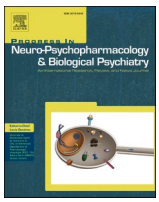
Progress in Neuropsychopharmacology & Biological Psychiatry 130 (2024) 110912

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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



Behavioural traits related with resilience or vulnerability to the development of cocaine-induced conditioned place preference after exposure of female mice to vicarious social defeat

Maria Ángeles Martínez-Caballero [a], Claudia Calpe-López [a], Maria Pilar García-Pardo [b], Maria Carmen Arenas [c], Jose Enrique de la Rubia Ortí [d], Raquel Bayona-Babiloni [d], Maria Asunción Aguilar [a,*]

[a] Neurobehavioural Mechanisms and Endophenotypes of Addictive Behaviour Research Unit, Department of Psychobiology, University of Valencia, Valencia, Spain
[b] Department of Psychology and Sociology, Faculty of Social Sciences, University of Zaragoza, Teruel, Spain
[c] Department of Psychobiology, University of Valencia, Valencia, Spain.
[d] Department of Basic Medical Sciences, Catholic University of Valencia San Vicente Martir, Valencia, Spain

ARTICLE INFO

Keywords:
Cocaine
Conditioned place preference
Female mice
Resilience
Vicarious social defeat

ABSTRACT

Exposure to stress induced by intermittent repeated social defeat (IRSD) increases vulnerability to the development of cocaine-induced conditioned place preference (CPP) among male mice; however, some defeated mice are resilient to these effects of stress. In the present study we evaluated the effects of vicarious IRSD (VIRSD) in female mice and explored behavioural traits that are potentially predictive of resilience. C57BL/6 female mice (n = 28) were exposed to VIRSD, which consisted of the animals witnessing a short experience of social defeat by a male mouse on postnatal day (PND) 47, 50, 53 and 56. The control group (n = 10) was not exposed to stress. Blood samples were collected on PND 47 and 56 for corticosterone and interleukin-6 determinations. On PND 57–58, female mice performed several behavioural tests (elevated plus maze, hole-board, object recognition, social interaction, TST and splash tests). Three weeks later, the effects of cocaine (1.5 mg/kg) on the CPP paradigm were assessed. VIRSD decreased corticosterone levels (on PND 56), increased interleukin-6 levels, enhanced novelty-seeking, improved recognition memory and induced anxiety- and depression-like symptoms. Control and VIRSD female mice did not acquire CPP, although some stressed individuals with certain behavioural traits - including a high novelty-seeking profile or the development of depression-like behaviour in the splash test shortly after VIRSD - acquired cocaine CPP. Our results confirm that some behavioural traits of female mice are associated with vulnerability or resilience to the long-term effects of social stress on cocaine reward, as previously observed in males.

1. Introduction

Research over the years has demonstrated that a combination of biological and environmental factors, including social stress, is associated with drug addiction (Aguilar et al., 2013; Ruisoto and Contador, 2019; Volkow and Boyle, 2018). Several studies in our laboratory have demonstrated that exposure of male mice to intermittent repeated social defeat (IRSD), an animal model of social stress, during early and late adolescence induces short-term effects such as anxiety- and depression-like behaviour (Calpe-López et al., 2020; Calpe-López et al., 2022a; Calpe-López et al., 2022b) and enhances vulnerability to different psychostimulant drugs in adulthood, thereby increasing their rewarding effects in the conditioned place preference (CPP) paradigm (García-Pardo et al., 2015; García-Pardo et al., 2019). However, we have observed that not all mice are equally vulnerable to the effects of stress; in fact, some are resilient to the effects of IRSD (Calpe-López et al., 2020). Resilience to the effects of social stress on the rewarding properties of drugs of abuse has been poorly studied (Calpe-López et al., 2022c), but we have demonstrated that several behavioural traits are associated with resilience to the potentiation of cocaine CPP observed in the long term after IRSD exposure (Calpe-López et al., 2020).

The procedure of IRSD is a useful tool to model social stress in male

* Corresponding author.
E-mail address: asuncion.aguilar@uv.es (M.A. Aguilar).

https://doi.org/10.1016/j.pnpbp.2023.110912
Received 1 October 2023; Received in revised form 30 November 2023; Accepted 7 December 2023
Available online 13 December 2023

rodents, but it has an important limitation; namely, it is difficult to implement in female animals, as they express lower levels of aggression than males. This is of relevance, since it is very important to study the consequences of social stress in female rodents for several reasons. Mental illnesses such as anxiety and depression are more prevalent in women (Altemus et al., 2014; Kiely et al., 2019; Bangasser and Cuarenta, 2021), they are more prone than men to develop disorders after stress (Bangasser and Wiersielis, 2018; Swaab and Bao, 2020) and there are sex differences regarding cocaine addiction (Bobzean et al., 2014; Knouse and Brian, 2021). A modification of the classical model of social defeat, the vicarious social defeat stress (VSDS), has been shown to be an effective way of evaluating the physiological and behavioural effects of social stress in both male and female animals (Qi et al., 2022; Iñiguez et al., 2018; Warren et al., 2020; Sial et al., 2016; Sial et al., 2021). In this procedure a rodent (male or female) witnesses a physical defeat episode of a conspecific male from the safety of a compartment adjacent to the area where the interaction between the two males takes place. The witness and the physically defeated animal develop similar behavioural alterations (Warren et al., 2020; Sial et al., 2016).

In female rats, exposure to VSDS induces anxiety-like behaviour, anhedonia and behavioural despair, increases arterial pressure, heart rate and corticotropin-releasing factor, and enhances peripheral cytokines and interleukin (IL)-1β in the central amygdala (Finnell et al., 2018). In female mice, VSDS reduces social behaviour, decreases preference for sucrose, increases immobility in the tail suspension test (TST), enhances levels of corticosterone and decreases body weight (Iñiguez et al., 2018). Moreover, VSDS-exposed females display a reduction of social interaction in the three-chamber test (Pagliusi Jr et al., 2022; Morais-Silva et al., 2023). Recently, Franco et al. (Franco et al., 2022) demonstrated that the VSDS procedure is useful for evaluating the effects of social stress on free-choice fentanyl consumption in female mice and for discriminating between mice that are resilient and vulnerable to these effects of stress (Franco et al., 2022).

Thus, the aim of this work was to assess the short-term effects of vicarious IRSD (VIRSD) stress on different behavioural, cognitive and emotional parameters in female mice, such as novelty seeking behaviour, social interaction, recognition memory, and anxiety- and depression-like behaviour. In addition, we decided to evaluate the long-term effects of VIRSD on the sensitivity of female mice to cocaine reward. For these purposes, a group of late adolescent female mice was exposed to VIRSD, while another group did not undergo stress. The behaviour of the mice in both groups was compared in a series of tests carried out shortly after the last episode of VIRSD. Three weeks after the last episode of defeat, acquisition of CPP was evaluated following conditioning with a low dose of cocaine. Our hypothesis was that VIRSD stress would induce anxiety- and depression-like behaviour, alterations in novelty-seeking behaviour and memory disturbances, as well as enhanced sensitivity to the rewarding effects of cocaine. Moreover, based on our previous study in male mice, we expected to observe two subpopulations among the female mice exposed to VIRSD - one vulnerable and another resilient to the long-term effects of stress - and to find traits that were predictive of resilience. Finally, in a separate set of female mice, we evaluated the effects of the first and fourth episode of vicarious defeat on plasma levels of corticosterone and the proinflammatory cytokine IL-6.

2. Methods and materials

2.1. Subjects

Female ($n = 55$) and male ($n = 28$) mice of the C57BL/6 J strain, and male mice of the OF1 strain (n = 28) were supplied by Charles River (France). For details about arrival and housing conditions see the Supplementary material. All experimental protocols were conducted according to Directive 210/63/EU and were approved by the Ethics Committee in Experimental Research of the University of Valencia (A20210217012657, 2021-VSC-PEA-0083).

2.2. Drugs

Animals were injected intraperitoneally with 1.5 mg/kg of cocaine (Alcaliber Laboratory, Madrid, Spain) or physiological saline (NaCl 0.9%). The same physiological saline was also used to dissolve the cocaine (see more details about volume and dose in Supplementary Material).

2.3. Experimental design

For behavioural experiments, female mice were assigned to two groups: one control group ($n = 10$) and another exposed to social stress through VIRSD ($n = 28$). The VIRSD sample was larger because we subsequently segregated the group into two subgroups (see details in Supplementary Material). Shortly after the last episode of VIRSD (24–48 h), both groups of female mice underwent different behavioural tests: the elevated plus maze (EPM), hole-board (HB), social interaction (SI), object recognition (OR), splash test (SPT) and TST. There was an interval of one hour between each test (see Supplementary material). Following this, all the mice were left undisturbed in the vivarium for 3 weeks, after which they underwent the CPP procedure (see Fig. 1). The measures registered in each test are listed in Supplementary Table 1.

For biochemical experiments, a separate set of female mice was assigned to a control group ($n = 6$) or exposed to VIRSD ($n = 11$). 15–30 min after exposure to the first and last episode of exploration (control group) or vicarious defeat, blood sampling was performed for determination of plasma levels of corticosterone and IL-6 (see Fig. 1).

2.4. Experimental protocols

2.4.1. Vicarious Intermittent Repeated Social Defeat (VIRSD)

The vicarious social defeat procedure induces emotional/psychological stress by means of the perception of non-physical sensory stimuli of an episode of defeat (Iñiguez et al., 2018). Our VIRSD protocol consisted of four episodes, each lasting five minutes and separated by intervals of 72 h (PND 47, 50, 53 and 56). In each episode the experimental mice observed the confrontation between a male mouse of the same strain (C57 intruder) and a male mouse of the OF1 strain (resident) through a perforated methacrylate wall that divided the cage into two separate compartments and permitted the perception of visual, olfactory and chemosensory stimuli. Intruder mice were exposed to a different resident mouse during each episode of social defeat. The first and fourth episodes of VIRSD were videotaped and the behaviour of the females was evaluated using a computerized system (Raton Time 1.0 software; Fixma SL, Valencia, Spain). The locomotor activity (number of times that a female crossed a line that divides the floor into nine squares) and the frequency and time that female mice paid attention to the interaction between male mice were measured. The control (non-stressed) group underwent the same protocol without the presence of male mice (exploration).

2.4.2. Behavioural tests

On PND 57, female mice were tested in the EPM, HB and SI to evaluate the effects of VIRSD on anxiety, novelty-seeking and social behaviour, respectively. All apparatuses, procedures and behavioural measurements are previously described in detail (Calpe-López et al., 2020). It is important to note that the HB test was carried out in a square box with 16 equidistant holes in the floor. Each mouse can explore the box for 10 min and the number of times that it introduces its head in a hole (dip) and latency to perform the first dip are recorded. Frequency and latency of dips are usually considered a measure of the level of novelty-seeking of the animals. Since the animal explored the box only once and for a short period of time, it was assumed that spatial memory did not influence behaviour in the HB test.

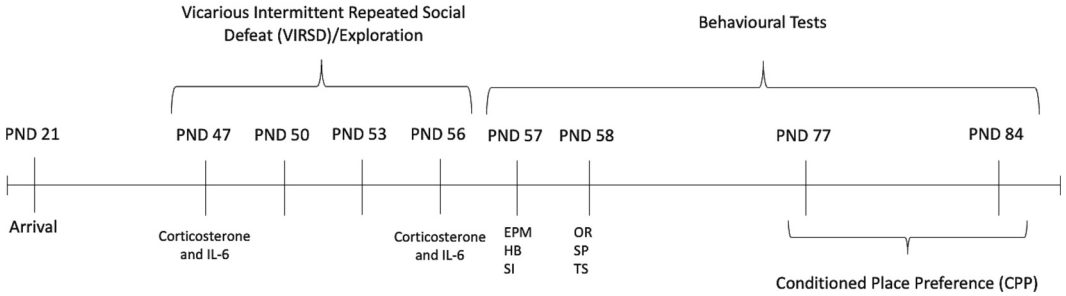


Fig. 1. Experimental Design. Two groups of female mice were used, one of which was exposed to vicarious intermittent repeated social defeat (VIRSD, $n = 39$). On postnatal day (PND) 47, 50, 53 and 56, female mice observed the social defeat of an intruder male mouse of the same strain by a resident OF1 male mouse. On the same PND, the female mice in the other group (Control, $n = 16$) simply explored an empty cage. After the first (PND 47) and fourth (PND 56) episode of vicarious defeat, blood samples were collected from a set of females exposed to vicarious defeat (VIRSD, $n = 11$) or exploration (Control, $n = 6$) in order to evaluate their levels of corticosterone and IL-6. The remaining female mice (VIRSD, $n = 28$; Control, $n = 10$) were used for behavioural experiments. On PND 57, VIRSD and Control females performed the elevated plus maze (EPM), hole board (HB) and social interaction (SI) tests. On PND 58, the same mice performed the object recognition (OR), splash (SP) and TST. After an interval of 3 weeks, VIRSD and Control female mice underwent the conditioned place preference (CPP) paradigm (PND 77–84).

On PND 58, female mice performed the OR test to evaluate the effects of VIRSD on explicit memory following the procedure previously described (Montesinos et al., 2015); see more details in the Supplementary material. Next, the female mice performed the SPT and the TST and the presence of depressive-like behaviour was assessed. Details about the apparatuses, procedures and behavioural measurements of these tests can be found in Calpe-López et al. (Calpe-López et al., 2020).

On PND 77–84 female mice underwent the CPP procedure to evaluate the effects of VIRSD on the rewarding properties of cocaine (1.5 mg/kg). The equipment and CPP protocol are previously described (Calpe-López et al., 2020). The criterion used to consider that a group had acquired CPP was the existence of significant differences between the time spent in the drug-paired compartment in Pre-Conditioning versus Post-Conditioning.

2.4.3. Corticosterone and IL-6 determination

Tests were carried out on blood obtained from the saphenous vein between 10 a.m. 1 p.m. and collected in BD Vacutainer Plus serum blood collection tubes (ref. 367,815). Once the test was finished, blood samples were kept on ice and plasma was separated from whole blood by centrifugation (5 min, 5000 *g*) and transferred to sterile 2 ml microcentrifuge tubes. Plasma samples were stored at −80 °C until determination of corticosterone and IL-6. The concentration of IL-6 in plasma was analysed with the Mouse IL-6 ELISA Kit (Catalog no.: ab100712, Abcam, Cambridge, UK), while plasma corticosterone values were analysed with CORT ImmunoAssay Enzo (ADI-900-097, Enzo Life Sciences, Plymouth meeting, PA, USA), following the manufacturer's instructions.

2.5. Statistical analysis

The effects of VIRSD on physiological and behavioural measurements were evaluated by means of ANOVA and Student *t*-tests (see Table 1).

The group of stressed female mice was separated into two subgroups according to the data obtained during the VIRSD episodes and in the behavioural tests performed shortly after VIRSD (EPM, HB, SI, OR, SPT, TST). Differences between subgroups were evaluated with Student *t*-tests and ANOVA (see Table 1 and Supplementary material).

Pearson correlation tests were used to determinate relationships among the performances of female mice in the different procedures. In the case of CPP, the conditioning score (time spent in Post-C minus time spent in Pre—C) was calculated. It is important to note that we performed Pearson correlations between all the behavioural measures obtained rather than merely performing planned correlations between selected measures that we expected to be causally related.

All statistical analyses were performed with the SPP programme.

Table 1
Statistical analysis employed.

	Statistical test	Variables	Levels
Physiological effects of VIRSD (Corticosterone, IL-6)	Repeated measures two-way ANOVA	Within-subjects: Episode Between-subjects: Stress	First vs Fourth Control vs VIRSD
Short-term behavioural effects (EPM, HB, SI, OR, SPT, TST)	Student t-test	Stress	Control vs VIRSD
Long-term behavioural effects (CPP)	Repeated measures two-way ANOVA	Within-subjects: Days Between-subjects: Stress	Pre-C vs Post-C Control vs VIRSD
Behavioural profile during episodes (LA1, LA4, FAtt1, FAtt4, Tatt1, TAtt4)	Student t-test	Score	Low vs High
Behavioural profile in short-term tests (EPM, HB, SI, OR, SPT, TST)	One-way ANOVA (non repeated)	Between-subjects: Group	Control, Low, High
Influence of behavioural profile on vulnerability to cocaine CPP	Repeated measures two-way ANOVA	Within-subjects: Days Between-subjects: Group	Pre-C vs Post-C Low vs High

After ANOVAs, post hoc comparisons were performed with Bonferroni.

3. Results

3.1. Biochemical effects of VIRSD exposure

ANOVA of the corticosterone data (Fig. 2A) revealed that the variable Stress [$F(1, 15)=5.281$; $p < 0.05$] and the Interaction Days x Stress [$F(1, 15)=8.028$; $p < 0.05$] were significant. In the group of stressed females, corticosterone levels were lower after the fourth episode of vicarious defeat than after the first episode ($p < 0.01$). Furthermore, stressed females showed lower corticosterone levels than control females after the fourth episode ($p < 0.01$). ANOVA of the IL-6 data (Fig. 2B) revealed that only the variable Stress was significant [$F(1, 15)=6.410$; $p < 0.05$], while stressed females showed higher IL-6 levels

Fig. 2. Biochemical effects of vicarious intermittent repeated social defeat (VIRSD). Plasmatic levels of corticosterone (A) and IL-6 (B) in female mice 15–30 min after the first (1st) and fourth (4th) episodes of vicarious defeat (VIRSD, $n = 11$) or exploration (Control, $n = 6$). Bars represent mean (±SEM) values. * $p < 0.05$, ** $p < 0.01$, significant difference with respect to the control group. ## $p < 0.01$, significant difference with respect to the first episode of defeat.

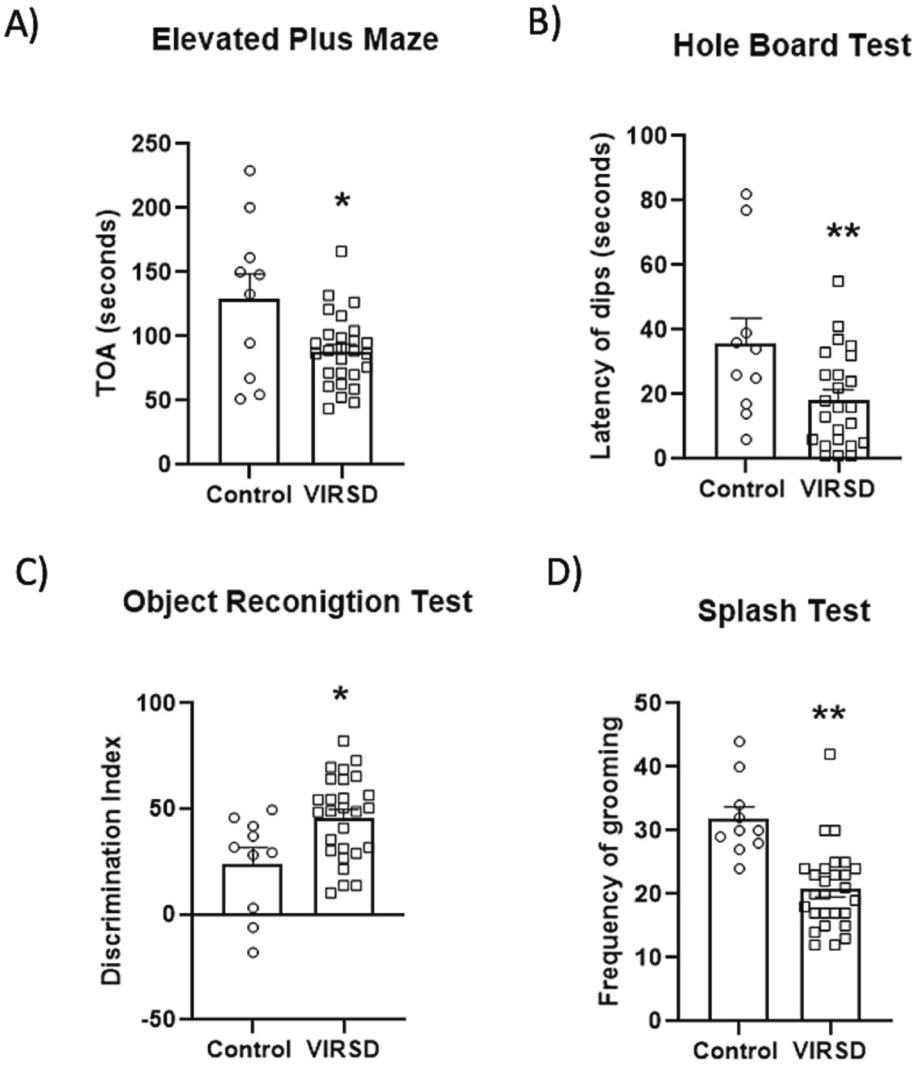


Fig. 3. Short-term behavioural effects of vicarious intermittent repeated social defeat (VIRSD). One group of late adolescent female mice was exposed to vicarious intermittent repeated social defeat (VIRSD, $n = 28$) on PND 47, 50, 53 and 56 while the other group was not exposed to stress (Control, $n = 10$). Bars represent mean (±SEM) values. A) Effects on the elevated plus maze (EPM). VIRSD reduced the time spent in the open arms (TOA) of the EPM. B) Effects on the hole board (HB) test. VIRSD reduced the latency to perform the first dip in the HB test. C) Effects on the object recognition (OR) test. VIRSD increased the discrimination index in the OR test. D) Effects in the splash SPT. VIRSD reduced the frequency of grooming behaviour in the SPT. *$p < 0.05$, **$p < 0.01$, significant difference with respect to the Control group.

than control females ($p < 0.05$).

3.2. Behavioural effects of VIRSD exposure

In terms of the short-term effects of VIRSD, in comparison to controls stressed females showed a decrease in the time [$t(10.65) = 2.13$; $p < 0.05$] (Fig. 3A) and percentage of time [$t(11.9) = 1.76$; $p < 0.05$] (Supplementary Fig. 1A) spent in the open arms of the EPM, a reduction in the latency to perform the first dip in the HB [$t(33)=2.605$; $p < 0.01$] (Fig. 3B), an increase in DI in the OR test [$t(36)= -2.321$; $p < 0.05$] (Fig. 3C), and a reduction in the frequency of grooming in the SPT [$t(36)=4.738$; $p < 0.01$] (Fig. 3D).

No significant effects of VIRSD were observed in the SI and TST (see Supplementary Fig. 1B and C). Regarding the long-term effects of exposure to VIRSD on the CPP induced by cocaine, ANOVA of the CPP data revealed no significant effects (Supplementary Fig. 2).

3.3. Behavioural profile of female mice during VIRSD and cocaine CPP

Stressed female mice (VIRSD group) were segregated into two subgroups in function of their locomotor activity (LA) during the first episode of vicarious defeat (Low or High LA) (Supplementary Fig. 3 A). ANOVA of the CPP data for these groups showed that only the Interaction Days x Group was significant [$F(2, 34)=3.425$; $p < 0.05$]; namely, the High LA group spent more time in the drug-paired compartment in Post-C than in Pre-C ($p < 0.01$) (Fig. 4A). Segregation of stressed females in function of their frequency of attention (FAtt) or time in attention (TAtt) to male interactions did not reveal significant differences in the CPP (data not shown).

In terms of behaviour in the fourth episode of VIRSD, only the segregation of stressed female mice in function of the frequency of attention (FAtt) (Supplementary Fig. 3B) was associated with differences in the CPP. ANOVA of the CPP data for the Low and High FAtt groups showed that the variable Days [$F(1, 34)=6.424$; $p < 0.05$] and the Interaction Days x Group [$F(2, 34)=3.560$; $p < 0.05$] were significant. Post hoc comparisons revealed that only the High FAtt group developed CPP ($p < 0.01$) (Fig. 4B).

3.4. Behavioural profile of stressed female mice in the behavioural tests performed shortly after VIRSD and cocaine CPP

In order to evaluate whether the novelty-seeking (NS) profile of female mice in the HB test influences the susceptibility of mice to develop cocaine CPP, stressed females were divided into two subgroups (Low or High NS) according to their dip score (Supplementary Fig. 4A). ANOVA of the CPP data for the two subgroups of females exposed to VIRSD (Low and High NS) revealed a significant effect of the variable Days [$F(1, 22)=13.399$; $p < 0.001$] and of the Interaction Days X Group [$F(1, 22)=4.319$; $p < 0.05$]. Post hoc comparisons revealed that only the High NS group developed CPP ($p < 0.001$) (Fig. 5A).

The behavioural profile of female mice in the SI test (Supplementary Fig. 4B) was also associated with the susceptibility of mice to develop cocaine CPP. ANOVA of the CPP data for the Low and High ISI groups revealed a significant effect of the variable Days [$F(1, 25)=10.521$; $p < 0.01$] and of the Interaction Days X Group [$F(1, 25)=4.993$; $p < 0.05$]. Post hoc comparisons revealed that only the Low ISI group developed CPP ($p < 0.001$) (Fig. 5B).

Finally, the behavioural profile of female mice in the SPT (Supplementary Fig. 4C) was associated with the susceptibility of mice to develop cocaine CPP. ANOVA of the CPP data for the Low and High TGr groups revealed a significant effect of the variable Days [$F(1, 25)=9.301$; $p < 0.01$] and of the Interaction Days X Group [$F(1, 25)=4.326$; $p < 0.05$]. Post hoc comparisons revealed that only the Low TGr group developed CPP ($p < 0.01$) (Fig. 5C).

The behavioural profile of female mice in the other tests (EPM, TST and OR test) was not associated with vulnerability or resilience to the effects of VIRSD on cocaine reward (see Supplementary Figs. 5–7).

3.5. Correlations between behavioural measurements

Pearson correlations between the data obtained for all animals (control and stressed females) revealed significant correlations between several measures of the different behavioural tests (Supplementary Tables 2 and 3). In addition, correlations between the measures taken during the episodes of VIRSD and during behavioural tests were detected (Table 2).

4. Discussion

As we expected, our VIRSD procedure proved to be useful for evaluating the effects of social stress in female mice and for discriminating between resilient and vulnerable animals. Exposure to VIRSD reduced the corticosterone response and induced inflammation. Short-term behavioural effects of VIRSD included anxiety-like symptoms in the

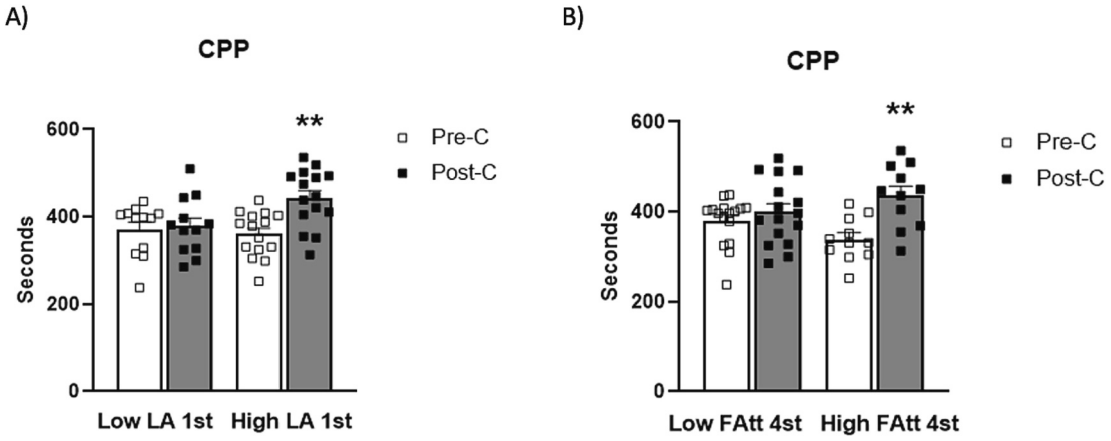


Fig. 4. Behaviour profile during episodes of vicarious defeat and cocaine reward. Bars represent the mean (±SEM) time spent in the drug-paired compartment in the pre-conditioning test (Pre—C, empty symbols) and in the post-conditioning test (Post-C, filled symbols). A) Effects of VIRSD on the CPP induced by cocaine (1.5 mg/kg) according to the level of locomotor activity (LA) shown by female mice in the 1st episode of vicarious defeat (see Fig.S3A). Only stressed female mice with High LA in the 1st episode of vicarious defeat acquired CPP. B) Effects of VIRSD on the CPP induced by cocaine (1.5 mg/kg) according to the frequency of attention (FAtt) shown by female mice to the male interactions in the 4th episode of vicarious defeat (see Fig.S3B). Only stressed female mice with High FAtt in the 4th episode of vicarious defeat acquired CPP. ** $p < 0.01$, significant difference in the time spent in the drug-paired compartment in Post-C vs. Pre-C test.

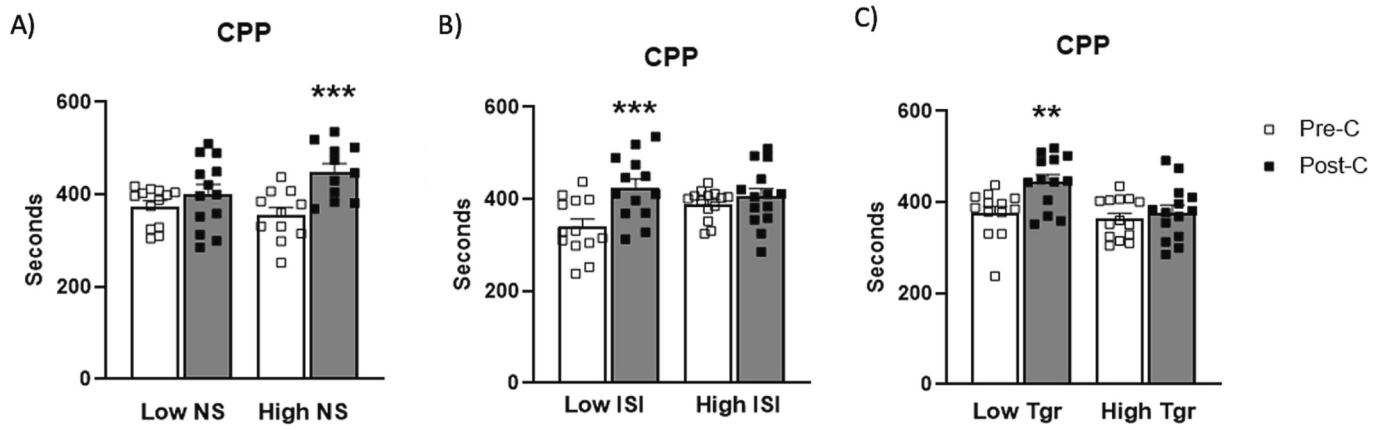


Fig. 5. Behaviour profile in the behavioural tests performed shortly after VIRSD and cocaine reward. Bars represent the mean (±SEM) time spent in the drug-paired compartment in the pre-conditioning test (Pre—C, empty symbols) and post-conditioning test (Post-C, filled symbols). A) Effects of VIRSD on the CPP induced by cocaine (1.5 mg/kg) according to the level of novelty-seeking (NS) shown by female mice in the hole-board test (see Fig.S4A). Only stressed female mice with High NS acquired CPP. B) Effects of VIRSD on the CPP induced by cocaine (1.5 mg/kg) according to the index of social interaction (ISI) shown by female mice in the social interaction test (see Fig. S4B). Only stressed female mice with Low ISI (indicative of depression-like behaviour) acquired CPP. C) Effects of VIRSD on the CPP induced by cocaine (1.5 mg/kg) according to the time spent grooming (Tgr) by female mice in the splash test (see Fig. S4C). Only stressed female mice with Low Tgr (indicative of depression-like behaviour) acquired CPP. ** $p < 0.01$, *** $p < 0.001$, significant difference in the time spent in the drug-paired compartment in Post-C vs. Pre-C test.

Table 2
Pearson correlations between behavioural measurements during the first and fourth episodes of vicarious social defeat and measurements of the different behavioural tests performed in the short- and long-term after VIRSD.

	AM1	AM4	FrAt1	FrAt4	TAt1	TAt4	TCA	Dips	Immob	Lat Imm	T Gr	Lat Gr	DI	CPP
AM1		ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	+
AM4	ns		ns	ns	ns	ns	ns	ns	+	ns	ns	ns	ns	ns
FrAt1	ns	ns		ns	+	ns	ns	−	ns	ns	−	ns	ns	ns
FrAt4	ns	ns	ns		ns	+	ns	ns	ns	ns	ns	ns	−	+
TAt1	ns	ns	0.001	ns		+	+	−	ns	−	−	+	−	ns
TAt4	ns	ns	ns	0.001	0.001		+	ns	ns	ns	−	+	−	ns
TCA	ns	ns	ns	ns	0.01	0.05		ns	ns	ns	−	+	ns	ns
Dips	ns	ns	0.01	ns	0.001	ns	ns		ns	ns	ns	ns	ns	ns
Immob	ns	0.01	ns	ns	ns	ns	ns	ns		ns	ns	ns	ns	ns
Lat Immob	ns	ns	ns	ns	0.05	ns	ns	ns	ns		+	−	ns	ns
T Gr	ns	ns	0.05	ns	0.001	0.01	0.01	ns	ns	0.05		−	ns	ns
Lat Gr	ns	ns	ns	ns	0.001	0.05	0.001	ns	ns	0.01	0.001		ns	ns
DI	ns	ns	ns	0.01	0.01	0.01	ns	ns	ns	ns	ns	ns		ns
CPP	0.05	ns	ns	0.01	ns	ns	ns	ns	ns	ns	ns	ns	ns	

+ positive correlation; − negative correlation; ns, no significant correlation. 0.05, 0.01 and 0.001, correlation is significant at the 0.05, 0.01 and 0.001 level (bilateral), respectively.

EPM and depression-like symptoms in the SPT, increased novelty-seeking behaviour and improved recognition memory. In addition, VIRSD induced long-term effects in a subgroup of vulnerable female mice that showed a potentiation of the rewarding effects of cocaine in the CPP paradigm. Some behavioural traits were associated with vulnerability or resilience to the effects of VIRSD on cocaine reward, such as the behaviour displayed during the episodes of social defeat, the novelty-seeking trait, and the development of short-term depression-like symptoms after stress.

4.1. Short-term effects of VIRSD exposure in late adolescence

Our protocol of VIRSD did not increase corticosterone levels, in contrast with that reported by other studies (18, 27). It is likely that our protocol (only four experiences of witness defeat, each lasting 5 min) was less stressful than those in which females were exposed to ten consecutive days of witness defeat (Iñiguez et al., 2018) or in which the agonistic encounter between males lasted longer (Ródenas-González et al., 2023) and the female mouse remained in the aggressor's cage after each episode of vicarious defeat. Nevertheless, our VIRSD protocol definitely altered the corticosterone response, since stressed females exhibited lower levels of corticosterone than controls after the fourth episode. In our opinion, this effect on corticosterone is not specific of our stress protocol, since similar results were observed by Marchette et al. (Marchette et al., 2018) in female mice exposed to repeated restraint stress; they found no differences between control and stressed mice on day 1, while corticosterone was reduced after 21 days of restraint. Importantly, the strain of mouse could have had an influence on the effects of stress on corticosterone levels. The study of Marchette et al. (Marchette et al., 2018) demonstrated that, in comparison to Swiss female mice, C57BL/6 female mice were more vulnerable to repeated restraint, which induces an anhedonic state (lower sucrose preference) accompanied by reduced plasma corticosterone and increased levels of glucocorticoid receptor (GR) and glial fibrillary acid protein (GFAP, a marker of astrocyte activation) in the hippocampus. Thus, in C57BL/6 female mice, stress dysregulated the hypothalamus-pituitary-adrenal axis, leading to a pro-inflammatory state (Marchette et al., 2018). In parallel with these results, the inhibition of corticosterone we have observed in the present study could be related with the increase in levels of the proinflammatory cytokine IL-6 observed in VIRSD -exposed female mice, a result in accordance with previous reports (Finnell et al., 2018). Alternatively, the reduction in the levels of corticosterone

observed after the fourth episode of vicarious defeat could be due to the habituation of mice to the stressor.

Regarding the short-term behavioural effects of vicarious defeat, female mice exposed to VIRSD showed anxiety-like behaviour in the EPM, in line with a recent study that used a similar protocol of VIDS (Ródenas-González et al., 2023) and with results obtained in VSDS-exposed rats in the burying paradigm (Finnell et al., 2018). In addition, VIRSD increased novelty-seeking, since stressed female mice showed lower latencies to perform the first dip in the HB. The effects of VSDS on novelty-seeking have not been evaluated to date, but exposure to other paradigms of stress during adolescence has been shown to increase novelty-seeking behaviours in female rats (Toledo-Rodriguez and Sandi, 2011; Sexton et al., 2022). Furthermore, VIRSD reduced the frequency of grooming in the SPT, which is indicative of depression-like behaviour, in line with reports of a reduction in the time spent engaged in back grooming by female mice exposed to VISD (Ródenas-González et al., 2023).

However, our VIRSD procedure did not affect other measures related with depression and reported to be influenced by VSDS in female mice, such as immobility in the TST (Iñiguez et al., 2018) and social interaction (Iñiguez et al., 2018; Pagliusi Jr et al., 2022; Morais-Silva et al., 2023). In this regard, it is important to point out that, in the study by Ródenas-González et al. (Ródenas-González et al., 2023), VIRSD did not induce effects in the TST or SI test. Such divergences among studies are probably related with the different levels of stress induced by VSDS or VIRSD.

Surprisingly, our female mice exposed to VIRSD showed a significant increase in DI in the OR test, suggesting that this kind of stress facilitates recognition memory. To date, no studies have evaluated the effects of vicarious defeat on OR, but recent research has shown that unpredictable chronic mild stress (UCMS) does not affect adult female mice cognition in the object recognition and location recognition tests (Madison et al., 2022) and that perinatal psychological stress enhances the performance of adolescent female mice in the object recognition test (Oshiro et al., 2022). In fact, contrasting data have been reported regarding the effects of stress on cognitive function in female rats (Bowman et al., 2022). The increase in object discrimination after vicarious stress observed in our study is in line with the previously reported improvement in the spatial memory of female mice exposed to UCMS on day 2 of training in a Morris water maze versus non-stressed females. It suggests that exposure to mild stress can improve cognitive function in females (Madison et al., 2022).

4.2. Long-term effects of VIRSD exposure in late adolescence on the CPP induced by cocaine in adulthood

Exposure to VIRSD did not modify the subsequent sensitivity of adult female mice to the rewarding effects of cocaine, since control and VIRSD-exposed female mice did not develop CPP after conditioning with 1.5 mg/kg of cocaine. It is important to note that, as in our previous studies with male mice (Calpe-López et al., 2020; Calpe-López et al., 2022a; Calpe-López et al., 2022b; García-Pardo et al., 2019), we used a low dose of cocaine that was ineffective in control mice in order to detect any potentiation of the rewarding effects of the drug in stressed animals. In future studies it would be of interest to evaluate the effects of VIRSD on the CPP induced by a slightly higher dose of cocaine (for example, 2 mg/kg) in order to assess how the stress-induced potentiation of CPP depends on the dose administered. The lack of effects of our VIRSD protocol on cocaine reward is probably related with the fact that the vicarious experience of defeat in females is less stressful than the physical interaction of the male mouse with an aggressive opponent. Only two recent studies have evaluated how vicarious defeat affects drug reward in female mice (Franco et al., 2022; Ródenas-González et al., 2023); in contrast with our results, exposure to VIRSD induced a potentiation of the rewarding effects of cocaine (Ródenas-González et al., 2023). These divergent results could be explained by differences between the VIRSD protocols employed; although both consisted of four intermittent experiences of vicarious defeat, in the study by Ródenas-Gónzalez et al. the agonistic encounter between males lasted longer and the female mouse remained in the aggressor's cage for 24 h after each episode of vicarious defeat (Ródenas-González et al., 2023). On the other hand, in the study by Franco et al., exposure to 10 consecutive days of VSDS did not modify fentanyl consumption or preference in a 15-day drinking paradigm (Franco et al., 2022). Interestingly, an increase in the consumption of fentanyl on day 15 in comparison with day 5 was observed in a subgroup of stressed susceptible females (which showed social avoidance in a SI test), while stressed resilient females (which maintained their sociability) did not increase fentanyl consumption (Franco et al., 2022). In the same line, we have observed that the segregation of female mice in function of their behavioural profile allowed us to detect stressed females that developed CPP after conditioning with a low dose of cocaine, while other females remained resilient and did not acquire cocaine CPP.

4.3. Behavioural traits associated with vulnerability or resilience to the effects of VIRSD on cocaine reward

Two behavioural traits shown by female mice during VIRSD episodes were associated with their subsequent vulnerability or resilience to develop cocaine CPP. Stressed mice that displayed a low level of locomotor activity during the first episode of defeat did not develop CPP; they were resilient to stress, thus reproducing the behaviour of the control group. Conversely, stressed mice with a high level of locomotor activity acquired CPP, and these two measures correlated positively. The mechanism underlying this correlation between hyperactivity and cocaine CPP is likely to be due to the fact that both effects depend on the activity of the dopaminergic neurons (in the nigrostriatal and mesolimbic DA pathways, respectively). The high locomotor activity in the first episode of VIRSD could be interpreted as reactivity to novelty (females were introduced into a novel cage for a short time), a trait that predicts higher vulnerability to cocaine CPP in female mice (Vidal-Infer et al., 2012; Arenas et al., 2014). In line with this, positive correlations between hyperactivity in a novel environment, plasma corticosterone concentration and cocaine CPP have been observed in male mice (Kähler et al., 2021). It would be of interest for future studies to evaluate if mice displaying high locomotion during the first vicarious defeat episode also have higher corticosterone levels.

Another behavioural trait that predicted greater vulnerability to cocaine CPP was the higher frequency of attention to the agonistic encounter between males in the fourth episode of VIRSD. The positive correlations between frequency of attention, CPP score, and the time spent in attention in the first and fourth episodes of VIRSD suggested that female mice with higher levels of stress (due to a greater visualization of defeat experience) were more vulnerable to cocaine reward. In addition, the correlation between the time spent in attention and other behavioural measures suggested that females which paid more attention to defeat also displayed depression-like symptoms in the TST (lower latency of immobility) and SPT (less time engaged in and higher latency of grooming) and less memory in the OR test. The mechanism behind these correlations is that visualization of a social defeat is assumed to induce stress; thus, the more attention paid by females to this stressful event, the more negative are the consequences.

The behavioural profile of stressed female mice in the HB, SI and SPT was also predictive of vulnerability or resilience to cocaine CPP. Firstly, stressed female mice with a more pronounced novelty-seeking behaviour were more sensitive to the effects of cocaine, since only the High NS group (which performed more dips than the Low NS and control groups) acquired CPP. These results are in accordance with those previously observed in male mice exposed to IRSD (Calpe-López et al., 2020). Secondly, stressed female mice that displayed an increase in social interaction were resilient to the long-term effects of stress and did not acquire cocaine CPP. These results reflect those previously observed in

male mice exposed to IRSD, since only defeated mice with a lower ISI acquired CPP (Calpe-López et al., 2020). This leads us to believe that maintenance of sociability was associated with resilience in both sexes. Indeed, cocaine dopaminergic activation and cocaine CPP are known to be reduced by social interaction (Ribeiro Do Cuoto et al., 2009; Tzeng et al., 2016; Zerning and Pinheiro, 2015). Thirdly, the absence of depression-like symptoms in the SPT was associated with resilience to cocaine CPP. Some stressed female mice remained resilient to VIRSD and even spent more time engaged in grooming than the control group; subsequently, these resilient females did not show CPP. Again, we have previously observed that only vulnerable male mice displaying a reduced frequency of grooming behaviour acquire cocaine CPP (Calpe-López et al., 2020). Similarly, only male mice with anhedonia (lower sucrose preference) acquired cocaine CPP (Krishnan et al., 2007). Finally, in our study anxiety-like behaviour did not predict resilience in female mice, in agreement with that observed using a model of female social defeat (Takahashi et al., 2017).

A limitation of the present study is that we have not evaluated the possible influence of oestrous cycle phase on the vulnerability or resilience to VIRSD. This might be relevant to ensure that animals with high activity or a high frequency of attention, and which also displayed CPP, were in the same phase than those displaying low activity and a low frequency of attention. It is important to bear in mind that, although there are various methods to determine the phase of the oestrous cycle in rodents (Ajayi and Akhigbe, 2020), all induce stress and thus can induce significant behavioural changes and affect the results obtained. In addition, exposure to male pheromones elicits oestrous synchrony among female mice that live together, a phenomenon known as "the Whitten effect" (Zakaria and Sukardi, 2019). As all the female mice underwent VIRSD episodes and behavioural tests on the same day, we can assume that all were in the same phase of the oestrous cycle.

In conclusion, the present study demonstrates that exposure to vicarious social defeat induces different biochemical and behavioural effects in female mice, and that there are several behavioural traits that confer resilience to the effects of this kind of stress on cocaine reward, such as reduced motor activity in the first episode of defeat and decreased attention to male interactions during the fourth episode of defeat. In addition, female mice that do not show an increase in novelty-seeking behaviour or depression-like symptoms after VIRSD do not subsequently develop cocaine CPP.

Role of the funding source

This work is part of the R+D+i project PID2020-118945RB-I00, financed by the Spanish Government MCIN/AEI/10.13039/501100011033 (Maria Aó Aguilar). Maria A Martínez-Caballero is granted by University of Valencia ("Atracció de talent").

Welfare of animals

All the procedures involving the mice and their care complied with national, regional, and local laws and regulations, which are in accordance with the Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes. The protocols were approved by the Ethics Committee in Experimental Research of the University of Valencia and Generalitat Valenciana (A20210217012657, 2021-VSC-PEA-0083).

CRediT authorship contribution statement

Maria Ángeles Martínez-Caballero: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Claudia Calpe-López:** Formal analysis, Visualization, Writing – original draft. **Maria Pilar García-Pardo:** Formal analysis, Writing – review & editing. **Maria Carmen Arenas:** Methodology, Writing – review & editing. **Jose Enrique de la Rubia Ortí:** Formal analysis, Writing – review & editing. **Raquel Bayona-Babiloni:** Investigation, Visualization. **Maria Asunción Aguilar:** Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

All the authors declare no financial/personal interest that could affect the objectivity of their work.

Data availability

Data will be made available on request.

Acknowledgements

This work is part of the R + D + i project PID2020-118945RB-I00, financed by the Spanish Government MCIN/AEI/10.13039/501100011033 (Maria A Aguilar). Maria A Martínez-Caballero is granted by University of Valencia ("Atracció de talent").

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110912.

References

Aguilar, M.A., García-Pardo, M.P., Montagud-Romero, S., Miñarro, J., Do Couto, B.R., 2013. Impact of social stress in addiction to psychostimulants: what we know from animal models. Curr. Pharm. Des. 19, 7009–7025. https://doi.org/10.2174/13816128194013120912470 8.

Ajayi, A.F., Akhigbe, R.E., 2020. Staging of the estrous cycle and induction of estrus in experimental rodents: an update. Fertil. Res. Pract. 6, 5. https://doi.org/10.1186/s40738-020-00074-3.

Altemus, M., Sarvaiya, N., Epperson, C.N., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35, 320–330. https://doi.org/10.1016/j.yfrne.2014.05.004.

Arenas, M.C., Daza-Losada, M., Vidal-Infer, A., Aguilar, M.A., Miñarro, J., Rodríguez-Arias, M., 2014. Capacity of novelty-induced locomotor activity and the hole-board test to predict sensitivity to the conditioned rewarding effect of cocaine. Physiol. Behav. 133, 152–160. https://doi.org/10.1016/j.physbeh.2014.05.028.

Bangasser, D.A., Cuarenta, A., 2021. Sex differences in anxiety and depression: circuits and mechanisms. Nat. Rev. Neurosci. 22, 674–684. https://doi.org/10.1038/s41583-021-00513-0.

Bangasser, D.A., Wiersielis, K.R., 2018. Sex differences in stress responses: a critical role for corticotropin-releasing factor. Hormones (Athens) 17, 5–13. https://doi.org/10.1007/s42000-018-0002-z.

Bobzean, S.A.M., DeNobrega, A.K., Perrotti, L.I., 2014. Sex differences in the neurobiology of drug addiction. Exp. Neurol. 259, 64–74. https://doi.org/10.1016/j.expneurol.2014.01.022.

Bowman, R., Frankfurt, M., Luine, V., 2022. Sex differences in cognition following variations in endocrine status. Learn. Mem. 29 (9), 234–245. https://doi.org/10.1101/lm.053509.121.

Calpe-López, C., García-Pardo, M.P., Martínez-Caballero, M.A., Santos-Ortíz, A., Aguilar, M.A., 2020. Behavioral traits associated with resilience to the effects of repeated social defeat on cocaine-induced conditioned place preference in mice. Front. Behav. Neurosci. 13, 278. https://doi.org/10.3389/fnbeh.2019.00278.

Calpe-López, C., Martínez-Caballero, M.A., García-Pardo, M.P., Aguilar, M.A., 2022a. Brief maternal separation inoculates against the effects of social stress on depression-like behavior and cocaine reward in mice. Front. Pharmacol. 13, 825522 https://doi.org/10.3389/fphar.2022.825522.

Calpe-López, C., Martínez-Caballero, M.A., García-Pardo, M.P., Aguilar, M.A., 2022b. Intermittent voluntary wheel running promotes resilience to the negative consequences of repeated social defeat in mice. Physiol. Behav. 254, 113916 https://doi.org/10.1016/j.physbeh.2022.113916.

Calpe-López, C., Martínez-Caballero, M.A., García-Pardo, M.P., Aguilar, M.A., 2022c. Resilience to the effects of social stress on vulnerability to developing drug addiction. World J. Psychiatry 12, 24–58. https://doi.org/10.5498/wjp.v12.i1.24.

Finnell, J.E., Muniz, B.L., Padi, A.R., Lombard, C.M., Moffitt, C.M., Wood, C.S., et al., 2018. Essential role of ovarian hormones in susceptibility to the consequences of witnessing social defeat in female rats. Biol. Psychiatry 84, 372–382. https://doi.org/10.1016/j.biopsych.2018.01.013.

Franco, D., Wulff, A.B., Lobo, M.K., Fox, M.E., 2022. Chronic physical and vicarious psychosocial stress alter fentanyl consumption and nucleus accumbens rho GTPases in male and female C57BL/6 mice. Front. Behav. Neurosci. 16, 821080 https://doi.org/10.3389/fnbeh.2022.821080.

García-Pardo, M.P., Blanco-Gandía, M.C., Valiente-Lluch, M., Rodríguez Arias, M., Miñarro, J., Ma, Aguilar, 2015. Long-term effects of repeated social stress on the conditioned place preference induced by MDMA in mice. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 63, 98–109. https://doi.org/10.1016/j.pnpbp.2015.06.006.

García-Pardo, M.P., Calpe-López, C., Miñarro, J., Aguilar, M.A., 2019. Role of N-methyl-D-aspartate receptors in the long-term effects of repeated social defeat stress on the rewarding and psychomotor properties of cocaine in mice. Behav. Brain Res. 361, 95–103. https://doi.org/10.1016/j.bbr.2018.12.025.

Iñiguez, S.D., Flores-Ramirez, F.J., Riggs, L.M., Alipio, J.B., García-Carachure, I., Hernández, M.A., et al., 2018. Vicarious social defeat stress induces depression-related outcomes in female mice. Biol. Psychiatry 83, 9–17. https://doi.org/10.1016/j.biopsych.2017.07.014.

Kähler, B., Romswinkel, E.V., Jakovcevski, M., Moses, A., Schachner, M., Morellini, F., 2021. Hyperfunction of the stress response system and novelty-induced hyperactivity correlate with enhanced cocaine-induced conditioned place preference in NCAM-deficient mice. Addict. Biol. 26 (2), e12887 https://doi.org/10.1111/adb.12887.

Kiely, K.M., Brady, B., Byles, J., 2019. Gender, mental health and ageing. Maturitas 129, 76–84. https://doi.org/10.1016/j.maturitas.2019.09.004.

Knouse, M.C., Brian, L.A., 2021. Behavioral sex differences in cocaine and opioid use disorders: the role of gonadal hormones. Neurosci. Biobehav. Rev. 128, 358–366. https://doi.org/10.1016/j.neubiorev.2021.06.038.

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

Madison, C.A., Debler, R.A., Vardeleon, N.I., Hillbrick, L., Jayaraman, A., Safe, E., et al., 2022. Sex-dependent differences in the stress mitigating and antidepressant effects of selective aryl hydrocarbon receptor modulators. J. Affect. Disord. 319, 213–220. https://doi.org/10.1016/j.jad.2022.09.155.

Marchette, R.C.N., Bicca, M.A., Santos, E.C.D.S., de Lima, T.C.M., 2018. Distinctive stress sensitivity and anxiety-like behavior in female mice: strain differences matter. Neurobiol. Stress 9, 55–63. https://doi.org/10.1016/j.ynstr.2018.08.002.

Montesinos, J., Pascual, M., Pla, A., Maldonado, C., Rodríguez-Arias, M., Miñarro, J., et al., 2015. TLR4 elimination prevents synaptic and myelin alterations and long-term cognitive dysfunctions in adolescent mice with intermittent ethanol treatment. Brain Behav. Immun. 45, 233–244. https://doi.org/10.1016/j.bbi.2014.11.015.

Morais-Silva, G., Campbell, R.R., Nam, H., Basu, M., Pagliusi, M., Fox, M.E., et al., 2023. Molecular, circuit, and stress response characterization of ventral pallidum Npas1-neurons. J. Neurosci. 43, 405–418. https://doi.org/10.1523/JNEUROSCI.0971-22.2022.

Oshiro, W.M., McDaniel, K.L., Beasley, T.E., Moser, V., Herr, D.W., 2022. Impacts of a perinatal exposure to manganese coupled with maternal stress in rats: learnin, memory and attentional function in exposed offspring. Neurotoxicol. Teratol. 91, 107077 https://doi.org/10.1016/j.ntt.2022.107077.

Pagliusi Jr., M., Franco, D., Cole, S., Morais-Silva, G., Chandra, R., Fox, M.E., et al., 2022. The BDNF-TrkB pathway acts through nucleus accumbens D2 expressing neurons to mediate stress susceptible outcomes. Front. Psychol. 13, 854494 https://doi.org/10.3389/fpsyt.2022.854494.

Qi, G., Zhang, P., Li, T., Li, M., Zhang, Q., He, F., et al., 2022. NAc-VTA circuit underlies emotional stress-induced anxiety-like behavior in the three-chamber vicarious social defeat stress mouse model. Nat. Commun. 13, 577. https://doi.org/10.1038/s41467-022-28190-2.

Ribeiro Do Cuoto, B., Aguilar, M.A., Luch, J., Rodríguez-Arias, M., Miñarro, J., 2009. Social experiences affect reinstatement of cocaine-induced place preference in mice. Psychopharmacology 207 (3), 485–498. https://doi.org/10.1007/s00213-009-1678-1.

Ródenas-González, F., Arenas, M.C., Blanco-Gandía, M.C., Manzanedo, C., Rodríguez-Arias, M., 2023. Vicarious social defeat increases conditioned rewarding effects of cocaine and ethanol intake in female mice. Biomedicines 11 (2), 502. https://doi.org/10.3390/biomedicines11020502.

Ruisoto, P., Contador, I., 2019. The role of stress in drug addiction. An integrative review. Physiol. Behav. 202, 62–68. https://doi.org/10.1016/j.physbeh.2019.01.022.

Sexton, H.G., Olszewski, N.A., Risher, M.L., 2022. The effects of rosiglitazone on task specific anxiety-like behavior and novelty seeking in a model of chronic adolescent unpredictable stress. Front. Behav. Neurosci. 16, 830310 https://doi.org/10.3389/fnbeh.2022.830310.

Sial, O.K., Warren, B.L., Alcantara, L.F., Parise, E.M., Bolaños-Guzmán, C.A., 2016. Vicarious social defeat stress: bridging the gap between physical and emotional stress. J. Neurosci. Methods 258, 94–103. https://doi.org/10.1016/j.jneumeth.2015.10.012.

Sial, O.K., Gnecco, T., Cardona-Acosta, A.M., Vieregg, E., Cardoso, E.A., Parise, L.F., et al., 2021. Exposure to vicarious social defeat stress and Western-style diets during adolescence leads to physiological dysregulation, decreases in reward sensitivity, and reduced antidepressant efficacy in adulthood. Front. Neurosci. 15, 701919 https://doi.org/10.3389/fnins.2021.701919.

Swaab, D.F., Bao, A.M., 2020. Sex differences in stress-related disorders: major depressive disorder, bipolar disorder, and posttraumatic stress disorder. Handb. Clin. Neurol. 175, 335–358. https://doi.org/10.1016/B978-0-444-64123-6.00023-0.

Takahashi, A., Chung, J.-R., Zhang, S., Zhang, H., GrossmanY, Aleyasin H., et al., 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.

Toledo-Rodriguez, M., Sandi, C., 2011. Stress during adolescence increases novelty seeking and risk-taking behavior in male and female rats. Front. Behav. Neurosci. 5, 17. https://doi.org/10.3389/fnbeh.2011.00017.

Tzeng, W.Y., Cherng, C.F.G., Wang, S.W., Yu, L., 2016. Familiar companions diminish cocaine conditioning and attenuate cocaine-stimulated dopamine release in the nucleus accumbens. Behav. Brain Res. 306, 146–153. https://doi.org/10.1016/j.bbr.2016.03.034.

Vidal-Infer, A., Arenas, M.C., Daza-Losada, M., Aguilar, M.A., Miñarro, J., Rodríguez-Arias, M., 2012. High novelty-seeking predicts greater sensitivity to the conditioned rewarding effects of cocaine. Pharmacol. Biochem. Behav. 102 (1), 124–132. https://doi.org/10.1016/j.pbb.2012.03.031.

Volkow, N.D., Boyle, M., 2018. Neuroscience of addiction: relevance to prevention and treatment. Am. J. Psychiatry 175, 729–740. https://doi.org/10.1176/appi.ajp.2018.17101174.

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. Psychiatry 88, 381–391. https://doi.org/10.1016/j.biopsych.2020.02.004.

Zakaria, N.H., Sukardi, S., 2019. Determination of the Whitten effect based on vaginal cell characteristics, vulva appearance and behavior in grouped female mice. Life Sci. Med. Biomed. 3, 8. https://doi.org/10.28916/lsmb.3.8.2019.56.

Zerning, G., Pinheiro, B.S., 2015. Dyadic social interaction inhibits cocaine-conditioned place preference and the associated activation of the accumbens corridor. Behav. Pharmacol. 26 (6), 580–594. https://doi.org/10.1097/FBP.0000000000000167.