopsych.2014.07.036.Enhancement.

Keeler, J.F., Robbins, T.W., 2011. Translating cognition from animals to humans. Biochem. Pharmacol. 81 (12), 1356–1366. https://doi.org/10.1016/j.bcp.2010.12.028.

Kelley, D.B., 1988. Sexually dimorphic behaviors. Annu. Rev. Neurosci. 11, 225–251. https://doi.org/10.1146/annurev.ne.11.030188.001301.

Kemble, E.D., Blanchard, D.C., Blanchard, R.J., 1993. Chapter 21 - methods in behavioral pharmacology: measurement of aggression. In: Frans (Ed.), Methods in Behavioral Pharmacology, vol. 10. Elsevier, pp. 539–559. https://doi.org/10.1016/B978-0-444-81444-9.50026-2.

Kemeny, M.E., Schedlowski, M., 2007. Understanding the interaction between psychosocial stress and immune-related diseases: a stepwise progression. Brain Behav. Immun. 21 (8), 1009–1018. https://doi.org/10.1016/j.bbi.2007.07.010.

Kendler, K.S., Hettema, J.M., Butera, F., Gardner, C.O., Prescott, C.A., 2003. Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. Arch. Gen. Psychiatr. 60 (8), 789–796. https://doi.org/10.1001/archpsyc.60.8.789.

Koolhaas, J.M., Korte, S.M., De Boer, S.F., Van Der Vegt, B.J., Van Reenen, C.G., Hopster, H., Blokhuis, H.J., 1999. Coping styles in animals: current status in behavior and stress-physiology. Neurosci. Biobehav. Rev. 23 (7), 925–935. https://doi.org/10.1016/s0149-7634(99)00026-3.

Koolhaas, J.M., de Boer, S.F., Buwalda, B., van Reenen, K., 2007. Individual variation in coping with stress: a multidimensional approach of ultimate and proximate mechanisms. Brain Behav. Evol. 70 (4), 218–226. https://doi.org/10.1159/000105485.

Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci. Biobehav. Rev. 29 (1), 3–38. https://doi.org/10.1016/j.neubiorev.2004.08.009.

Krishnan, V., Han, M.H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., Nestler, E.J., 2007. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131 (2), 391–404. https://doi.org/10.1016/j.cell.2007.09.018.

Kudryavtseva, N.N., Bakshtanovskaya, I.V., Koryakina, L.A., 1991. Social model of depression in mice of C57BL/6J strain. Pharmacol. Biochem. Behav. 38 (2), 315–320. https://doi.org/10.1016/0091-3057(91)90284-9.

Laine, M.A., Sokolowska, E., Dudek, M., Callan, S.A., Hyytiä, P., Hovatta, I., 2017. Brain activation induced by chronic psychosocial stress in mice. Sci. Rep. 7 (1), 15061. https://doi.org/10.1038/s41598-017-15422-5.

Laine, M.A., Trontti, K., Misiewicz, Z., Sokolowska, E., Kulesskaya, N., Heikkinen, A., Hovatta, I., 2018. Genetic control of myelin plasticity after chronic psychosocial stress. eNeuro 5 (4). https://doi.org/10.1523/ENEURO.0166-18.2018.

Langgartner, D., Füchsl, A.M., Uschold-Schmidt, N., Slattery, D.A., Reber, S.O., 2015. Chronic subordinate colony housing paradigm: a mouse model to characterize the consequences of insufficient glucocorticoid signaling. Front. Psychiatr. 6, 18. https://doi.org/10.3389/fpsyt.2015.00018.

Lazarus, R.S., Folkman, S., 1984. Stress, Appraisal, and Coping.

Leclair, K.B., Chan, K.L., Kaster, M.P., Parise, L.F., Burnett, C.J., Russo, S.J., 2021. Individual history of winning and hierarchy landscape influence stress susceptibility in mice: social rank and stress susceptibility. Elife 10, 1–19. https://doi.org/10.7554/eLife.71401.

Marchetti, C., Drent, P.J., 2000. Individual differences in the use of social information in foraging by captive great tits. Anim. Behav. 60 (1), 131–140. https://doi.org/10.1006/anbe.2000.1443.

Moal, M.L., 2016. Individual vulnerabilities relative for potential pathological conditions. Brain Res. 1645, 65–67. https://doi.org/10.1016/j.brainres.2015.12.037.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097. https://doi.org/10.1371/journal.pmed.1000097.

Montagud-Romero, S., Reguilon, M.D., Roger-Sanchez, C., Pascual, M., Aguilar, M.A., Guerri, C., Rodríguez-Arias, M., 2016. Role of dopamine neurotransmission in the long-term effects of repeated social defeat on the conditioned rewarding effects of cocaine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 71, 144–154. https://doi.org/10.1016/j.pnpbp.2016.07.008.

Moynihan, J.A., Brenner, G.J., Cocke, R., Karp, J.D., Breneman, S.M., Dopp, J.M., Felten, S.Y., 1994. 1 - stress-induced modulation of immune function in mice. In: Glaser, R., Kiecolt-Glaser, J.K. (Eds.), Handbook of Human Stress and Immunity. Academic Press, pp. 1–22.

Murison, R., 2016. Chapter 2 - the neurobiology of stress. In: Mustafa al'Absi, F., Arve, Magne (Eds.), Neuroscience of Pain, Stress, and Emotion. Academic Press, pp. 29–49. https://doi.org/10.1016/B978-0-12-800538-5.00002-9.

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. Neurobiol. Stress 17. https://doi.org/10.1016/j.ynstr.2022.100437.

Newman, E.L., Covington, H.E., Suh, J., Bicakci, M.B., Ressler, K.J., DeBold, J.F., Miczek, K.A., 2019. Fighting females: neural and behavioral consequences of social defeat stress in female mice. Biol. Psychiatr. 86 (9), 657–668. https://doi.org/10.1016/j.biopsych.2019.05.005.

O'Connor, D.B., Thayer, J.F., Vedhara, K., 2021. Stress and health: a review of psychobiological processes. Annu. Rev. Psychol. 72, 663–688. https://doi.org/10.1146/annurev-psych-062520-122331.

Obrist, P.A., 1981. Cardiovascular psychophysiology: a perspective. Psychol. Med. 12 (1), 218-218.

Oh, H.J., Song, M., Kim, Y.K., Bae, J.R., Cha, S.Y., Bae, J.Y., Maeng, S., 2018. Age-related decrease in stress responsiveness and proactive coping in male mice. Front. Aging Neurosci. 10, 128. https://doi.org/10.3389/fnagi.2018.00128.

Ortega-Saez, I., Díez-Solinska, A., Grífols, R., Martí, C., Zamora, C., Muñoz-Culla, M., Azkona, G., 2023. Individualized housing modifies the immune-endocrine system in CD1 adult male mice. Animals 13 (6). https://doi.org/10.3390/ani13061026.

Øverli, Ø., Sørensen, C., Pulman, K.G., Pottinger, T.G., Korzan, W., Summers, C.H., Nilsson, G.E., 2007. Evolutionary background for stress-coping styles: relationships between physiological, behavioral, and cognitive traits in non-mammalian vertebrates. Neurosci. Biobehav. Rev. 31 (3), 396–412. https://doi.org/10.1016/j.neubiorev.2006.10.006.

Palermo-Neto, J., Fonseca, E.S.M., Quinteiro-Filho, W.M., Correia, C.S.C., Sakai, M., 2008. Effects of individual housing on behavior and resistance to Ehrlich tumor growth in mice. Physiol. Behav. 95 (3), 435–440. https://doi.org/10.1016/j.physbeh.2008.07.006.

Pereira, V.H., Campos, I., Sousa, N., 2017. The role of autonomic nervous system in susceptibility and resilience to stress. Curr. Opin. Behav. Sci. 14, 102–107. https://doi.org/10.1016/j.cobeha.2017.01.003.

Pérez-Tejada, J., Arregi, A., Gómez-Lázaro, E., Vegas, O., Azpiroz, A., Garmendia, L., 2013. Coping with chronic social stress in mice: hypothalamic-pituitary-adrenal/sympathetic-adrenal-medullary axis activity, behavioral changes and effects of antalarmin treatment: implications for the study of stress-related psychopathologies. Neuroendocrinology 98 (1), 73–88. https://doi.org/10.1159/000353620.

Pérez-Tejada, J., Arregi, A., Azpiroz, A., Beitia, G., Gómez-Lázaro, E., Garmedia, L., 2016. Central immune alterations in passive strategy following chronic defeat stress. Behav. Brain Res. 298 (Pt B), 291–300. https://doi.org/10.1016/j.bbr.2015.11.015.

Perez-Tejada, J., Garmendia, L., Labaka, A., Vegas, O., Gómez-Lazaro, E., Arregi, A., 2019. Active and passive coping strategies: comparing psychological distress, cortisol, and proinflammatory cytokine levels in breast cancer survivors. Clin. J. Oncol. Nurs. 23 (6), 583–590. https://doi.org/10.1188/19.CJON.583-590.

Prevot, T.D., Chatterjee, D., Knoch, J., Codeluppi, S., Misquitta, K.A., Fee, C.J.E., Banasr, M., 2021. Dynamic Behavioral and Molecular Changes Induced by Chronic Stress Exposure in Mice.

Reber, S.O., Neumann, I.D., 2008. Defensive behavioral strategies and enhanced state anxiety during chronic subordinate colony housing are accompanied by reduced hypothalamic vasopressin, but not oxytocin, expression. Ann. N. Y. Acad. Sci. 1148, 184–195. https://doi.org/10.1196/annals.1410.003.

Reber, S.O., Siebler, P.H., Donner, N.C., Morton, J.T., Smith, D.G., Kopelman, J.M., Perez, G.L., 2016. Immunization with a heat-killed preparation of the environmental bacterium Mycobacterium vaccae promotes stress resilience in mice. Proc. Natl. Acad. Sci. U.S.A. 113 (22), 3130–3139. https://doi.org/10.1073/pnas.1600324113.

Reguilón, M.D., Ballestín, R., Miñarro, J., Rodríguez-Arias, M., 2022. Resilience to social defeat stress in adolescent male mice. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 119, 110591. https://doi.org/10.1016/j.pnpbp.2022.110591.

Ródenas-González, F., Blanco-Gandía, M.D.C., Miñarro López, J., Rodriguez-Arias, M., 2021. Behavioral and neuroimmune characterization of resilience to social stress: rewarding effects of cocaine. Adicciones 33 (4), 319–332. https://doi.org/10.20882/adicciones.1348.

Rodríguez-Arias, M., Miñarro, J., Aguilar, M.A., Pinazo, J., Simón, V.M., 1998. Effects of risperidone and SCH 23390 on isolation-induced aggression in male mice. Eur. Neuropsychopharmacol 8 (2), 95–103. https://doi.org/10.1016/s0924-977x(97)00051-5.

Rodríguez-Arias, M., Montagud-Romero, S., Rubio-Araiz, A., Aguilar, M.A., Martín-García, E., Cabrera, R., Miñarro, J., 2017. Effects of repeated social defeat on adolescent mice on cocaine-induced CPP and self-administration in adulthood: integrity of the blood-brain barrier. Addiction Biol. 22 (1), 129–141. https://doi.org/10.1111/adb.12301.

Rosado, A.F., Bevilacqua, L.M., Moreira, E.L.G., Kaster, M.P., 2023. Behavioral flexibility impacts on coping and emotional responses in male mice submitted to social defeat stress. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 123, 110696. https://doi.org/10.1016/j.pnpbp.2022.110696.

Saccheri, I., Hanski, I., 2006. Natural selection and population dynamics. Trends Ecol. Evol. 21 (6), 341–347. https://doi.org/10.1016/j.tree.2006.03.018.

Sapolsky, R.M., 1994. Individual differences and the stress response. Semin. Neurosci. 6 (4), 261–269. https://doi.org/10.1006/smns.1994.1033.

Sapolsky, R.M., 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch. Gen. Psychiatr. 57 (10), 925–935. https://doi.org/10.1001/archpsyc.57.10.925.

Savignac, H.M., Finger, B.C., Pizzo, R.C., O'Leary, O.F., Dinan, T.G., Cryan, J.F., 2011a. Increased sensitivity to the effects of chronic social defeat stress in an innately anxious mouse strain. Neuroscience 192, 524–536. https://doi.org/10.1016/j.neuroscience.2011.04.054.

Savignac, H.M., Hyland, N.P., Dinan, T.G., Cryan, J.F., 2011b. The effects of repeated social interaction stress on behavioural and physiological parameters in a stress-sensitive mouse strain. Behav. Brain Res. 216 (2), 576–584. https://doi.org/10.1016/j.bbr.2010.08.049.

Schmidt, M.V., Sterlemann, V., Müller, M.B., 2008. Chronic stress and individual vulnerability. Ann. N. Y. Acad. Sci. 1148, 174–183. https://doi.org/10.1196/annals.1410.017.

Schneiderman, N., Ironson, G., Siegel, S.D., 2005. Stress and health: psychological, behavioral, and biological determinants. Annu. Rev. Clin. Psychol. 1, 607–628. https://doi.org/10.1146/annurev.clinpsy.1.102803.144141.

Scott, K.A., Melhorn, S.J., Sakai, R.R., 2012. Effects of chronic social stress on obesity. Curr. Obes. Rep. 1 (1), 16–25. https://doi.org/10.1007/s13679-011-0006-3.

Sgoifo, A., Carnevali, L., Grippo, A.J., 2014. The socially stressed heart. Insights from studies in rodents. Neurosci. Biobehav. Rev. 39, 51–60. https://doi.org/10.1016/j.neubiorev.2013.12.005.

Sih, A., Bell, A., Johnson, J.C., 2004. Behavioral syndromes: an ecological and evolutionary overview. Trends Ecol. Evol. 19 (7), 372–378. https://doi.org/10.1016/j.tree.2004.04.009.

Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol. Bull. 140 (3), 774–815. https://doi.org/10.1037/a0035302.

Soskin, D.P., Carl, J.R., Alpert, J., Fava, M., 2012. Antidepressant effects on emotional temperament: toward a biobehavioral research paradigm for major depressive disorder. CNS Neurosci. Ther. 18 (6), 441–451. https://doi.org/10.1111/j.1755-5949.2012.00318.x.

Southwick, S.M., Vythilingam, M., Charney, D.S., . The psychobiology of depression and resilience to stress: implications for prevention and treatment. Annu. Rev. Clin. Psychol. 1, 255–291. https://doi.org/10.1146/annurev.clinpsy.1.102803.143948.

Steimer, T., Driscoll, P., 2005. Inter-individual vs line/strain differences in psychogenetically selected Roman High-(RHA) and Low-(RLA) Avoidance rats: neuroendocrine and behavioural aspects. Neurosci. Biobehav. Rev. 29 (1), 99–112. https://doi.org/10.1016/j.neubiorev.2004.07.002.

Takahashi, A., Chung, J.R., Zhang, S., Zhang, H., Grossman, Y., Aleyasin, H., Russo, S.J., 2017. Establishment of a repeated social defeat stress model in female mice. Sci. Rep. 7 (1), 12838. https://doi.org/10.1038/s41598-017-12811-8.

Tornatzky, W., Miczek, K.A., 1993. Long-term impairment of autonomic circadian rhythms after brief intermittent social stress. Physiol. Behav. 53 (5), 983–993. https://doi.org/10.1016/0031-9384(93)90278-n.

Tran, I., Gellner, A.K., 2023. Long-term effects of chronic stress models in adult mice. J. Neural. Transm. 130 (9), 1133–1151. https://doi.org/10.1007/s00702-023-02598-6.

Van der Hallen, R., Jongerling, J., Godor, B.P., 2020. Coping and resilience in adults: a cross-sectional network analysis. Hist. Philos. Logic 33 (5), 479–496. https://doi.org/10.1080/10615806.2020.1772969.

Van Loo, P.L., Van Zutphen, L.F., Baumans, V., 2003. Male management: coping with aggression problems in male laboratory mice. Lab. Anim. 37 (4), 300–313. https://doi.org/10.1258/002367703322389870.

Vegas, O., Fano, E., Brain, P.F., Alonso, A., Azpiroz, A., 2006. Social stress, coping strategies and tumor development in male mice: behavioral, neuroendocrine and immunological implications. Psychoneuroendocrinology 31 (1), 69–79. https://doi.org/10.1016/j.psyneuen.2005.05.013.

Viveros, M.-P., Mendrek, A., Paus, T., López-Rodríguez, A.B., Marco, E.M., Yehuda, R., Wagner, E.J., 2012. A comparative, developmental, and clinical perspective of neurobehavioral sexual dimorphisms. Front. Neurosci. 6. https://doi.org/10.3389/fnins.2012.00084.

Võikar, V., Kõks, S., Vasar, E., Rauvala, H., 2001. Strain and gender differences in the behavior of mouse lines commonly used in transgenic studies. Physiol. Behav. 72 (1–2), 271–281. https://doi.org/10.1016/S0031-9384(00)00405-4.

Warren, B.L., Mazei-Robison, M.S., Robison, A.J., Iñiguez, S.D., 2020. Can I get a witness? Using vicarious defeat stress to study mood-related illnesses in traditionally understudied populations. Biol. Psychiatr. 88 (5), 381–391. https://doi.org/10.1016/j.biopsych.2020.02.004.

Wood, S.K., 2014. Individual differences in the neurobiology of social stress: implications for depression-cardiovascular disease comorbidity. Curr. Neuropharmacol. 12 (2), 205–211. https://doi.org/10.2174/1570159X11666131120224413.

Wood, S.K., Bhatnagar, S., 2015. Resilience to the effects of social stress: evidence from clinical and preclinical studies on the role of coping strategies. Neurobiol. Stress 1, 164–173. https://doi.org/10.1016/j.ynstr.2014.11.002.

Yaribeygi, H., Panahi, Y., Sahraei, H., Johnston, T.P., Sahebkar, A., 2017. The impact of stress on body function: a review. EXCLI J. 16, 1057–1072. https://doi.org/10.17179/excli2017-480.

Yu, T., Guo, M., Garza, J., Rendon, S., Sun, X.-L., Zhang, W., Lu, X.-Y., 2011. Cognitive and neural correlates of depression-like behaviour in socially defeated mice: an animal model of depression with cognitive dysfunction. Int. J. Neuropsychopharmacol. 14 (3), 303–317. https://doi.org/10.1017/S1461145710000945.

Zamudio, S.R., Quevedo-Corona, L., Garcés, L., De La Cruz, F., 2009. The effects of acute stress and acute corticosterone administration on the immobility response in rats. Brain Res. Bull. 80 (6), 331–336. https://doi.org/10.1016/j.brainresbull.2009.09.005.

Zhang, H., Chaudhury, D., Nectow, A.R., Friedman, A.K., Zhang, S., Juarez, B., Han, M.-H., 2019. α1- and β3-adrenergic receptor–mediated mesolimbic homeostatic plasticity confers resilience to social stress in susceptible mice. Biol. Psychiatr. 85 (3), 226–236. https://doi.org/10.1016/j.biopsych.2018.08.020.