Proceedings of 3rd International Conference on Interdisciplinary Humanities and Communication Studies
DOI: 10.54254/2753-7064/40/20242331

Neuroplasticity and Cocaine Exposure During Adolescence

Xinyi Zeng[1,a,*]

[1]*School of Social Sciences, University of California Irvine, California, United States*
a. Zengx14@uci.edu
**corresponding author*

Abstract: The adolescent brain is particularly vulnerable to the effects of cocaine exposure due to ongoing neurodevelopment especially in areas that are crucial for cognitive and emotional regulation. This review explores the multifaceted impact of cocaine on neuroplasticity during adolescence, thereby highlighting both the immediate and long-term consequences of drug exposure. Key findings from recent studies indicate that cocaine use during adolescence leads to significant alterations in synaptic plasticity, dendritic spine morphology, and neurotransmitter systems, which may persist into adulthood and contribute to addictive behaviors. Additionally, the interaction between genetic predispositions, environmental stressors, and drug exposure is emphasized. The review also analyzed the risks of early-life stress and social isolation on cocaine-induced neuroplasticity, which can render anxiety-related behaviors and lead to neurological changes. Future studies should incorporate longitudinal design to understand the long-term trajectory of neuroplasticity induced by cocaine. This paper can provide some suggestions to the development of prevention and intervention programs for adolescents at risk.

Keywords: neuroplasticity, cocaine exposure, adolescence.

1. Introduction

The importance of studying neuroplasticity and cocaine exposure during adolescence is multifaceted. First, understanding the developmental stage of adolescence is crucial because this period is marked by profound brain maturation and increased vulnerability to substance abuse. The prefrontal cortex, responsible for executive functions such as decision-making, impulse control, and risk assessment, is still developing during adolescence. This developmental stage is critical for shaping lifelong cognitive and behavioral patterns. Second, investigating the impact of cocaine on neuroplasticity during adolescence is important for identifying the specific neural mechanisms that undergo within addiction and its long-term consequences. This knowledge can contribute to the development of targeted interventions and prevention strategies aimed at mitigating the adverse effects of cocaine on the adolescent brain [1]. Finally, studying this topic can lead to the improvement of intervention programs and systems designed for adolescents at risk of substance abuse. By understanding how cocaine exposure affects neuroplasticity during this critical developmental period, researchers and clinicians can develop more effective therapeutic approaches to support recovery and promote healthy brain development [2].

Existing research on neuroplasticity and cocaine exposure during adolescence has identified several key trends and theories. One prominent trend is the focus on the effects of cocaine on synaptic

DOI: 10.54254/2753-7064/40/20242331

plasticity, particularly in the prefrontal cortex and limbic regions of the brain. Studies have shown that cocaine use during adolescence can lead to alterations in synaptic strength, dendritic spine morphology, and neurotransmitter systems, which can persist into adulthood and contribute to addictive behaviors [1-2].

The main theories in this field revolve around the concept of drug-induced neuroplasticity and its role in addiction. The "reward pathway" theory suggests that cocaine enhances synaptic plasticity in the brain's reward circuitry leading to increased drug-seeking behavior and reinforcing the addictive cycle. Additionally, the "developmental neuroplasticity" theory posits that adolescence is a period of heightened vulnerability to drug-induced changes in neural circuits, which can have long-lasting effects on behavior and cognition [1]. Despite the significant progress in understanding the effects of cocaine on neuroplasticity during adolescence, several gaps remain in this field. One major gap is the limited research on the long-term effects of adolescent cocaine exposure on cognitive and behavioral outcomes in humans. While animal studies have provided important insights, translating these findings to human populations requires further investigation [1].

Another gap is the lack of research on the interaction between genetic and environmental factors in modulating the effects of cocaine on neuroplasticity during adolescence. Understanding the interplay between genetic predispositions and environmental influences, such as stress and peer pressure, can provide a more comprehensive understanding of the risk factors and protective mechanisms associated with cocaine use in adolescents 1. Additionally, there is a need for research on the effectiveness of specific interventions and treatment strategies for adolescents with a history of cocaine use. While various therapeutic approaches have been explored, including behavioral therapies and pharmacological treatments, their efficacy in promoting neuroplasticity and recovery in adolescent populations remains understudied [1].

This review aims to address these gaps by synthesizing existing research on neuroplasticity and cocaine exposure during adolescence and highlighting studies that focus on the long-term effects, genetic and environmental interactions, and intervention strategies. The relevant studies in terms of their methodologies and findings will be discussed in this paper, which could possibly provide a comprehensive overview of the current state of knowledge in this field. By identifying the gaps and proposing directions for future research, this review aims to contribute to the development of more effective interventions and support systems for adolescents at risk of cocaine abuse [1-2].

Understanding the impact of cocaine exposure on neuroplasticity during adolescence is crucial for developing targeted interventions and prevention strategies. By addressing the gaps in existing research and exploring the complex interactions between genetic, environmental, and developmental factors, it’s helpful in enhancing understanding of the neural mechanisms underlying addiction and promote healthier outcomes for adolescents [2].

2. Cocaine Exposure During Adolescence: Long-Term Impact on Neuroplasticity

Cocaine exposure during adolescence has a significant impact on neuroplasticity, which could possibly lead to lasting changes in brain function that can persist into adulthood. This period of brain development is marked by heightened plasticity, making it particularly vulnerable to external influences such as drug use. Research has shown that cocaine use during this critical time can lead to alterations in neural circuitry, including changes in synaptic plasticity and neurotransmitter systems, which are associated with long-term behavioral consequences.

The study conducted by Parsegian and other researchers examined the long-term effects of cocaine exposure during adolescence on neuroplasticity using a rat model. The researchers administered a 7-day cocaine injection to adolescent high-responder rats. They found that cocaine exposure led to persistent psychomotor sensitization and significant alterations in histone modifications within the nucleus accumbens (NAc) including a decrease in repressive H3K9me3 and an increase in permissive

DOI: 10.54254/2753-7064/40/20242331

acH3K9 [3]. This study combined detailed behavioral assessments with targeted epigenetic analyses, which highlights the effects of adolescent cocaine use on brain structure and function, and underscoring the importance of early prevention strategies. Adolescence is a developmental period marked by heightened neuroplasticity, during which the brain is particularly vulnerable to external influences such as drug exposure. The persistence of psychomotor sensitization and epigenetic changes observed in the study indicates that cocaine use during adolescence can lead to substantial alterations in brain function, which may expose individuals to the harm of addiction. The decrease in repressive histone and the increase in permissive ones suggest that cocaine exposure during this period can fundamentally alter gene expression patterns, thereby locking in a heightened vulnerability to addictive behaviors. These molecular changes also reinforce the idea that interventions during adolescence are crucial. This research suggests the need for implementing prevention strategies such as careful education, early intervention programs, and strict policies that limit adolescents' access to drugs, which could reduce the likelihood of long-term addiction and related mental health issues.

3. Genetic and Environmental Influences on Adolescent Neuroplasticity: The Role of PDE4 in Cocaine-Induced Vulnerability

Adolescence is critical for healthy cognitive and emotional development. Also, the combination of genetic vulnerability and environmental stress during adolescence can increase the vulnerability to neuroplasticity induced by cocaine exposures. In the study conducted by Hikida and other researchers who genetically modified rats to carry a dominant-negative mutation in the DISC1 gene, making them prone to neuropsychiatric disorders. These genetically vulnerable rats were subjected to social isolation during adolescence to simulate environmental stress, creating a gene-environment interaction (GXE) as the independent variable. The dependent variables were locomotor activity following cocaine administration and conditioned place preference (CPP), both of which measure drug-induced neuroplastic changes [4].

The results showed that GXE mice exhibited significantly greater locomotor sensitization and a stronger preference for the cocaine-paired environment compared to controls. The study also found a significant increase in PDE4 activity in the nucleus accumbens (NAc) of GXE mice, suggesting altered cAMP signaling, which contributes to their enhanced cocaine sensitivity and the persistence of addictive behaviors. Importantly, administering rolipram, a PDE4 inhibitor, before cocaine exposure blocked these effects, indicating that PDE4 could be a potential therapeutic target for preventing cocaine addiction in individuals with genetic vulnerability and environmental stress during adolescence. The study emphasizes the importance of gene-environment interactions in addiction development and identifies PDE4 as a key molecular target for intervention.

These results strongly support the idea that the interaction between genetic predisposition and environmental stress during adolescence not only heightens the brain’s vulnerability to cocaine but also induces long-term molecular changes that could perpetuate addictive behaviors even after the cessation of drug use. It also underscores the importance of understanding these interactions to develop effective interventions that target the molecular pathways involved in addiction, particularly during the critical period of adolescence. By highlighting the role of PDE4 in these processes, the research provides a specific target for therapeutic interventions aimed at reversing or preventing the neuroplastic changes associated with cocaine addiction.

4. The Role of Early-Life Stress in Modulating Cocaine-Induced Neuroplasticity and Negative Affect

Early-life stress, an adverse experiences or environmental challenges occurred during critical period of developments especially childhood and adolescence, exacerbates the long-term neuroplastic and

DOI: 10.54254/2753-7064/40/20242331

behavioral effects of cocaine exposure during adolescence, thereby creating a compounded risk for the development of addiction and negative affective states. In 2021, Bis-Humbert and other researchers examined the combined effects of early-life stress and adolescent cocaine exposure on behavioral and neurochemical outcomes in female rats. In the experiment, female Sprague-Dawley rats were subjected to maternal deprivation on postnatal day 9 and then exposed to a 7-day cocaine regimen during adolescence (postnatal days 33–39) [5]. The results indicated that early-life stress alone did not significantly alter behavior during adolescence. However, when it combined with cocaine exposure, it led to a pronounced increase in negative affect during adulthood. This was evidenced by increased immobility in the forced swim test and reduced exploratory behavior in the open field test, signaling a pro-depressive state. Moreover, the combination of stress and cocaine exposure resulted in elevated levels of the neuroplasticity marker FADD in the hippocampus, suggesting long-lasting structural changes in the brain that contribute to the observed behavioral alterations. The elevated levels of neuroplasticity markers like FADD in the hippocampus suggest that these stressors lead to lasting changes in brain structure, increasing vulnerability to negative affect and addiction in adulthood. The observed pro-depressive behaviors indicate that the brain's response to these combined stressors may predispose individuals to psychiatric disorders. This highlights the importance of early interventions aimed at reducing stress to intervene or prevent this factor from being the possible influencer that causes future development of drug addiction and related mental health issues.

4.1. Long-Term Consequences of Chronic Social Stress During Adolescence on Anxiety-Related Behaviors

If stress is not be resolved in time, it will become chronic stress. Chronic social stress during adolescence has long-term effects on anxiety-related behaviors, which suggests that this critical period is particularly sensitive to stressors that can alter emotional regulation later in life. Research shows that the prolonged exposure to social stress during this developmental stage can lead to persistent changes in brain regions associated with anxiety, thereby resulting in producing anxiety-related behaviors in adulthood. In 2019, Caffino and other researchers explored the long-term effects of chronic social stress on anxiety behaviors in adolescent rats and its impact in adulthood. The independent variable was exposure to chronic social stress during adolescence, while the dependent variables included anxiety-related behaviors measured through tests like the elevated plus maze and open field test, and changes in neurobiological markers such as corticotropin-releasing factor (CRF) expression in the brain [6].

This study involved subjecting adolescent rats to social or isolation stress over several weeks. After this the rats matured into adulthood without further stressors, which allowed researchers to attribute any long-term behavioral changes directly to the adolescent stress experience. Behavioral assessments were conducted to evaluate anxiety, and brain tissues were analyzed to investigate changes in CRF expression and other stress-related biomarkers. The results showed that rats exposed to chronic social stress during adolescence exhibited significantly higher levels of anxiety-related behaviors in adulthood compared to controls who have fewer stress. These behaviors were linked to increased CRF expression in brain regions associated with anxiety, such as the amygdala and prefrontal cortex. The persistence of these changes into adulthood suggests that chronic social stress during adolescence can lead to lasting alterations in the stress response system, potentially predisposing individuals to anxiety disorders.

The changes in adulthood suggest that chronic social stress during adolescence can lead to alterations in the stress response system, potentially predisposing individuals to anxiety disorders. This study underscores the critical impact of adolescent stress on long-term mental health, as the heightened neuroplasticity during this developmental period makes the brain particularly susceptible

DOI: 10.54254/2753-7064/40/20242331

to external influences. The increased expression of CRF in key brain regions like the amygdala and prefrontal cortex indicates that the stress system is being reprogrammed in a way that sustains heightened anxiety responses well into adulthood.

These findings highlight the importance of early interventions designed to mitigate the effects of chronic stress during adolescence. By addressing stressors early on, it may be possible to prevent the reprogramming of the stress response system and reduce the risk of developing anxiety-related disorders later in life. Interventions could include therapeutic strategies to enhance resilience, supportive environments, or even pharmacological approaches to modulate stress-related neurobiological changes. Ultimately, this research emphasizes that safeguarding adolescent mental health through early intervention is crucial for preventing long-term psychological consequences.

Chronic social stress during adolescence not only heightens anxiety-related behaviors in adulthood but also leads to lasting alterations in neuroplasticity that underpin these behavioral changes. The interplay between prolonged stress exposure and the developing brain during this critical period sets the stage for enduring neurobiological vulnerabilities, as evidenced by alterations in key neural circuits involved in emotion regulation and stress response. In 2020, Caffino and other researchers examined the long-term effects of chronic social stress during adolescence on anxiety behaviors and neuroplasticity. The study's independent variable was the exposure to chronic social stress while the dependent variables included anxiety-related behaviors. Research was measured through elevated maze and open field tests, and changes in neural markers like brain-derived neurotrophic factor (BDNF) expression in the hippocampus [7].

Adolescent rats were exposed to chronic social stress over an extended period, and after the stress exposure, they were allowed to mature without further stressors. This approach ensured that any observed changes in adulthood could be directly attributed to the earlier stress experience. Behavioral assessments indicated significantly higher anxiety levels in adulthood for the stressed rats compared to non-stressed controls. This increased anxiety was linked to reduced BDNF expression in the hippocampus, a region critical for emotion regulation and memory. The study suggests that chronic social stress during adolescence leads to lasting modifications in brain plasticity, increasing vulnerability to anxiety disorders later in life.

These findings underscore the crucial role that adolescence plays in brain development and the brain's response to stress. During this period, the brain undergoes significant neuroplastic changes, making it particularly sensitive to external stressors like chronic social stress. The research demonstrates that stress during adolescence can lead to enduring changes in brain regions critical for emotion regulation, such as the hippocampus, where reduced BDNF expression was observed. This reduction in BDNF, a key player in supporting neuroplasticity and cognitive function, suggests that chronic stress during this formative period can disrupt normal brain development, leading to heightened anxiety and other emotional disorders that persist into adulthood. These findings underscore the long-term risks of chronic stress during adolescence, as anxiety-related behaviors persisting into adulthood indicate lasting changes in brain plasticity. This highlights the need for early interventions to mitigate social stress during this critical period, potentially preventing enduring brain alterations that increase the risk of anxiety disorders later in life.

4.2. The Impact of Combined Early-Life Stress and Adolescent Cocaine Exposure on Long-Term Anxiety and Neuroplasticity

The combined effects of early-life stress and cocaine exposure during adolescence on anxiety-related behaviors and neuroplasticity highlight the importance of multiple stressors during critical periods of brain development. This concept is supported by evidence showing that early-life stress can exacerbate the long-term behavioral and neurobiological effects of adolescent drug exposure, which lead to increased anxiety and neuroplasticity in adulthood.

DOI: 10.54254/2753-7064/40/20242331

In Bis-Humbert and other researchers' study, the long-term effects of combining early-life maternal deprivation with adolescent cocaine exposure were examined in male rats. This study was measured through forced swim tests and other behavioral assays, and changes in the expression of neuroplasticity markers, such as Fas-associated protein with death domain (FADD) in the hippocampus [8]. It is also involved in subjecting male Sprague-Dawley rats to a single episode of maternal deprivation on postnatal day 9 followed by a 7-day cocaine regimen during adolescence (postnatal days 33–39) [8]. Behavioral tests aimed to assess anxiety-related behaviors during both adolescence and adulthood and hippocampal tissue was analyzed for changes in FADD expression. The results indicated that the combination of early-life stress and adolescent cocaine exposure led to a significant increase in anxiety-related behaviors in adulthood as it was evidenced by increased immobility in the forced swim test and altered performance in other anxiety-related tasks. Additionally, these rats showed a dysregulation of FADD expression in the hippocampus, with maternal deprivation increasing FADD content during adolescence, but a decrease in FADD levels was observed in adulthood after prolonged cocaine withdrawal. This suggests that the combined stressors induced a long-lasting impact on neuroplasticity, contributing to the persistent anxiety-related behaviors observed. These findings underscore the critical nature of the adolescent period for brain development and the compounding effects of multiple stressors and highlight the importance of considering both early-life experiences and adolescent drug exposure in understanding the development of anxiety disorders and other mental health issues.

4.3. The Long-Term Impact of Social Isolation on Anxiety and Neuroplasticity

Social isolation during adolescence significantly impacts anxiety-related behaviors and neuroplasticity, thereby leading to persistent changes in brain structure and function that extend into adulthood. This concept is supported by evidence showing that prolonged social isolation during critical developmental periods can lead to alterations in brain regions involved in stress and emotion regulation, ultimately resulting in heightened anxiety and other behavioral disturbances. Researchers examined the effects of social isolation on adolescent rats and its long-term impact on anxiety-related behaviors and neuroplasticity. The independent variable in this study was the duration of social isolation during adolescence while the dependent variables included measures of anxiety-related behaviors and neuroplastic changes in the brain such as alterations in synaptic vesicle glycoprotein 2A (SV2A) density in the hippocampus.

This study involved subjecting adolescent rats to prolonged social isolation and then assessing their behavior and brain structure in adulthood. Behavioral tests, such as the elevated plus maze and open field test, were conducted to evaluate anxiety levels. Additionally, brain tissue was analyzed to measure SV2A density, a marker of synaptic activity, in key regions associated with anxiety and stress response, in the hippocampus [9]. The results indicated that rats exposed to social isolation during adolescence exhibited significantly higher levels of anxiety-related behaviors in adulthood compared to socially housed controls. This increased anxiety was accompanied by changes in SV2A density in the hippocampus, suggesting that social isolation led to long-lasting alterations in synaptic activity and neuroplasticity. Specifically, the study found that isolated rats had increased SV2A density in the dorsal and ventral hippocampus, which persisted long after the isolation period had ended. These findings highlight the critical role of social experiences during adolescence in shaping long-term brain development and emotional health. The persistent changes in neuroplasticity observed in the hippocampus suggest that social isolation during this critical period can have enduring effects on the brain's ability to regulate stress and anxiety.

Adolescent social isolation has a significant and lasting impact on both anxiety-related behaviors and the brain's response to cocaine, emphasizing the critical role of early social experiences in shaping long-term mental health outcomes. This relationship is particularly evident in how social isolation

DOI: 10.54254/2753-7064/40/20242331

alters neurobiological pathways that regulate stress and reward, leading to heightened vulnerability to anxiety and substance use disorders in adulthood.

In another study, researchers examined the effects of a brief period of social isolation during adolescence on anxiety-like behaviors and cocaine-induced neuroplasticity in male rats. The independent variable was the exposure to social isolation during adolescence, while the dependent variables included anxiety-related behaviors measured in adulthood and changes in the Wnt/β-catenin signaling pathway, particularly in the prefrontal cortex (PFC) and nucleus accumbens (NAcc), which are crucial regions for emotion regulation and reward processing [10]. This research involved isolating male rats for five days during adolescence (postnatal days 30 to 35) and then assessing their behavior and brain structure in adulthood. Behavioral tests, including the open field test and conditioned place preference (CPP) for cocaine, were conducted to evaluate anxiety levels and cocaine sensitivity. In addition, molecular analyses were performed to measure the activity of the Wnt/β-catenin pathway in the PFC and NAcc [10].

The results revealed that social isolation during adolescence led to a significant increase in anxiety-like behaviors in adulthood, as evidenced by reduced time spent in the center of the open field test, indicating higher anxiety levels. Furthermore, the study found that isolated rats displayed enhanced behavioral sensitization to cocaine, demonstrated by an increased preference for the cocaine-paired environment in the CPP test. At the molecular level, these behavioral changes were associated with decreased activity of the Wnt/β-catenin pathway in the PFC shortly after isolation, which persisted into adulthood, and increased activity of this pathway in the NAcc following cocaine exposure. These findings showcased the profound impact of social isolation during adolescence on long-term anxiety and drug sensitivity. The alteration in the Wnt/β-catenin signaling pathway highlights a potential molecular mechanism through which early-life social experiences can influence vulnerability to anxiety and addiction. This research suggests that interventions aimed at enhancing social interactions during adolescence could be crucial in preventing the development of these disorders.

5. Conclusion

The interaction between genetic predispositions, environmental stress, and drug exposure during adolescence plays a pivotal role in shaping the long-term vulnerability to addiction. Adolescence is a critical developmental stage characterized by significant neuroplasticity, making the brain more adaptable yet also more vulnerable to external influences, such as drug exposure. The introduction of cocaine during this period can lead to profound and enduring changes in neural circuitry, particularly in areas associated with reward and motivation, such as the nucleus accumbens (NAc). Studies have shown that cocaine use during adolescence can alter synaptic strength, dendritic spine morphology, and neurotransmitter systems, which can persist into adulthood and contribute to addictive behaviors. While animal models provide valuable insights, translating these findings to human populations remains a significant challenge. It's important to consider both genetic and environmental factors when assessing the risk of addiction in adolescents. However, there is a need for further research involving human subjects to validate these findings and explore their clinical implications. Additionally, understanding how these interactions manifest in diverse populations with varying genetic backgrounds and environmental exposures is crucial for developing targeted prevention and intervention strategies.

While the current study provides significant insights into the long-term effects of social isolation and cocaine exposure during adolescence on anxiety-related behaviors and neuroplasticity, there are several limitations that must be acknowledged. First, the use of animal models, while informative, may not fully capture the complexity of human experiences and the full range of environmental influences that contribute to anxiety and substance use disorders. Additionally, the study focused primarily on male rats, leaving the potential sex differences in response to social isolation and cocaine

DOI: 10.54254/2753-7064/40/20242331

exposure underexplored. Future research should include both male and female subjects to determine if there are sex-specific effects that could inform more tailored intervention strategies. Another limitation is the relatively limited time duration of the social isolation period (five days), which, while effective in inducing significant behavioral and neurobiological changes, may not fully represent the chronic stress experienced by some individuals during adolescence. Future studies should explore the effects of varying durations and intensities of social isolation to better understand the dose-response relationship and its implications for long-term mental health outcomes.

The findings of these studies demonstrate the critical impact of adolescent social isolation on long-term anxiety and susceptibility to cocaine-induced neuroplasticity. The results suggest that early-life social experiences play a pivotal role in shaping the brain's response to stress and reward, with significant implications for the development of anxiety disorders and substance use disorders in adulthood. The study also emphasizes the importance of early social interactions in promoting healthy brain development and preventing long-term psychological issues. Given the limitations of the current research, future studies should explore sex differences, the effects of varying durations of social isolation, and additional molecular pathways involved in these processes. Ultimately, a deeper understanding of the neurobiological consequences of adolescent social isolation will inform more effective prevention and treatment strategies for anxiety and addiction, improving long-term outcomes for individuals exposed to social stress during critical periods of development.

References

[1] *Piazza, P.V. and Deroche-Gamonet, V. (2013). A multistep general theory of transition to addiction. Psychopharmacology, 229, 387-413.*

[2] *Feltenstein, M.W. and See, R.E. (2013). Systems level neuroplasticity in drug addiction. Cold Spring Harbor Perspectives in Medicine, 3(5), a011916.*

[3] *Parsegian, A., García-Fuster, M.J., Hebda-Bauer, E., Watson, S.J., Flagel, S.B. and Akil, H. (2022). Adolescent cocaine differentially impacts psychomotor sensitization and epigenetic profiles in adult male rats with divergent affective phenotypes. Frontiers in psychiatry, 13, 1024617.*

[4] *Hikida, T., Morita, M., Kuroiwa, M., Macpherson, T., Shuto, T., Sotogaku, N. and Nishi, A. (2020). Adolescent psychosocial stress enhances sensitization to cocaine exposure in genetically vulnerable mice. Neuroscience research, 151, 38-45.*

[5] *Bis-Humbert, C. and García-Fuster, M.J. (2021). Adolescent cocaine induced persistent negative affect in female rats exposed to early-life stress. Psychopharmacology, 238(12), 3399–3410. https://doi.org/10.1007/s00213-021-05955-z*

[6] *Caffino, L., Giannotti, G., Messa, G., Mottarlini, F. and Fumagalli, F. (2019). Repeated cocaine exposure dysregulates BDNF expression and signaling in the mesocorticolimbic pathway of the adolescent rat. The World Journal of Biological Psychiatry, 20(7), 531-544.*

[7] *Caffino, L., Moro, F., Mottarlini, F., Targa, G., Di Clemente, A., Toia, M. and Cervo, L. (2021). Repeated exposure to cocaine during adolescence enhances the rewarding threshold for cocaine-conditioned place preference in adulthood. Addiction Biology, 26(5), e13012.*

[8] *Bis-Humbert, C., García-Cabrerizo, R. and García-Fuster, M.J. (2021). Increased negative affect when combining early-life maternal deprivation with adolescent, but not adult, cocaine exposure in male rats: regulation of hippocampal FADD. Psychopharmacology, 238, 411-420.*

[9] *Rossi, R., Bærentzen, S.L., Thomsen, M.B., Real, C.C., Wegener, G., Grassi-Oliveira, R. and Landau, A.M. (2024). A single dose of cocaine raises SV2A density in hippocampus of adolescent rats. Acta Neuropsychiatrica, 36(2), 109-117.*

[10] *Cuesta, S., Funes, A. and Pacchioni, A.M. (2020). Social isolation in male rats during adolescence inhibits the Wnt/β-catenin pathway in the prefrontal cortex and enhances anxiety and cocaine-induced plasticity in adulthood. Neuroscience Bulletin, 36(6), 611-624.*