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Original Research Article

Comparative Effect of Fluoxetine and Imipramine on Social Defeat Stress Model of Depression in Mice

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ABSTRACT

Fluoxetine and imipramine are antidepressant drugs used in the management of depression. This study aimed to evaluate the comparative effect of fluoxetine and imipramine on social defeat stress (SDS)-induced depression in mice. Twenty-eight mice were divided into four groups as follows: **1** - Control (distilled water), **2** - untreated SDS, **3** - SDS + fluoxetine (10 mg/kg), and **4** - SDS + imipramine (10 mg/kg). Fluoxetine and imipramine were administered orally once daily for 14 days. At the end of treatment period, behavioural tests, including tail suspension test (TST), forced swim test (FST), sucrose splash test (SST), and social interaction test (SIT) were conducted, after which the animals were sacrificed, and blood samples were collected for biochemical analysis. Mice brain were harvested for immune-histochemical and histological analysis. Results showed that fluoxetine decreased immobility time significantly ($p < 0.05$) in the TST and FST compared to imipramine, while in SST, imipramine increased sucrose preference significantly ($p < 0.05$) compared to fluoxetine. Both drugs boosted antioxidant levels in SDS mice, but fluoxetine had a better effect on catalase than imipramine. Both drugs increased levels of corticosterone and norepinephrine to similar extent in the prefrontal cortex (PFC). Fluoxetine significantly ($p < 0.05$) increased serotonin levels compared to imipramine. Both drugs significantly increased neuronal density to similar extent in the medial PFC, hippocampus, and adrenal gland of SDS mice compared to the untreated SDS mice. This study has revealed that fluoxetine had a better antidepressant effect than imipramine as shown in the behavioural models.

Keywords: Depression, Social Defeat Stress, Immobility, Fluoxetine, Imipramine.

Introduction

In recent times, there is an increased focus on mental health, especially among teenagers.[1] It is estimated that 1 in 7 children between the ages of 10 and 19 suffers from mental health disorders, which makes approximately 13% of the disease burden in this age range worldwide.[2] Of all mental health disorders, depression accounts for the greatest percentage (37.3%), with anxiety coming second.[3]

According to estimates, 26.9% of adolescents in sub-Saharan Africa suffer from depressive disorder.[4] Undoubtedly, depression is a prevalent mental health issue among children and teenagers, mostly presenting as a continuous decline in academic performance, emotional instability such as feeling of worthlessness, challenges in forming friendships, and inadequate sleep patterns.[1] Teenage depression is a widespread condition that has a significant impact on the social, intellectual, physical, and mental well-being of teenagers.[5] Severe depression may even be fatal.[5] Depression is the primary cause of suicide among teenagers, and suicide is the third most common cause of mortality among children and adolescents.[6] Various variables, such as bullying and traumatic events, can lead to changes in the physical, emotional, and social routines of adolescents.[7]

Bullying has a wide range of negative effects on its victims, including mental illness, physical health issues, and academic difficulties.[8] Teens that experience bullying are more likely to experience mental health issues, which can have a detrimental effect on their day-to-day functioning.[9] Another study revealed that the risk of depressive disorder is 1.8 times higher in adolescents who have experienced bullying than in adolescents who have not.[10] Additionally, studies has also revealed that school-age children who experienced bullying are more likely to have depression.[11] The frequency of bullying increases the likelihood of severe mental health issues in teenagers.

Research on the pathophysiology of depression, requires animal models with an absolute propensity to accurately forecast, and mimic the disease as it occurs in humans. The lipopolysaccharide (LPS) model, social defeat stress, and chronic mild stress in animals have all shown similarities in neurochemical, structural, and behavioral changes, even if the animal models may not fully fit the criteria.[12] These models have been applied to understand the nature of depression, and perform antidepressant screening.[12]

Stress related to social failure can result in mood-related disorders like anxiety and depression.[3] Social conflict between members of the same species is the source of social defeat stress, sometimes referred to as the resident intruder test, which produces emotional and psychological strain. It is interesting to note that mice suffering from social defeat stress exhibit altered behavior, which includes less social contact and

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less satisfaction.[13] Given the detrimental effects of bullying-induced depression in adolescent, this study aims to determine a better antidepressant to be used in this condition by comparing the effects of imipramine and fluoxetine on social defeat stress model of depression in mice.

Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI). Fluoxetine works by selectively inhibiting the serotonin transporter (SERT), preventing the reuptake of serotonin (5-HT) into the presynaptic neuron. This leads to an increased concentration of serotonin in the synaptic cleft and enhances serotonergic neurotransmission in the brain, particularly in regions associated with mood regulation such as the prefrontal cortex and hippocampus.[14] Imipramine on the other hand is a Tricyclic Antidepressant (TCA). Imipramine inhibits the reuptake of both serotonin (SER) and norepinephrine (NE). Additionally, it blocks various receptors including muscarinic cholinergic, histaminergic (H1), and alpha-adrenergic receptors, which contributes to its side effect profile.[15] The dual inhibition of serotonin transporter (SERT) and norepinephrine transporter (NET) enhances both serotonergic and noradrenergic neurotransmission.

Materials and Methods

Experimental animal

Twenty-eight (28) male albino mice weighing between 14 and 18 g were used for the study and they were obtained from the Central Animal House, Delta State University, Abraka. The animals were housed in an environment with controlled air temperature (23 ± 2ºC), a 12-hour light and 12-hour dark cycle, relative humidity between 40 and 70%, and unlimited access to food and water. The animals were acclimatized for 2 weeks in the animal house. Ethical approval (Reference number: RBC/FBMC/DELSU/24/550) was granted by the Faculty of Basic Medical Science Research and Ethics Committee, Delta State University, Abraka, Nigeria. All procedures adhered to the NIH Guidelines for the Care and Use of Laboratory Animals.

The animals were assigned into four groups (Groups 1-4), each with seven animals (n = 7):

Group 1: (control) received vehicle only, i.e., distilled water.

Group 2: Induced with depression via social defeat stress (untreated SDS)

Group 3: Induced with depression via social defeat stress and treated with fluoxetine (10 mg/kg)

Group 4: Induced with depression via social defeat stress and treated with imipramine (10 mg/kg).

All administrations were done once daily orally via an oro-gastric syringe for 14 consecutive days.

Drug preparation

Doses of fluoxetine (10 mg/kg) and imipramine (10mg/kg) were prepared in stock solution. The doses administered were selected from previous literatures.[16]

Induction of depression

Before the induction of depression in groups 2, 3, and 4 mice, another set of mice (10 adult male mice) were kept in isolation in ten separate cages. These ten male mice were allowed to acclimatize for about 30 days prior to the induction of depression. The isolation was necessary to induce aggression in the mice that were housed singly.[17] At the end of the 30 days, isolation period, a young intruder male mouse was introduced into the resident cage. Both animals were allowed ten minutes of physical interaction, followed by a ten minutes' threat thereafter, intruder mice were returned to their home cages. This procedure was repeated for seven consecutive days. Depression was characterized by submission, supine posture, emitting frequent calls of distress and exhibiting freezing behaviour.[18] At the end of induction of depression period, animals in groups 3 and 4 were treated orally with Fluoxetine (10 mg/kg) and Imipramine (10 mg/kg), respectively for 14 consecutive days. Thereafter, different behavioural test such as social interaction test, Tail suspension test, Light and dark phase test, elevated plus maze, and forced swim test were conducted on animals in the different groups.

At the end of the behavioral tests, animals were decapitated, blood samples were collected via cardiac puncture for corticosterone analysis, and different brain regions were collected for biochemical and histological analysis.

Behavioral assays

Tail suspension test

On day 15, the tail suspension test (TST) was carried out according to the procedure described by Cryan et al. (2005) [19] and Steru et al. (1985). [20]. The animals were suspended individually on a retort stand, placed 50 cm above the floor with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. The total duration of immobility was recorded during the last 4 min of the 6 min test. Animals were considered to be immobile when it did not show any movement of the body and hangs passively.

Sucrose splash test (SST)

On day 15, immediately after the tail suspension test, the sucrose splash test was evaluated according to the method previously described by Burstein et al. (2018).[21] In the sucrose splash test, mice were placed in a separate cage and the 10% sucrose solution was sprayed on the back of the animal. Animals were observed for 5 min and the frequency and length of grooming was recorded.

Forced swim test (FST)

On day 16, the Forced swim test was conducted and the test lasted for 1 hour. Forced swim test was evaluated according to the method previously described by Aluko et al. (2015).[22] Each mouse was forced to swim individually in a glass jar of height 20 cm, diameter 10 cm, and filled with water to a depth of 15 cm and the water was maintained at room temperature. The duration of immobility (the total time during which the animal was immobile) during the last 4 min of a 6 min observation period was measured. A mouse was judged to be immobile when it remained floating in an upright position with the head above the water level.

Social interaction test (SIT)

This particular test is used to measure the social interactive behavior of animals. This test was evaluated according to the method previously described by File and Deakin. (1980).[23] This test involves the use of a test chamber consisting of a 60 × 40 cm Plexiglas box divided into three chambers (A, B, and C). Mice move between chambers through a small opening (6 × 6 cm) in the dividers. An iron restraining cage was placed in each of the two side chambers (A and C). A test (experimental) mouse was placed in the center chamber (chamber B) and allowed 5 minutes of exploration time in all chambers. At the end of the 5-minute exploration time, the test mouse was removed, and an unfamiliar, same-sex probe mouse from the same experimental group was placed in one of two restraining cages in chamber A, while chamber C was without mice.

Thereafter, the test mouse was placed back into chamber B and allowed to explore between chambers A (containing the probe mouse) and chamber C (without the mouse) in the social test box. The time spent exploring chambers A and C was measured with different stopwatches, and the social preference was defined as follows:

$$\frac{Time\ spent\ with\ novel\ mouse}{Time\ spent\ with\ novel\ mouse + empty\ chamber} \times \frac{100}{1}$$

Biochemical analysis

Determination of catalase activity

Catalase activity was determined according to the method previously described by Ben-Azu et al. (2022).[24] Aliquots of mouse brain supernatant (0.1 mL) was added to 2 mL of sodium phosphate buffer (0.05 M; pH 7.4) and 0.9 mL of H_2O_2 (800 µM). The reacting mixture was mixed by a gentle swirling motion at room temperature and 1 mL of this mixture was added to 2 mL dichromate/acetic acid reagent. The absorbance was read using a spectrophotometer at a wavelength of 570 nm and change in absorbance was recorded at 60 seconds intervals. The catalase activity was expressed as µM of hydrogen peroxide (H_2O_2) decomposed per minute per mg protein.

Determination of glutathione (GSH) concentration
Aliquots of brain supernatant of individual mouse in the respective treatment groups was taken and GSH concentration was determined using the Moron' method as cited by [25] Equal volume (0.4 mL) of brain homogenate and 20% tricarboxylic acid (0.4 mL) was mixed and then centrifuged using a cold centrifuge at 10,000 rpm at 4°C for 20 min. The supernatant (0.25 mL) was added to 2 mL of 0.6 mM 5,5-dithio-bis-(nitrobenzoic acid) and the final volume was made up to 3 mL with phosphate buffer (0.2 M, pH 8.0). The absorbance was read at 412 nm against blank reagent using a spectrophotometer. The concentrations of GSH in the brain tissues was expressed as micromoles per gram tissue (µmol/g tissue).

Monoamine assay
Monoamines (serotonin and noradrenaline) were assayed. The sandwich enzyme-linked immunosorbent test kit was pre-coated with primary antibodies, specifically mouse neurotransmitter monoclonal antibodies. Following sample addition (15 µL), the antibody-precoated wells were incubated. The development of an immunological complex occurs when biotin-labeled anti-receptive neurotransmitter antibodies and streptavidin-HRP were added to the plate following the incubation period. After adding the incubation substrate to the plates, the unbound enzymes were eliminated by washing the plate. Acid will cause the solution to first turn blue and then turn yellow. After that, the neurotransmitter levels were measured using a commercial kit in accordance with the manufacturer's instructions.

Corticosterone assay
Before usage, all materials and reagents were brought to room temperature, and all reagents were mixed without foaming. As directed by the manufacturer, duplicate assays were carried out. There was a sufficient quantity of microplate wells prepared to hold calibrators and samples. Ten microliters of every calibrator, sample, and control were injected into the relevant wells using fresh disposable tips. The incubation buffer (100 µL) was then added to each well, followed by the addition of 50 µL enzyme conjugate. The plates were incubated on a microplate mixer (>600 rpm) for two hours at room temperature. The solutions in the wells were discarded, and the wells were rinsed four times with a diluted wash solution, the contents of the wells were removed by beating the microplate on absorbent paper. Each well received 200 µL of substrate solution, and the wells were allowed to stand at room temperature for 30 min in the dark without being shaken. To halt the reaction, 50 µL of the stop solution was added to each well. The absorbance of the content of each well was measured at 450 nm.
Preparation of brain tissues for immunohistochemistry and histology
After the behavioural tests, mice (n = 3) in the respective groups were decapitated. The adrenal gland and different brain regions like prefrontal cortex, and hippocampus (*cornu ammonis*) were harvested and fixed with 10% phosphate buffered formaldehyde used for perfusion. The brain regions were subjected to the routine method for paraffin wax embedment to obtain paraffin wax embedded tissue blocks. Transverse sections (5 - 6 µm thick) of the prefrontal cortex, hippocampus and adrenal gland were obtained with the aid of microtome (Leica, Germany) and the sections was fixed on glass slides.
Cyclic AMP response element-binding protein (CREB) assay
CREB assay was done using the mice medial prefrontal cortex according to method previously described by Shaywitz and Greenberg (1999).[26] The protocol for assaying CREB using immunohistochemistry involved perfusing anesthetized mice with phosphate buffered saline (PBS) and 4% paraformaldehyde (PFA), followed by post-fixation in PFA overnight. The brains were then cryoprotected using a sucrose gradient, embedded in optimal cutting temperature (OCT) compound, and sectioned at 10–20 µm using a cryostat before being stored at -20°C. Antigen retrieval was performed when necessary, using citrate buffer, and non-specific binding was blocked with 5% normal goat serum containing Triton X-100. The sections were incubated overnight with an anti-CREB or anti-phospho-CREB primary antibody, followed by incubation with a biotinylated secondary antibody and an avidin-biotin complex (ABC) reaction. Visualization was achieved using DAB staining, and the sections were counterstained with hematoxylin, dehydrated with an ethanol gradient, cleared with xylene, and mounted. Imaging was performed using a light microscope, with a focus on regions such as the hippocampus, prefrontal cortex, and amygdala, while ImageJ software was used for quantification. Increased CREB or phospho-CREB staining indicated enhanced neuronal plasticity and transcriptional activity, whereas decreased levels were associated with cognitive deficits and neuropsychiatric disorders. This method allowed for the assessment of CREB activation in brain regions involved in learning, memory, and synaptic plasticity.

Extracellular Signal-regulated Kinases (ERK) Assay
ERK assay was done using mice medial prefrontal cortex according to the method previously described by Osmond et al. (2005).[27] The protocol for assaying ERK using immunohistochemistry involved perfusing anesthetized mice with PBS and 4% paraformaldehyde (PFA), followed by post-fixation in PFA overnight. The brains were then cryoprotected using a sucrose gradient (10% and 30%), embedded in OCT, and sectioned at 10–20 µm using a cryostat before being stored at −20°C. For immunohistochemistry, antigen retrieval was performed with citrate buffer when necessary, and non-specific binding was blocked with 5% normal goat serum containing Triton X-100. The sections were incubated overnight with an anti-pERK1/2 primary antibody (1:500), followed by incubation with a biotinylated secondary antibody and an avidin-biotin complex (ABC) reaction. Visualization was achieved using DAB staining, and sections were counterstained with hematoxylin, dehydrated through an ethanol gradient, cleared with xylene, and mounted. Imaging was performed using a light microscope, focusing on regions such as the hippocampus, prefrontal cortex, and amygdala, while ImageJ software was used to quantify DAB staining intensity. Increased pERK staining indicated heightened synaptic activity, learning, and stress response, whereas reduced levels were associated with neurodegeneration and cognitive decline. This method provided insights into ERK activation in brain regions involved in memory, learning, and neuropsychiatric disorders.

Statistical analysis
Data were presented as mean ± standard error of the mean (S.E.M.). Differences between means were analysed using a one-way ANOVA, followed by Turkey's post hoc test. Statistically significant difference was established at $p < 0.05$. Graph pad prism (Version 8.0) was used for statistical analysis.

Results and Discussion

Effect of fluoxetine and imipramine on depressive-like behaviour in social defeat stress mice
In animal models, depression is typically caused by persistent stress or other approaches that mirror human depressive states. The tail suspension test (TST), forced-swim test (FST), social interaction test (SIT) and sucrose splash test (SST) are valid animal models of depression.[28-30] The effect of fluoxetine and imipramine on immobility time in the tail suspension test and forced-swim test is presented in Figures 1 and 2, respectively. There were significant differences between treatment groups. The untreated SDS group had significantly ($p < 0.05$) increased immobility time when compared to the control group, while the immobility time for SDS + Fluoxetine (10 mg/kg) group and SDS + Imipramine (10 mg/kg) group were significantly ($p < 0.05$) lower compared to the untreated SDS group. SDS + Fluoxetine group showed a significant ($p < 0.05$) decrease in immobility time when compared to SDS + Imipramine group (Figures 1 and 2). In the TST and FST, mice exhibiting depressive-like behaviour demonstrated increased immobility time, suggesting a state of behavioural despair. This increased immobility is assumed to indicate a lack of drive to flee or a sense of hopelessness, akin to symptoms reported in clinical depression.[31] In the present study, it was observed that fluoxetine and imipramine reduced immobility time due to social defeat stress in TST and FST with fluoxetine exhibiting a more significant reduction in immobility time. This reduction in immobility time may be attributed to increase serotonergic transmission as an increase in serotonin level is

connected with enhanced mood and reduced depressive symptoms.[32] Although, some researcher suggests that imipramine may elicit a more

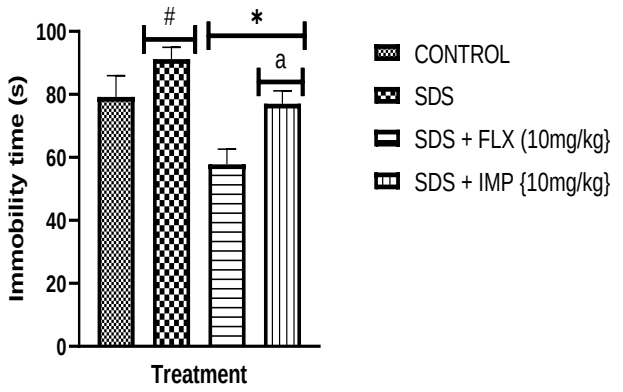

Figure 1: The effect of fluoxetine and imipramine on depressive-like behaviour in social defeat stress mice using the tail suspension test. Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ compared to the control group. * $p < 0.05$ compared to the pathologic group. [a] $p < 0.05$ compared to SDS + fluoxetine group. SDS = Social-defeat stress.

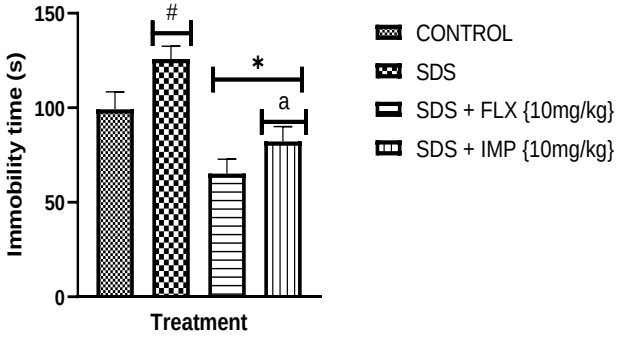

Figure 2: The effect of fluoxetine and imipramine on depressive-like behaviour in social defeat stress mice using the forced swim test (FST).
Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ compared to the control group. * $p < 0.05$ compared to the pathologic group. [a] $p < 0.05$ compared to SDS + fluoxetine group. SDS = Social-defeat stress.

robust reduction in immobility compared to fluoxetine, presumably due to its broader action on neurotransmitter systems.[33] This is however contrary to the findings from the present study, as fluoxetine demonstrated a superior reduction of immobility time compared to imipramine in the tail suspension test and forced swim test. Several investigations have also indicated that fluoxetine administration leads to a considerable decrease in immobility time in the TST, demonstrating its efficacy as an antidepressant.[34] Fluoxetine's specific impact on serotonin makes it a preferred choice for patients with mild to moderate depression.

As shown in Figure 3, untreated SDS group showed a significant ($p<0.05$) reduction in sociability as depicted by a reduced social interaction when compared to the control group. Fluoxetine (10 mg/kg) and imipramine (10 mg/kg) both produced a significant ($p < 0.05$) increase in sociability when compared with untreated SDS group. The mean social interaction time for SDS + fluoxetine group was almost the same as that of the control group (group 1), but was lower in the SDS + imipramine group compared to both the control and SDS + fluoxetine groups (Figure 3). This is consistent with a previous study which reported that rodents subjected to prolonged stress often display reduced social contact, corresponding to the social withdrawal reported in depressed individuals.[35] In the present study, fluoxetine and imipramine were effective in boosting social interaction time with fluoxetine demonstrating a significant increase in social interaction time compared to imipramine. The significant increase in sociability seen with fluoxetine may be due to the fact that fluoxetine selectively increases serotonin levels in the brain and increase in serotonin has been linked to enhanced social behavior and mood regulation whereas imipramine's action on norepinephrine may cause activation of the sympathetic nervous system which may interfere with social behavior. The improvement in social behaviour following fluoxetine treatment underscores its potential in addressing the social deficiencies reported in depressive illnesses.

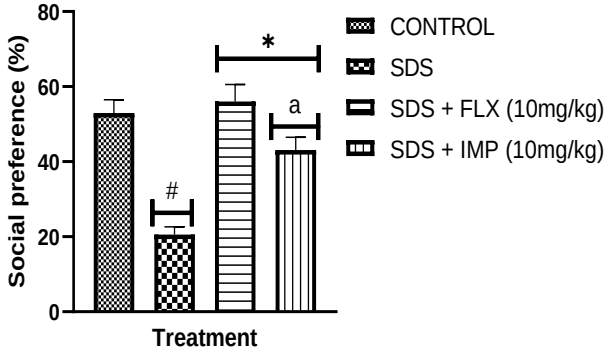

Figure 3: The effect of fluoxetine and imipramine on depressive-like behaviour in social defeat stress mice using the social interaction test (SIT). Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ compared to the control group. * $p < 0.05$ compared to the pathologic group. [a] $p < 0.05$ compared to SDS + fluoxetine group. SDS = Social-defeat stress.

Depressed mice often display decreased grooming behaviour in the sucrose splash test (SST). This reduction in self-care is considered equivalent to the lower interest in personal cleanliness and other activities typically found in depressed individuals.[36] As shown in Figure 4, results from this study demonstrated that fluoxetine and imipramine significantly ($p < 0.05$) increased grooming behaviour, with imipramine having a better significant increase in grooming time compared to fluoxetine.

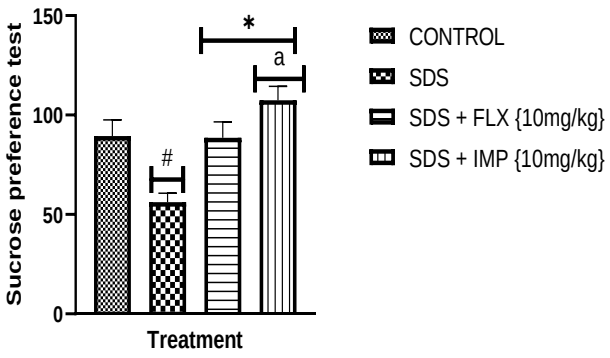

Figure 4: The effect of fluoxetine and imipramine on depressive-like behaviour in social defeat stress mice using the sucrose preference test (SPT). Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ compared to the control group. * $p < 0.05$ compared to the pathologic group. [a] $p < 0.05$ compared to SDS + fluoxetine group. SDS = Social-defeat stress.

The increase in sucrose preference associated with imipramine is caused by dopamine as increased norepinephrine may affect dopamine signaling, particularly in the prefrontal cortex. Enhanced dopamine levels can increase sucrose preference by amplifying the reward response to pleasurable stimuli. Although, both fluoxetine and imipramine are beneficial in enhancing grooming behaviour in the SST, their effects may vary depending on the underlying neurochemical underpinnings of the depressive-like behaviour. Fluoxetine's selective action on serotonin may make it particularly effective in cases where anhedonia is closely linked to serotonergic system.[37]

Effect of fluoxetine and imipramine on antioxidative systems in social defeat stress mice

Depression is associated with an imbalance in oxidative and antioxidative systems, leading to increased oxidative stress, particularly in brain regions such as the prefrontal cortex and hippocampus. The prefrontal cortex (PFC) is important in executive functioning and emotion control, whereas the hippocampus plays a vital role in memory and learning. Both regions are especially sensitive to oxidative injury due to their high metabolic activity and inadequate levels of antioxidant defense. Results from this study demonstrated reduced levels of catalase (CAT) and glutathione (GSH) in the prefrontal cortex and hippocampus of untreated social defeat stress mice (Figures 5 and 6).

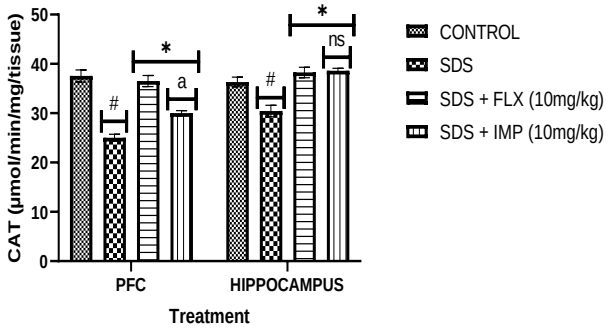

Figure 5: The effect of fluoxetine and imipramine on catalase in social defeat stress mice. Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$), while 'a' denotes statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P < 0.05$). SDS = Social-defeat stress.

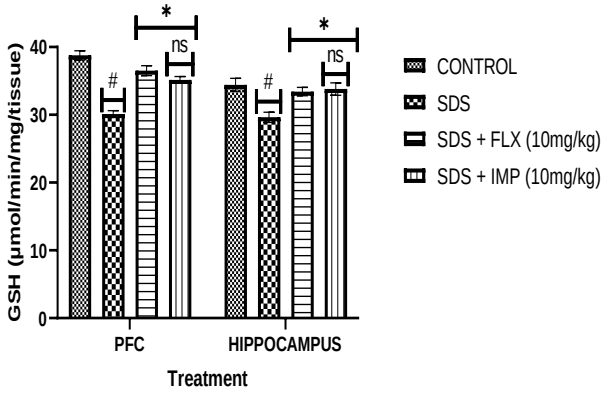

Figure 6: The effect of fluoxetine and imipramine on glutathione in social defeat stress mice. Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$), while 'a' denotes statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P < 0.05$). SDS = Social-defeat stress.

This is in congruence with the research conducted by [38] which found that people with depression commonly display lower levels of CAT and GSH. Low CAT activity in depression can result in inadequate detoxification of hydrogen peroxide, further leading to oxidative damage.[39] GSH, a tripeptide containing cysteine, is a key intracellular antioxidant that directly scavenges free radicals and regenerates other antioxidants. Depressed patients commonly demonstrate lower GSH levels, which might weaken cellular defenses against oxidative stress and worsen brain damage.[40] The drop in GSH levels has been connected with increased vulnerability to oxidative stress, leading to neuronal death and reduced synaptic plasticity, which are the hallmarks of depression.[41] Result from this study demonstrated that fluoxetine and imipramine were able to boost significantly ($P < 0.05$) CAT and GSH levels in social-defeat stress mice compared to the untreated SDS mice (Figures 5 and 6). Although, both drugs showed the potential to boost the levels of CAT and GSH, fluoxetine appears to have a better effect on catalase level in the prefrontal cortex compared to imipramine, because it tends to modulate mitochondrial function and reduce ROS (reactive oxygen species) generation.

Effect of fluoxetine and imipramine on corticosterone levels in social defeat stress mice

The results from the present study showed that there was a significantly higher ($p < 0.05$) corticosterone level in untreated social defeat stress mice compared to the control (Figure 7). This increased corticosterone level may be caused by the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Other investigations done in both humans and rodents have likewise consistently shown higher corticosterone (or cortisol) levels, demonstrating the dysregulation of HPA under stressful conditions.[42] Studies have revealed that both fluoxetine and imipramine have the ability to restore the hyperactivity of the HPA axis. This investigation highlighted that the influence of fluoxetine and imipramine were similar.

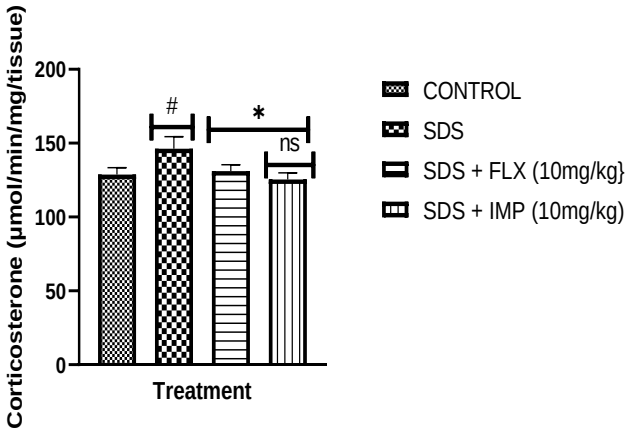

Figure 7: The effect of fluoxetine and imipramine on corticosterone levels in social defeat stress mice. Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

Effect of fluoxetine and imipramine on norepinephrine and serotonin levels in social defeat stress mice

In depression, there is often dysregulation of the noradrenergic system, resulting in altered norepinephrine levels in the PFC. Studies have demonstrated that depression is connected with reduced norepinephrine transmission in the PFC, which can contribute to symptoms such as low energy, impaired focus, and anhedonia (inability to perceive pleasure).[43] As shown in Figure 8, result from this study showed that social defeat stress as a kind of bullying-generated depression tends to lower norepinephrine levels substantially, while fluoxetine and imipramine raise the levels of norepinephrine, but the effect of imipramine on norepinephrine was higher compared to that of fluoxetine, but not significant. Imipramine, as a tricyclic anti-depressant, has also been observed to elevate norepinephrine directly by inhibiting its reuptake.[44] Chronic therapy with imipramine leads to sustained increase in norepinephrine level in the PFC, resulting in improvements in mood, attention, and motivation.[45] This rise in norepinephrine in the prefrontal cortex can attenuate symptoms of depression by altering attention, arousal, and working memory.

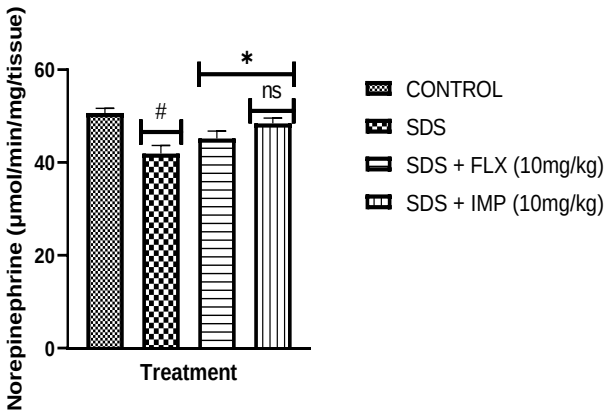

Figure 8: The effect of fluoxetine and imipramine on norepinephrine level in social defeat stress mice. Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

Apart from reduced norepinephrine, this study has also shown that depression via social defeat stress decreases serotonin level in the prefrontal cortex (Figure 9). Both fluoxetine and imipramine boosted the levels of serotonin considerably whereas fluoxetine had a better influence on serotonin level compared to imipramine. Fluoxetine, a selective serotonin reuptake inhibitor has been observed to selectively inhibit the reuptake of serotonin and this action tends to lower anxiety, enhance mood and promote flexibility hence relieving the symptoms of depression.[44]

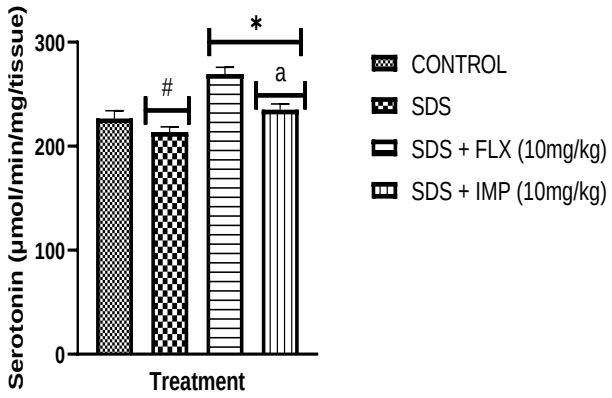

Figure 9: The effect of fluoxetine and imipramine on serotonin level in social defeat stress mice. Data represent the mean ± S.E.M, (n = 5). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'a' denotes statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P < 0.05$). SDS = Social-defeat stress.

Effect of fluoxetine and imipramine on the prefrontal cortex of social defeat stress mice

Depression is associated with severe structural changes in the medial prefrontal cortex (mPFC), including neuronal atrophy, diminished dendritic complexity, and a decrease in synaptic density. These changes contribute to the cognitive and emotional deficiencies noticed in depressed individuals. As shown in Figure 10b, this study showed that social defeat stress produced atrophy and angulation of neurons. This can be due to the fact that social defeat stress lowers Brain-derived neurotrophic factor (BDNF) expression in the mPFC, which is closely associated with neuronal shrinkage. The loss in BDNF affects synaptic plasticity and leads to the structural degeneration of neurons in the mPFC, resulting in decreased dendritic branching and spine density.[47] In addition to atrophy, social defeat stress can produce morphological alterations in the structure of neurons, including the angulation of dendrites. This angulation is hypothesized to arise from the retraction and restructuring of dendrites as a reaction to chronic stress.[48]

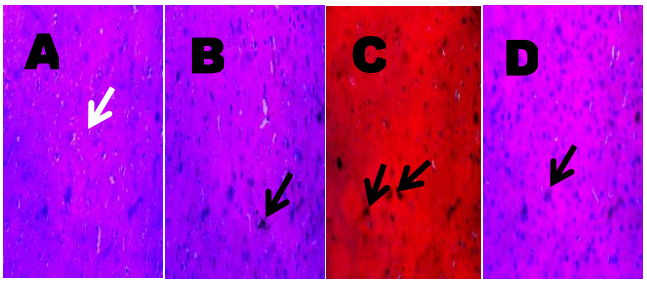

Figure 10a: Representative photomicrographs (H & E stained sections) of prefrontal cortex of SDS mice showing the effect of fluoxetine and imipramine on the prefrontal cortex. Magnification = HE x400. **A** = Control, **B** = SDS (untreated), **C** = SDS + fluoxetine (10 mg/kg) and **D** = SDS + imipramine (10 mg/kg)

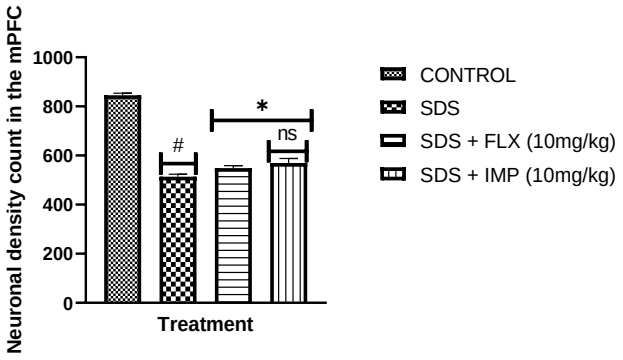

Figure 10b: The effect of fluoxetine and imipramine on neuronal density count in medial prefrontal cortex of social defeat stress mice
Data are presented as mean ± SEM, (n = 3). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

This angulation could impede neural connection and signal transmission, contributing to the behavioural impairments reported in stress-related diseases. Although, study conducted by [45] demonstrated that fluoxetine and imipramine were able to repair stress-induced neuronal atrophy in the mPFC by promoting dendritic development, and increasing spine density. This is in contrast to the findings from the present study, in which fluoxetine and imipramine were not able to repair stress-induced neuronal damage. This may be due to the duration of administration of both drugs, and/or slow onset of action of both drugs.[46] In rare situations, excessive doses or persistent usage of imipramine could potentially lead to severe effects, including neurotoxicity. However, the neurotoxic effects would more likely emerge in peripheral systems rather than centrally, particularly in the mPFC.[47] The photomicrographs showed the effect of fluoxetine and imipramine on the medial prefrontal cortex of SDS mice. Slide A showed no observable lesion, Slides B - D revealed atrophy of the neurons (Figure 10a). White arrow represents viable neurons while black arrows represent atrophy of the neurons.

Effect of fluoxetine and imipramine on the hippocampus of social defeat stress mice

Findings from the present study demonstrated that SDS produced atrophy in the *cornu ammonis* (CA1) region of the hippocampus (Figure 11). This is congruent with the study conducted by Köhler et al. (2018)[48] which indicated that chronic stress, a significant contributing factor to depression can lead to hippocampal shrinkage, impaired neurogenesis and decreased neuronal density specifically in the CA1 region. Administration of imipramine was able to reverse the detrimental effect of chronic stress (SDS) in the CA1 region.

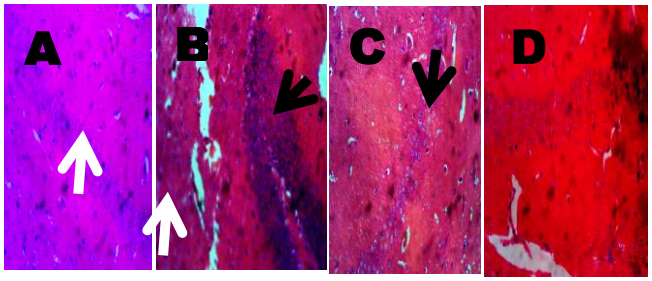

Figure 11a: Representative photomicrographs (H & E stained sections) of the CA1 region of the hippocampus showing the effect of fluoxetine and imipramine on the CA1 of SDS mice. Magnification = HE x400. **A** = Control, **B** = SDS (untreated), **C** = SDS + fluoxetine (10 mg/kg) and **D** = SDS + imipramine (10 mg/kg).

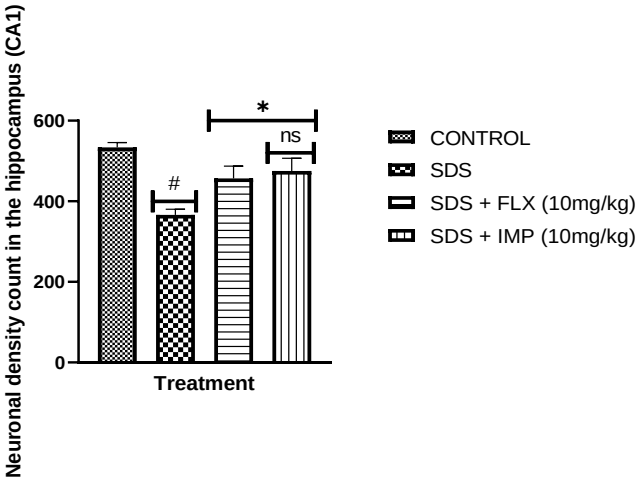

Figure 11b: The effect of fluoxetine and imipramine on hippocampal neuronal density count (*cornu ammonis* 1) in social defeat stress mice
Data are presented as mean ± SEM, (n = 3). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

This is also consistent with the study conducted by Chakrapani et al. (2020)[49] which reported imipramine to increase the expression of brain-derived neurotrophic factor (BDNF) and this is associated with enhanced neurogenesis and subsequent increase in neuronal density in the CA1 region. In this study, fluoxetine was not able to reverse the detrimental effect caused by SDS in the CA1 region. This is in contrast to the findings from the research conducted by Li et al. (2021)[50] which revealed fluoxetine to have enhanced dendritic complexity and spine density in the CA1 region, suggesting a protective impact against depression-induced neurodegeneration. The localized degeneration of pyramidal neurons reported after administration of fluoxetine may be attributed to the dosage of fluoxetine. High dosages of fluoxetine can lead to overstimulation of serotonin receptors, particularly the 5-HT2A receptors, which are densely distributed in the hippocampus. Over activation of these receptors can result in excitotoxicity, a process where excessive glutamate release causes neuronal damage and death.[54]
The photomicrographs showed the effect of fluoxetine and imipramine on the CA1 region of the hippocampus of SDS mice. Slide A showed no observable lesion in the CA1 region of the hippocampus. Slide B revealed atrophy of neurons in the CA1 region of the hippocampus. Slide C revealed focal degeneration of pyramidal neurons in the CA1 region of the hippocampus, Slide D showed no observable lesion in the CA1 region of the hippocampus (Figure 11a). White arrows represent viable neurons while black arrows represent atrophy of the neurons.

Effect of fluoxetine and imipramine on adrenal gland of social defeat stress mice

The patchy degradation of glandular cells seen in the *zona fasciculata* of SDS mice may be connected to the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.[47] Both fluoxetine and imipramine were able to reverse this effect since both medicines had similar effect on the adrenal gland. A study has also demonstrated that both fluoxetine and imipramine reduced adrenal hypertrophy and normalize cellular density in the adrenal cortex by regulating the HPA axis.[48]

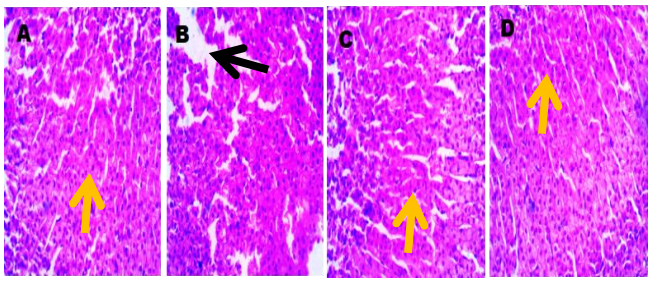

Figure 12a: Representative photomicrographs (H & E stained sections) of the effect of fluoxetine and imipramine on the *zona fasciculata* of SDS mice. Magnification = HE x400. **A** = Control, **B** = SDS (untreated), **C** = SDS + fluoxetine (10 mg/kg) and **D** = SDS + imipramine (10 mg/kg)

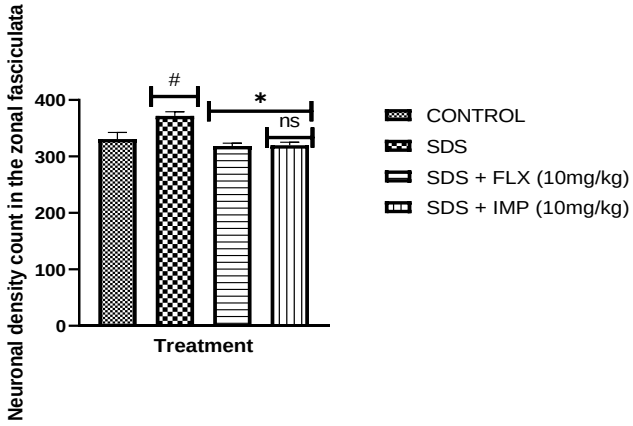

Figure 12b: The effect of fluoxetine and imipramine on adrenal gland (*zona fasciculata*) neuronal density in SDS mice.

Data are presented as mean ± SEM, (n = 3). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

The photomicrographs showed the effect of fluoxetine and imipramine on the *zona fasciculata* of SDS mice. Slide A showed no observable lesion in the *zona fasciculata*. Slide B revealed patchy degeneration of glandular cells in the *zona fasciculata*. Slides C and D showed no observable lesion in the *zona fasciculata* (Figure 12a). Yellow arrows denote viable neurons while black arrows denote patchy degeneration of glandular cells.

Effect of fluoxetine and imipramine on CREB expression in social defeat stress mice

Cyclic AMP response element-binding protein **(**CREB) is a transcription factor that regulates the expression of genes involved in synaptic plasticity, learning, and memory, such as brain-derived neurotrophic factor (BDNF). Activation of CREB in the PFC is necessary for the long-term therapeutic effects of antidepressants.[55] Results from this study revealed that both fluoxetine and imipramine significantly ($p < 0.05$) elevated CREB phosphorylation in the prefrontal cortex in comparison with the control (Figure 13). Increasing CREB phosphorylation in the prefrontal cortex can improve neuroplasticity and resilience against stress-induced neuronal damage.[55]

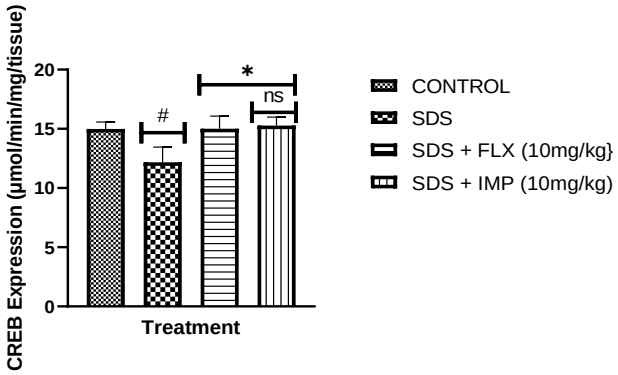

Figure 13: The effect of fluoxetine and imipramine on CREB in social defeat stress mice. Data are presented as mean ± SEM, (n = 3). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

Effect of fluoxetine and imipramine on the prefrontal cortex ERK expression in social defeat stress mice

The lower extracellular signal-regulated kinase (ERK) expression reported in untreated SDS mice can be attributed to poor synaptic plasticity and neurogenesis (Figure 14).

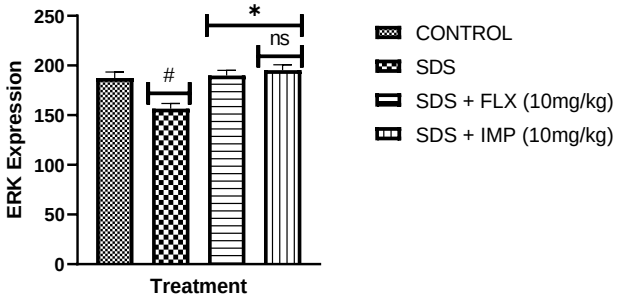

Figure 14: The effect of fluoxetine and imipramine on the prefrontal cortex extracellular signal-regulated kinase (ERK) expression in social defeat stress mice. Data are presented as mean ± SEM, (n = 3). # $p < 0.05$ for the control (group 1) compared to untreated SDS group. * $P < 0.05$ for the SDS + fluoxetine and SDS + imipramine groups when compared to SDS (untreated) group. 'ns' denotes no statistically significant difference between SDS + fluoxetine group and SDS + imipramine group ($P > 0.05$). SDS = Social-defeat stress.

Studies have demonstrated that chronic stress, a key contributor to depression, results in decreased phosphorylation of ERK1/2, which is necessary for the activation of downstream targets involved in neural plasticity.[56] The lower ERK activity in the mPFC can lead to the cognitive impairments and mood disorders observed in depression. Again, both fluoxetine and imipramine boosted ERK expressions considerably. Both medications exhibited similar effect in restoring ERK signaling in the mPFC through boosting ERK1/2 phosphorylation, which boosts synaptic plasticity and promotes neurogenesis, leading to their antidepressant effects.[56]

Conclusion

The findings from the present study has shown that both fluoxetine and imipramine improve behavioural response in social defeat stress (SDS)-induced depression in mice, with fluoxetine exhibiting a better effect

than imipramine. Both drugs boosted antioxidant levels in SDS mice, but fluoxetine had a better effect on catalase than imipramine. Both drugs also increased levels of serotonin, corticosterone and norepinephrine in the prefrontal cortex, with fluoxetine increasing serotonin levels more significantly compared to imipramine. Both drugs significantly increased neuronal density to similar extent in the medial PFC, hippocampus, and adrenal gland of SDS mice compared to the untreated SDS mice. Overall, fluoxetine has proven to be a better antidepressant than imipramine as it tends to increase sociability and improve mood through its effect on serotonin levels, although more research is needed in this area.

Conflict of interest
The author reports no conflicts of interest in this work.

Authors' Declaration
The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References
1. Hazell P. Updates in treatment of depression in children and adolescents. Curr Opin Psychiatry. 2021; 34(6):593-599.
2. Vasileva M, Graf RK, Reinelt T, Petermann U, Petermann F. Research review: A meta-analysis of the international prevalence and comorbidity of mental disorders in children between 1 and 7 years. J Child Psychol Psychiatry. 2021; 62(4):372-381.
3. Tyagi R, Chen X, Dhar A, Yang B, Zhou W, Reheman A, Cao G. Chronic social defeat stress-induced depression reduces BCG efficacy by promoting regulatory T-cell levels in mice. Anim Dis. 2023; 3(1):40.
4. Jörns-Presentati A, Napp AK, Dessauvagie AS, Stein DJ, Jonker D, Breet E, Charles W, Swart RL, Lahti M, Suliman S, Jansen R. The prevalence of mental health problems in sub-Saharan adolescents: A systematic review. Plos One. 2021; 16(5):0251689.
5. Beck A, LeBlanc JC, Morissette K, Hamel C, Skidmore B, Colquhoun H, Lang E, Moore A, Riva JJ, Thombs BD, Patten S, Bragg H, Colman I, Goldfield GS, Nicholls SG, Pajer K, Potter BK, Meeder R, Vasa P, Hutton B, Shea BJ, Graham E, Little J, Moher D, Stevens A. Screening for depression in children and adolescents: a protocol for a systematic review update. Syst Rev. 2021; 10(1):24.
6. Xu M, Liu S, Chen J, Yin A, He Q, Jiang Z, Liu J. Relationships among life events, emotional symptoms and non-suicidal self-injury behaviors in adolescents with depression. Psychiatry J. 2020; 33(6):420-423.
7. Waasdorp TE, Mehari KR, Milam AJ, Bradshaw CP. Health-related risks for involvement in bullying among middle and high school youth. J child fam stud. 2019; 28:2606-2617.
8. Armitage R. Bullying in children: impact on child health. BMJ paediatr open. 2021; 5(1):e000939.
9. Hartley SM. Assessment of Behaviors and Beliefs Exhibited by African American Practicing Physicians Toward Clinical Trial Research (Doctoral dissertation, Capella University). 2021; 28321065: 1–24 pp.
10. Jadambaa A, Thomas HJ, Scott JG, Graves N, Brain D, Pacella R. Prevalence of traditional bullying and cyberbullying among children and adolescents in Australia: A systematic review and meta-analysis. Aust N Z J Psychiatry. 2019; 53(9):878-888.
11. Ngo AT, Nguyen LH, Dang AK, Hoang MT, Nguyen THT, Vu GT, Ho CS. Bullying experience in urban adolescents: Prevalence and correlations with health-related quality of life and psychological issues. PloS One. 2021; 16(6):e0252459.
12. Demin KA, Sysoev M, Chernysh MV, Savva AK, Koshiba M, Wappler-Guzzetta EA, Song C, De Abreu MS, Leonard B, Parker MO, Harvey BH. Animal models of major depressive disorder and the implications for drug discovery and development. Expert Opin Drug Discov. 2019; 14(4):365-378.
13. Browne CA, Falcon E, Robinson SA, Berton O, Lucki I. Reversal of stress-induced social interaction deficits by buprenorphine. Int J Neuropsychopharmacol. 2018; 21(2):164-174.
14. Trivedi MH, Rush AJ, Wisniewski SR. Treatment and outcomes of depression. Am J Psychiatry. 2021; 178(10):899–915.
15. Dold M, Kasper S, Zajkowska Z. Efficacy and tolerability of imipramine in the treatment of major depression: a meta-analysis of randomized controlled trials. CNS Drugs. 2016; 30(3):243–258.
16. Saikarthik J, Gunapriya R, Saraswathi I, Vijayakumar J, Vijayaraghavan R. Effect of fluoxetine on hippocampus of Wistar Albino Rats in cold restraint stress model. J Clin Diagn Res. 2017; 11(6):AF01-AF06
17. Malick JB. The pharmacology of isolation-induced aggressive behavior in mice. *Curr Dev Psychopharmacol*. 1979; 5:1-27.
18. Blanchard RJ and Blanchard DC. Aggressive behavior in the rat. Behav Biol. 1977; 21(2):197-224.
19. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev. 2005; 29(4-5):571-625.
20. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacol. 1985; 85(3):367-370.
21. Burstein O and Doron R. The unpredictable chronic mild stress protocol for inducing anhedonia in mice. J Vis Exp. 2018; (140):58184.
22. Aluko OM, Umukoro S, Annafi OS, Adewole FA, Omorogbe O. Effects of methyl jasmonate on acute stress responses in mice subjected to forced swim and anoxic tests. Sci Pharm. 2015; 83(4):635-644.
23. File SE and Deakin JFW. Chemical lesions of both dorsal and median raphe nuclei and changes in social and aggressive behaviour in rats. Pharmacol Biochem Behav. 1980; 12(6):855-859.
24. Ben-Azu B, Adebayo OG, Wopara I, Aduema W, Onyeleonu I, Umoren EB, Kolawole TA, Ebo OT, Akpotu AE, Ajibo DN, Onuoha OG. Lead acetate induces hippocampal pyramidal neuron degeneration in mice via up-regulation of executioner caspase-3, oxido-inflammatory stress expression and decreased BDNF and cholinergic activity: Reversal effects of *Gingko biloba* supplement. J Trace Elem Med Biol. 2022; 71:126919.
25. Xie J, Cheng D, Li P, Xu Z, Zhu X, Zhang Y, Yao S. Au/metal–organic framework nanocapsules for electrochemical determination of glutathione. ACS Appl Nano Mater. 2021; 4(5):4853-4862.
26. Shaywitz AJ and Greenberg ME. CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. Annu Rev Biochem. 1999; 68:821-861.
27. Osmond RIW, Sheehan A, Borowicz R, Barnett E, Harvey G, Turner C, Brown A, Crouch MF, Dyer AR. GPCR Screening via ERK1/2: A Novel Platform for screening G protein-coupled receptors. J Biomol. 2005; 10(7):730-737.
28. Halverson NG. "Frozen": Tonic Immobility and Posttraumatic Outcomes Among Survivors of Sexual Assault. University of Montana. 2023.
29. Sbrini G, Brivio P, Bosch K, Homberg JR, Calabrese F. Enrichment environment positively influences depression-and anxiety-like behavior in serotonin transporter knockout rats through the modulation of neuroplasticity, spine, and GABAergic markers. Genes. 2020; 11(11):1248.
30. Bullich S, Delcourte S, Haddjeri N, Guiard BP. Learned immobility produces enduring impairment of the HPA axis reactivity in mice without replicating the broad spectrum of depressive-like phenotype. Int J Mol Sci. 2021; 22(2):937.
31. Dos Santos BM, Pereira GC, Piton E, Fialho MFP, Becker G, da Silva Carlotto M, Camargo LFM, Ramanzini LG, Oliveira SM,

Trevisan G, Zanchet EM. Lower antidepressant response to fluoxetine is associated with anxiety-like behavior, hippocampal oxidative imbalance, and increase on peripheral IL-17 and IFN-γ levels. Behav Brain Res. 2022; 425:113815.
32. Rincón-Cortés M and Grace AA.. Antidepressant effects of ketamine on depression-related phenotypes and dopamine dysfunction in rodent models of stress. Behav Brain Res. 2022; 379:112367.
33. Riegel B, Dunbar SB, Fitzsimons D, Freedland KE, Lee CS, Middleton S, Stromberg A, Vellone E, Webber DE, Jaarsma T. Self-care research: where are we now? Where are we going? Int J Nurs Stud. 2021; 116:103402.
34. McLaughlin L. A Review of Serotonin's Role in Depression and Modern Perspectives. 2022.
35. Ugwu PI, Ben-Azu B, Ugwu SU, Uruaka CI, Nworgu CC, Okorie PO, Okafor KO, Anachuna KK, Elendu MU, Ugwu AO, Anyaehie UB, Nwankwo AA, Osim EE. Preventive putative mechanisms involved in the psychopathologies of mice passively coping with psychosocial defeat stress by quercetin. Brain Res Bull. 2022; 183:127-141.
36. Barbosa ML, Melo de Meneses AP, Sousa de Aguiar RP, Marcelo de Castro e Sousa J, Cavalcante AACM, Maluf SW. Oxidative stress, antioxidant defense and depressive disorders: a systematic review of biochemical and molecular markers. Neurol Psychiatry *Brain* Res. 2020; 36(1):65-72.
37. Cecerska-Heryć E, Polikowska A, Serwin N, Roszak M, Grygorcewicz B, Heryć R, Michalczyk A, Dołęgowska B. Importance of oxidative stress in the pathogenesis, diagnosis, and monitoring of patients with neuropsychiatric disorders, a review. Neurochem. Int. 2022; 153:105269.
38. Nandam LS, Brazel M, Zhou M, Jhaveri DJ. Cortisol and major depressive disorder—translating findings from humans to animal models and back. Front Psychiatry. 2020; 10:974.
39. Coccurello R. Anhedonia in depression symptomatology: Appetite dysregulation and defective brain reward processing. Behav Brain Res. 2019; 372:112041.
40. Asensi-Cantó A, López-Abellán MD, Castillo-Guardiola V, Hurtado AM, Martínez-Penella M, Luengo-Gil G, Conesa-Zamora P. Antitumoral effects of tricyclic antidepressants: beyond neuropathic pain treatment. Cancers. 2022; 14(13):3248.
41. Khushboo Siddiqi NJ, de Lourdes Pereira M, Sharma B. Neuroanatomical, biochemical, and functional modifications in brain induced by treatment with antidepressants. Mol Neurobiol. 2022; 59(6):3564-3584.
42. Williams R and Cleare A. Drug and Physical Treatments of Depression. In: Kingdon D, Rowlands P, Stein G, eds. Seminars in General Adult Psychiatry. College Seminars Series. Cambridge University Press; 2024. 108-146 p.
43. Yan Z and Rein B. Mechanisms of synaptic transmission dysregulation in the prefrontal cortex: pathophysiological implications. Mol Psychiatry. 2022; 27(1):445-465.
44. Dandi E, Spandou E, Tata DA. Investigating the role of environmental enrichment initiated in adolescence against the detrimental effects of chronic unpredictable stress in adulthood: Sex-specific differences in behavioral and neuroendocrinological findings. Behav Processes. 2022; 200:104707.
45. Machado-Santos AR, Loureiro-Campos E, Patrício P, Araújo B, Alves ND, Mateus-Pinheiro A, Correia JS, Morais M, Bessa JM, Sousa N, Rodrigues AJ. Beyond new neurons in the adult hippocampus: imipramine acts as a pro-astrogliogenic factor and rescues cognitive impairments induced by stress exposure. Cells. 2022; 11(3):390.
46. Scotton WJ, Hill LJ, William AC, Barnes NM. Serotonin syndrome: pathophysiology, clinical features, management, and potential future directions. Int J Tryptophan Res. 2019; 12:1178646919873925.
47. Kummer KK, Mitrić M, Kalpachidou T, Kress M. The medial prefrontal cortex as a central hub for mental comorbidities associated with chronic pain. Int J Mol Sci. 2022; 21(10):3440.
48. Köhler CA, Freitas TH, Stubbs B, Maes M, Solmi M, Veronese N, de Andrade NQ, Morris G, Fernandes BS, Brunoni AR, Herrmann N. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: systematic review and meta-analysis. Mol Neurobiol. 2018; 55(5):4195-4206.
49. Chakrapani S, Eskander N, De Los Santos LA, Omisore BA, Mostafa JA. Neuroplasticity and the biological role of brain derived neurotrophic factor in the pathophysiology and management of depression. Cureus. 2020; 12(11):e11396.
50. Li W, Ali T, He K, Liu Z, Shah FA, Ren Q, Liu Y, Jiang A, Li S. Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. Brain Behav Immun. 2021; 92:10-24.
51. Rišňovská D. The effect of agonist of the metabotropic glutamate receptors LY 379268 in an animal model of psychosis. Charles University Digital Repository. 2020. Available from: https://dspace.cuni.cz/handle/20.500.11956/122223.
52. Sze WC. BMP3b expression and role in zonation and tumourigenesis in the adrenal cortex (Doctoral dissertation, Queen Mary University of London). 2020.
53. Machado-Santos AR, Loureiro-Campos E, Patrício P, Araújo B, Alves ND, Mateus-Pinheiro A, Correia JS, Morais M, Bessa JM, Sousa N, Rodrigues AJ. Beyond new neurons in the adult hippocampus: imipramine acts as a pro-astrogliogenic factor and rescues cognitive impairments induced by stress exposure. Cells. 2022; 11(3):390.
54. Misrani, A, Tabassum S, Wang M, Chen J, Yang L, Long C. Citalopram prevents sleep-deprivation-induced reduction in CaMKII-CREB-BDNF signaling in mouse prefrontal cortex. Brain Res Bull. 2020; 155:11-18.
55. Tarai S, Mukherjee R, Gupta S, Rizvanov AA, Palotás A, Chandrasekhar Pammi VS, Bit A. Influence of pharmacological and epigenetic factors to suppress neurotrophic factors and enhance neural plasticity in stress and mood disorders. Cogn. Neurodyn. 2019; 13(3):219-237.
56. Wang G, An T, Lei C, Zhu X, Yang L, Zhang L, Zhang R. Antidepressant-like effect of ginsenoside Rb1 on potentiating synaptic plasticity via the miR-134–mediated BDNF signaling pathway in a mouse model of chronic stress-induced depression. J Ginseng Res. 2022; 46(3):376-386.