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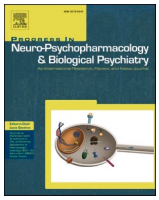

Dose-dependent modulation of social and motivational behavior by lurasidone in a rat model of social defeat

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ABSTRACT

Chronic psychosocial stress is a key risk factor for psychiatric disorders, often causing motivational and social impairments poorly responsive to conventional pharmacotherapies. The present study investigated the effects of chronic lurasidone treatment on behavioral and molecular alterations induced by prolonged social defeat (SD) stress in adult male rats. Rats underwent resident–intruder SD paradigm for approximately seven weeks and treated orally with lurasidone (1 or 3 mg/kg/day) during the final three weeks. Motivational drive was assessed using sucrose self-administration under fixed and progressive ratio schedules, while sociability was evaluated through social interaction tests. Molecular analysis quantified DARPP-32 dopaminergic response to social stimuli and gene expression [immediate early genes (Arc, c-Fos, Npas4, Zif268) and glucocorticoid-responsive genes (Sgk1, Fkbp5, Dusp1, Nr4a1)] across corticolimbic regions, including the nucleus accumbens and prefrontal cortex.

SD stress caused anhedonia and social withdrawal. Treatment with lurasidone at 3 mg/kg, but not 1 mg/kg, effectively restored motivational performance, as indicated by normalized breaking points in the progressive ratio task. Both doses ameliorated the stress-induced social deficits, and DARPP-32 responses, although with different magnitudes. At the molecular level, SD disrupted activity-dependent and glucocorticoid-responsive transcription and functional coupling between brain regions. Lurasidone reinstated coordinated network activation, particularly during social stimulation, suggesting a dose- and context-dependent facilitation of neuronal plasticity.

Overall, chronic lurasidone treatment counteracts stress-induced impairments in motivation and sociability through the restoration of corticolimbic network activity. Such effects may underlie its clinical efficacy in addressing negative and motivational symptoms across affective and psychotic disorders.

1. Introduction

Anhedonia is a core transdiagnostic feature of several psychiatric disorders, most prominently depression and psychosis. Clinically, it presents a marked reduction in interest or pleasure across nearly all activities, diminished responsiveness to rewarding stimuli, and a lack of motivation to pursue rewards. These deficits are associated with poorer treatment outcomes and an overall worse prognosis, encompassing physical, psychological, and functional impairments (Wong et al., 2024). Motivational anhedonia, reflecting impairments in the willingness to exert effort for reward, has been linked to reduced responsiveness of mesolimbic dopaminergic pathways (Treadway and Zald, 2011). Importantly, the presence of anhedonia is associated with increased suicide risk and, when expressed during adolescence, is considered a significant predictor of later psychopathology (Yang et al., 2022; Gooding et al., 2017; Gabbay et al., 2015; Olino et al., 2015).

Among the multiple factors contributing to anhedonia, chronic psychosocial stress stands out as a major risk factor. Psychosocial stress plays a principal role in the onset and progression of different psychiatric conditions, including major depression, anxiety disorders, and

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schizophrenia (Hammen, 2005; Riboni and Belzung, 2017; Duchaine et al., 2020). Repeated exposure to negative social events disrupts neural circuits governing reward processing and goal-directed behavior, leading to motivational impairments such as anhedonia, social withdrawal, and reduced engagement in everyday activities. Social impairment is especially debilitating, as it diminishes functional recovery, sometimes persists during remission and profoundly affects quality of life (Kupferberg et al., 2016; Porcelli et al., 2020).

Despite its clinical relevance, effective prevention and treatment strategies for the different forms of anhedonia remain limited. Standard antidepressants and antipsychotics may improve mood or psychotic symptoms but rarely normalize goal-directed behavior or restore social engagement. This therapeutic gap highlights the need for compounds with pro-motivational properties capable of reversing stress-induced impairments in reward-related behavior without worsening other psychiatric symptoms.

Lurasidone is a second-generation antipsychotic drug characterized by a multi-receptor profile with high affinity for dopamine D_2 and serotonin 5-HT_7, 5-HT_{2A} and 5-HT_{1A} receptors, which may confer antidepressant properties in addition to its antipsychotic activity. Consistent with this profile, lurasidone has demonstrated efficacy in reducing depressive symptoms in schizophrenia and other psychiatric disorders (Fiorillo et al., 2024; Feng et al., 2024). Moreover, the receptor profile of lurasidone suggests the potential to modulate motivational processes via mesolimbic and mesocortical pathways. In line with this, recent work from our group demonstrated that chronic lurasidone treatment effectively reversed an anhedonic phenotype and motivational deficits in the unavoidable chronic stress paradigm based on nociceptive stimulation, restoring dopaminergic responses to salient cues within the mesolimbic circuit (Corridori et al., 2025). In line with these data, lurasidone attenuated the negative consequences of social isolation stress in male mice via modulation of dopaminergic transmission (Umamichi et al., 2026). Additional evidence shows that lurasidone relieves anhedonia and enhances neuroplasticity in rodent chronic mild stress models (Luoni et al., 2015; Calabrese et al., 2020; Cattaneo et al., 2020).

These findings raise the question of whether lurasidone can also mitigates motivational deficits arising specifically from psychosocial forms of stress. To address this, the present study employs the social defeat (SD) paradigm, an ethologically relevant model of social stress, to characterize stress-induced impairments in reward-related and social behaviors. We assessed whether long-term lurasidone administration mitigates motivational anhedonia and social dysfunction and restores reactivity to positive stimuli, such as social interaction. Furthermore, we examined activation and functional co-activation patterns across four brain regions central to motivation and sociability, the prefrontal cortex (PFC), amygdala (AMY), ventral hippocampus (VH), and nucleus accumbens (NAc), both at baseline and following a social interaction task. In parallel, we evaluated glucocorticoid-responsive gene expression to assess stress-related transcriptional adaptations across treatment conditions. Together, these analyses aim to clarify whether lurasidone possesses pro-motivational properties capable of counteracting the behavioral and neurobiological consequences of chronic psychosocial stress.

2. Materials and methods

2.1. Animals

Experiments were performed on male Sprague-Dawley rats (Charles River, Calco, Italy), 9–10 weeks old at the beginning of the study that were group-housed (4–5 per cage) for the entire experiment unless otherwise specified. Adult male retired breeder Long Evans rats, single-housed, were used as resident aggressors for the social defeat stress paradigm (Becker et al., 2008). All rats were housed under controlled conditions (temperature 21–24 °C, humidity 40–60%) with ad libitum access to food and water and maintained on a reversed 12 h light/dark cycle (dark phase 07:00–19:00). Before testing, animals were habituated for 10 min to the housing environment, handling, and the behavioral testing rooms to minimize anxiety and stress. Animals were allocated to experimental groups using a weight-balanced procedure to ensure comparable mean body weights across groups at baseline. Behavioral testing and outcome assessments were conducted by experimenters blinded to group allocation whenever feasible; however, blinding was not possible during procedures requiring direct intervention (e.g., stress induction). Sample size was determined based on previous studies employing similar experimental paradigms and endpoints.

All procedures were conducted in accordance with European Directive (2010/63/EU) and Italian legislation (D. Lgs. 26/2014) on the use and care of laboratory animals and were approved by the University of Siena Animal Welfare Body and the Italian Ministry of Health (Authorization No. 366/2022-PR). Every effort was made to minimize animal suffering and to reduce the number of animals used.

2.2. Drugs and chemicals

Lurasidone (kindly supplied by Sumitomo Pharma) was dissolved in a vehicle solution consisting of deionized water with 1% (*w/v*) hydroxyethylcellulose (HEC). The compound was delivered once daily by oral gavage at doses of 1 or 3 mg/kg, using a final administration volume of 1 mL/kg body weight. Control animals received an equivalent volume of vehicle solution. Lurasidone doses (1 and 3 mg/kg) were selected based on previous evidence of behavioral efficacy at 3 mg/kg (Corridori et al., 2025) and to define the minimal effective dose endowed with pro-motivational and pro-social properties.

2.3. Social defeat stress paradigm

The chronic stress was induced through the resident-intruder paradigm (Koolhaas et al., 2013; Liu et al., 2017) and outlined in Fig. 1. Male Sprague-Dawley rats (*intruders*) were exposed to an aggressive adult male Long-Evans rat (*resident*) every other day. At the beginning of each session, the *intruder* was placed in the home cage of a *resident* for direct physical interaction lasting up to 5 min. To protect the *intruder,* the interaction was interrupted as soon as it displayed a submissive posture or an immobilized behavior for approximately 5 s. At this point, the animals were separated by a perforated Plexiglas barrier that remained in place for 55 min, allowing continuous visual, olfactory, and auditory contact without further physical aggression. Different *residents* were used across sessions to avoid habituation. This procedure reliably induces a state of submission and psychosocial stress (social defeat) that persists throughout the experimental protocol (Crawford et al., 2013; Koolhaas et al., 1997). The exposure continued every other day until the end of the experiment, for approximately 8 weeks.

2.4. Sucrose self-administration

The sucrose self-administration experiments were conducted, according to Scheggi et al., 2018b, in operant conditioning chambers (MED Associates Inc., St. Albans, VT, USA) equipped with two levers: pressing the active lever delivered a sucrose pellet (unflavored dustless precision pellets 45 mg, Bio-Serv, Frenchtown, NJ, USA) into the food receptacle, whereas the inactive lever produced no programmed consequence. Experimental events and data collection were managed using MED Associates software (MED Associates Inc.). All rats had free access to the standard diet before and after the sessions and were never food deprived. Rats' training began under a fixed ratio 1 (FR1) schedule until control rats reached a criterion of $\geq$50 responses/session for two consecutive days, and the schedule was shifted to FR5. Once the control group reached $\geq$40 responses/session under FR5, all animals were tested under a progressive ratio (PR) schedule, in which the response requirement increased by three lever presses (PR3) for each successive reward. Sessions under FR1 and FR5 lasted 15 min, whereas PR sessions

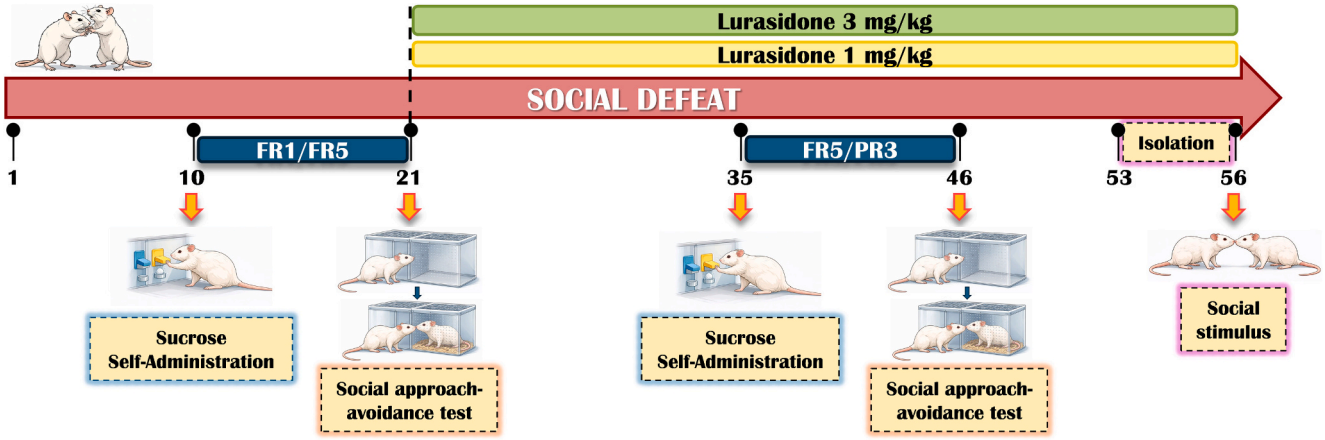

Fig. 1. Outline of the experimental protocol.
Rats were assigned to a non-stressed control group (CTR, $n = 16$) or a social defeat stress group (SD, $n = 43$). On day 10, both groups began operant training for sucrose self-administration (FR1 and FR5). On day 21, animals were randomized to receive vehicle (CTR + Vehicle, n = 16; SD + Vehicle, $n = 18$) or lurasidone (SD + Lurasidone 1 mg/kg, $n = 11$; SD + Lurasidone 3 mg/kg, $n = 12$). Stress exposure and drug treatment continued to the end of the experiments. After 14 days of treatment, sucrose self-administration was resumed (FR5 and PR), followed by social interaction and social avoidance tests. After behavioral testing, animals were isolated for 72 h, and half were then exposed to a social stimulus for subsequent neurochemical analyses. FR, fixed ratio; PR, progressive ratio.

terminated when no reinforcer was obtained within 5 min. The breaking point (BP), defined as the number of lever presses in the last completed ratio (Hodos, 1961), was used as an index of motivation (Larson et al., 2011; Ducasse et al., 2021), reflecting the maximum effort the subject is willing to exert to pursue a reward. Since rats were nonfood deprived, sucrose seeking was not influenced by caloric need. A motivational deficit was defined as a lever-pressing rate below 60% of the control group in FR1 and FR5 schedules (Marchese et al., 2013; Scheggi et al., 2015, 2016, 2018b). Rats exposed to the chronic stress procedure underwent stress sessions in the afternoon, 3–4 h after the end of self-administration.

2.5. Social approach-avoidance test

The social approach-avoidance test, modified from (Haller and Bakos, 2002), was conducted in a clean cage (84 × 57 × 40 cm) placed in an unfamiliar room. A wire mesh cage was positioned along one side wall. Each experimental rat was transferred to the test room and allowed to explore the cage freely for 2 min. Then, during the first test session (5 min), an empty wire mesh cage (No target) was positioned along one side wall, and the rat was free to explore the cage. In the following second session (5 min), the experimental rat was reintroduced to the same cage, but the wire mesh cage now contained an unfamiliar conspecific rat (Target). Behavioral parameters were measured, including time spent exploring the No target and the Target, the time spent avoiding the target or remaining in the "safe" zone of the cage. Preference for social interaction (social interaction ratio) was calculated by comparing exploration time of the Target versus No target.

2.6. Social interaction test

To evaluate the ability to interact with a specific novel, social stimulus, one week after the end of the behavioral experiments, all animals were housed individually for 3 days and on the fourth day in a novel clean cage rats were exposed for 10 min to a conspecific never encountered before (social stimulus, +) or were not exposed to the stimulus (control, −). A total of 10 animals (not used in any procedure) were used as a social stimulus for each experimental protocol. The time spent interacting with the social stimulus and avoidance behavior were measured. It is important to underline that in addition to quantitative reduction in social interaction, socially defeated rats exhibited also a qualitatively different pattern of social behavior, characterized by predominant freezing, avoidance and submissive posture (Fig. S1 - Supplementary). After 30 min from the exposure to the stimulus (or to the same context without the stimulus), rats were sacrificed by decapitation.

2.7. Brain sampling

Different brain regions such as the prefrontal cortex (PFC), nucleus accumbens (NAc), ventral hippocampus (VH), and amygdala (AMY) were rapidly excised using the head-freeze dissection technique from slices identified based on the Atlas of the Rat Brain (Paxinos and Watson, 2007). The following coordinates were used: PFC: AP +2.70 mm, ML ±1.0 mm, DV ~5.0 mm, corresponding to plate 9; NAc: AP +1.70 mm, ML ±1.0 mm, DV ~6.5 mm, corresponding to plate 11; AMY: AP −2.80 mm, ML ±5.0 mm, DV ~8.0 mm, corresponding to plate 31; VH: AP −5.20 mm, ML ±5.0 mm, DV ~6.0 mm, corresponding to plate 40. The samples were snap-frozen on dry ice and stored at −80 °C until RNA extraction or immunoblotting.

2.8. Immunoblotting

Immunoblotting was performed as detailed in Scheggi et al., 2020. Briefly, brain tissues were sonicated in 10 volumes of RIPA buffer containing protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA), 50 mM sodium fluoride (NaF), 4 mM phenylmethylsulfonyl fluoride (PMSF), then centrifuged at 12,000 ×*g* for 10 min at 4 °C to remove cell debris. The samples, containing 30 μg of total protein, were loaded on precast polyacrylamide gels (4%–15% Criterion TGX Stain-Free Precast Gel; Bio-Rad Laboratories, Milan, Italy) and separated by electrophoresis (SDS-PAGE) at 130 V for 60–90 min. Subsequently, the proteins were transferred to a nitrocellulose membrane using the Trans-Blot Turbo Transfer system (Bio-Rad Laboratories). The membranes were then blocked for 2 h at room temperature with 3% BSA (Sigma-Aldrich) in TRIS-buffered saline (20 mM Tris Base, 150 mM NaCl) containing 0.1% Tween 20, followed by overnight incubation with primary antibodies at 4 °C. The membranes were probed with the following antibodies: anti-DARPP-32 (Cell Signaling Technology, Beverly, MA, USA, #2302), anti-phospho-Thr34 DARPP-32 (PhosphoSolutions, Aurora, CO, USA, #p1025–34) and anti-β-actin (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA, #MA5–11869). Following three 10-min washes, the membranes were incubated with HRP-conjugated secondary antibodies. Antibody binding was detected using Clarity ECL

substrate (Bio-Rad Laboratories). Band intensities were quantified using the Image Lab software and Gel Doc XRS+ system (Bio-Rad Laboratories). Phospho-protein levels were normalized to those of total unphosphorylated protein, while total protein levels were normalized to β-actin levels. The values expressed in arbitrary units were then calculated as a percentage of the non-stressed + vehicle group (CTR + VEH).

2.9. Real time PCR analyses

Total RNA was extracted from the different brain regions (PFC, NAc, VH and AMY) of all animals.

RNA extraction was performed using the PureZol reagent (Bio-Rad Laboratories) according to the manufacturer's protocol. Next, the RNA was submitted to DNase treatment to avoid DNA contamination. RNA concentration was measured at NanoDrop spectrophotometer (Thermo Fisher Scientific) and further diluted at 10 ng/ul for quantitative real-time polymerase chain reaction (qRT-PCR) (CFX384 real-time system, Bio-Rad Laboratories). All samples were run in a 384 wells plate in triplicates with GAPDH as internal control (housekeeping gene). Primers and probes were purchased from Thermo Fisher Scientific or Eurofins Genomics (Ebersberg, Germany), and their ID's or sequences are shown in Table S1 (supplementary). The efficiency corrected model was used for qRT-PCR analysis, in which the amplification efficiencies of target and housekeeping genes were considered. Data are presented as fold change % compared to the CTR + VEH group (set at 100%).

2.10. Statistical analyses

Statistical analyses were performed on commercially available software (GraphPad Prism 8 statistical package, GraphPad, San Diego, CA). Normality and homoscedasticity of data distribution were tested using Kolmogorov–Smirnov and Bartlett's tests. Behavioral data were analyzed by unpaired Student's *t*-test or multiple ANOVA, as appropriate, for variables with normal distribution, followed by Bonferroni's multiple comparison test; otherwise, the groups were compared using the Kruskal-Wallis test and Dunn's post hoc analysis. Data from self-administration experiments (FR1 and FR5 protocols) were analyzed by two-way repeated measures ANOVA (RM ANOVA), with condition (stress or/and lurasidone treatment) as the between-subject factor and session as the within-subject factor. Data from the PR schedule of self-administration experiments and social interaction were analyzed using one-way ANOVA. The neurochemical data (phosphorylation levels of Thr34 DARPP-32) were subjected to two-way ANOVA with condition (stress or/and lurasidone treatment) as the between-subject factor and social interaction as the within-subject factor. Data are presented as mean ± SEM. Statistical significance was set at $p < 0.05$.

Correlation analyses and simple linear regressions were performed to investigate the relationship between sucrose preference tasks (FR5 and BP) and the social interaction task. To further assess potential group differences in functional restoration, we employed an ANCOVA-based approach to compare regression lines for both BP and FR5. Specifically, we tested the equality of slopes and elevations (intercepts). When the null hypothesis of equal slopes was not rejected ($P > 0.05$), a pooled slope was calculated to determine the common rate of change across groups, which subsequently allowed for the comparison of elevations.

For an integrated molecular overview, a *Z*-score value was calculated considering the immediate early genes (IEGs: *Arc, Npas4, cFos* and *Zif268*) or the glucocorticoid-responsive genes (GCs: *Sgk1, Fkbp5, Dusp-1,* and *Nr4a1*) that were analyzed by qRT-PCR. The individual z-score per animal in each gene was obtained by utilizing the following formula: z-score = (x-μ)/σ; where x is the individual gene expression value of each animal, μ is the average gene expression of the control group, and σ is the standard deviation of the control group. To specifically underscore the effect of the social stimulus, the Z-score was also calculated relative to the mean (μ) and standard deviation (σ) of their respective baseline groups (same experimental condition without social stimulus). Next, the average of all IEGs or GCs Z-score per animal was calculated when the expression data for at least three genes were available.

For an integrated analysis of brain activation, correlation matrices for cerebral areas z-score of IEGs were computed using non-parametric Spearman Rank-Order correlations (ρ). To perform this statistical analysis and to plot the obtained data as heatmap GraphPad Prism 8 was utilized.

3. Results

3.1. Exposure of rats to the social defeat paradigms produces distinct behavioral alterations

SD exposure diminished social interaction (Fig. 2A–C) and motivation for sucrose reward (Fig. 2D–F). In the social approach-avoidance test, SD animals spent significantly less time interacting with a conspecific (target) (Fig. 2A, $t(57) = 10.10$, $p < 0.0001$, unpaired *t*-test), whereas exploration of the empty cage (no target) was unaffected by stress exposure (Fig. 2B, $t(57) = 10.10$, $p = 0.1156$,unpaired *t*-test), indicating preserved locomotor and exploratory activity. Consequently, SD rats showed a diminished preference for social over non-social stimuli, reflected in a lower social interaction ratio (Kim et al., 2017) (Fig. 2C, $t(57) = 7.67$, $p < 0.0001$, unpaired *t*-test). In the operant task under both FR1 (Fig. 2D) and FR5 (Fig. 2E) reinforcement schedules, the SD group displayed a markedly reduced tendency to press the active lever for sucrose rewards compared with the unstressed control group (RM Two-way ANOVA, FR1: stress: $F_{1, 55} = 64.82$, $p < 0.0001$; session: $F_{4, 220} = 20.91$, $p < 0.0001$; interaction: $F_{4, 220} = 7.77$, $p < 0.0001$; FR5: stress: $F_{1, 55} = 51.91$, $p < 0.0001$; session: $F_{2, 110} = 19.59$, $p < 0.0001$; interaction: $F_{2, 110} = 12.44$, $p < 0.0001$). Post hoc comparisons indicate that SD rats exhibited a marked reduction in lever presses across all sessions ($p < 0.01$ at session 1 in FR1, $p < 0.0001$ in all other sessions. Importantly, the number of incomplete trials was unaffected by stress, indicating that the performance deficit was not attributable to alterations in locomotor activity (Fig. S2 - supplementary).

We next evaluated a possible relationship between social and anhedonic-like behavioral alterations induced following the SD procedure (Fig. 2F). To this end, we correlated the time spent interacting with the social target during the social approach-avoidance test with the number of lever presses in the FR5 schedule. A strong positive correlation was observed between social interaction time and lever pressing in FR5 indicating that animals exhibiting lower social interaction also showed the highest reduction in motivational performance ($p = 0.004$). Notably, SD animals performed significantly worse than CTR animals across both behavioral domains.

3.2. Chronic treatment with lurasidone ameliorates motivational and social anhedonia observed in rats exposed to the social defeat paradigm

On day 21, once a condition of anhedonia and social impairment was established, animals belonging to the SD group were randomized to receive the antipsychotic drug lurasidone at doses of 1 or 3 mg/kg, while the remaining received vehicle.

As shown in Fig. 3 (A–B), lurasidone restored sucrose seeking only at the dose of 3 mg/kg (FR5, RM Two-way ANOVA: group: $F_{3, 53} = 16.23$, $p < 0.0001$; session: $F_{4, 212} = 36.36$, $p < 0.0001$; interaction: $F_{12, 212} = 10.55$, $p < 0.0001$; PR, One-way ANOVA: $F_{3, 53} = 16.50$, $p < 0.0001$). Under FR5 protocol (Fig. 3A), lurasidone 3 mg/kg significantly increased the number of lever presses to obtain sucrose pellets, thus leading to an attenuation of stress-induced motivational anhedonia already by the 4th session ($p < 0.05$ vs SD + VEH group), completely restoring the appetitive responses at session 5th ($p < 0.001$ vs SD + VEH group). Consistently, in the PR schedule of reinforcement (Fig. 3B, One-way ANOVA, $F_{3, 53} = 16.50$, $p < 0.0001$), lurasidone 3 mg/kg increased the appetitive motivation disrupted by social defeat ($p < 0.01$ vs SD + VEH) as shown by increased BP, while lurasidone 1 mg/kg did not

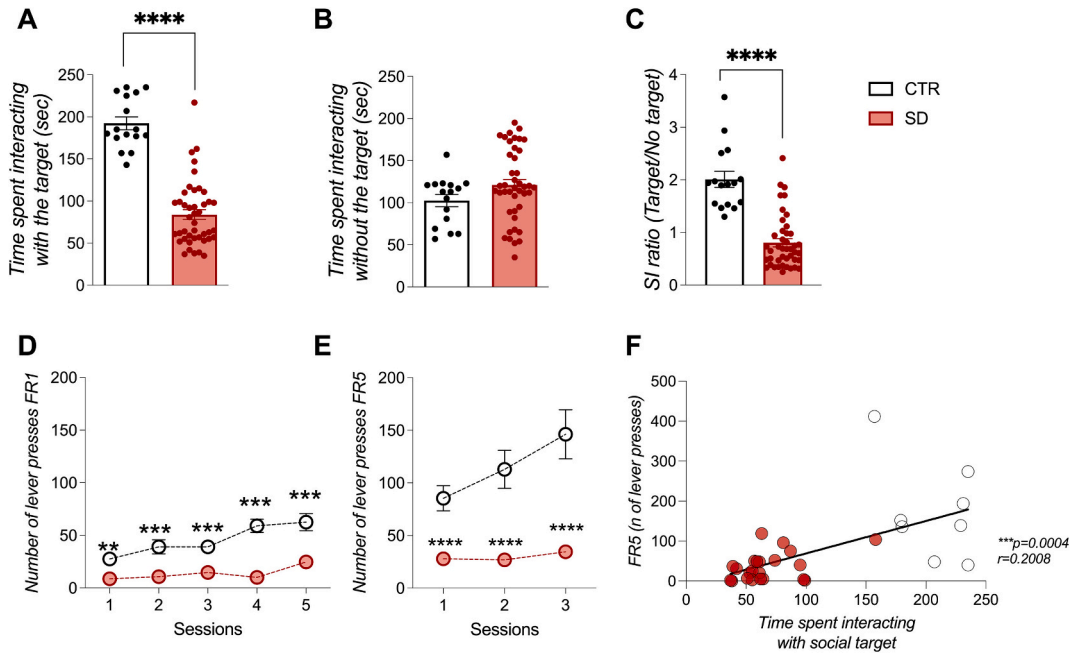

Fig. 2. Exposure to social defeat stress produces a reduction in social interaction and motivational performance.
(A–C) Sociability was assessed by the time spent with the social target (A), time spent without the social target (B), and the social interaction ratio (C) in control (CTR) and social defeat stress (SD) rats before treatment starts. ****$p < 0.0001$, unpaired Student's *t*-test.
(D–E) Sucrose self-administration was measured under FR1 (D) and FR5 (E) schedules. **$p < 0.01$, ***$p < 0.0001$, two-way RM ANOVA followed by Bonferroni's multiple comparisons test.
(F) Correlation between social interaction and FR5 performance. ***$p = 0.0004$, Simple linear regression. Data are presented as mean ± SEM of 16 CTR and 43 SD animals.

induce significant improvement in the anhedonic behavior. However, lurasidone 1 mg/kg showed partial effects limited to reward output measures without a significant impact on motivational breakpoint-related responding (Supplementary materials, Fig. S3). Lastly, at the end of the SA protocol, the animals were tested for changes in social interaction and avoidance behavior (Fig. 3C-E). Lurasidone at both doses significantly improved the social impairment, as evidenced by the increased time spent exploring the target (One-way ANOVA, $F_{3, 53} = 32.75$, $p < 0.0001$; $p < 0.001$ vs SD + LURA1 and SD + LURA3, Fig. 3D) or the social interaction ratio (One-way ANOVA, $F_{3, 53} = 18.00$, $p < 0.0001$; $p < 0.0001$ vs SD + LURA 1 and $p < 0.05$ vs SD + LURA3, Fig. 3E). In addition, the effect on social interaction seemed to be more pronounced in SD rats receiving lurasidone at the lower dose (1 mg/kg) ($p < 0.05$ SD + LURA1 compared to SD + LURA3, Fig. 3E). Remarkably, the effects of lurasidone at both doses on the time spent avoiding the target or remaining in the "safe" zone of the cage were less noticeable (One-way ANOVA, $F_{3, 53} = 3.163$, $p = 0.0319$, Fig. 3F). These findings suggest that lurasidone may exert stronger effects on behavioral activation than on behavioral inhibition.

Next, to integrate the results obtained in the previous tests and to attain an overall score of the effect of lurasidone on motivation toward natural stimuli we calculated a composite emotional Z score based on BP, time spent interacting with the target and social avoidance (Bordes et al., 2023), Fig. 3G. This emotionality index calculates *z*-scores for each behavioral test by normalizing individual rat in relation to control averages and the standard deviation for that specific behavior (Guilloux et al., 2011). The results showed that lurasidone significantly ameliorated impaired emotionality (One-way ANOVA, $F_{3, 53} = 27.90$, $p < 0.0001$). SD + VEH rats exhibited a markedly impaired behavioral profile compared to unstressed rats ($p < 0.0001$ vs CTR + VEH). In contrast, the treatment with lurasidone 3 mg/kg robustly restored both social and appetitive motivation ($p < 0.0001$ SD + LURA3 vs SD + VEH), whereas the 1 mg/kg dose produced only a partial improvement ($p < 0.01$ SD + LURA 1 vs SD + VEH).

Interestingly, as shown in Fig. 3H–I, the positive association between social interaction and motivational performance observed before treatment onset (see Fig. 2F) remained preserved following pharmacological intervention ($p < 0.0001$). Our linear regression analysis further supported this, revealing consistent response dynamics across groups, as indicated by non-significant differences in slopes for both FR5 and BP ($p > 0.05$). This finding suggests that improvements in social and motivational domains are functionally linked in socially defeated animals treated with lurasidone although, at the lower dose, the antipsychotic drug selectively enhanced social behavior without fully restoring motivational performance, as indicated by the increased dispersion of data points for this experimental group in the correlation plots.

To better understand the active response to a social challenge and correlate it to the modulation of specific neuronal circuits, half of the rats from the previous experiments were isolated for 72 h, exposed to a 10-min social interaction test, and sacrificed 30 min afterward (Fig. 4). In the response to reciprocal social interaction, only chronic lurasidone treatment at 3 mg/kg produced a significant increase of interaction time (Fig. 4A, One-way ANOVA: $F_{3, 25} = 8.864$, $p = 0.0004$; Bonferroni's multiple comparison test: $p = 0.003$ SD+ VEH vs CTR + VEH; $p = 0.0085$ SD + VEH vs SD + LURA3) and an attenuation of freezing behavior (Fig. 4B, Kruskal-Wallis test: $H_3 = 22.39$, $p < 0.0001$; Dunn's multiple comparisons test: $p < 0.0001$, SD+ VEH vs CTR + VEH; $p = 0.028$, SD + VEH vs SD + LURA3; $p = 0.176$, SD + VEH vs SD + LURA1; Fig. 4B). These results suggest that both doses effectively increase social behavior in response to passive social target (Fig. 3D-E), but only lurasidone 3 mg/kg is effective in the contexts requiring active, reciprocal social interaction with direct contact. Moreover, both doses were not significantly effective in reducing the number of submissive postures (Fig. 4C, Kruskal-Wallis test: $H_3 = 12.15$, $p < 0.01$), although a string trend was observed for the 3 mg/kg dose (Dunn's multiple comparisons test: $p = 0.079$, SD + LURA3 vs SD + VEH; $p = 0.505$, SD + LURA1 vs SD + VEH). These findings confirm that lurasidone may be more effective in improving SD-induced motivational deficits rather than submissive and

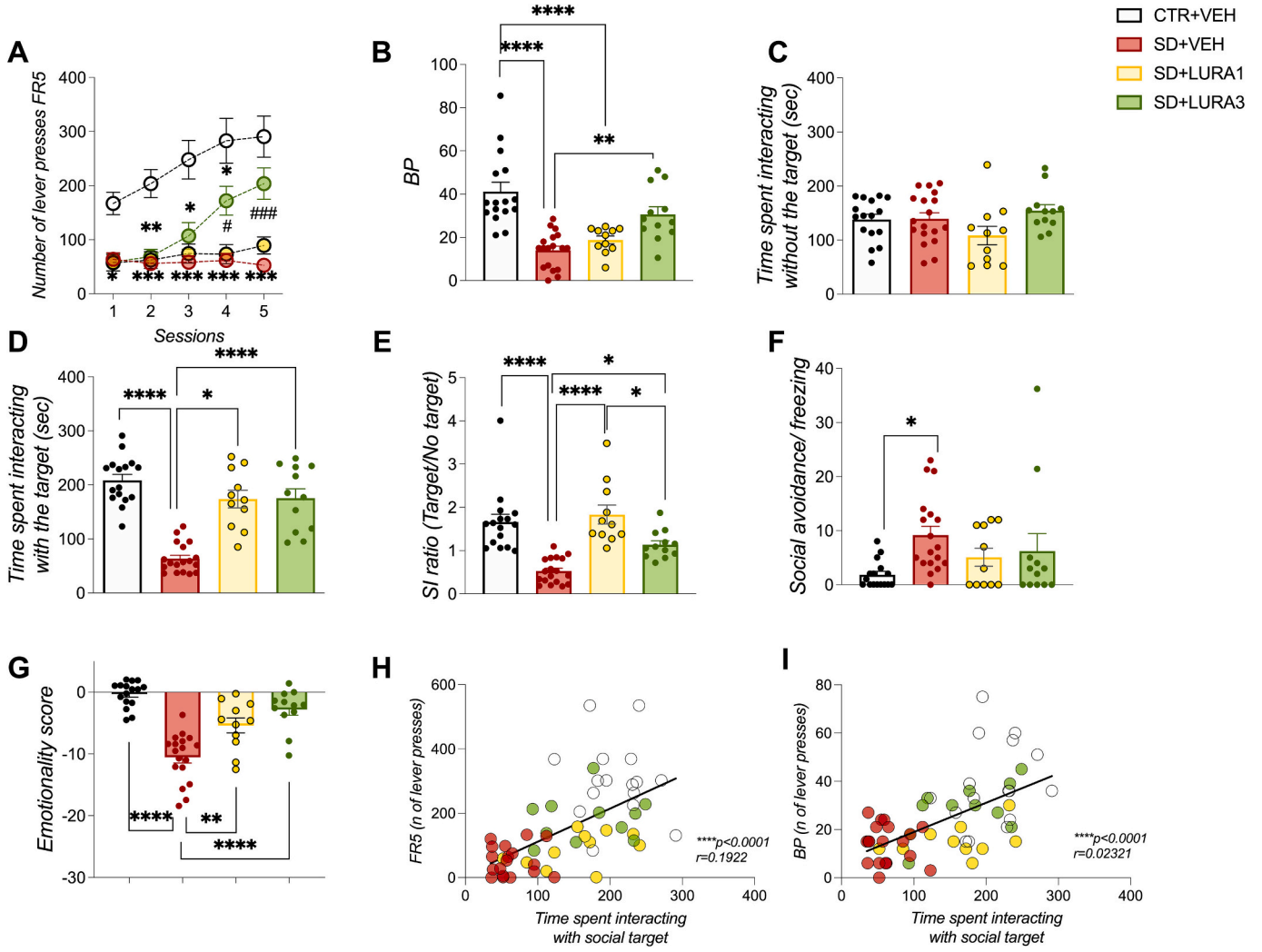

Fig. 3. Effects of lurasidone treatment on social defeat–induced impairments in sucrose self-administration and social interaction performance.
Behavioral analyses were performed in control animals (CTR + VEH) and in rats exposed to social defeat and treated with vehicle (SD + VEH) or lurasidone (1 mg/kg, SD + LURA1; 3 mg/kg, SD + LURA3) to assess motivation (A, B) and sociability (C–G). (A) Sucrose self-administration under the FR5 schedule; (B) Breaking point under the PR3 schedule; (C) Time spent without the target during social interaction; (D) Time spent with the target during social interaction; (E) Social interaction ratio; (F) Social avoidance; (G) Emotionality composite z-score based on breaking point, social interaction with target, and social avoidance. (H) Correlation between social interaction and FR5 performance. (I) Correlation between social interaction and breaking point.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$.
Data are presented as mean ± SEM of 11–16 animals per group.

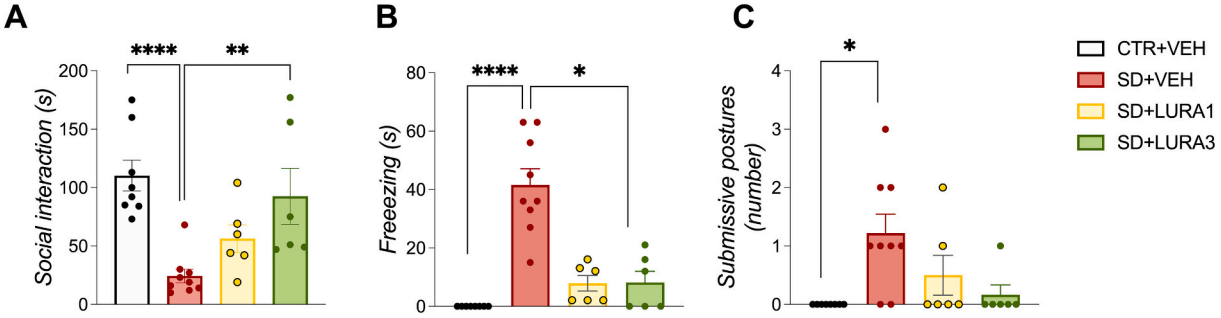

Fig. 4. Lurasidone dose-dependently rescues social interaction with a novel conspecific and reduces defensive behaviors in animals exposed to the social defeat stress.
The following parameters were assessed in control animals (CTR + VEH) and in rats exposed to social defeat and treated with vehicle (SD + VEH) or lurasidone (1 mg/kg, SD + LURA1; 3 mg/kg, SD + LURA3): (A) social interaction time; (B) freezing time; and (C) number of submissive episodes. $^{*}p < 0.05$, p < 0.01, $^{**}p <$ 0.0001; one-way ANOVA followed by Bonferroni's multiple comparison test (A) or Kruskal-Wallis test followed by Dunn's multiple comparison test (B, C). Data are presented as mean ± SEM of 6–9 animals per group.

defensive behavior.

Social interaction elicited a significant increase in DARPP-32 phosphorylation in the PFC (Fig. 5A) and NAc (Fig. 5B) of control animals, an effect that was blunted by social defeat stress. Remarkably, lurasidone restored the stress-impaired DARPP-32 phosphorylation response to social cues. Specifically, in the PFC, only the 3 mg/kg dose significantly increased DARPP-32 phosphorylation ($p < 0.0001$ vs SD + VEH + SI), restoring levels comparable to those observed in control rats (two-way ANOVA: group, $F_{3,\ 49} = 6.67$, $p = 0.0007$; social interaction, $F_{1,\ 49} = 13.70$, $p = 0.0005$; interaction, $F_{3,\ 49} = 4.92$, $p = 0.0045$). In contrast, in the NAc, both lurasidone doses were sufficient to reinstate phosphorylation responses to social interaction ($p < 0.05$ vs SD + VEH + SI), indicating a full recovery of reward sensitivity (two-way ANOVA: group, $F_{3,\ 49} = 3.42$, $p = 0.024$; social interaction, $F_{1,\ 49} = 5.52$, $p = 0.022$; interaction, $F_{3,\ 49} = 5.11$, $p = 0.0037$). No differences were detected in total DARPP-32 protein levels across groups (Fig. S4 - supplementary).

3.3. Analysis of activity-dependent gene expression patterns in animals exposed to social defeat and modulation by lurasidone treatment

To examine regional expression patterns in response to a social challenge as a function of prior stress exposure and lurasidone treatment, we analyzed the expression of four immediate early genes (IEGs) – Arc, c-Fos, Npas4, and Zif268 – as markers of neuronal activation (Fig. S5 – Supplementary). These genes were selected as sensitive molecular markers of neuronal activation and synaptic plasticity, reflecting early transcriptional responses to environmental stimuli. Transcript levels were quantified in the PFC, AMY, VH and NAc, which form a core network involved in emotional regulation, motivation, and stress adaptation. To visualize region-specific activation patterns, expression values were standardized using z-score transformation and represented in heatmaps, providing a quantitative overview of IEG activity across experimental conditions following social defeat and lurasidone treatment (Fig. 6A-B).

At baseline condition (Fig. 6A), SD animals displayed a comparable IEGs activation compared to CTR baseline (z-scores approximating zero or negative values across brain regions, SD + VEH vs. CTR + VEH). Low-dose lurasidone treatment (SD + LURA1) appeared to modulate IEG expression, with moderate increases observed in the NAc (3.81), whereas high-dose lurasidone (SD + LURA3) was associated with minor changes in expression (z-scores < 1.4 across brain regions, SD + LURA3 vs. CTR + VEH).

When analyzing the activity-dependent response to social interaction (SI) relative to the baseline condition (Fig. 6B), SI elicited distinct patterns of regional IEG activation across experimental groups. In control animals (CTR + VEH + SI vs. CTR + VEH), significant activation was observed throughout the different brain regions (z-score range: 1.9–3.07), suggesting the engagement of corticolimbic and mesolimbic circuits during social behavior. When considering socially defeated animals, SI resulted in a selective activation of these networks, with marked increases in the PFC (3.45) and NAc (2.54), and noticeable activation in the VH (2.57). In SD animals treated with the low dose of lurasidone (SD + LURA1), SI was associated with a pronounced increase in IEG activation, most notably in the VH (5.97) and AMY (3.72), together with a more limited response of the PFC (1.14). Similarly, SI was associated with robust activation in SD treated with the high dose of lurasidone (SD + LURA3) throughout the different brain regions (z-score range: 2.43–4.18).

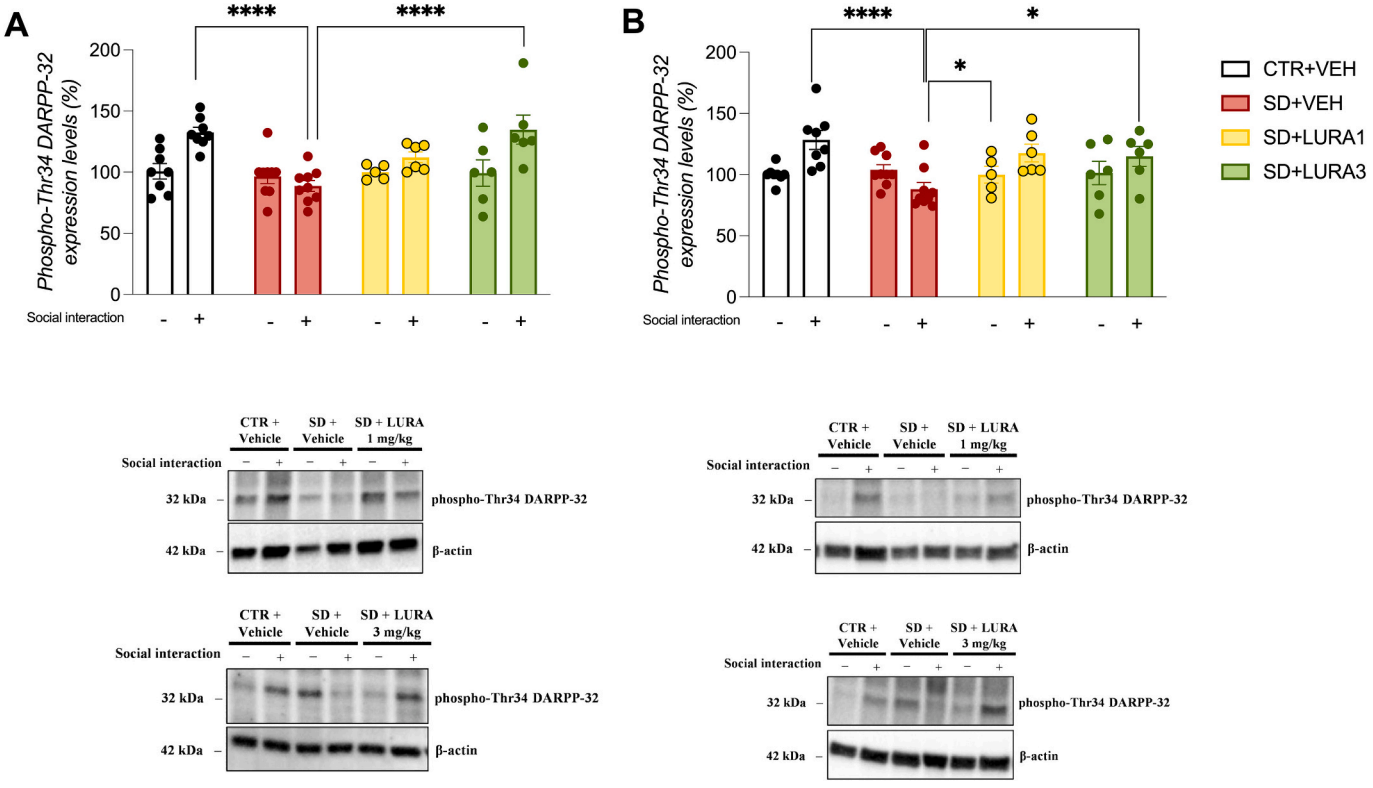

Fig. 5. Effects of lurasidone treatment on social cue–induced DARPP-32 phosphorylation in cortico-striatal regions after social defeat stress.
Phospho-Thr34 DARPP-32 levels were measured in PFC (A) and NAc (B) under basal conditions (no social interaction, SI−) and after social interaction with a novel conspecific (SI+) in control (CTR) and socially defeated (SD) animals treated with vehicle (VEH) or lurasidone (1 mg/kg, SD + LURA1; 3 mg/kg, SD + LURA3. Data are presented as mean ± SEM of 5–9 animals per group and are shown as percentage of CTR + VEH baseline values (SI−). *p < 0.05, ***p < 0.0001, two-way ANOVA followed by Bonferroni's multiple comparison test.

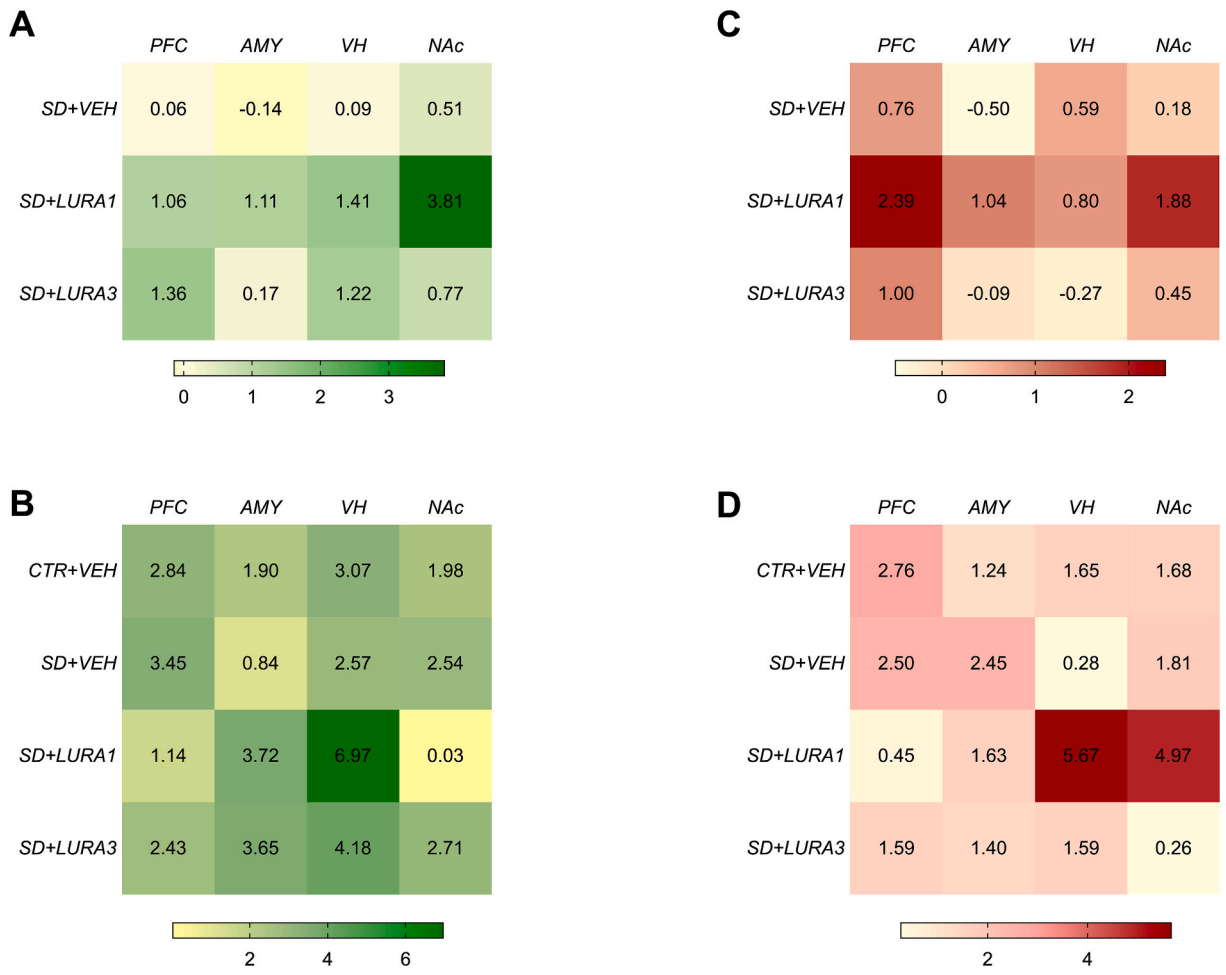

Fig. 6. Z-score heatmaps of brain activity and glucocorticoid-dependent transcription under basal conditions and following the social interaction test. Heatmaps show control animals (CTR + VEH) and rats exposed to social defeat and treated with vehicle (SD + VEH) or lurasidone (1 mg/kg, SD + LURA1; 3 mg/kg, SD + LURA3). (A) Basal neuronal activity, assessed by immediate early gene expression (Arc, c-Fos, Zif268, Npas4), expressed relative to CTR + VEH baseline values. (B) Neuronal activity after the social interaction test, expressed relative to baseline within each group. (C) Basal glucocorticoid-dependent transcription, assessed by GC-responsive genes (Sgk1, Fkbp5, Dusp-1, Nr4a1), expressed relative to CTR + VEH baseline values. (D) Glucocorticoid-dependent transcription after the social interaction test, expressed relative to baseline within each group. Positive and negative z-scores indicate increased or decreased activity or transcription, respectively. Data were analyzed by one-way ANOVA followed by Tukey's multiple comparisons test and visualized in GraphPad Prism 8.

3.4. Analysis of glucocorticoid responsive gene expression patterns in animals exposed to social defeat and modulation by lurasidone treatment

We next assessed the expression of glucocorticoid (GC)-responsive genes as molecular sensors of the physiological stress response (Fig. 6C-D). These genes provide an integrated readout of hypothalamic–pituitary–adrenal (HPA) axis engagement and its downstream impact on neural circuits. We first quantified their expression under baseline conditions to determine how exposure to social defeat and/or lurasidone treatment reshape the tonic responsiveness of the GR pathway (Fig. S4 - Supplementary). Analysis of the mean *Z*-scores for GC-responsive genes (SGK1, FKBP5, DUSP-1, NR4A1) revealed significant regional and condition-dependent modulation of gene expression relative to control animals. Under baseline conditions (Fig. 6C), social defeat alone produced z-score values close to those of CTR animals, with the AMY showing a slight decrease ($Z = -0.50$) and the NAc showing a small increase ($Z = 0.18$). Treatment with low-dose lurasidone (SD + LURA1) shifted baseline activation upward, as reflected by increased Z-scores across regions, particularly in the PFC ($Z = 2.39$) and in the NAc ($Z = 1.88$). In contrast, high-dose lurasidone (SD + LURA3) produced Z-scores that remained close to those observed in SD animals, with slight decreases in the VH ($Z = -0.27$).

We then examined the mean z-score expression of GC-responsive genes across the same brain regions, focusing specifically on the effect of social interaction relative to each group's basal levels (Fig. 6D). Control animals exposed to social interaction (CTR + VEH + SI) showed a moderate induction of GC responsive genes across all brain regions, indicating a coordinated GC transcriptional response to social engagement. Socially defeated rats exposed to social interaction (SD + VEH + SI) displayed elevated GC-gene expression in the PFC (=2.50), AMY (=2.45), and NAc (=1.81), but a markedly attenuated response in the VH (=0.28). This pattern suggests that SD selectively blunts hippocampal GC transcriptional reactivity while maintaining responsiveness in frontal and limbic regions. SD animals treated with the low-dose of lurasidone (SD + LURA1) display the most robust GC-gene activation following social interaction, with a pronounced induction in the VH (=5.67) and in the NAc (=4.97), along with elevated expression in the AMY (=1.63). When examining SD rats treated with the higher lurasidone dose (SD + LURA3), GC-gene transcription following SI remained moderate across all brain regions, indicating a positive, though less selective engagement of GC activation.

3.5. Anatomical patterns of co-activation in animals exposed to social defeat and modulation by lurasidone treatment (rho transformation)

To better understand how these brain regions interacted during the

different experimental conditions, we transformed the z-score values into correlation coefficients (ρ) to measure how strongly the activity of each region was related to the others. This analysis made it possible to identify patterns of co-activation and functional coordination across the PFC, AMY, VH and NAc (Fig. 7).

At baseline, CT animals displayed strong positive correlations among corticolimbic regions, notably between the PFC and NAc ($\rho = 0.93$) and VH and NAc ($\rho = 0.76$), reflecting a coordinated transcriptional profile. SD disrupted these associations, resulting in negative PFC–NAc coupling ($\rho = -0.56$) and overall reduction in inter-regional coordination, indicative of transcriptional dysregulation following stress exposure. Low-dose lurasidone treatment (SD + LURA1) partially modulated this coupling, with PFC–NAc correlation being zero and VH–NAc showing a modest positive correlation ($\rho \approx 0.10$), suggesting only limited normalization of these co-activation patterns. Conversely, SD animals treated with the high-dose of lurasidone (SD + LURA3) showed a strong negative correlation between VH and NAc ($\rho = -0.83$) and a modest reduction in PFC-NAc coupling ($\rho = -0.10$).

When analyzing the pattern of co-activation following the social interaction (SI) test, CTR animals maintained positive co-expression patterns, particularly in the PFC–NAc axis ($\rho = 0.69$), reflecting a standard pattern of coordinated activity-related gene expression. SD rats showed a negative correlation of VH-NAc ($\rho = -0.48$) indicating a disruption on the mesolimbic transcriptional profile. Interestingly, low-dose lurasidone combined with social interaction (SD + LURA1 + SI) re-established coherent co-expression across multiple pairs, including PFC–NAc ($\rho = 0.66$), suggesting a normalization of functional integration. In contrast, high-dose lurasidone combined with social interaction (SD + LURA3 + SI) displayed mixed effects, with strengthened AMY–NAc coupling ($\rho = 0.60$) but persistent negative coupling between VH and NAc ($\rho = -0.60$).

4. Discussion

The findings of this study provide new evidence that lurasidone restores motivational drive and sociability in this social defeat model, suggesting potential relevance for anhedonia- and social dysfunction-related phenotypes. Importantly, these domains are modulated in a dose-dependent fashion, supporting the idea that lurasidone engages distinct behavioral processes across different dosing conditions. Moreover, our data suggest that lurasidone may facilitate plasticity-related processes which, in conjunction with behavioral activation, could promote the adaptive re-engagement of neural systems involved in stress regulation, reward processing, and cognitive function that are disrupted by stress exposure. In this context, lurasidone may contribute to improved adaptive functioning in the face of stress (Dong et al., 2022).

Aversive and stressful experiences can exert profound consequences on motivational and emotional states, affecting reward processing, reinforcement learning, and decision making. Diminished responsiveness to rewarding stimuli may underlie motivational anhedonia, a core, and still clinically challenging, symptom across psychotic and mood disorders. In the present study, we adopted the social defeat stress paradigm, a validated model of psychosocial stress, to further investigate motivational dysfunction arising from socially driven stressors, as well as the potential of lurasidone to reverse these alterations. Psychosocial stress markedly reduced the motivation of rats to press a lever for reward. Notably, socially defeated rats treated with lurasidone at 3 mg/kg exerted greater effort to obtain sucrose pellets under both FR5 and PR schedules, indicating enhanced motivation toward the reward and reversal of motivational anhedonia. By contrast, the lower dose of lurasidone was ineffective on motivational outcomes, mirroring the lack of efficacy observed with the 10 mg/kg dose in the chronic unavoidable stress paradigm (Corridori et al., 2025). Together, these results suggest that optimal modulation of motivation may require a dose-dependent balance of lurasidone action at receptor level. Because lurasidone influences both phasic and tonic dopamine signaling through multiple mechanisms [(e.g. direct D2 receptor antagonism, indirect modulation via 5-HT2A and 5-HT7 receptor blockade, and, at lower doses, presynaptic dopamine autoreceptor inhibition (Wolke et al., 2019), different doses likely produce distinct patterns of receptor occupancy, resulting in dose-dependent behavioral effects. Importantly, the doses used in the present study fall within the lower range of clinically relevant exposure. In this context, lower doses—associated with a more limited D2 receptor occupancy—may preferentially modulate behavioral domains such as motivation and social functioning, supporting the idea that dose-dependent effects of lurasidone reflect distinct circuit-level mechanisms.

Fig. 7. Heatmaps of brain region co-activation under baseline conditions or following exposure to social interaction.
Heatmaps show pairwise co-activation patterns in control animals (CTR + VEH) and rats exposed to social defeat and treated with vehicle (SD + VEH) or lurasidone (1 mg/kg, SD + LURA1; 3 mg/kg, SD + LURA3) under basal conditions (top) and after the social interaction test (bottom). Co-activation was assessed in the PFC, AMY, VH, and NAc using Spearman's correlation coefficients (ρ) derived from z-score values of immediate early gene expression (Arc, c-Fos, Zif268, and Npas4) within each group. Positive and negative ρ values indicate increased or decreased co-activation between regions, respectively. Correlation matrices were visualized in GraphPad Prism 8.

The efficacy of lurasidone in reversing stress-induced motivational deficits aligns with our previous studies using different rodent stress paradigms. Repeated lurasidone administration has been shown to normalize consummatory anhedonia and cognitive impairment through different molecular pathways (Calabrese et al., 2020; Creutzberg et al., 2023; Luoni et al., 2015; Rossetti et al., 2016; Rossetti et al., 2018). More recently, in a model of nociceptive stress-induced anhedonia, repeated treatment with lurasidone at 3 mg/kg (but not 10 mg/kg) restored motivational deficits via activation of D1 dopaminergic signaling in the mPFC (Corridori et al., 2025). Some clinical findings also suggest that lurasidone enhances motivation in psychiatric patients. As an example, lurasidone combined with sulpiride improved psychosocial functioning and motivation/energy scores in schizophrenics (Zhao et al., 2025). Real-world data similarly show reductions in positive and negative symptoms, including anhedonia, abulia, and affective flattening, along with improved quality of life (De Filippis et al., 2024; Mora et al., 2025).

Our results also provide compelling evidence that both doses of lurasidone (1 and 3 mg/kg) alleviated stress-induced social deficits, a result of particular importance given the central role of sociability impairments across many psychiatric conditions. Exposure to the social defeat paradigm led to marked reductions in social interaction, increased avoidance of social contact, and heightened freezing and submissive behaviors. In our cohort, animals exposed to the SD protocol exhibited robust social deficits with a very low prevalence of stress resilience (only 2 animals showed resilience and were excluded from the analysis). This contrasts with reports from mouse models of SD stress, in which resilience rates of approximately 30–40% have been described (Krishnan et al., 2007). Indeed, social defeat stress affected both the quantity and the quality of social interactions, resulting in a behavioral profile dominated by defensive and submissive responses rather than reciprocal social engagement (Fig. S1). Notably, in rats exposed to SD, lurasidone restored social interaction with conspecifics, although it was less effective in diminishing avoidance responses. In this context, it is worth to emphasize that lurasidone at both doses facilitates social approach behavior toward a social stimulus per se. However, only lurasidone at 3 mg/kg was effective in attenuating social deficits in a paradigm involving bidirectional, physically interactive social engagement. Clinical research has increasingly emphasized patient-reported outcomes that reflect meaningful functional goals. Among these, life engagement has emerged as a multidimensional construct encompassing motivation, vitality, and broader emotional, physical, social, and cognitive aspects of well-being. Life engagement captures positive health capacities such as pleasure, well-being, and participation in family, social, and community activities, contributing substantially to functional recovery beyond symptom remission. Consistent with this framework, post-hoc analyses from the JEWEL study show that lurasidone improves both the PANSS life-engagement subscale (Maruyama et al., 2024) and the PANSS prosocial subscale (Miura et al., 2024), each reflecting the ability to re-establish meaningful social roles. Similarly, in bipolar disorder, lurasidone has been associated with significant improvements in social relationships compared with placebo (Dembek et al., 2022).

It is worth noting that while both doses improved sociability, only the 3 mg/kg dose enhanced motivation. This pattern suggests that motivational and social deficits may stem from partially distinct neural circuits that are differentially sensitive to lurasidone in a dose-dependent and circuit-specific manner.

The dose-dependent behavioral effects were mirrored by corresponding changes in DARPP-32 phosphorylation within the NAc and PFC following exposure to social cues. We have previously shown that lurasidone normalizes stress-induced reductions in DARPP-32 phosphorylation at Thr34, highlighting its capacity to modulate dopamine-dependent processes involved in motivation and emotional regulation (Corridori et al., 2025). In the present study, socially defeated animals exhibited a blunted DARPP-32 phosphorylation response to social interaction in both the PFC and NAc. Notably, treatment with lurasidone at 3 mg/kg restored Thr34 phosphorylation to levels comparable to non-defeated controls. These findings are consistent with previous reports showing that interventions capable of reinstating Thr34 phosphorylation in the NAc in animal models of anhedonia often reinstate motivation for rewards, underscoring the link between dopamine signaling and motivational drive mediated through this pathway (Scheggi et al., 2018a, 2018b). Interestingly, lurasidone at 1 mg/kg, which was effective in improving sociability but not motivation, was nonetheless able to enhance the stress-compromised phosphorylation response in the NAc. Overall, our data highlight a potential link between motivational and social dysfunction and, for the first time, demonstrate that lurasidone can ameliorate both domains, despite dose-dependent differences in sensitivity across behavioral measures.

To understand the mechanisms underlying lurasidone efficacy in the animals exposed to SD, we investigated how chronic stress modifies transcriptional activity and coordinated expression patterns within corticolimbic–mesolimbic regions during a social challenge, and how pharmacological treatment modifies these stress-induced changes. At baseline, SD displayed comparable immediate early gene activation across prefrontal, hippocampal, amygdalar, and accumbal regions compared to control animals as reflected by z-scores approximating zero. This finding is consistent with evidence that social defeat primarily manifests as altered stimulus- or stress-induced responsivity, rather than as stable changes in basal transcriptional activity. Indeed, chronic social defeat has been shown to leave baseline IEG expression largely intact, while modifying the magnitude and spatial coordination of activity-dependent gene induction following environmental or pharmacological challenges (Paul et al., 2011; Ritger et al., 2023). In parallel, glucocorticoid-responsive gene expression at baseline showed modest, region-specific alterations rather than a global suppression (Göver and Slezak, 2024). When exposed to the social cue, control animals showed coordinated activation across corticolimbic–mesolimbic regions, whereas defeated animals displayed only partial expression patterns, suggesting a constrained capacity for transcriptional coordination following chronic stress.

Lurasidone facilitated neural activation primarily in a dose-dependent manner: low-dose lurasidone was associated with higher IEG expression within the NAc, a key region for social reward and motivation. In contrast, the higher dose resulted in minor changes in expression across regions, indicating a non-linear response. These findings align with recent evidence of positioning lurasidone as a potent modulator of neuroplastic signaling, particularly through its action on 5-HT7 and D2 receptors, which may facilitate the gene expression changes observed during social challenges (Wolke et al., 2019). Following social interaction, the drug appears to be associated with an altered responsiveness to social stimuli. In SD animals, both doses coincided with a pronounced induction of IEGs within the VH and AMY; however, while the higher dose was associated with engagement of subcortical limbic hubs, PFC activation remained modest. These results suggest that lurasidone may promote experience-dependent plasticity by modulating the threshold of activation in regions associated with social salience and emotional processing, rather than simply normalizing baseline activity.

At baseline, low dose lurasidone (1 mg/kg) exerts a “priming” effect by modulating GC pathways in the PFC and NAc. This basal elevation may prepare these regions for a more efficient transcriptional response to subsequent social challenges, selectively optimizing neuroendocrine integration within emotion and reward circuits (Luoni et al., 2014). Conversely, the high dose (3 mg/kg) fails to induce this pre-conditioning at baseline, resulting in a more attenuated and generalized transcriptional profile following social interaction. This “inverted U-shape” response - where lower doses outperform higher ones- is a feature of several psychotropic compounds (Creutzberg et al., 2023).

At the system level, SD disrupted the coordinated activation patterns within fronto-mesolimbic regions, in line with alterations in motivational and social processing. When combined with social interaction, lurasidone partially restored these coherent activation patterns in a

dose-dependent manner, with lower doses exerting a more favorable effect on regional co-expression than higher doses. This suggests that optimal recovery of these coordinated profiles may depend on balanced pharmacological modulation rather than maximal receptor engagement. These findings support a model in which chronic social defeat constrains neural activation and regional coordination, while pharmacological intervention can facilitate adaptive activation patterns only when paired with behavioral activation. This mechanism may be particularly relevant to defeat-like states, where impaired recruitment of these pathways, rather than permanent structural damage, is a defining feature.

Despite the robustness of behavioral and molecular findings, some limitations should be acknowledged. It is important to note that the use of IEG expression as a marker of neuronal activation is indirect since it provides a snapshot of transcriptional activity that does not equate to real-time neuronal firing or direct measurements of circuit dynamics. Furthermore, our approach relies on correlation-based analyses of gene expression patterns; while useful for identifying coordinated transcriptional profiles across regions, these data should not be equated with functional connectivity or established circuit-level interactions in the absence of direct validation, such as in vivo electrophysiology, imaging, or optogenetic manipulation.

Additionally, while our analysis identified coordinated activation patterns, these correlation matrices cannot confirm directional or causal network interactions. Although the social defeat paradigm is a well-established model of psychosocial stress, it does not fully capture the complexity of human psychiatric disorders. Moreover, although social stress models are valuable tools to investigate sex-specific factors underlying psychopathology, the present study was limited to male rats, as the effects of social defeat in adult females are often weaker and less consistent, thereby limiting generalizability across sexes (Kuske and Trainor, 2022). Female rats exhibit lower levels of spontaneous territorial aggression and less stable dominance hierarchies, and resident males typically do not attack female intruders. Consequently, establishing ethologically valid social defeat protocols applicable to both sexes remains challenging without substantial methodological adaptations (Solomon, 2017).

Molecular analyses were restricted to a selected gene panel, and the dose-dependent effects of lurasidone indicate complex pharmacokinetic and receptor-level mechanisms that remain to be fully characterized. Future studies integrating these behavioral and transcriptional findings with electrophysiological or imaging techniques will be essential to provide definitive evidence of circuit-level reorganization. Finally, the absence of a comparator drug represents an additional limitation of the study. Future investigations will be important to assess whether similar effects can be observed with other psychotropic compounds, thereby clarifying the generalizability of these mechanisms in relation to their receptor profiles.

In summary, chronic social defeat stress induces persistent impairments in motivation, sociability, and corticolimbic network responsiveness, modeling core dimensions of stress-related psychopathology. Chronic lurasidone treatment effectively counteracted these deficits, restoring social engagement and motivational drive through dose-dependent modulation of stress- and reward-related circuits. Rather than simply normalizing baseline neural activity, lurasidone appears to facilitate experience-dependent re-engagement of dysfunctional networks, promoting behavioral recovery in domains that are critical for functional outcomes in psychiatric disorders.

Importantly, these effects should be interpreted within the context of lurasidone-specific pharmacology, as antipsychotic compounds differ substantially in their receptor profiles and mechanisms of action. From a translational perspective, they suggest that targeting specific behavioral domains through dose-tailored interventions may represent a promising strategy for the development of more selective and functionally relevant treatments.

AI disclosure

Open AI-assisted tools were used to refine illustrative images depicting the behavioral test paradigms; the prompts were developed by the authors, all scientific content was verified and approved by the authors.

CRediT authorship contribution statement

Eleonora Corridori: Writing – original draft, Visualization, Investigation, Formal analysis. **Alessia Marchesin:** Writing – original draft, Visualization, Investigation, Formal analysis. **Camilla Amato:** Investigation. **Veronica Begni:** Investigation. **Sara Salviati:** Investigation. **Carla Gambarana:** Writing – review & editing. **Marco Andrea Riva:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Simona Scheggi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.A.R. has received compensation as speaker/consultant from Angelini, Exeltis, Lundbeck, Otzuka and Sumitomo Pharma, and he has received research grants from Sumitomo Pharma. All the other authors declare no financial interests or potential conflicts of interest.

All procedures were conducted in accordance with European Directive (2010/63/EU) and Italian legislation (D. Lgs. 26/2014) on the use and care of laboratory animals and were approved by the University of Siena Animal Welfare Body and the Italian Ministry of Health (Authorization No. 366/2022-PR). Every effort was made to minimize animal suffering and to reduce the number of animals used.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2026.111756.

Data availability

Data will be made available on request.

References

Becker, C., Zeau, B., Rivat, C., Blugeot, A., Hamon, M., Benoliel, J.J., 2008. Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin. Mol. Psychiatry 13 (12), 1079–1092. https://doi.org/10.1038/sj.mp.4002097.

Bordes, J., Miranda, L., Reinhardt, M., Narayan, S., Hartmann, J., Newman, E.L., Brix, L. M., van Doeselaar, L., Engelhardt, C., Dillmann, L., Mitra, S., Ressler, K.J., Pütz, B., Agakov, F., Müller-Myhsok, B., Schmidt, M.V., 2023. Automatically annotated motion tracking identifies a distinct social behavioral profile following chronic social defeat stress. Nat. Commun. 14 (1), 4319. https://doi.org/10.1038/s41467-023-40040-3.

Calabrese, F., Brivio, P., Sbrini, G., Gruca, P., Lason, M., Litwa, E., Niemczyk, M., Papp, M., Riva, M.A., 2020. Effect of lurasidone treatment on chronic mild stress-induced behavioural deficits in male rats: the potential role for glucocorticoid receptor signalling. J. Psychopharmacol. (Oxford, England) 34 (4), 420–428. https://doi.org/10.1177/0269881119895547.

Cattaneo, A., Suderman, M., Cattane, N., Mazzelli, M., Begni, V., Maj, C., D'Aprile, I., Pariante, C.M., Luoni, A., Berry, A., Wurst, K., Hommers, L., Domschke, K., Cirulli, F., Szyf, M., Menke, A., Riva, M.A., 2020. Long-term effects of stress early in life on microRNA-30a and its network: preventive effects of lurasidone and potential implications for depression vulnerability. Neurobiol. Stress 13, 100271. https://doi.org/10.1016/j.ynstr.2020.100271.

Corridori, E., Salviati, S., Begni, V., Marchesin, A., Gambarana, C., Riva, M.A., Scheggi, S., 2025. Restorative properties of chronic lurasidone treatment on emotional dysfunction in rats exposed to chronic unavoidable stress: a role for medial prefrontal cortex - nucleus accumbens network. Neuropharmacology 267, 110302. https://doi.org/10.1016/j.neuropharm.2025.110302.

Crawford, L.K., Rahman, S.F., Beck, S.G., 2013. Social stress alters inhibitory synaptic input to distinct subpopulations of raphe serotonin neurons. ACS Chem. Neurosci. 4 (1), 200–209. https://doi.org/10.1021/cn300238j.

Creutzberg, K.C., Begni, V., Marchisella, F., Papp, M., Riva, M.A., 2023. Early effects of lurasidone treatment in a chronic mild stress model in male rats. Psychopharmacology 240 (4), 1001–1010. https://doi.org/10.1007/s00213-023-06343-5.

De Filippis, S., Vita, A., Cuomo, A., Amici, E., Giovanetti, V., Lombardozzi, G., Pardossi, S., Altieri, L., Cicale, A., Dosoli, M., Galluzzo, A., Invernizzi, E., Rodigari, P., Mascagni, P., Santini, C., Falsetto, N., Manes, M.A., Micillo, M., Fagiolini, A., 2024. Treatment satisfaction and effectiveness of Lurasidone on quality of life and functioning in adult patients with schizophrenia in the real-world Italian clinical practice: a prospective 3-month observational study. Ann. General Psychiatry 23 (1), 43. https://doi.org/10.1186/s12991-024-00531-z.

Dembek, C., Fan, Q., Niu, X., Mao, Y., Anupindi, V.R., Laubmeier, K., Tocco, M., 2022. Impact of lurasidone on health-related quality of life in adults with bipolar depression: a post-hoc analysis. Curr. Med. Res. Opin. 38 (9), 1613–1619. https://doi.org/10.1080/03007995.2022.2083400.

Dong, D., Ironside, M., Belleau, E.L., Sun, X., Cheng, C., Xiong, G., Nickerson, L.D., Wang, X., Yao, S., Pizzagalli, D.A., 2022. Sex-specific neural responses to acute psychosocial stress in depression. Transl. Psychiatry 12 (1), 2. https://doi.org/10.1038/s41398-021-01768-y.

Ducasse, D., Dubois, J., Jaussent, I., Azorin, J.M., Etain, B., Gard, S., Henry, C., Bougerol, T., Kahn, J.P., Aubin, V., Bellivier, F., Belzeaux, R., Dubertret, C., Dubreucq, J., Llorca, P.M., Loftus, J., Passerieux, C., Polosan, M., Samalin, L., Leboyer, M., Courtet, P., 2021. Association between anhedonia and suicidal events in patients with mood disorders: a 3-year prospective study. Depress. Anxiety 38 (1), 17–27. https://doi.org/10.1002/da.23072.

Duchaine, C.S., Aubé, K., Gilbert-Ouimet, M., Vézina, M., Ndjaboué, R., Massamba, V., Talbot, D., Lavigne-Robichaud, M., Trudel, X., Pena-Gralle, A.B., Lesage, A., Moore, L., Milot, A., Laurin, D., Brisson, C., 2020. Psychosocial stressors at work and the risk of sickness absence due to a diagnosed mental disorder: a systematic review and meta-analysis. JAMA Psychiatry 77 (8), 842–851. https://doi.org/10.1001/jamapsychiatry.2020.0322.

Feng, X.Z., Li, Z., Li, Z.Y., Wang, K., Tan, X., Zhao, Y.Y., Mi, W.F., Zhu, W.L., Bao, Y.P., Lu, L., Li, S.X., 2024. Effectiveness and safety of second-generation antipsychotics for psychiatric disorders apart from schizophrenia: a systematic review and meta-analysis. Psychiatry Res. 332, 115637. https://doi.org/10.1016/j.psychres.2023.115637.

Fiorillo, A., Sampogna, G., Albert, U., Bondi, E., De Giorgi, S., Fagiolini, A., Pompili, M., Serafini, G., Volpe, U., Vita, A., 2024. The role of lurasidone in managing depressive symptoms in people with schizophrenia: a review. Brain Sci. 14 (3), 225. https://doi.org/10.3390/brainsci14030225.

Gabbay, V., Johnson, A.R., Alonso, C.M., Evans, L.K., Babb, J.S., Klein, R.G., 2015. Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. J. Child Adolesc. Psychopharmacol. 25 (3), 194–200. https://doi.org/10.1089/cap.2014.0105.

Gooding, D.C., Padrutt, E.R., Pflum, M.J., 2017. The predictive value of the NEO-FFI items: parsing the nature of social anhedonia using the revised social anhedonia scale and the ACIPS. Front. Psychol. 8, 147. https://doi.org/10.3389/fpsyg.2017.00147.

Göver, T., Slezak, M., 2024. Targeting glucocorticoid receptor signaling pathway for treatment of stress-related brain disorders. Pharmacol. Rep.PR 76 (6), 1333–1345. https://doi.org/10.1007/s43440-024-00654-w.

Guilloux, J.P., Seney, M., Edgar, N., Sibille, E., 2011. Integrated behavioral z-scoring increases the sensitivity and reliability of behavioral phenotyping in mice: relevance to emotionality and sex. J. Neurosci. Methods 197 (1), 21–31. https://doi.org/10.1016/j.jneumeth.2011.01.019.

Haller, J., Bakos, N., 2002. Stress-induced social avoidance: a new model of stress-induced anxiety? Physiol. Behav. 77 (2–3), 327–332. https://doi.org/10.1016/s0031-9384(02)00860-0.

Hammen, C., 2005. Stress and depression. Annu. Rev. Clin. Psychol. 1, 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938.

Hodos, W., 1961. Progressive ratio as a measure of reward strength. Science (New York, N.Y.) 134 (3483), 943–944. https://doi.org/10.1126/science.134.3483.943.

Kim, H.D., Call, T., Carotenuto, S., Johnson, R., Ferguson, D., 2017. Testing depression in mice: a chronic social defeat stress model. Bio-protocol 7 (7), e2203. https://doi.org/10.21769/BioProtoc.2203.

Koolhaas, J.M., De Boer, S.F., De Rutter, A.J., Meerlo, P., Sgoifo, A., 1997. Social stress in rats and mice. Acta Physiol. Scand. Suppl. 640, 69–72.

Koolhaas, J.M., Coppens, C.M., de Boer, S.F., Buwalda, B., Meerlo, P., Timmermans, P.J., 2013. The resident-intruder paradigm: a standardized test for aggression, violence and social stress. J. Visual. Exp. 77, e4367. https://doi.org/10.3791/4367.

Krishnan, V., Han, M.H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., Laplant, Q., Graham, A., Lutter, M., Lagace, D.C., Ghose, S., Reister, R., Tannous, P., Green, T.A., Neve, R.L., Chakravarty, S., Kumar, A., Eisch, A.J., Self, D.W., Lee, F.S., 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.

Kupferberg, A., Bicks, L., Hasler, G., 2016. Social functioning in major depressive disorder. Neurosci. Biobehav. Rev. 69, 313–332. https://doi.org/10.1016/j.neubiorev.2016.07.002.

Kuske, J.X., Trainor, B.C., 2022. Mean girls: social stress models for female rodents. Curr. Top. Behav. Neurosci. 54, 95–124. https://doi.org/10.1007/7854_2021_247.

Larson, E.B., Graham, D.L., Arzaga, R.R., Buzin, N., Webb, J., Green, T.A., Bass, C.E., Neve, R.L., Terwilliger, E.F., Nestler, E.J., Self, D.W., 2011. Overexpression of CREB in the nucleus accumbens shell increases cocaine reinforcement in self-administering rats. J. Neurosci. 31 (45), 16447–16457. https://doi.org/10.1523/JNEUROSCI.3070-11.2011.

Liu, Y.Y., Zhou, X.Y., Yang, L.N., Wang, H.Y., Zhang, Y.Q., Pu, J.C., Liu, L.X., Gui, S.W., Zeng, L., Chen, J.J., Zhou, C.J., Xie, P., 2017. Social defeat stress causes depression-like behavior with metabolite changes in the prefrontal cortex of rats. PLoS One 12 (4), e0176725. https://doi.org/10.1371/journal.pone.0176725.

Luoni, A., Berry, A., Calabrese, F., Capoccia, S., Bellisario, V., Gass, P., Cirulli, F., Riva, M.A., 2014. Delayed BDNF alterations in the prefrontal cortex of rats exposed to prenatal stress: preventive effect of lurasidone treatment during adolescence. Eur. Neuropsychopharmacol. 24 (6), 986–995. https://doi.org/10.1016/j.euroneuro.2013.12.010.

Luoni, A., Macchi, F., Papp, M., Molteni, R., Riva, M.A., 2015. Lurasidone exerts antidepressant properties in the chronic mild stress model through the regulation of synaptic and neuroplastic mechanisms in the rat prefrontal cortex. Int. J. Neuropsychopharmacol. 18 (4), pyu061. https://doi.org/10.1093/ijnp/pyu061.

Marchese, G., Scheggi, S., Secci, M.E., De Montis, M.G., Gambarana, C., 2013. Anti-anhedonic activity of long-term lithium treatment in rats exposed to repeated unavoidable stress. Int. J. Neuropsychopharmacol. 16 (7), 1611–1621. https://doi.org/10.1017/S1461145712001654.

Maruyama, H., Sano, F., Sakaguchi, R., Okamoto, K., Miura, I., 2024. Effect of lurasidone on life engagement in schizophrenia: post-hoc analysis of the JEWEL study. Neuropsychiatr. Dis. Treat. 20, 1453–1463. https://doi.org/10.2147/NDT.S466479.

Miura, I., Sano, F., Sakaguchi, R., Okamoto, K., Maruyama, H., 2024. Effect of lurasidone on social functioning in schizophrenia: post hoc analysis of the JEWEL study. J. Clin. Psychiatry 85 (1), 23m14881. https://doi.org/10.4088/JCP.23m14881.

Mora, F., Gómez Sánchez-Lafuente, C., De Iceta, M., Roset, C., Cárdenas, A., Pérez, D., Álvarez-Barón, E., Gabarda-Inat, I., Savana Research Group, 2025. Lurasidone uses and dosages in Spain: RETROLUR, a real-world retrospective analysis using artificial intelligence. Front. Psychiatry 15, 1506142. https://doi.org/10.3389/fpsyt.2024.1506142.

Olino, T.M., Silk, J.S., Osterritter, C., Forbes, E.E., 2015. Social reward in youth at risk for depression: a preliminary investigation of subjective and neural differences. J. Child Adolesc. Psychopharmacol. 25 (9), 711–721. https://doi.org/10.1089/cap.2014.0165.

Paul, E.D., Hale, M.W., Lukkes, J.L., Valentine, M.J., Sarchet, D.M., Lowry, C.A., 2011. Repeated social defeat increases reactive emotional coping behavior and alters functional responses in serotonergic neurons in the rat dorsal raphe nucleus. Physiol. Behav. 104 (2), 272–282. https://doi.org/10.1016/j.physbeh.2011.01.006.

Paxinos, G., Watson, C., 2007. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York.

Porcelli, S., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Mendlewicz, J., Merlo Pich, E., Pollentier, S., Penninx, B.W.J.H., Serretti, A., 2020. Social dysfunction in mood disorders and schizophrenia: clinical modulators in four independent samples. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 99, 109835. https://doi.org/10.1016/j.pnpbp.2019.109835.

Riboni, F.V., Belzung, C., 2017. Stress and psychiatric disorders: from categorical to dimensional approaches. Curr. Opin. Behav. Sci. 14, 72–77. https://doi.org/10.1016/j.cobeha.2016.12.011.

Ritger, A.C., Stickling, C.P., Ferrara, N.C., 2023. The impact of social defeat on basomedial amygdala neuronal activity in adult male rats. Behav. Brain Res. 446, 114418. https://doi.org/10.1016/j.bbr.2023.114418.

Rossetti, A.C., Papp, M., Gruca, P., Paladini, M.S., Racagni, G., Riva, M.A., Molteni, R., 2016. Stress-induced anhedonia is associated with the activation of the inflammatory system in the rat brain: restorative effect of pharmacological intervention. Pharmacol. Res. 103, 1–12. https://doi.org/10.1016/j.phrs.2015.10.022.

Rossetti, A.C., Paladini, M.S., Colombo, M., Gruca, P., Lason-Tyburkiewicz, M., Tota-Glowczyk, K., Papp, M., Riva, M.A., Molteni, R., 2018. Chronic stress exposure reduces parvalbumin expression in the rat hippocampus through an imbalance of redox mechanisms: restorative effect of the antipsychotic lurasidone. Int. J. Neuropsychopharmacol. 21 (9), 883–893. https://doi.org/10.1093/ijnp/pyy046.

Scheggi, S., Pelliccia, T., Ferrari, A., De Montis, M.G., Gambarana, C., 2015. Impramine, fluoxetine and clozapine differently affected reactivity to positive and negative stimuli in a model of motivational anhedonia in rats. Neuroscience 291, 189–202. https://doi.org/10.1016/j.neuroscience.2015.02.006.

Scheggi, S., Melis, M., De Felice, M., Aroni, S., Muntoni, A.L., Pelliccia, T., Gambarana, C., De Montis, M.G., Pistis, M., 2016. PPARα modulation of mesolimbic dopamine transmission rescues depression-related behaviors. Neuropharmacology 110 (Pt A), 251–259. https://doi.org/10.1016/j.neuropharm.2016.07.024.

Scheggi, S., De Montis, M.G., Gambarana, C., 2018a. DARPP-32 in the orchestration of responses to positive natural stimuli. J. Neurochem. 147 (4), 439–453. https://doi.org/10.1111/jnc.14558.

Scheggi, S., Pelliccia, T., Gambarana, C., De Montis, M.G., 2018b. Aripiprazole relieves motivational anhedonia in rats. J. Affect. Disord. 227, 192–197. https://doi.org/10.1016/j.jad.2017.10.032.

Scheggi, S., Guzzi, F., Braccagni, G., De Montis, M.G., Parenti, M., Gambarana, C., 2020. Targeting PPARα in the rat valproic acid model of autism: focus on social motivational impairment and sex-related differences. Mol. Autism. 11 (1), 62. https://doi.org/10.1186/s13229-020-00358-x.

Solomon, M.B., 2017. Evaluating social defeat as a model for psychopathology in adult female rodents. J. Neurosci. Res. 95 (1–2), 763–776. https://doi.org/10.1002/jnr.23971.

Treadway, M.T., Zald, D.H., 2011. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci. Biobehav. Rev. 35 (3), 537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006.

Umamichi, K., Furukawa, T., Sato, C., Miura, H., Hatakenaka, K., Nunomura, T., Mikami, M., Koeda, S., Yamada, J., 2026. Voluntary wheel running improves cognitive deficits and abnormal agonistic behavior induced by social isolation stress in mice. Physiol. Behav. 304, 115176. https://doi.org/10.1016/j.physbeh.2025.115176.

Wolke, S.A., Mehta, M.A., O'Daly, O., Zelaya, F., Zahreddine, N., Keren, H., O'Callaghan, G., Young, A.H., Leibenluft, E., Pine, D.S., Stringaris, A., 2019. Modulation of anterior cingulate cortex reward and penalty signalling in medication-naive young-adult subjects with depressive symptoms following acute dose lurasidone. Psychol. Med. 49 (8), 1365–1377. https://doi.org/10.1017/S0033291718003306.

Wong, S., Le, G.H., Phan, L., Rhee, T.G., Ho, R., Meshkat, S., Teopiz, K.M., Kwan, A.T.H., Mansur, R.B., Rosenblat, J.D., McIntyre, R.S., 2024. Effects of anhedonia on health-related quality of life and functional outcomes in major depressive disorder: a systematic review and meta-analysis. J. Affect. Disord. 356, 684–698. https://doi.org/10.1016/j.jad.2024.04.086.

Yang, X., Guo, Y., Harrison, P., Liu, X., 2022. Social and general anhedonia in adolescents: Stability and associations with other symptoms. J. Adolesc. 94 (3), 380–389. https://doi.org/10.1002/jad.12029.

Zhao, J.J., Han, C.Y., Xu, G.X., Zhou, M., Jin, Z.M., 2025. Effect of lurasidone plus sulpiride on treatment efficacy, psychiatric manifestations, and quality of life among patients with schizophrenia. World J. Psychiatry 15 (10), 105932. https://doi.org/10.5498/wjp.v15.i10.105932.