



Maternal Substance Use and Early-Life Adversity: Inducing Drug Dependence in Offspring, Interactions, Mechanisms, and Treatments

Maysam Fadaei-Kenarsary^{1*}, Khadijeh Esmailpour^{1,2}, Mohammad Shabani¹, Vahid Sheibani¹

¹Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

²Department of Health Sciences, Faculty of Health, University of Waterloo, Waterloo, Ontario, Canada

*Corresponding Authors: Vahid Sheibani, Emails: vsheibani2@yahoo.com, v_sheibani@kmu.ac.ir and Maysam Fadaei-kenarsary, Email: fadaeikenarsary@gmail.com

Abstract

The likelihood of substance dependency in offspring is increased in cases when there is a family history of drug or alcohol use. Mothering is limited by maternal addiction because of the separation. Maternal separation (MS) leads to the development of behavioural and neuropsychiatric issues in the future. Despite the importance of this issue, empirical investigations of the influences of maternal substance use and separation on substance use problems in offspring are limited, and studies that consider both effects are rare. This study aims to review a few studies on the mechanisms, treatments, genetics, epigenetics, molecular and psychological alterations, and neuroanatomical regions involved in the dependence of offspring who underwent maternal addiction and separation. The PubMed database was used. A total of 95 articles were found, including the most related ones in the review. The brain's lateral paragigantocellularis (LPGi), nucleus accumbens (NAc), caudate-putamen (CPU), prefrontal cortex (PFC), and hippocampus, can be affected by MS. Dopamine receptor subtype genes, alcohol biomarker minor allele, and preproenkephalin mRNA may be affected by alcohol or substance use disorders. After early-life adversity, histone acetylation in the hippocampus may be linked to brain-derived neurotrophic factor (BDNF) gene epigenetics and glucocorticoid receptors (GRs). The adverse early-life experiences differ in offspring's genders and rewire the brain's dopamine and endocannabinoid circuits, making offspring more susceptible to dependence. Related psychological factors rooted in early-life stress (ELS) and parental substance use disorder (SUD). Treatments include antidepressants, histone deacetylase inhibitors, lamotrigine, ketamine, choline, modafinil, methadone, dopamine, cannabinoid 1 receptor agonists/antagonists, vitamins, oxytocin, tetrahydrocannabinol, SR141716A, and dronabinol. Finally, the study emphasizes the need for multifaceted strategies to prevent these outcomes.

Keywords: Addiction, Drug dependence, Maternal separation, Early-life adversity, Early-life stress

Citation: Fadaei-kenarsary M, Esmailpour K, Shabani M, Sheibani V. Maternal substance use and early-life adversity: inducing drug dependence in offspring, interactions, mechanisms, and treatments. *Addict Health*. 2024;16(1):51-66. doi:10.34172/ahj.2024.1478

Received: July 3, 2023, **Accepted:** August 11, 2023, **ePublished:** February 29, 2024

Introduction

Addiction is one of the major issues facing human society and is particularly prevalent in developing nations. Moreover, it contributes to family, societal, and personal issues.¹ Addiction to opioids and opioid use disorders are global epidemics. Sixteen million individuals worldwide have or are currently experiencing opioid use disorder.² Worldwide, opioid use disorders claim the lives of around 120 000 individuals each year.³ With 10% of the population affected, drug use and dependence place substantial health costs on our society.⁴ Approximately 50% of children admitted to hospitals for mental illnesses also have parents diagnosed with substance use disorders (SUDs).⁵ Child maltreatment and parental SUD are linked.⁶ Many types of substance use cause long-lasting

alterations in synaptic transmission and brain circuit function.⁷ Therefore, it would be very useful to directly address possible mechanisms and alterations regarding the increased risk of dependence symptoms in animals and humans exposed to maternal addiction or separation. The alcohol-drinking behaviour of young adult males is impacted by parental factors from early childhood, including active parenting (such as monitoring, setting rules, and being aware of their places) and the perception of their parents' SUD. Consequently, in alcohol prevention initiatives, health practitioners should emphasize the significance of active parenting and parental drug use prevention.⁸ A family history of addiction is a risk factor for SUD. A greater frequency of externalizing disorders, reward processing impairments, and impulsivity are all



present in youth with a family history of SUDs. High-risk adolescents, including those with attention-deficit/hyperactivity disorder and parental SUD, have the highest levels of accuracy and learning impairment.⁹

Parental psychopathology, family environment, sibling, and peer behaviors affect child psychopathology subtypes.¹⁰ Adolescents with drug-dependent parents are at high risk for drug use and dependence. Psychological and interpersonal variables may influence the relationship between parents' psychoactive SUD and adolescent drug use.¹¹ In a study, 18.4% of teenagers reported family member substance or alcohol use, including 50.6% parental alcohol usage and 19.1% parental drug use. Parental drug usage influences the severity of substance dependence, major depressive disorder (MDD), and post-traumatic stress disorder (PTSD).¹² An established risk factor for teenage and adult substance use is a familial history of drug use.¹³ Parental drug use problems, antisocial conduct, and children's disruptive disorders are strongly linked.¹⁴ Parental death and separation may cause drug use.¹⁵ Owing to parental grief, sickness, mental stress, or drug use, sometimes children replace parental duties. If these kids have to over-function as adults, their development may fail.¹⁶ Among different adverse childhood experiences, parental drug use was the only significant explanatory risk factor for nicotine dependence in females.¹⁷ Parental opioid addiction has been linked to a weaker mother-child attachment.¹⁸ People with alcohol and SUDs report more maternal separation (MS), particularly owing to marital discord and parental separations. Paternal separations may not cause drinking, although marital discord may cause opiate addiction.¹⁵

To the best of our knowledge and based on the

searches, the impact of mother drug use, both before and during pregnancy and lactation, as well as MS, on the likelihood of children dependency in terms of molecular, neurobiological, neuroanatomical, and psychological factors and possible interventions would be of importance but are not well understood. Despite the importance of this issue, empirical investigations of the influences of maternal substance use and MS on substance use problems in offspring are sparse and studies that take into account both effects are rare.

Therefore, this review aims to first examine the independent effects of maternal addiction and MS on dependence criteria in offspring and then their combined effects. Secondly, this review summarizes the multiple, interconnected neuroanatomical circuitry, molecular, and psychological factors related to substance-using mothers exposing their offspring to dependence. Thirdly, pre- or post-natal interventions targeting the complex and numerous proximal and distal risk factors crucial to the development of offspring dependence are reviewed. Figure 1 illustrates these factors and their interplay with maternal substance use and offspring dependence, while Table 1 provides a summary of the relevant literature.

Methods

The PubMed database was used. After duplicate deletions, a total of 95 articles were found, of which the most related ones were included in the review. The data were analyzed using content analysis.

Search strategies included:
 ("maternal morphine exposure"[Text Word] OR "maternal separation"[Text Word]) AND "dependence"[Text Word]

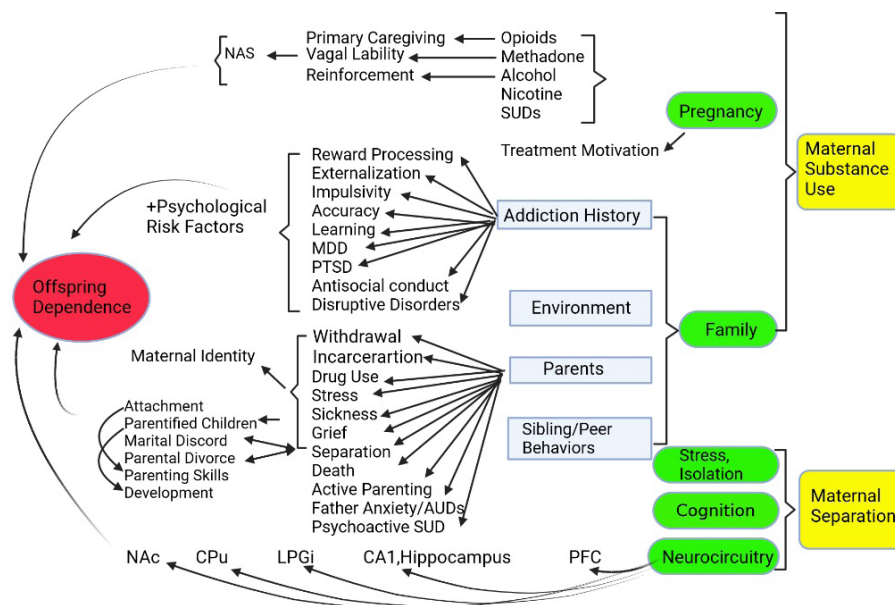


Figure 1. Risk factors crucial to the development of offspring dependence and their interplay with maternal substance use and separation. Substance use disorder(s) (SUD(s)), neonatal abstinence syndrome (NAS), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), alcohol use disorder (AUDs), prefrontal cortex (PFC), cornu ammonis area 1 (CA1), lateral paraventricular nucleus (LPGi), caudate-putamen (CPu), nucleus accumbens (NAc)

Table 1. A summary of the relevant literature on the effects of maternal substance use and separation on the offspring’s drug/alcohol dependence

Species	Age	Gender	Drug type	Model/task/tool	Drug dose/route/duration	MS	Lactation	Study type	Changes in criteria assessed
HS	Neonates	B	Heroin	History and/or physical examination in mothers, narcotic withdrawal in neonates	NR	N	N	R	Forty-one neonates (61%) exhibited withdrawal symptoms. Tremors, agitation, and high-pitched crying were the most prevalent signs. Also, poor feeding, diarrhea, and vomiting were reported. ¹⁹
HS	Before 15 years of age	B	Drugs and alcohol	Family history of alcoholism (brief screening questionnaire) or other drug problems	Most users inject (IV) between 0.5 and 1 g of heroin every day. The typical use period is 12 months, with minimum usage of 6 months and maximum usage of 10 years. All had used other illegal substances, and most had a history of poly-drug misuse before heroin dependency.	Y	N	R	Antisocial personality is associated with early grief and alcohol and substance use. Male sex was associated with more frequent paternal losses and narcotic addiction. Addicts lose more. Alcoholics separated more for most reasons. ¹⁵
HS	16 years or over	M	Alcohol	Semistructured psychiatric interview: the TOSHI	NR	Y	N	CC	Alcohol-dependent males and healthy controls had similar rates of parental death and separation. ²⁰
HS	3 points in time into adulthood	B	Drugs and alcohol	Interview	Maternal smoking 10 or more cigarettes or more nearly every day while pregnant	N	Y	10-year LS	More than five-fold incidence of adolescent-onset drug dependency in girls. ²¹
HS	Adolescence	B	SUDs	SCID	32% of parents had SUDs. Drug use disorders were 17%, alcohol 25%, and drug and alcohol 30%. 29% of children exposed to a drug use disorder, had at least one parent with cannabis use.	N	N	5-year Follow up	Parental SUDs are nonspecific, putting kids at risk for SUDs. Parental SUDs are one of numerous environmental risk factors for SUDs. ²²
HS		B	Methadone, alcohol and substance use	Views of self as a parent	At a mean dosage of 79.4 mg, the average time on methadone maintenance was 3.3 years.	N	N	RCT	A decrease in concurrent alcohol use, and maintenance dose of methadone. ²³
HS	Adolescence	B	Alcohol	C-SSAGA-A) SARAH The SARAH items include both parental alcohol and drug use	Alcohol was consumed by 69% of the mothers and 89% of the dads. 11% of the moms and 20% of the dads engaged in drug usage.	N	N	CS	Adolescent alcohol dependency was highly correlated with father's drug usage. Mother's anger and avoidance while drinking or using drugs were both strongly linked to teenage alcohol dependency; Mother's anger predicted alcohol dependence for females but not for boys. ²⁴
Rr	Adult	M	Morphine	Self-administration of morphine (25 mg/L) utilizing the two-bottle choice paradigm and preference	Oral 2 or 5 mg/kg morphine	Y	Y	A	Although non-deprived animals need 5 mg/kg of morphine to induce conditioning, deprived rats only required 2 mg/kg of morphine to do so. ²⁵
Rr	Adult	M	Morphine, ethanol, amphetamine and cocaine	Long-term continuous free choice self-administration paradigm	Morphine (25 mg/L), ethanol (10%), amphetamine (25 mg/L) and cocaine (100 mg/L) Route	Y	Y	A	78% of the deprived rats demonstrated a gradual reduction in aversion to morphine as their consumption of the morphine rose. Deprived rats exhibited a minor but considerable increase in oral amphetamine intake. ²⁶
HS	12-17	B	Alcohol or drugs	CATI technology/surveys	NR	N	N	CS-Census	Parental drug abuse has identified as a moderating factor for Substance abuse/dependence. ¹²
Rr	2.5–3 months of age	M	Morphine	CPP	Morphine (5 mg/kg) during conditioning to offspring Route	Y	Y	A	BP 897 (0.5 or 2 mg/kg), a selective partial D3 receptor agonist, increased the expression of morphine conditioning in control rats. Same dosages had no effect on rats' morphine conditioning. ²⁷
HS	Neonates		Heroin, Methadone or their combination, barbiturates, benzodiazepines, and marijuana	Type of drug, Neonatal abstinence syndrome	Among the 85 pregnant addicts, 51 (60%) used heroin, 6 (7%) used methadone alone, and 9 (11%) used both heroin and methadone. 15 women (19%) reported using benzodiazepines in conjunction with heroin and/or methadone that was the most common.	N	Y	R, Co	Seventy-one percent incidence of NAS, mostly among infants delivered to heroin and methadone dependent mothers. ²⁸

Table 1. Continued.

Species	Age	Gender	Drug type	Model/task/tool	Drug dose/route/duration	MS	Lactation	Study type	Changes in criteria assessed
Rr	Adolescence	M	Chronic dronabinol (natural THC)	Place preference and oral self-administration over 12 weeks employing a two-bottle choice paradigm	Exposure to dronabinol during postnatal days 35-49. The administration of morphine at a dose of 1 mL/kg with a concentration of 25 mg/L, together with dronabinol, was carried out during a period of abstinence and at higher doses (5 mg/kg or 10 mg/kg i.p.) among postpartum days 35-48.	Y	Y	A	A decrease in PPE mRNA expression in the striatum is associated with an increase in oral morphine self-administration behavior and preference. ²⁹
Mm	8 months and early adulthood (approximately 4 years)	B	Alcohol	Voluntary ethanol consumption experiment, mother- vs. peer-raising paradigm	Two weeks (1 h/d) ethanol solution (final concentration, 8.4% v/v), 7-week voluntary ethanol (5 days/week) experimental phase	Y	Y	A	The dopamine D1 receptor gene may have a role in regulating alcohol use, particularly in the setting of early environmental stress. Males heterozygous for the T gene and without a mother consumed substantially more ethanol. ³⁰
Rr	Adolescent and adult	M	Chronic THC/morphine consumption	Oral morphine self-administration	Oral Morphine (25mg/L) self-administration, Using a two-bottle choice paradigm for 14 weeks. For two weeks, SR141716A, a cannabinoid CB1 receptor antagonist/inverse agonist, was injected chronically at doses of 3 mg/kg and 1 mL/kg.	Y	Y	PS	Alterations in brain endocannabinoid levels in a model of maternal deprivation may be responsible for the increase in morphine consumption. ³¹
HS	Children and adolescents	B	Drugs or alcohol	DAST-20 and AUDIT	Less than 13% of caregivers in the sample reported harmful use or dependence on drugs or alcohol	NCR	NCR	L,R	The incidence of drug problems would be much greater among parents whose children were first taken from the family following an inquiry or evaluation. Caseworkers were less likely to recognize drug misuse when their caseloads were large and when dads were the primary caretakers. 102 (68%) of the youngsters had drug abuse or exposure allegations. ³²
HS	17.9 ± 4.20 years	F	Alcohol or drugs of abuse	Structured psychiatric interviews	Diverse	NCR	NCR	Co	Parental drug use may increase the risk of SUD in these adolescents. Offspring exposed to their mother's drug use problem were 7.40 times more likely to acquire a drug use disorder. ³³
HS	Adolescents and young adults.	B	Alcohol, alcohol/cannabis, nicotine	Telephone-administered diagnostic interviews	NR	NCR	NCR	CS	Offspring with any pattern of comorbidity were more likely to have dads who were not presently married to the biological mother (separated, divorced, or never married). Regarding parental drug use, mother marijuana abuse/dependence was remarkably high in the SUD-CD class (15.2%) and paternal (but not maternal) smoking history was more prevalent in all affected classes. ¹⁰
HS	Adolescents		Alcohol and drugs of abuse	Reward region response to anticipated monetary reward and pictures of alcohol. Structured Clinical Interview for DSM-IV Axis I Disorders, fMRI	26 adolescents among 128 had a parental record of drug use problems (46.2% males, 86% father record, 7% mother record, and 7% father and mother record).	NR	Excluded	CS, Imaging	The brain regions implicated in reward are more responsive in adolescents at risk of future SUDs. ³⁴

Table 1. Continued.

Species	Age	Gender	Drug type	Model/task/tool	Drug dose/route/duration	MS	Lactation	Study type	Changes in criteria assessed
HS	Young (mean age 19.51 years)	M	Drugs or alcohol	Abstention, RSOD, volume drinking and dependence	Just 5.8% of Swiss conscripts said they did not drink. Of those who did not abstain, 50.1% reported engaging in RSOD behavior, while 6.9% reported drinking in excess. Of those who did not abstain, 50.1% reported engaging in RSOD behavior, while 6.9% reported drinking in excess. An alcohol dependency was found in 11% of the patients.	NCR	NCR	Co	Self-reported parental characteristics are related with self-reported alcohol use. Both heavy drinking and dependency were much more frequent among young males who reported parental substance abuse. Active parenting was connected with decreased alcohol dependency. ⁸
HS	Mean age of 5.9 years (ranging from 3 months to 20 years)	B	Methadone maintenance treatment	Data collection interviews	NCR	Y	NCR	MM	There was also diminished maternal identity in the subtheme of interrupted mothering or long-term separation of mother and child due to physical separation or inability to provide child care due to illness or withdrawal symptoms. ³⁵
HS	Childhood and adolescence	B	Alcohol, drug, and cigarette	K-SADS CIDI-SAM DSM-III (childhood) or DSM-IV (young adult) criteria (APA, 2000)	N	NCR	Y	L,P (Co)	Cigarette use in kids was predicted by prenatal exposure to cigarettes. Alcohol intake during pregnancy was linked to a greater likelihood of SUD in the child. Family record of SUD increases risk for substance use. ³⁶
HS	Preadolescent (≤ 12) or adolescent (> 12) years) to young adulthood	B	Non-nicotine SUD and Alcohol	Cox proportional hazard models	Diverse	NCR	NCR	L, CC + 10-year follow-up (Co)	Prenatal alcohol exposure was linked to an increased risk for offspring SUD. Prenatal cigarette exposure predicted offspring cigarette smoking. Risk of drug use rises in families with SUD. ³⁷
Rr	Adult	M	Alcohol	Continuous voluntary alcohol drinking protocol (two-bottle choice) and food self-administration	Started on PND 130. Over a 10-day period, single-housed rats had continuous access to water and 10% (w/v) alcohol	Y	Y	A	• High alcohol intake is linked to MD, high anxiety, high CB1R expression in the NAc, and low CB1R production in the PFC. ³⁸
Rr	Adult	M	Alcohol	Continuous voluntary alcohol drinking (two-bottle choice) for 10 days (grams of alcohol/ body weight (kg) and percent preference for alcohol relative to liquid intake)	Continuous voluntary alcohol drinking (10 % alcohol solution (w/v)) started on PND 64 and lasted until PND 74	Y	Y	A	In addition to increasing D2R, D3R, and CB1R expression in the NAc, MS, aSI, and MS + aSI significantly increased anxiety and alcohol consumption. More alcohol was taken in and favored by MS rats. aSI rats had higher desire for and consumption of alcohol. ³⁹
HS	13–17 years	B	Nicotine	European Addiction Severity Index, seven-item mFTQ for assessment of the level of ND, modified Fagerström Tolerance	Alcohol, drugs or other substances Doses and duration: NCR	Parental divorce	NCR	CS, R	Regular smoking in teenage females was linked to violent ACEs, including: witnessing domestic violence, physical and sexual abuse by parent(s), parental divorce, and drug use. Just one kind of ACE, parental drug use disorders, accompanied by frequent, moderate, or high levels of ND. The characteristics of regular smokers were old age, drug use, and conduct disorders. ¹⁷

Abbreviations: APA, American Psychiatric Association; HS, *Homo sapiens*; Rr, *Rattus rattus*; Y, Yes; N, No; NCR, Not clearly reported; L, Longitudinal study; P, Prospective; R, Retrospective; CC, Case-Control; CS, Cross-sectional; A, Animal; RCT, Randomized clinical trial; Co, Cohort; MM, Mixed method; Mm, *Macaca mulatta*; IV, Intravenous; SD, Standard deviation; SUD, substance use disorder; CD, conduct disorder; EPM, elevated plus maze; g, gram; IV, Intravenous; NAS, Neonatal abstinence syndrome; PPE, Preproenkephalin; mRNA, Messenger ribonucleic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; fourth edition; CB1R, Cannabinoid receptor type 1; D2R, Dopamine D2 receptor; D3R, Dopamine D3 receptor; NAc, Nucleus Accumbens; TOSHI, Time-Ordered Stress and Health Interview; SCID, Structured Clinical Interview for the DSM-IV; C-SSAGA-A, Comprehensive Semi-Structured Assessment for the Genetics of Alcoholism for Adolescents; SARA, Structured Assessment Record of Alcoholic Homes; CATI, Computer Assisted Telephone Interviewing; CPP, conditioned place preference; THC, delta-9 tetrahydrocannabinol; DAST-20, Drug Abuse Screening Test; AUDIT, Alcohol Use Disorders Identification Test; RSOD, risky single occasion drinking; aSI, adolescent social isolation; ACEs, adverse childhood experiences; ND, nicotine dependence; CIDI-SAM, CIDI-Substance Abuse Module.

(“maternal substance use”[Text Word] OR “maternal separation”[Text Word]) AND “dependence”[Text Word]

(“maternal addiction”[Text Word] OR “maternal separation”[Text Word]) AND “dependence”[Text Word]

(“maternal substance abuse”[Text Word] OR “maternal separation”[Text Word]) AND “dependence”[Text Word]

(“maternal substance use”[Text Word] OR “maternal deprivation”[Text Word]) AND “dependence”[Text Word]

(“parental substance use”[Text Word] OR “maternal deprivation”[Text Word]) AND “dependence”[Text Word]

(“parental addiction”[Text Word] OR “maternal separation”[Text Word]) AND “dependence”[Text Word]

(“parental addiction”[Text Word] AND “maternal separation”[Text Word] AND “dependence”[Text Word])

The data were collected on all dates. Preclinical or human studies that clearly referred to the effects of maternal substance use and/or separation or deprivation (interventions, mechanisms, prevention, or treatment strategies) on offspring dependence were included in the present study. Articles that indirectly referred to addiction or were restricted to one aspect of addiction or comorbidities (not related to maternal substance use, separation or offspring dependence) were excluded.

Results

Maternal substance use

Prenatal alcohol, cigarette, and other drug exposures have several negative effects on offspring, including an increased risk for substance use and addiction.³⁶ Even when accounting for psychopathology, only 38% of opioid-using mothers remained primary-caregiver of their children throughout the 10 years compared to other mothers (81%).⁴⁰ Children born to mothers who smoked during pregnancy had an increased possibility of having fathers with alcohol and/or anxiety disorders, while simultaneously displaying a decreased probability of developing substance abuse difficulties themselves. The association between mother smoking during pregnancy, early-onset conduct disorder in males, and drug use in girls was not influenced by the father’s diagnosis.²¹ Alcohol use disorder (AUD) rises with prenatal, infant, and adolescent ethanol exposure. Early exposure to ethanol’s positive and negative reinforcing effects may cause this.⁴¹ The most relevant literature is summarized in [Table 1](#).

Public health necessitates that pregnant women should avoid alcohol and tobacco. A family history of alcoholism tends to increase maternal drug use during pregnancy.³⁶ Moreover, women who experienced vagal tone

reactivity (activation or suppression) after methadone at the end of pregnancy had babies with more severe neonatal abstinence syndrome (NAS). Nevertheless, it has been found that no relationships exist between NAS expression and maternal methadone maintenance characteristics such as trimester of commencement, duration, methadone exposure throughout pregnancy, and maternal drug use before pregnancy.⁴²

Pregnancy offers substance-using moms a “window of opportunity” for treatment motivation.⁴³ Prenatal therapies that focus on the maternal-fetal attachment link and the mother’s capacity to reflect on her baby, mothering, and attachment history also help substance-using women acquire parenting skills. Addiction pregnancies are infrequent but high-risk. Proper obstetric and neonatal care can reduce pregnancy complications and improve perinatal outcomes.²⁸ Additionally, it has been suggested that there are worldwide deficiencies in neurological and substance-related caregiving systems. They should be addressed throughout pregnancy by encouraging abstinence, emerging motherhood, and a bond with the fetus.⁴⁴ The literature on prenatal opioid exposure takes into account that this is not just a one-time occurrence but rather a cycle of events that can span across generations. Various mechanisms of transmission from one generation to the next are identified, including gut-brain axis and biological factors such as genetics, and epigenetics. Furthermore, this intergenerational cascade is influenced by various parent-child interactions, such as past events of child maltreatment, the level of parenting quality, infant behaviors, the diagnosis of neonatal opioid withdrawal, and wider environmental concerns such as stigmatization by society and destitution, engagement with childcare agencies, and exposure to aggression.⁴⁵

Summary

A family record of using alcohol or drugs heightens the likelihood of dependence and NAS in offspring. Proper obstetric and neonatal care and encouraging abstinence can reduce pregnancy complications and improve motherhood and perinatal outcomes.

Maternal separation

Parental loss, abuse, and social deprivation are rodent and primate models of early trauma.⁴⁶ Stress, inflammation, and starvation in early childhood may cause psychopathology or cognitive impairments in maturity. Childhood trauma causes antisocial behavior and drug use. Antisocial people often use drugs.¹⁵ Maternal care deficits harm CNS development and offspring mental health.⁴⁷ The MS animal paradigm has been accepted as a preclinical model of early-life stress (ELS), an essential determinant for mental disorders.⁴⁸ There are two models, which have been given the name “MS”, vary in ways that distinctly shift the stress between

the mother and her offspring units. The distinction is that early maternal deprivation (MD) separates pups on an individual basis, while the mother is left with a portion of her littermates at home rather than being left alone. The alternative variant, designated MS, separates the pups while isolating the mother in a unique cage.⁴⁹ Since MS and MD might differ in some aspects, the usage form of each word in the manuscript was based on the original reference.

Mother-pup interaction affects mammalian development. Behavioral and neuropsychiatric issues might result from MS. Maternal morphine exposure may exacerbate MS-induced spatial learning and locomotor activity in adolescent male rats.⁵⁰ MS causes long-term brain development changes and hippocampus-related neuropsychiatric, cognitive, learning, and memory impairments.⁵¹⁻⁵³ MS may impede CA1 hippocampal long-term potentiation (LTP) induction in adolescent female rats.⁵¹ External effects appear highest during times of experience-based development or natural oxytocin oscillations.⁵⁴ Furthermore, MD from post-natal days (PND) one to 14 (pups were separated from 13:00 to 16:00) extends morphine conditioned place preference (CPP).²⁷ MD rats have increased susceptibility to the pleasurable effects of morphine, making them an appropriate candidate for investigating their behavior using a two-bottle-choice experimental setup. During the plateau phase of the experiment, MD rats had a morphine consumption rate that, compared to rats who were not deprived, was double as high.²⁵ Brief MS may protect mice against alcohol addiction, but protracted neonatal separations may dose-dependently increase adult alcohol consumption.^{4,55} Postnatal environment modification increases morphine dependence and hypersensitivity to its reinforcing effects.⁴ People with AUDs had greater maternal losses than controls. They also had longer and more frequent losses and were more likely to lose a mother. 25% of people with AUDs and 9% of controls had parental separations.¹⁵ However, there is evidence that childhood parental loss and alcohol use are not directly related. Alcohol-dependent males and healthy controls had similar rates of parent death and separation.²⁰

Summary

MS increases polydrug self-administration and sensitivity in adulthood. Hence, MS may be a valid paradigm for the evaluation of drug addiction therapies in traumatized children.⁴ MD in rodents is a viable model of ELS that causes significant anxiety, motivation,³⁸ and cognitive⁵⁰ changes, which may enhance sensitivity to alcohol³⁸ and drug dependence.

Combination of maternal addiction and MS

Early MD and morphine use impair brain development. Hence, early morphine and MD may alter core phenotypic

traits that are adaptive in adulthood.⁵⁶ Addiction weakens parental identity by limiting mothering and interrupting it due to separation. Reduced maternal identity was evident in cases of interrupted mothering or prolonged mother-child separation brought on by illness, physical separation, or withdrawal symptoms. The act of separating from their children greatly distressed the mothers. Some women stopped caring for their children or chose to separate from them altogether as a result of committing crimes such as check fraud or robbery in order to acquire funds for drugs. Additionally, many mothers were separated from their children due to being incarcerated.³⁵

Children who experienced their mother smoking when she was pregnant had a 1.75-fold increased risk of experiencing parental divorce and a 2-fold increased risk of seeing conflict between parents and children (Risk ratio [RR]=2.03). Male kids had a higher risk of conduct disorder (CD) at prepubertal onset (RR=5.67), whereas female offspring had a higher risk of drug use/dependence at teenage onset (RR=4.68). 70% of drug-using women utilized several substances. Only parental divorce was related to male prepubertal-onset CD and significantly lowered maternal smoking's effect size. Males who experienced their mother smoking while pregnant showed a greater frequency of prepubertal-onset CD (RR=4.1) even after adjusting for divorce. CD and substance use/dependence models incorporated interaction factors for alcohol, smoking, and coffee consumption of mother during pregnancy.²¹

Summary

Maternal addiction diminishes parental identity by restricting and halting mothering due to separation. MS enhances male prepubertal-onset CD and female adolescent drug dependence.

Neurocircuitry involved in the effects of MS

In MD animals, it was shown that lateral paragigantocellularis (LPGi) neuron interspike interval variability was reduced in both inhibitory and excitatory responses at baseline. Deprived animals had less morphine-induced discharge inhibition. The observations suggest that acute morphine use in MD during their early years alters LPGi neuronal activity over the long run. Hence, MD may change adult opiate use risk.⁵⁷ MD rats showed decreased preproenkephalin (PPE) mRNA in their nucleus accumbens (NAc) and anterior caudate-putamen (CPu) nuclei. In the NAc, MD rats displayed a similar drop in PPE mRNA levels in the four main subregions. MD may lower striatal PPE mRNA levels. Variations may be explained by differences in methodology (separation procedure, quantification of peptides, brain regions, and origins of peptides).²⁵ Dronabinol restored normal levels of PPE reduction in

the striatum, morphine consumption, and susceptibility to morphine conditioning in MD rats.²⁹ MD induces inflammatory biomarkers (in the prefrontal cortex [PFC] and hippocampus),⁵⁸ long-term changes in hippocampal microglia, spatial memory, and depressive-like behavior via synaptic gene expression.⁵⁹ MS can also impair average field excitatory post-synaptic potentials, induction of early LTP, and maintenance in the CA1 area of the offspring's hippocampus.⁶⁰ MD affects neuroendocrine responses to stress by dysregulating the hypothalamic-pituitary-adrenal (HPA) axis.⁶¹ MS reduces the number of c-Fos positive cells and plastic capacity of the medial amygdala, paraventricular nucleus of the hypothalamus, lateral septum (LS), NAc, and medial PFC.⁶² LS contributes to the regulation of NAc function.⁶³ Taken together, these neuroanatomical structures seemed to be linked to the neural networks of maternal behavior,⁶⁴ anxiety,⁶⁵ and reward circuits. Hence, animal models can shed light on the underlying neuroanatomical circuits modified by MS. Family, psychological risk factors, and neuroanatomical regions involved in maternal substance dependence and separation effects on the offspring's substance dependence are summarized in [Figure 1](#).

Summary

Many brain structures, including the LPGi, NAc, CPu, PFC, and hippocampus, can be affected by MS.

Sex differences in maternal substance use and separation outcomes

After unfavorable childhood experiences, girls smoke more and become more nicotine dependent than boys. Why adolescent boys develop no such habits is unknown.¹⁷ However, males under stress exhibit increased susceptibility to the stimulating effects of alcohol and are more inclined to initiate drinking for its pleasurable outcomes; thus, the genetic influence is primarily seen in them.³⁰ MS affects male rats' alcohol intake more than females, according to most investigations.⁵⁵ Notable exceptions to the models of parents and peers' effects on externalizing behavior and drug use were found according to gender.⁶⁶ Only MD males showed depressive-like behavior in the forced swimming test, while both sexes showed a reduction in grooming time. Gender affects treatment responsiveness to MDD induced by ELS. Treatments including electroconvulsive stimulation with ketamine or escitalopram had a gender-dependent impact (e.g., a reduction of catalase activity only in females' hippocampi were reported).⁵⁸

Summary

Following negative early experiences, girls may be more susceptible to developing SUDs and nicotine addiction compared to boys. Men with high levels of stress are more likely to drink alcohol due to its higher perceived reward

value. MD has been shown to induce behaviors similar to depression in animals. Moreover, an individual's gender can influence their response to therapy for MDD.

Role of genetics in offspring dependence induced by maternal substance use and separation

Pregnant women from SUD households are more likely to use drugs.³⁶ Prenatal nicotine exposure is linked to several adult-onset, basal metabolic index, and weight-related health issues in 235 children from families stratified for familial/genetic risk for alcohol and smoking dependence.⁶⁷

On the other side, dopamine receptor subtype genes are promising potential loci for understanding alcohol dependence and its associated behavioral phenotypes. A genotype-gender-environmental interaction has been reported. The dopamine D1 receptor (DRD1) locus's effect on alcohol intake is modest and only phenotypically quantifiable in certain gender and rearing condition combinations. The alcohol biomarker minor allele (T) influences MD men and works as a biomarker of susceptibility to alcohol use. The DRD1 locus may make people more likely to use alcohol as an anxiolytic. The D1 receptor modulates alcohol consumption in primates and non-primates. D1 receptor gene alterations may influence alcohol intake and motivating behaviors in a rhesus model. This research found a DRD1 restriction site polymorphism near the transcription start point. It is not clear whether the consequences of this polymorphism are functional.³⁰

In MD rats' NAc and CPu nuclei, PPE mRNA expression decreased significantly.²⁵ Extended treatment of dronabinol in AFR rats heightened their susceptibility to morphine conditioning in the place preference model. It reduced the PPE mRNA concentration in the NAc and CPu nuclei, but it didn't change the preference for oral morphine.²⁹ Yet, a strong heritable general liability causes parent-child transmission of externalizing psychopathology¹⁴ that is related to offspring substance dependence.^{66,68} A graphical abstract sums up the evidence from genomics, epigenomics, proteomics, and metabolomics about how SUD and MS in the mother affect substance dependence in the child and how they might interact with each other as shown in [Figure 2](#).

Summary

Adult-onset health problems have been found to be associated with prenatal exposure to nicotine in children from families classified based on their familial or genetic dependence on alcohol and smoking. The dopamine receptor subtype genes, the DRD1 locus, the restriction site polymorphism, and the T allele alcohol biomarker in men with MD are all genetic factors that are affected by AUD or SUD. Additionally, alcohol or SUDs have an impact on PPE mRNA and the parent-child transmission of externalizing psychopathology.

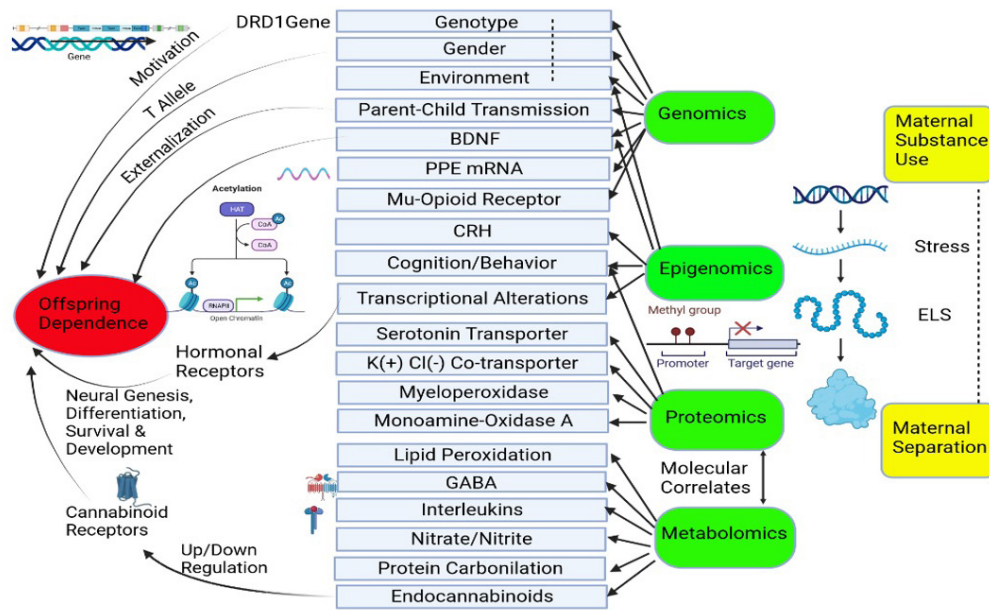


Figure 2. Genomics, epigenomics, proteomics, and metabolomics mechanisms involved in the effects of maternal SUD (Substance Use Disorder(s)) and MS (Maternal Separation) on the offspring's substance dependence and possible interactions among them

Epigenetic regulation in the context of maternal separation

Evidence suggests that ELS has diverse molecular and behavioral effects over the lifespan. Epigenetic processes may contribute to temporally specific transcriptional alterations after ELS.⁶⁹ Glucocorticoid receptor (GR) activation is one way these stressful events alter brain development. Hormone receptors are key epigenetic targets for developmental program changes. Transcription factors are the principal hormonal receptors. Neurogenesis, neural fate, differentiation, and survival are all linked to such receptors.⁷⁰ Some transcription factors include the transcription factor nerve growth factor inducible protein A, STAT5, and heat shock transcription factor 1.⁷¹ Childhood maltreatment in humans is associated with a reduction in hippocampus GR expression and an increase in stress responses throughout adulthood. The aforementioned effects are modulated by epigenetic processes, namely DNA methylation and hydroxymethylation within the GR gene's promoter regions. The elucidation of histone post-translational changes occurring in the promoter region of the GR in the hippocampus of rats has been described.⁷²

MS induces transgenerational behavioral impairments that could be inherited via epigenetic mechanisms.⁷³ MS produces long-term brain epigenetic alterations and enhances adult traumatic events sensitivity. The epigenetic fingerprints of the brain-derived neurotrophic factor (BDNF) genes may be associated to histone acetylation in the hippocampus as a reaction to stress, which may be useful for people exposed to stress-related psychopathologies.⁷⁴ Expression of the transcription factor cAMP response element-binding protein and

neuropeptide Y and a reduction of Jun-B mRNA have been reported after MS. Jun-B is one of four genes in the activator protein-1 complex that could be epigenetically regulated.⁷⁵ ELS triggers epigenetic modifications in genes outside the HPA axis, including BDNF, the serotonin transporter (5-HTT or Slc6a4) gene, the estrogen receptor- α gene, glutamate decarboxylase-1, and Reelin genes.⁷¹

The amount and quality of early-life maternal care are major contributors to lasting, bidirectional changes in gene expression patterns. These include glucocorticoids and corticotropin-releasing hormone (CRH) which are associated with phenotypes that are resistant or sensitive. Several essential questions remain unanswered. The mechanism by which maternal-derived signals reach specific neuronal populations that regulate gene expression through epigenetic mechanisms is not yet fully understood. The available data on this topic is still limited. It is not yet clear how neurons "switch on" the epigenetic machinery. The question of how gene expression impacts function remains an active area of research. However, recent studies have shown that CRH-expressing hypothalamic neurons that regulate stress response amplitude can be affected by recurring bursts of sensory input from the mother, which is commonly referred to as "mother's love".⁷⁶

Summary

Following exposure to ELS, epigenetic mechanisms can have a temporal impact on transcription. Stress can activate GRs, leading to changes in brain development. MS has been shown to cause long-term alterations in brain epigenetics. There is evidence to suggest that stress-induced histone acetylation in the hippocampus may

be linked to the epigenetics of the BDNF gene. Despite these findings, there are still critical questions that have not been fully answered. One of these questions is how maternal-derived signals reach neuronal populations that regulate epigenetic mechanisms.

Mechanisms of different responses to drug types after MS
MD may induce opposing outcomes.²⁹ MS also variably alters adult reactions to psychostimulants, in line with the extent of its MS history.⁴ Morphine-dependent rats with a history of MS had higher somatic withdrawal ratings.⁷⁷ The oral self-administration testing in a free choice paradigm showed that MD rats finally took more morphine than AFR animals. Compared to AFR rats, MD rats took somewhat more amphetamine but not cocaine or ethanol. Control and MD rats consumed and preferred cocaine and ethanol similarly. Gustative and post-digestive characteristics and monoaminergic system processes may explain the distinctions between these two psychostimulants. Amphetamine increases extracellular monoamine levels, whereas cocaine prevents monoamine reuptake. Amphetamine and cocaine also have different effects due to their dopamine release mechanisms, dependence, and dopamine transporter surface expression regulation.²⁶ Repeated and irregular exposure to rising tetrahydrocannabinol (THC) dosages throughout adolescence changed adult rats' enkephalinergic systems. This is seen in changes in PPE mRNA levels and morphine sensitivity. MS amplifies opiates' acute stimulating and reinforcing characteristics and may increase susceptibility to their dependence-associated hypohedonic effects.⁴ MS additionally sensitizes rats to heroin's acute regulation of lateral hypothalamus intracranial self-stimulation thresholds, causing threshold elevations at moderate dosages.⁷⁸ The somatodendritic autoreceptors in adult MS rats are more sensitive, while the binding of 5-HT1A receptor in the dorsal raphe nucleus remains unchanged.⁷⁹ After female mice are kept in solitude, MS increases their demand for ethanol.⁸⁰

Early life trauma rewires the brain's dopamine and endocannabinoid circuits, making people more susceptible to anxiety, alcohol, and drug dependence.^{38,39}

Summary

MD rats have been found to consume more morphine and amphetamine compared to non-deprived rats. MS has been shown to enhance the acutely stimulating and reinforcing effects of opiates. Exposure to THC has been linked to changes in PPE mRNA levels and morphine sensitivity. The effects of MD on drug responses are complex and can vary depending on the type of drug. Some unique drug responses observed after MS may be attributed to differences in the pharmacological and neurobiological properties of the drugs or alcohol. Adverse early-life experiences can rewire the dopamine

and endocannabinoid circuits in the brain, which may increase susceptibility to substance dependence.

Molecular correlates of MS/MD

MS has a substantial effect on the regulation of genes associated with histone methylation, β -catenin, neurotrophin, endogenous opioid, and glucocorticoid signalling pathways.⁸¹ A possible case in terms of MS molecular etiology (after drug or alcohol use) is the DRD1 receptor gene. Possible involvement of the DRD1 gene has been shown in alcohol use, particularly in early environmental stress. Parental deprivation may change the lives of those who inherit a gene variation that influences dopamine transmission. Since macaques that are carriers of the T allele get higher rewards, they may consume more alcohol.³⁰ At a distance, amphetamine self-administration between MD and control rats cannot be accounted for by expression of dopamine transporter.⁸² Amphetamine injection "paradoxically" impacts corticosterone secretion exclusively in deprived individuals. MD may "sensitize" the HPA system, disinhibiting several corticosterone secretion processes.⁸³ Recurrent early MS may alter the HPA axis, permitting ethanol ingestion.⁸⁴ Moreover, the endogenous oxytocin system may affect stress, anxiety, addiction, and mental health sensitivity.⁵⁴

Adolescent MD rats showed higher baseline anandamide levels in the NAc, CPU nuclei, and mesencephalon compared to adolescent AFR rats, while adult MD rats had higher anandamide and 2-arachidonoylglycerol levels.³¹ Exposure to maternal care deficits affects the endocannabinoid system region-specifically, downregulating cannabinoid 1 receptor (CB1R) in the PFC and upregulating it in the NAc.³⁸

MD increases protein carbonylation, lipid peroxidation, nitrite/nitrate content, and activity of myeloperoxidase in both male and female PFC and hippocampus while decreasing interleukin-10 in both groups.⁵⁸ MS delays the hippocampal γ -aminobutyric acid (GABA) switch and suppresses membrane K (+)-Cl (-) co-transporter (KCC2) expression until adolescence.⁸⁵ Astrocytes' role in early-life adversity-induced brain programming has recently been recognized. Early-life adversity affects astrocytes short- and long-term.⁸⁴ MD enhances intrinsic sensitivity to dependence, especially for opiates, making it an excellent model to research environmentally driven interindividual vulnerability to opiate addiction.⁸²

Summary

MD has been found to increase intrinsic sensitivity to drug dependence. Various genes, including DRD1, serotonin transporter genes, μ -opioid receptor, CRH, MAOA, oxytocin, anandamide, CB1R, myeloperoxidase, interleukin-10, superoxide dismutase, and catalase, as well as neurotransmitters such as GABA and KCC2, and

nitrite/nitrate content, are thought to be involved in the effects of MS on substance dependence.

Psychological risk factors affecting offspring dependence in the context of maternal substance use and separation

Violence-exposed teens with parental alcohol or drug use had the highest rates of mental illness.¹² ELS influences several brain components, including the link between prenatal multi-hit and subsequent neurological problems.⁸⁶ Family unity reduces psychoactive SUDs and adolescent drug addiction. Parental psychological concerns increase alcohol use but not drug addiction, according to research. Psychoactive SUD is linked with teenage drug and alcohol use when adolescents have inadequate self-esteem, greater depressive symptoms, more stressful life events, low family integration, and socializing with drug-using peers.¹¹

Maternal smoking and CD are influenced by parental antisocial personality disorder as a confounding factor.²¹ Maternal drug use is linked to insensitive and poor parenting behavior when mothers interact with their infants; however, this is mostly due to comorbid maternal psychopathology, notably antisocial and related personality disorders.⁴⁰

Anxiety and impulsivity, risk factors for AUD, may result from MD. Alcohol may be used for its anxiolytic effects rather than its euphoric, sedative, and rewarding effects.³⁰ Both family drug and alcohol use are separately linked to a heightened risk of various externalizing disorders in teenage kids.⁶⁸ The path from unsupportive parenting to adolescent externalizing behaviors was mediated by deviant peer behavior, and the path to drug use was mediated by peer drug use.⁶⁶

Drug use is higher in those with PTSD. PTSD patients commonly have comorbid stress and drug use problems, which burden health care without appropriate treatments. The long-term impact of chronic stress on drug self-administration should be studied. MS, foot shock, and social defeat may be useful models for treating co-occurring PTSD and addiction. Medication for drug issues might target stress response systems.⁴ In rodent models, stresses increase acute responses, drug intake,⁴ and the return to morphine dependence.⁸⁷

Depression scores were highest in people with SUDs and then in people with AUDs.¹⁵ Some mothers suffer from severe depression, life challenges, and family dysfunction. High-depressive women reported hostile parenting, which may indicate their limited emotional or “mechanical” caring.⁸⁸ Depression is prevalent after opioid agonist therapy.

Summary

Psychological factors such as depression, violence, adverse early life experiences, psychoactive SUD, family cohesion, stress, self-esteem, anxiety, impulsivity, social defeat

stress, and antisocial and related personality disorders are closely associated with maternal and offspring addiction and separation (Figure 1).

Treatments and interventions for improving offspring dependence induced by maternal substance use and separation

Venlafaxine as an antidepressant may improve depression-induced reinstatement of morphine dependence.⁸⁷ Lamotrigine reduced immobility in MD rats. Lamotrigine restored amygdala BDNF levels in MD rats treated with saline.⁸⁹ Ketamine alleviates MD-induced male depression and prevents male MD-induced lipid peroxidation. It reduces protein carbonylation in both genders. ELS may cause behavioral, neuroimmune, and oxidative stress, depending on sex and brain region. Ketamine has anti-inflammatory and antioxidant qualities and may be an option for those who are resistant to conventional therapies. Ketamine reduced nitrite/nitrate in male PFCs but not in females. Male and female-deprived and ketamine-treated groups had lower antioxidant enzymes (superoxide dismutase, and catalase) activity. Ketamine reduces MD-induced myeloperoxidase activity and interleukin-6 levels in men.⁹⁰ Moreover, lithium reduces dose-dependently ethanol-induced developmental toxicities, including morphological changes, cognitive retention, and oxidative stress in brain tissue.⁹¹ Choline supplementation during periadolescence may reduce newborn stress-induced memory loss.⁹²

Mothers are less likely to participate in methadone maintenance therapy (MMT), the addiction treatment of choice. To involve mothers in MMT, we must understand how mothers experience addiction and recovery.³⁵ Child protection system engagement was substantially related to mental health issues, parental support, and child number.⁹³ Mothers gradually become aware of the impact of addiction on their ability to be good mothers and choose rehabilitation and MMT to benefit their children and preserve their identity. Most mothers redefined their maternal identity and enhanced mothering and mother-child connections after MMT and recovery.³⁵

Environment enrichment (EE) therapy may prevent drug addiction and help adults recover from neonatal MS-related cognitive impairments.⁹⁴ Moreover, EE may completely compensate for the harmful effects of stress. Stressed people with EE performed comparably to enriched people without stress manipulation.⁹⁵

Morphine CPP alters D2/D3 receptor function. Early alterations of infant-mother bonding may affect opioidergic and dopaminergic neurotransmission and disclose pharmacological features of dopamine receptor partial agonists or antagonists that might be used therapeutically.²⁷ A nonhuman monkey model explores the role of the mesolimbic dopamine system in alcohol and other μ -opioid receptor reward and genetic diversity

in the DRD1 locus for drug discovery.³⁰

THC's homeostatic modulator effects impair morphine's reward effects on naive animals but improve them in MD rats. These data suggest cannabis medication postnatally in adverse environments.²⁹ In MD rats, prolonged THC exposure inhibits morphine dependence in adolescents (PND 35–48).²⁹

SR141716A chronically prevented morphine intake increases in adolescent MD rats. Selective CB1 receptor antagonists/inverse agonists may assist teenage people with opiate dependence to SUDs quit, especially those in stressful postnatal environments.³¹

Dronabinol treatment in MD animals increased morphine conditioning tolerance in CPP and suppressed oral morphine self-administration test escalation.²⁹ Early, short-term micronutrients supplementation may avoid ELS's long-term consequences.⁹⁶ Further on, a study reported that treatments involving children are not useful.⁹⁷ The role of histone deacetylase enzymes in cognitive and affective changes caused by binge alcohol use during gestation and breastfeeding suggests that histone deacetylase inhibitors may help certain elements of fetal alcohol spectrum disorders.⁹⁸ Modafinil improves newborn MS-induced memory deficits.⁹⁹ Oxytocin-targeted interventions during or after adversity may be protective.⁵⁴ Handling lowers adult cocaine self-administration at all dosages.¹⁰⁰ It also decreases adult male rats' sensitivity to amphetamine's rewarding effects, blunting their choice for the drug-paired chamber in a CPP test.¹⁰¹ Family counseling seems to uncover issues and bring some emotional comfort.¹⁶ Pre- and postnatal care education for mothers, particularly teens, may improve mother and baby perinatal outcomes.^{28,44,102}

Although some interventions like family counseling, EE, modafinil, oxytocin, THC, and CB1 receptor antagonists/inverse agonists may have more known effects on both MS and SUD, there are few or rare studies that discuss their effects on the combination of maternal substance use and MS outcomes. It doesn't mean that other interventions may only affect one of MS or SUD. On the other side, stress, maternal identity, and reward seem to bridge the gap between each intervention and have indirect effects on the combination of maternal substance use and MS.

Summary

Antidepressants may reduce depression-induced drug dependence. Handling also reduces adult drug dependence. Lithium and histone deacetylase inhibitors reduce some alcohol-induced disorders. Lamotrigine and ketamine reduce MD-related deficits. Choline or modafinil may improve neonatal MS memory loss. MMT and recovery, family counseling, education, and dopamine receptor partial agonists or antagonists may improve mother-offspring bonding and perinatal

outcomes. Vitamin or oxytocin supplementation may prevent ELS's effects. THC, SR141716A, and dronabinol reduce morphine dependence in MD animals. EE treatment may prevent drug addiction and aid individuals with neonatal MS cognitive deficits. Teenage people with opiate dependence and SUDs in stressful postnatal circumstances may benefit from selective CB1 receptor antagonists/inverse agonists.

Future suggestions for studies about offspring dependence induced by maternal substance use and separation

Several animal experiments use a rank-dependent access prevention method to provide all animals with unrestricted and voluntary access to medicines or alcohol.^{30,50} Whether rank-dependence or dominance happens in communities or groups, the outcome is unclear. Future studies are suggested to focus on disseminating parenting principles and incorporating advice into everyday life.⁸ Substance-use therapy for women should include mental health and parenting measures.^{40,44} New comorbid disorder treatments should be prioritized.⁴ Considering gender-dependent differences and agents against oxidative stress and inflammation⁵⁸ may open up new horizons for more targeted treatments for MS outcomes.

Conclusion

An MS vulnerability model might provide useful insights into the neurological dysfunctions associated with addiction and facilitate the development of novel preventive and therapeutic strategies to reduce susceptibility during maternal addiction and after childbirth. Although not derived from the same group of research participants, these studies suggest that maternal addiction and MS play a significant role in brain programming in offspring and that maternal addiction and separation predispose progeny to drug dependence in both animals and humans. The mechanisms, interventions, psychological, neuroanatomical, and molecular correlates reviewed here might comprehensively encapsulate these phenomena, although it should be noted that all of these events occurred after maternal addiction and separation. This study emphasizes the importance of maternal addiction and separation outcomes and emphasizes the necessity for innovative and comprehensive strategies to avoid or solve these consequences. Therefore, clinicians, clinical social workers, medical practitioners, psychiatrists, and all staff involved in addiction prevention, rehabilitation, and therapy are suggested to consider this vulnerability.

Acknowledgments

This study is extracted from Maysam Fadaei-kenarsary Ph.D. thesis approved (Study Number: 97-53) by Kerman Neuroscience Research Center (KNRC), Kerman University of Medical Sciences (KMU). The authors acknowledge Dr. Hoda Ranjbar (KNRC, KMU) for some technical consults and Dr. Maryam Okhovati (Medical Informatics Research Center, KMU) for search strategies.

Authors' Contribution**Conceptualization:** Vahid Sheibani.**Data curation:** Maysam Fadaei-Kenarsary.**Formal analysis:** Maysam Fadaei-Kenarsary.**Funding acquisition:** Vahid Sheibani.**Investigation:** Maysam Fadaei-Kenarsary, Vahid Sheibani.**Methodology:** Vahid Sheibani, Mohammad Shabani, Khadijeh Esmaeilpour.**Project administration:** Maysam Fadaei-Kenarsary, Vahid Sheibani.**Resources:** Vahid Sheibani, Khadijeh Esmaeilpour, Maysam Fadaei-Kenarsary.**Software:** Maysam Fadaei-Kenarsary.**Supervision:** Vahid Sheibani, Khadijeh Esmaeilpour.**Validation:** Vahid Sheibani, Khadijeh Esmaeilpour.**Visualization:** Maysam Fadaei-Kenarsary.**Writing—original draft:** Maysam Fadaei-Kenarsary.**Writing—review & editing:** Vahid Sheibani, Khadijeh Esmaeilpour, Mohammad Shabani, Maysam Fadaei-Kenarsary.**Competing Interests**

The authors declare no competing or conflicting interests.

Data Availability Statement

Data are contained within the article and are available from the corresponding authors upon reasonable request.

Ethical Approval

Not Applicable.

Funding

This research received no external funding.

References

- Parvaz N, Mazhari S, Nazari-Noghabi M. Frequency of psychiatric disorders in children of opioid or methamphetamine-dependent patients. *Addict Health*. 2015;7(3-4):140-8.
- Azadfar M, Huecker MR, Leaming JM. Opioid addiction. In: *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing; 2022.
- Theisen K, Jacobs B, Macleod L, Davies B. The United States opioid epidemic: a review of the surgeon's contribution to it and health policy initiatives. *BJU Int*. 2018;122(5):754-9. doi: [10.1111/bju.14446](https://doi.org/10.1111/bju.14446).
- Logrip ML, Zorrilla EP, Koob GF. Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder. *Neuropharmacology*. 2012;62(2):552-64. doi: [10.1016/j.neuropharm.2011.07.007](https://doi.org/10.1016/j.neuropharm.2011.07.007).
- Christoffersen MN, Sothill K. The long-term consequences of parental alcohol abuse: a cohort study of children in Denmark. *J Subst Abuse Treat*. 2003;25(2):107-16. doi: [10.1016/s0740-5472\(03\)00116-8](https://doi.org/10.1016/s0740-5472(03)00116-8).
- Young NK, Boles SM, Otero C. Parental substance use disorders and child maltreatment: overlap, gaps, and opportunities. *Child Maltreat*. 2007;12(2):137-49. doi: [10.1177/1077559507300322](https://doi.org/10.1177/1077559507300322).
- Yalçın B, Pomrenze MB, Malacon K, Chau JJ, Taylor KR, Ni L, et al. Myelin plasticity in ventral tegmental area is required for opioid reward. *bioRxiv* [Preprint]. September 3, 2022. Available from: <https://www.biorxiv.org/content/10.1101/2022.09.01.506263v1>.
- Steiner S, Schori D, Gmel G. Excessive alcohol consumption in young men: is there an association with their earlier family situation? A baseline-analysis of the C-SURF-study (Cohort Study on Substance Use Risk Factors). *Swiss Med Wkly*. 2014;144:w14007. doi: [10.4414/smw.2014.14007](https://doi.org/10.4414/smw.2014.14007).
- Parvaz MA, Kim K, Froudust-Walsh S, Newcorn JH, Ivanov I. Reward-based learning as a function of severity of substance abuse risk in drug-naïve youth with ADHD. *J Child Adolesc Psychopharmacol*. 2018;28(8):547-53. doi: [10.1089/cap.2018.0010](https://doi.org/10.1089/cap.2018.0010).
- McCutcheon VV, Scherrer JF, Grant JD, Xian H, Haber JR, Jacob T, et al. Parent, sibling and peer associations with subtypes of psychiatric and substance use disorder comorbidity in offspring. *Drug Alcohol Depend*. 2013;128(1-2):20-9. doi: [10.1016/j.drugalcdep.2012.07.015](https://doi.org/10.1016/j.drugalcdep.2012.07.015).
- Hoffmann JP, Cerbone FG. Parental substance use disorder and the risk of adolescent drug abuse: an event history analysis. *Drug Alcohol Depend*. 2002;66(3):255-64. doi: [10.1016/s0376-8716\(02\)00005-4](https://doi.org/10.1016/s0376-8716(02)00005-4).
- Hanson RF, Self-Brown S, Fricker-Elhai A, Kilpatrick DG, Saunders BE, Resnick H. Relations among parental substance use, violence exposure and mental health: the national survey of adolescents. *Addict Behav*. 2006;31(11):1988-2001. doi: [10.1016/j.addbeh.2006.01.012](https://doi.org/10.1016/j.addbeh.2006.01.012).
- Cummings JR, Lumeng JC, Miller AL, Hyde LW, Siada R, Gearhardt AN. Parental substance use and child reward-driven eating behaviors. *Appetite*. 2020;144:104486. doi: [10.1016/j.appet.2019.104486](https://doi.org/10.1016/j.appet.2019.104486).
- Bornoalova MA, Hicks BM, Iacono WG, McGue M. Familial transmission and heritability of childhood disruptive disorders. *Am J Psychiatry*. 2010;167(9):1066-74. doi: [10.1176/appi.ajp.2010.09091272](https://doi.org/10.1176/appi.ajp.2010.09091272).
- Tennant C, Bernardi E. Childhood loss in alcoholics and narcotic addicts. *Br J Addict*. 1988;83(6):695-703. doi: [10.1111/j.1360-0443.1988.tb02600.x](https://doi.org/10.1111/j.1360-0443.1988.tb02600.x).
- Bekir P, McLellan T, Childress AR, Gariti P. Role reversals in families of substance misusers: a transgenerational phenomenon. *Int J Addict*. 1993;28(7):613-30. doi: [10.3109/10826089309039652](https://doi.org/10.3109/10826089309039652).
- Penttinen R, Hakko H, Riiipinen P, Isohookana R, Riala K. Associations of adverse childhood experiences to smoking and nicotine dependence among adolescent psychiatric inpatients. *Community Ment Health J*. 2020;56(2):333-7. doi: [10.1007/s10597-019-00476-8](https://doi.org/10.1007/s10597-019-00476-8).
- Romanowicz M, Vande Voort JL, Shekunov J, Oesterle TS, Thusius NJ, Rummans TA, et al. The effects of parental opioid use on the parent-child relationship and children's developmental and behavioral outcomes: a systematic review of published reports. *Child Adolesc Psychiatry Ment Health*. 2019;13:5. doi: [10.1186/s13034-019-0266-3](https://doi.org/10.1186/s13034-019-0266-3).
- Vargas GC, Pildes RS, Vidyasagar D, Keith LG. Effect of maternal heroin addiction on 67 liveborn neonates. Withdrawal symptoms, small body size, and small head circumference were frequent findings. *Clin Pediatr (Phila)*. 1975;14(8):751-7. doi: [10.1177/000992287501400811](https://doi.org/10.1177/000992287501400811).
- Furukawa T, Harai H, Hirai T, Fujihara S, Kitamura T, Takahashi K. Childhood parental loss and alcohol dependence among Japanese men: a case-control study. Group for Longitudinal Affective Disorders Study (GLADS). *Acta Psychiatr Scand*. 1998;97(6):403-7. doi: [10.1111/j.1600-0447.1998.tb10022.x](https://doi.org/10.1111/j.1600-0447.1998.tb10022.x).
- Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *J Am Acad Child Adolesc Psychiatry*. 1999;38(7):892-9. doi: [10.1097/00004583-199907000-00020](https://doi.org/10.1097/00004583-199907000-00020).
- Biederman J, Faraone SV, Monuteaux MC, Feighner JA. Patterns of alcohol and drug use in adolescents can be predicted by parental substance use disorders. *Pediatrics*. 2000;106(4):792-7. doi: [10.1542/peds.106.4.792](https://doi.org/10.1542/peds.106.4.792).
- Dawe S, Harnett PH, Rendalls V, Staiger P. Improving

- family functioning and child outcome in methadone-maintained families: the Parents Under Pressure programme. *Drug Alcohol Rev.* 2003;22(3):299-307. doi: [10.1080/0959523031000154445](https://doi.org/10.1080/0959523031000154445).
24. Ohannessian CM, Hesselbrock VM, Kramer J, Bucholz KK, Schuckit MA, Kuperman S, et al. Parental substance use consequences and adolescent psychopathology. *J Stud Alcohol.* 2004;65(6):725-30. doi: [10.15288/jsa.2004.65.725](https://doi.org/10.15288/jsa.2004.65.725).
 25. Vazquez V, Penit-Soria J, Durand C, Besson MJ, Giros B, Daugé V. Maternal deprivation increases vulnerability to morphine dependence and disturbs the encephalineric system in adulthood. *J Neurosci.* 2005;25(18):4453-62. doi: [10.1523/jneurosci.4807-04.2005](https://doi.org/10.1523/jneurosci.4807-04.2005).
 26. Vazquez V, Giros B, Daugé V. Maternal deprivation specifically enhances vulnerability to opiate dependence. *Behav Pharmacol.* 2006;17(8):715-24. doi: [10.1097/FBP.0b013e3280116e6f](https://doi.org/10.1097/FBP.0b013e3280116e6f).
 27. Vazquez V, Weiss S, Giros B, Martres MP, Daugé V. Maternal deprivation and handling modify the effect of the dopamine D3 receptor agonist, BP 897 on morphine-conditioned place preference in rats. *Psychopharmacology (Berl).* 2007;193(4):475-86. doi: [10.1007/s00213-007-0789-9](https://doi.org/10.1007/s00213-007-0789-9).
 28. Vucinovic M, Roje D, Vucinovic Z, Capkun V, Bucat M, Banovic I. Maternal and neonatal effects of substance abuse during pregnancy: our ten-year experience. *Yonsei Med J.* 2008;49(5):705-13. doi: [10.3349/ymj.2008.49.5.705](https://doi.org/10.3349/ymj.2008.49.5.705).
 29. Morel LJ, Giros B, Daugé V. Adolescent exposure to chronic delta-9-tetrahydrocannabinol blocks opiate dependence in maternally deprived rats. *Neuropsychopharmacology.* 2009;34(11):2469-76. doi: [10.1038/npp.2009.70](https://doi.org/10.1038/npp.2009.70).
 30. Newman TK, Parker CC, Suomi SJ, Goldman D, Barr CS, Higley JD. DRD1 5'UTR variation, sex and early infant stress influence ethanol consumption in rhesus macaques. *Genes Brain Behav.* 2009;8(6):626-30. doi: [10.1111/j.1601-183X.2009.00507.x](https://doi.org/10.1111/j.1601-183X.2009.00507.x).
 31. Naudon L, Piscitelli F, Giros B, Di Marzo V, Daugé V. Possible involvement of endocannabinoids in the increase of morphine consumption in maternally deprived rat. *Neuropharmacology.* 2013;65:193-9. doi: [10.1016/j.neuropharm.2012.10.008](https://doi.org/10.1016/j.neuropharm.2012.10.008).
 32. Chuang E, Wells R, Belletiere J, Cross TP. Identifying the substance abuse treatment needs of caregivers involved with child welfare. *J Subst Abuse Treat.* 2013;45(1):118-25. doi: [10.1016/j.jsat.2013.01.007](https://doi.org/10.1016/j.jsat.2013.01.007).
 33. Yule AM, Wilens TE, Martelon MK, Simon A, Biederman J. Does exposure to parental substance use disorders increase substance use disorder risk in offspring? A 5-year follow-up study. *Am J Addict.* 2013;22(5):460-5. doi: [10.1111/j.1521-0391.2013.12048.x](https://doi.org/10.1111/j.1521-0391.2013.12048.x).
 34. Stice E, Yokum S. Brain reward region responsivity of adolescents with and without parental substance use disorders. *Psychol Addict Behav.* 2014;28(3):805-15. doi: [10.1037/a0034460](https://doi.org/10.1037/a0034460).
 35. Secco L, Letourneau N, Campbell MA, Craig S, Colpitts J. Stresses, strengths, and experiences of mothers engaged in methadone maintenance treatment. *J Addict Nurs.* 2014;25(3):139-47. doi: [10.1097/jan.0000000000000038](https://doi.org/10.1097/jan.0000000000000038).
 36. O'Brien JW, Hill SY. Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. *Alcohol Clin Exp Res.* 2014;38(12):2952-61. doi: [10.1111/acer.12569](https://doi.org/10.1111/acer.12569).
 37. Yule AM, Wilens TE, Martelon M, Rosenthal L, Biederman J. Does exposure to parental substance use disorders increase offspring risk for a substance use disorder? A longitudinal follow-up study into young adulthood. *Drug Alcohol Depend.* 2018;186:154-8. doi: [10.1016/j.drugalcdep.2018.01.021](https://doi.org/10.1016/j.drugalcdep.2018.01.021).
 38. Amancio-Belmont O, Becerril Meléndez AL, Ruiz-Contreras AE, Méndez-Díaz M, Prospéro-García O. Opposed cannabinoid 1 receptor (CB1R) expression in the prefrontal cortex vs. nucleus accumbens is associated with alcohol consumption in male rats. *Brain Res.* 2019;1725:146485. doi: [10.1016/j.brainres.2019.146485](https://doi.org/10.1016/j.brainres.2019.146485).
 39. Amancio-Belmont O, Becerril Meléndez AL, Ruiz-Contreras AE, Méndez-Díaz M, Prospéro-García O. Maternal separation plus social isolation during adolescence reprogram brain dopamine and endocannabinoid systems and facilitate alcohol intake in rats. *Brain Res Bull.* 2020;164:21-8. doi: [10.1016/j.brainresbull.2020.08.002](https://doi.org/10.1016/j.brainresbull.2020.08.002).
 40. Hans SL, Bernstein VJ, Henson LG. The role of psychopathology in the parenting of drug-dependent women. *Dev Psychopathol.* 1999;11(4):957-77. doi: [10.1017/s0954579499002400](https://doi.org/10.1017/s0954579499002400).
 41. Pautassi RM, Camarini R, Quadros IM, Miczek KA, Israel Y. Genetic and environmental influences on ethanol consumption: perspectives from preclinical research. *Alcohol Clin Exp Res.* 2010;34(6):976-87. doi: [10.1111/j.1530-0277.2010.01172.x](https://doi.org/10.1111/j.1530-0277.2010.01172.x).
 42. Jansson LM, Dipietro JA, Elko A, Velez M. Maternal vagal tone change in response to methadone is associated with neonatal abstinence syndrome severity in exposed neonates. *J Matern Fetal Neonatal Med.* 2007;20(9):677-85. doi: [10.1080/14767050701490327](https://doi.org/10.1080/14767050701490327).
 43. Le TL, Kenaszchuk C, Milligan K, Urbanoski K. Levels and predictors of participation in integrated treatment programs for pregnant and parenting women with problematic substance use. *BMC Public Health.* 2019;19(1):154. doi: [10.1186/s12889-019-6455-4](https://doi.org/10.1186/s12889-019-6455-4).
 44. Flykt MS, Salo S, Pajulo M. "A window of opportunity": parenting and addiction in the context of pregnancy. *Curr Addict Rep.* 2021;8(4):578-94. doi: [10.1007/s40429-021-00394-4](https://doi.org/10.1007/s40429-021-00394-4).
 45. Conradt E, Camerota M, Maylott S, Lester BM. Annual Research Review: prenatal opioid exposure - a two-generation approach to conceptualizing neurodevelopmental outcomes. *J Child Psychol Psychiatry.* 2023;64(4):566-78. doi: [10.1111/jcpp.13761](https://doi.org/10.1111/jcpp.13761).
 46. Sánchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev Psychopathol.* 2001;13(3):419-49. doi: [10.1017/s0954579401003029](https://doi.org/10.1017/s0954579401003029).
 47. Courtiol E, Wilson DA, Shah R, Sullivan RM, Teixeira CM. Maternal regulation of pups' cortical activity: role of serotonergic signaling. *eNeuro.* 2018;5(4):ENEURO.0093-18.2018. doi: [10.1523/eneuro.0093-18.2018](https://doi.org/10.1523/eneuro.0093-18.2018).
 48. Wang X, Wang X, Xie F, Sun Z, Guo B, Li F, et al. Leucine mediates cognitive dysfunction in early life stress-induced mental disorders by activating autophagy. *Front Cell Neurosci.* 2022;16:1060712. doi: [10.3389/fncel.2022.1060712](https://doi.org/10.3389/fncel.2022.1060712).
 49. Zimmerberg B, Sageser KA. Comparison of two rodent models of maternal separation on juvenile social behavior. *Front Psychiatry.* 2011;2:39. doi: [10.3389/fpsy.2011.00039](https://doi.org/10.3389/fpsy.2011.00039).
 50. Fadaei-Kenarsary M, Esmaeilpour K, Shabani M, Joushi S, Sheibani V. Chronic morphine exposure and maternal separation induce impairments in cognition and locomotor activity of male adolescent rats. *Int J Dev Neurosci.* 2023;83(3):235-47. doi: [10.1002/jdn.10251](https://doi.org/10.1002/jdn.10251).
 51. Heydari A, Esmaeilpour K, Sheibani V. Maternal separation impairs long term-potential in CA3-CA1 synapses in adolescent female rats. *Behav Brain Res.* 2019;376:112239. doi: [10.1016/j.bbr.2019.112239](https://doi.org/10.1016/j.bbr.2019.112239).
 52. Shahraiki S, Esmaeilpour K, Shabani M, Sepehri G, Rajizadeh MA, Maneshian M, et al. Choline chloride modulates learning, memory, and synaptic plasticity impairments in

- maternally separated adolescent male rats. *Int J Dev Neurosci*. 2022;82(1):19-38. doi: [10.1002/jdn.10155](https://doi.org/10.1002/jdn.10155).
53. Talani G, Biggio F, Gorule AA, Licheri V, Saolini E, Colombo D, et al. Sex-dependent changes of hippocampal synaptic plasticity and cognitive performance in C57BL/6j mice exposed to neonatal repeated maternal separation. *Neuropharmacology*. 2023;222:109301. doi: [10.1016/j.neuropharm.2022.109301](https://doi.org/10.1016/j.neuropharm.2022.109301).
 54. Johnson JL, Buisman-Pijlman FT. Adversity impacting on oxytocin and behaviour: timing matters. *Behav Pharmacol*. 2016;27(8):659-71. doi: [10.1097/fbp.0000000000000269](https://doi.org/10.1097/fbp.0000000000000269).
 55. Roman E, Gustafsson L, Hyytiä P, Nylander I. Short and prolonged periods of maternal separation and voluntary ethanol intake in male and female ethanol-preferring AA and ethanol-avoiding ANA rats. *Alcohol Clin Exp Res*. 2005;29(4):591-601. doi: [10.1097/01.alc.0000158933.70242.fc](https://doi.org/10.1097/01.alc.0000158933.70242.fc).
 56. de Oliveira C, Scarabelot VL, Vercelino R, Silveira NP, Adachi LNS, Regner GG, et al. Morphine exposure and maternal deprivation during the early postnatal period alter neuromotor development and nerve growth factor levels. *Int J Dev Neurosci*. 2017;63:8-15. doi: [10.1016/j.ijdevneu.2017.09.001](https://doi.org/10.1016/j.ijdevneu.2017.09.001).
 57. Masroui H, Azadi M, Semnani S, Azizi H. Early life maternal deprivation attenuates morphine induced inhibition in lateral paraventricular neurons in adult rats. *Brain Res Bull*. 2021;169:128-35. doi: [10.1016/j.brainresbull.2021.01.011](https://doi.org/10.1016/j.brainresbull.2021.01.011).
 58. Abelaira HM, Rosa T, de Moura AB, Andrade NM, Martinello NS, Maciel LR, et al. Combination of electroconvulsive stimulation with ketamine or escitalopram protects the brain against inflammation and oxidative stress induced by maternal deprivation and is critical for associated behaviors in male and female rats. *Mol Neurobiol*. 2022;59(3):1452-75. doi: [10.1007/s12035-021-02718-x](https://doi.org/10.1007/s12035-021-02718-x).
 59. Bachiller S, Paulus A, Vázquez-Reyes S, García-Domínguez I, Deierborg T. Maternal separation leads to regional hippocampal microglial activation and alters the behavior in the adolescence in a sex-specific manner. *Brain Behav Immun Health*. 2020;9:100142. doi: [10.1016/j.bbih.2020.100142](https://doi.org/10.1016/j.bbih.2020.100142).
 60. Fadaei-Kenarsary M, Esmaeilpour K, Shabani M, Sheibani V. Chronic maternal morphine exposure and early-life adversity induce impairment in synaptic plasticity of adolescent male rats. *Neurosci Lett*. 2023;812:137365. doi: [10.1016/j.neulet.2023.137365](https://doi.org/10.1016/j.neulet.2023.137365).
 61. Čater M, Majdič G. How early maternal deprivation changes the brain and behavior? *Eur J Neurosci*. 2022;55(9-10):2058-75. doi: [10.1111/ejn.15238](https://doi.org/10.1111/ejn.15238).
 62. Mejía-Chávez S, Venebra-Muñoz A, García-García F, Corona-Morales AA, Orozco-Vargas AE. Maternal separation modifies the activity of social processing brain nuclei upon social novelty exposure. *Front Behav Neurosci*. 2021;15:651263. doi: [10.3389/fnbeh.2021.651263](https://doi.org/10.3389/fnbeh.2021.651263).
 63. Sheehan TP, Chambers RA, Russell DS. Regulation of affect by the lateral septum: implications for neuropsychiatry. *Brain Res Brain Res Rev*. 2004;46(1):71-117. doi: [10.1016/j.brainresrev.2004.04.009](https://doi.org/10.1016/j.brainresrev.2004.04.009).
 64. Orikasa C. Social network plasticity of mice parental behavior. *Front Neurosci*. 2022;16:882850. doi: [10.3389/fnins.2022.882850](https://doi.org/10.3389/fnins.2022.882850).
 65. Linsambarth S, Moraga-Amaro R, Quintana-Donoso D, Rojas S, Stehberg J. The amygdala and anxiety. In: Ferry B, ed. *The Amygdala*. Rijeka: IntechOpen; 2017. p. 7. doi: [10.5772/intechopen.68618](https://doi.org/10.5772/intechopen.68618).
 66. Cox R. Differential effects of parents and peers on externalizing behavior and drug use. *Acta Investig Psicol*. 2014;4(2):1491-509. doi: [10.1016/s2007-4719\(14\)70389-8](https://doi.org/10.1016/s2007-4719(14)70389-8).
 67. Hill SY, Shen S, Locke Wellman J, Rickin E, Lowers L. Offspring from families at high risk for alcohol dependence: increased body mass index in association with prenatal exposure to cigarettes but not alcohol. *Psychiatry Res*. 2005;135(3):203-16. doi: [10.1016/j.psychres.2005.04.003](https://doi.org/10.1016/j.psychres.2005.04.003).
 68. Marmorstein NR, Iacono WG, McGue M. Alcohol and illicit drug dependence among parents: associations with offspring externalizing disorders. *Psychol Med*. 2009;39(1):149-55. doi: [10.1017/s0033291708003085](https://doi.org/10.1017/s0033291708003085).
 69. Suri D, Bhattacharya A, Vaidya VA. Early stress evokes temporally distinct consequences on the hippocampal transcriptome, anxiety and cognitive behaviour. *Int J Neuropsychopharmacol*. 2014;17(2):289-301. doi: [10.1017/s1461145713001004](https://doi.org/10.1017/s1461145713001004).
 70. Viveros MP, Llorente R, Suarez J, Llorente-Berzal A, López-Gallardo M, de Fonseca FR. The endocannabinoid system in critical neurodevelopmental periods: sex differences and neuropsychiatric implications. *J Psychopharmacol*. 2012;26(1):164-76. doi: [10.1177/0269881111408956](https://doi.org/10.1177/0269881111408956).
 71. Jawahar MC, Murgatroyd C, Harrison EL, Baune BT. Epigenetic alterations following early postnatal stress: a review on novel aetiological mechanisms of common psychiatric disorders. *Clin Epigenetics*. 2015;7:122. doi: [10.1186/s13148-015-0156-3](https://doi.org/10.1186/s13148-015-0156-3).
 72. Zhang TY, Labonté B, Wen XL, Turecki G, Meaney MJ. Epigenetic mechanisms for the early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. *Neuropsychopharmacology*. 2013;38(1):111-23. doi: [10.1038/npp.2012.149](https://doi.org/10.1038/npp.2012.149).
 73. Joushi S, Esmaeilpour K, Taherizadeh Z, Taheri F, Sheibani V. Intergenerational effects of maternal separation on cognitive abilities of adolescent rats. *Int J Dev Neurosci*. 2020;80(8):687-98. doi: [10.1002/jdn.10066](https://doi.org/10.1002/jdn.10066).
 74. Sun H, Zhang X, Kong Y, Gou L, Lian B, Wang Y, et al. Maternal separation-induced histone acetylation correlates with BDNF-programmed synaptic changes in an animal model of PTSD with sex differences. *Mol Neurobiol*. 2021;58(4):1738-54. doi: [10.1007/s12035-020-02224-6](https://doi.org/10.1007/s12035-020-02224-6).
 75. Lundgaard Donovan L, Henningsen K, Flou Kristensen A, Wiborg O, Nieland JD, Lichota J. Maternal separation followed by chronic mild stress in adulthood is associated with concerted epigenetic regulation of AP-1 complex genes. *J Pers Med*. 2021;11(3):209. doi: [10.3390/jpm11030209](https://doi.org/10.3390/jpm11030209).
 76. Korosi A, Baram TZ. The pathways from mother's love to baby's future. *Front Behav Neurosci*. 2009;3:27. doi: [10.3389/neuro.08.027.2009](https://doi.org/10.3389/neuro.08.027.2009).
 77. Kalinichev M, Easterling KW, Holtzman SG. Early neonatal experience of Long-Evans rats results in long-lasting changes in morphine tolerance and dependence. *Psychopharmacology (Berl)*. 2001;157(3):305-12. doi: [10.1007/s002130100806](https://doi.org/10.1007/s002130100806).
 78. Matthews K, Robbins TW. Early experience as a determinant of adult behavioural responses to reward: the effects of repeated maternal separation in the rat. *Neurosci Biobehav Rev*. 2003;27(1-2):45-55. doi: [10.1016/s0149-7634\(03\)00008-3](https://doi.org/10.1016/s0149-7634(03)00008-3).
 79. Arborelius L, Hawks BW, Owens MJ, Plotsky PM, Nemeroff CB. Increased responsiveness of presumed 5-HT cells to citalopram in adult rats subjected to prolonged maternal separation relative to brief separation. *Psychopharmacology (Berl)*. 2004;176(3-4):248-55. doi: [10.1007/s00213-004-1883-x](https://doi.org/10.1007/s00213-004-1883-x).
 80. Advani T, Hensler JG, Koek W. Effect of early rearing conditions on alcohol drinking and 5-HT1A receptor function in C57BL/6j mice. *Int J Neuropsychopharmacol*. 2007;10(5):595-607. doi: [10.1017/s1461145706007401](https://doi.org/10.1017/s1461145706007401).
 81. Sachs BD, Tran HL, Folse E, Caron MG. Brain-region-specific molecular responses to maternal separation and social defeat stress in mice. *Neuroscience*. 2018;373:122-36. doi: [10.1016/j.neuroscience.2018.03.045](https://doi.org/10.1016/j.neuroscience.2018.03.045).

- [10.1016/j.neuroscience.2018.01.018](https://doi.org/10.1016/j.neuroscience.2018.01.018).
82. Vazquez DM, Bailey C, Dent GW, Okimoto DK, Steffek A, López JF, et al. Brain corticotropin-releasing hormone (CRH) circuits in the developing rat: effect of maternal deprivation. *Brain Res*. 2006;1121(1):83-94. doi: [10.1016/j.brainres.2006.08.104](https://doi.org/10.1016/j.brainres.2006.08.104).
 83. Cirulli F, Laviola G. Paradoxical effects of D-amphetamine in infant and adolescent mice: role of gender and environmental risk factors. *Neurosci Biobehav Rev*. 2000;24(1):73-84. doi: [10.1016/s0149-7634\(99\)00047-0](https://doi.org/10.1016/s0149-7634(99)00047-0).
 84. Abbink MR, van Deijk AF, Heine VM, Verheijen MH, Korosi A. The involvement of astrocytes in early-life adversity induced programming of the brain. *Glia*. 2019;67(9):1637-53. doi: [10.1002/glia.23625](https://doi.org/10.1002/glia.23625).
 85. Furukawa M, Tsukahara T, Tomita K, Iwai H, Sonomura T, Miyawaki S, et al. Neonatal maternal separation delays the GABA excitatory-to-inhibitory functional switch by inhibiting KCC2 expression. *Biochem Biophys Res Commun*. 2017;493(3):1243-9. doi: [10.1016/j.bbrc.2017.09.143](https://doi.org/10.1016/j.bbrc.2017.09.143).
 86. Sarkar T, Patro N, Patro IK. Cumulative multiple early life hits-a potent threat leading to neurological disorders. *Brain Res Bull*. 2019;147:58-68. doi: [10.1016/j.brainresbull.2019.02.005](https://doi.org/10.1016/j.brainresbull.2019.02.005).
 87. Fadaei-Kenarsary M, Fathi Moghaddam H, Mansouri SM, Farbood Y. Administration of venlafaxine after chronic methadone detoxification blocks post-depression relapse in rats. *Braz Arch Biol Technol*. 2017;60:e17160436. doi: [10.1590/1678-4324-2017160436](https://doi.org/10.1590/1678-4324-2017160436).
 88. Barr JA. Postpartum depression, delayed maternal adaptation, and mechanical infant caring: a phenomenological hermeneutic study. *Int J Nurs Stud*. 2008;45(3):362-9. doi: [10.1016/j.ijnurstu.2006.10.002](https://doi.org/10.1016/j.ijnurstu.2006.10.002).
 89. Abelaira HM, Réus GZ, Ribeiro KF, Zappellini G, Cipriano AL, Scaini G, et al. Lamotrigine treatment reverses depressive-like behavior and alters BDNF levels in the brains of maternally deprived adult rats. *Pharmacol Biochem Behav*. 2012;101(3):348-53. doi: [10.1016/j.pbb.2012.01.019](https://doi.org/10.1016/j.pbb.2012.01.019).
 90. Abelaira HM, Veron DC, de Moura AB, Carlessi AS, Borba LA, Botelho ME, et al. Sex differences on the behavior and oxidative stress after ketamine treatment in adult rats subjected to early life stress. *Brain Res Bull*. 2021;172:129-38. doi: [10.1016/j.brainresbull.2021.04.021](https://doi.org/10.1016/j.brainresbull.2021.04.021).
 91. Ahmad M, Abu Taweel GM. Ameliorating effects of lithium on the perinatal ethanol-induced behavioral and cognitive dysfunction and brain oxidative stress in postnatal developing mice pups. *Curr Pharm Biotechnol*. 2020;21(13):1325-32. doi: [10.2174/1389201021666200615170644](https://doi.org/10.2174/1389201021666200615170644).
 92. Moreno Gudiño H, Carías Picón D, de Brugada Sauras I. Dietary choline during periadolescence attenuates cognitive damage caused by neonatal maternal separation in male rats. *Nutr Neurosci*. 2017;20(6):327-35. doi: [10.1080/1028415x.2015.1126444](https://doi.org/10.1080/1028415x.2015.1126444).
 93. Taplin S, Mattick RP. Mothers in methadone treatment and their involvement with the child protection system: a replication and extension study. *Child Abuse Negl*. 2013;37(8):500-10. doi: [10.1016/j.chiabu.2013.01.003](https://doi.org/10.1016/j.chiabu.2013.01.003).
 94. Mohammadian J, Najafi M, Miladi-Gorji H. Effect of enriched environment during adolescence on spatial learning and memory, and voluntary consumption of morphine in maternally separated rats in adulthood. *Dev Psychobiol*. 2019;61(4):615-25. doi: [10.1002/dev.21808](https://doi.org/10.1002/dev.21808).
 95. Macartney EL, Lagisz M, Nakagawa S. The relative benefits of environmental enrichment on learning and memory are greater when stressed: a meta-analysis of interactions in rodents. *Neurosci Biobehav Rev*. 2022;135:104554. doi: [10.1016/j.neubiorev.2022.104554](https://doi.org/10.1016/j.neubiorev.2022.104554).
 96. Naninck EF, Oosterink JE, Yam KY, de Vries LP, Schierbeek H, van Goudoever JB, et al. Early micronutrient supplementation protects against early stress-induced cognitive impairments. *FASEB J*. 2017;31(2):505-18. doi: [10.1096/fj.201600834R](https://doi.org/10.1096/fj.201600834R).
 97. McGovern R, Newham JJ, Addison MT, Hickman M, Kaner EF. Effectiveness of psychosocial interventions for reducing parental substance misuse. *Cochrane Database Syst Rev*. 2021;3(3):CD012823. doi: [10.1002/14651858.CD012823.pub2](https://doi.org/10.1002/14651858.CD012823.pub2).
 98. Montagud-Romero S, Cantacorps L, Valverde O. Histone deacetylases inhibitor trichostatin A reverses anxiety-like symptoms and memory impairments induced by maternal binge alcohol drinking in mice. *J Psychopharmacol*. 2019;33(12):1573-87. doi: [10.1177/0269881119857208](https://doi.org/10.1177/0269881119857208).
 99. Garcia VA, Hirotsu C, Matos G, Alvarenga T, Pires GN, Kapczinski F, et al. Modafinil ameliorates cognitive deficits induced by maternal separation and sleep deprivation. *Behav Brain Res*. 2013;253:274-9. doi: [10.1016/j.bbr.2013.07.029](https://doi.org/10.1016/j.bbr.2013.07.029).
 100. Moffett MC, Harley J, Francis D, Sanghani SP, Davis WI, Kuhar MJ. Maternal separation and handling affects cocaine self-administration in both the treated pups as adults and the dams. *J Pharmacol Exp Ther*. 2006;317(3):1210-8. doi: [10.1124/jpet.106.101139](https://doi.org/10.1124/jpet.106.101139).
 101. Campbell J, Spear LP. Effects of early handling on amphetamine-induced locomotor activation and conditioned place preference in the adult rat. *Psychopharmacology (Berl)*. 1999;143(2):183-9. doi: [10.1007/s002130050934](https://doi.org/10.1007/s002130050934).
 102. Malamitsi-Puchner A, Boutsikou T. Adolescent pregnancy and perinatal outcome. *Pediatr Endocrinol Rev*. 2006;3 Suppl 1:170-1.