



# UNIVERSITÀ DI PARMA

## ARCHIVIO DELLA RICERCA

University of Parma Research Repository

Early parent-child interactions and substance use disorder: An attachment perspective on a biopsychosocial entanglement

This is the peer reviewed version of the following article:

*Original*

Early parent-child interactions and substance use disorder: An attachment perspective on a biopsychosocial entanglement / Gerra, Maria Lidia; Gerra, MARIA CARLA; Tadonio, Leonardo; Pellegrini, Pietro; Marchesi, Carlo; Mattfeld, Elizabeth; Ossola, Paolo; Gerra, Gilberto. - In: NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS. - ISSN 0149-7634. - ottobre:1(2021), pp. 560-580. [10.1016/j.neubiorev.2021.09.052]

*Availability:*

This version is available at: 11381/2901865 since: 2024-12-16T22:27:15Z

*Publisher:*

Elsevier

*Published*

DOI:10.1016/j.neubiorev.2021.09.052

*Terms of use:*

Anyone can freely access the full text of works made available as "Open Access". Works made available

*Publisher copyright*

note finali coverpage

(Article begins on next page)

02 May 2026

# Neuroscience and Biobehavioral Reviews

## Early Parent-Child Interactions and Substance Use Disorder: an Attachment Perspective in a Biopsychosocial Entanglement --Manuscript Draft--

<b>Manuscript Number:</b>	NEUBIOREV-D-21-00456R2		
<b>Article Type:</b>	Review Article		
<b>Keywords:</b>	Attachment; Substance use; genetic; Epigenetic; neuroendocrine		
<b>Corresponding Author:</b>	Paolo Ossola, M.D. Universita degli Studi di Parma Parma, Emilia-Romagna ITALY		
<b>First Author:</b>	Maria Lidia Gerra, M.D., PhD		
<b>Order of Authors:</b>	Maria Lidia Gerra, M.D., PhD Maria Carla Gerra, PhD Leonardo Tadonio Pietro Pellegrini, M.D. Carlo Marchesi, M.D. Elizabeth Mattfeld Gilberto Gerra, M.D. Paolo Ossola, M.D.		
<b>Abstract:</b>	<p>This review aims to elucidate environmental and genetic factors, as well as their epigenetic and neuroendocrine moderators, that may underlie the association between early childhood experiences and Substance Use Disorders (SUD), through the lens of parental attachment.</p> <p>Here we review those attachment-related studies that examined the monoaminergic systems, the hypothalamic pituitary adrenal stress response system, the oxytoninergic system, and the endogenous opioid system from a genetic, epigenetic, and neuroendocrine perspective.</p> <p>Overall, the selected studies point to a moderating effect of insecure attachment between genetic vulnerability and SUD, reasonably through epigenetic modifications. Preliminary evidence suggests that vulnerability to SUDs is related with hypo-methylation (e.g. hyper-expression) of high-risk polymorphisms on the monoaminergic and hypothalamic pituitary adrenal system and hyper-methylation (e.g. hypo-expressions) of protective polymorphisms on the opioid and oxytocin system. These epigenetic modifications may induce a cascade of neuroendocrine changes contributing to the subclinical and behavioral manifestations that precede the clinical onset of SUD. Protective and supportive parenting could hence represent a key therapeutic target to prevent addiction and moderate insecure attachment.</p>		
<b>Suggested Reviewers:</b>	Icro Maremmani, M.D. Professor, University of Pisa: Universita degli Studi di Pisa icromaremmani@med.unipi.it	Adam Bisaga, M.D. professor, Columbia University Adam.Bisaga@nyspi.columbia.edu	Massimiliano Buoli, M.D. professor, University of Milan: Universita degli Studi di Milano massimiliano.buoli@unimi.it
<b>Response to Reviewers:</b>			



# UNIVERSITÀ DI PARMA

DIPARTIMENTO DI MEDICINA E CHIRURGIA

Via Gramsci, 14 - 43126 Parma

Tel: +39 0521 033184 fax: +39 0521 033185

e-mail: [amministrazione.dimec@unipr.it](mailto:amministrazione.dimec@unipr.it) - PEC: [DipMedicina@pec.unipr.it](mailto:DipMedicina@pec.unipr.it)

Parma, September 2021

Dear Prof La Viola,

Thank you for considering our manuscript, now entitled "Early Parent-Child Interactions and Substance Use Disorder: an Attachment Perspective in a Biopsychosocial Entanglement" for publication in *Neuroscience & Biobehavioral Reviews*.

We were encouraged by the fewer revisions suggested in this second round and we addressed almost every query. Specifically after an extensive discussion with the other authors we included also the studies that evaluated attachment styles as requested by Reviewer #4.

We would like to thank the reviewers for a thorough and thoughtful commentary on our work. Incorporating their suggestions has strengthened the manuscript which we hope is now suitable for publication in *Neuroscience & Biobehavioral Reviews*. To ensure we address all of the Reviewers' comments, and for ease of reference, we include their reviews below followed by our response to each concern.

Yours sincerely,

Gilberto Gerra  
AUSL of Parma

Paolo Ossola  
University of Parma

Dear Prof Laviola,

Thank you for considering our manuscript, now entitled "Early parent-child interactions and substance use disorder: a biopsychosocial entanglement" for publication in Neuroscience & Biobehavioral Reviews.

In this second round of revision, the Reviewers also raised a couple of conceptual and technical problems that needed to be addressed. We were able to address all of these issues in the revised manuscript. In particular, we further clarified the search strategy and added a flow diagram to guarantee the reproducibility of the revision. We clarified the developmental trajectory of attachment from infancy through adulthood in the introduction and we also included in the review the studies that considered adult attachment style. We also changed the main study figure that now includes more information regarding the proposed neurobiological pathways.

We would like to thank the reviewers for their commentary on our work. Incorporating their suggestions has strengthened the manuscript which we hope is now suitable for publication in Neuroscience & Biobehavioral Reviews. To ensure we address all of the Reviewers' comments, and for ease of reference, we include their reviews below followed by our response to each concern.

### **Essential Revisions:**

#### **Reviewer #2:**

The authors addressed all my comments and improved the manuscript that in my opinion can be accepted for publication. Only a typesetting error in the clean copy page 5 line 15 "literature seems to agree" instead of "seem to agree"

- Thank you for this comment. We corrected the error.

#### **Reviewer #3:**

The authors have addressed many of my concerns.

Please add the search strategy to the paper. For example, you could add a paragraph explaining what you did and a PRISMA flow diagram.

- We further clarified the search strategy in the methods and added the flow chart following diagram, which is reported in Figure 1.

The figure seems a bit simple compared to the amount of information in the text. I think that it could include many more relevant results of the paper.

- We agree that a more comprehensive figure would help in understanding the results. As suggested, we enriched Figure 2, adding some of the information reported in the text. Specifically we included more details regarding the four hypothesised pathways in our model.

#### **Reviewer #3:**

The manuscript has undergone substantial revision and has improved in many respects. There are, however, a couple of issues that I still find puzzling.

First, the manuscript focus still does not seem to be adequately expressed. While the title state "Parent-child attachment and substance use disorder (SUD)", the paper does not deal with attachment as a whole and includes topics that are not attachment, though they are related to attachment. The author's decision to leave out the literature on attachment styles and SUD does not fit with a paper on attachment and SUD and cannot be justified

by the appeal to a developmental approach. There is continuity, as demonstrated from longitudinal studies, from attachment in infancy and romantic attachment in adulthood as measured by attachment styles. Also, adult attachment styles are linked to infant attachment in a similar way as adult state of mind about attachment relationships with parents. Therefore, it would be quite easy to incorporate the literature on attachment styles and SUD by making reference to the two-dimensional model of attachment, that is strongly supported by research data. Research indeed suggests that there are two major dimensions underlying adult attachment style, called attachment-related anxiety and avoidance. The first refers to the fear of being abandoned or not loved enough, the second to discomfort with intimacy and the expression of emotions. What is extremely interesting is that there are striking parallels between these dimensions and a number of continuous coding scales assessing the behaviour of infants during Ainsworth's "Strange Situation". The first dimension has a parallel in infant distress after separation from the mother and anger at reunion, while the second dimension relates to less distress after separation and avoidance of and lack of closeness to mother. Observations such as these make very clear why incorporating attachment styles in the manuscript would not violate its ambition to take a developmental approach.

It is important to note that the authors refer to a bidimensional model of attachment, but they refer to a model in which one dimension is insecurity and the other is coping strategies. While I would not argue about the fact that this model has been proposed, almost every textbook about attachment contains a figure illustrating the two-dimensional model based on anxiety and avoidance, which is by and large the dominating model. The readers may wonder why a relatively unknown model is used as reference in place of the established model. Also, the established model would make it easy for the authors to incorporate the findings from the attachment style literature. An excellent textbook that may guide them through this recommended process is Mikulincer and Shaver's *Attachment in Adulthood. Structure, Dynamics, and Change* by the Guilford Press.

Second, there is still confusion about the use of the term "attachment". Attachment, in the theoretical meaning of the term, is a very specific concept. It is not synonym with parent-child relationship, parental style, and similar concepts. Individual differences in attachment are meaningfully related to the way parents treated the child, and to the experiences that the child faced, but are not determined by these factors in a causal and completely predictable way. Genes have their fair share of effect, as well as other individual factors. Thus, assessment instruments such as the Parental Bonding Instrument, which is listed among instruments that would measure "parental attachment and state of mind about attachment with parents in adulthood" do not measure attachment; rather, the PBI measures parental style as recollected by an adult. No attachment researcher or theoreticians would sign up that the PBI measures attachment in the strict meaning of the term. The scope of the paper, in its current form, is not parent-child attachment but rather topics such "child experiences", "family experiences in childhood", "parent-child interactions". Definitely, not parent-child attachment.

I would therefore recommend the authors to make the review more comprehensive by including the literature on adult attachment style and more focused by excluding studies on topics that, though related to attachment, are not attachment. Or, alternatively, to change the title in order to remove the word "attachment" and replace it with a concept that would better fit with the content of the paper. It would be a pity to lose the richness of the adult attachment style literature and to have a loosening of the focus away from attachment towards other constructs, but at least the topic of the paper would be properly expressed.

- We thank the reviewer for this thoughtful comment. After an extensive discussion with the other authors, as suggested, we agreed to incorporate all the studies that adopted questionnaires and interviews that assess the attachment style in our review. As a results:
  - we added a paragraph on attachment styles in adulthood, paralleling insecure infant attachments (ambivalent and avoidant) with insecure adult attachment styles (preoccupied and dismissing). We also referred to the most common two-dimensional model of attachment (page 5).
  - we modified the title in “Early parent-child experiences and substance use disorder: a biopsychosocial entanglement”, in order to include early experiences that, although not directly definable “attachment”, are related and influence it. Our decision to include this literature, despite the risk to loose the specific focus on attachment has two order of reasons. On one hand parental styles, as those measured by the PBI for example, can be crucial in the development of a specific attachment. On the other hand the paucity of studies that adopted “strict” measure of attachment in neurobiological studies would not allow a comprehensive overview of the topic. In fact only 8 out of 58 studies (14%) adopted classic measures of attachment as those listed in the Mikulincer and Shaver's book.
  - for completeness, in the limitation section we added a paragraph on the stability in attachment patterns from infancy to adulthood in longitudinal data. This should strengthen our choice of including parental experiences as there may be discontinuities in attachment pattern according life circumstances (Mikulincer e Shaver, 2016; Fraley et al., 2020). With this in mind the trajectories are more uneven and less predictable in children whose early experiences include adversity and maltreatment (Prior & Glaser, 2006) (page 34).

Finally, concerning the Conclusions, the authors start by noting that at least four different mechanisms, not included in the review because of lack of experimental studies, might be involved, and then discuss these mechanisms. Later, they make statements such as "the four main proposed pathways are not acting in isolation but are strictly interconnected" and "Up to now we described how gene and environment interact to shape the early attachment and hence increase the vulnerability to SUD". These statements seem to describe proven facts, rather than mere hypotheses. How could statements such as these be justified if there is not a single study to support them? These four pathways are only suggested pathways, and every statement about them should be very prudent and avoid any implication of certainty and causal inferences.

- In line with the reviewer suggestion, we moderated the assertiveness of the statements that reported still hypothetical associations, avoiding implication of certainty and causal inferences. We also highlighted in the discussion that the proposed model need further empirical validation (page 35).

Indeed, the Conclusions of the paper would much benefit from including a list of suggestions for future research. It would be very useful for other researchers if the authors, having conducted such a thorough review and identified a number of serious research gaps, would indicate which steps should be taken to advance our understanding of this topic.

- *We agree that suggestions for future projects would be helpful for researcher planning to conduct studies in this field. Our hypotheses in this regard have been added in the conclusions.*

## **Highlights**

- Substance use disorders vulnerability is rooted in neurobiological developmental pathways
- Insecure attachment and trauma are greater risk factors for developing substance use disorders
- Vulnerability to substance use disorders involve genetic, epigenetic and neuroendocrine changes
- Parenting represents a therapeutic target for prevention of addiction

## **Abstract**

This review aims to elucidate environmental and genetic factors, as well as their epigenetic and neuroendocrine moderators, that may underlie the association between early childhood experiences and Substance Use Disorders (SUD), through the lens of parental attachment.

Here we review those attachment-related studies that examined the monoaminergic systems, the hypothalamic pituitary adrenal stress response system, the oxytoninergic system, and the endogenous opioid system from a genetic, epigenetic, and neuroendocrine perspective.

Overall, the selected studies point to a moderating effect of insecure attachment between genetic vulnerability and SUD, reasonably through epigenetic modifications. Preliminary evidence suggests that vulnerability to SUDs is related with hypo-methylation (e.g. hyper-expression) of high-risk polymorphisms on the monoaminergic and hypothalamic pituitary adrenal system and hyper-methylation (e.g. hypo-expressions) of protective polymorphisms on the opioid and oxytocin system. These epigenetic modifications may induce a cascade of neuroendocrine changes contributing to the subclinical and behavioral manifestations that precede the clinical onset of SUD. Protective and supportive parenting could hence represent a key therapeutic target to prevent addiction and moderate insecure attachment.

**Keywords.** attachment; Substance use; genetic; epigenetic; neuroendocrine;

1  
2  
3  
4 **EARLY PARENT-CHILD INTERACTIONS AND SUBSTANCE**  
5  
6  
7 **USE DISORDER: AN ATTACHMENT PERSPECTIVE ON A**  
8  
9  
10 **BIOPSYCHOSOCIAL ENTANGLEMENT.**

11  
12 Maria Lidia Gerra <sup>a</sup>, Maria Carla Gerra <sup>b</sup>, Leonardo Tadonio <sup>a</sup>, Pietro Pelligini <sup>a</sup>, Carlo Marchesi <sup>c</sup>,  
13  
14 Elizabeth Mattfeld <sup>d</sup>, Gilberto Gerra <sup>a</sup>, Paolo Ossola <sup>b\*</sup>

15  
16  
17  
18  
19  
20 (a) Department of Mental Health, AUSL of Parma, Parma, Italy

21  
22 [magera@ausl.pr.it](mailto:magera@ausl.pr.it), [ltadonio@ausl.pr.it](mailto:ltadonio@ausl.pr.it); [ppellegrini@ausl.pr.it](mailto:ppellegrini@ausl.pr.it); [ggerra@ausl.pr.it](mailto:ggerra@ausl.pr.it);

23  
24  
25 (b) Center for Neuroplasticity and Pain (CNAP), SMI@, Department of Health Science and Technology,  
26  
27 Aalborg University, Aalborg, Denmark.

28  
29  
30 [mcg@hst.aau.dk](mailto:mcg@hst.aau.dk)

31  
32 (c) Psychiatry Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy

33  
34  
35 [paolo.ossola@unipr.it](mailto:paolo.ossola@unipr.it); [carlo.marchesi@unipr.it](mailto:carlo.marchesi@unipr.it);

36  
37 (d) Drug Prevention and Health Branch, Prevention Treatment and Rehabilitation Section, United  
38  
39 Nations Office on Drugs and Crime, Vienna, Austria

40  
41  
42 [Elizabeth.mattfeld@un.org](mailto:Elizabeth.mattfeld@un.org)

43  
44  
45  
46 \* Paolo Ossola, MD

47  
48  
49 Psychiatry Unit, Department of Medicine and Surgery, University of Parma

50  
51  
52 Padiglione Braga #21

53  
54  
55 Via Antonio Gramsci 14

56  
57  
58 43126 Parma (PR) Italy

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**Abstract**

This review aims to elucidate environmental and genetic factors, as well as their epigenetic and neuroendocrine moderators, that may underlie the association between early childhood experiences and Substance Use Disorders (SUD), through the lens of parental attachment.

Here we review those attachment-related studies that examined the monoaminergic systems, the hypothalamic pituitary adrenal stress response system, the oxytoninergic system, and the endogenous opioid system from a genetic, epigenetic, and neuroendocrine perspective.

Overall, the selected studies point to a moderating effect of insecure attachment between genetic vulnerability and SUD, reasonably through epigenetic modifications. Preliminary evidence suggests that vulnerability to SUDs is related with hypo-methylation (e.g. hyper-expression) of high-risk polymorphisms on the monoaminergic and hypothalamic pituitary adrenal system and hyper-methylation (e.g. hypo-expressions) of protective polymorphisms on the opioid and oxytocin system. These epigenetic modifications may induce a cascade of neuroendocrine changes contributing to the subclinical and behavioral manifestations that precede the clinical onset of SUD. Protective and supportive parenting could hence represent a key therapeutic target to prevent addiction and moderate insecure attachment.

**Keywords.** attachment; Substance use; genetic; epigenetic; neuroendocrine;

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## 1. Introduction

In many societies, addiction is still unrecognized as a health problem and many people suffering from it are stigmatized with limited or no access to diagnosis, treatment and rehabilitation. This dramatic discrimination reflects a moralistic view, which considers addiction as a failure of righteous values and subjects with Substance Use Disorder (SUD) as people with simply a dysfunctional personality (Pickard, 2017).

Two opposing theories attempt to define the behavioural component of substance use disorders. On one side some authors, based on classic models of learning from reward, suggested that addiction is a voluntary behaviour, governed by universal principles of choice and motivation and influenced by preferences and goals (Heyman, 2009; Frank & Nagel, 2017; Henden et al, 2013). By contrast other authors pointed that addiction is deeply rooted in neurobiological modification (Volkow et al., 2016) that imply a primary impairment in decision-making, self-control and emotion regulation. According to the latter becoming addicted involves a transition from voluntary to non-voluntary compulsive drug use (Mollick & Kober, 2020).

Although moving from a moralistic to a biological model had strong implications for public attitudes and policies, the belief that SUD could be explained ultimately in terms of specific dysfunctional neurobiological conditions risks to be a reductionist explanation, which may underestimate the social and psychological causes and consequences of addiction (Borsboom et al. 2019).

Indeed, a growing body of evidence suggests a greater complexity in the pathogenesis of addiction, which begins early after conception and involves concurring genetic, epigenetic and neuroendocrine modifications. In this view, SUD is conceptualized as a “developmental disorder”, with genetic, and environmental antecedents (McCrorry and Mayes, 2015).

The dynamic in the early relationships seems to impact mostly on the future vulnerability to SUD (Knudsen et al., 2004). Hence here we decided to focus on the early parental attachment that may

1  
2  
3  
4 represent the very first potential protective element acting against vulnerabilities toward SUD, not simply  
5  
6 a risk factor.  
7

### 8 ***1.1. Attachment***

9  
10 Attachment has been defined as a bond between an individual and a caregiver, based on the need for  
11  
12 safety and protection (Bowlby, 1969).  
13

14  
15 A secure attachment emerges from the encounter between the temperamental characteristics of the infant  
16  
17 and the sensitivity of the caregiver, intended as responding with availability and responsiveness to child  
18  
19 signals (Holmes & Holmes, 2014). The secure child is able to use the parent as a secure base from which  
20  
21 to explore the environment and is easy to console after separation or when otherwise stressed (Ainsworth  
22  
23 et al., 1978).  
24  
25

26  
27 By contrast, an insecure attachment develops as a form of adaptation to mis-attuned parenting. Insecure  
28  
29 attachment emerges when infants have difficulty using the caregivers as a secure base, because at times  
30  
31 the parent or caregiver responses are intrusive or they are emotionally unavailable. Based on the infant  
32  
33 response behaviour when the caregiver interacts with strangers or leaves them alone, insecure  
34  
35 attachments are divided into avoidant or ambivalent. It is defined avoidant attachment when infants do  
36  
37 not exhibit distress upon separation and do not seek contact after the caregiver's return. Children with  
38  
39 ambivalent attachment, instead, are extremely distressed when left alone and alternate behaviours of  
40  
41 seeking contact with and resisting to the caregivers after separation.  
42  
43  
44  
45  
46  
47

48 Disorganized attachment is the most extreme of insecure attachments; this is often a consequence of a  
49  
50 trauma, such as interpersonal neglect or psychological, physical or sexual abuse, with aspects of  
51  
52 neurodevelopment vulnerability in the child (Main et al., 2005). The children exhibit contradictory and  
53  
54 unpredictable behavioural patterns of interaction with the caregiver, in the form of wandering, confusion,  
55  
56 freezing, and undirected movements.  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 Attachment research extended into adolescence and adulthood has suggested that there is continuity from  
5  
6 attachment in infancy and romantic attachment in adulthood. In line with this evidences adolescents and  
7  
8 adults' mental representations of attachment to their parents during childhood are the foundation on  
9  
10 which state of mind with respect to one's current relationship partners during adulthood is constructed.  
11  
12 Dismissing (i.e., avoidant) adults play down the importance of attachment relationships and tend to recall  
13  
14 few concrete episodes of emotional interactions with parent. They experience discomfort with closeness  
15  
16 and dependence on relationship partners, preferring emotional distance and self-reliance and using  
17  
18 deactivating strategies to deal with insecurity and distress. On the other side, preoccupied (i.e.,  
19  
20 ambivalent) individuals are entangled in worries and angry feelings about parents, are hypersensitive to  
21  
22 attachment experiences, and can easily retrieve negative memories. In romantic relationship they are  
23  
24 concerned with a strong desire for closeness and protection, intense worries about partner availability  
25  
26 and one's own value to the partner and use of hyper-activating strategies to deal with insecurity and  
27  
28 distress. Finally, fearful avoidant attachment represents the extreme degree of attachment insecurity in  
29  
30 adulthood, paralleling disorganization in infancy. Fearful avoidant individuals easily came from abusive  
31  
32 or dysfunctional families and they may report physical or sexual abuse or other attachment-related  
33  
34 traumas. They are the least secure, least trusting and most troubled of adolescents and adults because  
35  
36 they use mixed deactivating and hyper activating attachment strategies to deal with insecurity: like  
37  
38 dismissing individuals they often distance themselves from relationship partners, to avoid the possible  
39  
40 negative consequences of reliance on others, but, as the preoccupied counterpart, they continue to  
41  
42 experience anxiety, ambivalence, and the desire for their relationship partners' love and support  
43  
44 (Mikulincer and Shaver, 2016).  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

56 Within the developmental psychopathology framework, many longitudinal studies have examined the  
57  
58 connection between insecure and disorganized attachment patterns and the occurrence of  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 psychopathology (Dutra & Lyons-Ruth, 2005; Englund et al., 2011; Grossmann et al., 2005; Lyons-Ruth  
5  
6 et al., 2013; Shi et al., 2012; Sroufe, 2005). Although the exact ways in which early attachment  
7  
8 experiences lead to the development of specific forms of psychopathology remain unclear, literature  
9  
10 seems to agree with a causal relationship (Cassidy and Shaver, 2016). Well-replicated results supported  
11  
12 links between avoidant attachment and anxiety disorders in adolescence and between disorganized  
13  
14 attachment and dissociative symptoms in adolescence and early adulthood. Moreover, a meta-analysis  
15  
16 conducted by Bakermans-Kranenburg and Van IJzendoorn's (2009) highlighted that  
17  
18 ambivalent/avoidant attachment relations are usually associated with subsequent externalizing  
19  
20 behaviours, such as antisocial personality and conduct disorders, while disorganized attachment increases  
21  
22 risk for internalizing problems, like borderline personality disorders. Mixed results on the association  
23  
24 between attachment and other psychopathologies (e.g., depression, schizophrenia, anxiety disorders and  
25  
26 eating disorders) could be due to their heterogeneity or the presence of comorbidities.  
27  
28  
29  
30  
31

### 32 33 ***1.2. Association between parental attachment and SUD*** 34

35  
36 Several studies have explored the association between attachment and SUD, suggesting that moderate to  
37  
38 strong evidence supports the assumption of insecure/disorganized attachment being a risk factor for SUD,  
39  
40 accounting for about 30% of the risk (Jordan and Sack, 2009). Effect size was also moderate when  
41  
42 evaluating the prospective association between insecure attachment and SUD in longitudinal studies  
43  
44 (Fairbairn et al., 2018).  
45  
46

47  
48 People who are relatively secure in their attachments are more likely than those who are not to manage  
49  
50 conflict effectively and be better adjusted psychologically. Attachment theory suggests a developmental  
51  
52 pathway from insecure attachment to SUD. Substance use can be understood as an attempt to compensate  
53  
54 for lacking attachment strategies. With increasing insecurity, individuals face more difficulties in  
55  
56 regulating emotions and stress. Psychotropic substance use may then become attractive as a means to  
57  
58 “self-medicate” attachment needs, to regulate emotions, or to cope with stress (Gill, 2017).  
59  
60  
61

1  
2  
3  
4 As for the attachment figures people experience positive emotions when reunited and restlessness and  
5  
6 preoccupation when separated, similar emotional responses occur in the context of addiction with the  
7  
8 preferred substance (Fairbairn et al., 2018). This pattern seems to parallel also the neurobiological basis  
9  
10 of substance use in which the binge/intoxication is followed by a stress-like response during withdrawal  
11  
12 that, through an inefficient emotion regulation, leads to a new intoxication, perpetrating the cycle and  
13  
14 contributing to abuse (Koob and Volkow, 2016).  
15  
16  
17

18  
19 According with a recent theoretical model (Schindler, 2019) the identification of coping strategies to  
20  
21 threats and stressors could allow to split the insecure, maladaptive, attachment into avoidant and  
22  
23 ambivalent. We can hypothesise that individuals with ambivalent and avoidant patterns use different  
24  
25 substances to compensate for the lack of a secure base. Specifically subjects with avoidant strategies look  
26  
27 for emotional distancing (e.g. heroin) whereas subjects with ambivalent strategies seek an affectively  
28  
29 hyperactivating substances (e.g. cocaine) to seek closeness to important others. Even though this is an  
30  
31 appealing hypothesis, the abovementioned systematic review did not confirm an association between the  
32  
33 type of insecure attachment and specific substances nor with the level of insecurity and the SUD severity  
34  
35 (Schindler, 2019).  
36  
37  
38

39  
40 The studies that explored the association between parental attachment and SUD can be divided into  
41  
42 studies that evaluated substance use in healthy subjects and studies that employed clinical groups with  
43  
44 SUD.  
45  
46  
47

48  
49 Studies in healthy subjects showed a cross-sectional association between maladaptive parental  
50  
51 attachment and substance use (Gattamorta et al., 2017; McLaughlin et al., 2016; Taylor-Seehafer et al.,  
52  
53 2008; Borelli et al., 2010; Nakhoul et al. 2020), alcohol (Abar et al., 2012), tobacco (Wise et al., 2017)  
54  
55 and behavioural addiction (Badenes et al., 2019; Ghasempour et al., 2015; Eichenberg et al., 2017, 2019;  
56  
57 Monacis et al., 2018; Remondi et al., 2020). A recent meta-analysis in healthy controls also confirmed  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 the association between parental attachment and substance use when including only the studies with a  
5  
6 longitudinal design (Fairbairn et al., 2018).  
7

8  
9 Overlapping results were found when considering clinical populations with SUD (Delvecchio et al.,  
10  
11 2016; Torresani et al., 2000, Lindberg et al., 2015, Schindler et al., 2005; Thorberg et al., 2006; Harnic  
12  
13 et al., 2010; Fumaz et al., 2019; Potik et al., 2014) where a poor attachment was associated with addiction  
14  
15 severity, an earlier age at onset (Icick et al., 2013) and a lower willingness to seek treatment (Caspers et  
16  
17 al., 2006; Berry et al., 2017). Interestingly, parental attachment seems differentially associated with the  
18  
19 type of drug (Hosseinfard et al., 2015). For example crack users perceive mothers as neglectful, and  
20  
21 fathers as controlling and affectionless (Pettenton et al., 2014). When exploring specifically their  
22  
23 perception of self and others, the heroin users showed a fearful pattern (negative model of self and  
24  
25 others), ecstasy users were more preoccupied (negative model of self and positive model of other) and  
26  
27 cannabis users were mainly dismissing (positive model of self, negative model of other) (Schindler et al.,  
28  
29 2009). In terms of treatment a more secure attachment was also related to a higher treatment retention  
30  
31 and lower relapse rate (Marshall et al., 2017), and methadone users reported significantly lower anxiety  
32  
33 about being rejected than drug-free addicts (Torres et al., 2019).  
34  
35  
36  
37  
38  
39

40  
41 The few neuroimaging studies available (Fuchshuber et al., 2020; Unterrainer et al., 2017; Unterrainer et  
42  
43 al., 2016) seem to point out to a diminished white matter integrity as a neurobiological marker of  
44  
45 attachment in substance use disorder.  
46

### 47 ***1.3. Aims***

48  
49  
50 The association between parental attachment and SUD, however, is not so linear and several moderators  
51  
52 have been suggested as taking part in this relationship. To better understand drug dependence, as a  
53  
54 “complex multifactorial health disorder, characterized by a chronic and relapsing nature” (UNGASS,  
55  
56 2016), we embrace a developmental perspective, suggesting that environmental and genetic factors could  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 interact with early adverse experiences in shaping parental attachment relationships. The latter result in  
5  
6 a potential vulnerability to addiction, by way of epigenetic and neuroendocrine mechanisms.  
7  
8

## 9 **2. Methods**

10  
11 Although this paper represents a comprehensive overview of the available literature on genetic,  
12  
13 epigenetic and neuroendocrine factors, that may underlie the association between attachment and SUD,  
14  
15 we adopted a semi-systematic approach.  
16  
17

18  
19 The strategy was developed in MEDLINE combining the following keywords:  
20

21 Set 1: (a) attachment; (b) maltreatment OR childhood OR neglect.  
22

23 Set 2: (a) substance OR addict\* OR dependence; (b) alcohol OR opiate OR opioid OR cocaine OR  
24  
25 cannab\* OR methamphetamine\* OR heroin\* OR stimulant\* OR tobacco OR cigarette\* OR ecstasy.  
26  
27

28 Set 3: (a) HPA OR cortisol OR stress hormone; (b) Oxytocin\* OR OT OR neuropeptide; (c) endogenous  
29  
30 opioid OR beta-endorphin; (d) dopamine\* OR homovanillic acid; (e) serotonin\* OR 5HT OR 5-  
31  
32 hydroxytryptamine OR 5-hydroxyindolacetic acid.  
33  
34

35 Set 4: (a) gene OR genetic; (b) epigenetic OR polymorph\* OR methylat\*  
36  
37

38 To evaluate which were the environmental factors involved in the association between attachment and  
39  
40 SUD we combined the keywords of Set 1a [Title/Abstract] and Set 2a [Title] retrieving n=493 abstracts.  
41  
42

43 We then combined the keywords of Sets 1, 2, and 3 [Title/Abstract] retrieving n=550 abstracts to draft  
44  
45 the paragraph on the neuroendocrine mechanism. Lastly to select the papers exploring the genetic and  
46  
47 epigenetic factors associated with early adverse experiences and SUD we combined the keywords of Sets  
48  
49 1 and 2 [Title/Abstract] and Set 4 [Title] retrieving n=355 abstracts. The abstracts have been screened  
50  
51 based on the appropriateness to the review topic. Studies published in English through March 2021 were  
52  
53 included. In addition, further studies were retrieved from reference listing of relevant articles and  
54  
55 consultation with experts in the field. The flowchart is depicted in **Figure 1**.  
56  
57  
58

59  
60 - Figure 1 approximately here -  
61  
62  
63  
64  
65

1  
2  
3  
4 As noted, because of the paucity of studies considering the classic attachment interviews and  
5  
6 questionnaires (Mikulincer and Shaver, 2016) in epi/genetic and neurobiological studies, when searching  
7  
8 in this literature we also included semi-structured interviews and questionnaires explicitly assessing early  
9  
10 environmental dynamics, traumatic experiences in childhood and parental styles, which could contribute  
11  
12 to the development of insecure attachment organization. These are for instance the Childhood Experience  
13  
14 of Care and Abuse questionnaire (CECA-Q) (Bifulco et al., 2005), the Childhood Trauma Questionnaire  
15  
16 (CTQ) (Bernstein et al., 1998) and the Parental Bonding Instrument (PBI) (Parker, Tupling, & Brown,  
17  
18 1979).

### 23 **3. Pathways from early experiences to vulnerability to SUD**

#### 26 **3.1. Environmental factors**

27  
28 Although listing all the environmental risk factors that predispose to SUD goes beyond the scope of the  
29  
30 current review, we will briefly summarize the results of the current literature. Environmental factors  
31  
32 contributing to risks of SUD can be divided into three main categories: individual, familial and social  
33  
34 (Whitesell et al., 2013).

##### 38 **3.1.1. Individual factors**

39  
40 Individual factors that moderate the association between attachment and SUD encompass both stable  
41  
42 trait-like dimensions (e.g., temperament and character) and transient state-dependent phenomena (e.g.,  
43  
44 psychopathology symptoms).

45  
46 Cross-sectional studies in healthy subjects, for example, noted that both higher temperamental novelty  
47  
48 seeking (Cornellà-Font et al., 2018) and maladaptive coping strategies (Andres et al., 2014; Estevez et  
49  
50 al., 2019; Gerra et al., 2004; Lee et al., 2003; Lyvers et al., 2019; Walsh et al., 1995; Kassel et al., 2007;  
51  
52 Liese et al., 2020, Zakhour et al., 2020; Serra et al., 2019; Starks et al., 2015) separately increase the risk  
53  
54 of SUD and behavioural addiction (Liu et al., 2019; Monacis et al., 2017) when controlling for parental  
55  
56 attachment. Similar results were found when evaluating emotion dysregulation in a cohort of subjects  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 with SUD and comorbid borderline personality disorder (Schindler & Sack, 2015, Hiebler-Ragger et al.,  
5  
6 2016). Longitudinal studies in healthy subjects yielded similar results (Brook et al., 1993), with some  
7  
8 suggesting that temperamental dimensions of dysregulation mediate the association between attachment  
9  
10 and SUD (Zhai et al., 2014; Rovai et al., 2017; Maremmani et al., 2009; Fuchshuber et al., 2018).

11  
12  
13  
14 This means that subjects with higher levels of persistence (Arnau et al., 2008), greater emotion-regulation  
15  
16 (Kober, 2014, Karimi et al., 2019, Zdankiewicz-Scigala et al., 2018) and metacognitive abilities (Outcalt  
17  
18 et al., 2016) and more mature coping strategies (Willis, Wallston, & Johnson, 2001) have a lower risk of  
19  
20 developing a SUD, even when their parental attachment is insecure (Gerra et al., 2004).

21  
22  
23 Slightly more complex is the moderating effect of internalising psychopathology (i.e., depression and  
24  
25 anxiety). In fact, this would open the debate of whether this association is a pure comorbidity, a merely  
26  
27 diagnostic comorbidity, related to item overlap, or an aetiopathogenic comorbidity, in which the  
28  
29 relationship between internalising symptoms and SUD is causal (Feinstein, 1970). Independently from  
30  
31 which is the true meaning of this association, literature seems to agree that internalising symptoms  
32  
33 increase the risk of substance use beyond a maladaptive attachment in healthy subjects (Niyonsenga et  
34  
35 al., 2012; Pellerone et al., 2016; Kim et al., 2017; Shin et al., 2011; Meredith et al., 2020; Greger et al.,  
36  
37 2017; Chen et al., 2020) and clinical populations (De Palo et al., 2014; Miljkovitch et al., 2005; Musetti  
38  
39 et al., 2016; Schindler et al., 2007; Vismara et al., 2019; Wedekind et al., 2013; Thorberg et al., 2010;  
40  
41 De Rick et al., 2009; Fowler et al., 2013; Owens et al., 2018), also longitudinally (Gidhagen et al., 2018).

### 42 43 44 45 46 47 *3.1.2. Familial factors*

48  
49  
50 Considering familial moderators, several cross-sectional studies in healthy subjects showed that a  
51  
52 problematic family environment (Cleveland et al., 2014; De Wit et al., 1999; Estevez et al., 2017; Hayre  
53  
54 et al., 2019; Kanamori et al., 2016; Kostecky et al., 2005; Luk et al., 2015; Scragg et al., 2008  
55  
56 Zdankiewicz-Scigala et al., 2019; Winham et al., 2015; Vungkhanching et al., 2004; Massey et al., 2014;  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 Jones et al., 2015; Zeinali et al., 2011; Dishon-Brown et al., 2017) might moderate the association  
5  
6 between maladaptive attachment and substance use. This association was confirmed also in longitudinal  
7  
8 studies on healthy subjects (Heerde et al., 2019; Branstetter et al., 2009; VanderVost et al., 2006),  
9  
10 suggesting that a caring environment might be protective for SUD in those subjects with an insecure  
11  
12 attachment.  
13  
14

### 15 16 *3.1.3. Social factors* 17

18  
19 Finally, as children progress into adolescence, family becomes less influential and peers become the  
20  
21 more dominant socialization unit and hence a contributing factor to SUD development (Hahm et al.,  
22  
23 2003; Henry, 2008; Henry et al., 2009; Guo et al., 2020; Hocking et al., 2017; Liu et al., 2020). Peer drug  
24  
25 use in fact has a relatively strong effects on adolescent drug use, even when controlling for family climate  
26  
27 and attachment styles (Bahr et al., 2005). It is therefore important that programs targeting risk factors  
28  
29 and resilience to substance use incorporate the school environment and social domain in their skill  
30  
31 training.  
32  
33

### 34 35 *3.2. Genetic factors* 36

37  
38 Although heritability has been repeatedly demonstrated, SUDs show considerable evidence of  
39  
40 environmental influence, especially during early stages of life (Enoch, 2012; Dick et al., 2012). Recent  
41  
42 domain of research, usually entitled “gene-environment interplay”, showed that the study of  
43  
44 environmental risk factors is not in contradiction with a genetic approach of addictive disorders  
45  
46 (Gorwood et al., 2007).  
47  
48

49  
50 Here we considered the studies in which genetic factors and adverse parenting experiences interact and  
51  
52 contribute to or predispose to SUD.  
53  
54

55  
56 The majority of Candidate Gene Association Studies (CGAS), based on *a priori* assumptions, revealed  
57  
58 variants associated with the dopaminergic, serotonergic and opioids’ pathways, and with the  
59  
60 hypothalamic pituitary adrenal (HPA) axis (**Table 1**).  
61  
62

1  
2  
3  
4 *3.2.1. Monoamines*  
5

6 The main variants related to dopaminergic pathways belong to the dopamine receptors, and specifically  
7 to *DRD4* and *DRD2*.  
8

9  
10 The most frequently studied polymorphism of the *DRD4* gene is a 48-base-pair variable number tandem  
11 repeats (VNTR) (Van Tol et al., 1992). Subjects with long alleles (7 or more repeats) may have a reduced  
12 *DRD4* gene expression (Schoots & Van Tol, 2003) as well as receptors with reduced reactivity to  
13 endogenous dopamine. Adolescent and young adult carriers of 7 or more repeats (7R+) of the variable  
14 number tandem repeat (48-bp VNTR III exon) of *DRD4* were shown to have a major risk of alcohol  
15 dependence in the presence of environmental risks such as childhood adversity (Park et al., 2011) or a  
16 greater risk of tobacco and cannabis use when the attachment was insecure (Olsson et al., 2011). This  
17 was also confirmed by a longitudinal study in a cohort of male adolescents, in which being 7R+ increased  
18 the risk of any substance use, but protective parenting practices prevented this outcome (Brody et al.,  
19 2014)  
20  
21

22 Concerning the *DRD2* gene, the most attractive genetic variants has been the Taq1A polymorphism,  
23 located about 10 kb downstream from the *DRD2* gene within the ankyrin repeat and kinase domain  
24 containing 1, *ANKK1* gene) (Neville et al., 2004). Children carriers of Taq1 A allele (rs1800497-T,  
25 *ANKK1/DRD2*) differed in their sensitivity to both negative and positive feedback. Being insensitive to  
26 a regularly offered positive reinforcement may predispose the child to seek other types of reward  
27 increasing the neuronal release of dopamine and subsequently counteracting the negative feelings  
28 (Althaus et al., 2009). Consistently with the hypothesized altered reward processing of Taq1A  
29 polymorphism, adolescent carriers of the A1/T allele, and with parents highly permissive, were found to  
30 use significantly more alcohol over time compared with adolescents without these risk factors (van der  
31 Zwaluw et al., 2010). Moreover, this allele was found significantly associated to cannabis use in an adult  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 population with parental neglect being the greatest risk factors for cannabis use, beyond the genetic  
5  
6 influence (Gerra, et al., 2019).  
7

8  
9 Several CGAS also explored the role of 5-HTTLPR polymorphism as a risk factor for substance use,  
10  
11 depending on parental care perception. The short allele of 5-HTTLPR has been shown to have lower  
12  
13 transcriptional activity of the serotonin transporter than the long allele and resulted in higher risk of  
14  
15 alcohol use (Su et al., 2019), cocaine or illegal psychotropic drugs use (Gerra et al., 2007; Gerra et al.,  
16  
17 2010). In all these studies, however, supportive parenting (Su et al., 2019; Brody et al., 2009) and also  
18  
19 the perceived paternal and maternal care (Gerra et al., 2007, Gerra et al., 2010) attenuated or completely  
20  
21 eliminated the link between the genetic risk and the longitudinal increase in substance use.  
22  
23

24  
25 The association between 5-HTTLPR and marijuana specifically seems moderated by gender, with  
26  
27 females having a higher risk of misuse when neglected (Vaske et al., 2012). Ossola and coworkers,  
28  
29 exploring both the 5-HTTLPR and Taq1A/DRD2 polymorphisms in a sample of adults, children of  
30  
31 alcoholic parents, demonstrated that an early caring environment might lower the genetic risk of  
32  
33 developing an Alcohol Use Disorder (AUD), especially in males (Ossola et al., 2021).  
34  
35

36  
37 Beyond the transporters and receptors, also the enzymes involved in monoamine metabolism such as the  
38  
39 Catechol-O-methyltransferase (COMT) and the Monoamine oxidases (MAO) have been considered to  
40  
41 identify potential genetic variants conferring risk to substance use.  
42  
43

44  
45 Favourable parenting was identified as a protective factor for alcohol abuse in adolescents homozygous  
46  
47 for the Met allele of the *COMT* Val(158)Met polymorphism (Laucht et al., 2012). A substitution of  
48  
49 methionine (Met) in place of valine (Val) in this gene results in a 3- to 4-fold decrease in the activity of  
50  
51 the COMT enzyme (Lachman et al., 1996). The two possible variants however have differential  
52  
53 association with neurobiology of emotion regulation and executive functions. Whereas the low-activity  
54  
55 Met allele is related to a greater activation in limbic brain regions, the high-activity Val allele is  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 associated to impaired prefrontal activation (Mier, Kirsch, & Meyer-Lindenberg, 2010). For example,  
5  
6 carriers of the homozygous genotype Val/Val who used cannabis were more likely to experience  
7  
8 psychotic symptoms in presence of past childhood maltreatment (Vinkers et al., 2013). The role of  
9  
10 childhood trauma was also associated to an increased risk of heroin use when the subjects had another  
11  
12 polymorphism of the *COMT* gene (i.e., TT genotype of *rs737866*) (Li et al., 2012).  
13  
14

15  
16 A shorter allele in the promoter region of the monoamine oxidase type A (*MAOA*) is associated with a  
17  
18 lower functioning of the enzyme. Previous studies already tested the role of this variant in moderating  
19  
20 the association between childhood trauma and both psychopathology (Caspi et al., 2002) and brain  
21  
22 connectivity (Hart et al., 2018).  
23  
24

25  
26 A more recent study showed that physical and emotional abuse were associated with tobacco and  
27  
28 cannabis use lifetime if the carriers of the high-activity *MAOA* allele were female. On the other hand,  
29  
30 males had a greater risk of tobacco consumption in presence of a low-activity *MAOA* allele (Fite et al.,  
31  
32 2019)  
33  
34

### 35 36 3.2.2. HPA axis 37

38  
39 Genetic factors per se contribute to the stress regulatory HPA-axis and related cortisol reactivity and the  
40  
41 latter might influence the parent-infant attachment relationship. Genes involved in these pathways have  
42  
43 been identified on both central and peripheral receptors involving the corticotropin-releasing hormone  
44  
45 (CRH) and the glucocorticoids receptors.  
46  
47

48  
49 The corticotropin-releasing hormone receptor 1 (CRHR1) seems to mediate behavioural stress responses  
50  
51 (Heinrichs & Koob, 2004). Specific polymorphisms of its promoter have been associated with increased  
52  
53 CRH-R1 density and a greater alcohol preference (Hansson et al., 2006). Haplotype-tagging SNPs (the  
54  
55 *rs1876831* C allele and the *rs242938A* allele) in the *CRHR1* gene were associated with a greater  
56  
57 consumption of alcohol after stressful events and also with an earlier age of drinking initiation (Schmid  
58  
59 et al., 2010)  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 The FK506-binding protein 5 (FKBP5) is a glucocorticoid receptor co-chaperone that can decrease its  
5  
6 affinity for glucocorticoids and hence modulate the response to stress. The TT genotype carriers of the  
7  
8 intronic variant *rs1360780*, that have twice the amount of FKBP5 protein levels, were more likely to  
9  
10 develop into a problematic drinking behaviour or pattern in the presence of a poor relationship between  
11  
12 the child and parents (Nylander et al., 2017).  
13  
14

15  
16 A dysregulation of the HPA axis has been also associated with craving and relapse in cocaine-abstinent  
17  
18 addicts (Brady et al., 2009), probably toward an interaction between both mineralocorticoid and  
19  
20 glucocorticoid receptors (Joels et al., 2008; Oitzl et al., 2010). Polymorphisms in mineralocorticoid and  
21  
22 glucocorticoid receptor genes (*NR3C2* and *NR3C1*, respectively) associated with lowered efficiency of  
23  
24 cortisol, but not aldosterone, as a ligand, increased the risk of crack/cocaine addiction in the presence of  
25  
26 childhood physical neglect. The same polymorphisms and were also associated with greater  
27  
28 crack/cocaine withdrawal symptoms independently from adverse childhood experiences (Rovaris et al.,  
29  
30 2015).  
31  
32  
33

### 34 35 36 3.2.3. *Opioids* 37

38 Several studies in mammals suggest that opioids are central in the development of infant-mother  
39  
40 attachment (Nelson & Panksepp, 1998) and, in humans, mu-opioid receptor availability is correlated with  
41  
42 attachment avoidance (Nummenmaa et al., 2015). Most of the literature that explored this association  
43  
44 from a genetic perspective focused on the missense variant A118G, *rs1799971* of mu-opioid receptor  
45  
46 gene (*OPRM1*). Expressing the G allele of this polymorphism results in up to 10- fold lower levels of  
47  
48 mu-opioid receptors compared to the A allele (Zhang et al., 2005). The G allele, seems to be associated  
49  
50 to better parent-child relations compared with A/A subjects in case of familiarity for SUD (Copeland et  
51  
52 al., 2011), whereas the A carriers showed lower scores of self-directedness, cooperativeness, and  
53  
54 predictive substance abuse even in response to higher maternal protection (Noto et al., 2020). However,  
55  
56 not all the results are consistent; the G allele for example was also associated with insecure attachment,  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 less care in mothers and predisposing to psychopathological symptoms development (Cimino et al.,  
5  
6 2020).

#### 9 3.2.4. *Oxytocin and other pathways*

10  
11 Oxytocin has received much attention as a prosocial and anxiolytic neuropeptide. In human studies, the  
12  
13 G-allele of a common variant (*rs53576*) in the oxytocin receptor gene (*OXTR*) has been associated with  
14  
15 protective properties such as reduced stress response and higher receptiveness for social support.  
16  
17 However, when including environmental factors into the model, the G-allele increased the susceptibility  
18  
19 to detrimental effects of childhood adversities. GG homozygotes exposed to childhood adversities  
20  
21 reported lower reward dependence and increased responsiveness to emotional stimuli suggesting an  
22  
23 attunement for social cues in early adverse conditions (Dannlowski et al., 2016)

24  
25 It is also worth reminding about a few other variants that might affect SUD development in the context  
26  
27 of altered attachment. These include: (1) the *rs604300* polymorphism of the monoglyceride lipase gene  
28  
29 (*MGLL*), an enzyme involved in the signalling within the endocannabinoid system (Carey et al., 2015)  
30  
31 (2) the *rs2072660* polymorphism of the Cholinergic Receptor Nicotinic Beta 2 Subunit (*CHRN2*), that  
32  
33 was significantly associated with nicotine dependence (Csala et al., 2015); and (3) the *rs2290045* of the  
34  
35 Vesicular Glutamate Transporter 2 (*VGLUT2*) a broadly expressed transporter in brain areas involved in  
36  
37 the reward system (Meyers et al., 2015).

38  
39 Beyond the pharmacodynamics, specific polymorphisms can also affect the pharmacokinetics of  
40  
41 substances, such as the *rs1229984* polymorphism of the Alcohol dehydrogenase 1B (*ADH1B*). The A  
42  
43 allele, compared to the G allele, greatly increases the activity of the ADH1B enzyme and this has been  
44  
45 consistently associated with a protective effect against alcoholism (Zaso et al., 2019). This association is  
46  
47 moderated by childhood adversity, so that those exposed to neglect or abuse during the first years and  
48  
49 with a GG homozygosity had more severe AUD (Vrettou et al., 2019).

1  
2  
3  
4 Interestingly, non-supportive parenting seemed also to affect telomere length and this was mediated by  
5  
6 the escalation of drinking and smoking in young adulthood (Beach et al., 2014).  
7  
8

9 Only one Genome Wide Association Study (GWAS) investigated specific variants interacting with  
10  
11 traumatic childhood experience and SUD. A “TG” deletion (del-1:15511771) in the *TMEM5* gene,  
12  
13 encoding a multi-pass transmembrane protein highly expressed in the brain, was shown to be associated  
14  
15 with cocaine use in subjects who had non-traditional parental care (Sun et al., 2020). Other GWAS found  
16  
17 potential genetic variants on genes related to synaptic transmission and cation transport (Pappa et al.,  
18  
19 2015) and in transcriptions regulatory genes (Dalvie et al., 2020) associated to parental attachment styles  
20  
21 or childhood trauma but they did not explore the interaction with SUD development.  
22  
23  
24

25  
26 - Table 1 approximately here -  
27

### 28 ***3.3. Epigenetic mechanisms***

29  
30  
31 Literature seems to agree that stressful or supportive early social environments, such as adverse  
32  
33 childhood experiences or protective parenting, affect epigenetic changes (Jiang et al., 2019; Garg et al  
34  
35 2018). Among all the epigenetic changes, the majority of the studies focus on DNA methylation. This  
36  
37 modification consists in the transfer of a methyl group to the cytosine of the DNA to form 5-methyl-  
38  
39 cytosine and it is generally associated with gene repression (Moore et al., 2013).  
40  
41

42  
43 In this paragraph we will focus on the epigenetic modifications that, interacting with attachment-related  
44  
45 factors, might entail regulatory implications for SUD. All the studies analysed DNA methylation in  
46  
47 peripheral tissues, in genes related to dopamine, opioids, HPA axis and oxytocin (**Table 2**).  
48  
49

#### 50 ***3.3.1. Monoamines***

51  
52  
53 Two studies evaluated specifically the epigenetic modifications in monoamine related genes. One that  
54  
55 regulates monoamine degradation through Monoamine Oxidase (MAO) (Bendre et al., 2018) and the  
56  
57 other that controls the dopamine reuptake (DAT) (De Nardi et al., 2020).  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 Brendre and colleagues (2018) investigated whether the methylations levels in the functional variable  
5  
6 number tandem repeats in the promoter region of the *MAOA* gene (*MAOA-uVNTR*) affects alcohol  
7  
8 consumption in a sample of male adolescents/young adults. The authors focused on 16 candidate sites  
9  
10 for methylation where cytosine lies next to guanine in the DNA sequence (CpGs) within part of the  
11  
12 *MAOA* first exon and intron. The methylation of these regions is usually inversely correlated with gene  
13  
14 expression. They found that the risk of alcohol use was associated with both carrying the *MAOA-uVNTR*  
15  
16 *S* allele and having experienced maltreatment, but depended on the degree of first-intron *MAOA*  
17  
18 methylation: among *S* carriers who experienced maltreatment, those who displayed lower levels of  
19  
20 intronic *MAOA* methylation reported more alcohol-related problems than those who displayed higher  
21  
22 levels of intronic *MAOA* methylation. Therefore subjects with high-risk genotype (*S* allele), who  
23  
24 experienced maltreatment, have a greater risk of alcohol-related problems, unless their *S* allele was  
25  
26 silenced by methylation. By contrast, having a protective *MAOA-uVNTR L* allele did not completely  
27  
28 prevent the risk of alcohol-related problems in fact intronic *MAOA* methylation could inactivate the  
29  
30 transcription of the protective allele among those who experience maltreatment.  
31  
32  
33  
34  
35  
36  
37

38 The authors also investigated the association between alcohol consumption and *MAOA* exonic-  
39  
40 methylation. They showed that subjects among those consuming high levels of alcohol exonic *MAOA*  
41  
42 methylation was lower in high-risk genotype (*S* allele) carriers than the *L*-allele carriers. These results  
43  
44 suggest that exonic *MAOA* methylation may be a biomarker of alcohol related problems, but still in a  
45  
46 genotype-dependent manner.  
47  
48  
49

50 A key player in dopamine (DA) neurotransmission is the dopamine transporter (DAT), a protein located  
51  
52 in the synapsis that regulates the release and reuptake of dopamine. The human *DAT1* gene, encoding for  
53  
54 the dopamine transporter, has a variable number of tandem repeats (VNTR) polymorphism in the 3'-  
55  
56 untranslated region (3'-UTR) in which the base pairs can be repeated 9 or 10 times. The 3' UTR 9-repeat  
57  
58 allele has been related with higher DAT binding and subsequently reduced downstream DA signalling,  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 conferring relative protection from becoming a stimulant user (Haile et al., 2007). However, the  
5  
6 dynamics of methylation within the 5'-untranslated region (5'-UTR) of the DAT1 gene could modify the  
7  
8 gene expression. According with the recent paper by Nardi and colleagues (2020), subjects with internet  
9  
10 addiction were more likely to have the 10-repeat allele and an insecure attachment style. However,  
11  
12 considering individuals in the control group, without internet addition, homozygous for the 10-repeat  
13  
14 allele, DNA CpG5 methylation percentage at 5'-UTR was not matched with CpG6 methylation, as  
15  
16 compared with controls with 9/x genotype. This result from the CpG5–CpG6 comparison suggests an  
17  
18 unexplored 5'-UTR intra-motif link that could represent, again, an epigenetic silencing mechanism on  
19  
20 the expression of high-risk genotype (De Nardi et al., 2020).  
21  
22  
23  
24  
25

### 26 3.3.2. HPA axis

27  
28 Several research groups have demonstrated that DNA methylation in HPA axis genes interacts with  
29  
30 childhood-negative experiences (Bosmans et al., 2018; Mudler et al., 2017; Ein-Dor et al., 2018). To our  
31  
32 knowledge, only one study specifically explored whether DNA methylation in the glucocorticoid  
33  
34 receptor gene *NR3C1* was associated with SUD in case of childhood maltreatment (Tyrka et al., 2016).  
35  
36 The glucocorticoid receptor (GR) gene has a regulatory role of the GR in hypothalamic–pituitary–adrenal  
37  
38 (HPA) axis function. Lower methylation of *NR3C1* is associated with increased gene expression, greater  
39  
40 GR numbers and, consistently, with enhanced glucocorticoid negative feedback and reduced cortisol  
41  
42 responses. The authors noted that in subjects with a SUD history, childhood adversities were negatively  
43  
44 related to gene methylation and associated to a blunted cortisol response to dexamethasone/corticotropin-  
45  
46 releasing hormone test.  
47  
48  
49  
50  
51  
52

### 53 3.3.3. Opioid

54  
55 When examining the childhood adversity-associated DNA methylation changes in Alcohol Dependent  
56  
57 patients, the promoters region of three genes results hyper-methylated (Zhang et al., 2013). These genes  
58  
59 are the aldehyde dehydrogenase gene (*ALDH1A1*), involved in alcohol metabolism, the regulator of G-

1  
2  
3  
4 protein signalling 19 (*RGS19*), and, the Opioid Related Nociceptin Receptor 1 gene (*OPRL1*), which  
5  
6 regulates behavioural responses to alcohol. Animal models suggested that the nociceptin receptor,  
7  
8 encoded by *OPRL1*, might be an interesting target for treatment, reducing ethanol intake in alcohol-  
9  
10 preferring rats and abolishes the rewarding properties of ethanol (Ciccocioppo 2004). DNA methylation  
11  
12 in the *OPRL1* gene, was further investigated in 660 adolescents (Ruggeri et al., 2018), with contradictory  
13  
14 results. The authors did not find associations between single nucleotide polymorphisms (SNPs) contained  
15  
16 in the *OPRL1* gene, which were previously associated with alcohol-use disorders, and binge drinking or  
17  
18 *OPRL1* methylation profile. Moreover, in contrast with their previous results (Ruggeri et al., 2015),  
19  
20 found that lifetime stressful life events are associated with lower methylation in the first intron of the  
21  
22 *OPRL-1*, which in turn was found associated with higher frequency of binge drinking. Therefore these  
23  
24 results should be interpreted cautiously.  
25  
26  
27  
28  
29

30  
31 DNA hydroxymethylation is an intermediate in the demethylation process mainly associated with  
32  
33 transcriptional activation rather than gene silencing. It has been observed that childhood abuse is  
34  
35 associated with a decreased hydroxymethylation and hence with a downregulation of the Kappa opioid  
36  
37 receptor. It is possible that this mechanism is mediated in the amygdala by glucocorticoid receptor  
38  
39 binding demonstrating the well-established interactions between endogenous opioids and stress (Lutz et  
40  
41 al., 2018). However, no studies investigated its potential impact on SUD development.  
42  
43  
44

#### 45 46 3.3.4. *Oxytocin* 47

48 Allelic variations of the oxytocin receptor gene (*OXTR*) influence neural responses to rewards, regulating  
49  
50 mesolimbic dopamine release, which may inhibit approach behaviors towards rewards (Wang et al.,  
51  
52 2013). By contrast, other *OXTR* polymorphisms are associated with risk for substance use in adolescents  
53  
54 and adults (Vaht et al., 2016),.  
55  
56

57 Previous studies suggested that expression of *OXTR* may be epigenetically regulated by DNA  
58  
59 methylation: increased *OXTR* methylation in CpG island spanning exons 1 to 3 is associated with  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 decreased OXTR expression (Kumsta et al., 2013), by contrast methylation of the third intronic region  
5  
6 of *OXTR* is associated with transcriptional repression of the gene (Mizumoto et al., 1997; Gregory et al.,  
7  
8 2009).

10  
11 Although the specific environmental modulators of *OXTR* activity remained unexplored and no direct  
12  
13 association of childhood maltreatment with *OXTR* methylation has been found (Parade et al., 2021), the  
14  
15 studies did report indirect or moderation effects of childhood adversities on OXTR methylation status  
16  
17 (Cecil et al., 2014; Unternaehrer et al., 2015).

20  
21 Only one study focused on OXTR methylation as the mechanism linking early social environments to  
22  
23 substance abuse (Kogan et al., 2018). The results showed that methylation at exons 1 to 3 of OXTR  
24  
25 increases SUD symptoms, suggesting a protective role of OT in modulating the rewarding effects of  
26  
27 drugs. Moreover, also in this study early adversities were associated with OXTR methylation indirectly  
28  
29 via contemporary prosocial relationships: childhood trauma and other forms of adversity may contribute  
30  
31 to problems with establishing and maintaining salutary relationships, which in turn affect OXTR  
32  
33 methylation status.  
34  
35  
36

37  
38 - Table 2 approximately here -  
39

### 40 41 **3.4. Neuroendocrine mechanisms**

42  
43 Neuroendocrine mechanisms have been demonstrated to represent one of the fundamental  
44  
45 neurobiological pathways underlying the relationship between genetic predisposition, early experiences  
46  
47 and susceptibility to addiction (Strathearn et al., 2019).

48  
49 Reviewing the current literature, three neuroendocrine pathways have been identified. These include the  
50  
51 hypothalamic-pituitary-adrenal (HPA) axis that is a proxy of our stress response system, the  
52  
53 monoaminergic system and the oxytocin-related system (**Table 3**).

#### 54 55 **3.4.1. Monoamine**

56  
57 Dopamine, serotonin and norepinephrine neurotransmission has been implicated in reward, impulsivity,  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 negative affectivity, and drug-seeking behaviour among patients with SUDs (Koob and Volkow, 2016).

5  
6 Following the hypothesis that monoaminergic dysfunctions pre-exist to SUD and could be related to  
7  
8 early stressful experiences, six studies focused on altered dopaminergic/serotonergic  
9  
10 neurotransmission as mediators between early stressful experiences and vulnerability to SUD.  
11

12  
13  
14 One neuroendocrine method to study the monoaminergic activity was to measure monoamine end-point  
15  
16 metabolite concentrations in the cerebrospinal fluid and plasma in patients with opioids (Gerra et al.,  
17  
18 2007), Alcohol (Virkkunen et al., 1996) and Cocaine Use Disorders (Roy, 2002; Gerra et al., 2009a). In  
19  
20 these studies dopamine metabolite homovanillic acid (HVA) and serotonin metabolite 5-  
21  
22 hydroxyindoleacetic acid (5-HIAA) concentrations showed significant negative correlations with  
23  
24 childhood neglect, poor parenting perception and a family history positive for paternal violence in SUD.  
25  
26

27  
28 Moreover, both dopamine and serotonin are thought to be independently involved in the central control  
29  
30 of prolactin (PRL) secretion: dopamine exerts tonic inhibitory control over PRL secretion, while  
31  
32 serotonin stimulates PRL secretion. Among cocaine addicted patients, higher basal levels of circulating  
33  
34 PRL, interpreted as an expression of reduced dopaminergic activity, have been found to be related to  
35  
36 neglect and poor parenting perception (Gerra et al., 2009a). In another study focused on the  
37  
38 serotonergic activity, after oral administration of a selective serotonin reuptake inhibitor (Citalopram),  
39  
40 alcohol-dependent individuals with childhood experience of emotional abuse had significantly lower  
41  
42 delta PRL response compared with those who did not report such abuse (Berglund et al., 2013).  
43  
44  
45  
46

47  
48 Finally, a positron emission tomography study in humans showed that a greater number of traumatic  
49  
50 events and altered caregiving were each associated with a higher ventral striatal dopamine response to  
51  
52 amphetamine, suggesting that early trauma may lead to enhanced dopaminergic sensitivity to psycho-  
53  
54 stimulants and that this mechanism may underlie increased vulnerability for drug use (Oswald et al.,  
55  
56 2014).  
57  
58

59  
60 These preliminary findings suggest that dopaminergic/serotonergic neuroendocrine alterations may be  
61  
62

1  
2  
3  
4 pre-existing to SUD and related to childhood adverse experience and poor parenting, rather than represent  
5  
6 just a consequence of prolonged substance exposure, which could also be responsible for a consistent  
7  
8 reduction in monoamine neurotransmission in SUD.  
9

### 10 11 3.4.2. HPA axis 12

13  
14 The HPA axis is a central component of the neuroendocrine response to stress, which can be measured  
15  
16 during basal functioning (HPA axis basal activity) or during stressful situations (HPA axis reactivity).  
17

18  
19 As indicated in **Table 3**, we were able to find 19 papers, which investigated the relationship between  
20  
21 problematic parenting/insecure attachment/early adverse experiences, HPA axis dysfunction and  
22  
23 vulnerability to addiction (Gerra et al., 2010).  
24

25  
26 Considering the HPA axis basal activity, the majority of the studies found positive correlations between  
27  
28 adverse childhood experiences and cortisol levels in patients with cocaine (Roy, 2002; Gerra et al., 2008;  
29  
30 Gerra et al. 2009a), opioids (Gerra et al., 2008; Gerra et al., 2014), alcohol (Schäfer et al., 2010), nicotine  
31  
32 (Gerra et al., 2016) and methamphetamine (Pirnia et al., 2019) use disorders as well as among adolescents  
33  
34 experimenting with tobacco use, particularly smoking (Doan et al., 2014) and illegal drugs (Gerra et al.,  
35  
36 2009b). However, other studies found no effect of childhood maltreatment exposure on cortisol plasma  
37  
38 levels, in a sample of females who use crack cocaine (Levandowski et al., 2016) or negative associations  
39  
40 between family dysfunction and baseline concentration of salivary cortisol among sons of SUD parents  
41  
42 (Dawes et al., 1999).  
43  
44  
45  
46  
47

48 Recently, greater consensus emerged on the supposition that the earlier risk factors that predict SUD also  
49  
50 predict a blunted HPA axis reactivity to pharmacological and social challenges. Accordingly, HPA axis  
51  
52 activity did not increase either after auditory evoked potential in preadolescents with father's with  
53  
54 substance use disorders (Dawes et al., 1999), or after unpleasant slide set viewing in opioids-dependent  
55  
56 patients tested for ACE (Gerra et al., 2009), or after dexamethasone/corticotropin-releasing hormone  
57  
58 challenge among cocaine-dependent patients with early life stress (Moran-Santa Maria et al., 2010).  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 Considering the studies that used the Trier Social Stress Tasks, blunted cortisol reactivity has been found  
5  
6 in a longitudinal study in girls who developed subsequent more pubertal change and substance use  
7  
8 (Negriff et al, 2015), in alcohol-dependent patients with and without childhood maltreatment (Muehlhan  
9  
10 et al., 2018), in higher smoking adolescents with colder parenting (Marceau et al., 2019), in young adults  
11  
12 who had experienced parental divorce and reported binge drinking (Hagan et al., 2019), in female  
13  
14 smokers with higher ACE scores (Hood et al., 2020). Again, although negative or conflicting results have  
15  
16 been reported in other samples (Moran-Santa Maria et al., 2010; Flanagan et al., 2015; Groh et al., 2020),  
17  
18 the effects of early life stress in patients at risk of SUD seem to manifest later in life in the form of HPA  
19  
20 axis dysregulation, which frequently involves dampening or blunting reactivity to stress.  
21  
22  
23

24  
25 Overall, although conflicting findings, perhaps due to different studies' designs, multiple substances  
26  
27 examined, different measures of HPA axis functioning and the complex nature of early experiences,  
28  
29 accumulating evidence seem to support the hypothesis that early stressful experiences could have  
30  
31 activated a persistent and unjustified corticotropin releasing hormone secretion also in front of non-  
32  
33 salient stimuli. This induces a permanent HPA axis basal hyperactivity, with poor ability to react to  
34  
35 contingent stressful conditions among individuals at risk of SUD (Gerra et al., 2014).  
36  
37  
38

### 39 40 41 *3.4.3. Opioid*

42  
43 The endogenous opioid system (EOS) includes the different opioid receptors and their endogenous  
44  
45 peptide ligands. The opioids  $\mu$ ,  $\kappa$  and  $\delta$  receptors belong to the superfamily of seven transmembrane  
46  
47 domain G protein-coupled receptors, whose activation inhibits neuronal activity and reduces  
48  
49 neurotransmitter release. The endogenous opioid ligands, including  $\beta$ -endorphin, met- and leu-  
50  
51 enkephalin, dynorphins and neo-endorphins, are active peptides with an N-terminal sequence (Tyr-Gly-  
52  
53 Gly-Phe-Met-Leu), indispensable to activate opioid receptors, although they have different affinity for  
54  
55 the different receptors (Trigo et al., 2010).  
56  
57  
58

59  
60 The EOS seems to play an important role in the development of addiction, influencing personality traits  
61  
62  
63  
64  
65

1  
2  
3  
4 that confer vulnerability or resiliency against risky behaviours such as the predisposition to develop  
5  
6 substance use disorders (Love et al., 2009). Moreover, in nonhuman primates, this system has been  
7  
8 demonstrated to be involved in social interactions between mothers and infants, like grooming and  
9  
10 attachment. However, evidence from humans is lacking due to practical difficulties associated with both  
11  
12 the assaying of endogenous opioid levels from human cerebro-spinal fluid or with Positron Emission  
13  
14 Tomography (PET) and the administration of opioid receptor antagonists and agonist (Machin et al.,  
15  
16 2011).  
17  
18  
19

20  
21 We found only one recent study (Groh et al. 2020) that evaluated the interrelationship between the serum  
22  
23 level of  $\beta$ -endorphin and childhood trauma, in a sample of 15 patients with Opioid Use Disorders,  
24  
25 challenged with diamorphine. The authors found a strong correlation between severe trauma and  
26  
27 significantly lower levels of  $\beta$ -endorphin, suggesting that reduced endogenous opioid peptides could  
28  
29 have a role in the altered in stress response, among SUD patients.  
30  
31

#### 32 33 *3.4.4. Oxytocin* 34

35  
36 More recently, research focused on oxytocin (OT), a nonapeptide hormone synthesized primarily in  
37  
38 hypothalamic nuclei and both secreted into the general circulation and released within the brain.  
39  
40 Neurobiological models suggested that emotional neglect and abuse in childhood dysregulate the  
41  
42 development of the OT system (Tops et al., 2014), which has been linked to a greater susceptibility to  
43  
44 develop drug addiction (Baracz et al., 2020). However, few studies in humans examined the individual  
45  
46 variability of the endogenous oxytocin system in patients with SUD, in relations with early  
47  
48 experiences/attachment measures. Huang et al. (2018) found a distinctively reduced OT plasma level in  
49  
50 ketamine-dependent patients, during early abstinence, but no association has been found with measures  
51  
52 of childhood trauma. In contrast, another study showed that poli-drug users on maintenance therapy  
53  
54 found higher levels of peripheral plasma OT, as compared to HC, at baseline, with non-significant  
55  
56 differences in OT-reactivity to an attachment related stimulus (Fuchshuber & Unterrainer , 2020). Gerra  
57  
58  
59  
60  
61

1  
2  
3  
4 et al. (2017) found that OT serum levels, among abstinent patients affected by opioid use disorder, were  
5  
6 unexpectedly higher and positively correlated with mother neglect scores, suggesting that oxytocinergic  
7  
8 signalling may exert different effects on attachment and bonding depending on the safe or dangerous  
9  
10 environmental conditions (Dannowski et al., 2016; Carter, 2017).  
11  
12

13  
14 These contradictory findings suggest that OT system is part of a more complex mechanism (Ellis et al.,  
15  
16 2021), which involves the interaction with other unexplored neuroendocrine mechanisms that might  
17  
18 mediate the relationship between early adversities and the pathogenesis of SUD. Among the suggested  
19  
20 pathways there are the endogenous opioids, the glutamate and immune systems (Buisman-Pijlman et al.,  
21  
22 2014; Uvnäs Moberg et al., 2019; Sundar et al., 2021).  
23  
24

25  
26 - Table 3 approximately here -  
27

## 28 **4. Discussion**

29  
30 In this review we focused on gene variants, epigenetic modifications and neuroendocrine changes that  
31  
32 affect the glucocorticoid-related, monoaminergic, opioidergic and oxytocinergic pathways that might  
33  
34 link early adverse childhood experiences with substance use.  
35  
36

### 37 **4.1. Possible neglected mechanisms**

38  
39 In most of the described papers the specific mechanism, being it environmental, genetic, epigenetic or  
40  
41 neuroendocrine, interacted with the early caring environment in shaping the risk of SUD. However, the  
42  
43 picture seems not so simplistic. At least four different mechanisms, not included in this review because  
44  
45 of lack of experimental studies, might be involved. These are: the multiple mechanisms of action of a  
46  
47 single gene, the gene-environment interaction, the gate control over epigenetic modifications and the  
48  
49 interaction with other pathways.  
50  
51

#### 52 **4.1.1. Same gene, different mechanisms**

53  
54 Heritability has been repeatedly demonstrated in SUD, with a risk due to genetic differences between  
55  
56 individuals ranging from 40% to 70% across different psychoactive substances, suggesting that polygenic  
57  
58  
59  
60  
61

1  
2  
3  
4 (quantitative) influences account for about 50% of the risk of developing SUD (Prom-Wormley et al,  
5  
6 2017). Despite the successes of genome-wide association (GWA) research in identify different molecular  
7  
8 markers, beyond the usual candidate genes (Deak and Johnson, 2021), the GWA studies on SUD are still  
9  
10 characterized by a heritability gap between molecular and quantitative genetic studies. Twin and adoption  
11  
12 studies estimated for approximately 50% of heritability (Kendler et al., 2012) however the effect sizes  
13  
14 found in GWAS are very small and hence we are far from explaining all the heritability factors through  
15  
16  
17  
18  
19  
20 GWAS studies.

21  
22 The complexity is further compounded because specific polymorphisms could code for the same protein  
23  
24 with different activity. The reader might then suppose that, as in the case of aldehyde dehydrogenase, a  
25  
26 lower metabolism of aldehyde would result in higher concentration of this compound with the alcohol  
27  
28 consumption and hence in a more severe hangover. In reality each single protein might increase the risk  
29  
30 of substance use through different mechanisms, not necessarily directly related with the protein function.  
31  
32 For example, a single genetic variation in GABA<sub>A</sub> receptor subunits is able to increase the risk of alcohol  
33  
34 consumption by at least three different mechanisms. First, it increases the ethanol-induced impulsive  
35  
36 behaviour, leading to a greater consumption after the first beers; second it attenuates the sensitivity to  
37  
38 the sedative effects of drugs and hence it keeps the subjects awake and ready to consume; lastly it raises  
39  
40 the dopamine firing, associated with reward, priming the dependence circle (Stojakovic et al., 2018).  
41  
42  
43  
44

#### 45 46 *4.1.2. Gene-Environment interactions*

47  
48 Beyond the aforementioned genetic risks, SUD show considerable evidence of environmental influences,  
49  
50 especially during early stages of life (Enoch, 2012, Dick & Kendler., 2012). According to theoretical  
51  
52 models, genetic differences affect both the sensitivity (gene-environment interaction model, GXE) and  
53  
54 exposure to environmental risk factors (gene-environment correlation model, rGE).  
55  
56

57  
58 Gene-environment interaction (GxE) occurs when adverse environments may create a risk, depending  
59  
60 on genetic susceptibility factors. The GxE model has been tested in SUD with twin studies (van der  
61  
62  
63  
64  
65

1  
2  
3  
4 Zwaluw and Engels, 2009; Vink, 2016), which demonstrated that the genetic load could be moderated  
5  
6 by environmental factors that confer risk and protection. Although findings are inconsistent across  
7  
8 studies, specific gene variants seem to interact mainly with parenting behaviours and peer influences,  
9  
10 and the effectiveness of interventions may vary by genotype (Milaniak et al., 2015).  
11  
12

13  
14 Few studies, instead, have focused on gene-environment correlation (rGE) model for SUDs. Three main  
15  
16 categories of rGE have been identified (Hines et al., 2015).  
17  
18

19 Passive rGE occurs to individuals who are passively exposed to environments that are correlated with  
20  
21 their genetic predispositions. For example children can both inherit the genetic vulnerability and develop  
22  
23 insecure attachment because the parents have a SUD. Active rGE occurs when individuals select, modify  
24  
25 or construct experiences that are correlated with their genetic predisposition mechanisms.  
26  
27 Temperamental characteristics, for example, may lead the child to seek out contexts associated with  
28  
29 greater risk; this includes a greater propensity to try new things but also engaging with equally  
30  
31 extroverted peers. Evocative rGE occurs when the individual's genotype elicits a certain response from  
32  
33 the environment around them. As in the previous example, children with high levels of extroversion and  
34  
35 low self-control, not only will seek novelty environment but also might evoke, because of these  
36  
37 genetically determined traits, negative responses from their parents. These patterns of behaviour can  
38  
39 shape the attachment relationships and further exacerbate risk for SUD (Hicks et al., 2013). Evidence of  
40  
41 these evocative mechanisms often emerges in the clinical practice, when the parents of SUD's patients  
42  
43 remembered their children as hard, frustrating and "unattuned", since the first days of life.  
44  
45  
46  
47  
48  
49

#### 50 *4.1.3. Epigenetic as a future target*

51

52 This "gene environment interplay" may be further complicated by epigenetic variations, which are still  
53  
54 poorly investigated. Epigenetics is defined as "mitotically and/or meiotically heritable change in gene  
55  
56 function that cannot be explained by changes in the DNA sequence" (Riggs and Porter, 1996). Inter-  
57  
58 individual variation has been demonstrated to characterize the epigenome and this inherited epigenetic  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 individuality may have high impact on phenotypic outcomes in health and diseases. Studies reported  
5  
6 differential DNA methylation, RNA expression, chromatin structure and chromatin modifications  
7  
8 associated to both SUDs (Nestler and Lüscher, 2019) and attachment (Robakis et al., 2020). Moreover,  
9  
10 environmental effects on the epigenome could lead to sustained changes in gene transcription and thus  
11  
12 early environment might affect these molecular processes later in life.  
13  
14

15  
16 Considering the short allele *S* of the serotonin transporter promoter (5-HTTLPR), previous studies found  
17  
18 associations with temperament and personality traits at risk for substance abuse (Gerra et al., 2004a,  
19  
20 2004b) with an increased availability to experiment with non-medical use of drugs among adolescents  
21  
22 (Gerra et al., 2005), and with greater psychological sensitivity to environmental stressors (Caspi et al.,  
23  
24 2003; Kilpatrick et al., 2007). Nevertheless, meta-analytic findings showed that there is variability in the  
25  
26 success of replicating such findings (Risch et al., 2009, Munafò et al., 2009).  
27  
28  
29

30  
31 One potential explanation for the variability in results is the level of methylation in the 5-HTTLPR, which  
32  
33 may reduce mRNA transcription. Specifically, van Ijzendoorn and colleagues (2010) found that the  
34  
35 ability of the short variant of 5-HTTLPR genotype to predict a stressful response was dependent on  
36  
37 methylation density. The *s* allele predicted a stressful response, but only when the levels of methylation  
38  
39 were low, while higher levels of methylation of the *s* variant were associated with less stressful responses  
40  
41

42  
43 On the other hand, methylation of alleles carrying the long 5-HTTLPR variant (*l*), usually protective in  
44  
45 regard of any psychopathology, hampered its expression, increasing the risk of a stressful response in  
46  
47 individuals that were supposed to be resilient because of their genotype.  
48  
49

50  
51 It is also possible that specific genes act as a gate on the stress-related modification of the epigenome.

52  
53 In this case the association between stress and epigenetic methylation, for example, can be moderated  
54  
55 by a specific polymorphism that confers resilience or allows the stressor to carry out its deleterious  
56  
57 effects on other genes transcription (Lewis and Olive, 2014).  
58  
59  
60  
61  
62

1  
2  
3  
4 Therefore, the importance of including epigenetics in genetic and environmental epidemiology studies  
5  
6 lies in the double role epigenetic marks may play, as mediators in regulatory processes and mediators of  
7  
8 vulnerability (Ladd-Acosta and Fallin, 2016). Histone modifications, DNA methylation changes, and  
9  
10 miRNAs expression have already been shown to be the key players in the development of addiction to  
11  
12 cocaine and other substances (Nestler, 2014). Moreover, epigenetics modifications induced by a negative  
13  
14 parenting scenario or early adverse experience may mediate lifelong vulnerability to SUDs (Jiang et al.,  
15  
16  
17  
18  
19 2021).

20  
21 Epigenetics can mediate the genetic or environmental risk, or represent the biological mechanism to  
22  
23 explain how genetic and environmental factors, in combination, may be involved in the addiction process.  
24  
25 Even when it is not clear if the identified epigenetic changes are causal or a consequence of a specific  
26  
27 phenotypes, these marks might serve as biomarkers of addiction or vulnerability to addiction.  
28  
29

#### 30 31 *3.1.4. Interaction with other pathways*

32  
33 We should keep in mind that the four main identified pathways are not likely acting in isolation, but they  
34  
35 may be strictly interconnected. Moreover, other biological systems might increase the risk of developing  
36  
37 SUD when the early environment is predisposed to a maladaptive attachment; these includes but are not  
38  
39 limited to the glutamatergic, GABAergic, enzymatic, immune and inflammatory pathways (Strathearn et  
40  
41 al., 2019).  
42  
43  
44

#### 45 46 *4.2. Clinical implications*

47  
48 Up to now we tried to delineate a hypothetical model, which is currently only partially empirically  
49  
50 validated, to describe how gene and environment may interact to shape the early attachment and hence  
51  
52 increase the vulnerability to SUD.  
53  
54

55  
56 Whereas epigenetic factors and hormones might represent a fascinating therapeutic target, significantly  
57  
58 more studies focused on how to reduce SUD risk through parenting (Allen et al., 2016). Parenting, in  
59  
60  
61  
62

1  
2  
3  
4 fact, has been suggested as a crucial target, not only in preventing SUD, but also as a critical mechanism  
5  
6 in healthy emotional development (Holmes et al., 2017).  
7

8  
9 It is well-known that parents' SUD is a risk factor for substance use in their children (Bailey et al., 2006).  
10  
11 However, from a preventive point of view, is more useful to understand what parents, independently  
12  
13 from their relationship with the substances, can do to reduce the risk and increase the resilience or  
14  
15 protective factors in their children. Because of the high vulnerability of subjects during the developmental  
16  
17 age, most of the prevention programs focused on school-aged youth (Tremblay et al., 2020).  
18  
19

20  
21 This is even more relevant from an attachment point of view. In fact, although attachment is not a  
22  
23 parenting style, literature suggest that a secure attachment is a function of children's experience of  
24  
25 parenting (Cummings & Cummings, 2002).  
26  
27

28  
29 A recent meta-analysis (Garcia-Huidobro et al., 2018) showed that offering parenting guidance to all  
30  
31 families with adolescent children was effective in reducing youth substance use. Parenting programs  
32  
33 generally educate parents and build skills related to improving family management, reducing family  
34  
35 conflict, effective monitoring of their children and increasing positive parent-child interactions (Sandler  
36  
37 et al., 2011).  
38  
39

40  
41 The authors, however, concludes that studies including adolescents older than 14 years are lacking, and  
42  
43 few studies target adolescents from racial/ethnic minority groups. Considering what was noted above  
44  
45 related to peer influence in this age range, it is possible that older adolescent might benefit more from  
46  
47 specific skills training programs aimed at improving emotion management and self-regulation (Tremblay  
48  
49 et al., 2020).  
50  
51

52  
53 The three main family protective factors for SUD in children and adolescents are: a positive parent/child  
54  
55 relationship, a consistent discipline, and clear parental attitudes related to non-use of substances. Most  
56  
57 of family-based interventions grounded on these three pillars had a greater effect size in reducing the risk  
58  
59 of SUD than simple children-based approaches that focus on effective education, drug education and  
60  
61

1  
2  
3  
4 skills training (Kumpfer et al., 2003). A combined approach of family- and children-focused  
5  
6 interventions guarantees an even greater efficacy (Kumpfer et al., 2003) because the combination satisfy  
7  
8 all the requirement for an effective preventing program: parenting skills; reductions in short-term  
9  
10 problems through an adaptation to stress; and an improvement of the context (Sandler et al., 2011).  
11  
12

13  
14 Parenting programs do not act simply by improving the attachment style and increasing the emotion  
15  
16 regulation abilities but also through epigenetic mechanism. Two recent reviews (Craig et al., 2021;  
17  
18 Darling Rasmussen & Storebø, 2021) found a total of 16 studies pointing to a link between early  
19  
20 childhood adversity, attachment processes, and epigenetic changes. The authors suggest that DNA  
21  
22 methylation on attachment-related genes might affect the development of stress regulation systems and  
23  
24 social-emotional capacities, thus contributing to the emerging phenotypic outcomes. We can hypothesise  
25  
26 that parenting could reduce the genetic and environmental risk factors through epigenetic modifications  
27  
28 increasing the resilience to SUD but unfortunately any of the included studies investigated specifically  
29  
30 the association with substance misuse (**Figure 2**).  
31  
32

33  
34  
35  
36 - Figure 2 approximately here -  
37

### 38 ***4.3. Limitation and future directions***

39  
40 We highlight that, despite our specific focus on attachment, the majority of the studies investigating the  
41  
42 relation between early parent-child experiences and SUD did not include only measurement strictly  
43  
44 related to attachment. We extended our research to adverse parent-child experiences, which are known  
45  
46 to have a potential effect on attachment, because although longitudinal data reveal a moderate degree of  
47  
48 stability in attachment patterns from infancy to adulthood, there may be discontinuities in attachment  
49  
50 pattern depending on life circumstances (Mikulincer e Shaver, 2016; Fraley et al., 2020). In fact,  
51  
52 attachment trajectories are more uneven and less predictable in children whose early experiences include  
53  
54 adversity and maltreatment (Prior & Glaser, 2006).  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4     Secondarily, it is worth noting, that all epigenetic studies focused on DNA methylation. However  
5  
6     multiple regulatory epigenetic elements in conjunction seem to orchestrate gene expression and  
7  
8     regulation, including non-coding RNAs and chromatin modifications. In addition, some research  
9  
10    hypothesized transcriptional changes, however, none of them explore if the detected epigenetic  
11  
12    modification corresponded to gene expression alterations.  
13

14  
15  
16    Another important aspect that should be considered is the fact that almost all the studies focused on  
17  
18    peripheral samples. Comparative studies should better explore the largely unknown correspondence  
19  
20    between buccal/blood and neuronal methylation profiles in order to use surrogate tissues for brain-based  
21  
22    phenotype research. Potential targets of these studies could be the clock genes that contribute to the  
23  
24    development of different psychiatric disorders and are characterized by an epigenetic synchronization  
25  
26    between periphery and central nervous (Liu and Chung, 2015).  
27  
28  
29

30  
31    Even if these studies do not evidence a unique epigenetic signature of attachment and SUD, often because  
32  
33    the lack of rigorous study design, the obtained findings should not be left out and set aside. New research  
34  
35    considering different types of tissues, integrating the high-throughput sequencing technologies and the  
36  
37    large amount of data analysis through sophisticated algorithms, might reveal new marks or confirm the  
38  
39    marks we have only started to explore.  
40  
41

42  
43    The epigenomic data will provide a chance to discover their role during attachment/parenting and  
44  
45    addiction development, with two fundamental impacts. First, specific epigenetic marks could reveal  
46  
47    molecular mechanisms underpinning the neurobiology of substance abuse. Moreover, the reversible  
48  
49    nature of epigenetic modifications could pave the way for the development of novel therapeutic targets.  
50  
51

#### 52    **4.4. Conclusions**

53  
54  
55    In conclusion, our review highlights genes that increase vulnerability to SUD may act through a direct  
56  
57    and an indirect pathway. The indirect pathway, through evocative mechanisms, affects the ability of the  
58  
59    caregiver to appropriately perceive and respond to the infant's emotional cues, determining the quality of  
60  
61

1  
2  
3  
4 parent-child attachment relationships. Adverse childhood experiences may aggravate the situation  
5  
6 through epigenetic modifications, determining changes in gene expression. These molecular variations,  
7  
8 related to early life experience and to patterns of childhood attachment, may induce a cascade of  
9  
10 neuroendocrine changes in glucocorticoid-related, monoaminergic, opioidergic and oxytocinergic  
11  
12 systems. Other still unexplored neurobiological pathways may contribute to risk, resulting in  
13  
14 externalizing/internalizing symptoms, emotional dysregulation and social dysfunctioning that, at the  
15  
16 behavioural level, precede the clinical onset of SUD.  
17  
18  
19

20  
21 This complex view of the etiopathogenesis of SUD, deeply rooted in early attachment relationships,  
22  
23 needs experimental confirmation in future studies, which combine different approaches. Longitudinal  
24  
25 studies following-up cohorts of healthy children, screened for genotypes at risk for SUD are needed.  
26  
27 These observational studies should include neurobiological (e.g. epigenetic, neuroimaging and  
28  
29 neuroendocrine), environmental assessment, and clinical interviews at each time point. This approach  
30  
31 would allow identifying developmental trajectories of vulnerability to SUD, intertwined with the  
32  
33 development of adult attachment styles. Clarifying these mechanisms, keeping in mind the relevance of  
34  
35 time and context (Hitchcock et al., 2021), could reveal novel potential therapeutic targets for preventing  
36  
37 the non-medical use of substances, drug dependence and drug use disorders.  
38  
39  
40  
41  
42  
43  
44

## 45 **References**

- 46  
47  
48 Abar, C.C., Jackson, K.M., Colby, S.M., Barnett, N.P., 2015. Parent-Child Discrepancies in Reports of  
49 Parental Monitoring and Their Relationship to Adolescent Alcohol-Related Behaviors. *J Youth*  
50 *Adolesc.* 44, 1688-1701. <https://doi:10.1007/s10964-014-0143-6>  
51  
52  
53 Ainsworth, M. D. S., Blehar, M. C, Waters, E., & Wall, S., 1978. Patterns of attachment: A psychological  
54 study of the strange situation. Hillsdale, NJ: Erlbaum.  
55  
56 Allen, M.L., Garcia-Huidobro, D., Porta, C., Curran, D., Patel, R., Miller, J., Borowsky, I., 2016.  
57 Effective Parenting Interventions to Reduce Youth Substance Use: A Systematic Review. *Pediatrics*  
58 138, e20154425. <https://doi.org/10.1542/peds.2015-4425>  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Althaus, M., Groen, Y., Wijers, A.A., Mulder, L.J.M., Minderaa, R.B., Kema, I.P., Dijck, J.D.A.,  
5 Hartman, C.A., Hoekstra, P.J., 2009. Differential effects of 5-HTTLPR and DRD2/ANKK1  
6 polymorphisms on electrocortical measures of error and feedback processing in children. *Clin.*  
7 *Neurophysiol.* 120, 93–107. <https://doi.org/10.1016/j.clinph.2008.10.012>  
8  
9  
10 Andres, F., Castanier, C., Le Scanff, C., 2014. Attachment and alcohol use amongst athletes: The  
11 mediating role of conscientiousness and alexithymia. *Addict. Behav.* 39, 487–490.  
12 <https://doi.org/10.1016/j.addbeh.2013.10.022>  
13  
14 Arnau, M.M., Mondon, S., Santacreu, J.J., 2008. Using the temperament and character inventory (TCI)  
15 to predict outcome after inpatient detoxification during 100 days of outpatient treatment. *Alcohol*  
16 *Alcohol.* 43, 583–588. <https://doi.org/10.1093/alcalc/agn047>  
17  
18 Badenes-Ribera, L., Fabris, M.A., Gastaldi, F.G.M., Prino, L.E., Longobardi, C., 2019. Parent and peer  
19 attachment as predictors of facebook addiction symptoms in different developmental stages (early  
20 adolescents and adolescents). *Addict. Behav.* 95, 226–232.  
21 <https://doi.org/10.1016/j.addbeh.2019.05.009>  
22  
23 Bahr, S.J., Hoffmann, J.P., Yang, X., 2005. Parental and peer influences on the risk of adolescent drug  
24 use. *J Prim Prev.* 26, 529–551. <https://doi.org/10.1007/s10935-005-0014-8>  
25  
26 Bailey, J.A., Hill, K.G., Oesterle, S., Hawkins, J.D., 2006. Linking Substance Use and Problem Behavior  
27 Across Three Generations. *J. Abnorm. Child Psychol.* 34, 263–282. [https://doi.org/10.1007/s10802-](https://doi.org/10.1007/s10802-006-9033-z)  
28 [006-9033-z](https://doi.org/10.1007/s10802-006-9033-z)  
29  
30 Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H., 2009. The first 10,000 adult attachment  
31 interviews: Distributions of adult attachment representations in clinical and non-clinical groups.  
32 *Attachment and Human Development*, 11(3), 223–263. <https://doi.org/10.1080/14616730902814762>  
33  
34 Baracz, S.J., Everett, N.A., Robinson, K.J., Campbell, G.R., Cornish, J.L., 2020. Maternal separation  
35 changes maternal care, anxiety-like behaviour and expression of paraventricular oxytocin and  
36 corticotrophin-releasing factor immunoreactivity in lactating rats. *J. Neuroendocrinol.* 32, 12861.  
37 <https://doi.org/10.1111/jne.12861>  
38  
39 Beach, S.R.H., Lei, M.K., Brody, G.H., Yu, T., Philibert, R.A., 2014. Nonsupportive parenting affects  
40 telomere length in young adulthood among african americans: Mediation through substance use. *J.*  
41 *Fam. Psychol.* 28, 967–972. <https://doi.org/10.1037/fam0000039>  
42  
43 Bendre, M., Comasco, E., Checknita, D., Tiihonen, J., Hodgins, S., Nilsson, K.W., 2018. Associations  
44 Between MAOA-uVNTR Genotype, Maltreatment, MAOA Methylation, and Alcohol Consumption  
45 in Young Adult Males. *Alcohol. Clin. Exp. Res.* 42, 508–519. <https://doi.org/10.1111/acer.13578>  
46  
47 Berglund, K.J., Balldin, J., Berggren, U., Gerdner, A., Fahlke, C., 2013. Childhood Maltreatment Affects  
48 the Serotonergic System in Male Alcohol-Dependent Individuals. *Alcohol. Clin. Exp. Res.* 37, 757–  
49 762. <https://doi.org/10.1111/acer.12023>  
50  
51 Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J., 1998. Childhood trauma questionnaire.  
52 Assessment of family violence: A handbook for researchers and practitioners. APA PsycTests.  
53 <https://doi.org/10.1037/t02080-000>  
54  
55 Berry, K., Palmer, T., Gregg, L., Barrowclough, C., Lobban, F., 2018. Attachment and therapeutic  
56 alliance in psychological therapy for people with recent onset psychosis who use cannabis. *Clin*  
57 *Psychol Psychother.* 25, 440–445. <https://doi.org/10.1002/cpp.2178>  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Bifulco, A., Bernazzani, O., Moran, P. M., & Jacobs, C., 2005. The childhood experience of care and  
5 abuse questionnaire (CECA. Q): validation in a community series. *Br J Clin Psychol* British Journal  
6 of Clinical Psychology, 44(4), 563-581. <https://doi.org/10.1348/014466505X35344>  
7
- 8 Borelli, J.L., Goshin, L., Joestl, S., Clark, J., Byrne, M.W., 2011. Attachment Organization in a Sample  
9 of Incarcerated Mothers. *Attach. Hum. Dev.* 12, 355-374.  
10 <https://doi.org/10.1080/14616730903416971>.  
11
- 12 Borsboom, D., Cramer, A., Kalis, A., 2018. Brain disorders? Not really... Why network structures block  
13 reductionism in psychopathology research. *Behav. Brain Sci.* 119, 1-54.  
14 <https://doi.org/10.1017/S0140525X17002266>  
15
- 16 Bosmans, G., Young, J.F., Hankin, B.L., 2018. NR3C1 methylation as a moderator of the effects of  
17 maternal support and stress on insecure attachment development. *Dev. Psychol.* 54, 29-38.  
18 <https://doi.org/10.1037/dev0000422>  
19
- 20 Bowlby, J. (1969). *Attachment and Loss, Volume 1-3, Attachment*. New York: Basic Books.  
21
- 22 Brady, K.T., McRae, A.L., Maria, M.M.M.S., DeSantis, S.M., Simpson, A.N., Waldrop, A.E., Back,  
23 S.E., Kreek, M.J., 2009. Response to corticotropin-releasing hormone infusion in cocaine-dependent  
24 individuals. *Arch. Gen. Psychiatry* 66, 422-430. <https://doi.org/10.1001/archgenpsychiatry.2009.9>  
25
- 26 Branstetter, S.A., Furman, W., Cottrell, L., 2009. The influence of representations of attachment,  
27 maternal-adolescent relationship quality, and maternal monitoring on adolescent substance use: A 2-  
28 year longitudinal examination. *Child Dev.* 80, 1448-1462. [https://doi.org/10.1111/j.1467-  
29 8624.2009.01344.x](https://doi.org/10.1111/j.1467-8624.2009.01344.x)  
30
- 31 Brody, G.H., Beach, S.R.H., Philibert, R.A., Chen, Y. fu, Lei, M.K., Murry, V.M.B., Brown, A.C., 2009.  
32 Parenting Moderates a Genetic Vulnerability Factor in Longitudinal Increases in Youths' Substance  
33 Use. *J. Consult. Clin. Psychol.* 77, 1-11. <https://doi.org/10.1037/a0012996>  
34
- 35 Brody, G.H., Chen, Y. fu, Beach, S.R.H., Kogan, S.M., Yu, T., DiClemente, R.J., Wingood, G.M.,  
36 Windle, M., Philibert, R.A., 2014. Differential sensitivity to prevention programming: A  
37 dopaminergic polymorphism-enhanced prevention effect on protective parenting and adolescent  
38 substance use. *Heal. Psychol.* 33, 182-191. <https://doi.org/10.1037/a0031253>  
39
- 40 Brook, J.S., Whiteman, M., Finch, S., 1993. Role of Mutual Attachment in Drug Use: A Longitudinal  
41 Study. *J. Am. Acad. Child Adolesc. Psychiatry* 32, 982-989. [https://doi.org/10.1097/00004583-  
42 199309000-00015](https://doi.org/10.1097/00004583-199309000-00015)  
43
- 44 Buisman-Pijlman, F.T.A., Sumracki, N.M., Gordon, J.J., Hull, P.R., Carter, C.S., Tops, M., 2014.  
45 Individual differences underlying susceptibility to addiction: Role for the endogenous oxytocin  
46 system. *Pharmacol. Biochem. Behav.* 119, 22-38. <https://doi.org/10.1016/j.pbb.2013.09.005>  
47
- 48 Carey, C.E., Agrawal, A., Zhang, B., Conley, E.D., Degenhardt, L., Heath, A.C., Li, D., Lynskey, M.T.,  
49 Martin, N.G., Montgomery, G.W., Wang, T., Bierut, L.J., Hariri, A.R., Nelson, E.C., Bogdan, R.,  
50 2015. Monoacylglycerol lipase (MGLL) polymorphism rs604300 interacts with childhood adversity  
51 to predict cannabis dependence symptoms and amygdala habituation: Evidence from an  
52 endocannabinoid system-level analysis. *J. Abnorm. Psychol.* 124, 860-877.  
53 <https://doi.org/10.1037/abn0000079>  
54
- 55 Carter, C.S., 2017. The role of oxytocin and vasopressin in attachment. *Psychodyn. Psychiatry* 45, 499-  
56 518. <https://doi.org/10.1521/pdps.2017.45.4.499>  
57

- 1  
2  
3  
4 Caspers, K.M., Yucuis, R., Troutman, B., Spinks, R., 2006. Attachment as an organizer of behavior:  
5 Implications for substance abuse problems and willingness to seek treatment. *Subst. Abus. Treat. Prev.*  
6 *Policy* 1. <https://doi.org/10.1186/1747-597X-1-32>  
7  
8 Caspi, A., 2002. Role of Genotype in the Cycle of Violence in Maltreated Children. *Science* (80-. ). 297,  
9 851–854. <https://doi.org/10.1126/science.1072290>  
10  
11 Caspi, A., 2003. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT  
12 Gene. *Science* (80-. ). 301, 386–389. <https://doi.org/10.1126/science.1083968>  
13  
14 Cassidy, J., & Shaver, P. R., 2016. *Handbook of attachment: Theory, research, and clinical applications.*  
15 (Eds.) New York: Guilford Press.  
16  
17 Cavaiola, A.A., Fulmer, B.A., Stout, D., 2015. The Impact of Social Support and Attachment Style on  
18 Quality of Life and Readiness to Change in a Sample of Individuals Receiving Medication-  
19 Assisted Treatment for Opioid Dependence. *Subst Abus.* 36, 183-91.  
20 <https://doi.org/10.1080/08897077.2015.1019662>  
21  
22 Cecil, C.A.M., Lysenko, L.J., Jaffee, S.R., Pingault, J.-B., Smith, R.G., Relton, C.L., Woodward, G.,  
23 McArdle, W., Mill, J., Barker, E.D., 2014. Environmental risk, Oxytocin Receptor Gene (OXTR)  
24 methylation and youth callous-unemotional traits: A 13-year longitudinal study. *Molec. psychiatry* 19,  
25 1071–1077. <https://doi.org/10.1038/mp.2014.95>  
26  
27 Chen, Y., Li, R., Zhang, P., Liu, X., 2020. The Moderating Role of State Attachment Anxiety and  
28 Avoidance Between Social Anxiety and Social Networking Sites Addiction. *Psychol.* 123, 633-  
29 647. <https://doi.org/10.1177/0033294118823178>  
30  
31 Ciccocioppo, R., Economidou, D., Fedeli, A., Angeletti, S., Weiss, F., Heilig, M., Massi, M., 2004.  
32 Attenuation of ethanol self-administration and of conditioned reinstatement of alcohol-seeking  
33 behaviour by the antiopioid peptide nociceptin/orphanin FQ in alcohol-preferring rats.  
34 *Psychopharmacology (Berl)* 172:170–178. <https://doi.org/10.1007/s00213-003-1645-1>  
35  
36 Cimino, S., Carola, V., Cerniglia, L., Bussone, S., Bevilacqua, A., Tambelli, R., 2020. The  $\mu$ -opioid  
37 receptor gene A118G polymorphism is associated with insecure attachment in children with disruptive  
38 mood regulation disorder and their mothers. *Brain Behav.* 10. <https://doi.org/10.1002/brb3.1659>  
39  
40 Cleveland, M.J., Reavy, R., Mallett, K.A., Turrisi, R., White, H.R., 2014. Moderating effects of positive  
41 parenting and maternal alcohol use on emerging adults' alcohol use: Does living at home matter?  
42 *Addict. Behav.* 39, 869–878. <https://doi.org/10.1016/j.addbeh.2014.01.028>  
43  
44 Copeland, W.E., Sun, H., Costello, E.J., Angold, A., Heilig, M.A., Barr, C.S., 2011. Child-opioid  
45 receptor gene variant influences parent-child relations. *Neuropsychopharmacology* 36, 1165–1170.  
46 <https://doi.org/10.1038/npp.2010.251>  
47  
48 Cornellà-Font, M.G., Viñas-Poch, F., Juárez-López, J.R., Martín-Perpiñá, M.D.L.M., Malo-Cerrato, S.,  
49 2018. Temperament and attachment as predictive factors for the risk of addiction to substances in  
50 adolescents. *Rev. Psicopatol. y Psicol. Clin.* 23, 179–187.  
51 <https://doi.org/10.5944/rppc.vol.23.num.3.2018.21423>  
52  
53 Craig, F., Tenuta, F., Rizzato, V., Costabile, A., Trabacca, A., Montirosso, R., 2021. Attachment-related  
54 dimensions in the epigenetic era: A systematic review of the human research. *Neurosci Biobehav Rev.*  
55 2021 Jun;125, :654-666. <https://doi.org/10.1016/j.neubiorev.2021.03.006>  
56  
57 Csala, I., Egervari, L., Dome, P., Faludi, G., Dome, B., Lazary, J., 2015. The possible role of maternal  
58 bonding style and CHRNA2 gene polymorphisms in nicotine dependence and related depressive  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 phenotype. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 59, 84–90.  
5 <https://doi.org/10.1016/j.pnpbp.2015.01.012>  
6

7 Cummings, E. M., & Cummings, J. S., 2002. Parenting and attachment. In M. H. Bornstein (Ed.),  
8 *Handbook of parenting: Practical issues in parenting* (p. 35–58). Lawrence Erlbaum Associates  
9 Publishers.  
10

11 Dalvie, S., Maihofer, A.X., Coleman, J.R.I., Bradley, B., Breen, G., Brick, L.A., Chen, C.-Y., Choi,  
12 K.W., Duncan, L.E., Guffanti, G., Haas, M., Harnal, S., Liberzon, I., Nugent, N.R., Provost, A.C.,  
13 Ressler, K.J., Torres, K., Amstadter, A.B., Bryn Austin, S., Baker, D.G., Bolger, E.A., Bryant, R.A.,  
14 Calabrese, J.R., Delahanty, D.L., Farrer, L.A., Feeny, N.C., Flory, J.D., Forbes, D., Galea, S., Gautam,  
15 A., Gelernter, J., Hammamieh, R., Jett, M., Junglen, A.G., Kaufman, M.L., Kessler, R.C., Khan, A.,  
16 Kranzler, H.R., Lebois, L.A.M., Marmar, C., Mavissakalian, M.R., McFarlane, A., Donnell, M.O.,  
17 Orcutt, H.K., Pietrzak, R.H., Risbrough, V.B., Roberts, A.L., Rothbaum, A.O., Roy-Byrne, P.,  
18 Ruggiero, K., Seligowski, A. V., Sheerin, C.M., Silove, D., Smoller, J.W., Stein, M.B., Teicher, M.H.,  
19 Ursano, R.J., Van Hooff, M., Winternitz, S., Wolff, J.D., Yehuda, R., Zhao, H., Zoellner, L.A., Stein,  
20 D.J., Koenen, K.C., Nievergelt, C.M., 2020. Genomic influences on self-reported childhood  
21 maltreatment. *Transl. Psychiatry* 10, 38. <https://doi.org/10.1038/s41398-020-0706-0>  
22  
23

24  
25 Dannlowski, U., Kugel, H., Grotegerd, D., Redlich, R., Opel, N., Dohm, K., Zaremba, D., Grögler, A.,  
26 Schwieren, J., Suslow, T., Ohrmann, P., Bauer, J., Krug, A., Kircher, T., Jansen, A., Domschke, K.,  
27 Hohoff, C., Zwitserlood, P., Heinrichs, M., Arolt, V., Heindel, W., Baune, B.T., 2016. Disadvantage  
28 of Social Sensitivity: Interaction of Oxytocin Receptor Genotype and Child Maltreatment on Brain  
29 Structure. *Biol. Psychiatry* 80, 398–405. <https://doi.org/10.1016/j.biopsych.2015.12.010>  
30  
31

32 Darling Rasmussen, P., & Storebø, O. J. (2021). Attachment and Epigenetics: A Scoping Review of  
33 Recent Research and Current Knowledge. *Psychological Reports*, 124(2), 479-501.;  
34 <https://doi.org/10.1177/0033294120901846>  
35

36 Dawes, M., Clark, D., Moss, H., Kirisci, L., Tarter, R., 1999. Family and peer correlates of behavioral  
37 self-regulation in boys at risk for substance abuse. *Am. J. Drug Alcohol Abuse* 25, 219–237.  
38 <https://doi.org/10.1081/ADA-100101857>  
39

40 De Nardi, L., Carpentieri, V., Pascale, E., Pucci, M., D'addario, C., Cerniglia, L., Adriani, W., Cimino,  
41 S., 2020. Involvement of DAT1 gene on internet addiction: Cross-correlations of methylation levels  
42 in 5'-utr and 3'-UTR genotypes, interact with impulsivity and attachment-driven quality of  
43 relationships. *Int. J. Environ. Res. Public Health* 17, 1–11. <https://doi.org/10.3390/ijerph17217956>  
44

45 De Palo, F., Capra, N., Simonelli, A., Salcuni, S., Di Riso, D., 2014. Parenting quality in drug-addicted  
46 mothers in a therapeutic mother-child community: The contribution of attachment and personality  
47 assessment. *Front. Psychol.* 5, 1–13. <https://doi.org/10.3389/fpsyg.2014.01009>  
48  
49

50 De Rick, A., Vanheule, S., Verhaeghe, P., 2009. Alcohol addiction and the attachment system: an  
51 empirical study of attachment style, alexithymia, and psychiatric disorders in alcoholic inpatients.  
52 *Subst Use Misuse*. 44,99-114. <https://doi.org/10.1080/10826080802525744>  
53

54 De Wit, M.L., Embree, B.G., De Wit, D., 1999. Determinants of the risk and timing of alcohol and illicit  
55 drug use onset among natives and non-natives: Similarities and differences in family attachment  
56 processes. *Soc. Biol.* 46, 100–121. <https://doi.org/10.1080/19485565.1999.9988990>  
57

58 Deak, J. D., & Johnson, E. C., 2021. Genetics of substance use disorders: a review. *Psychological*  
59 *medicine*, 1-12. <https://doi.org/10.1017/S0033291721000969>  
60  
61

- 1  
2  
3  
4 Delvecchio, E., Di Riso, D., Lis, A., Salcuni, S., 2016. Adult Attachment, Social Adjustment, and Well-  
5 Being in Drug-Addicted Inpatients. *Psychol. Rep.* 118, 587–607.  
6 <https://doi.org/10.1177/0033294116639181>  
7  
8 Dick, D.M., & Kendler, K.S., 2012. The impact of gene-environment interaction on alcohol use  
9 disorders. *Alcohol Res.* 34, 318-24. PMID: 23134047; PMCID: PMC3606909.  
10  
11 Dishon-Brown, A., Golder, S., Renn, T., Winham, K., Higgins, GE., Logan, TK., 2017. Childhood  
12 Victimization, Attachment, Coping, and Substance Use Among Victimized Women on Probation  
13 and Parole. *Violence Vict.* 32,431-451. <https://doi.org/10.1891/0886-6708.VV-D-15-00100>  
14  
15 Doan, S.N., Dich, N., Evans, G.W., 2014. Childhood cumulative risk and later allostatic load: Mediating  
16 role of substance use. *Heal. Psychol.* 33, 1402–1409. <https://doi.org/10.1037/a0034790>  
17  
18 Dutra, L., & Lyons-Ruth, K., (2005., April). Maltreatment, maternal and child psychopathology, and  
19 quality of early care as predictors of adolescent dissociation. In biennial meeting of the Society for  
20 Research in Child Development, Atlanta, GA.  
21  
22 Eichenberg, C., Dyba, J., Schott, M., 2017. Bindungsstile, Nutzungsmotive und Internetsucht  
23 [Attachment Style, Motives for Use and Internet Addiction]. *Psychiatr Prax.* 44,41-46.  
24 <https://doi.org/10.1055/s-0041-110025>.  
25  
26 Eichenberg, C., Schott, M., Decker, O., Sindelar, B., 2017. Attachment Style and Internet Addiction: An  
27 Online Survey. *J Med Internet Res.* 19, e170. <https://doi.org/10.2196/jmir.6694>  
28  
29 Ein-Dor, T., Verbeke, W.J.M.I., Mokry, M., Vrtička, P., 2018. Epigenetic modification of the oxytocin  
30 and glucocorticoid receptor genes is linked to attachment avoidance in young adults. *Attach. Hum.*  
31 *Dev.* 20, 439–454. <https://doi.org/10.1080/14616734.2018.1446451>  
32  
33 Ellis, B.J., Horn, A.J., Carter, C.S., van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., 2021.  
34 Developmental programming of oxytocin through variation in early-life stress: Four meta-analyses  
35 and a theoretical reinterpretation. *Clin. Psychol. Rev.* 86, 101985.  
36 <https://doi.org/10.1016/j.cpr.2021.101985>  
37  
38 Englund, M. M., Kuo, S. I. C., Puig, J., & Collins, W. A., (2011). Early roots of adult competence: The  
39 significance of close relationships from infancy to early adulthood. *Int. J. Behav. Dev.* International  
40 journal of behavioral development, 35(6), 490-496. <https://doi.org/10.1177/0165025411422994>  
41  
42 Enoch, M.A., 2012. The influence of gene-environment interactions on the development of alcoholism  
43 and drug dependence. *Curr. Psychiatry Rep.* 14, 150–158. [https://doi.org/10.1007/s11920-011-0252-](https://doi.org/10.1007/s11920-011-0252-9)  
44 [9](https://doi.org/10.1007/s11920-011-0252-9)  
45  
46 Estevez, A., Jauregui, P., Lopez-Gonzalez, H., 2019. Attachment and behavioral addictions in  
47 adolescents: The mediating and moderating role of coping strategies. *Scand. J. Psychol.* 60, 348–360.  
48 <https://doi.org/10.1111/sjop.12547>  
49  
50 Estévez, A., Jáuregui, P., Sánchez-Marcos, I., López-González, H., Griffiths, M.D., 2017. Attachment  
51 and emotion regulation in substance addictions and behavioral addictions. *J. Behav. Addict.* 6, 534–  
52 544. <https://doi.org/10.1556/2006.6.2017.086>  
53  
54 Fairbairn, C.E., Briley, D.A., Kang, D., Fraley, R.C., Hankin, B.L., Ariss, T., 2018. A meta-analysis of  
55 longitudinal associations between substance use and interpersonal attachment security. *Psychol. Bull.*  
56 144, 532–555. <https://doi.org/10.1037/bul0000141>  
57  
58 Feinstein, A.R., 1970. The pre-therapeutic classification of co-morbidity in chronic disease. *J. Chronic*  
59 *Dis.* 23, 455–468. [https://doi.org/10.1016/0021-9681\(70\)90054-8](https://doi.org/10.1016/0021-9681(70)90054-8)  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Fite, P.J., Brown, S., Hossain, W., Manzardo, A., Butler, M.G., Bortolato, M., 2019. Tobacco and  
5 cannabis use in college students are predicted by sex-dimorphic interactions between MAOA  
6 genotype and child abuse. *CNS Neurosci. Ther.* 25, 101–111. <https://doi.org/10.1111/cns.13002>  
7  
8 Flanagan, J.C., Baker, N.L., McRae-Clark, A.L., Brady, K.T., Moran-Santa Maria, M.M., 2015. Effects  
9 of adverse childhood experiences on the association between intranasal oxytocin and social stress  
10 reactivity among individuals with cocaine dependence. *Psychiatry Res.* 229, 94–100.  
11 <https://doi.org/10.1016/j.psychres.2015.07.064>  
12  
13 Fowler, J.C., Groat, M., Ulanday, M., 2013. Attachment style and treatment completion among  
14 psychiatric inpatients with substance use disorders. *Am J Addict.* 22, 14-7.  
15 <https://doi.org/10.1111/j.1521-0391.2013.00318.x>  
16  
17 Fraley, R. C., 2019. Attachment in adulthood: Recent developments, emerging debates, and future  
18 directions. *Annual review of psychology*, 70, 401–422. <https://doi.org/10.1146/annurev-psych-010418-102813>  
19  
20 Frank, L.E., & Nagel, S.K., 2017. Addiction and Moralization: the Role of the Underlying Model of  
21 Addiction. *Neuroethics* 10, 129–139. <https://doi.org/10.1007/s12152-017-9307-x>.  
22  
23 Fuchshuber, J., & Unterrainer, H.F., 2020. Childhood Trauma, Personality, and Substance Use Disorder:  
24 The Development of a Neuropsychanalytic Addiction Model. *Front. Psychiatry* 11, 1–21.  
25 <https://doi.org/10.3389/fpsy.2020.00531>  
26  
27 Fuchshuber, J., Hiebler-Ragger, M., Ragger, K., Rinner, A., Kapfhammer, H.P., Unterrainer, H.F., 2018.  
28 Increased attachment security is related to early therapy drop-out in substance use disorders.  
29 *BMC Res Notes.* 11,141. <https://doi.org/10.1186/s13104-018-3251-7>.  
30  
31 Fuchshuber, J., Unterrainer, H.F., Hiebler-Ragger, M., Koschutnig, K., Papousek, I., Weiss, EM., Fink,  
32 A., 2020 Pinpointing Neural Correlates of Attachment in Poly-Drug Use: A Diffusion Tensor  
33 Imaging Study., *Front Neurosci.* 11;14:596. <https://doi.org/10.3389/fnins.2020.00596>.  
34  
35 Fumaz, C.R., Muñoz-Moreno, J.A., Ferrer, MJ., Ornelas, A., Coll, J., Clotet, B., 2020. Attachment Styles,  
36 Condomless Sex, and Drugs in HIV-Positive Gay and Bisexual Men. *J Sex Marital Ther.* 46, 35-  
37 42. <https://doi.org/10.1080/0092623x.2019.1626308>  
38  
39 Garcia-Huidobro, D., Doty, J.L., Davis, L., Borowsky, I.W., Allen, M.L., 2018. For Whom Do Parenting  
40 Interventions to Prevent Adolescent Substance Use Work? *Prev. Sci.* 19, 570–578.  
41 <https://doi.org/10.1007/s11121-017-0853-6>  
42  
43 Garg, E., Chen, L., Nguyen, T.T.T., Pokhvisneva, I., Chen, L.M., Unternaehrer, E., MacIsaac, J.L.,  
44 McEwen, L.M., Mah, S.M., Gaudreau, H., Levitan, R., Moss, E., Sokolowski, M.B., Kennedy, J.L.,  
45 Steiner, M.S., Meaney, M.J., Holbrook, J.D., Silveira, P.P., Karnani, N., Kobor, M.S., O'Donnell,  
46 K.J., 2018. The early care environment and DNA methylome variation in childhood. *Dev.*  
47 *Psychopathol.* 30, 891–903. <https://doi.org/10.1017/S0954579418000627>  
48  
49 Gattamorta, K.A., Varela, A., McCabe, B.E., Mena, M.P., Santisteban, D.A., 2017. Psychiatric  
50 Symptoms, Parental Attachment, and Reasons for Use as Correlates of Heavy Substance Use Among  
51 Treatment-Seeking Hispanic Adolescents. *Subst. Use Misuse* 52, 392–400.  
52 <https://doi.org/10.1080/10826084.2016.1229338>  
53  
54 Gerra, G., Angioni, L., Zaimovic, A., Moi, G., Bussandri, M., Bertacca, S., Santoro, G., Gardini, S.,  
55 Caccavari, R., Nicoli, M.A., 2004. Substance Use among High-School Students: Relationships with  
56 Temperament, Personality Traits, and Parental Care Perception. *Subst. Use Misuse* 39, 345–367.  
57 <https://doi.org/10.1081/JA-120028493>  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Gerra, G., Garofano, L., Santoro, G., Bosari, S., Pellegrini, C., Zaimovic, A., Moi, G., Bussandri, M.,  
5 Moi, A., Brambilla, F., Donnini, C., 2004. Association between Low-Activity Serotonin Transporter  
6 Genotype and Heroin Dependence: Behavioral and Personality Correlates. *Am. J. Med. Genet. -*  
7 *Neuropsychiatr. Genet.* 126 B, 37–42. <https://doi.org/10.1002/ajmg.b.20111>  
8  
9  
10 Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell’Agnello, G., Manfredini, M., Somaini, L.,  
11 Petracca, F., Caretti, V., Saracino, M.A., Raggi, M.A., Donnini, C., 2007. Homovanillic acid (HVA)  
12 plasma levels inversely correlate with attention deficit-hyperactivity and childhood neglect measures  
13 in addicted patients. *J. Neural Transm.* 114, 1637–1647. <https://doi.org/10.1007/s00702-007-0793-6>  
14  
15 Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell’Agnello, G., Manfredini, M., Somaini, L.,  
16 Petracca, F., Caretti, V., Baroni, C., Donnini, C., 2008. Adrenocorticotrophic hormone and cortisol  
17 plasma levels directly correlate with childhood neglect and depression measures in addicted patients.  
18 *Addict. Biol.* 13, 95–104. <https://doi.org/10.1111/j.1369-1600.2007.00086.x>  
19  
20 Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell’Agnello, G., Manfredini, M., Somaini, L.,  
21 Petracca, F., Caretti, V., Raggi, M.A., Donnini, C., 2009. Childhood neglect and parental care  
22 perception in cocaine addicts: Relation with psychiatric symptoms and biological correlates. *Neurosci.*  
23 *Biobehav. Rev.* 33, 601–610. <https://doi.org/10.1016/j.neubiorev.2007.08.002>  
24  
25 Gerra, G., Manfredini, M., Somaini, L., Milano, G., Ciccocioppo, R., Donnini, C., 2016. Perceived  
26 parental care during childhood, ACTH, cortisol and nicotine dependence in the adult. *Psychiatry Res.*  
27 245, 458–465. <https://doi.org/10.1016/j.psychres.2016.09.001>  
28  
29  
30 Gerra, G., Somaini, L., Manfredini, M., Raggi, M.A., Saracino, M.A., Amore, M., Leonardi, C., Cortese,  
31 E., Donnini, C., 2014. Dysregulated responses to emotions among abstinent heroin users: Correlation  
32 with childhood neglect and addiction severity. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 48,  
33 220–228. <https://doi.org/10.1016/j.pnpbp.2013.10.011>  
34  
35 Gerra, G., Zaimovic, A., Castaldini, L., Garofano, L., Manfredini, M., Somaini, L., Leonardi, C., Gerra,  
36 M.L., Donnini, C., 2010. Relevance of perceived childhood neglect, 5-HTT gene variants and  
37 hypothalamus-pituitary-adrenal axis dysregulation to substance abuse susceptibility. *Am. J. Med.*  
38 *Genet. Part B Neuropsychiatr. Genet.* 153, 715–722. <https://doi.org/10.1002/ajmg.b.31038>  
39  
40 Gerra, G., Zaimovic, A., Garofano, L., Ciusa, F., Moi, G., Avanzini, P., Talarico, E., Gardini, F.,  
41 Brambilla, F., Manfredini, M., Donnini, C., 2007. Perceived parenting behavior in the childhood of  
42 cocaine users: Relationship with genotype and personality traits. *Am. J. Med. Genet. Part B*  
43 *Neuropsychiatr. Genet.* 144, 52–57. <https://doi.org/10.1002/ajmg.b.30388>  
44  
45 Gerra, M.C., Manfredini, M., Cortese, E., Antonioni, M.C., Leonardi, C., Magnelli, F., Somaini, L.,  
46 Jayanthi, S., Cadet, J.L., Donnini, C., 2019. Genetic and Environmental Risk Factors for Cannabis  
47 Use: Preliminary Results for the Role of Parental Care Perception. *Subst. Use Misuse* 54, 670–680.  
48 <https://doi.org/10.1080/10826084.2018.1531430>  
49  
50 Ghasempour, A., Mahmoodi-Aghdam, M., 2015.n.d. The Role of Depression and Attachment Styles in  
51 Predicting Students’ Addiction to Cell Phones. *Addict. Heal.* 7, 192–7. PMID: 26885356  
52  
53  
54  
55 Gidhagen, Y., Holmqvist, R., Philips, B., 2018. Attachment style among outpatients with substance use  
56 disorders in psychological treatment. *Psychol Psychother.* 91,490-508.  
57 <https://doi.org/10.1111/papt.12172>.  
58  
59 Gill, R., 2017. Addictions from an Attachment Perspective: Do Broken Bonds and Early Trauma Lead  
60 to Addictive Behavior. New York, NY: Routledge  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Gorwood, P., Wohl, M., Le Strat, Y., Rouillon, F., 2007. Gene-environment interactions in addictive  
5 disorders: epidemiological and methodological aspects. *Comptes Rendus - Biol.* 330, 329–338.  
6 <https://doi.org/10.1016/j.crvi.2007.02.017>  
7
- 8 Greenberg, M.T., Siegel, J.M., Leitch, C.J., 1983. The nature and importance of attachment relationships  
9 to parents and peers during adolescence. *J. Youth Adolesc.* 12, 373–386.  
10 <https://doi.org/10.1007/BF02088721>  
11
- 12 Greger, H.K., Myhre, A.K., Klöckner, C.A., Jozefiak, T., 2017. Childhood maltreatment,  
13 psychopathology and well-being: The mediator role of global self-esteem, attachment difficulties  
14 and substance use. *Child Abuse Negl.* 70,122-133. <https://doi.org/10.1016/j.chiabu.2017.06.012>.  
15
- 16 Groh, A., Rhein, M., Roy, M., Gessner, C., Lichtinghagen, R., Heberlein, A., Hillemacher, T., Bleich,  
17 S., Walter, M., Frieling, H., 2020. Trauma Severity in Early Childhood Correlates with Stress and  
18 Satiety Hormone Levels in a Pilot Cohort Receiving Diamorphine Maintenance Treatment. *Eur.*  
19 *Addict. Res.* 26, 103–108. <https://doi.org/10.1159/000505293>  
20
- 21 Grossmann, K. E., Grossmann, K., & Waters, E. (Eds.), 2005. Attachment from infancy to adulthood:  
22 The major longitudinal studies. New York: Guilford Press.  
23
- 24 Guo, J., Zhu, Y., Fang ,L., Zhang, B., Liu, D., Fu, M., Wang, X.,2020. The Relationship Between Being  
25 Bullied and Addictive Internet Use Among Chinese Rural Adolescents: The Mediating Effect of  
26 Adult Attachment. *J Interpers Violence.* 21:886260520966681.  
27 <https://doi.org/10.1177/0886260520966681>  
28
- 29 Hagan, M.J., Modecki, K., Tan, L.M., Luecken, L., Wolchik, S., Sandler, I., 2019. Binge drinking in  
30 adolescence predicts an atypical cortisol stress response in young adulthood.  
31 *Psychoneuroendocrinology*, 100, 137–144. <https://doi.org/10.1016/j.psyneuen.2018.10.002>  
32
- 33 Hahm, H.C., Lahiff, M., Guterman, N.B., 2003. Acculturation and parental attachment in Asian-  
34 American adolescents' alcohol use. *J. Adolesc. Health* 33, 119–129. [https://doi.org/10.1016/S1054-  
35 139X\(03\)00058-2](https://doi.org/10.1016/S1054-139X(03)00058-2)  
36
- 37 Haile, C. N., Kosten, T. R., & Kosten, T. A., 2007. Genetics of dopamine and its contribution to cocaine  
38 addiction. *Behav. Genet.*Behavior genetics, 37(1), 119-145. [https://doi.org/10.1007/s10519-006-  
39 9115-2](https://doi.org/10.1007/s10519-006-9115-2)  
40
- 41 Hansson, A.C., Cippitelli, A., Sommer, W.H., Fedeli, A., Björk, K., Soverchia, L., Terasmaa, A., Massi,  
42 M., Heilig, M., Ciccocioppo, R., 2006. Variation at the rat *Crhr1* locus and sensitivity to relapse into  
43 alcohol seeking induced by environmental stress. *Proc. Natl. Acad. Sci. U. S. A.* 103, 15236–15241.  
44 <https://doi.org/10.1073/pnas.0604419103>  
45
- 46 Harnic, D., Digiacomantonio, V., Innamorati, M., Mazza, M., Di Marzo, S., Sacripanti, F., Saioni, R.,  
47 Cardella, A., Di Felice, C., Girardi, P., Janiri L., 2010. Temperament and attachment in alcohol  
48 addicted patients of type 1 and 2. *Riv Psichiatr.* 45, 311-319.  
49
- 50 Hart, H., Lim, L., Mehta, M.A., Curtis, C., Xu, X., Breen, G., Simmons, A., Mirza, K., Rubia, K., 2018.  
51 Altered Functional Connectivity of Fronto-Cingulo-Striatal Circuits during Error Monitoring in  
52 Adolescents with a History of Childhood Abuse. *Front. Hum. Neurosci.* 12, 7.  
53 <https://doi.org/10.3389/fnhum.2018.00007>  
54
- 55 Hayre, R.S., Goulter, N., Moretti, M.M., 2019. Maltreatment, attachment, and substance use in  
56 adolescence: Direct and indirect pathways. *Addict. Behav.* 90, 196–203.  
57 <https://doi.org/10.1016/j.addbeh.2018.10.049>  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Heerde, J.A., Bailey, J.A., Toumbourou, J.W., Catalano, R.F., 2019. Longitudinal Associations Between  
5 the Adolescent Family Environment and Young Adult Substance Use in Australia and the United  
6 States. *Front. Psychiatry* 10, 1–10. <https://doi.org/10.3389/fpsy.2019.00821>  
7  
8 Heinrichs, S.C., Koob, G.F., 2004. Corticotropin-releasing factor in brain: A role in activation, arousal,  
9 and affect regulation. *J. Pharmacol. Exp. Ther.* 311, 427–440. <https://doi.org/10.1124/jpet.103.052092>  
10  
11 Henden, E., Melberg, H.O., Røgeberg, O.J., 2013. Addiction: Choice or Compulsion? *Front. Psychiatry*  
12 4. <https://doi.org/10.3389/fpsy.2013.00077>  
13  
14 Henry, K.L., 2008. Low Prosocial Attachment, Involvement With Drug-Using Peers, and Adolescent  
15 Drug Use: A Longitudinal Examination of Mediational Mechanisms. *Psychol. Addict. Behav.* 22,  
16 302–308. <https://doi.org/10.1037/0893-164X.22.2.302>  
17  
18 Henry, K.L., Oetting, E.R., Slater, M.D., 2009. The Role of Attachment to Family, School, and Peers in  
19 Adolescents' Use of Alcohol: A Longitudinal Study of Within-Person and Between-Persons Effects.  
20 *J. Couns. Psychol.* 56, 564–572. <https://doi.org/10.1037/a0017041>  
21  
22 Heyman, G.M., 2009. *Addiction: A disorder of choice.*, *Addiction: A disorder of choice.* Harvard  
23 University Press, Cambridge, MA, US.  
24  
25 Hicks, B. M., Johnson, W., Durbin, C. E., Blonigen, D. M., Iacono, W. G., & McGue, M., 2013. Gene-  
26 environment correlation in the development of adolescent substance abuse: Selection effects of child  
27 personality and mediation via contextual risk factors. *Dev. Psychopathol.*, 25(1), 119.  
28 <https://doi.org/10.1017/S0954579412000946>  
29  
30 Hiebler-Ragger, M., Unterrainer, H.F., Rinner, A., Kapfhammer, H.P., 2016. Insecure Attachment Styles  
31 and Increased Borderline Personality Organization in Substance Use Disorders.  
32 *Psychopathology.* 49, 341-344. <https://doi.org/10.1159/000448177>  
33  
34 Hines, L.A., Morley, K.I., Mackie, C., Lynskey, M., 2015. Genetic and Environmental Interplay in  
35 Adolescent Substance Use Disorders. *Curr. Addict. Rep.* 2, 122-129. <https://doi.org/10.1007/s40429-015-0049-8>  
36  
37  
38 Hitchcock, P., Fried, E. I., & Frank, M. (2021). Computational Psychiatry Needs Time and Context.  
39 *Annual Review of Psychology*, 73. <https://doi.org/10.1146/annurev-psych-021621-124910>  
40  
41 Hocking, E.C., Simons, R.M., Simons, J.S., Freeman, H., 2018. Adult attachment and drinking context  
42 as predictors of alcohol problems and relationship satisfaction in college students. *Am J Drug*  
43 *Alcohol Abuse.* 44, 339-347. <https://doi.org/10.1080/00952990.2017.1344682>  
44  
45 Holmes, J., & Holmes, J., 2014. *John Bowlby and Attachment Theory* (2nd ed.). Routledge.  
46 <https://doi.org/10.4324/9781315879772>  
47  
48 Hood, C.O., Tomko, R.L., Baker, N.L., Tuck, B.M., Flanagan, J.C., Carpenter, M.J., Gray, K.M., Saladin,  
49 M.E., McClure, E.A., 2020. Examining sex, adverse childhood experiences, and oxytocin on  
50 neuroendocrine reactivity in smokers. *Psychoneuroendocrinology* 120, 104752.  
51 <https://doi.org/10.1016/j.psyneuen.2020.104752>  
52  
53 Hosseinifard, S.M., Kaviani, N., 2015. Comparing the Early Maladaptive Schemas, Attachment and  
54 Coping Styles in Opium and Stimulant Drugs Dependent Men in Kerman, Iran. *Addict Health.* 7,  
55 30-36 <https://www.ncbi.nlm.nih.gov/pubmed/26322208>  
56  
57 Huang, M.-C., Chen, L.-Y., Chang, H.-M., Liang, X.-Y., Chen, C.-K., Cheng, W.-J., Xu, K., 2018.  
58 Decreased Blood Levels of Oxytocin in Ketamine-Dependent Patients During Early Abstinence.  
59 *Front. Psychiatry* 9, 633. <https://doi.org/10.3389/fpsy.2018.00633>  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Icick, R., Lauer, S., Romo, L., Dupuy, G., Lépine, J.P., Vorspan, F., 2013. Dysfunctional parental styles  
5 perceived during childhood in outpatients with substance use disorders. *Psychiatry Res.* 210, 522-528.  
6 <https://doi.org/10.1016/j.psychres.2013.06.041>  
7
- 8 Iglesias, E. B., Fernández del Río, E., Calafat, A., & Fernández-Hermida, J. R., 2014. Attachment and  
9 substance use in adolescence: a review of conceptual and methodological aspects. *Adicciones*, 26,  
10 77–86.  
11
- 12 Jiang, N., Xu, J., Li, X., Wang, Y., Zhuang, L., Qin, S., 2021. Negative Parenting Affects Adolescent  
13 Internalizing Symptoms Through Alterations in Amygdala-Prefrontal Circuitry: A Longitudinal Twin  
14 Study. *Biol. Psychiatry* 89, 560–569. <https://doi.org/10.1016/j.biopsych.2020.08.002>  
15
- 16 Jiang, S., Postovit, L., Cattaneo, A., Binder, E.B., Aitchison, K.J., 2019. Epigenetic Modifications in  
17 Stress Response Genes Associated With Childhood Trauma. *Front. Psychiatry* 10.  
18 <https://doi.org/10.3389/fpsy.2019.00808>  
19
- 20 Joëls, M., Karst, H., DeRijk, R., de Kloet, E.R., 2008. The coming out of the brain mineralocorticoid  
21 receptor. *Trends Neurosci.* 31, 1–7. <https://doi.org/10.1016/j.tins.2007.10.005>  
22
- 23 Jones, J.D., Ehrlich K.B., Lejuez, C.W., Cassidy J., 2015. Parental knowledge of adolescent activities:  
24 links with parental attachment style and adolescent substance use. *J Fam Psychol.* 29,191-200.  
25 <https://doi.org/10.1037/fam0000070>  
26
- 27 Jordan, S., Sack, P.M., 2009. Schutz- und Risikofaktoren [Protective factors and risk factors]. In:  
28 Thomasius, R., Schulte-Markwort, M., Küstner, U.J., and Riedesser, P., editors. *Suchtstörungen im*  
29 *Kindes- und Jugendalter–Das Handbuch: Grundlagen und Praxis.* Stuttgart, Germany: Schattauer. p.  
30 127–38.  
31
- 32 Kanamori, M., Weissman, J., De La Rosa, M., Trepka, M.J., Rojas, P., Cano, M.A., Melton, J.,  
33 Unterberger, A., 2016. Latino Mother/Daughter Dyadic Attachment as a Mediator for Substance Use  
34 Disorder and Emotional Abuse. *J. Immigr. Minor. Heal.* 18, 896–903. [https://doi.org/10.1007/s10903-](https://doi.org/10.1007/s10903-015-0312-z)  
35 [015-0312-z](https://doi.org/10.1007/s10903-015-0312-z)  
36
- 37 Karimi, Z., Haghshenas, L., Mohtashami, T., Dehkordi, M.A., 2019. Investigating the role of attachment  
38 styles, dysfunctional attitudes, and spirituality in predicting membership in addicted and non-  
39 addicted groups. *Psych J.* 8, 169-179. <https://doi.org/10.1002/pchj.254>  
40
- 41 Kassel, J.D., Wardle, M., Roberts, J.E., 2007. Adult attachment security and college student substance  
42 use. *Addict Behav.* 32, 1164-76. <https://doi.org/10.1016/j.addbeh.2006.08.005>  
43
- 44 Kendler, K. S., Sundquist, K., Ohlsson, H., PalmÚr, K., Maes, H., Winkleby, M. A., & Sundquist, J.  
45 (2012). Genetic and familial environmental influences on the risk for drug abuse: a national Swedish  
46 adoption study. *Archives of general psychiatry*, 69(7), 690-697.  
47 <https://doi.org/10.1001/archgenpsychiatry.2011.2112>  
48
- 49 Kendler, K.S., Myers, J., Prescott, C.A., 2000. Parenting and adult mood, anxiety and substance use  
50 disorders in female twins: An epidemiological, multi-informant, retrospective study. *Psychol. Med.*  
51 30, 281–294. <https://doi.org/10.1017/S0033291799001889>  
52
- 53 Kilpatrick, D.G., Koenen, K.C., Ruggiero, K.J., Acerno, R., Galea, S., Resnick, H.S., Roitzsch, J., Boyle,  
54 J., Gelernter, J., 2007. The serotonin transporter genotype and social support and moderation of  
55 posttraumatic stress disorder and depression in hurricane-exposed adults. *Am. J. Psychiatry* 164,  
56 1693–1699. <https://doi.org/10.1176/appi.ajp.2007.06122007>  
57
- 58 Knudsen, E.I., 2004. Sensitive periods in the development of the brain and behavior. *J. Cogn. Neurosci.*  
59 16, 1412–1425. <https://doi.org/10.1162/0898929042304796>  
60
- 61  
62  
63  
64  
65

- 1  
2  
3  
4 Kober, H., 2014. Emotion regulation in substance use disorders. In J. J. Gross (Ed.), Handbook of  
5 emotion regulation. The Guilford Press, pp 428–446.  
6
- 7 Kogan, S.M., Cho, J., Beach, S.R.H., Smith, A.K., Nishitani, S., 2018. Oxytocin receptor gene  
8 methylation and substance use problems among young African American men. *Drug Alcohol Depend.*  
9 192, 309–315. <https://doi.org/10.1016/j.drugalcdep.2018.08.022>  
10
- 11 Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. *The lancet.*  
12 *Psychiatry* 3, 760–773. [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8)  
13
- 14 Kostelecky, K.L., 2005. Parental attachment, academic achievement, life events and their relationship to  
15 alcohol and drug use during adolescence. *J. Adolesc.* 28, 665–669.  
16 <https://doi.org/10.1016/j.adolescence.2004.12.006>  
17
- 18 Kumpfer K.L., Alvarado R., Whiteside H.O., 2003. Family-based interventions for substance use and  
19 misuse prevention. *Subst Use Misuse* 38, 1759-1787. <https://doi.org/10.1081/ja-120024240>  
20
- 21 Lachman, H.M., Papolos, D.F., Saito, T., Yu, Y.M., Szumlanski, C.L., Weinshilboum, R.M., 1996.  
22 Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism  
23 and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 6, 243–250.  
24 <https://doi.org/10.1097/00008571-199606000-00007>  
25
- 26 Ladd-Acosta, C. & Fallin, M.D., 2016., 'The role of epigenetics in genetic and environmental  
27 epidemiology', *Epigenomics* 8, 271-283. <https://doi.org/10.2217/epi.15.102>  
28
- 29 Laucht, M., Blomeyer, D., Buchmann, A.F., Treutlein, J., Schmidt, M.H., Esser, G., Jennen-Steinmetz,  
30 C., Rietschel, M., Zimmermann, U.S., Banaschewski, T., 2012. Catechol-O-methyltransferase Val  
31 158 met genotype, parenting practices and adolescent alcohol use: Testing the differential  
32 susceptibility hypothesis. *J. Child Psychol. Psychiatry Allied Discip.* 53, 351–359.  
33 <https://doi.org/10.1111/j.1469-7610.2011.02408.x>  
34
- 35 Lee, J.M., & Bell, N.J., 2003. Individual differences in attachment-autonomy configurations: Linkages  
36 with substance use and youth competencies. *J. Adolesc.* 26, 347–361. [https://doi.org/10.1016/S0140-1971\(03\)00018-6](https://doi.org/10.1016/S0140-1971(03)00018-6)  
37
- 38 Levandowski, M.L., Viola, T.W., Prado, C.H., Wieck, A., Bauer, M.E., Brietzke, E., Grassi-Oliveira, R.,  
39 2016. Distinct behavioral and immunoendocrine parameters during crack cocaine abstinence in  
40 women reporting childhood abuse and neglect. *Drug Alcohol Depend.* 167, 140–148.  
41 <https://doi.org/10.1016/j.drugalcdep.2016.08.010>  
42
- 43 Levitt, A., Leonard, K.E., 2015. Insecure attachment styles, relationship-drinking contexts, and marital  
44 alcohol problems: Testing the mediating role of relationship-specific drinking-to-cope motives.  
45 *Psychol Addict Behav.* 29,696-705. <https://dx.doi.org/10.1037/adb0000064>  
46
- 47 Lewis, C. R., & Olive, M. F., 2014. Early life stress interactions with the epigenome: potential  
48 mechanisms driving vulnerability towards psychiatric illness. *Behav. Pharmacol.*, 25(5 0 6), 341.  
49 <https://doi.org/10.1097/FBP.0000000000000057>  
50
- 51 Li, T., Du, J., Yu, S., Jiang, H., Fu, Y., Wang, D., Sun, H., Chen, H., Zhao, M., 2012. Pathways to Age  
52 of Onset of Heroin Use: A Structural Model Approach Exploring the Relationship of the COMT Gene,  
53 Impulsivity and Childhood Trauma. *PLoS One* 7, e48735.  
54 <https://doi.org/10.1371/journal.pone.0048735>  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Liese, B.S., Kim ,H.S., Hodgins, D.C., 2020. Insecure attachment and addiction: Testing the mediating  
5 role of emotion dysregulation in four potentially addictive behaviors. *Addict Behav.* 107, 106432.  
6 <https://doi.org/10.1016/j.addbeh.2020.106432>  
7  
8 Lindberg, M.A., Fugett, A., Carter, J.E., 2015. Tests of the attachment and clinical issues questionnaire  
9 as it applies to alcohol dependence. *J. Addict. Med.* 9, 286–295.  
10 <https://doi.org/10.1097/ADM.0000000000000131>  
11  
12 Lindberg, M.A., Thomas, S.W., 2011. The attachment and clinical issues questionnaire (ACIQ): Scale  
13 development. *J. Genet. Psychol.* 172, 329–352. <https://doi.org/10.1080/00221325.2010.541382>  
14  
15 Liu .C., Ma, J.L., 2019. Adult Attachment Style, Emotion Regulation, and Social Networking Sites  
16 Addiction. *Front Psychol.* 10, 2352. <https://doi.org/10.3389/fpsyg.2019.02352>.  
17  
18 Liu, C., & Chung, M., 2015. Genetics and epigenetics of circadian rhythms and their potential roles in  
19 neuropsychiatric disorders. *Neuroscience bulletin*, 31(1), 141-159. [https://doi.org/10.1007/s12264-](https://doi.org/10.1007/s12264-014-1495-3)  
20 [014-1495-3](https://doi.org/10.1007/s12264-014-1495-3)  
21  
22 Liu, C., Ma, J.L., 2019. Adult Attachment Orientations and Social Networking Site Addiction: The  
23 Mediating Effects of Online Social Support and the Fear of Missing Out. *Front Psychol.* 10, 2629.  
24 <https://doi.org/10.3389/fpsyg.2019.02629>.  
25  
26 Love, T. M., Stohler, C. S., & Zubieta, J. K. (2009). Positron emission tomography measures of  
27 endogenous opioid neurotransmission and impulsiveness traits in humans. *Archives of general*  
28 *psychiatry*, 66(10), 1124-1134. <https://doi:10.1001/archgenpsychiatry.2009.134>  
29  
30 Luk, J.W., Patock-Peckham, J.A., King, K.M., 2015. Are Dimensions of Parenting Differentially Linked  
31 to Substance Use Across Caucasian and Asian American College Students? *Subst. Use Misuse* 50,  
32 1360–1369. <https://doi.org/10.3109/10826084.2015.1013134>  
33  
34 Lutz, P.E., Gross, J.A., Dhir, S.K., Maussion, G., Yang, J., Bramouille, A., Meaney, M.J., Turecki, G.,  
35 2018. Epigenetic Regulation of the Kappa Opioid Receptor by Child Abuse. *Biol. Psychiatry* 84, 751–  
36 761. <https://doi.org/10.1016/j.biopsych.2017.07.012>  
37  
38 Lyons-Ruth, K., Bureau, J. F., Holmes, B., Easterbrooks, A., & Brooks, N. H., 2013. Borderline  
39 symptoms and suicidality/self-injury in late adolescence: Prospectively observed relationship  
40 correlates in infancy and childhood. *Psychiatry research*, 206(2-3), 273-281.  
41 <https://doi.org/10.1016/j.psychres.2012.09.030>  
42  
43 Lyvers, M., Mayer, K., Needham, K., Thorberg, F.A., 2019. Parental bonding, adult attachment, and  
44 theory of mind: A developmental model of alexithymia and alcohol-related risk. *J. Clin. Psychol.* 75,  
45 1288–1304. <https://doi.org/10.1002/jclp.22772>  
46  
47 Machin, A. J., & Dunbar, R. I., 2011. The brain opioid theory of social attachment: a review of the  
48 evidence. *Behaviour*, 148(9-10), 985-1025. <https://doi.org/10.1163/000579511X596624>  
49  
50 Main, M., Hesse, E., & Kaplan, N., 2005. Predictability of Attachment Behavior and Representational  
51 Processes at 1, 6, and 19 Years of Age: The Berkeley Longitudinal Study. In K. E. Grossmann, K.  
52 Grossmann, & E. Waters (Eds.), *Attachment from infancy to adulthood: The major longitudinal*  
53 *studies*. Guilford Publications, pp. 245–304.  
54  
55 Marceau, K., Brick, L.A., Knopik, V.S., Reijneveld, S.A., 2020. Developmental Pathways from Genetic,  
56 Prenatal, Parenting and Emotional/Behavioral Risk to Cortisol Reactivity and Adolescent Substance  
57 Use: A TRAILS Study. *J. Youth Adolesc.* 49, 17–31. <https://doi.org/10.1007/s10964-019-01142-8>  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Maremmani, I., Pacini, M., Popovic, D., Romano, A., Maremmani, A.G., Perugi, G., Deltito, J., Akiskal,  
5 K., Akiskal, H., 2009. Affective temperaments in heroin addiction. *J Affect Disord.* 117, 186-92.  
6 <https://doi.org/10.1016/j.jad.2009.01.007>  
7  
8 Marshall, S.W., Albery, I.P., Frings, D., 2018. Who stays in addiction treatment groups? Anxiety and  
9 avoidant attachment styles predict treatment retention and relapse. *Clin Psychol Psychother.* 25,  
10 525-531. <https://doi.org/10.1002/cpp.2187>.  
11  
12 Massey, S.H., Compton, M.T., Kaslow, N.J., 2014. Attachment security and problematic substance use  
13 in low-income, suicidal, African American women. *Am J Addict.* 23, 294-299.  
14 <https://doi.org/10.1111/j.1521-0391.2014.12104.x>  
15  
16 McCrory, E.J., Mayes, L., 2015. Understanding Addiction as a Developmental Disorder: An Argument  
17 for a Developmentally Informed Multilevel Approach. *Curr. Addict. Reports* 2, 326–330.  
18 <https://doi.org/10.1007/s40429-015-0079-2>  
19  
20 McLaughlin, A., Campbell, A., McColgan, M., 2016. Adolescent Substance Use in the Context of the  
21 Family: A Qualitative Study of Young People’s Views on Parent-Child Attachments, Parenting Style  
22 and Parental Substance Use. *Subst. Use Misuse* 51, 1846–1855.  
23 <https://doi.org/10.1080/10826084.2016.1197941>  
24  
25 Meredith, P., Moyle, R., Kerley, L., 2020. Substance Use: Links with Sensory Sensitivity, Attachment  
26 Insecurity, and Distress in Young Adults. *Subst Use Misuse.* 55, 1817-1824.  
27 <https://doi.org/10.1080/10826084.2020.1766502>  
28  
29 Meyers, J.L., Shmulewitz, D., Wall, M.M., Keyes, K.M., Aharonovich, E., Spivak, B., Weizman, A.,  
30 Frisch, A., Edenberg, H.J., Gelernter, J., Grant, B.F., Hasin, D., 2015. Childhood adversity moderates  
31 the effect of ADH1B on risk for alcohol-related phenotypes in Jewish Israeli drinkers. *Addict. Biol.*  
32 20, 205–214. <https://doi.org/10.1111/adb.12102>  
33  
34 Mier D, Kirsch P, Meyer-Lindenberg A. 2010. Neural substrates of pleiotropic action of genetic variation  
35 in COMT: a meta-analysis. *Mol Psychiatry.*15, 918-927. <https://doi:10.1038/mp.2009.36>  
36  
37 Mikulincer, M., & Shaver, P. R. (2016). *Attachment in adulthood: Structure, dynamics, and change.*  
38 Guilford Press.  
39  
40 Milaniak, I., Watson, B. & Jaffee, S.R., 2015. Gene-Environment Interplay and Substance Use: A  
41 Review of Recent Findings. *Curr Addict Rep* 2, 364–371. [https://doi.org/10.1007/s40429-015-0069-](https://doi.org/10.1007/s40429-015-0069-4)  
42 [4](https://doi.org/10.1007/s40429-015-0069-4)  
43  
44 Miljkovitch, R., Pierrehumbert, B., Karmaniola, A., Bader, M., Halfon, O., 2005. Assessing attachment  
45 cognitions and their associations with depression in youth with eating or drug misuse disorders. *Subst.*  
46 *Use Misuse* 40, 605–623. <https://doi.org/10.1081/JA-200055349>  
47  
48 Mollick, J.A., Kober, H., 2020. Computational models of drug use and addiction: A review. *J. Abnorm.*  
49 *Psychol.* 129, 544–555. <https://doi.org/10.1037/abn0000503>  
50  
51 Monacis, L., de Palo, V., Griffiths, M.D., Sinatra, M., 2017. Exploring Individual Differences in Online  
52 Addictions: the Role of Identity and Attachment. *Int J Ment Health Addict.* 15, 853-868.  
53 <https://doi.org/10.1007/s11469-017-9768-5>.  
54  
55 Monacis, L., de Palo, V., Griffiths, M.D., Sinatra, M., 2017. Social networking addiction, attachment  
56 style, and validation of the Italian version of the Bergen Social Media Addiction Scale. *J Behav*  
57 *Addict.* 6, 178-186. <https://doi.org/10.1556/2006.6.2017.023>.  
58  
59 Moore, L. D., Le, T., & Fan, G., 2013. DNA methylation and its basic function.  
60 *Neuropsychopharmacology*, 38(1), 23-38. <https://doi.org/10.1038/npp.2012.112>  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Moran-Santa Maria MM, McRae-Clark AL, Back SE, DeSantis SM, Baker NL, Spratt EG, Simpson AN,  
5 Brady KT. 2010., Influence of cocaine dependence and early life stress on pituitary-adrenal axis  
6 responses to CRH and the Trier social stressor. *Psychoneuroendocrinology* 35, 1492-500.  
7 <https://doi.org/10.1016/j.psyneuen.2010.05.001>  
8  
9 Muehlhan, M., Höcker, A., Miller, R., Trautmann, S., Wiedemann, K., Lotzin, A., Barnow, S., Schäfer,  
10 I., 2020. HPA axis stress reactivity and hair cortisol concentrations in recently detoxified alcoholics  
11 and healthy controls with and without childhood maltreatment. *Addict. Biol.* 25, 1–8.  
12 <https://doi.org/10.1111/adb.12681>  
13  
14 Mulder, R.H., Rijlaarsdam, J., Luijk, M.P.C.M., Verhulst, F.C., Felix, J.F., Tiemeier, H., Bakermans-  
15 Kranenburg, M.J., Van Ijzendoorn, M.H., 2017. Methylation matters: FK506 binding protein 51  
16 (FKBP5) methylation moderates the associations of FKBP5 genotype and resistant attachment with  
17 stress regulation. *Dev. Psychopathol.* 29, 491–503. <https://doi.org/10.1017/S095457941700013X>  
18  
19 Munafò, M.R., Freimer, N.B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Järvelin, M.R., Taanila, A.,  
20 Flint, J., 2009. 5-HTTLPR genotype and anxiety-related personality traits: A meta-analysis and new  
21 data. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 150, 271–281.  
22 <https://doi.org/10.1002/ajmg.b.30808>  
23  
24 Musetti, A., Terrone, G., Corsano, P., Magnani, B., Salvatore, S., 2016. Exploring the link among state  
25 of mind concerning childhood attachment, attachment in close relationships, parental bonding, and  
26 psychopathological symptoms in substance users. *Front. Psychol.* 7, 1–9.  
27 <https://doi.org/10.3389/fpsyg.2016.01193>  
28  
29 Nakhoul, L., Obeid, S., Sacre, H., Haddad, C., Soufia, M., Hallit, R., Akel, M., Salameh, P., Hallit, S.,  
30 2020. Attachment style and addictions (alcohol, cigarette, waterpipe and internet) among  
31 Lebanese adolescents: a national study. *BMC Psychol.* 8, 33. [https://doi.org/10.1186/s40359-](https://doi.org/10.1186/s40359-020-00404-6)  
32 [020-00404-6](https://doi.org/10.1186/s40359-020-00404-6) .  
33  
34 Negriff, S., Saxbe, D.E., Trickett, P.K., 2015. Childhood maltreatment, pubertal development, HPA axis  
35 functioning, and psychosocial outcomes: An integrative biopsychosocial model. *Dev. Psychobiol.* 57,  
36 984–993. <https://doi.org/10.1002/dev.21340>  
37  
38 Nelson, E.E., Panksepp, J., 1998. Brain substrates of infant-mother attachment: Contributions of opioids,  
39 oxytocin, and norepinephrine. *Neurosci. Biobehav. Rev.* 22, 437–452. [https://doi.org/10.1016/S0149-](https://doi.org/10.1016/S0149-7634(97)00052-3)  
40 [7634\(97\)00052-3](https://doi.org/10.1016/S0149-7634(97)00052-3)  
41  
42 Nestler, E.J., 2014. Epigenetic mechanisms of drug addiction. *Neuropharmacology* 76, 259–268.  
43 <https://doi.org/10.1016/j.neuropharm.2013.04.004>  
44  
45 Nestler, E.J., Lüscher, C., 2019. The Molecular Basis of Drug Addiction: Linking Epigenetic to Synaptic  
46 and Circuit Mechanisms. *Neuron* 102, 48–59. <https://doi.org/10.1016/j.neuron.2019.01.016>  
47  
48 Neville, M. J., Johnstone, E. C., & Walton, R. T., 2004. Identification and characterization of ANKK1:  
49 a novel kinase gene closely linked to DRD2 on chromosome band 11q23. 1. *Hum. Mutat.*, 23(6), 540-  
50 545. <https://pubmed.ncbi.nlm.nih.gov/15146457/>  
51  
52 Niyonsenga, T., Blackson, T.C., De La Rosa, M., Rojas, P., Dillon, F., Ganapati, E.N., 2012. Social  
53 support, attachment, and chronic stress as correlates of latina mother and daughter drug use behaviors.  
54 *Am. J. Addict.* 21, 157–167. <https://doi.org/10.1111/j.1521-0391.2011.00202.x>  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Noto, K., Suzuki, A., Shirata, T., Matsumoto, Y., Takahashi, N., Goto, K., Otani, K., 2020. Mu-opioid  
5 receptor polymorphism moderates sensitivity to parental behaviors during characterization of  
6 personality traits. *Neuropsychiatr. Dis. Treat.* 16, 2161–2167. <https://doi.org/10.2147/NDT.S265774>  
7
- 8 Nummenmaa, L., Manninen, S., Tuominen, L., Hirvonen, J., Kalliokoski, K.K., Nuutila, P., Jääskeläinen,  
9 I.P., Hari, R., Dunbar, R.I.M., Sams, M., 2015. Adult attachment style is associated with cerebral  $\mu$ -  
10 opioid receptor availability in humans. *Hum. Brain Mapp.* 36, 3621–3628.  
11 <https://doi.org/10.1002/hbm.22866>  
12
- 13 Nylander, I., Todkar, A., Granholm, L., Vrettou, M., Bendre, M., Boon, W., Andershed, H., Tuvblad, C.,  
14 Nilsson, K.W., Comasco, E., 2017. Evidence for a Link Between Fkbp5/FKBP5, Early Life Social  
15 Relations and Alcohol Drinking in Young Adult Rats and Humans. *Mol. Neurobiol.* 54, 6225–6234.  
16 <https://doi.org/10.1007/s12035-016-0157-z>  
17
- 18 Oitzl, M.S., Champagne, D.L., van der Veen, R., de Kloet, E.R., 2010. Brain development under stress:  
19 hypotheses of glucocorticoid actions revisited. *Neurosci. Biobehav. Rev.* 34, 853–66.  
20 <https://doi.org/10.1016/j.neubiorev.2009.07.006>  
21
- 22 Olsson, C.A., Moyzis, R.K., Williamson, E., Ellis, J.A., Parkinson-Bates, M., Patton, G.C., Dwyer, T.,  
23 Romaniuk, H., Moore, E.E., 2011. Gene-environment interaction in problematic substance use:  
24 Interaction between DRD4 and insecure attachments. *Addict. Biol.* 18, 717–726.  
25 <https://doi.org/10.1111/j.1369-1600.2011.00413.x>  
26
- 27 Ossola, P., Gerra, M.C., Gerra, M.L., Milano, G., Zatti, M., Zavan, V., Volpi, R., Marchesi, C., Donnini,  
28 C., Gerra, G., Di Gennaro, C., 2020. Alcohol use disorders among adult children of alcoholics  
29 (ACOAs): Gene-environment resilience factors. *Prog. Neuro-Psychopharmacology Biol. Psychiatry*  
30 108. <https://doi.org/10.1016/j.pnpbp.2020.110167>  
31
- 32 Oswald, L.M., Wand, G.S., Kuwabara, H., Wong, D.F., Zhu, S., Brasic, J.R., 2014. History of childhood  
33 adversity is positively associated with ventral striatal dopamine responses to amphetamine.  
34 *Psychopharmacology (Berl)*. 231, 2417–2433. <https://doi.org/10.1007/s00213-013-3407-z>  
35
- 36 Outcalt, J., Dimaggio, G., Popolo, R., Buck, K., Chaudoin-Patzoldt, K.A., Kukla, M., Olesek, K.L.,  
37 Lysaker, P.H., 2016. Metacognition moderates the relationship of disturbances in attachment with  
38 severity of borderline personality disorder among persons in treatment of substance use disorders.  
39 *Compr Psychiatry*. 64, 22-28. <https://doi.org/10.1016/j.comppsy.2015.10.002>  
40
- 41 Owens, G.P., Held, P., Blackburn, L., Auerbach, J.S., Clark, A.A., Herrera, C.J., Cook, J., Stuart, G.L.,  
42 2014. Differences in relationship conflict, attachment, and depression in treatment-seeking  
43 veterans with hazardous substance use, PTSD, or PTSD and hazardous substance use. *J Interpers*  
44 *Violence*. 29, 1318-37. <https://doi.org/10.1177/0886260513506274>  
45
- 46 Pappa, I., Szekely, E., Mileva-Seitz, V.R., Luijk, M.P.C.M., Bakermans-Kranenburg, M.J., van  
47 IJzendoorn, M.H., Tiemeier, H., 2015. Beyond the usual suspects: a multidimensional genetic  
48 exploration of infant attachment disorganization and security. *Attach. Hum. Dev.* 17, 288–301.  
49 <https://doi.org/10.1080/14616734.2015.1037316>  
50
- 51 Parade, S. H., Huffhines, L., Daniels, T. E., Stroud, L. R., Nugent, N. R., & Tyrka, A. R. (2021). A  
52 systematic review of childhood maltreatment and DNA methylation: candidate gene and epigenome-  
53 wide approaches. *Translational psychiatry*, 11(1), 1-33.  
54
- 55 Park, A., Sher, K.J., Todorov, A.A., Heath, A.C., 2011. Interaction between the DRD4 VNTR  
56 polymorphism and proximal and distal environments in alcohol dependence during emerging and  
57 young adulthood. *J. Abnorm. Psychol.* 120, 585–595. <https://doi.org/10.1037/a0022648>  
58

- 1  
2  
3  
4 Parker, G., Tupling, H., Brown, L.B., 1979. A Parental Bonding Instrument. *Br. J. Med. Psychol.* 52, 1–  
5 10. <https://doi.org/10.1111/j.2044-8341.1979.tb02487.x>  
6  
7 Pellerone, M., Tolini, G., Polopoli, C., 2016. Parenting, identity development, internalizing symptoms,  
8 and alcohol use: A cross-sectional study in a group of Italian adolescents. *Neuropsychiatr. Dis. Treat.*  
9 12, 1769–1778. <https://doi.org/10.2147/NDT.S106791>  
10  
11 Pettenon, M., Kessler, F.H.P., Guimarães, L.S.P., Pedroso, R.S., Hauck, S., Pechansky, F., 2014.  
12 Perceptions of parental bonding in freebase cocaine users versus non-illicit drug users. *Indian J. Med.*  
13 *Res.* 139, 835–840.  
14  
15 Pickard, H., 2017. Responsibility without Blame for Addiction. *Neuroethics* 10, 169–180.  
16 <https://doi.org/10.1007/s12152-016-9295-2>.  
17  
18 Pirnia, B., Khosravani, V., Maleki, F., Kalbasi, R., Pirnia, K., Malekanmehr, P., Zahiroddin, A., 2020.  
19 The role of childhood maltreatment in cortisol in the hypothalamic–pituitary–adrenal (HPA) axis in  
20 methamphetamine-dependent individuals with and without depression comorbidity and suicide  
21 attempts. *J. Affect. Disord.* 263, 274–281. <https://doi.org/10.1016/j.jad.2019.11.168>  
22  
23 Potik, D., Peles, E., Abramsohn, Y., Adelson, M., Schreiber, S., 2014. The relationship between  
24 vulnerable attachment style, psychopathology, drug abuse, and retention in treatment among  
25 methadone maintenance treatment patients. *J Psychoactive Drugs.* 46,325-333.  
26 <https://doi.org/10.1080/02791072.2014.944290>  
27  
28 Prior, V., & Glaser, D., 2006. Understanding attachment and attachment disorders: Theory, evidence and  
29 practice. Jessica Kingsley Publishers. Plotka R., 2011. Adult Attachment Interview (AAI). In:  
30 Goldstein S., Naglieri J.A. (eds) *Encyclopedia of Child Behavior and Development*. Springer, Boston,  
31 MA. [https://doi.org/10.1007/978-0-387-79061-9\\_68](https://doi.org/10.1007/978-0-387-79061-9_68)  
32  
33 Prom-Wormley, E. C., Ebejer, J., Dick, D. M., & Bowers, M. S., 2017. The genetic epidemiology of  
34 substance use disorder: a review. *Drug and alcohol dependence*, 180, 241-259.  
35  
36 Remondi, C., Compare, A., Tasca, G.A., Greco, A., Pievani, L., Poletti, B., Brugnera, A., 2020. Insecure  
37 Attachment and Technology Addiction Among Young Adults: The Mediating Role of  
38 Impulsivity, Alexithymia, and General Psychological Distress. *Cyberpsychol Behav Soc Netw.*  
39 23, 761-767. <https://doi.org/10.1089/cyber.2019.0747>  
40  
41 Remondi, C., Compare, A., Tasca, G.A., Greco, A., Pievani, L., Poletti, B., Brugnera, B., 2020. Insecure  
42 Attachment and Technology Addiction Among Young Adults: The Mediating Role of  
43 Impulsivity, Alexithymia, and General Psychological Distress. *Cyberpsychol Behav Soc Netw.*  
44 23, 761-767. <https://doi.org/10.1089/cyber.2019.0747>  
45  
46 Riggs A.D. & Porter T.N., 1996. Overview of epigenetic mechanisms. In *Epigenetic mechanisms of gene*  
47 *regulation* (eds. Russo VEA, Martienssen R, Riggs AD), Cold Spring Harbor Laboratory Press, Cold  
48 Spring Harbor, NY, pp. 29–45.  
49  
50 Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR.,  
51 2009. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk  
52 of depression: a meta-analysis. *JAMA.* 301, 2462-71. <https://doi.org/10.1001/jama.2009.878>. Erratum  
53 in: *JAMA.* 2009 302, 492. PMID: 19531786; PMCID: PMC2938776.  
54  
55 Robakis, T.K., Zhang, S., Rasgon, N.L., Li, T., Wang, T., Roth, M.C., Humphreys, K.L., Gotlib, I.H.,  
56 Ho, M., Khechaduri, A., Watson, K., Roat-Shumway, S., Budhan, V. V., Davis, K.N., Crowe, S.D.,  
57 Ellie Williams, K., Urban, A.E., 2020. Epigenetic signatures of attachment insecurity and childhood  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 adversity provide evidence for role transition in the pathogenesis of perinatal depression. *Transl. Psychiatry* 10, 1–14. <https://doi.org/10.1038/s41398-020-0703-3>

7 Rovai L., Maremmani AGI, Bacciardi S., Gazzarrini D., Pallucchini A., Spera V., Perugi G., Maremmani I., 2017. Opposed Effect of Hyperthymic and Cyclothymic Temperament in Substance Use Disorder (Heroin or Alcohol Dependent Patients). *Journal of Affective Disorders*. 218: 339-345. <https://doi.org/10.1016/j.jad.2017.04.041>

12 Rovaris, D.L., Mota, N.R., Bertuzzi, G.P., Aroche, A.P., Callegari-Jacques, S.M., Guimarães, L.S.P., Pezzi, J.C., Viola, T.W., Bau, C.H.D., Grassi-Oliveira, R., 2015. Corticosteroid receptor genes and childhood neglect influence susceptibility to crack/cocaine addiction and response to detoxification treatment. *J. Psychiatr. Res.* 68, 83–90. <https://doi.org/10.1016/j.jpsychires.2015.06.008>

18 Roy, A., 2002. Self-rated childhood emotional neglect and CSF monoamine indices in abstinent cocaine-abusing adults: Possible implications for suicidal behavior. *Psychiatry Res.* 112, 69–75. [https://doi.org/10.1016/S0165-1781\(02\)00176-2](https://doi.org/10.1016/S0165-1781(02)00176-2)

22 Ruggeri, B., Macare, C., Stopponi, S., Jia, T., Carvalho, F.M., Robert, G., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Büchel, C., Cattrell, A., Conrod, P.J., Desrivières, S., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.L., Martinot, M.L.P., Nees, F., Papadopoulos-Orfanos, D., Paus, T., Poustka, L., Smolka, M.N., Vetter, N.C., Walter, H., Whelan, R., Sommer, W.H., Bakalkin, G., Ciccocioppo, R., Schumann, G., 2018. Methylation of OPR1L1 mediates the effect of psychosocial stress on binge drinking in adolescents. *J. Child Psychol. Psychiatry Allied Discip.* 59, 650–658. <https://doi.org/10.1111/jcpp.12843>

31 Ruggeri, B., Nymberg, C., Vuoksima, E., Lourdasamy, A., Wong, C. P., Carvalho, F. M., ... & IMAGEN Consortium. (2015). Association of protein phosphatase PPM1G with alcohol use disorder and brain activity during behavioral control in a genome-wide methylation analysis. *American Journal of Psychiatry*, 172(6), 543-552.

36 Sandler, I.N., Schoenfelder, E.N., Wolchik, S.A., MacKinnon, D.P., 2011. Long-term impact of prevention programs to promote effective parenting: Lasting effects but uncertain processes. *Annu. Rev. Psychol.* 62, 299–329. <https://doi.org/10.1146/annurev.psych.121208.131619>

41 Schäfer, I., Teske, L., Schulze-Thüsing, J., Homann, K., Reimer, J., Haasen, C., Hissbach, J., Wiedemann, K., 2010. Impact of childhood trauma on hypothalamus-pituitary-adrenal axis activity in alcohol-dependent patients. *Eur. Addict. Res.* 16, 108–114. <https://doi.org/10.1159/000294362>

45 Schindler, A., 2019. Attachment and Substance Use Disorders—Theoretical Models, Empirical Evidence, and Implications for Treatment. *Front. Psychiatry* 10, 1–13. <https://doi.org/10.3389/fpsy.2019.00727>

49 Schindler, A., Bröning, S., 2015. A Review on Attachment and Adolescent Substance Abuse: Empirical Evidence and Implications for Prevention and Treatment. *Subst. Abus.* 36, 304–13. <https://doi.org/10.1080/08897077.2014.983586>

53 Schindler, A., Sack, P.M., 2015. Exploring attachment patterns in patients with comorbid borderline personality and substance use disorders. *J. Nerv. Ment. Dis.* 203, 820–826. <https://doi.org/10.1097/NMD.0000000000000377>

57 Schindler, A., Thomasius, R., Petersen, K., Sack, P.M., 2009. Heroin as an attachment substitute? Differences in attachment representations between opioid, ecstasy and cannabis abusers. *Attach. Hum. Dev.* 11, 307–330. <https://doi.org/10.1080/14616730902815009>

- 1  
2  
3  
4 Schindler, A., Thomasius, R., Sack, P.M., Gemeinhardt, B., Küstner, U., 2007. Insecure family bases and  
5 adolescent drug abuse: A new approach to family patterns of attachment. *Attach. Hum. Dev.* 9, 111–  
6 126. <https://doi.org/10.1080/14616730701349689>  
7  
8 Schmid, B., Blomeyer, D., Treutlein, J., Zimmermann, U.S., Buchmann, A.F., Schmidt, M.H., Esser, G.,  
9 Rietschel, M., Banaschewski, T., Schumann, G., Laucht, M., 2010. Interacting effects of CRHR1 gene  
10 and stressful life events on drinking initiation and progression among 19-year-olds. *Int. J.*  
11 *Neuropsychopharmacol.* 13, 703–714. <https://doi.org/10.1017/S146114570990290>  
12  
13 Schoots, O., Van Tol, H.H.M., 2003. The human dopamine D4 receptor repeat sequences modulate  
14 expression. *Pharmacogenomics J.* 3, 343–348. <https://doi.org/10.1038/sj.tpj.6500208>  
15  
16 Scragg, R., Reeder, A.I., Wong, G., Glover, M., Nosa, V., 2008. Attachment to parents, parental tobacco  
17 smoking and smoking among Year 10 students in the 2005 New Zealand national survey. *Aust. N. Z.*  
18 *J. Public Health* 32, 348–353. <https://doi.org/10.1111/j.1753-6405.2008.00253.x>  
19  
20 Şenormancı, Ö., Şenormancı, G., Güçlü, O., Konkan, R., 2014. Attachment and family functioning in  
21 patients with internet addiction. *Gen Hosp Psychiatry.* 36, 203-207.  
22 <https://doi.org/10.1016/j.genhosppsy.2013.10.012>  
23  
24 Serra, W., Chatard, A., Tello, N., Harika-Germaneau, G., Noël, X., Jaafari, N., 2019. Mummy, daddy,  
25 and addiction: Implicit insecure attachment is associated with substance use in college students.  
26 *Exp Clin Psychopharmacol.* 27, 522-529. <https://doi.org/10.1037/pha0000266>  
27  
28 Shi, Z., Bureau, J. F., Easterbrooks, M. A., Zhao, X., & Lyons- Ruth, K., 2012. Childhood maltreatment  
29 and prospectively observed quality of early care as predictors of antisocial personality disorder  
30 features. *Infant Mental Health Journal*, 33(1), 55-69. <https://doi.org/10.1002/imhj.20295>  
31  
32 Shin, S.E., Kim, N.S., Jang, E.Y., 2011. Comparison of problematic internet and alcohol use and  
33 attachment styles among industrial workers in Korea. *Cyberpsychol Behav Soc Netw.* 14, 665-  
34 72. <https://doi.org/10.1089/cyber.2010.0470> .  
35  
36 Sroufe LA, Carlson EA, Levy AK, Egeland B. 1999. Implications of attachment theory for  
37 developmental psychopathology. *Dev Psychopathol.* 11, 1-13.  
38 <https://doi.org/10.1017/s0954579499001923>  
39  
40 Sroufe, L. A., 2005. Attachment and development: A prospective, longitudinal study from birth to  
41 adulthood. *Attachment & human development*, 7(4), 349-367.  
42 <https://doi.org/10.1080/14616730500365928>  
43  
44 Starks, T.J., Millar, B.M., Tuck, A.N., Wells, B.E., 2015. The role of sexual expectancies of substance  
45 use as a mediator between adult attachment and drug use among gay and bisexual men. *Drug*  
46 *Alcohol Depend.* 153, 187-93. <https://doi.org/10.1016/j.drugalcdep.2015.05.028> .  
47  
48 Stojakovic, A., Walczak, M., Cieślak, P.E., Trenk, A., Sköld, J., Zajdel, J., Mirrasekhian, E., Karlsson,  
49 C., Thorsell, A., Heilig, M., Parkitna, J.R., Błasiak, T., Engblom, D., 2018. Several behavioral traits  
50 relevant for alcoholism are controlled by  $\gamma 2$  subunit containing GABAA receptors on dopamine  
51 neurons in mice. *Neuropsychopharmacology* 43, 1548–1556. <https://doi.org/10.1038/s41386-018-0022-z>  
52  
53 Strathearn, L., Mertens, C.E., Mayes, L., Rutherford, H., Rajhans, P., Xu, G., Potenza, M.N., Kim, S.,  
54 2019. Pathways Relating the Neurobiology of Attachment to Drug Addiction. *Front. Psychiatry* 10,  
55 1–15. <https://doi.org/10.3389/fpsy.2019.00737>  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Su, J., Supple, A.J., Leerkes, E.M., Kuo, S.I.C., 2019. Latent trajectories of alcohol use from early  
5 adolescence to young adulthood: Interaction effects between 5-HTTLPR and parenting quality and  
6 gender differences. *Dev. Psychopathol.* 31, 457–469. <https://doi.org/10.1017/S095457941800024X>  
7  
8 Sun, J., Kranzler, H.R., Gelernter, J., Bi, J., 2020. A genome-wide association study of cocaine use  
9 disorder accounting for phenotypic heterogeneity and gene–environment interaction. *J. Psychiatry*  
10 *Neurosci.* 45, 34–44. <https://doi.org/10.1503/jpn.180098>  
11  
12 Sundar, M., Patel, D., Young, Z., & Leong, K. C., 2021. Oxytocin and Addiction: Potential Glutamatergic  
13 Mechanisms. *Int. J. Mol. Sci.*, 22(5), 2405. <https://doi.org/10.3390/ijms22052405>  
14  
15 Taylor-Seehafer, M., Jacobvitz, D., Steiker, L.H., 2008. Patterns of attachment organization, social  
16 connectedness, and substance use in a sample of older homeless adolescents: Preliminary findings.  
17 *Fam. Community Heal.* 31, S81-8. <https://doi.org/10.1097/01.FCH.0000304021.05632.a1>  
18  
19 Thorberg, F.A., Lyvers, M., 2006. Attachment, fear of intimacy and differentiation of self among clients  
20 in substance disorder treatment facilities. *Addict Behav.* 31, 732-737.  
21 <https://doi.org/10.1016/j.addbeh.2005.05.050>  
22  
23 Thorberg, F.A., Young, R.M., Sullivan, K.A., Lyvers, M., Connor, J.P., Feeney, G.F. *Addict Behav.*,  
24 2011. Alexithymia, craving and attachment in a heavy drinking population. 36, 427-30.  
25 <https://doi.org/10.1016/j.addbeh.2010.12.016>  
26  
27 Tops, M., Koole, S.L., Ijzerman, H., Buisman-Pijlman, F.T.A., 2014. Why social attachment and  
28 oxytocin protect against addiction and stress: Insights from the dynamics between ventral and dorsal  
29 corticostriatal systems. *Pharmacol. Biochem. Behav.* 119, 39–48.  
30 <https://doi.org/10.1016/j.pbb.2013.07.015>  
31  
32 Torresani, S., Favaretto, E., Zimmermann, C., 2000. Parental representations in drug-dependent patients  
33 and their parents. *Compr. Psychiatry* 41, 123–129. [https://doi.org/10.1016/S0010-440X\(00\)90145-7](https://doi.org/10.1016/S0010-440X(00)90145-7)  
34  
35 Tremblay, M., Baydala, L., Khan, M., Currie, C., Morley, K., Burkholder, C., Davidson, R., Stillar, A.,  
36 2020. Primary Substance Use Prevention Programs for Children and Youth: A Systematic Review.  
37 *Pediatrics* 146, e20192747. <https://doi.org/10.1542/peds.2019-2747>  
38  
39 Tyrka, A.R., Parade, S.H., Welch, E.S., Ridout, K.K., Price, L.H., Marsit, C., Philip, N.S., Carpenter,  
40 L.L., 2016. Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations  
41 with early adversity and depressive, anxiety and substance-use disorders. *Transl. Psychiatry* 6, e848.  
42 <https://doi.org/10.1038/tp.2016.112>  
43  
44 UN General Assembly, 2016. Resolution adopted by the General Assembly on 19 April 2016. S-30/1.  
45 Our joint commitment to effectively addressing and countering the world drug problem. *Ungass*  
46 56350, 1–27.  
47  
48 Unternaehrer E, Meyer AH, Burkhardt SCA, Dempster E, Staehli S, Theill N, Lieb R, Meinschmidt G,  
49 2015. Childhood maternal care is associated with DNA methylation of the genes for brain-derived  
50 neurotrophic factor (BDNF) and oxytocin receptor (OXR) in peripheral blood cells in adult men and  
51 women. *Stress* 18, 451–461.  
52  
53 Unterrainer, H.F., Hiebler, M., Ragger, K., Froehlich, L., Koschutnig, K., Schoeggl, H., Kapfhammer,  
54 H.P., Papousek, I., Weiss, E.M., Fink, A. 2016. White matter integrity in polydrug users in relation to  
55 attachment and personality: a controlled diffusion tensor imaging study. *Brain Imaging Behav.*  
56 10:1096-1107. doi: 10.1007/s11682-015-9475-4.  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Unterrainer, H.F., Hiebler-Ragger, M., Koschutnig, K., Fuchshuber, J., Tscheschner, S., Url, M.,  
5 Wagner-Skacel, J., Reininghaus, E.Z., Papousek, I., Weiss, E.M., Fink, A., 2017. Addiction as an  
6 attachment disorder: White matter impairment is linked to increased negative affective states in poly-  
7 drug use. *Front. Hum. Neurosci.* 11, 1–11. <https://doi.org/10.3389/fnhum.2017.00208>  
8  
9  
10 Unterrainer, H.F., Hiebler-Ragger, M., Roggen, L., Kapfhammer, H.P., 2018. Addiction as an attachment  
11 disorder. *Der Nervenarzt* . 89, 1043-1048. <https://doi.org/10.1007/s00115-017-0462-4>.  
12  
13 Vaht, M., Kurrikoff, T., Laas, K., Veidebaum, T., & Harro, J. (2016). Oxytocin receptor gene variation  
14 rs53576 and alcohol abuse in a longitudinal population representative study.  
15 *Psychoneuroendocrinology*, 74, 333-341.  
16  
17 Van Der Vorst, H., Engels, R.C.M.E., Meeus, W., Deković, M., Vermulst, A., 2006. Parental attachment,  
18 parental control, and early development of alcohol use: A longitudinal study. *Psychol. Addict. Behav.*  
19 20, 107–116. <https://doi.org/10.1037/0893-164X.20.2.107>  
20  
21 van der Zwaluw, C. S., & Engels, R. C. M. E., 2009. Gene–environment interactions and alcohol use and  
22 dependence: Current status and future challenges. *Addiction* 104, 907–914.  
23 <https://doi.org/10.1111/j.1360-0443.2009.02563.x>  
24  
25 Van Der Zwaluw, C.S., Engels, R.C.M.E., Vermulst, A.A., Franke, B., Buitelaar, J., Verkes, R.J.,  
26 Scholte, R.H.J., 2010. Interaction between dopamine D2 receptor genotype and parental rule-setting  
27 in adolescent alcohol use: Evidence for a gene-parenting interaction. *Mol. Psychiatry* 15, 727–735.  
28 <https://doi.org/10.1038/mp.2009.4>  
29  
30 Van Ijzendoorn, M.H., Caspers, K., Bakermans-Kranenburg, M.J., Beach, S.R.H., Philibert, R., 2010.  
31 Methylation matters: Interaction between methylation density and serotonin transporter genotype  
32 predicts unresolved loss or trauma. *Biol. Psychiatry* 68, 405–407.  
33 <https://doi.org/10.1016/j.biopsych.2010.05.008>  
34  
35 Van Tol, H. H., Wu, C. M., Guan, H. C., Ohara, K., Bunzow, J. R., Civelli, O., Kennedy, J., Seeman, P.,  
36 Niznik, H. B., & Jovanovic, V. 1992. Multiple dopamine D4 receptor variants in the human  
37 population. *Nature*. 358, 149-152. <https://doi:10.1038/358149a0>  
38  
39 Vaske, J., Newsome, J., Wright, J.P., 2012. Interaction of serotonin transporter linked polymorphic  
40 region and childhood neglect on criminal behavior and substance use for males and females. *Dev.*  
41 *Psychopathol.* 24, 181–193. <https://doi.org/10.1017/S0954579411000769>  
42  
43 Vink, J.M., 2016. Genetics of addiction: Future focus on gene × environment interaction? *J. Stud.*  
44 *Alcohol Drugs* 77, 684–687. <https://doi.org/10.15288/jsad.2016.77.684>  
45  
46 Vinkers, C.H., Van Gastel, W.A., Schubart, C.D., Van Eijk, K.R., Luykx, J.J., Van Winkel, R., Joëls,  
47 M., Ophoff, R.A., Boks, M.P.M., 2013. The effect of childhood maltreatment and cannabis use on  
48 adult psychotic symptoms is modified by the COMT Val158Met polymorphism. *Schizophr. Res.* 150,  
49 303–311. <https://doi.org/10.1016/j.schres.2013.07.020>  
50  
51 Virkkunen, M., Eggert, M., Rawlings, R., Linnoila, M., 1996. A prospective follow-up study of alcoholic  
52 violent offenders and fire setters. *Arch. Gen. Psychiatry* 53, 523–529.  
53 <https://doi.org/10.1001/archpsyc.1996.01830060067009>  
54  
55 Vismara, L., Presaghi, F., Bocchia, M., Ricci, R.V., Ammaniti, M., 2019. Attachment Patterns in Subjects  
56 Diagnosed With a Substance Use Disorder: A Comparison of Patients in Outpatient Treatment and  
57 Patients in Therapeutic Communities. *Front. Psychiatry* 10, 1–12.  
58 <https://doi.org/10.3389/fpsy.2019.00807>  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic Advances from the Brain Disease  
5 Model of Addiction. *N. Engl. J. Med.* 374, 363–371. <https://doi.org/10.1056/nejmra1511480>.  
6
- 7 Vrettou, M., Nilsson, K.W., Tuvblad, C., Rehn, M., Åslund, C., Andershed, A.K., Wallén-Mackenzie,  
8 Å., Andershed, H., Hodgins, S., Nylander, I., Comasco, E., 2019. VGLUT2 rs2290045 genotype  
9 moderates environmental sensitivity to alcohol-related problems in three samples of youths. *Eur.*  
10 *Child Adolesc. Psychiatry* 28, 1329–1340. <https://doi.org/10.1007/s00787-019-01293-w>  
11
- 12 Vungkhanching, M., Sher, K.J., Jackson, K.M., Parra, G.R., 2004. Relation of attachment style to family  
13 history of alcoholism and alcohol use disorders in early adulthood. *Drug Alcohol Depend.* 75,  
14 47-53. <https://doi.org/10.1016/j.drugalcdep.2004.01.013>  
15
- 16 Walsh, A., 1995. Parental attachment, drug use, and facultative sexual strategies. *Soc. Biol.* 42, 95–107.  
17 <https://doi.org/10.1080/19485565.1995.9988890>  
18
- 19 Wang, J., Qin, W., Liu, B., Wang, D., Zhang, Y., Jiang, T., & Yu, C. (2013). Variant in OXTR gene and  
20 functional connectivity of the hypothalamus in normal subjects. *Neuroimage*, 81, 199-204.  
21
- 22 Wedekind, D., Bandelow, B., Heitmann, S., Havemann-Reinecke, U., Engel, K.R., Huether, G., 2013.  
23 Attachment style, anxiety coping, and personality-styles in withdrawn alcohol addicted  
24 inpatients. *Subst Abuse Treat Prev Policy.* 8,1. <https://doi.org/10.1186/1747-597X-8-1>  
25
- 26 Whitesell, M., Bachand, A., Peel, J., Brown, M., 2013. Familial, Social, and Individual Factors  
27 Contributing to Risk for Adolescent Substance Use. *J. Addict.* 2013, 1–9.  
28 <https://doi.org/10.1155/2013/579310>  
29
- 30 Willis, A.S., Wallston, K.A., & Johnson, K.R. S., 2001. Tobacco and alcohol use among young adults:  
31 Exploring religious faith, locus of health control, and coping strategies as predictors. In T. G. Plante,  
32 & A. C. Sherman (Eds.), *Faith and health: Psychological perspectives*, Guilford Press, New York, pp.  
33 213-239.  
34
- 35 Winham, K.M., Engstrom, M., Golder, S., Renn, T., Higgins, G.E., Logan, T.K., 2015. Childhood  
36 victimization, attachment, psychological distress, and substance use among women on probation  
37 and parole. *Am J Orthopsychiatry.* 85, 45-158. <https://doi.org/10.1037/ort0000038>  
38
- 39 Wise, M.H., Weierbach, F., Cao, Y., Phillips, K., 2017. Tobacco Use and Attachment Style in  
40 Appalachia. *Issues Ment Health Nurs.* 38, 562-569.  
41 <https://doi.org/10.1080/01612840.2017.1312651>  
42
- 43 Zakhour, M., Haddad, C., Salameh, P., Akel, M., Fares, K., Sacre, H., Hallit, S., Obeid, S., 2020. Impact  
44 of the interaction between alexithymia and the adult attachment styles in participants with alcohol  
45 use disorder. *Alcohol.* 83, 1-8. <https://doi.org/10.1016/j.alcohol.2019.08.007>  
46
- 47 Zaso, M.J., Goodhines, P.A., Wall, T.L., Park, A., 2019. Meta-Analysis on Associations of Alcohol  
48 Metabolism Genes with Alcohol Use Disorder in East Asians. *Alcohol Alcohol.* 54, 216–224.  
49 <https://doi.org/10.1093/alcalc/agz011>  
50
- 51 Zdankiewicz-Ścigała, E., Ścigała, D.K., 2020. Attachment Style, Early Childhood Trauma, Alexithymia,  
52 and Dissociation Among Persons Addicted to Alcohol: Structural Equation Model of  
53 Dependencies. *Front Psychol.* 10, 2957. <https://doi.org/10.3389/fpsyg.2019.02957>  
54
- 55 Zdankiewicz-Ścigała, E., Ścigała, D.K., 2018. Relationship Between Attachment Style in  
56 Adulthood, Alexithymia, and Dissociation in Alcohol Use Disorder Inpatients. *Mediational*  
57 *Model. Psychol.* 9, 2039. <https://doi.org/10.3389/fpsyg.2018.02039>  
58
- 59 Zeinali, A., Sharifi, H., Enayati, M., Asgari, P., Pasha, G., 2011. The mediational pathway among  
60 parenting styles, attachment styles and self-regulation with addiction susceptibility of  
61  
62  
63  
64  
65

1  
2  
3  
4 adolescents. J Res Med Sci. 16, 1105-1121.

5 <http://www.ncbi.nlm.nih.gov/pmc/articles/pmc3430035/>

6 Zhai, Z.W., Kirisci, L., Tarter, R.E., Ridenour, T.A., 2014. Psychological dysregulation during  
7 adolescence mediates the association of parent-child attachment in childhood and substance use  
8 disorder in adulthood. Am. J. Drug Alcohol Abuse 40, 67–74.  
9 <https://doi.org/10.3109/00952990.2013.848876>

10  
11 Zhang, H., Wang, F., Kranzler, H.R., Zhao, H., Gelernter, J., 2013. Profiling of childhood adversity-  
12 associated DNA methylation changes in alcoholic patients and healthy controls. PLoS One 8, e65648.  
13 <https://doi.org/10.1371/journal.pone.0065648>

14  
15 Zhang, Y., Wang, D., Johnson, A.D., Papp, A.C., Sadée, W., 2005. Allelic expression imbalance of  
16 human mu opioid receptor (OPRM1) caused by variant A118G. J. Biol. Chem. 280, 32618–32624.  
17 <https://doi.org/10.1074/jbc.M504942200>  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## Figure Captions

**Figure 1.** PRISMA Flow diagram

**Figure 2.** Addiction is not a self-fulfilling prophecy.

**Note.** Environmental and genetic factors, alongside adverse childhood experiences, could concur to determine, through parental attachment relationships, a potential vulnerability to substance use, by way of epigenetic and neuroendocrine mechanisms. High risk genotypes could influence early environment through active, passive and evocative gene\*environment correlations (rGE). Gene-environment interplay, in turn, could activate a cascade of neuroendocrine changes in monoaminergic, HPA-axis, opioidergic and oxytocinergic systems, which ultimately determine vulnerability to addiction. Epigenetic changes induced by the early exposure to high risk environment seem to further exacerbate the burden of genetic predisposition. We hypothesized that epigenetic changes, induced by positive and caring parenting, could change these trajectories, reducing the expression of the high risk genotypes and potentiating the expression of protective ones. ACEs: Adverse Childhood experiences; COMT: Catechol-O-Methyltransferase and the Monoamine Oxidases A genes; CRH-R1: Corticotropin-Releasing Hormone Receptor 1 gene; DAT1: Dopamine Transporter 1 gene; DRD4 and DRD2: Dopamine Receptor D4 and D2 genes; FKBP5: glucocorticoid receptor co-chaperone FK506-binding protein 5 gene; GR-NR3C1: Glucocorticoid Receptor gene; 5-HIAA: Serotonin metabolite 5-hydroxyindoleacetic Acid 5-HTTLPR: Serotonin Transporter Linked Promoter Region gene; HVA: Dopamine metabolite Homovanillic Acid; MAOA: Monoamine Oxidase A gene; OPRL1: Opioid Related Nociceptin Receptor 1 gene; OPRM1: mu-Opioid Receptor 1 gene; OXTR: Oxytocin Receptor gene; PRL: prolactine

14  
15  
16  
17  
18  
19 **Tables.**

20  
21 **Table 1.** Studies on the genetic factors associated with attachment and Substance Use Disorder  
22  
23

24  
25  
26  
27  
28  
29

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
<b>Monoamines</b>								
Althaus et al., 2009	The Netherlands	65	Children with Pervasive Developmental Disorder or Attention Deficit Hyperactivity Disorder and healthy controls, aged 10-12	Potential correlation with a reward deficit syndrome	Dopamine receptor gene (DRD2) / ankyrin repeat and kinase domain containing 1 (ANKK1): Taq1 A allele polymorphism	Attachment	Electrocortical event-related potentials	Cross-sectional
Brody et al., 2014	USA	502	Youths, aged 16 through 18	Any substances	Dopamine receptor gene (DRD4): alleles with 7 or more repeats (7R+)	Parenting	Strong African American Families-Teen program	Longitudinal
Fite et al., 2018	USA	500	Adults, aged 18-25	Cannabis and tobacco	Monoamine oxidase A gene (MAO-A): upstream variable number tandem repeat (uVNRT) polymorfism	ACEs	-	Cross-sectional
Gerra et al., 2007	Italy	96	Male patients with cocaine use disorder, aged 19-25 years	Cocaine	Serotonin transporter promoter gene (5-HTTLPR)	Parenting	-	Cross-sectional
Gerra et al., 2010	Italy	187	Youths, aged 14-19	Any illicit substances	Serotonin transporter promoter gene (5-HTTLPR)	ACEs	-	Cross-sectional
Gerra et al., 2019	Italy	185	Patients with cannabis use disorder and healthy	Cannabis	Dopamine receptor gene (DRD2) / ankyrin	ACEs and parenting	-	Cross-sectional

30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

			controls, aged 19-25		repeat and kinase domain containing 1 (ANKK1): Taq1 A allele polymorphism			
Laucht et al., 2012	Germany	285	Youths, aged 15-19	Alcohol	Catechol-O-methyltransferase (COMT) gene: Val(158)Met polymorphism	Parenting	-	Longitudinal
Li et al., 2012	China	450	Patients with opioid use disorder, aged 26-41	Heroin	Catechol-O-methyltransferase (COMT) gene: rs737866 single nucleotide polymorphism	ACEs	-	Cross-sectional
Olsson et al., 2011	Australia	839	Youths, aged 14 through 24	Nicotine, cannabis and alcohol	Dopamine receptor gene (DRD4): alleles with 7 or more repeats (7R+)	Attachment	-	Longitudinal
Ossola et al., 2021	Italy	107	Adult Children of Alcoholic Parents (ACOAs)	Alcohol	Serotonin transporter promoter gene (5-HTTLPR); dopamine receptor gene (DRD2) / ankyrin repeat and kinase domain containing 1 (ANKK1): Taq1 A allele polymorphism	ACEs	-	Cross-sectional
Park et al., 2011	USA	234	Adults, aged 18 through 34	Alcohol	Dopamine receptor gene (DRD4): 4 variable number tandem repeat (VNTR) polymorphism	ACEs	-	Longitudinal
Vaske et al., 2012	USA	2403	Youths, aged 11 through 26	Cannabis	Serotonin transporter promoter gene (5-HTTLPR)	ACEs	-	Longitudinal
Vinkers et al., 2013	The Netherlands	918	Adults, aged 18-25	Cannabis	Catechol-O-methyltransferase (COMT) gene: Val(158)Met polymorphism	ACEs	-	Cross-sectional
<b>Hypothalamic-Pituitary-Adrenal axis</b>								

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Nylander et al., 2017	Sweden	838	Male adults, aged 20-24	Alcohol	FK506-binding protein (FKBP5): rs1360780 single nucleotide polymorphism	Attachment	-	Cross-sectional
Rovaris et al., 2015	Brazil	139	Female patients with cocaine use disorder, aged 25-35	Cocaine	Mineralocorticoid (NR3C2) and glucocorticoid (NR3C1) receptor genes: rs5522 and rs6198 single nucleotide polymorphisms	ACEs	-	Cross-sectional
Schmid et al., 2010	Germany	270	Youths, aged 15 through 19	Alcohol	Corticotropin-releasing hormone receptor 1 (CRHR1): rs242938 and rs1876831 single nucleotide polymorphisms	ACEs	-	Longitudinal
<b>Opioids</b>								
Cimino et al., 2020	Italy	150	Children, aged 8-9	- (general psychopathology)	$\mu$ -opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Copeland et al., 2011	USA	226	Children, aged 9-17	Any substances	$\mu$ -opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Noto et al., 2020	Japan	725	Healthy adults, aged 18-35	- (personality traits)	$\mu$ -opioid receptor gene: A118G single nucleotide polymorphism	Parenting	-	Cross-sectional
<b>Oxytocin</b>								
Dannlowski et al., 2016	Germany	309	Healthy adults, aged 18-59	-	Oxytocin receptor gene (OXTR): rs53576 single nucleotide polymorphism of G-allele	ACEs	Facial emotions responsiveness in fMRI	Cross-sectional
<b>Others</b>								
Carey et al., 2015	USA	1,558	Patients with Opioid or Alcohol Use Disorders and	Cannabis	6 endocannabinoid (eCB) genes: anabolism (DAGLA, DAGLB, NAPEPLD),	ACEs	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

			healthy controls, aged 18-50		catabolism (MGLL, FAAH), binding (CNR1)			
Csala et al., 2015	Hungary	232	Patients with Nicotine Use Disorder, aged 38-64	Nicotine	Neural nicotinic acetylcholinergic receptors gene (nAChR): rs2072660 single nucleotide polymorphism of $\beta 2$ subunit	Parenting	-	Cross-sectional
Vrettou et al., 2019	Sweden	3612	Youths, aged 14-22	Alcohol	Vesicular Glutamate Transporter 2 gene (VGLUT2): rs2290045 single nucleotide polymorphism	Attachment and ACEs	-	Cross-sectional
Beach et al., 2015	USA	183	Young adult, aged 17 through 22	Alcohol and nicotine	Telomere length	Parenting	-	Longitudinal
Sun et al., 2020	USA	9965	Adults, aged 25-55	Cocaine	Genome-Wide Association Study (GWAS)	ACEs	-	Cross-sectional

**Note.** ACEs= Adverse Childhood Experiences: retrospective scales on perceived maltreatment, physical/sexual abuse and neglect were included.

Attachment: includes retrospective measures of child-parents relationship, as well as direct measures of attachment in childhood

Parenting: evaluations of positive and negative parenting were included.

**Table 2.** Studies on the epigenetic mechanisms associated with attachment and Substance Use Disorder.

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
<b>Monamines</b>								
Bendre et al., 2018	Sweden	53	Male patients with Substance Use Disorders, aged 16 through 21	Alcohol	Monoamine oxidase A gene (MAO-A): methylation of the first exon and intron of the upstream variable number of tandem repeats (VNTR)	ACEs and parenting	-	Longitudinal

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

De Nardi et al., 2020	Italy	79	Youths, aged 18-34	Internet addiction	Dopamine transporter gene (DAT1): methylation of the 5'-untranslated region (UTR) variable number of tandem repeats (VNTR)	Attachment	-	Cross-sectional
<b>Hypothalamic-Pituitary-Adrenal axis</b>								
Tyrka et al., 2016	USA	340	Adults, aged 18-65	Any substance	Glucocorticoid receptor gene (NR3C1): methylation of exon 1F of the promoter region	ACEs	Dexamethasone/corticotropin releasing hormone test	Cross-sectional
<b>Opioids</b>								
NONE								
<b>Oxytocin</b>								
Kogan et al., 2018	USA	358	Adults, aged 18 through 19	Any substance	Oxytocin receptor gene (OXTR): methylation of the promoter region	ACEs	-	Longitudinal

**Table 3.** Studies on the neuroendocrine mechanisms associated with attachment and Substance Use Disorder

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
<b>Monoamines</b>								
Berglund et al., 2013	Sweden	18	Male patients with Alcohol Use Disorder, aged 35-55	Alcohol	Serum prolactine reactivity	ACEs	Prolactin response to a selective 5-HT reuptake inhibitor (citalopram)	Cross-sectional
Gerra et al. 2007	Italy	126	Patients with Opioid and Cocaine Use Disorder and healthy control, aged 22-35	Opioid and cocaine	Serum homovanillic acid	ACEs	-	Cross-sectional
Gerra et al. 2009a	Italy	94	Male patients with Cocaine Use	Cocaine	Serum homovanillic acid, prolactine,	ACEs and parenting	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

			Disorder and healthy controls, aged 20-36		adrenocorticotrophic hormone (ACTH) and cortisol			
Oswald et al., 2014	USA	28	Adults, aged 18-29	Amphetamine	Intrasynaptic dopamine release observed with the positron emission tomography (PET)	ACEs	-	Cross-sectional
Roy et al. 2002	USA	29	Male patients with Cocaine Use Disorder, aged 35-45	Cocaine	Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid	ACEs	-	Cross-sectional
Virkkunen et al. 1996	Finland	114	Male offenders with Cocaine Use Disorder, aged 18-45	Alcohol	Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid	ACEs	-	Cross-sectional
<b>Hypothalamic-Pituitary-Adrenal axis</b>								
Dawes et al. 1999	USA	297	Sons of fathers with substance abuse disorders and healthy controls, aged 10-22	Any substance	Serum testosterone, dehydrotestosterone and cortisol reactivity	ACEs	Auditory evoked potential task	Cross-sectional
Doan et al. 2014	USA	162	Children, aged 8 through 17	Any substance	Serum cortisol, epinephrine, norepinephrine	ACEs	-	Longitudinal
Flanagan et al. 2015	USA	31	Patients with Cocaine Use Disorder, aged 33-51	Cocaine	Salivary cortisol and dehydroepiandrosterone reactivity	ACEs	Intranasal oxytocin and Trier Social Stress Test (TSST)	Cross-sectional
Gerra et al. 2008	Italy	126	Patients with Opioid and Cocaine Use Disorder and healthy control, aged 22-35	Opioid and cocaine	Serum adrenocorticotrophic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional
Gerra et al. 2009a	Italy	94	Male patients with Cocaine Use Disorder and healthy controls, aged 20-36	Cocaine	Serum homovanillic acid, prolactine, adrenocorticotrophic hormone (ACTH) and cortisol	ACEs and parenting	-	Cross-sectional
Gerra et al. 2009b	Italy	187	Youths experimenters of illegal drugs and healthy controls, aged 14-19	Any illicit substance	Serum adrenocorticotrophic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Gerra et al. 2014	Italy	30	Male patients with Opioid Use Disorder, aged 22-35	Opioid	Serum adrenocorticotrophic hormone (ACTH) and cortisol reactivity	ACEs	Neutral and unpleasant pictures selected from the International Affective Picture System Self-assessment Manikin procedure	Cross-sectional
Gerra et al. 2016	Italy	100	Male patients with Nicotine Use Disorder and healthy controls, aged 20-50	Nicotine	Serum adrenocorticotrophic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotrophic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides $\alpha$ -melanocyte stimulating hormone (MSH) and $\beta$ -endorphin (END)	ACEs	Treatment with diamorphine	Cross-sectional
Hagan et al. 2019	USA	160	Adults, aged 24-28	Alcohol	Salivary cortisol reactivity	ACEs	Modified Trier Social Stress Test (TSST)	Cross-sectional
Hood et al. 2020	USA	144	Adults, aged 18-45	Nicotine	Salivary cortisol reactivity	ACEs	Intranasal oxytocin and Trier Social Stress Test (TSST)	Cross-sectional
Levandowski et al. 2016	Brazil	132	Female patients with Cocaine Use Disorder and healthy controls, aged 18-55	Cocaine	Serum cortisol and cytokines	ACEs	-	Cross-sectional
Marceau et al. 2019	The Netherlands	591	Youths, aged 16	Alcohol, nicotine and marijuana	Salivary cortisol reactivity	Parenting	Trier Social Stress Test (TSST)	Cross-sectional
Moran-Santa Maria et al. 2010	USA	85	Patients with Cocaine Use Disorder and healthy controls, aged 24-51	Cocaine	Serum ACTH and cortisol reactivity	ACEs	Corticotropin-releasing hormone (CRH) challenge and Trier Social Stress Test (TSST)	Cross-sectional
Muehlhan et al. 2018	Germany	130	Patients with Alcohol Use Disorder and healthy controls, aged 18-65	Alcohol	Salivary and serum ACTH and cortisol reactivity and hair cortisol concentrations (HCC)	ACEs	Trier Social Stress Test (TSST)	Cross-sectional
Negriff et al. 2015	USA	254	Youths, aged 10 through 18	Alcohol and cannabis	Salivary cortisol reactivity	ACEs	Trier Social Stress Test (TSST) modified for children	Longitudinal

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Pirnia et al. 2019	Iran	195	Patients with Methamphetamine Use Disorder, aged 18-35	Methamphetamine	Salivary cortisol	ACEs	-	Cross-sectional
Roy et al. 2002	USA	29	Male patients with Cocaine Use Disorder, aged 35-45	Cocaine	Urinary free cortisol (UFC)	ACEs	-	Cross-sectional
Schäfer et al. 2010	Germany	38	Patients with Alcohol Use Disorder, aged 18-65	Alcohol	Serum ACTH and cortisol	ACEs	-	Cross-sectional
<b>Opioids</b>								
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotrophic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides $\alpha$ -melanocyte stimulating hormone (MSH) and $\beta$ -endorphin (END)	ACEs	Treatment with diamorphine	Cross-sectional
<b>Oxytocin</b>								
Fuchshuber et al, 2020	United Kingdom	48	Male patients with poly-Substance Use Disorder and healthy control, aged 19-38	Any substance	Serum OT reactivity	Attachment	Adult Attachment Projective Picture System (AAP)	Cross-sectional
Gerra et al. 2017	Italy	18	Male patients with Opioid Use Disorder and healthy control, aged 21-48	Opioid	Serum OT	ACEs	-	Cross-sectional
Huang et al. 2018	Taiwan	130	Patients with Ketamine Use Disorder and healthy control, aged 18-60	Ketamine	Serum OT	ACEs	-	Cross-sectional

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**EARLY PARENT-CHILD ATTACHMENT INTERACTIONS AND SUBSTANCE USE DISORDER: AN —ATTACHMENT PERSPECTIVE ON A—AS BIOPSYCHOSOCIAL ENTANGLEMENT.**

Maria Lidia Gerra <sup>a</sup>, Maria Carla Gerra <sup>b</sup>, Leonardo Tadonio <sup>a</sup>, Pietro Pellergini <sup>a</sup>, Carlo Marchesi <sup>c</sup>, Elizabeth Mattfeld <sup>d</sup>, Gilberto Gerra <sup>a</sup>, Paolo Ossola <sup>b\*</sup>

(a) Department of Mental Health, AUSL of Parma, Parma, Italy

[magerra@ausl.pr.it](mailto:magerra@ausl.pr.it); [ltadonio@ausl.pr.it](mailto:ltadonio@ausl.pr.it); [ppellegrini@ausl.pr.it](mailto:ppellegrini@ausl.pr.it); [ggerra@ausl.pr.it](mailto:ggerra@ausl.pr.it);

(b) Center for Neuroplasticity and Pain (CNAP), SMI®, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark.

[mcg@hst.aau.dk](mailto:mcg@hst.aau.dk)

(c) Psychiatry Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy

[paolo.ossola@unipr.it](mailto:paolo.ossola@unipr.it); [carlo.marchesi@unipr.it](mailto:carlo.marchesi@unipr.it);

(d) Drug Prevention and Health Branch, Prevention Treatment and Rehabilitation Section, United Nations Office on Drugs and Crime, Vienna, Austria

[Elizabeth.mattfeld@un.org](mailto:Elizabeth.mattfeld@un.org)

\* Paolo Ossola, MD

Psychiatry Unit, Department of Medicine and Surgery, University of Parma

Padiglione Braga #21

Via Antonio Gramsci 14

43126 Parma (PR) Italy

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**Abstract**

This review aims to elucidate environmental and genetic factors, as well as their epigenetic and neuroendocrine moderators, that may underlie the association between early childhood experiences and Substance Use Disorders (SUD), through the lens of parental attachment.

Here we review those attachment-related studies that examined the monoaminergic systems, the hypothalamic pituitary adrenal stress response system, the oxytoninergic system, and the endogenous opioid system from a genetic, epigenetic, and neuroendocrine perspective.

Overall, the selected studies point to a moderating effect of insecure attachment between genetic vulnerability and SUD, reasonably through epigenetic modifications. Preliminary evidence suggests that vulnerability to SUDs is related with hypo-methylation (e.g. hyper-expression) of high-risk polymorphisms on the monoaminergic and hypothalamic pituitary adrenal system and hyper-methylation (e.g. hypo-expressions) of protective polymorphisms on the opioid and oxytocin system. These epigenetic modifications may induce a cascade of neuroendocrine changes contributing to the subclinical and behavioral manifestations that precede the clinical onset of SUD. Protective and supportive parenting could hence represent a key therapeutic target to prevent addiction and moderate insecure attachment.

**Keywords.** ~~Parental~~ attachment; Substance use; genetic; epigenetic; neuroendocrine;

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**1. Introduction**

In many societies, addiction is still unrecognized as a health problem and many people suffering from it are stigmatized with limited or no access to diagnosis, treatment and rehabilitation. This dramatic discrimination reflects a moralistic view, which considers addiction as a failure of righteous values and subjects with Substance Use Disorder (SUD) as people with simply a dysfunctional personality (Pickard, 2017).

Two opposing theories attempt to define the behavioural component of substance use disorders. On one side some authors, based on classic models of learning from reward, suggested that addiction is a voluntary behaviour, governed by universal principles of choice and motivation and influenced by preferences and goals (Heyman, 2009; Frank & Nagel, 2017; Henden et al, 2013). By contrast other authors pointed that addiction is deeply rooted in neurobiological modification (Volkow et al., 2016) that imply a primary impairment in decision-making, self-control and emotion regulation. According to the latter becoming addicted involves a transition from voluntary to non-voluntary compulsive drug use (Mollick & Kober, 2020).

Although moving from a moralistic to a biological model had strong implications for public attitudes and policies, the belief that SUD could be explained ultimately in terms of specific dysfunctional neurobiological conditions risks to be a reductionist explanation, which may underestimate the social and psychological causes and consequences of addiction (Borsboom et al. 2019).

Indeed, a growing body of evidence suggests a greater complexity in the pathogenesis of addiction, which begins early after conception and involves concurring genetic, epigenetic and neuroendocrine modifications. In this view, SUD is conceptualized as a “developmental disorder”, with genetic, and environmental antecedents (McCrorry and Mayes, 2015).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

The dynamic in the early relationships seems to impact mostly on the future vulnerability to SUD (Knudsen et al., 2004). Hence here we decided to focus on the early parental attachment that may represent the very first potential protective element acting against vulnerabilities toward SUD, not simply a risk factor.

**1.1. Attachment**

Attachment has been defined as a bond between an individual and a caregiver, based on the need for safety and protection (Bowlby, 1969).

A secure attachment emerges from the encounter between the temperamental characteristics of the infant and the sensitivity of the caregiver, intended as responding with availability and responsiveness to child signals (Holmes & Holmes, 2014). The secure child is able to use the parent as a secure base from which to explore the environment and is easy to console after separation or when otherwise stressed (Ainsworth et al., 1978).

By contrast, an insecure attachment develops as a form of adaptation to mis-attuned parenting. Insecure attachment emerges when infants have difficulty using the caregivers as a secure base, because at times the parent or caregiver responses are intrusive or they are emotionally unavailable. Based on the infant response behaviour when the caregiver interacts with strangers or leaves them alone, insecure attachments are divided into avoidant ~~or~~ ambivalent ~~or disorganized~~. It is defined avoidant attachment when infants do not exhibit distress upon separation and do not seek contact after the caregiver's return. Children with ambivalent attachment, instead, are extremely distressed when left alone and alternate behaviours of seeking contact with and resisting to the caregivers after separation.

Disorganized attachment is the most extreme of insecure ~~attachments, attachments~~; this is often a consequence of a trauma, such as interpersonal neglect or psychological, physical or sexual abuse, with aspects of neurodevelopment vulnerability in the child (Main et al., 2005). The children exhibit

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

contradictory and unpredictable behavioural patterns of interaction with the caregiver, in the form of wandering, confusion, freezing, and undirected movements.

Attachment research extended into adolescence and adulthood has suggested that there is continuity from attachment in infancy and romantic attachment in adulthood. In line with this evidences adolescents and adults' mental representations of attachment to their parents during childhood are the foundation on which state of mind with respect to one's current relationship partners during adulthood is constructed. Dismissing (i.e., avoidant) adults play down the importance of attachment relationships and tend to recall few concrete episodes of emotional interactions with parent. They experience discomfort with closeness and dependence on relationship partners, preferring emotional distance and self-reliance and using deactivating strategies to deal with insecurity and distress. On the other side, preoccupied (i.e., ambivalent) individuals are entangled in worries and angry feelings about parents, are hypersensitive to attachment experiences, and can easily retrieve negative memories. In romantic relationship they are concerned with a strong desire for closeness and protection, intense worries about partner availability and one's own value to the partner and use of hyper-activating strategies to deal with insecurity and distress. Finally, fearful avoidant attachment represents the extreme degree of attachment insecurity in adulthood, paralleling disorganization in infancy. Fearful avoidant individuals easily came from abusive or dysfunctional families and they may report physical or sexual abuse or other attachment-related traumas. They are the least secure, least trusting and most troubled of adolescents and adults because they use mixed deactivating and hyper activating attachment strategies to deal with insecurity: like dismissing individuals they often distance themselves from relationship partners, to avoid the possible negative consequences of reliance on others, but, as the preoccupied counterpart, they continue to experience anxiety, ambivalence, and the desire for their relationship partners' love and support (Mikulincer and Shaver, 2016).

---

Formatted: Left, Line spacing: single, Tab stops: 2.63", Left

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Within the developmental psychopathology framework, many longitudinal studies have examined the connection between insecure and disorganized attachment patterns and the occurrence of psychopathology (Dutra & Lyons-Ruth, 2005; Englund et al., 2011; Grossmann et al., 2005; Lyons-Ruth et al., 2013; Shi et al., 2012; Sroufe, 2005). Although the exact ways in which early attachment experiences lead to the development of specific forms of psychopathology remain unclear, literature seems to agree with a causal relationship (Cassidy and Shaver, 2016). Well-replicated results supported links between avoidant attachment and anxiety disorders in adolescence and between disorganized attachment and dissociative symptoms in adolescence and early adulthood. Moreover, a meta-analysis conducted by Bakermans-Kranenburg and Van IJzendoorn's (2009) highlighted that ambivalent/avoidant attachment relations are usually associated with subsequent externalizing behaviours, such as antisocial personality and conduct disorders, while disorganized attachment increases risk for internalizing problems, like borderline personality disorders. Mixed results on the association between attachment and other psychopathologies (e.g., depression, schizophrenia, anxiety disorders and eating disorders) could be due to their heterogeneity or the presence of comorbidities.

### ***1.2. Association between parental attachment and SUD***

Several studies have explored the association between attachment and SUD, suggesting that moderate to strong evidence supports the assumption of insecure/disorganized attachment being a risk factor for SUD, accounting for about 30% of the risk (Jordan and Sack, 2009). Effect size was also moderate when evaluating the prospective association between insecure attachment and SUD in longitudinal studies (Fairbairn et al., 2018).

People who are relatively secure in their attachments are more likely than those who are not to manage conflict effectively and be better adjusted psychologically. Attachment theory suggests a developmental pathway from insecure attachment to SUD. Substance use can be understood as an attempt to compensate for lacking attachment strategies. With increasing insecurity, individuals face more difficulties in

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

regulating emotions and stress. Psychotropic substance use may then become attractive as a means to “self-medicate” attachment needs, to regulate emotions, or to cope with stress (Gill, 2017).

As for the attachment figures people experience positive emotions when reunited and restlessness and preoccupation when separated, similar emotional responses occur in the context of addiction with the preferred substance (Fairbairn et al., 2018). This pattern seems to parallel also the neurobiological basis of substance use in which the binge/intoxication is followed by a stress-like response during withdrawal that, through an inefficient emotion regulation, leads to a new intoxication, perpetrating the cycle and contributing to abuse (Koob and Volkow, 2016).

~~As we have seen earlier, we can categorise attachment on two dimensions. One that move along a bipolar continuum, from secure to insecure and includes disorganised attachment, and the other that defines the coping mechanisms splitting the insecure, maladaptive, attachment into avoidant and ambivalent (Schindler, 2019). In line with this~~ According with a recent approach theoretical model (Schindler, 2019) the identification of coping strategies to threats and stressors could allow to split the insecure, maladaptive, attachment into avoidant and ambivalent. We can hypothesise that individuals with ambivalent and avoidant patterns use different substances to compensate for the lack of a secure base. Specifically subjects with avoidant strategies look for emotional distancing (e.g. heroin) whereas subjects with ambivalent strategies seek an affectively hyperactivating substances (e.g. cocaine) to seek closeness to important others. Even though this is an appealing hypothesis, ~~the abovementioned a recent~~ systematic review did not confirm an association between the type of insecure attachment and specific substances nor with the level of insecurity and the SUD severity (Schindler, 2019).

~~Most of the published systematic reviews in adults (Iglesias et al., 2014; Schindler & Bröning., 2015; Unterrainer et al., 2017; Schindler, 2019) and adolescents (Schindler et al., 2015) included adult attachment styles. These, rather than a measure of early environmental dynamics, define the way the subjects interact and bond with others in their adult life, representing an outcome of the early attachment~~

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

~~experiences. In this review, instead, we will focus specifically on parental attachment and on state of mind about attachment with parents in adulthood, as explored by semi-structured interviews and questionnaires explicitly assessing the relationship with parents during childhood. These are for example the Adult Attachment Interview (AAI) (Plotka, 2011), Childhood Experience of Care and Abuse questionnaire (CECA-Q) (Bifulco et al., 2005), the Attachment and Clinical Issues Questionnaire (ACIQ) (Lindberg & Thomas, 2011), the Inventory of Parent and Peer Attachment (IPPA) (Greenberg, Seigel, & Leich, 1983), the Parental Bonding Instrument (PBI) (Parker, Tupling, & Brown, 1979).~~

The studies that explored the association between parental attachment and SUD can be divided into studies that evaluated substance use in healthy subjects and studies that employed clinical groups with SUD.

Studies in healthy subjects showed a cross-sectional association between maladaptive parental attachment and substance use (Gattamorta et al., 2017; McLaughlin et al., 2016; Taylor-Seehafer et al., 2008; Borelli et al., 2010; [Nakhoul et al. 2020](#)), alcohol (Abar et al., 2012), [tobacco \(Wise et al., 2017\)](#) and behavioural addiction (Badenes et al., 2019; Ghasempour et al., 2015; [Eichenberg et al., 2017, 2019;](#) [Monacis et al., 2018;](#) [Remondi et al., 2020](#)). A recent meta-analysis in healthy controls also confirmed the association between parental attachment and substance use when including only the studies with a longitudinal design (Fairbairn et al., 2018).

Overlapping results were found when considering clinical populations with SUD (Delvecchio et al., 2016; Torresani et al., 2000, Lindberg et al., 2015, Schindler et al., 2005; [Thorberg et al., 2006;](#) [Harnic et al., 2010;](#) [Fumaz et al., 2019;](#) [Potik et al., 2014](#)) where a poor attachment was associated with addiction severity, an earlier age at onset (Icick et al., 2013) and a lower willingness to seek treatment (Caspers et al., 2006; [Berry et al., 2017](#)). Interestingly, parental attachment seems differentially associated with the type of drug ([Hosseinfard et al., 2015](#)). For example crack users perceive mothers as neglectful, and fathers as controlling and affectionless (Pettenton et al., 2014). When exploring specifically their

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

perception of self and others, the heroin users showed a fearful pattern (negative model of self and others), ecstasy users were more preoccupied (negative model of self and positive model of other) and cannabis users were mainly dismissing (positive model of self, negative model of other) (Schindler et al., 2009). In terms of treatment a more secure attachment was also related to a higher treatment retention and lower relapse rate (Marshall et al., 2017), and methadone users reported significantly lower anxiety about being rejected than drug-free addicts (Torres et al., 2019).

The few neuroimaging studies available (Fuchshuber et al., 2020; Unterrainer et al., 2017; Unterrainer et al., 2016) seem to point out to a diminished white matter integrity as a neurobiological marker of attachment in substance use disorder.

Formatted: Not Highlight  
Formatted: Not Highlight  
Formatted: Not Highlight

**1.3. Aims**

The association between parental attachment and SUD, however, is not so linear and several moderators have been suggested as taking part in this relationship. To better understand drug dependence, as a “complex multifactorial health disorder, characterized by a chronic and relapsing nature” (UNGASS, 2016), we embrace a developmental perspective, suggesting that environmental and genetic factors could interact with early adverse experiences in shaping parental attachment relationships. The latter result in a potential vulnerability to addiction, by way of epigenetic and neuroendocrine mechanisms.

**2. Methods**

Although this paper represents a comprehensive overview of the available literature on genetic, epigenetic and neuroendocrine factors, that may underlie the association between ~~early childhood experiences~~ attachment and SUD, we adopted a semi-systematic approach.

The strategy was developed in MEDLINE combining the following keywords:

- Set 1: (a) attachment; (b) maltreatment OR childhood OR neglect.
- Set 2: (a) substance OR addict\* OR dependence; (b) alcohol OR opiate OR opioid OR cocaine OR cannabis\* OR methamphetamine\* OR heroin\* OR stimulant\* OR tobacco OR cigarette\* OR ecstasy.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Set 3: (a) HPA OR cortisol OR stress hormone; (b) Oxytocin\* OR OT OR neuropeptide; (c) endogenous opioid OR beta-endorphin; (d) dopamine\* OR homovanillic acid; (e) serotonin\* OR 5HT OR 5-hydroxytryptamine OR 5-hydroxyindolacetic acid.

Set 4: (a) gene OR genetic; (b) epigenetic OR polymorph\* OR methylat\*

To evaluate which were the environmental factors involved in the association between attachment and SUD we combined the keywords of Set 1a [Title/Abstract] and Set 2a [Title] retrieving n=493 abstracts. We then combined the keywords of Sets 1, 2, and 3 [Title/Abstract] retrieving n=550 abstracts to draft the paragraph on the neuroendocrine mechanism. Lastly to select the papers exploring the genetic and epigenetic factors associated with early adverse experiences and SUD we combined the keywords of Sets 1 and 2 [Title/Abstract] and Set 4 [Title] retrieving n=355 abstracts. The abstracts haves been screened based on the appropriateness to the review topic. Studies published in English through March 2021 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field. The flowchart is depicted in Figure 1.

Formatted: Font: Bold

- Figure 1 approximately here -

As noted, because of the paucity of studies considering the classic attachment interviews and questionnaires (Mikulincer and Shaver, 2016) in epi/genetic and neurobiological studies, when searching in this literature we did not considered only strictly attachment measures, but we also included semi-structured interviews and questionnaires explicitly assessing early environmental dynamics, traumatic experiences in childhood and parental styles, which could contribute to the development of insecure attachment organization. These are for instance the Childhood Experience of Care and Abuse questionnaire (CECA-Q) (Bifulco et al., 2005), the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1998) and the Parental Bonding Instrument (PBI) (Parker, Tupling, & Brown, 1979).

Formatted: Font: Not Bold, English (United States)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

### 3. Pathways from early experiences to vulnerability to SUD

#### 3.1. Environmental factors

Although listing all the environmental risk factors that predispose to SUD goes beyond the scope of the current review, we will briefly summarize the results of the current literature. Environmental factors contributing to risks of SUD can be divided into three main categories: individual, familial and social (Whitesell et al., 2013).

##### 3.1.1. Individual factors

Individual factors that moderate the association between attachment and SUD encompass both stable trait-like dimensions (e.g., temperament and character) and transient state-dependent phenomena (e.g., psychopathology symptoms).

Cross-sectional studies in healthy subjects, for example, noted that both higher temperamental novelty seeking (Cornellà-Font et al., 2018) and maladaptive coping strategies (Andres et al., 2014; Estevez et al., 2019; Gerra et al., 2004; Lee et al., 2003; Lyvers et al., 2019; Walsh et al., 1995; [Kassel et al., 2007](#); [Liese et al., 2020](#), [Zakhour et al., 2020](#); [Serra et al., 2019](#); [Starks et al., 2015](#)), separately increase the risk of SUD and behavioural addiction (Liu et al., 2019; [Monacis et al., 2017](#)) when controlling for parental attachment. Similar results were found when evaluating emotion dysregulation in a cohort of subjects with SUD and comorbid borderline personality disorder (Schindler & Sack, 2015, [Hiebler-Ragger et al., 2016](#)). Longitudinal studies in healthy subjects yielded similar results (Brook et al., 1993), with some suggesting that temperamental dimensions of dysregulation mediate the association between attachment and SUD (Zhai et al., 2014; Rovai et al., 2017; Maremmani et al., 2009; [Fuchshuber et al., 2018](#)).

This means that subjects with higher levels of persistence (Arнау et al., 2008), greater emotion-regulation (Kober, 2014, [Karimi et al., 2019](#), [Zdankiewicz-Scigala et al., 2018](#)) and metacognitive abilities ([Outcalt et al., 2016](#)) and more mature coping strategies (Willis, Wallston, & Johnson, 2001) have a lower risk of developing a SUD, even when their parental attachment is insecure (Gerra et al., 2004).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Slightly more complex is the moderating effect of internalising psychopathology (i.e., depression and anxiety). In fact, this would open the debate of whether this association is a pure comorbidity, a merely diagnostic comorbidity, related to item overlap, or an aetiopathogenic comorbidity, in which the relationship between internalising symptoms and SUD is causal (Feinstein, 1970). Independently from which is the true meaning of this association, literature seems to agree that internalising symptoms increase the risk of substance use beyond a maladaptive attachment in healthy subjects (Niyonsenga et al., 2012; Pellerone et al., 2016; [Kim et al., 2017](#); [Shin et al., 2011](#); [Meredith et al., 2020](#); [Greger et al., 2017](#); [Chen et al., 2020](#)) and clinical populations (De Palo et al., 2014; Miljkovitch et al., 2005; Musetti et al., 2016; Schindler et al., 2007; Vismara et al., 2019; [Wedekind et al., 2013](#); [Thorberg et al., 2010](#); [De Rick et al., 2009](#); [Fowler et al., 2013](#); [Owens et al., 2018](#)), also longitudinally- ([Gidhagen et al., 2018](#)).

### 3.1.2. *Familial factors*

Considering familial moderators, several cross-sectional studies in healthy subjects showed that a problematic family environment (Cleveland et al., 2014; De Wit et al., 1999; Estevez et al., 2017; Hayre et al., 2019; Kanamori et al., 2016; Kostelecky et al., 2005; Luk et al., 2015; Scragg et al., 2008; [Zdankiewicz-Scigala et al., 2019](#); [Winham et al., 2015](#); [Vungkhanching et al., 2004](#); [Massey et al., 2014](#); [Jones et al., 2015](#); [Zeinali et al., 2011](#); [Dishon-Brown et al., 2017](#)) might moderate the association between maladaptive attachment and substance use. This association was confirmed also in longitudinal studies on healthy subjects (Heerde et al., 2019; Branstetter et al., 2009; VanderVost et al., 2006), suggesting that a caring environment might be protective for SUD in those subjects with an insecure attachment.

### 3.1.3. *Social factors*

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Finally, as children progress into adolescence, family becomes less influential and peers become the more dominant socialization unit and hence a contributing factor to SUD development (Hahm et al., 2003; Henry, 2008; Henry et al., 2009; [Guo et al., 2020](#); [Hocking et al., 2017](#); [Liu et al., 2020](#)). Peer drug use in fact has a relatively strong effects on adolescent drug use, even when controlling for family climate and attachment styles (Bahr et al., 2005). It is therefore important that programs targeting risk factors and resilience to substance use incorporate the school environment and social domain in their skill training.

### 3.2. Genetic factors

Although heritability has been repeatedly demonstrated, SUDs show considerable evidence of environmental influence, especially during early stages of life (Enoch, 2012; Dick et al., 2012). Recent domain of research, usually entitled “gene-environment interplay”, showed that the study of environmental risk factors is not in contradiction with a genetic approach of addictive disorders (Gorwood et al., 2007).

Here we considered the studies in which genetic factors and adverse parenting experiences interact and contribute to or predispose to SUD.

The majority of Candidate Gene Association Studies (CGAS), based on *a priori* assumptions, revealed variants associated with the dopaminergic, serotonergic and opioids’ pathways, and with the hypothalamic pituitary adrenal (HPA) axis (**Table 1**).

#### 3.2.1. Monoamines

The main variants related to dopaminergic pathways belong to the dopamine receptors, and specifically to *DRD4* and *DRD2*.

The most frequently studied polymorphism of the *DRD4* gene is a 48-base-pair variable number tandem repeats (VNTR) (Van Tol et al., 1992). Subjects with long alleles (7 or more repeats) may have a reduced *DRD4* gene expression (Schoots & Van Tol, 2003) as well as receptors with reduced reactivity to

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

endogenous dopamine. Adolescent and young adult carriers of 7 or more repeats (7R+) of the variable number tandem repeat (48-bp VNTR III exon) of *DRD4* were shown to have a major risk of alcohol dependence in the presence of environmental risks such as childhood adversity (Park et al., 2011) or a greater risk of tobacco and cannabis use when the attachment was insecure (Olsson et al., 2011). This was also confirmed by a longitudinal study in a cohort of male adolescents, in which being 7R+ increased the risk of any substance use, but protective parenting practices prevented this outcome (Brody et al., 2014)

Concerning the *DRD2* gene, the most attractive genetic variants has been the Taq1A polymorphism, located about 10 kb downstream from the *DRD2* gene within the ankyrin repeat and kinase domain containing 1, *ANKK1* gene) (Neville et al., 2004). Children carriers of Taq1 A allele (rs1800497-T, *ANKK1/DRD2*) differed in their sensitivity to both negative and positive feedback. Being insensitive to a regularly offered positive reinforcement may predispose the child to seek other types of reward increasing the neuronal release of dopamine and subsequently counteracting the negative feelings (Althaus et al., 2009). Consistently with the hypothesized altered reward processing of Taq1A polymorphism, adolescent carriers of the A1/T allele, and with parents highly permissive, were found to use significantly more alcohol over time compared with adolescents without these risk factors (van der Zwaluw et al., 2010). Moreover, this allele was found significantly associated to cannabis use in an adult population with parental neglect being the greatest risk factors for cannabis use, beyond the genetic influence (Gerra, et al., 2019).

Several CGAS also explored the role of 5-HTTLPR polymorphism as a risk factor for substance use, depending on parental care perception. The short allele of 5-HTTLPR has been shown to have lower transcriptional activity of the serotonin transporter than the long allele and resulted in higher risk of alcohol use (Su et al., 2019), cocaine or illegal psychotropic drugs use (Gerra et al., 2007; Gerra et al., 2010). In all these studies, however, supportive parenting (Su et al., 2019; Brody et al., 2009) and also

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

the perceived paternal and maternal care (Gerra et al., 2007, Gerra et al., 2010) attenuated or completely eliminated the link between the genetic risk and the longitudinal increase in substance use.

The association between 5-HTTLPR and marijuana specifically seems moderated by gender, with females having a higher risk of misuse when neglected (Vaske et al., 2012). Ossola and coworkers, exploring both the 5-HTTLPR and Taq1A/DRD2 polymorphisms in a sample of adults, children of alcoholic parents, demonstrated that an early caring environment might lower the genetic risk of developing an Alcohol Use Disorder (AUD), especially in males (Ossola et al., 2021).

Beyond the transporters and receptors, also the enzymes involved in monoamine metabolism such as the Catechol-O-methyltransferase (COMT) and the Monoamine oxidases (MAO) have been considered to identify potential genetic variants conferring risk to substance use.

Favourable parenting was identified as a protective factor for alcohol abuse in adolescents homozygous for the Met allele of the *COMT* Val(158)Met polymorphism (Laucht et al., 2012). A substitution of methionine (Met) in place of valine (Val) in this gene results in a 3- to 4-fold decrease in the activity of the COMT enzyme (Lachman et al., 1996). The two possible variants however have differential association with neurobiology of emotion regulation and executive functions. Whereas the low-activity Met allele is related to a greater activation in limbic brain regions, the high-activity Val allele is associated to impaired prefrontal activation (Mier, Kirsch, & Meyer-Lindenberg, 2010). For example, carriers of the homozygous genotype Val/Val who used cannabis were more likely to experience psychotic symptoms in presence of past childhood maltreatment (Vinkers et al., 2013). The role of childhood trauma was also associated to an increased risk of heroin use when the subjects had another polymorphism of the *COMT* gene (i.e., TT genotype of *rs737866*) (Li et al., 2012).

A shorter allele in the promoter region of the monoamine oxidase type A (*MAOA*) is associated with a lower functioning of the enzyme. Previous studies already tested the role of this variant in moderating

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

the association between childhood trauma and both psychopathology (Caspi et al., 2002) and brain connectivity (Hart et al., 2018).

A more recent study showed that physical and emotional abuse were associated with tobacco and cannabis use lifetime if the carriers of the high-activity *MAOA* allele were female. On the other hand, males had a greater risk of tobacco consumption in presence of a low-activity *MAOA* allele (Fite et al., 2019)

### 3.2.2. *HPA axis*

Genetic factors per se contribute to the stress regulatory HPA-axis and related cortisol reactivity and the latter might influence the parent-infant attachment relationship. Genes involved in these pathways have been identified on both central and peripheral receptors involving the corticotropin-releasing hormone (CRH) and the glucocorticoids receptors.

The corticotropin-releasing hormone receptor 1 (CRHR1) seems to mediate behavioural stress responses (Heinrichs & Koob, 2004). Specific polymorphisms of its promoter have been associated with increased CRH-R1 density and a greater alcohol preference (Hansson et al., 2006). Haplotype-tagging SNPs (the *rs1876831* C allele and the *rs242938A* allele) in the *CRHRI* gene were associated with a greater consumption of alcohol after stressful events and also with an earlier age of drinking initiation (Schmid et al., 2010)

The FK506-binding protein 5 (FKBP5) is a glucocorticoid receptor co-chaperone that can decrease its affinity for glucocorticoids and hence modulate the response to stress. The TT genotype carriers of the intronic variant *rs1360780*, that have twice the amount of FKBP5 protein levels, were more likely to develop into a problematic drinking behaviour or pattern in the presence of a poor relationship between the child and parents (Nylander et al., 2017).

A dysregulation of the HPA axis has been also associated with craving and relapse in cocaine-abstinent addicts (Brady et al., 2009), probably toward an interaction between both mineralocorticoid and

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

glucocorticoid receptors (Joels et al., 2008; Oitzl et al., 2010). Polymorphisms in mineralocorticoid and glucocorticoid receptor genes (*NR3C2* and *NR3C1*, respectively) associated with lowered efficiency of cortisol, but not aldosterone, as a ligand, increased the risk of crack/cocaine addiction in the presence of childhood physical neglect. The same polymorphisms and were also associated with greater crack/cocaine withdrawal symptoms independently from adverse childhood experiences (Rovaris et al., 2015).

3.2.3. *Opioids*

Several studies in mammals suggest that opioids are central in the development of infant-mother attachment (Nelson & Panksepp, 1998) and, in humans, mu-opioid receptor availability is correlated with attachment avoidance (Nummenmaa et al., 2015). Most of the literature that explored this association from a genetic perspective focused on the missense variant A118G, *rs1799971* of mu-opioid receptor gene (*OPRM1*). Expressing the G allele of this polymorphism results in up to 10- fold lower levels of mu-opioid receptors compared to the A allele (Zhang et al., 2005). The G allele, seems to be associated to better parent-child relations compared with A/A subjects in case of familiarity for SUD (Copeland et al., 2011), whereas the A carriers showed lower scores of self-directedness, cooperativeness, and predictive substance abuse even in response to higher maternal protection (Noto et al., 2020). However, not all the results are consistent; the G allele for example was also associated with insecure attachment, less care in mothers and predisposing to psychopathological symptoms development (Cimino et al., 2020).

3.2.4. *Oxytocin and other pathways*

Oxytocin has received much attention as a prosocial and anxiolytic neuropeptide. In human studies, the G-allele of a common variant (*rs53576*) in the oxytocin receptor gene (*OXTR*) has been associated with protective properties such as reduced stress response and higher receptiveness for social support. However, when including environmental factors into the model, the G-allele increased the susceptibility

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

to detrimental effects of childhood adversities. GG homozygotes exposed to childhood adversities reported lower reward dependence and increased responsiveness to emotional stimuli suggesting an attunement for social cues in early adverse conditions (Dannowski et al., 2016)

It is also worth reminding about a few other variants that might affect SUD development in the context of altered attachment. These include: (1) the *rs604300* polymorphism of the monoglyceride lipase gene (*MGLL*), an enzyme involved in the signalling within the endocannabinoid system (Carey et al., 2015) (2) the *rs2072660* polymorphism of the Cholinergic Receptor Nicotinic Beta 2 Subunit (*CHRN2*), that was significantly associated with nicotine dependence (Csala et al., 2015); and (3) the *rs2290045* of the Vesicular Glutamate Transporter 2 (*VGLUT2*) a broadly expressed transporter in brain areas involved in the reward system (Meyers et al., 2015).

Beyond the pharmacodynamics, specific polymorphisms can also affect the pharmacokinetics of substances, such as the *rs1229984* polymorphism of the Alcohol dehydrogenase 1B (*ADH1B*). The A allele, compared to the G allele, greatly increases the activity of the ADH1B enzyme and this has been consistently associated with a protective effect against alcoholism (Zaso et al., 2019). This association is moderated by childhood adversity, so that those exposed to neglect or abuse during the first years and with a GG homozygosis had more severe AUD (Vrettou et al., 2019).

Interestingly, non-supportive parenting seemed also to affect telomere length and this was mediated by the escalation of drinking and smoking in young adulthood (Beach et al., 2014).

Only one Genome Wide Association Study (GWAS) investigated specific variants interacting with traumatic childhood experience and SUD. A “TG” deletion (del-1:15511771) in the *TMEM5* gene, encoding a multi-pass transmembrane protein highly expressed in the brain, was shown to be associated with cocaine use in subjects who had non-traditional parental care (Sun et al., 2020). Other GWAS found potential genetic variants on genes related to synaptic transmission and cation transport (Pappa et al.,

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

2015) and in transcriptions regulatory genes (Dalvie et al., 2020) associated to parental attachment styles or childhood trauma but they did not explore the interaction with SUD development.

- Table 1 approximately here -

**3.3. Epigenetic mechanisms**

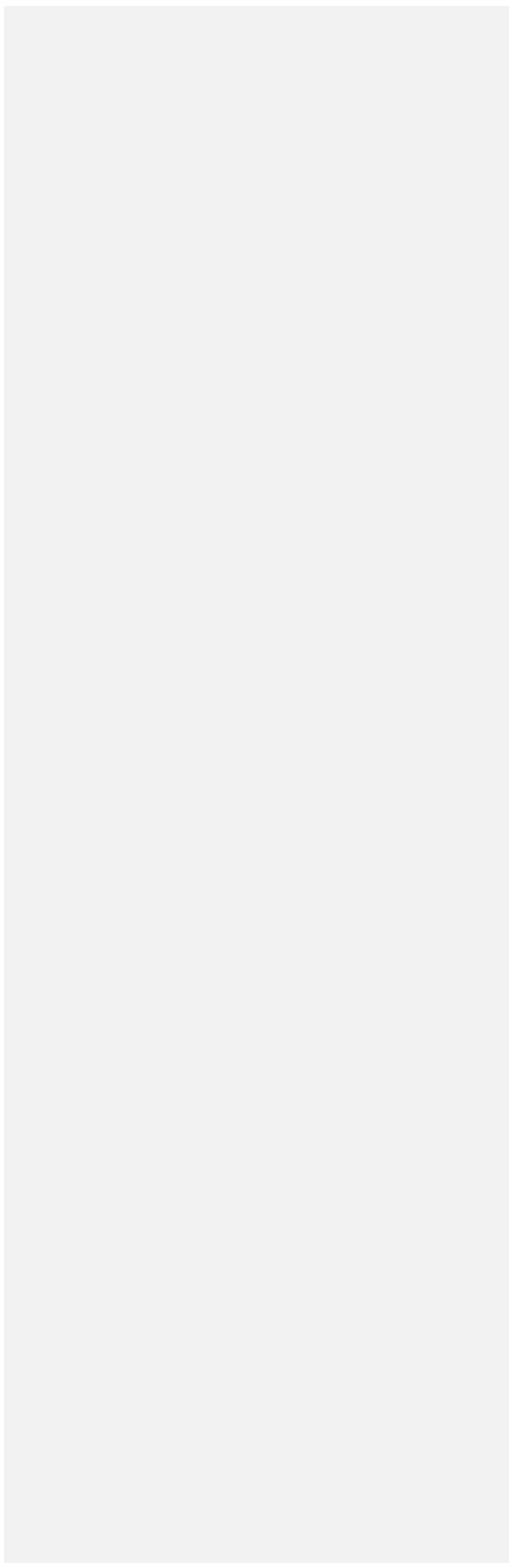
Literature seems to agree that stressful or supportive early social environments, such as adverse childhood experiences or protective parenting, affect epigenetic changes (Jiang et al., 2019; Garg et al 2018). Among all the epigenetic changes, the majority of the studies focus on DNA methylation. This modification consists in the transfer of a methyl group to the cytosine of the DNA to form 5-methyl-cytosine and it is generally associated with gene repression (Moore et al., 2013).

In this paragraph we will focus on the epigenetic modifications that, interacting with attachment-related factors, might entail regulatory implications for SUD. All the studies analysed DNA methylation in peripheral tissues, in genes related to dopamine, opioids, HPA axis and oxytocin (**Table 2**).

**3.3.1. Monoamines**

Two studies evaluated specifically the epigenetic modifications in monoamine related genes. One that regulates monoamine degradation through Monoamine Oxidase (MAO) (Bendre et al., 2018) and the other that controls the dopamine reuptake (DAT) (De Nardi et al., 2020).

Bendre and colleagues (2018) investigated whether the methylations levels in the functional variable number tandem repeats in the promoter region of the *MAOA* gene (*MAOA-uVNTR*) affects alcohol consumption in a sample of male adolescents/young adults. The authors focused on 16 candidate sites for methylation where cytosine lies next to guanine in the DNA sequence (CpGs) within part of the *MAOA* first exon and intron. The methylation of these regions is usually inversely correlated with gene expression. They found that the risk of alcohol use was associated with both carrying the *MAOA-uVNTR* S allele and having experienced maltreatment, but depended on the degree of first-intron *MAOA* methylation: among S carriers who experienced maltreatment, those who displayed lower levels of



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

intronic MAOA methylation reported more alcohol-related problems than those who displayed higher levels of intronic MAOA methylation. Therefore subjects with high-risk genotype (S allele), who experienced maltreatment, have a greater risk of alcohol-related problems, unless their S allele was silenced by methylation. By contrast, having a protective MAOA-uVNTR L allele did not completely prevent the risk of alcohol-related problems in fact intronic MAOA methylation could inactivate the transcription of the protective allele among those who experience maltreatment.

The authors also investigated the association between alcohol consumption and MAOA exonic methylation. They showed that subjects among those consuming high levels of alcohol exonic MAOA methylation was lower in high-risk genotype (S allele) carriers than the L-allele carriers. These results suggest that exonic MAOA methylation may be a biomarker of alcohol related problems, but still in a genotype-dependent manner.

A key player in dopamine (DA) neurotransmission is the dopamine transporter (DAT), a protein located in the synapsis that regulates the release and reuptake of dopamine. The human *DAT1* gene, encoding for the dopamine transporter, has a variable number of tandem repeats (VNTR) polymorphism in the 3'-untranslated region (3'-UTR) in which the base pairs can be repeated 9 or 10 times. The 3' UTR 9-repeat allele has been related with higher DAT binding and subsequently reduced downstream DA signalling, conferring relative protection from becoming a stimulant user (Haile et al., 2007). However, the dynamics of methylation within the 5'-untranslated region (5'-UTR) of the DAT1 gene could modify the gene expression. According with the recent paper by Nardi and colleagues (2020), subjects with internet addiction were more likely to have the 10-repeat allele and an insecure attachment style. However, considering individuals in the control group, without internet addition, homozygous for the 10-repeat allele, DNA CpG5 methylation percentage at 5'-UTR was not matched with CpG6 methylation, as compared with controls with 9/x genotype. This result from the CpG5–CpG6 comparison suggests an

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

unexplored 5'-UTR intra-motif link that could represent, again, an epigenetic silencing mechanism on the expression of high-risk genotype (De Nardi et al., 2020).

### 3.3.2. HPA axis

Several research groups have demonstrated that DNA methylation in HPA axis genes interacts with childhood-negative experiences (Bosmans et al., 2018; Mudler et al., 2017; Ein-Dor et al., 2018). To our knowledge, only one study specifically explored whether DNA methylation in the glucocorticoid receptor gene *NR3C1* was associated with SUD in case of childhood maltreatment (Tyrka et al., 2016). The glucocorticoid receptor (GR) gene has a regulatory role of the GR in hypothalamic–pituitary–adrenal (HPA) axis function. Lower methylation of *NR3C1* is associated with increased gene expression, greater GR numbers and, consistently, with enhanced glucocorticoid negative feedback and reduced cortisol responses. The authors noted that in subjects with a SUD history, childhood adversities were negatively related to gene methylation and associated to a blunted cortisol response to dexamethasone/corticotropin-releasing hormone test.

### 3.3.3. Opioid

When examining the childhood adversity-associated DNA methylation changes in Alcohol Dependent patients, the promoters region of three genes results hyper-methylated (Zhang et al., 2013). These genes are the aldehyde dehydrogenase gene (*ALDH1A1*), involved in alcohol metabolism, the regulator of G-protein signalling 19 (*RGS19*), and, the Opioid Related Nociceptin Receptor 1 gene (*OPRL1*), which regulates behavioural responses to alcohol. Animal models suggested that the nociceptin receptor, encoded by *OPRL1*, might be an interesting target for treatment, reducing ethanol intake in alcohol-preferring rats and abolishes the rewarding properties of ethanol (Ciccocioppo 2004). DNA methylation in the *OPRL1* gene, was further investigated in 660 adolescents (Ruggeri et al., 2018), with contradictory results. The authors did not find associations between single nucleotide polymorphisms (SNPs) contained in the *OPRL1* gene, which were previously associated with alcohol-use disorders, and binge drinking or

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

OPRL1 methylation profile. Moreover, in contrast with their previous results (Ruggeri et al., 2015), found that lifetime stressful life events are associated with lower methylation in the first intron of the OPRL-1, which in turn was found associated with higher frequency of binge drinking. Therefore these results should be interpreted cautiously.

DNA hydroxymethylation is an intermediate in the demethylation process mainly associated with transcriptional activation rather than gene silencing. It has been observed that childhood abuse is associated with a decreased hydroxymethylation and hence with a downregulation of the Kappa opioid receptor. It is possible that this mechanism is mediated in the amygdala by glucocorticoid receptor binding demonstrating the well-established interactions between endogenous opioids and stress (Lutz et al., 2018). However, no studies investigated its potential impact on SUD development.

3.3.4. *Oxytocin*

Allelic variations of the oxytocin receptor gene (*OXTR*) influence neural responses to rewards, regulating mesolimbic dopamine release, which may inhibit approach behaviors towards rewards (Wang et al., 2013). By contrast, other *OXTR* polymorphisms are associated with risk for substance use in adolescents and adults (Vaht et al., 2016),.

Previous studies suggested that expression of *OXTR* may be epigenetically regulated by DNA methylation: increased *OXTR* methylation in CpG island spanning exons 1 to 3 is associated with decreased *OXTR* expression (Kumsta et al., 2013), by contrast methylation of the third intronic region of *OXTR* is associated with transcriptional repression of the gene (Mizumoto et al., 1997; Gregory et al., 2009).

Although the specific environmental modulators of *OXTR* activity remained unexplored and no direct association of childhood maltreatment with *OXTR* methylation has been found (Parade et al., 2021), the studies did report indirect or moderation effects of childhood adversities on *OXTR* methylation status (Cecil et al., 2014; Unternaehrer et al., 2015).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Only one study focused on OXTR methylation as the mechanism linking early social environments to substance abuse (Kogan et al., 2018). The results showed that methylation at exons 1 to 3 of OXTR increases SUD symptoms, suggesting a protective role of OT in modulating the rewarding effects of drugs. Moreover, also in this study early adversities were associated with OXTR methylation indirectly via contemporary prosocial relationships: childhood trauma and other forms of adversity may contribute to problems with establishing and maintaining salutary relationships, which in turn affect OXTR methylation status.

- Table 2 approximately here -

**3.4. Neuroendocrine mechanisms**

Neuroendocrine mechanisms have been demonstrated to represent one of the fundamental neurobiological pathways underlying the relationship between genetic predisposition, early experiences and susceptibility to addiction (Strathearn et al., 2019).

Reviewing the current literature, three neuroendocrine pathways have been identified. These include the hypothalamic-pituitary-adrenal (HPA) axis that is a proxy of our stress response system, the monoaminergic system and the oxytocin-related system (**Table 3**).

**3.4.1. Monoamine**

Dopamine, serotonin and norepinephrine neurotransmission has been implicated in reward, impulsivity, negative affectivity, and drug-seeking behaviour among patients with SUDs (Koob and Volkow, 2016).

Following the hypothesis that monoaminergic dysfunctions pre-exist to SUD and could be related to early stressful experiences, six studies focused on altered dopaminergic/serotonergic neurotransmission as mediators between early stressful experiences and vulnerability to SUD.

One neuroendocrine method to study the monoaminergic activity was to measure monoamine end-point metabolite concentrations in the cerebrospinal fluid and plasma in patients with opioids (Gerra et al., 2007), Alcohol (Virkkunen et al., 1996) and Cocaine Use Disorders (Roy, 2002; Gerra et al., 2009a). In

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

these studies dopamine metabolite homovanillic acid (HVA) and serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) concentrations showed significant negative correlations with childhood neglect, poor parenting perception and a family history positive for paternal violence in SUD.

Moreover, both dopamine and serotonin are thought to be independently involved in the central control of prolactin (PRL) secretion: dopamine exerts tonic inhibitory control over PRL secretion, while serotonin stimulates PRL secretion. Among cocaine addicted patients, higher basal levels of circulating PRL, interpreted as an expression of reduced dopaminergic activity, have been found to be related to neglect and poor parenting perception (Gerra et al., 2009a). In another study focused on the serotonergic activity, after oral administration of a selective serotonin reuptake inhibitor (Citalopram), alcohol-dependent individuals with childhood experience of emotional abuse had significantly lower delta PRL response compared with those who did not report such abuse (Berglund et al., 2013).

Finally, a positron emission tomography study in humans showed that a greater number of traumatic events and altered caregiving were each associated with a higher ventral striatal dopamine response to amphetamine, suggesting that early trauma may lead to enhanced dopaminergic sensitivity to psychostimulants and that this mechanism may underlie increased vulnerability for drug use (Oswald et al., 2014).

These preliminary findings suggest that dopaminergic/serotonergic neuroendocrine alterations may be pre-existing to SUD and related to childhood adverse experience and poor parenting, rather than represent just a consequence of prolonged substance exposure, which could also be responsible for a consistent reduction in monoamine neurotransmission in SUD.

#### 3.4.2. HPA axis

The HPA axis is a central component of the neuroendocrine response to stress, which can be measured during basal functioning (HPA axis basal activity) or during stressful situations (HPA axis reactivity).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

As indicated in **Table 3**, we were able to find 19 papers, which investigated the relationship between problematic parenting/insecure attachment/early adverse experiences, HPA axis dysfunction and vulnerability to addiction (Gerra et al., 2010).

Considering the HPA axis basal activity, the majority of the studies found positive correlations between adverse childhood experiences and cortisol levels in patients with cocaine (Roy, 2002; Gerra et al., 2008; Gerra et al. 2009a), opioids (Gerra et al., 2008; Gerra et al., 2014), alcohol (Schäfer et al., 2010), nicotine (Gerra et al., 2016) and methamphetamine (Pirnia et al., 2019) use disorders as well as among adolescents experimenting with tobacco use, particularly smoking (Doan et al., 2014) and illegal drugs (Gerra et al., 2009b). However, other studies found no effect of childhood maltreatment exposure on cortisol plasma levels, in a sample of females who use crack cocaine (Levandowski et al., 2016) or negative associations between family dysfunction and baseline concentration of salivary cortisol among sons of SUD parents (Dawes et al., 1999).

Recently, greater consensus emerged on the supposition that the earlier risk factors that predict SUD also predict a blunted HPA axis reactivity to pharmacological and social challenges. Accordingly, HPA axis activity did not increase either after auditory evoked potential in preadolescents with father's with substance use disorders (Dawes et al., 1999), or after unpleasant slide set viewing in opioids-dependent patients tested for ACE (Gerra et al., 2009), or after dexamethasone/corticotropin-releasing hormone challenge among cocaine-dependent patients with early life stress (Moran-Santa Maria et al., 2010).

Considering the studies that used the Trier Social Stress Tasks, blunted cortisol reactivity has been found in a longitudinal study in girls who developed subsequent more pubertal change and substance use (Negriff et al, 2015), in alcohol-dependent patients with and without childhood maltreatment (Muehlhan et al., 2018), in higher smoking adolescents with colder parenting (Marceau et al., 2019), in young adults who had experienced parental divorce and reported binge drinking (Hagan et al., 2019), in female smokers with higher ACE scores (Hood et al., 2020). Again, although negative or conflicting results have

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

been reported in other samples (Moran-Santa Maria et al., 2010; Flanagan et al., 2015; Groh et al., 2020), the effects of early life stress in patients at risk of SUD seem to manifest later in life in the form of HPA axis dysregulation, which frequently involves dampening or blunting reactivity to stress.

Overall, although conflicting findings, perhaps due to different studies' designs, multiple substances examined, different measures of HPA axis functioning and the complex nature of early experiences, accumulating evidence seem to support the hypothesis that early stressful experiences could have activated a persistent and unjustified corticotropin releasing hormone secretion also in front of non-salient stimuli. This induces a permanent HPA axis basal hyperactivity, with poor ability to react to contingent stressful conditions among individuals at risk of SUD (Gerra et al., 2014).

### 3.4.3. *Opioid*

The endogenous opioid system (EOS) includes the different opioid receptors and their endogenous peptide ligands. The opioids  $\mu$ ,  $\kappa$  and  $\delta$  receptors belong to the superfamily of seven transmembrane domain G protein-coupled receptors, whose activation inhibits neuronal activity and reduces neurotransmitter release. The endogenous opioid ligands, including  $\beta$ -endorphin, met- and leu-enkephalin, dynorphins and neo-endorphins, are active peptides with an N-terminal sequence (Tyr-Gly-Gly-Phe-Met-Leu), indispensable to activate opioid receptors, although they have different affinity for the different receptors (Trigo et al., 2010).

The EOS seems to play an important role in the development of addiction, influencing personality traits that confer vulnerability or resiliency against risky behaviours such as the predisposition to develop substance use disorders (Love et al., 2009). Moreover, in nonhuman primates, this system has been demonstrated to be involved in social interactions between mothers and infants, like grooming and attachment. However, evidence from humans is lacking due to practical difficulties associated with both the assaying of endogenous opioid levels from human cerebro-spinal fluid or with Positron Emission Tomography (PET) and the administration of opioid receptor antagonists and agonist (Machin et al.,

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

2011).

We found only one recent study (Groh et al. 2020) that evaluated the interrelationship between the serum level of  $\beta$ -endorphin and childhood trauma, in a sample of 15 patients with Opioid Use Disorders, challenged with diamorphine. The authors found a strong correlation between severe trauma and significantly lower levels of  $\beta$ -endorphin, suggesting that reduced endogenous opioid peptides could have a role in the altered stress response, among SUD patients.

#### 3.4.4. *Oxytocin*

More recently, research focused on oxytocin (OT), a nonapeptide hormone synthesized primarily in hypothalamic nuclei and both secreted into the general circulation and released within the brain. Neurobiological models suggested that emotional neglect and abuse in childhood dysregulate the development of the OT system (Tops et al., 2014), which has been linked to a greater susceptibility to develop drug addiction (Baracz et al., 2020). However, few studies in humans examined the individual variability of the endogenous oxytocin system in patients with SUD, in relations with early experiences/attachment measures. Huang et al. (2018) found a distinctively reduced OT plasma level in ketamine-dependent patients, during early abstinence, but no association has been found with measures of childhood trauma. In contrast, another study showed that poli-drug users on maintenance therapy found higher levels of peripheral plasma OT, as compared to HC, at baseline, with non-significant differences in OT-reactivity to an attachment related stimulus (Fuchshuber & Unterrainer, 2020). Gerra et al. (2017) found that OT serum levels, among abstinent patients affected by opioid use disorder, were unexpectedly higher and positively correlated with mother neglect scores, suggesting that oxytocinergic signalling may exert different effects on attachment and bonding depending on the safe or dangerous environmental conditions (Dannowski et al., 2016; Carter, 2017).

These contradictory findings suggest that OT system is part of a more complex mechanism (Ellis et al., 2021), which involves the interaction with other unexplored neuroendocrine mechanisms that might

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

mediate the relationship between early adversities and the pathogenesis of SUD. Among the suggested pathways there are the endogenous opioids, the glutamate and immune systems (Buisman-Pijlman et al., 2014; Uvnäs Moberg et al., 2019; Sundar et al., 2021).

- Table 3 approximately here -

**4. Discussion**

In this review we focused on gene variants, epigenetic modifications and neuroendocrine changes that affect the glucocorticoid-related, monoaminergic, opioidergic and oxytocinergic pathways that might link early adverse childhood experiences with substance use.

**4.1. Possible neglected mechanisms**

In most of the described papers the specific mechanism, being it environmental, genetic, epigenetic or neuroendocrine, interacted with the early caring environment in shaping the risk of SUD. However, the picture ~~is~~ seems not so simplistic. At least four different mechanisms, not included in this review because of lack of experimental studies, might be involved. These are: the multiple mechanisms of action of a single gene, the gene-environment interaction, the gate control over epigenetic modifications and the interaction with other pathways.

**4.1.1. Same gene, different mechanisms**

Heritability has been repeatedly demonstrated in SUD, with a risk due to genetic differences between individuals ranging from 40% to 70% across different psychoactive substances, suggesting that polygenic (quantitative) influences account for about 50% of the risk of developing SUD (Prom-Wormley et al, 2017). Despite the successes of genome-wide association (GWA) research in identify different molecular markers, beyond the usual candidate genes (Deak and Johnson, 2021), the GWA studies on SUD are still characterized by a heritability gap between molecular and quantitative genetic studies. Twin and adoption studies estimated for approximately 50% of heritability (Kendler et al., 2012) however the effect

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

sizes found in GWAS are very small and hence we are far from explaining all the heritability factors through GWAS studies.

The complexity is further compounded because specific polymorphisms could code for the same protein with different activity. The reader might then suppose that, as in the case of aldehyde dehydrogenase, a lower metabolism of aldehyde would result in higher concentration of this compound with the alcohol consumption and hence in a more severe hangover. In reality each single protein might increase the risk of substance use through different mechanisms, not necessarily directly related with the protein function. For example, a single genetic variation in GABA<sub>A</sub> receptor subunits is able to increase the risk of alcohol consumption by at least three different mechanisms. First, it increases the ethanol-induced impulsive behaviour, leading to a greater consumption after the first beers; second it attenuates the sensitivity to the sedative effects of drugs and hence it keeps the subjects awake and ready to consume; lastly it raises the dopamine firing, associated with reward, priming the dependence circle (Stojakovic et al., 2018).

*4.1.2. Gene-Environment interactions*

Beyond the aforementioned genetic risks, SUD show considerable evidence of environmental influences, especially during early stages of life (Enoch, 2012, Dick & Kendler., 2012). According to theoretical models, genetic differences affect both the sensitivity (gene-environment interaction model, GXE) and exposure to environmental risk factors (gene-environment correlation model, rGE).

Gene-environment interaction (GxE) occurs when adverse environments may create a risk, depending on genetic susceptibility factors. The GxE model has been tested in SUD with twin studies (van der Zwaluw and Engels, 2009; Vink, 2016), which demonstrated that the genetic load could be moderated by environmental factors that confer risk and protection. Although findings are inconsistent across studies, specific gene variants seem to interact mainly with parenting behaviours and peer influences, and the effectiveness of interventions may vary by genotype (Milaniak et al., 2015).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Few studies, instead, have focused on gene-environment correlation (rGE) model for SUDs. Three main categories of rGE have been identified (Hines et al., 2015).

Passive rGE occurs to individuals who are passively exposed to environments that are correlated with their genetic predispositions. For example children can both inherit the genetic vulnerability and develop insecure attachment because the parents have a SUD. Active rGE occurs when individuals select, modify or construct experiences that are correlated with their genetic predisposition mechanisms. Temperamental characteristics, for example, may lead the child to seek out contexts associated with greater risk; this includes a greater propensity to try new things but also engaging with equally extroverted peers. Evocative rGE occurs when the individual's genotype elicits a certain response from the environment around them. As in the previous example, children with high levels of extroversion and low self-control, not only will seek novelty environment but also might evoke, because of these genetically determined traits, negative responses from their parents. These patterns of behaviour can shape the attachment relationships and further exacerbate risk for SUD (Hicks et al., 2013). Evidence of these evocative mechanisms often emerges in the clinical practice, when the parents of SUD's patients remembered their children as hard, frustrating and "unattuned", since the first days of life.

#### 4.1.3. Epigenetic as a future target

This "gene environment interplay" ~~is~~ may be further complicated by epigenetic variations, which are still poorly investigated. Epigenetics is defined as "mitotically and/or meiotically heritable change in gene function that cannot be explained by changes in the DNA sequence" (Riggs and Porter, 1996). Inter-individual variation has been demonstrated to characterize the epigenome and this inherited epigenetic individuality may have high impact on phenotypic outcomes in health and diseases. Studies reported differential DNA methylation, RNA expression, chromatin structure and chromatin modifications associated to both SUDs (Nestler and Lüscher, 2019) and attachment (Robakis et al., 2020). Moreover,

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

environmental effects on the epigenome could lead to sustained changes in gene transcription and thus early environment might affect these molecular processes later in life.

Considering the short allele *S* of the serotonin transporter promoter (5-HTTLPR), previous studies found associations with temperament and personality traits at risk for substance abuse (Gerra et al., 2004a, 2004b) with an increased availability to experiment with non-medical use of drugs among adolescents (Gerra et al., 2005), and with greater psychological sensitivity to environmental stressors (Caspi et al., 2003; Kilpatrick et al., 2007). Nevertheless, meta-analytic findings showed that there is variability in the success of replicating such findings (Risch et al., 2009, Munafo et al., 2009).

One potential explanation for the variability in results is the level of methylation in the 5-HTTLPR, which may reduce mRNA transcription. Specifically, van Ijzendoorn and colleagues (2010) found that the ability of the short variant of 5-HTTLPR genotype to predict a stressful response was dependent on methylation density. The *s* allele predicted a stressful response, but only when the levels of methylation were low, while higher levels of methylation of the *s* variant were associated with less stressful responses. On the other hand, methylation of alleles carrying the long 5-HTTLPR variant (*l*), usually protective in regard of any psychopathology, hampered its expression, increasing the risk of a stressful response in individuals that were supposed to be resilient because of their genotype.

It is also possible that specific genes act as a gate on the stress-related modification of the epigenome. In this case the association between stress and epigenetic methylation, for example, can be moderated by a specific polymorphism that confers resilience or allows the stressor to carry out its deleterious effects on other genes transcription (Lewis and Olive, 2014).

Therefore, the importance of including epigenetics in genetic and environmental epidemiology studies lies in the double role epigenetic marks may play, as mediators in regulatory processes and mediators of vulnerability (Ladd-Acosta and Fallin, 2016). Histone modifications, DNA methylation changes, and miRNAs expression have already been shown to be the key players in the development of addiction to

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

cocaine and other substances (Nestler, 2014). Moreover, epigenetics modifications induced by a negative parenting scenario or early adverse experience may mediate lifelong vulnerability to SUDs (Jiang et al., 2021).

Epigenetics can mediate the genetic or environmental risk, or represent the biological mechanism to explain how genetic and environmental factors, in combination, may be involved in the addiction process. Even when it is not clear if the identified epigenetic changes are causal or a consequence of a specific phenotypes, these marks might serve as biomarkers of addiction or vulnerability to addiction.

*3.1.4. Interaction with other pathways*

We should keep in mind that the four main ~~identified~~<sup>proposed</sup> pathways are not likely acting in isolation, but they may be strictly interconnected. Moreover, other biological systems might increase the risk of developing SUD when the early environment is predisposed to a maladaptive attachment; these includes but are not limited to the glutamatergic, GABAergic, enzymatic, immune and inflammatory pathways (Strathearn et al., 2019).

**4.2. Clinical implications**

Up to now we ~~described~~<sup>tried to delineate a hypothetical model, which is currently only partially empirically validated, to describe</sup> how gene and environment may interact to shape the early attachment and hence increase the vulnerability to SUD.

Whereas epigenetic factors and hormones might represent a fascinating therapeutic target, significantly more studies focused on how to reduce SUD risk through parenting (Allen et al., 2016). Parenting, in fact, has been suggested as a crucial target, not only in preventing SUD, but also as a critical mechanism in healthy emotional development (Holmes et al., 2017).

It is well-known that parents' SUD is a risk factor for substance use in their children (Bailey et al., 2006). However, from a preventive point of view, is more useful to understand what parents, independently from their relationship with the substances, can do to reduce the risk and increase the resilience or

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

protective factors in their children. Because of the high vulnerability of subjects during the developmental age, most of the prevention programs focused on school-aged youth (Tremblay et al., 2020).

This is even more relevant from an attachment point of view. In fact, although attachment is not a parenting style, literature suggest that a secure attachment is a function of children's experience of parenting (Cummings & Cummings, 2002).

A recent meta-analysis (Garcia-Huidobro et al., 2018) showed that offering parenting guidance to all families with adolescent children was effective in reducing youth substance use. Parenting programs generally educate parents and build skills related to improving family management, reducing family conflict, effective monitoring of their children and increasing positive parent-child interactions (Sandler et al., 2011).

The authors, however, concludes that studies including adolescents older than 14 years are lacking, and few studies target adolescents from racial/ethnic minority groups. Considering what was noted above related to peer influence in this age range, it is possible that older adolescent might benefit more from specific skills training programs aimed at improving emotion management and self-regulation (Tremblay et al., 2020).

The three main family protective factors for SUD in children and adolescents are: a positive parent/child relationship, a consistent discipline, and clear parental attitudes related to non-use of substances. Most of family-based interventions grounded on these three pillars had a greater effect size in reducing the risk of SUD than simple children-based approaches that focus on effective education, drug education and skills training (Kumpfer et al., 2003). A combined approach of family- and children-focused interventions guarantees an even greater efficacy (Kumpfer et al., 2003) because the combination satisfy all the requirement for an effective preventing program: parenting skills; reductions in short-term problems through an adaptation to stress; and an improvement of the context (Sandler et al., 2011).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Parenting programs do not act simply by improving the attachment style and increasing the emotion regulation abilities but also through epigenetic mechanism. Two recent reviews (Craig et al., 2021; Darling Rasmussen & Storebø, 2021) found a total of 16 studies pointing to a link between early childhood adversity, attachment processes, and epigenetic changes. The authors suggest that DNA methylation on attachment-related genes might affect the development of stress regulation systems and social-emotional capacities, thus contributing to the emerging phenotypic outcomes. We can hypothesise that parenting could reduce the genetic and environmental risk factors through epigenetic modifications increasing the resilience to SUD but unfortunately any of the included studies investigated specifically the association with substance misuse (Figure 21).

- Figure 22 approximately here -

**4.3. Limitation and future directions**

~~Among the limitation of our review we highlight that, despite our specific focus on attachment, the majority of the studies investigating the relation between early parent-child experiences and SUD, through genetic, epigenetic and neuroendocrine perspectives, did not include only measurement a strictly related to attachment measure. Therefore, to make our results more reliable, we extended our research to adverse parent-child experiences, which are known to have a potential effect on attachment, because a. Even because, although longitudinal data generally reveal a moderate degree of stability in attachment patterns from infancy to adulthood, there may be discontinuities in attachment pattern changing depending on life circumstances (Mikulincer e Shaver, 2016; Fraley et al., 2020). In fact, attachment and the trajectories are more uneven and less predictable in children whose early experiences include adversity and maltreatment (Prior & Glaser, 2006).~~  
Secondarily, it is worth noting, ~~as potential limitation on our findings,~~ that all epigenetic studies focused ~~only~~ on DNA methylation, ~~→~~ However multiple regulatory epigenetic elements in conjunction seem to orchestrate gene expression and regulation, including non-coding RNAs and chromatin modifications.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

In addition, some research hypothesized transcriptional changes, however, none of them explore if the detected epigenetic modification corresponded to gene expression alterations.

Another important aspect that should be considered is the fact that almost all the studies focused on peripheral samples. Comparative studies should better explore the largely unknown correspondence between buccal/blood and neuronal methylation profiles in order to use surrogate tissues for brain-based phenotype research. Potential targets of these studies could be the clock genes that contribute to the development of different psychiatric disorders and are characterized by an epigenetic synchronization between periphery and central nervous (Liu and Chung, 2015).

Even if these studies do not evidence a unique epigenetic signature of attachment and SUD, often because the lack of rigorous study design, the obtained findings should not be left out and set aside. New research considering different types of tissues, integrating the high-throughput sequencing technologies and the large amount of data analysis through sophisticated algorithms, might reveal new marks or confirm the marks we have only started to explore.

The epigenomic data will provide a chance to discover their role during attachment/parenting and addiction development, with two fundamental impacts. First, specific epigenetic marks could reveal molecular mechanisms underpinning the neurobiology of substance abuse. Moreover, the reversible nature of epigenetic modifications could pave the way for the development of novel therapeutic targets.

**4.4. Conclusions**

In conclusion, our review highlights genes that increase vulnerability to SUD may act through a direct and an indirect pathway. The indirect pathway, through evocative mechanisms, affects the ability of the caregiver to appropriately perceive and respond to the infant's emotional cues, determining the quality of parent-child attachment relationships. Adverse childhood experiences may aggravate the situation through epigenetic modifications, determining changes in gene expression. These molecular variations, related to early life experience and to patterns of childhood attachment, may induce a cascade of

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

neuroendocrine changes in glucocorticoid-related, monoaminergic, opioidergic and oxytocinergic systems. Other still unexplored neurobiological pathways may contribute to risk, resulting in externalizing/internalizing symptoms, emotional dysregulation and social dysfunctioning that, at the behavioural level, precede the clinical onset of SUD.

This complex view of the etiopathogenesis of SUD, deeply rooted in early attachment relationships, needs experimental confirmation in future studies, which combine different approaches. Longitudinal studies following-up cohorts of healthy children, screened for genotypes at risk for SUD are needed.

These observational studies should include neurobiological (e.g. epigenetic, neuroimaging and neuroendocrine), environmental assessment, and clinical interviews at each time point. This approach would allow identifying developmental trajectories of vulnerability to SUD, intertwined with the development of adult attachment styles. Clarifying these mechanisms, keeping in mind the relevance of time and context (Hitchcock et al., 2021), could reveal novel potential therapeutic targets for preventing the non-medical use of substances, drug dependence and drug use disorders.

~~In conclusion, our review highlights genes that increase vulnerability to SUD may act through a direct and an indirect pathway. The indirect pathway, through evocative mechanisms, affects the ability of the caregiver to appropriately perceive and respond to the infant's emotional cues, determining the quality of parent-child attachment relationships. Adverse childhood experiences may aggravate the situation through epigenetic modifications, determining changes in gene expression. These molecular variations, related to early life experience and to patterns of childhood attachment, may induce a cascade of neuroendocrine changes in glucocorticoid-related, monoaminergic, opioidergic and oxytocinergic systems. Other still unexplored neurobiological pathways may contribute to risk, resulting in externalizing/internalizing symptoms, emotional dysregulation and social dysfunctioning that, at the behavioural level, precede the clinical onset of SUD.~~

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

~~This complex view of the etiopathogenesis of SUD, deeply rooted in early attachment relationships, highlights the need for complex studies, which combine molecular, neuroendocrine and behavioural approaches. Clarifying these mechanisms keeping in mind the relevance of time and context (Hitchcock et al., 2021) could reveal novel potential therapeutic targets for preventing the non-medical use of substances, drug dependence and drug use disorders.~~

**References**

**References**

Abar, C.C., Jackson, K.M., Colby, S.M., Barnett, N.P., 2015. Parent-Child Discrepancies in Reports of Parental Monitoring and Their Relationship to Adolescent Alcohol-Related Behaviors. *J Youth Adolesc.* 44, 1688-1701. <https://doi.org/10.1007/s10964-014-0143-6>

Ainsworth, M. D. S., Blehar, M. C, Waters, E., & Wall, S., 1978. Patterns of attachment: A psychological study of the strange situation. Hillsdale, NJ: Erlbaum.

Allen, M.L., Garcia-Huidobro, D., Porta, C., Curran, D., Patel, R., Miller, J., Borowsky, I., 2016. Effective Parenting Interventions to Reduce Youth Substance Use: A Systematic Review. *Pediatrics* 138, e20154425. <https://doi.org/10.1542/peds.2015-4425>

Althaus, M., Groen, Y., Wijers, A.A., Mulder, L.J.M., Minderaa, R.B., Kema, I.P., Dijck, J.D.A., Hartman, C.A., Hoekstra, P.J., 2009. Differential effects of 5-HTTLPR and DRD2/ANKK1 polymorphisms on electrocortical measures of error and feedback processing in children. *Clin. Neurophysiol.* 120, 93–107. <https://doi.org/10.1016/j.clinph.2008.10.012>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Andres, F., Castanier, C., Le Scanff, C., 2014. Attachment and alcohol use amongst athletes: The mediating role of conscientiousness and alexithymia. *Addict. Behav.* 39, 487–490. <https://doi.org/10.1016/j.addbeh.2013.10.022>

Arnau, M.M., Mondon, S., Santacreu, J.J., 2008. Using the temperament and character inventory (TCI) to predict outcome after inpatient detoxification during 100 days of outpatient treatment. *Alcohol Alcohol.* 43, 583–588. <https://doi.org/10.1093/alcac/agn047>

Badenes-Ribera, L., Fabris, M.A., Gastaldi, F.G.M., Prino, L.E., Longobardi, C., 2019. Parent and peer attachment as predictors of facebook addiction symptoms in different developmental stages (early adolescents and adolescents). *Addict. Behav.* 95, 226–232. <https://doi.org/10.1016/j.addbeh.2019.05.009>

Bahr, S.J., Hoffmann, J.P., Yang, X., 2005. Parental and peer influences on the risk of adolescent drug use. *J Prim Prev.* 26, 529–551. <https://doi.org/10.1007/s10935-005-0014-8>

Bailey, J.A., Hill, K.G., Oesterle, S., Hawkins, J.D., 2006. Linking Substance Use and Problem Behavior Across Three Generations. *J. Abnorm. Child Psychol.* 34, 263–282. <https://doi.org/10.1007/s10802-006-9033-z>

Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H., 2009. The first 10,000 adult attachment interviews: Distributions of adult attachment representations in clinical and non-clinical groups. *Attachment and Human Development*, 11(3), 223–263. <https://doi.org/10.1080/14616730902814762>

Baracz, S.J., Everett, N.A., Robinson, K.J., Campbell, G.R., Cornish, J.L., 2020. Maternal separation changes maternal care, anxiety-like behaviour and expression of paraventricular oxytocin and corticotrophin-releasing factor immunoreactivity in lactating rats. *J. Neuroendocrinol.* 32, 12861. <https://doi.org/10.1111/jne.12861>

Beach, S.R.H., Lei, M.K., Brody, G.H., Yu, T., Philibert, R.A., 2014. Nonsupportive parenting affects telomere length in young adulthood among african americans: Mediation through substance use. *J. Fam. Psychol.* 28, 967–972. <https://doi.org/10.1037/fam0000039>

Bendre, M., Comasco, E., Checknita, D., Tiihonen, J., Hodgins, S., Nilsson, K.W., 2018. Associations Between MAOA-uVNTR Genotype, Maltreatment, MAOA Methylation, and Alcohol Consumption in Young Adult Males. *Alcohol. Clin. Exp. Res.* 42, 508–519. <https://doi.org/10.1111/acer.13578>

Berglund, K.J., Balldin, J., Berggren, U., Gerdner, A., Fahlke, C., 2013. Childhood Maltreatment Affects the Serotonergic System in Male Alcohol-Dependent Individuals. *Alcohol. Clin. Exp. Res.* 37, 757–762. <https://doi.org/10.1111/acer.12023>

Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J., 1998. Childhood trauma questionnaire. Assessment of family violence: A handbook for researchers and practitioners. APA PsycTests. <https://doi.org/10.1037/t02080-000>

Berry, K., Palmer, T., Gregg, L., Barrowclough, C., Lobban, F., 2018. Attachment and therapeutic alliance in psychological therapy for people with recent onset psychosis who use cannabis. *Clin Psychol Psychother.* 25, 440–445. <https://doi.org/10.1002/cpp.2178>

Bifulco, A., Bernazzani, O., Moran, P. M., & Jacobs, C., 2005. The childhood experience of care and abuse questionnaire (CECA. Q): validation in a community series. *Br J Clin Psychol/British Journal of Clinical Psychology*, 44(4), 563–581. <https://doi.org/10.1348/014466505X35344>

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Borelli, J.L., Goshin, L., Joestl, S., Clark, J., Byrne, M.W., 2011. Attachment Organization in a Sample of Incarcerated Mothers. *Attach. Hum. Dev.* 12, 355–374. <https://doi.org/10.1080/14616730903416971>.

Borsboom, D., Cramer, A., Kalis, A., 2018. Brain disorders? Not really... Why network structures block reductionism in psychopathology research. *Behav. Brain Sci.* 119, 1–54. <https://doi.org/10.1017/S0140525X17002266>

Bosmans, G., Young, J.F., Hankin, B.L., 2018. NR3C1 methylation as a moderator of the effects of maternal support and stress on insecure attachment development. *Dev. Psychol.* 54, 29–38. <https://doi.org/10.1037/dev0000422>

Bowlby, J. (1969). *Attachment and Loss, Volume 1-3, Attachment*. New York: Basic Books.

Brady, K.T., McRae, A.L., Maria, M.M.M.S., DeSantis, S.M., Simpson, A.N., Waldrop, A.E., Back, S.E., Kreek, M.J., 2009. Response to corticotropin-releasing hormone infusion in cocaine-dependent individuals. *Arch. Gen. Psychiatry* 66, 422–430. <https://doi.org/10.1001/archgenpsychiatry.2009.9>

Branstetter, S.A., Furman, W., Cottrell, L., 2009. The influence of representations of attachment, maternal-adolescent relationship quality, and maternal monitoring on adolescent substance use: A 2-year longitudinal examination. *Child Dev.* 80, 1448–1462. <https://doi.org/10.1111/j.1467-8624.2009.01344.x>

Brody, G.H., Beach, S.R.H., Philibert, R.A., Chen, Y. fu, Lei, M.K., Murry, V.M.B., Brown, A.C., 2009. Parenting Moderates a Genetic Vulnerability Factor in Longitudinal Increases in Youths' Substance Use. *J. Consult. Clin. Psychol.* 77, 1–11. <https://doi.org/10.1037/a0012996>

Brody, G.H., Chen, Y. fu, Beach, S.R.H., Kogan, S.M., Yu, T., DiClemente, R.J., Wingood, G.M., Windle, M., Philibert, R.A., 2014. Differential sensitivity to prevention programming: A dopaminergic polymorphism-enhanced prevention effect on protective parenting and adolescent substance use. *Heal. Psychol.* 33, 182–191. <https://doi.org/10.1037/a0031253>

Brook, J.S., Whiteman, M., Finch, S., 1993. Role of Mutual Attachment in Drug Use: A Longitudinal Study. *J. Am. Acad. Child Adolesc. Psychiatry* 32, 982–989. <https://doi.org/10.1097/00004583-199309000-00015>

Buisman-Pijlman, F.T.A., Sumracki, N.M., Gordon, J.J., Hull, P.R., Carter, C.S., Tops, M., 2014. Individual differences underlying susceptibility to addiction: Role for the endogenous oxytocin system. *Pharmacol. Biochem. Behav.* 119, 22–38. <https://doi.org/10.1016/j.pbb.2013.09.005>

Carey, C.E., Agrawal, A., Zhang, B., Conley, E.D., Degenhardt, L., Heath, A.C., Li, D., Lynskey, M.T., Martin, N.G., Montgomery, G.W., Wang, T., Bierut, L.J., Hariri, A.R., Nelson, E.C., Bogdan, R., 2015. Monoacylglycerol lipase (MGLL) polymorphism rs604300 interacts with childhood adversity to predict cannabis dependence symptoms and amygdala habituation: Evidence from an endocannabinoid system-level analysis. *J. Abnorm. Psychol.* 124, 860–877. <https://doi.org/10.1037/abn0000079>

Carter, C.S., 2017. The role of oxytocin and vasopressin in attachment. *Psychodyn. Psychiatry* 45, 499–518. <https://doi.org/10.1521/pdps.2017.45.4.499>

Caspers, K.M., Yucuis, R., Troutman, B., Spinks, R., 2006. Attachment as an organizer of behavior: Implications for substance abuse problems and willingness to seek treatment. *Subst. Abuse. Treat. Prev. Policy* 1. <https://doi.org/10.1186/1747-597X-1-32>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Caspi, A., 2002. Role of Genotype in the Cycle of Violence in Maltreated Children. *Science* (80-. ). 297, 851–854. <https://doi.org/10.1126/science.1072290>

Caspi, A., 2003. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science* (80-. ). 301, 386–389. <https://doi.org/10.1126/science.1083968>

Cassidy, J., & Shaver, P. R., 2016. *Handbook of attachment: Theory, research, and clinical applications.* (Eds.) New York: Guilford Press.

Cavaiola, A.A., Fulmer, B.A., Stout, D., 2015. The Impact of Social Support and Attachment Style on Quality of Life and Readiness to Change in a Sample of Individuals Receiving Medication-Assisted Treatment for Opioid Dependence. *Subst Abus.* 36, 183-91. <https://doi.org/10.1080/08897077.2015.1019662>

Cecil, C.A.M., Lysenko, L.J., Jaffee, S.R., Pingault, J.-B., Smith, R.G., Relton, C.L., Woodward, G., McArdle, W., Mill, J., Barker, E.D., 2014. Environmental risk, Oxytocin Receptor Gene (OXTR) methylation and youth callous-unemotional traits: A 13-year longitudinal study. *Molec. sychiatry* 19, 1071–1077. <https://doi.org/10.1038/mp.2014.95>

Chen, Y., Li, R., Zhang, P., Liu, X., 2020. The Moderating Role of State Attachment Anxiety and Avoidance Between Social Anxiety and Social Networking Sites Addiction. *Psychol.* 123, 633-647. <https://doi.org/10.1177/0033294118823178>

Ciccocioppo, R., Economidou, D., Fedeli, A., Angeletti, S., Weiss, F., Heilig, M., Massi, M., 2004. Attenuation of ethanol self-administration and of conditioned reinstatement of alcohol-seeking behaviour by the antiopioid peptide nociceptin/orphanin FQ in alcohol-preferring rats. *Psychopharmacology (Berl)* 172:170–178. <https://doi.org/10.1007/s00213-003-1645-1>

Cimino, S., Carola, V., Cerniglia, L., Bussone, S., Bevilacqua, A., Tambelli, R., 2020. The  $\mu$ -opioid receptor gene A118G polymorphism is associated with insecure attachment in children with disruptive mood regulation disorder and their mothers. *Brain Behav.* 10. <https://doi.org/10.1002/brb3.1659>

Cleveland, M.J., Reavy, R., Mallett, K.A., Turrissi, R., White, H.R., 2014. Moderating effects of positive parenting and maternal alcohol use on emerging adults' alcohol use: Does living at home matter? *Addict. Behav.* 39, 869–878. <https://doi.org/10.1016/j.addbeh.2014.01.028>

Copeland, W.E., Sun, H., Costello, E.J., Angold, A., Heilig, M.A., Barr, C.S., 2011. Child-opioid receptor gene variant influences parent-child relations. *Neuropsychopharmacology* 36, 1165–1170. <https://doi.org/10.1038/npp.2010.251>

Cornellà-Font, M.G., Viñas-Poch, F., Juárez-López, J.R., Martín-Perpiñá, M.D.L.M., Malo-Cerrato, S., 2018. Temperament and attachment as predictive factors for the risk of addiction to substances in adolescents. *Rev. Psicopatol. y Psicol. Clin.* 23, 179–187. <https://doi.org/10.5944/rppc.vol.23.num.3.2018.21423>

Craig, F., Tenuta, F., Rizzato, V., Costabile, A., Trabacca, A., Montirosso, R., 2021. Attachment-related dimensions in the epigenetic era: A systematic review of the human research. *Neurosci Biobehav Rev.* 2021 Jun;125, :654-666. <https://doi.org/10.1016/j.neubiorev.2021.03.006>

Csala, I., Egervari, L., Dome, P., Faludi, G., Dome, B., Lazary, J., 2015. The possible role of maternal bonding style and CHRN2 gene polymorphisms in nicotine dependence and related depressive phenotype. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 59, 84–90. <https://doi.org/10.1016/j.pnpbp.2015.01.012>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Cummings, E. M., & Cummings, J. S., 2002. Parenting and attachment. In M. H. Bornstein (Ed.), *Handbook of parenting: Practical issues in parenting* (p. 35–58). Lawrence Erlbaum Associates Publishers.

Dalvie, S., Maihofer, A.X., Coleman, J.R.I., Bradley, B., Breen, G., Brick, L.A., Chen, C.-Y., Choi, K.W., Duncan, L.E., Guffanti, G., Haas, M., Harnal, S., Liberzon, I., Nugent, N.R., Provost, A.C., Ressler, K.J., Torres, K., Amstadter, A.B., Bryn Austin, S., Baker, D.G., Bolger, E.A., Bryant, R.A., Calabrese, J.R., Delahanty, D.L., Farrer, L.A., Feeny, N.C., Flory, J.D., Forbes, D., Galea, S., Gautam, A., Gelernter, J., Hammamieh, R., Jett, M., Junglen, A.G., Kaufman, M.L., Kessler, R.C., Khan, A., Kranzler, H.R., Lebois, L.A.M., Marmar, C., Mavissakalian, M.R., McFarlane, A., Donnell, M.O., Orcutt, H.K., Pietrzak, R.H., Risbrough, V.B., Roberts, A.L., Rothbaum, A.O., Roy-Byrne, P., Ruggiero, K., Seligowski, A. V., Sheerin, C.M., Silove, D., Smoller, J.W., Stein, M.B., Teicher, M.H., Ursano, R.J., Van Hooff, M., Winternitz, S., Wolff, J.D., Yehuda, R., Zhao, H., Zoellner, L.A., Stein, D.J., Koenen, K.C., Nievergelt, C.M., 2020. Genomic influences on self-reported childhood maltreatment. *Transl. Psychiatry* 10, 38. <https://doi.org/10.1038/s41398-020-0706-0>

Dannlowski, U., Kugel, H., Grotegerd, D., Redlich, R., Opel, N., Dohm, K., Zaremba, D., Grögler, A., Schwieren, J., Suslow, T., Ohrmann, P., Bauer, J., Krug, A., Kircher, T., Jansen, A., Domschke, K., Hohoff, C., Zwieterlood, P., Heinrichs, M., Arolt, V., Heindel, W., Baune, B.T., 2016. Disadvantage of Social Sensitivity: Interaction of Oxytocin Receptor Genotype and Child Maltreatment on Brain Structure. *Biol. Psychiatry* 80, 398–405. <https://doi.org/10.1016/j.biopsych.2015.12.010>

Darling Rasmussen, P., & Storebø, O. J. (2021). Attachment and Epigenetics: A Scoping Review of Recent Research and Current Knowledge. *Psychological Reports*, 124(2), 479-501.; <https://doi.org/10.1177/0033294120901846>

Dawes, M., Clark, D., Moss, H., Kirisci, L., Tarter, R., 1999. Family and peer correlates of behavioral self-regulation in boys at risk for substance abuse. *Am. J. Drug Alcohol Abuse* 25, 219–237. <https://doi.org/10.1081/ADA-100101857>

De Nardi, L., Carpentieri, V., Pascale, E., Pucci, M., D’addario, C., Cerniglia, L., Adriani, W., Cimino, S., 2020. Involvement of DAT1 gene on internet addiction: Cross-correlations of methylation levels in 5’-utr and 3’-UTR genotypes, interact with impulsivity and attachment-driven quality of relationships. *Int. J. Environ. Res. Public Health* 17, 1–11. <https://doi.org/10.3390/ijerph17217956>

De Palo, F., Capra, N., Simonelli, A., Salcuni, S., Di Riso, D., 2014. Parenting quality in drug-addicted mothers in a therapeutic mother-child community: The contribution of attachment and personality assessment. *Front. Psychol.* 5, 1–13. <https://doi.org/10.3389/fpsyg.2014.01009>

De Rick, A., Vanheule, S., Verhaeghe, P., 2009. Alcohol addiction and the attachment system: an empirical study of attachment style, alexithymia, and psychiatric disorders in alcoholic inpatients. *Subst Use Misuse*. 44,99-114. <https://doi.org/10.1080/10826080802525744>

De Wit, M.L., Embree, B.G., De Wit, D., 1999. Determinants of the risk and timing of alcohol and illicit drug use onset among natives and non-natives: Similarities and differences in family attachment processes. *Soc. Biol.* 46, 100–121. <https://doi.org/10.1080/19485565.1999.9988990>

Deak, J. D., & Johnson, E. C., 2021. Genetics of substance use disorders: a review. *Psychological medicine*, 1-12. <https://doi.org/10.1017/S0033291721000969>

Delvecchio, E., Di Riso, D., Lis, A., Salcuni, S., 2016. Adult Attachment, Social Adjustment, and Well-Being in Drug-Addicted Inpatients. *Psychol. Rep.* 118, 587–607. <https://doi.org/10.1177/0033294116639181>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Dick, D.M., & Kendler, K.S., 2012. The impact of gene-environment interaction on alcohol use  
12 disorders. *Alcohol Res.* 34, 318-24. PMID: 23134047; PMCID: PMC3606909.
- 13 Dishon-Brown, A., Golder, S., Renn, T., Winham, K., Higgins, G.E., Logan, T.K., 2017. Childhood  
14 Victimization, Attachment, Coping, and Substance Use Among Victimized Women on Probation  
15 and Parole. *Violence Vict.* 32,431-451. <https://doi.org/10.1891/0886-6708.VV-D-15-00100>
- 16 Doan, S.N., Dich, N., Evans, G.W., 2014. Childhood cumulative risk and later allostatic load: Mediating  
17 role of substance use. *Heal. Psychol.* 33, 1402-1409. <https://doi.org/10.1037/a0034790>
- 18 Dutra, L., & Lyons-Ruth, K., (2005., April). Maltreatment, maternal and child psychopathology, and  
19 quality of early care as predictors of adolescent dissociation. In biennial meeting of the Society for  
20 Research in Child Development, Atlanta, GA.
- 21 Eichenberg, C., Dyba, J., Schott, M., 2017. Bindungsstile, Nutzungsmotive und Internetsucht  
22 [Attachment Style, Motives for Use and Internet Addiction]. *Psychiatr Prax.* 44,41-46.  
23 <https://doi.org/10.1055/s-0041-110025>.
- 24 Eichenberg, C., Schott, M., Decker, O., Sindelar, B., 2017. Attachment Style and Internet Addiction: An  
25 Online Survey. *J Med Internet Res.* 19, e170. <https://doi.org/10.2196/jmir.6694>
- 26 Ein-Dor, T., Verbeke, W.J.M.I., Mokry, M., Vrtička, P., 2018. Epigenetic modification of the oxytocin  
27 and glucocorticoid receptor genes is linked to attachment avoidance in young adults. *Attach. Hum.*  
28 *Dev.* 20, 439-454. <https://doi.org/10.1080/14616734.2018.1446451>
- 29 Ellis, B.J., Horn, A.J., Carter, C.S., van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., 2021.  
30 Developmental programming of oxytocin through variation in early-life stress: Four meta-analyses  
31 and a theoretical reinterpretation. *Clin. Psychol. Rev.* 86, 101985.  
32 <https://doi.org/10.1016/j.cpr.2021.101985>
- 33 Englund, M. M., Kuo, S. I. C., Puig, J., & Collins, W. A., (2011). Early roots of adult competence: The  
34 significance of close relationships from infancy to early adulthood. *Int. J. Behav. Dev.* International  
35 journal of behavioral development, 35(6), 490-496. <https://doi.org/10.1177/0165025411422994>
- 36 Enoch, M.A., 2012. The influence of gene-environment interactions on the development of alcoholism  
37 and drug dependence. *Curr. Psychiatry Rep.* 14, 150-158. <https://doi.org/10.1007/s11920-011-0252-9>
- 38  
39 Estevez, A., Jauregui, P., Lopez-Gonzalez, H., 2019. Attachment and behavioral addictions in  
40 adolescents: The mediating and moderating role of coping strategies. *Scand. J. Psychol.* 60, 348-360.  
41 <https://doi.org/10.1111/sjop.12547>
- 42 Estévez, A., Jáuregui, P., Sánchez-Marcos, I., López-González, H., Griffiths, M.D., 2017. Attachment  
43 and emotion regulation in substance addictions and behavioral addictions. *J. Behav. Addict.* 6, 534-  
44 544. <https://doi.org/10.1556/2006.6.2017.086>
- 45 Fairbairn, C.E., Briley, D.A., Kang, D., Fraley, R.C., Hankin, B.L., Ariss, T., 2018. A meta-analysis of  
46 longitudinal associations between substance use and interpersonal attachment security. *Psychol. Bull.*  
47 144, 532-555. <https://doi.org/10.1037/bul0000141>
- 48 Feinstein, A.R., 1970. The pre-therapeutic classification of co-morbidity in chronic disease. *J. Chronic*  
49 *Dis.* 23, 455-468. [https://doi.org/10.1016/0021-9681\(70\)90054-8](https://doi.org/10.1016/0021-9681(70)90054-8)
- 50 Fite, P.J., Brown, S., Hossain, W., Manzardo, A., Butler, M.G., Bortolato, M., 2019. Tobacco and  
51 cannabis use in college students are predicted by sex-dimorphic interactions between MAOA  
52 genotype and child abuse. *CNS Neurosci. Ther.* 25, 101-111. <https://doi.org/10.1111/cns.13002>
- 53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Flanagan, J.C., Baker, N.L., McRae-Clark, A.L., Brady, K.T., Moran-Santa Maria, M.M., 2015. Effects of adverse childhood experiences on the association between intranasal oxytocin and social stress reactivity among individuals with cocaine dependence. *Psychiatry Res.* 229, 94–100. <https://doi.org/10.1016/j.psychres.2015.07.064>

Fowler, J.C., Groat, M., Ulanday, M., 2013. Attachment style and treatment completion among psychiatric inpatients with substance use disorders. *Am J Addict.* 22, 14-7. <https://doi.org/10.1111/j.1521-0391.2013.00318.x>

Fraley, R. C., 2019. Attachment in adulthood: Recent developments, emerging debates, and future directions. *Annual review of psychology*, 70, 401–422. <https://doi.org/10.1146/annurev-psych-010418-102813>

Frank, L.E., & Nagel, S.K., 2017. Addiction and Moralization: the Role of the Underlying Model of Addiction. *Neuroethics* 10, 129–139. <https://doi.org/10.1007/s12152-017-9307-x>.

Fuchshuber, J., & Unterrainer, H.F., 2020. Childhood Trauma, Personality, and Substance Use Disorder: The Development of a Neuropsychanalytic Addiction Model. *Front. Psychiatry* 11, 1–21. <https://doi.org/10.3389/fpsyt.2020.00531>

Fuchshuber, J., Hiebler-Ragger, M., Ragger, K., Rinner, A., Kapfhammer, H.P., Unterrainer, H.F., 2018. Increased attachment security is related to early therapy drop-out in substance use disorders. *BMC Res Notes.* 11,141. <https://doi.org/10.1186/s13104-018-3251-7>.

Fuchshuber, J., Unterrainer, H.F., Hiebler-Ragger, M., Koschutnig, K., Papousek, I., Weiss, EM., Fink, A., 2020 Pinpointing Neural Correlates of Attachment in Poly-Drug Use: A Diffusion Tensor Imaging Study., *Front Neurosci.* 11;14:596. <https://doi.org/10.3389/fnins.2020.00596>.

Fumaz, C.R., Muñoz-Moreno, J.A., Ferrer, MJ., Ornelas, A., Coll, J., Clotet, B., 2020. Attachment Styles, Condomless Sex, and Drugs in HIV-Positive Gay and Bisexual Men. *J Sex Marital Ther.* 46, 35-42. <https://doi.org/10.1080/0092623x.2019.1626308>

Garcia-Huidobro, D., Doty, J.L., Davis, L., Borowsky, I.W., Allen, M.L., 2018. For Whom Do Parenting Interventions to Prevent Adolescent Substance Use Work? *Prev. Sci.* 19, 570–578. <https://doi.org/10.1007/s11121-017-0853-6>

Garg, E., Chen, L., Nguyen, T.T.T., Pokhvisneva, I., Chen, L.M., Unternaehrer, E., MacIsaac, J.L., McEwen, L.M., Mah, S.M., Gaudreau, H., Levitan, R., Moss, E., Sokolowski, M.B., Kennedy, J.L., Steiner, M.S., Meaney, M.J., Holbrook, J.D., Silveira, P.P., Kamani, N., Kobor, M.S., O'Donnell, K.J., 2018. The early care environment and DNA methylome variation in childhood. *Dev. Psychopathol.* 30, 891–903. <https://doi.org/10.1017/S0954579418000627>

Gattamorta, K.A., Varela, A., McCabe, B.E., Mena, M.P., Santisteban, D.A., 2017. Psychiatric Symptoms, Parental Attachment, and Reasons for Use as Correlates of Heavy Substance Use Among Treatment-Seeking Hispanic Adolescents. *Subst. Use Misuse* 52, 392–400. <https://doi.org/10.1080/10826084.2016.1229338>

Gerra, G., Angioni, L., Zaimovic, A., Moi, G., Bussandri, M., Bertacca, S., Santoro, G., Gardini, S., Caccavari, R., Nicoli, M.A., 2004. Substance Use among High-School Students: Relationships with Temperament, Personality Traits, and Parental Care Perception. *Subst. Use Misuse* 39, 345–367. <https://doi.org/10.1081/JA-120028493>

Gerra, G., Garofano, L., Santoro, G., Bosari, S., Pellegrini, C., Zaimovic, A., Moi, G., Bussandri, M., Moi, A., Brambilla, F., Donnini, C., 2004. Association between Low-Activity Serotonin Transporter Genotype and Heroin Dependence: Behavioral and Personality Correlates. *Am. J. Med. Genet. - Neuropsychiatr. Genet.* 126 B, 37–42. <https://doi.org/10.1002/ajmg.b.20111>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell’Agnello, G., Manfredini, M., Somaini, L., Petracca, F., Caretti, V., Saracino, M.A., Raggi, M.A., Donnini, C., 2007. Homovanillic acid (HVA) plasma levels inversely correlate with attention deficit-hyperactivity and childhood neglect measures in addicted patients. *J. Neural Transm.* 114, 1637–1647. <https://doi.org/10.1007/s00702-007-0793-6>

Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell’Agnello, G., Manfredini, M., Somaini, L., Petracca, F., Caretti, V., Baroni, C., Donnini, C., 2008. Adrenocorticotrophic hormone and cortisol plasma levels directly correlate with childhood neglect and depression measures in addicted patients. *Addict. Biol.* 13, 95–104. <https://doi.org/10.1111/j.1369-1600.2007.00086.x>

Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell’Agnello, G., Manfredini, M., Somaini, L., Petracca, F., Caretti, V., Raggi, M.A., Donnini, C., 2009. Childhood neglect and parental care perception in cocaine addicts: Relation with psychiatric symptoms and biological correlates. *Neurosci. Biobehav. Rev.* 33, 601–610. <https://doi.org/10.1016/j.neubiorev.2007.08.002>

Gerra, G., Manfredini, M., Somaini, L., Milano, G., Ciccocioppo, R., Donnini, C., 2016. Perceived parental care during childhood, ACTH, cortisol and nicotine dependence in the adult. *Psychiatry Res.* 245, 458–465. <https://doi.org/10.1016/j.psychres.2016.09.001>

Gerra, G., Somaini, L., Manfredini, M., Raggi, M.A., Saracino, M.A., Amore, M., Leonardi, C., Cortese, E., Donnini, C., 2014. Dysregulated responses to emotions among abstinent heroin users: Correlation with childhood neglect and addiction severity. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 48, 220–228. <https://doi.org/10.1016/j.pnpbp.2013.10.011>

Gerra, G., Zaimovic, A., Castaldini, L., Garofano, L., Manfredini, M., Somaini, L., Leonardi, C., Gerra, M.L., Donnini, C., 2010. Relevance of perceived childhood neglect, 5-HTT gene variants and hypothalamus-pituitary-adrenal axis dysregulation to substance abuse susceptibility. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 153, 715–722. <https://doi.org/10.1002/ajmg.b.31038>

Gerra, G., Zaimovic, A., Garofano, L., Ciusa, F., Moi, G., Avanzini, P., Talarico, E., Gardini, F., Brambilla, F., Manfredini, M., Donnini, C., 2007. Perceived parenting behavior in the childhood of cocaine users: Relationship with genotype and personality traits. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 144, 52–57. <https://doi.org/10.1002/ajmg.b.30388>

Gerra, M.C., Manfredini, M., Cortese, E., Antonioni, M.C., Leonardi, C., Magnelli, F., Somaini, L., Jayanthi, S., Cadet, J.L., Donnini, C., 2019. Genetic and Environmental Risk Factors for Cannabis Use: Preliminary Results for the Role of Parental Care Perception. *Subst. Use Misuse* 54, 670–680. <https://doi.org/10.1080/10826084.2018.1531430>

Ghasempour, A., Mahmoodi-Aghdam, M., 2015.n.d. The Role of Depression and Attachment Styles in Predicting Students’ Addiction to Cell Phones. *Addict. Heal.* 7, 192–7. PMID: 26885356

Gidhagen, Y., Holmqvist, R., Philips, B., 2018. Attachment style among outpatients with substance use disorders in psychological treatment. *Psychol Psychother.* 91,490-508. <https://doi.org/10.1111/papt.12172>.

Gill, R., 2017. Addictions from an Attachment Perspective: Do Broken Bonds and Early Trauma Lead to Addictive Behavior. New York, NY: Routledge

Gorwood, P., Wohl, M., Le Strat, Y., Rouillon, F., 2007. Gene-environment interactions in addictive disorders: epidemiological and methodological aspects. *Comptes Rendus - Biol.* 330, 329–338. <https://doi.org/10.1016/j.crv.2007.02.017>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Greenberg, M.T., Siegel, J.M., Leitch, C.J., 1983. The nature and importance of attachment relationships  
12 to parents and peers during adolescence. *J. Youth Adolesc.* 12, 373–386.  
13 <https://doi.org/10.1007/BF02088721>
- 14 Greger, H.K., Myhre, A.K., Klöckner, C.A., Jozefiak, T., 2017. Childhood maltreatment,  
15 psychopathology and well-being: The mediator role of global self-esteem, attachment difficulties  
16 and substance use. *Child Abuse Negl.* 70,122-133. <https://doi.org/10.1016/j.chiabu.2017.06.012>.
- 17 Groh, A., Rhein, M., Roy, M., Gessner, C., Lichtinghagen, R., Heberlein, A., Hillemacher, T., Bleich,  
18 S., Walter, M., Frieling, H., 2020. Trauma Severity in Early Childhood Correlates with Stress and  
19 Satiety Hormone Levels in a Pilot Cohort Receiving Diamorphine Maintenance Treatment. *Eur.*  
20 *Addict. Res.* 26, 103–108. <https://doi.org/10.1159/000505293>
- 21 Grossmann, K. E., Grossmann, K., & Waters, E. (Eds.), 2005. Attachment from infancy to adulthood:  
22 The major longitudinal studies. New York: Guilford Press.
- 23 Guo, J., Zhu, Y., Fang, L., Zhang, B., Liu, D., Fu, M., Wang, X., 2020. The Relationship Between Being  
24 Bullied and Addictive Internet Use Among Chinese Rural Adolescents: The Mediating Effect of  
25 Adult Attachment. *J Interpers Violence.* 21:886260520966681.  
26 <https://doi.org/10.1177/0886260520966681>
- 27 Hagan, M.J., Modecki, K., Tan, L.M., Luecken, L., Wolchik, S., Sandler, I., 2019. Binge drinking in  
28 adolescence predicts an atypical cortisol stress response in young adulthood.  
29 *Psychoneuroendocrinology*, 100, 137–144. <https://doi.org/10.1016/j.psyneuen.2018.10.002>
- 30 Hahn, H.C., Lahiff, M., Guterman, N.B., 2003. Acculturation and parental attachment in Asian-  
31 American adolescents' alcohol use. *J. Adolesc. Health* 33, 119–129. [https://doi.org/10.1016/S1054-139X\(03\)00058-2](https://doi.org/10.1016/S1054-139X(03)00058-2)
- 32  
33 Haile, C. N., Kosten, T. R., & Kosten, T. A., 2007. Genetics of dopamine and its contribution to cocaine  
34 addiction. *Behav. Genet. Behavior genetics*, 37(1), 119-145. <https://doi.org/10.1007/s10519-006-9115-2>
- 35  
36 Hansson, A.C., Cippitelli, A., Sommer, W.H., Fedeli, A., Björk, K., Soverchia, L., Terasmaa, A., Massi,  
37 M., Heilig, M., Ciccocioppo, R., 2006. Variation at the rat Crhr1 locus and sensitivity to relapse into  
38 alcohol seeking induced by environmental stress. *Proc. Natl. Acad. Sci. U. S. A.* 103, 15236–15241.  
39 <https://doi.org/10.1073/pnas.0604419103>
- 40 Harnic, D., Digiacomantonio, V., Innamorati, M., Mazza, M., Di Marzo, S., Sacripanti, F., Saioni, R.,  
41 Cardella, A., Di Felice, C., Girardi, P., Janiri L., 2010. Temperament and attachment in alcohol  
42 addicted patients of type 1 and 2. *Riv Psichiatri.* 45, 311-319.
- 43 Hart, H., Lim, L., Mehta, M.A., Curtis, C., Xu, X., Breen, G., Simmons, A., Mirza, K., Rubia, K., 2018.  
44 Altered Functional Connectivity of Fronto-Cingulo-Striatal Circuits during Error Monitoring in  
45 Adolescents with a History of Childhood Abuse. *Front. Hum. Neurosci.* 12, 7.  
46 <https://doi.org/10.3389/fnhum.2018.00007>
- 47 Hayre, R.S., Goulter, N., Moretti, M.M., 2019. Maltreatment, attachment, and substance use in  
48 adolescence: Direct and indirect pathways. *Addict. Behav.* 90, 196–203.  
49 <https://doi.org/10.1016/j.addbeh.2018.10.049>
- 50 Heerde, J.A., Bailey, J.A., Toumbourou, J.W., Catalano, R.F., 2019. Longitudinal Associations Between  
51 the Adolescent Family Environment and Young Adult Substance Use in Australia and the United  
52 States. *Front. Psychiatry* 10, 1–10. <https://doi.org/10.3389/fpsyt.2019.00821>
- 53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Heinrichs, S.C., Koob, G.F., 2004. Corticotropin-releasing factor in brain: A role in activation, arousal, and affect regulation. *J. Pharmacol. Exp. Ther.* 311, 427–440. <https://doi.org/10.1124/jpet.103.052092>

Henden, E., Melberg, H.O., Røgeberg, O.J., 2013. Addiction: Choice or Compulsion? *Front. Psychiatry* 4. <https://doi.org/10.3389/fpsy.2013.00077>

Henry, K.L., 2008. Low Prosocial Attachment, Involvement With Drug-Using Peers, and Adolescent Drug Use: A Longitudinal Examination of Mediational Mechanisms. *Psychol. Addict. Behav.* 22, 302–308. <https://doi.org/10.1037/0893-164X.22.2.302>

Henry, K.L., Oetting, E.R., Slater, M.D., 2009. The Role of Attachment to Family, School, and Peers in Adolescents' Use of Alcohol: A Longitudinal Study of Within-Person and Between-Persons Effects. *J. Couns. Psychol.* 56, 564–572. <https://doi.org/10.1037/a0017041>

Heyman, G.M., 2009. *Addiction: A disorder of choice.*, *Addiction: A disorder of choice.* Harvard University Press, Cambridge, MA, US.

Hicks, B. M., Johnson, W., Durbin, C. E., Blonigen, D. M., Iacono, W. G., & McGue, M., 2013. Gene-environment correlation in the development of adolescent substance abuse: Selection effects of child personality and mediation via contextual risk factors. *Dev. Psychopathol.*, 25(1), 119. <https://doi.org/10.1017/S0954579412000946>

Hiebler-Ragger, M., Unterrainer, H.F., Rinner, A., Kapfhammer, H.P., 2016. Insecure Attachment Styles and Increased Borderline Personality Organization in Substance Use Disorders. *Psychopathology.* 49, 341-344. <https://doi.org/10.1159/000448177>

Hines, L.A., Morley, K.I., Mackie, C., Lynskey, M., 2015. Genetic and Environmental Interplay in Adolescent Substance Use Disorders. *Curr. Addict. Rep.* 2, 122-129. <https://doi.org/10.1007/s40429-015-0049-8>

Hitchcock, P., Fried, E. I., & Frank, M. (2021). Computational Psychiatry Needs Time and Context. *Annual Review of Psychology*, 73. <https://doi.org/10.1146/annurev-psych-021621-124910>

Hocking, E.C., Simons, R.M., Simons, J.S., Freeman, H., 2018. Adult attachment and drinking context as predictors of alcohol problems and relationship satisfaction in college students. *Am J Drug Alcohol Abuse.* 44, 339-347. <https://doi.org/10.1080/00952990.2017.1344682>

Holmes, J., & Holmes, J., 2014. *John Bowlby and Attachment Theory* (2nd ed.). Routledge. <https://doi.org/10.4324/9781315879772>

Hood, C.O., Tomko, R.L., Baker, N.L., Tuck, B.M., Flanagan, J.C., Carpenter, M.J., Gray, K.M., Saladin, M.E., McClure, E.A., 2020. Examining sex, adverse childhood experiences, and oxytocin on neuroendocrine reactivity in smokers. *Psychoneuroendocrinology* 120, 104752. <https://doi.org/10.1016/j.psyneuen.2020.104752>

Hosseinfard, S.M., Kaviani, N., 2015. Comparing the Early Maladaptive Schemas, Attachment and Coping Styles in Opium and Stimulant Drugs Dependent Men in Kerman, Iran. *Addict Health.* 7, 30-36 <https://www.ncbi.nlm.nih.gov/pubmed/26322208>

Huang, M.-C., Chen, L.-Y., Chang, H.-M., Liang, X.-Y., Chen, C.-K., Cheng, W.-J., Xu, K., 2018. Decreased Blood Levels of Oxytocin in Ketamine-Dependent Patients During Early Abstinence. *Front. Psychiatry* 9, 633. <https://doi.org/10.3389/fpsy.2018.00633>

Icek, R., Lauer, S., Romo, L., Dupuy, G., Lépine, J.P., Vorspan, F., 2013. Dysfunctional parental styles perceived during childhood in outpatients with substance use disorders. *Psychiatry Res.* 210, 522-528. <https://doi:10.1016/j.psychres.2013.06.041>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Iglesias, E. B., Fernández del Río, E., Calafat, A., & Fernández-Hermida, J. R., 2014. Attachment and  
12 substance use in adolescence: a review of conceptual and methodological aspects. *Adicciones*, 26,  
13 77–86.
- 14 Jiang, N., Xu, J., Li, X., Wang, Y., Zhuang, L., Qin, S., 2021. Negative Parenting Affects Adolescent  
15 Internalizing Symptoms Through Alterations in Amygdala-Prefrontal Circuitry: A Longitudinal Twin  
16 Study. *Biol. Psychiatry* 89, 560–569. <https://doi.org/10.1016/j.biopsych.2020.08.002>
- 17 Jiang, S., Postovit, L., Cattaneo, A., Binder, E.B., Aitchison, K.J., 2019. Epigenetic Modifications in  
18 Stress Response Genes Associated With Childhood Trauma. *Front. Psychiatry* 10.  
19 <https://doi.org/10.3389/fpsyt.2019.00808>
- 20 Joëls, M., Karst, H., DeRijk, R., de Kloet, E.R., 2008. The coming out of the brain mineralocorticoid  
21 receptor. *Trends Neurosci.* 31, 1–7. <https://doi.org/10.1016/j.tins.2007.10.005>
- 22 Jones, J.D., Ehrlich K.B., Lejuez, C.W., Cassidy J., 2015. Parental knowledge of adolescent activities:  
23 links with parental attachment style and adolescent substance use. *J Fam Psychol.* 29,191-200.  
24 <https://doi.org/10.1037/fam0000070>
- 25 Jordan, S., Sack, P.M., 2009. Schutz- und Risikofaktoren [Protective factors and risk factors]. In:  
26 Thomasius, R., Schulte-Markwort, M., Küstner, U.J., and Riedesser, P., editors. *Suchtstörungen im*  
27 *Kindes- und Jugendalter–Das Handbuch: Grundlagen und Praxis.* Stuttgart, Germany: Schattauer. p.  
28 127–38.
- 29 Kanamori, M., Weissman, J., De La Rosa, M., Trepka, M.J., Rojas, P., Cano, M.A., Melton, J.,  
30 Unterberger, A., 2016. Latino Mother/Daughter Dyadic Attachment as a Mediator for Substance Use  
31 Disorder and Emotional Abuse. *J. Immigr. Minor. Heal.* 18, 896–903. [https://doi.org/10.1007/s10903-](https://doi.org/10.1007/s10903-015-0312-z)  
32 [015-0312-z](https://doi.org/10.1007/s10903-015-0312-z)
- 33 Karimi, Z., Haghshenas, L., Mohtashami, T., Dehkordi, M.A., 2019. Investigating the role of attachment  
34 styles, dysfunctional attitudes, and spirituality in predicting membership in addicted and non-  
35 addicted groups. *Psych J.* 8, 169-179. <https://doi.org/10.1002/pchj.254>
- 36 Kassel, J.D., Wardle, M., Roberts, J.E., 2007. Adult attachment security and college student substance  
37 use. *Addict Behav.* 32, 1164-76. <https://doi.org/10.1016/j.addbeh.2006.08.005>
- 38 Kendler, K. S., Sundquist, K., Ohlsson, H., PalmÚr, K., Maes, H., Winkleby, M. A., & Sundquist, J.  
39 (2012). Genetic and familial environmental influences on the risk for drug abuse: a national Swedish  
40 adoption study. *Arch. ives of gen.eral psychiatry*, 69(7), 690-697.  
41 <https://doi.org/10.1001/archgenpsychiatry.2011.2112>
- 42 Kendler, K.S., Myers, J., Prescott, C.A., 2000. Parenting and adult mood, anxiety and substance use  
43 disorders in female twins: An epidemiological, multi-informant, retrospective study. *Psychol. Med.*  
44 30, 281–294. <https://doi.org/10.1017/S0033291799001889>
- 45 Kilpatrick, D.G., Koenen, K.C., Ruggiero, K.J., Acierno, R., Galea, S., Resnick, H.S., Roitzsch, J., Boyle,  
46 J., Gelernter, J., 2007. The serotonin transporter genotype and social support and moderation of  
47 posttraumatic stress disorder and depression in hurricane-exposed adults. *Am. J. Psychiatry* 164,  
48 1693–1699. <https://doi.org/10.1176/appi.ajp.2007.06122007>
- 49 Knudsen, E.I., 2004. Sensitive periods in the development of the brain and behavior. *J. Cogn. Neurosci.*  
50 16, 1412–1425. <https://doi.org/10.1162/0898929042304796>
- 51 Kober, H., 2014. Emotion regulation in substance use disorders. In J. J. Gross (Ed.), *Handbook of*  
52 *emotion regulation.* The Guilford Press, pp 428–446.
- 53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Kogan, S.M., Cho, J., Beach, S.R.H., Smith, A.K., Nishitani, S., 2018. Oxytocin receptor gene methylation and substance use problems among young African American men. *Drug Alcohol Depend.* 192, 309–315. <https://doi.org/10.1016/j.drugalcdep.2018.08.022>

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry* 3, 760–773. [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8)

Kostelecky, K.L., 2005. Parental attachment, academic achievement, life events and their relationship to alcohol and drug use during adolescence. *J. Adolesc.* 28, 665–669. <https://doi.org/10.1016/j.adolescence.2004.12.006>

Kumpfer K.L., Alvarado R., Whiteside H.O., 2003. Family-based interventions for substance use and misuse prevention. *Subst Use Misuse* 38, 1759-1787. <https://doi.org/10.1081/ja-120024240>

Lachman, H.M., Papolos, D.F., Saito, T., Yu, Y.M., Szumlanski, C.L., Weinshilboum, R.M., 1996. Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 6, 243–250. <https://doi.org/10.1097/00008571-199606000-00007>

Ladd-Acosta, C. & Fallin, M.D., 2016., 'The role of epigenetics in genetic and environmental epidemiology', *Epigenomics* 8, 271-283. <https://doi.org/10.2217/epi.15.102>

Laucht, M., Blomeyer, D., Buchmann, A.F., Treutlein, J., Schmidt, M.H., Esser, G., Jennen-Steinmetz, C., Rietschel, M., Zimmermann, U.S., Banaschewski, T., 2012. Catechol-O-methyltransferase Val 158 met genotype, parenting practices and adolescent alcohol use: Testing the differential susceptibility hypothesis. *J. Child Psychol. Psychiatry Allied Discip.* 53, 351–359. <https://doi.org/10.1111/j.1469-7610.2011.02408.x>

Lee, J.M., & Bell, N.J., 2003. Individual differences in attachment-autonomy configurations: Linkages with substance use and youth competencies. *J. Adolesc.* 26, 347–361. [https://doi.org/10.1016/S0140-1971\(03\)00018-6](https://doi.org/10.1016/S0140-1971(03)00018-6)

Levandowski, M.L., Viola, T.W., Prado, C.H., Wieck, A., Bauer, M.E., Brietzke, E., Grassi-Oliveira, R., 2016. Distinct behavioral and immunoendocrine parameters during crack cocaine abstinence in women reporting childhood abuse and neglect. *Drug Alcohol Depend.* 167, 140–148. <https://doi.org/10.1016/j.drugalcdep.2016.08.010>

Levitt, A., Leonard, K.E., 2015. Insecure attachment styles, relationship-drinking contexts, and marital alcohol problems: Testing the mediating role of relationship-specific drinking-to-cope motives. *Psychol Addict Behav.* 29,696-705. <https://dx.doi.org/10.1037/adb0000064>

Lewis, C. R., & Olive, M. F., 2014. Early life stress interactions with the epigenome: potential mechanisms driving vulnerability towards psychiatric illness. *Behav. Pharmacol.*, 25(5 0 6), 341. <https://doi.org/10.1097/FBP.0000000000000057>

Li, T., Du, J., Yu, S., Jiang, H., Fu, Y., Wang, D., Sun, H., Chen, H., Zhao, M., 2012. Pathways to Age of Onset of Heroin Use: A Structural Model Approach Exploring the Relationship of the COMT Gene, Impulsivity and Childhood Trauma. *PLoS One* 7, e48735. <https://doi.org/10.1371/journal.pone.0048735>

Liese, B.S., Kim ,H.S., Hodgins, D.C., 2020. Insecure attachment and addiction: Testing the mediating role of emotion dysregulation in four potentially addictive behaviors. *Addict Behav.* 107, 106432. <https://doi.org/10.1016/j.addbeh.2020.106432>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Lindberg, M.A., Fugett, A., Carter, J.E., 2015. Tests of the attachment and clinical issues questionnaire as it applies to alcohol dependence. *J. Addict. Med.* 9, 286–295. <https://doi.org/10.1097/ADM.000000000000131>

Lindberg, M.A., Thomas, S.W., 2011. The attachment and clinical issues questionnaire (ACIQ): Scale development. *J. Genet. Psychol.* 172, 329–352. <https://doi.org/10.1080/00221325.2010.541382>

Liu, C., Ma, J.L., 2019. Adult Attachment Style, Emotion Regulation, and Social Networking Sites Addiction. *Front Psychol.* 10, 2352. <https://doi.org/10.3389/fpsyg.2019.02352>.

Liu, C., & Chung, M., 2015. Genetics and epigenetics of circadian rhythms and their potential roles in neuropsychiatric disorders. *Neuroscience bulletin*, 31(1), 141-159. <https://doi.org/10.1007/s12264-014-1495-3>

Liu, C., Ma, J.L., 2019. Adult Attachment Orientations and Social Networking Site Addiction: The Mediating Effects of Online Social Support and the Fear of Missing Out. *Front Psychol.* 10, 2629. <https://doi.org/10.3389/fpsyg.2019.02629>.

Love, T. M., Stohler, C. S., & Zubieta, J. K. (2009). Positron emission tomography measures of endogenous opioid neurotransmission and impulsiveness traits in humans. *Archives of general psychiatry*, 66(10), 1124-1134. <https://doi:10.1001/archgenpsychiatry.2009.134>

Luk, J.W., Patock-Peckham, J.A., King, K.M., 2015. Are Dimensions of Parenting Differentially Linked to Substance Use Across Caucasian and Asian American College Students? *Subst. Use Misuse* 50, 1360–1369. <https://doi.org/10.3109/10826084.2015.1013134>

Lutz, P.E., Gross, J.A., Dhir, S.K., Maussion, G., Yang, J., Bramouille, A., Meaney, M.J., Turecki, G., 2018. Epigenetic Regulation of the Kappa Opioid Receptor by Child Abuse. *Biol. Psychiatry* 84, 751–761. <https://doi.org/10.1016/j.biopsych.2017.07.012>

Lyons-Ruth, K., Bureau, J. F., Holmes, B., Easterbrooks, A., & Brooks, N. H., 2013. Borderline symptoms and suicidality/self-injury in late adolescence: Prospectively observed relationship correlates in infancy and childhood. *Psychiatry research*, 206(2-3), 273-281. <https://doi.org/10.1016/j.psychres.2012.09.030>

Lyvers, M., Mayer, K., Needham, K., Thorberg, F.A., 2019. Parental bonding, adult attachment, and theory of mind: A developmental model of alexithymia and alcohol-related risk. *J. Clin. Psychol.* 75, 1288–1304. <https://doi.org/10.1002/jclp.22772>

Machin, A. J., & Dunbar, R. I., 2011. The brain opioid theory of social attachment: a review of the evidence. *Behaviour*, 148(9-10), 985-1025. <https://doi.org/10.1163/000579511X596624>

Main, M., Hesse, E., & Kaplan, N., 2005. Predictability of Attachment Behavior and Representational Processes at 1, 6, and 19 Years of Age: The Berkeley Longitudinal Study. In K. E. Grossmann, K. Grossmann, & E. Waters (Eds.), *Attachment from infancy to adulthood: The major longitudinal studies*. Guilford Publications, pp. 245–304.

Marceau, K., Brick, L.A., Knopik, V.S., Reijneveld, S.A., 2020. Developmental Pathways from Genetic, Prenatal, Parenting and Emotional/Behavioral Risk to Cortisol Reactivity and Adolescent Substance Use: A TRAILS Study. *J. Youth Adolesc.* 49, 17–31. <https://doi.org/10.1007/s10964-019-01142-8>

Maremmani, I., Pacini, M., Popovic, D., Romano, A., Maremmani, A.G., Perugi, G., Deltito, J., Akiskal, K., Akiskal, H., 2009. Affective temperaments in heroin addiction. *J Affect Disord.* 117, 186-92. <https://doi.org/10.1016/j.jad.2009.01.007>

Formatted: Italian (Italy)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Marshall, S.W., Albery, I.P., Frings, D., 2018. Who stays in addiction treatment groups? Anxiety and avoidant attachment styles predict treatment retention and relapse. *Clin Psychol Psychother.* 25, 525-531. <https://doi.org/10.1002/cpp.2187>.

Massey, S.H., Compton, M.T., Kaslow, N.J., 2014. Attachment security and problematic substance use in low-income, suicidal, African American women. *Am J Addict.* 23, 294-299. <https://doi.org/10.1111/j.1521-0391.2014.12104.x>

McCrory, E.J., Mayes, L., 2015. Understanding Addiction as a Developmental Disorder: An Argument for a Developmentally Informed Multilevel Approach. *Curr. Addict. Reports* 2, 326–330. <https://doi.org/10.1007/s40429-015-0079-2>

McLaughlin, A., Campbell, A., McColgan, M., 2016. Adolescent Substance Use in the Context of the Family: A Qualitative Study of Young People’s Views on Parent-Child Attachments, Parenting Style and Parental Substance Use. *Subst. Use Misuse* 51, 1846–1855. <https://doi.org/10.1080/10826084.2016.1197941>

Meredith, P., Moyle, R., Kerley, L., 2020. Substance Use: Links with Sensory Sensitivity, Attachment Insecurity, and Distress in Young Adults. *Subst Use Misuse.* 55, 1817-1824. <https://doi.org/10.1080/10826084.2020.1766502>

Meyers, J.L., Shmulewitz, D., Wall, M.M., Keyes, K.M., Aharonovich, E., Spivak, B., Weizman, A., Frisch, A., Edenberg, H.J., Gelernter, J., Grant, B.F., Hasin, D., 2015. Childhood adversity moderates the effect of ADH1B on risk for alcohol-related phenotypes in Jewish Israeli drinkers. *Addict. Biol.* 20, 205–214. <https://doi.org/10.1111/adb.12102>

Mier D, Kirsch P, Meyer-Lindenberg A. 2010. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Mol Psychiatry.*15, 918-927. <https://doi:10.1038/mp.2009.36>

Mikulincer, M., & Shaver, P. R. (2016). *Attachment in adulthood: Structure, dynamics, and change.* Guilford Press.

Milaniak, I., Watson, B. & Jaffee, S.R., 2015. Gene-Environment Interplay and Substance Use: A Review of Recent Findings. *Curr Addict Rep* 2, 364–371. <https://doi.org/10.1007/s40429-015-0069-4>

Miljkovitch, R., Pierrehumbert, B., Karmaniola, A., Bader, M., Halfon, O., 2005. Assessing attachment cognitions and their associations with depression in youth with eating or drug misuse disorders. *Subst. Use Misuse* 40, 605–623. <https://doi.org/10.1081/JA-200055349>

Mollick, J.A., Kober, H., 2020. Computational models of drug use and addiction: A review. *J. Abnorm. Psychol.* 129, 544–555. <https://doi.org/10.1037/abn0000503>

Monacis, L., de Palo, V., Griffiths, M.D., Sinatra, M., 2017. Exploring Individual Differences in Online Addictions: the Role of Identity and Attachment. *Int J Ment Health Addict.* 15, 853-868. <https://doi.org/10.1007/s11469-017-9768-5>.

Monacis, L., de Palo, V., Griffiths, M.D., Sinatra, M., 2017. Social networking addiction, attachment style, and validation of the Italian version of the Bergen Social Media Addiction Scale. *J Behav Addict.* 6, 178-186. <https://doi.org/10.1556/2006.6.2017.023>.

Moore, L. D., Le, T., & Fan, G., 2013. DNA methylation and its basic function. *Neuropsychopharmacology*, 38(1), 23-38. <https://doi.org/10.1038/npp.2012.112>

Moran-Santa Maria MM, McRae-Clark AL, Back SE, DeSantis SM, Baker NL, Spratt EG, Simpson AN, Brady KT. 2010., Influence of cocaine dependence and early life stress on pituitary-adrenal axis

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

responses to CRH and the Trier social stressor. *Psychoneuroendocrinology* 35, 1492-500. <https://doi.org/10.1016/j.psyneuen.2010.05.001>

Muehlhan, M., Höcker, A., Miller, R., Trautmann, S., Wiedemann, K., Lotzin, A., Barnow, S., Schäfer, I., 2020. HPA axis stress reactivity and hair cortisol concentrations in recently detoxified alcoholics and healthy controls with and without childhood maltreatment. *Addict. Biol.* 25, 1–8. <https://doi.org/10.1111/adb.12681>

Mulder, R.H., Rijlaarsdam, J., Luijk, M.P.C.M., Verhulst, F.C., Felix, J.F., Tiemeier, H., Bakermans-Kranenburg, M.J., Van Ijzendoorn, M.H., 2017. Methylation matters: FK506 binding protein 51 (FKBP5) methylation moderates the associations of FKBP5 genotype and resistant attachment with stress regulation. *Dev. Psychopathol.* 29, 491–503. <https://doi.org/10.1017/S095457941700013X>

Munafò, M.R., Freimer, N.B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Järvelin, M.R., Taanila, A., Flint, J., 2009. 5-HTTLPR genotype and anxiety-related personality traits: A meta-analysis and new data. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 150, 271–281. <https://doi.org/10.1002/ajmg.b.30808>

Musetti, A., Terrone, G., Corsano, P., Magnani, B., Salvatore, S., 2016. Exploring the link among state of mind concerning childhood attachment, attachment in close relationships, parental bonding, and psychopathological symptoms in substance users. *Front. Psychol.* 7, 1–9. <https://doi.org/10.3389/fpsyg.2016.01193>

Nakhoul, L., Obeid, S., Sacre, H., Haddad, C., Soufia, M., Hallit, R., Akel, M., Salameh, P., Hallit, S., 2020. Attachment style and addictions (alcohol, cigarette, waterpipe and internet) among Lebanese adolescents: a national study. *BMC Psychol.* 8, 33. <https://doi.org/10.1186/s40359-020-00404-6>

Negriff, S., Saxbe, D.E., Trickett, P.K., 2015. Childhood maltreatment, pubertal development, HPA axis functioning, and psychosocial outcomes: An integrative biopsychosocial model. *Dev. Psychobiol.* 57, 984–993. <https://doi.org/10.1002/dev.21340>

Nelson, E.E., Panksepp, J., 1998. Brain substrates of infant-mother attachment: Contributions of opioids, oxytocin, and norepinephrine. *Neurosci. Biobehav. Rev.* 22, 437–452. [https://doi.org/10.1016/S0149-7634\(97\)00052-3](https://doi.org/10.1016/S0149-7634(97)00052-3)

Nestler, E.J., 2014. Epigenetic mechanisms of drug addiction. *Neuropharmacology* 76, 259–268. <https://doi.org/10.1016/j.neuropharm.2013.04.004>

Nestler, E.J., Luscher, C., 2019. The Molecular Basis of Drug Addiction: Linking Epigenetic to Synaptic and Circuit Mechanisms. *Neuron* 102, 48–59. <https://doi.org/10.1016/j.neuron.2019.01.016>

Neville, M. J., Johnstone, E. C., & Walton, R. T., 2004. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23. 1. *Hum. Mutat.*, 23(6), 540-545. <https://pubmed.ncbi.nlm.nih.gov/15146457/>

Niyonsenga, T., Blackson, T.C., De La Rosa, M., Rojas, P., Dillon, F., Ganapati, E.N., 2012. Social support, attachment, and chronic stress as correlates of latina mother and daughter drug use behaviors. *Am. J. Addict.* 21, 157–167. <https://doi.org/10.1111/j.1521-0391.2011.00202.x>

Noto, K., Suzuki, A., Shirata, T., Matsumoto, Y., Takahashi, N., Goto, K., Otani, K., 2020. Mu-opioid receptor polymorphism moderates sensitivity to parental behaviors during characterization of personality traits. *Neuropsychiatr. Dis. Treat.* 16, 2161–2167. <https://doi.org/10.2147/NDT.S265774>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Nummenmaa, L., Manninen, S., Tuominen, L., Hirvonen, J., Kalliokoski, K.K., Nuutila, P., Jääskeläinen,  
12 I.P., Hari, R., Dunbar, R.I.M., Sams, M., 2015. Adult attachment style is associated with cerebral  $\mu$ -  
13 opioid receptor availability in humans. *Hum. Brain Mapp.* 36, 3621–3628.  
14 <https://doi.org/10.1002/hbm.22866>
- 15 Nylander, I., Todkar, A., Granholm, L., Vrettou, M., Bendre, M., Boon, W., Andershed, H., Tuvblad, C.,  
16 Nilsson, K.W., Comasco, E., 2017. Evidence for a Link Between Fkbp5/FKBP5, Early Life Social  
17 Relations and Alcohol Drinking in Young Adult Rats and Humans. *Mol. Neurobiol.* 54, 6225–6234.  
18 <https://doi.org/10.1007/s12035-016-0157-z>
- 19 Oitzl, M.S., Champagne, D.L., van der Veen, R., de Kloet, E.R., 2010. Brain development under stress:  
20 hypotheses of glucocorticoid actions revisited. *Neurosci. Biobehav. Rev.* 34, 853–66.  
21 <https://doi.org/10.1016/j.neubiorev.2009.07.006>
- 22 Olsson, C.A., Moyzis, R.K., Williamson, E., Ellis, J.A., Parkinson-Bates, M., Patton, G.C., Dwyer, T.,  
23 Romaniuk, H., Moore, E.E., 2011. Gene-environment interaction in problematic substance use:  
24 Interaction between DRD4 and insecure attachments. *Addict. Biol.* 18, 717–726.  
25 <https://doi.org/10.1111/j.1369-1600.2011.00413.x>
- 26 Ossola, P., Gerra, M.C., Gerra, M.L., Milano, G., Zatti, M., Zavan, V., Volpi, R., Marchesi, C., Donnini,  
27 C., Gerra, G., Di Gennaro, C., 2020. Alcohol use disorders among adult children of alcoholics  
28 (ACOAs): Gene-environment resilience factors. *Prog. Neuro-Psychopharmacology Biol. Psychiatry*  
29 108. <https://doi.org/10.1016/j.pnpbp.2020.110167>
- 30 Oswald, L.M., Wand, G.S., Kuwabara, H., Wong, D.F., Zhu, S., Brasic, J.R., 2014. History of childhood  
31 adversity is positively associated with ventral striatal dopamine responses to amphetamine.  
32 *Psychopharmacology (Berl.)* 231, 2417–2433. <https://doi.org/10.1007/s00213-013-3407-z>
- 33 Outcalt, J., Dimaggio, G., Popolo, R., Buck, K., Chaudoin-Patzoldt, K.A., Kukla, M., Olesek, K.L.,  
34 Lysaker, P.H., 2016. Metacognition moderates the relationship of disturbances in attachment with  
35 severity of borderline personality disorder among persons in treatment of substance use disorders.  
36 *Compr Psychiatry*. 64, 22–28. <https://doi.org/10.1016/j.comppsy.2015.10.002>
- 37 Owens, G.P., Held, P., Blackburn, L., Auerbach, J.S., Clark, A.A., Herrera, C.J., Cook, J., Stuart, G.L.,  
38 2014. Differences in relationship conflict, attachment, and depression in treatment-seeking  
39 veterans with hazardous substance use, PTSD, or PTSD and hazardous substance use. *J Interpers*  
40 *Violence*. 29, 1318–37. <https://doi.org/10.1177/0886260513506274>
- 41 Pappa, I., Szekeley, E., Mileva-Seitz, V.R., Luijk, M.P.C.M., Bakermans-Kranenburg, M.J., van  
42 IJzendoorn, M.H., Tiemeier, H., 2015. Beyond the usual suspects: a multidimensional genetic  
43 exploration of infant attachment disorganization and security. *Attach. Hum. Dev.* 17, 288–301.  
44 <https://doi.org/10.1080/14616734.2015.1037316>
- 45 Parade, S. H., Huffhines, L., Daniels, T. E., Stroud, L. R., Nugent, N. R., & Tyrka, A. R. (2021). A  
46 systematic review of childhood maltreatment and DNA methylation: candidate gene and epigenome-  
47 wide approaches. *Translational psychiatry*, 11(1), 1-33.
- 48 Park, A., Sher, K.J., Todorov, A.A., Heath, A.C., 2011. Interaction between the DRD4 VNTR  
49 polymorphism and proximal and distal environments in alcohol dependence during emerging and  
50 young adulthood. *J. Abnorm. Psychol.* 120, 585–595. <https://doi.org/10.1037/a0022648>
- 51 Parker, G., Tupling, H., Brown, L.B., 1979. A Parental Bonding Instrument. *Br. J. Med. Psychol.* 52, 1–  
52 10. <https://doi.org/10.1111/j.2044-8341.1979.tb02487.x>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Pellerone, M., Tolini, G., Polopoli, C., 2016. Parenting, identity development, internalizing symptoms, and alcohol use: A cross-sectional study in a group of Italian adolescents. *Neuropsychiatr. Dis. Treat.* 12, 1769–1778. <https://doi.org/10.2147/NDT.S106791>

Pettenon, M., Kessler, F.H.P., Guimarães, L.S.P., Pedroso, R.S., Hauck, S., Pechansky, F., 2014. Perceptions of parental bonding in freebase cocaine users versus non-illicit drug users. *Indian J. Med. Res.* 139, 835–840.

Pickard, H., 2017. Responsibility without Blame for Addiction. *Neuroethics* 10, 169–180. <https://doi.org/10.1007/s12152-016-9295-2>.

Pirnia, B., Khosravani, V., Maleki, F., Kalbasi, R., Pirnia, K., Malekanmehr, P., Zahiroddin, A., 2020. The role of childhood maltreatment in cortisol in the hypothalamic–pituitary–adrenal (HPA) axis in methamphetamine-dependent individuals with and without depression comorbidity and suicide attempts. *J. Affect. Disord.* 263, 274–281. <https://doi.org/10.1016/j.jad.2019.11.168>

Potik, D., Peles, E., Abramsohn, Y., Adelson, M., Schreiber, S., 2014. The relationship between vulnerable attachment style, psychopathology, drug abuse, and retention in treatment among methadone maintenance treatment patients. *J Psychoactive Drugs.* 46,325-333. <https://doi.org/10.1080/02791072.2014.944290>

Prior, V., & Glaser, D., 2006. *Understanding attachment and attachment disorders: Theory, evidence and practice.* Jessica Kingsley Publishers.

Plotka R., 2011. Adult Attachment Interview (AAI). In: Goldstein S., Naglieri J.A. (eds) *Encyclopedia of Child Behavior and Development.* Springer, Boston, MA. [https://doi.org/10.1007/978-0-387-79061-9\\_68](https://doi.org/10.1007/978-0-387-79061-9_68)

Prom-Wormley, E. C., Ebejer, J., Dick, D. M., & Bowers, M. S., 2017. The genetic epidemiology of substance use disorder: a review. *Drug and alcohol dependence,* 180, 241-259.

Remondi, C., Compare, A., Tasca, G.A., Greco, A., Pievani, L., Poletti, B., Brugnera, A., 2020. Insecure Attachment and Technology Addiction Among Young Adults: The Mediating Role of Impulsivity, Alexithymia, and General Psychological Distress. *Cyberpsychol Behav Soc Netw.* 23, 761-767. <https://doi.org/10.1089/cyber.2019.0747>

Remondi, C., Compare, A., Tasca, G.A., Greco, A., Pievani, L., Poletti, B., Brugnera, B., 2020. Insecure Attachment and Technology Addiction Among Young Adults: The Mediating Role of Impulsivity, Alexithymia, and General Psychological Distress. *Cyberpsychol Behav Soc Netw.* 23, 761-767. <https://doi.org/10.1089/cyber.2019.0747>

Riggs A.D. & Porter T.N., 1996. Overview of epigenetic mechanisms. In *Epigenetic mechanisms of gene regulation* (eds. Russo VEA, Martienssen R, Riggs AD), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 29–45.

Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR., 2009. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA.* 301, 2462-71. <https://doi.org/10.1001/jama.2009.878>. Erratum in: *JAMA.* 2009 302, 492. PMID: 19531786; PMCID: PMC2938776.

Robakis, T.K., Zhang, S., Rasgon, N.L., Li, T., Wang, T., Roth, M.C., Humphreys, K.L., Gotlib, I.H., Ho, M., Khechaduri, A., Watson, K., Roat-Shumway, S., Budhan, V. V., Davis, K.N., Crowe, S.D., Ellie Williams, K., Urban, A.E., 2020. Epigenetic signatures of attachment insecurity and childhood adversity provide evidence for role transition in the pathogenesis of perinatal depression. *Transl. Psychiatry* 10, 1–14. <https://doi.org/10.1038/s41398-020-0703-3>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Rovai L., Maremmani AGI, Bacciardi S., Gazzarrini D., Pallucchini A., Spera V., Perugi G., Maremmani I., 2017. Opposed Effect of Hyperthymic and Cyclothymic Temperament in Substance Use Disorder (Heroin or Alcohol Dependent Patients). *Journal of Affective Disorders*. 218: 339-345. <https://doi.org/10.1016/j.jad.2017.04.041>

Rovaris, D.L., Mota, N.R., Bertuzzi, G.P., Aroche, A.P., Callegari-Jacques, S.M., Guimarães, L.S.P., Pezzi, J.C., Viola, T.W., Bau, C.H.D., Grassi-Oliveira, R., 2015. Corticosteroid receptor genes and childhood neglect influence susceptibility to crack/cocaine addiction and response to detoxification treatment. *J. Psychiatr. Res.* 68, 83–90. <https://doi.org/10.1016/j.jpsychires.2015.06.008>

Roy, A., 2002. Self-rated childhood emotional neglect and CSF monoamine indices in abstinent cocaine-abusing adults: Possible implications for suicidal behavior. *Psychiatry Res.* 112, 69–75. [https://doi.org/10.1016/S0165-1781\(02\)00176-2](https://doi.org/10.1016/S0165-1781(02)00176-2)

Ruggeri, B., Macare, C., Stopponi, S., Jia, T., Carvalho, F.M., Robert, G., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Büchel, C., Cattrell, A., Conrod, P.J., Desrivières, S., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.L., Martinot, M.L.P., Nees, F., Papadopoulos-Orfanos, D., Paus, T., Poustka, L., Smolka, M.N., Vetter, N.C., Walter, H., Whelan, R., Sommer, W.H., Bakalkin, G., Ciccocioppo, R., Schumann, G., 2018. Methylation of OPRL1 mediates the effect of psychosocial stress on binge drinking in adolescents. *J. Child Psychol. Psychiatry Allied Discip.* 59, 650–658. <https://doi.org/10.1111/jcpp.12843>

Ruggeri, B., Nymberg, C., Vuoksimaa, E., Lourdasamy, A., Wong, C. P., Carvalho, F. M., ... & IMAGEN Consortium. (2015). Association of protein phosphatase PPM1G with alcohol use disorder and brain activity during behavioral control in a genome-wide methylation analysis. *American Journal of Psychiatry*, 172(6), 543-552.

Sandler, I.N., Schoenfelder, E.N., Wolchik, S.A., MacKinnon, D.P., 2011. Long-term impact of prevention programs to promote effective parenting: Lasting effects but uncertain processes. *Annu. Rev. Psychol.* 62, 299–329. <https://doi.org/10.1146/annurev.psych.121208.131619>

Schäfer, I., Teske, L., Schulze-Thüsing, J., Homann, K., Reimer, J., Haasen, C., Hissbach, J., Wiedemann, K., 2010. Impact of childhood trauma on hypothalamus-pituitary-adrenal axis activity in alcohol-dependent patients. *Eur. Addict. Res.* 16, 108–114. <https://doi.org/10.1159/000294362>

Schindler, A., 2019. Attachment and Substance Use Disorders—Theoretical Models, Empirical Evidence, and Implications for Treatment. *Front. Psychiatry* 10, 1–13. <https://doi.org/10.3389/fpsyt.2019.00727>

Schindler, A., Bröning, S., 2015. A Review on Attachment and Adolescent Substance Abuse: Empirical Evidence and Implications for Prevention and Treatment. *Subst. Abus.* 36, 304–13. <https://doi.org/10.1080/08897077.2014.983586>

Schindler, A., Sack, P.M., 2015. Exploring attachment patterns in patients with comorbid borderline personality and substance use disorders. *J. Nerv. Ment. Dis.* 203, 820–826. <https://doi.org/10.1097/NMD.0000000000000377>

Schindler, A., Thomasius, R., Petersen, K., Sack, P.M., 2009. Heroin as an attachment substitute? Differences in attachment representations between opioid, ecstasy and cannabis abusers. *Attach. Hum. Dev.* 11, 307–330. <https://doi.org/10.1080/14616730902815009>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Schindler, A., Thomasius, R., Sack, P.M., Gemeinhardt, B., Küstner, U., 2007. Insecure family bases and adolescent drug abuse: A new approach to family patterns of attachment. *Attach. Hum. Dev.* 9, 111–126. <https://doi.org/10.1080/14616730701349689>

Schmid, B., Blomeyer, D., Treutlein, J., Zimmermann, U.S., Buchmann, A.F., Schmidt, M.H., Esser, G., Rietschel, M., Banaschewski, T., Schumann, G., Laucht, M., 2010. Interacting effects of CRHR1 gene and stressful life events on drinking initiation and progression among 19-year-olds. *Int. J. Neuropsychopharmacol.* 13, 703–714. <https://doi.org/10.1017/S1461145709990290>

Schoots, O., Van Tol, H.H.M., 2003. The human dopamine D4 receptor repeat sequences modulate expression. *Pharmacogenomics J.* 3, 343–348. <https://doi.org/10.1038/sj.tpj.6500208>

Scragg, R., Reeder, A.I., Wong, G., Glover, M., Nosa, V., 2008. Attachment to parents, parental tobacco smoking and smoking among Year 10 students in the 2005 New Zealand national survey. *Aust. N. Z. J. Public Health* 32, 348–353. <https://doi.org/10.1111/j.1753-6405.2008.00253.x>

Şenormancı, Ö., Şenormancı, G., Güçlü, O., Konkan, R., 2014. Attachment and family functioning in patients with internet addiction. *Gen Hosp Psychiatry.* 36, 203–207. <https://doi.org/10.1016/j.genhosppsych.2013.10.012>

Serra, W., Chatard, A., Tello, N., Harika-Germaneau, G., Noël, X., Jaafari, N., 2019. Mummy, daddy, and addiction: Implicit insecure attachment is associated with substance use in college students. *Exp Clin Psychopharmacol.* 27, 522–529. <https://doi.org/10.1037/pha0000266>

Shi, Z., Bureau, J. F., Easterbrooks, M. A., Zhao, X., & Lyons- Ruth, K., 2012. Childhood maltreatment and prospectively observed quality of early care as predictors of antisocial personality disorder features. *Infant Mental Health Journal*, 33(1), 55–69. <https://doi.org/10.1002/imhj.20295>

Shin, S.E., Kim, N.S., Jang, E.Y., 2011. Comparison of problematic internet and alcohol use and attachment styles among industrial workers in Korea. *Cyberpsychol Behav Soc Netw.* 14, 665–72. <https://doi.org/10.1089/cyber.2010.0470> .

Sroufe LA, Carlson EA, Levy AK, Egeland B. 1999. Implications of attachment theory for developmental psychopathology. *Dev Psychopathol.* 11, 1–13. <https://doi.org/10.1017/s0954579499001923>

Sroufe, L. A., 2005. Attachment and development: A prospective, longitudinal study from birth to adulthood. *Attachment & human development*, 7(4), 349–367. <https://doi.org/10.1080/14616730500365928>

Starks, T.J., Millar, B.M., Tuck, A.N., Wells, B.E., 2015. The role of sexual expectancies of substance use as a mediator between adult attachment and drug use among gay and bisexual men. *Drug Alcohol Depend.* 153, 187–93. <https://doi.org/10.1016/j.drugalcdep.2015.05.028> .

Stojakovic, A., Walczak, M., Cieślak, P.E., Trenk, A., Sköld, J., Zajdel, J., Mirrasekhian, E., Karlsson, C., Thorsell, A., Heilig, M., Parkitna, J.R., Błasiak, T., Engblom, D., 2018. Several behavioral traits relevant for alcoholism are controlled by  $\gamma 2$  subunit containing GABAA receptors on dopamine neurons in mice. *Neuropsychopharmacology* 43, 1548–1556. <https://doi.org/10.1038/s41386-018-0022-z>

Strathearn, L., Mertens, C.E., Mayes, L., Rutherford, H., Rajhans, P., Xu, G., Potenza, M.N., Kim, S., 2019. Pathways Relating the Neurobiology of Attachment to Drug Addiction. *Front. Psychiatry* 10, 1–15. <https://doi.org/10.3389/fpsy.2019.00737>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Su, J., Supple, A.J., Leerkes, E.M., Kuo, S.I.C., 2019. Latent trajectories of alcohol use from early adolescence to young adulthood: Interaction effects between 5-HTTLPR and parenting quality and gender differences. *Dev. Psychopathol.* 31, 457–469. <https://doi.org/10.1017/S095457941800024X>

Sun, J., Kranzler, H.R., Gelernter, J., Bi, J., 2020. A genome-wide association study of cocaine use disorder accounting for phenotypic heterogeneity and gene–environment interaction. *J. Psychiatry Neurosci.* 45, 34–44. <https://doi.org/10.1503/jpn.180098>

Sundar, M., Patel, D., Young, Z., & Leong, K. C., 2021. Oxytocin and Addiction: Potential Glutamatergic Mechanisms. *Int. J. Mol. Sci.*, 22(5), 2405. <https://doi.org/10.3390/ijms22052405>

Taylor-Seehafer, M., Jacobvitz, D., Steiker, L.H., 2008. Patterns of attachment organization, social connectedness, and substance use in a sample of older homeless adolescents: Preliminary findings. *Fam. Community Heal.* 31, S81-8. <https://doi.org/10.1097/01.FCH.0000304021.05632.a1>

Thorberg, F.A., Lyvers, M., 2006. Attachment, fear of intimacy and differentiation of self among clients in substance disorder treatment facilities. *Addict Behav.* 31, 732-737. <https://doi.org/10.1016/j.addbeh.2005.05.050>

Thorberg, F.A., Young, R.M., Sullivan, K.A., Lyvers, M., Connor, J.P., Feeney, G.F. *Addict Behav.*, 2011. Alexithymia, craving and attachment in a heavy drinking population. 36, 427-30. <https://doi.org/10.1016/j.addbeh.2010.12.016>

Tops, M., Koole, S.L., Ijzerman, H., Buisman-Pijlman, F.T.A., 2014. Why social attachment and oxytocin protect against addiction and stress: Insights from the dynamics between ventral and dorsal corticostriatal systems. *Pharmacol. Biochem. Behav.* 119, 39–48. <https://doi.org/10.1016/j.pbb.2013.07.015>

Torresani, S., Favaretto, E., Zimmermann, C., 2000. Parental representations in drug-dependent patients and their parents. *Compr. Psychiatry* 41, 123–129. [https://doi.org/10.1016/S0010-440X\(00\)90145-7](https://doi.org/10.1016/S0010-440X(00)90145-7)

Tremblay, M., Baydala, L., Khan, M., Currie, C., Morley, K., Burkholder, C., Davidson, R., Stillar, A., 2020. Primary Substance Use Prevention Programs for Children and Youth: A Systematic Review. *Pediatrics* 146, e20192747. <https://doi.org/10.1542/peds.2019-2747>

Tyrka, A.R., Parade, S.H., Welch, E.S., Ridout, K.K., Price, L.H., Marsit, C., Philip, N.S., Carpenter, L.L., 2016. Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations with early adversity and depressive, anxiety and substance-use disorders. *Transl. Psychiatry* 6, e848. <https://doi.org/10.1038/tp.2016.112>

UN General Assembly, 2016. Resolution adopted by the General Assembly on 19 April 2016. S-30/1. Our joint commitment to effectively addressing and countering the world drug problem. *Ungass* 56350, 1–27.

Unternaehrer E, Meyer AH, Burkhardt SCA, Dempster E, Staehli S, Theill N, Lieb R, Meinschmidt G, 2015. Childhood maternal care is associated with DNA methylation of the genes for brain-derived neurotrophic factor (BDNF) and oxytocin receptor (OXR) in peripheral blood cells in adult men and women. *Stress* 18, 451–461.

Unterrainer, H.F., Hiebler, M., Ragger, K., Froehlich, L., Koschutnig, K., Schoeggl, H., Kapfhammer, H.P., Papousek, I., Weiss, E.M., Fink, A. 2016. White matter integrity in polydrug users in relation to attachment and personality: a controlled diffusion tensor imaging study. *Brain Imaging Behav.* 10:1096-1107. doi: 10.1007/s11682-015-9475-4.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Unterrainer, H.F., Hiebler-Ragger, M., Koschutnig, K., Fuchshuber, J., Tscheschner, S., Url, M., Wagner-Skacel, J., Reininghaus, E.Z., Papousek, I., Weiss, E.M., Fink, A., 2017. Addiction as an attachment disorder: White matter impairment is linked to increased negative affective states in poly-drug use. *Front. Hum. Neurosci.* 11, 1–11. <https://doi.org/10.3389/fnhum.2017.00208>

Unterrainer, H.F., Hiebler-Ragger, M., Rogen, L., Kapfhammer, H.P., 2018. Addiction as an attachment disorder. *Der Nervenarzt* . 89, 1043-1048. <https://doi.org/10.1007/s00115-017-0462-4>.

Vaht, M., Kurrikoff, T., Laas, K., Veidebaum, T., & Harro, J. (2016). Oxytocin receptor gene variation rs53576 and alcohol abuse in a longitudinal population representative study. *Psychoneuroendocrinology*, 74, 333-341.

Van Der Vorst, H., Engels, R.C.M.E., Meeus, W., Deković, M., Vermulst, A., 2006. Parental attachment, parental control, and early development of alcohol use: A longitudinal study. *Psychol. Addict. Behav.* 20, 107–116. <https://doi.org/10.1037/0893-164X.20.2.107>

van der Zwaluw, C. S., & Engels, R. C. M. E., 2009. Gene–environment interactions and alcohol use and dependence: Current status and future challenges. *Addiction* 104, 907–914. <https://doi.org/10.1111/j.1360-0443.2009.02563.x>

Van Der Zwaluw, C.S., Engels, R.C.M.E., Vermulst, A.A., Franke, B., Buitelaar, J., Verkes, R.J., Scholte, R.H.J., 2010. Interaction between dopamine D2 receptor genotype and parental rule-setting in adolescent alcohol use: Evidence for a gene-parenting interaction. *Mol. Psychiatry* 15, 727–735. <https://doi.org/10.1038/mp.2009.4>

Van Ijzendoorn, M.H., Caspers, K., Bakermans-Kranenburg, M.J., Beach, S.R.H., Philibert, R., 2010. Methylation matters: Interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. *Biol. Psychiatry* 68, 405–407. <https://doi.org/10.1016/j.biopsych.2010.05.008>

Van Tol, H. H., Wu, C. M., Guan, H. C., Ohara, K., Bunzow, J. R., Civelli, O., Kennedy, J., Seeman, P., Niznik, H. B., & Jovanovic, V. 1992. Multiple dopamine D4 receptor variants in the human population. *Nature*. 358, 149-152. <https://doi:10.1038/358149a0>

Vaske, J., Newsome, J., Wright, J.P., 2012. Interaction of serotonin transporter linked polymorphic region and childhood neglect on criminal behavior and substance use for males and females. *Dev. Psychopathol.* 24, 181–193. <https://doi.org/10.1017/S0954579411000769>

Vink, J.M., 2016. Genetics of addiction: Future focus on gene × environment interaction? *J. Stud. Alcohol Drugs* 77, 684–687. <https://doi.org/10.15288/jsad.2016.77.684>

Vinkers, C.H., Van Gastel, W.A., Schubart, C.D., Van Eijk, K.R., Luykx, J.J., Van Winkel, R., Joëls, M., Ophoff, R.A., Boks, M.P.M., 2013. The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the COMT Val158Met polymorphism. *Schizophr. Res.* 150, 303–311. <https://doi.org/10.1016/j.schres.2013.07.020>

Virkkunen, M., Eggert, M., Rawlings, R., Linnoila, M., 1996. A prospective follow-up study of alcoholic violent offenders and fire setters. *Arch. Gen. Psychiatry* 53, 523–529. <https://doi.org/10.1001/archpsyc.1996.01830060067009>

Vismara, L., Presaghi, F., Bocchia, M., Ricci, R.V., Ammaniti, M., 2019. Attachment Patterns in Subjects Diagnosed With a Substance Use Disorder: A Comparison of Patients in Outpatient Treatment and Patients in Therapeutic Communities. *Front. Psychiatry* 10, 1–12. <https://doi.org/10.3389/fpsy.2019.00807>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic Advances from the Brain Disease  
12 Model of Addiction. *N. Engl. J. Med.* 374, 363–371. <https://doi.org/10.1056/nejmra1511480>.
- 13 Vrettou, M., Nilsson, K.W., Tuvblad, C., Rehn, M., Åslund, C., Andershed, A.K., Wallén-Mackenzie,  
14 Å., Andershed, H., Hodgins, S., Nylander, I., Comasco, E., 2019. VGLUT2 rs2290045 genotype  
15 moderates environmental sensitivity to alcohol-related problems in three samples of youths. *Eur.*  
16 *Child Adolesc. Psychiatry* 28, 1329–1340. <https://doi.org/10.1007/s00787-019-01293-w>
- 17 Vungkhanching, M., Sher, K.J., Jackson, K.M., Parra, G.R., 2004. Relation of attachment style to family  
18 history of alcoholism and alcohol use disorders in early adulthood. *Drug Alcohol Depend.* 75,  
19 47-53. <https://doi.org/10.1016/j.drugalcdep.2004.01.013>
- 20 Walsh, A., 1995. Parental attachment, drug use, and facultative sexual strategies. *Soc. Biol.* 42, 95–107.  
21 <https://doi.org/10.1080/19485565.1995.9988890>
- 22 Wang, J., Qin, W., Liu, B., Wang, D., Zhang, Y., Jiang, T., & Yu, C. (2013). Variant in OXTR gene and  
23 functional connectivity of the hypothalamus in normal subjects. *Neuroimage*, 81, 199-204.
- 24 Wedekind, D., Bandelow, B., Heitmann, S., Havemann-Reinecke, U., Engel, K.R., Huether, G., 2013.  
25 Attachment style, anxiety coping, and personality-styles in withdrawn alcohol addicted  
26 inpatients. *Subst Abuse Treat Prev Policy.* 8,1. <https://doi.org/10.1186/1747-597X-8-1>
- 27 Whitesell, M., Bachand, A., Peel, J., Brown, M., 2013. Familial, Social, and Individual Factors  
28 Contributing to Risk for Adolescent Substance Use. *J. Addict.* 2013, 1–9.  
29 <https://doi.org/10.1155/2013/579310>
- 30 Willis, A.S., Wallston, K.A., & Johnson, K.R. S., 2001. Tobacco and alcohol use among young adults:  
31 Exploring religious faith, locus of health control, and coping strategies as predictors. In T. G. Plante,  
32 & A. C. Sherman (Eds.), *Faith and health: Psychological perspectives*, Guilford Press, New York, pp.  
33 213-239.
- 34 Winham, K.M., Engstrom, M., Golder, S., Renn, T., Higgins, G.E., Logan ,T.K., 2015. Childhood  
35 victimization, attachment, psychological distress, and substance use among women on probation  
36 and parole. *Am J Orthopsychiatry.* 85, 45-158. <https://doi.org/10.1037/ort0000038>
- 37 Wise , M.H., Weierbach, F. , Cao, Y. , Phillips, K., 2017. Tobacco Use and Attachment Style in  
38 Appalachia. *Issues Ment Health Nurs.* 38, 562-569.  
39 <https://doi.org/10.1080/01612840.2017.1312651>
- 40 Zakhour, M., Haddad, C., Salameh, P., Akel, M., Fares, K., Sacre, H., Hallit, S., Obeid, S., 2020. Impact  
41 of the interaction between alexithymia and the adult attachment styles in participants with alcohol  
42 use disorder. *Alcohol.* 83, 1-8. <https://doi.org/10.1016/j.alcohol.2019.08.007>
- 43 Zaso, M.J., Goodhines, P.A., Wall, T.L., Park, A., 2019. Meta-Analysis on Associations of Alcohol  
44 Metabolism Genes with Alcohol Use Disorder in East Asians. *Alcohol Alcohol.* 54, 216–224.  
45 <https://doi.org/10.1093/alcac/agz011>
- 46 Zdankiewicz-Ścigała, E., Ścigała, D.K., 2020. Attachment Style, Early Childhood Trauma, Alexithymia,  
47 and Dissociation Among Persons Addicted to Alcohol: Structural Equation Model of  
48 Dependencies. *Front Psychol.* 10, 2957. <https://doi.org/10.3389/fpsyg.2019.02957>
- 49 Zdankiewicz-Ścigała, E., Ścigała, D.K. *Front .*, 2018. Relationship Between Attachment Style in  
50 Adulthood, Alexithymia, and Dissociation in Alcohol Use Disorder Inpatients. *Mediational*  
51 *Model. Psychol.* 9,2039. <https://doi.org/10.3389/fpsyg.2018.02039>
- 52 Zeinali, A., Sharifi, H., Enayati, M., Asgari, P., Pasha, G., 2011. The mediational pathway among  
53 parenting styles, attachment styles and self-regulation with addiction susceptibility of  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

adolescents. *J Res Med Sci.* 16, 1105-1121.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/pmc3430035/>

Zhai, Z.W., Kirisci, L., Tarter, R.E., Ridenour, T.A., 2014. Psychological dysregulation during adolescence mediates the association of parent-child attachment in childhood and substance use disorder in adulthood. *Am. J. Drug Alcohol Abuse* 40, 67–74.  
<https://doi.org/10.3109/00952990.2013.848876>

Zhang, H., Wang, F., Kranzler, H.R., Zhao, H., Gelernter, J., 2013. Profiling of childhood adversity-associated DNA methylation changes in alcoholic patients and healthy controls. *PLoS One* 8, e65648.  
<https://doi.org/10.1371/journal.pone.0065648>

Zhang, Y., Wang, D., Johnson, A.D., Papp, A.C., Sadée, W., 2005. Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. *J. Biol. Chem.* 280, 32618–32624.  
<https://doi.org/10.1074/jbc.M504942200>

~~Abar CC, Jackson KM, Colby SM, Barnett NP., 2015. Parent-Child Discrepancies in Reports of Parental Monitoring and Their Relationship to Adolescent Alcohol-Related Behaviors. *J Youth Adoles.* 44, 1688-1701.~~

~~Ainsworth, M. D. S., Blehar, M. C, Waters, E., & Wall, S., 1978. Patterns of attachment: A psychological study of the strange situation. Hillsdale, NJ: Erlbaum.~~

~~Allen, M.L., Garcia Huidobro, D., Porta, C., Curran, D., Patel, R., Miller, J., Borowsky, I., 2016. Effective Parenting Interventions to Reduce Youth Substance Use: A Systematic Review. *Pediatrics* 138, e20154425. <https://doi.org/10.1542/peds.2015-4425>~~

~~Althaus, M., Groen, Y., Wijers, A.A., Mulder, L.J.M., Minderaa, R.B., Kema, I.P., Dijk, J.D.A., Hartman, C.A., Hoekstra, P.J., 2009. Differential effects of 5-HTTLPR and DRD2/ANKK1 polymorphisms on electrocortical measures of error and feedback processing in children. *Clin. Neurophysiol.* 120, 93–107. <https://doi.org/10.1016/j.clinph.2008.10.012>~~

~~Andres, F., Castanier, C., Le Seanff, C., 2014. Attachment and alcohol use amongst athletes: The mediating role of conscientiousness and alexithymia. *Addict. Behav.* 39, 487–490. <https://doi.org/10.1016/j.addbeh.2013.10.022>~~

~~Arnau, M.M., Mondon, S., Santacreu, J.J., 2008. Using the temperament and character inventory (TCI) to predict outcome after inpatient detoxification during 100 days of outpatient treatment. *Alcohol* 43, 583–588. <https://doi.org/10.1093/alcale/agn047>~~

~~Badenes-Ribera, L., Fabris, M.A., Gastaldi, F.G.M., Prino, L.E., Longobardi, C., 2019. Parent and peer attachment as predictors of facebook addiction symptoms in different developmental stages (early adolescents and adolescents). *Addict. Behav.* 95, 226–232. <https://doi.org/10.1016/j.addbeh.2019.05.009>~~

~~Bailey, J.A., Hill, K.G., Oesterle, S., Hawkins, J.D., 2006. Linking Substance Use and Problem Behavior Across Three Generations. *J. Abnorm. Child Psychol.* 34, 263–282. <https://doi.org/10.1007/s10802-006-9033-z>~~

~~Bahr, S.J., Hoffmann, J.P., Yang, X., 2005. Parental and peer influences on the risk of adolescent drug use. *J Prim Prev.* 26, 529–551. <https://doi.org/10.1007/s10935-005-0014-8>~~

~~Bakermans Kranenburg, M. J., & Van IJzendoorn, M. H. 2009. The first 10,000 adult attachment interviews: Distributions of adult attachment representations in clinical and non-clinical groups. *Attachment and Human Development*, 11(3), 223–263. <https://doi.org/10.1080/14616730902814762>~~

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Baraez, S.J., Everett, N.A., Robinson, K.J., Campbell, G.R., Cornish, J.L., 2020. Maternal separation changes maternal care, anxiety like behaviour and expression of paraventricular oxytocin and corticotrophin releasing factor immunoreactivity in lactating rats. *J. Neuroendocrinol.* 32, 12861. <https://doi.org/10.1111/jne.12861>

Beach, S.R.H., Lei, M.K., Brody, G.H., Yu, T., Philibert, R.A., 2014. Nonsupportive parenting affects telomere length in young adulthood among african americans: Mediation through substance use. *J. Fam. Psychol.* 28, 967–972. <https://doi.org/10.1037/fam0000039>

Bendre, M., Comaseo, E., Checknita, D., Tiihonen, J., Hodgins, S., Nilsson, K.W., 2018. Associations Between MAOA-uVNTR Genotype, Maltreatment, MAOA Methylation, and Alcohol Consumption in Young Adult Males. *Alcohol. Clin. Exp. Res.* 42, 508–519. <https://doi.org/10.1111/acer.13578>

Berglund, K.J., Balldin, J., Berggren, U., Gerdner, A., Fahlke, C., 2013. Childhood Maltreatment Affects the Serotonergic System in Male Alcohol Dependent Individuals. *Alcohol. Clin. Exp. Res.* 37, 757–762. <https://doi.org/10.1111/acer.12023>

Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J., 1998. Childhood trauma questionnaire. Assessment of family violence: A handbook for researchers and practitioners.

Bifulco, A., Bernazzani, O., Moran, P. M., & Jacobs, C., 2005. The childhood experience of care and abuse questionnaire (CECA. Q): validation in a community series. *British Journal of Clinical Psychology*, 44(4), 563–581.

Borelli, J.L., Goshin, L., Joestl, S., Clark, J., Byrne, M.W., 2011. Attachment Organization in a Sample of Incarcerated Mothers. *Attach. Hum. Dev.* 12, 355–374. <https://doi.org/10.1080/14616730903416971>.

Borsboom, D., Cramer, A., Kalis, A., 2018. Brain disorders? Not really... Why network structures block reductionism in psychopathology research. *Behav. Brain Sci.* 119, 1–54. <https://doi.org/10.1017/S0140525X17002266>

Bosmans, G., Young, J.F., Hankin, B.L., 2018. NR3C1 methylation as a moderator of the effects of maternal support and stress on insecure attachment development. *Dev. Psychol.* 54, 29–38. <https://doi.org/10.1037/dev0000422>

Bowlby, J. (1969). *Attachment and Loss, Volume 1–3, Attachment.* New York: Basic Books.

Brady, K.T., McRae, A.L., Maria, M.M.M.S., DeSantis, S.M., Simpson, A.N., Waldrop, A.E., Back, S.E., Kreek, M.J., 2009. Response to corticotropin releasing hormone infusion in cocaine dependent individuals. *Arch. Gen. Psychiatry* 66, 422–430. <https://doi.org/10.1001/archgenpsychiatry.2009.9>

Branstetter, S.A., Furman, W., Cottrell, L., 2009. The influence of representations of attachment, maternal-adolescent relationship quality, and maternal monitoring on adolescent substance use: A 2-year longitudinal examination. *Child Dev.* 80, 1448–1462. <https://doi.org/10.1111/j.1467-8624.2009.01344.x>

Brody, G.H., Beach, S.R.H., Philibert, R.A., Chen, Y. fu, Lei, M.K., Murry, V.M.B., Brown, A.C., 2009. Parenting Moderates a Genetic Vulnerability Factor in Longitudinal Increases in Youths' Substance Use. *J. Consult. Clin. Psychol.* 77, 1–11. <https://doi.org/10.1037/a0012996>

Brody, G.H., Chen, Y. fu, Beach, S.R.H., Kogan, S.M., Yu, T., DiClemente, R.J., Wingood, G.M., Windle, M., Philibert, R.A., 2014. Differential sensitivity to prevention programming: A

Formatted: No underline, Font color: Auto

Formatted: No underline, Font color: Auto, English (United Kingdom)

Formatted: English (United Kingdom)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

dopaminergic polymorphism enhanced prevention effect on protective parenting and adolescent substance use. *Heal. Psychol.* 33, 182–191. <https://doi.org/10.1037/a0031253>

Brook, J.S., Whiteman, M., Finch, S., 1993. Role of Mutual Attachment in Drug Use: A Longitudinal Study. *J. Am. Acad. Child Adolesc. Psychiatry* 32, 982–989. <https://doi.org/10.1097/00004583-199309000-00015>

Buisman Pijlman, F.T.A., Sumracki, N.M., Gordon, J.J., Hull, P.R., Carter, C.S., Tops, M., 2014. Individual differences underlying susceptibility to addiction: Role for the endogenous oxytocin system. *Pharmacol. Biochem. Behav.* 119, 22–38. <https://doi.org/10.1016/j.pbb.2013.09.005>

Carey, C.E., Agrawal, A., Zhang, B., Conley, E.D., Degenhardt, L., Heath, A.C., Li, D., Lynskey, M.T., Martin, N.G., Montgomery, G.W., Wang, T., Bierut, L.J., Hariri, A.R., Nelson, E.C., Bogdan, R., 2015. Monoacylglycerol lipase (MGLL) polymorphism rs604300 interacts with childhood adversity to predict cannabis dependence symptoms and amygdala habituation: Evidence from an endocannabinoid system level analysis. *J. Abnorm. Psychol.* 124, 860–877. <https://doi.org/10.1037/abn0000079>

Carter, C.S., 2017. The role of oxytocin and vasopressin in attachment. *Psychodyn. Psychiatry* 45, 499–518. <https://doi.org/10.1521/pdps.2017.45.4.499>

Caspers, K.M., Yucuis, R., Troutman, B., Spinks, R., 2006. Attachment as an organizer of behavior: Implications for substance abuse problems and willingness to seek treatment. *Subst. Abuse. Treat. Prev. Policy* 1. <https://doi.org/10.1186/1747-597X-1-32>

Caspi, A., 2002. Role of Genotype in the Cycle of Violence in Maltreated Children. *Science* (80-.). 297, 851–854. <https://doi.org/10.1126/science.1072290>

Caspi, A., 2003. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science* (80-.). 301, 386–389. <https://doi.org/10.1126/science.1083968>

Cassidy, J., & Shaver, P. R., 2016. *Handbook of attachment: Theory, research, and clinical applications.* (Eds.) New York: Guilford Press.

Cecil CAM, Lysenko LJ, Jaffee SR, Pingault J B, Smith RG, Relton CL, Woodward G, McArdle W, Mill J, Barker ED, 2014. Environmental risk, Oxytocin Receptor Gene (OXTR) methylation and youth callous-unemotional traits: A 13-year longitudinal study. *Molec. psychiatry* 19, 1071–1077. <https://doi.org/10.1038/mp.2014.1659>

Ciccocioppo R, Economidou D, Fedeli A, Angeletti S, Weiss F, Heilig M, Massi M, 2004. Attenuation of ethanol self-administration and of conditioned reinstatement of alcohol-seeking behaviour by the antioioid peptide nociceptin/orphanin FQ in alcohol preferring rats. *Psychopharmacology (Berl)* 172:170–178. <https://doi.org/10.1002/brb3.1659>

Cimino, S., Carola, V., Cerniglia, L., Bussone, S., Bevilacqua, A., Tambelli, R., 2020. The  $\mu$  opioid receptor gene A118G polymorphism is associated with insecure attachment in children with disruptive mood-regulation disorder and their mothers. *Brain Behav.* 10. <https://doi.org/10.1002/brb3.1659>

Cleveland, M.J., Reavy, R., Mallett, K.A., Turrisi, R., White, H.R., 2014. Moderating effects of positive parenting and maternal alcohol use on emerging adults' alcohol use: Does living at home matter? *Addict. Behav.* 39, 869–878. <https://doi.org/10.1016/j.addbeh.2014.01.028>

Copeland, W.E., Sun, H., Costello, E.J., Angold, A., Heilig, M.A., Barr, C.S., 2011. Child opioid receptor gene variant influences parent-child relations. *Neuropsychopharmacology* 36, 1165–1170. <https://doi.org/10.1038/npp.2010.251>

Formatted: Italian (Italy)

Formatted: Italian (Italy)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Cornellà Font, M.G., Viñas Poch, F., Juárez López, J.R., Martín Perpiñá, M.D.L.M., Malo Cerrato, S., 2018. Temperament and attachment as predictive factors for the risk of addiction to substances in adolescents. *Rev. Psicopatol. y Psicol. Clin.* 23, 179–187. <https://doi.org/10.5944/rppe.vol.23.num.3.2018.21423>

Craig F, Tenuta F, Rizzato V, Costabile A, Trabacca A, Montiroso R. Attachment related dimensions in the epigenetic era: A systematic review of the human research. *Neurosci Biobehav Rev.* 2021 Jun;125:654–666. <https://doi.org/10.1016/j.neubiorev.2021.03.006>

Formatted: Italian (Italy)

Csala, I., Egervari, L., Dome, P., Faludi, G., Dome, B., Lazary, J., 2015. The possible role of maternal bonding style and CHRN2 gene polymorphisms in nicotine dependence and related depressive phenotype. *Prog. Neuro Psychopharmacology Biol. Psychiatry* 59, 84–90. <https://doi.org/10.1016/j.pnpbp.2015.01.012>

Cummings, E. M., & Cummings, J. S., 2002. Parenting and attachment. In M. H. Bornstein (Ed.), *Handbook of parenting: Practical issues in parenting* (p. 35–58). Lawrence Erlbaum Associates Publishers.

Dalvie, S., Maihofer, A.X., Coleman, J.R.I., Bradley, B., Breen, G., Brick, L.A., Chen, C. Y., Choi, K.W., Duncan, L.E., Guffanti, G., Haas, M., Harnal, S., Liberzon, I., Nugent, N.R., Provost, A.C., Ressler, K.J., Torres, K., Amstadter, A.B., Bryn Austin, S., Baker, D.G., Bolger, E.A., Bryant, R.A., Calabrese, J.R., Delahanty, D.L., Farrer, L.A., Feeny, N.C., Flory, J.D., Forbes, D., Galea, S., Gautam, A., Gelernter, J., Hammamich, R., Jett, M., Junglen, A.G., Kaufman, M.L., Kessler, R.C., Khan, A., Kranzler, H.R., Lebois, L.A.M., Marmar, C., Mavissakalian, M.R., McFarlane, A., Donnell, M.O., Oreutt, H.K., Pietrzak, R.H., Risbrough, V.B., Roberts, A.L., Rothbaum, A.O., Roy Byrne, P., Ruggiero, K., Seligowski, A. V., Sheerin, C.M., Silove, D., Smoller, J.W., Stein, M.B., Teicher, M.H., Ursano, R.J., Van Hooff, M., Winternitz, S., Wolff, J.D., Yehuda, R., Zhao, H., Zoellner, L.A., Stein, D.J., Koenen, K.C., Nievergelt, C.M., 2020. Genomic influences on self-reported childhood maltreatment. *Transl. Psychiatry* 10, 38. <https://doi.org/10.1038/s41398-020-0706-0>

Dannlowski, U., Kugel, H., Grotegerd, D., Redlich, R., Opel, N., Dohm, K., Zaremba, D., Grögler, A., Schwieren, J., Suslow, T., Ohrmann, P., Bauer, J., Krug, A., Kircher, T., Jansen, A., Domschke, K., Hohoff, C., Zwitserlood, P., Heinrichs, M., Arolt, V., Heindel, W., Baune, B.T., 2016. Disadvantage of Social Sensitivity: Interaction of Oxytocin Receptor Genotype and Child Maltreatment on Brain Structure. *Biol. Psychiatry* 80, 398–405. <https://doi.org/10.1016/j.biopsych.2015.12.010>

Darling Rasmussen, P., & Storebø, O. J. (2021). Attachment and Epigenetics: A Scoping Review of Recent Research and Current Knowledge. *Psychological Reports*, 124(2), 479–501; <https://doi.org/10.1177/0033294120901846>

Dawes, M., Clark, D., Moss, H., Kirisei, L., Tarter, R., 1999. Family and peer correlates of behavioral self-regulation in boys at risk for substance abuse. *Am. J. Drug Alcohol Abuse* 25, 219–237. <https://doi.org/10.1081/ADA-100101857>

De Nardi, L., Carpentieri, V., Pascale, E., Pucci, M., D'addario, C., Cerniglia, L., Adriani, W., Cimino, S., 2020. Involvement of DAT1 gene on internet addiction: Cross-correlations of methylation levels in 5' utr and 3' UTR genotypes, interact with impulsivity and attachment driven quality of relationships. *Int. J. Environ. Res. Public Health* 17, 1–11. <https://doi.org/10.3390/ijerph17217956>

Formatted: Highlight

De Palo, F., Capra, N., Simonelli, A., Saleuni, S., Di Riso, D., 2014. Parenting quality in drug addicted mothers in a therapeutic mother-child community: The contribution of attachment and personality assessment. *Front. Psychol.* 5, 1–13. <https://doi.org/10.3389/fpsyg.2014.01009>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

De Wit, M.L., Embree, B.G., De Wit, D., 1999. Determinants of the risk and timing of alcohol and illicit drug use onset among natives and non-natives: Similarities and differences in family attachment processes. *Soc. Biol.* 46, 100–121. <https://doi.org/10.1080/19485565.1999.9988990>

Deak, J. D., & Johnson, E. C., 2021. Genetics of substance use disorders: a review. *Psychological medicine*, 1–12.

Delvecchio, E., Di Riso, D., Lis, A., Saleuni, S., 2016. Adult Attachment, Social Adjustment, and Well-Being in Drug Addicted Inpatients. *Psychol. Rep.* 118, 587–607. <https://doi.org/10.1177/0033294116639181>

Dick DM, Kendler KS., 2012. The impact of gene-environment interaction on alcohol use disorders. *Alcohol Res.* 34, 318–24. PMID: 23134047; PMCID: PMC3606909.

Doan, S.N., Dich, N., Evans, G.W., 2014. Childhood cumulative risk and later allostatic load: Mediating role of substance use. *Heal. Psychol.* 33, 1402–1409. <https://doi.org/10.1037/a0034790>

Dutra, L., & Lyons Ruth, K. (2005, April). Maltreatment, maternal and child psychopathology, and quality of early care as predictors of adolescent dissociation. In biennial meeting of the Society for Research in Child Development, Atlanta, GA.

Ein-Dor, T., Verbeke, W.J.M.I., Mokry, M., Vrtička, P., 2018. Epigenetic modification of the oxytocin and glucocorticoid receptor genes is linked to attachment avoidance in young adults. *Attach. Hum. Dev.* 20, 439–454. <https://doi.org/10.1080/14616734.2018.1446451>

Ellis, B.J., Horn, A.J., Carter, C.S., van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., 2021. Developmental programming of oxytocin through variation in early-life stress: Four meta-analyses and a theoretical reinterpretation. *Clin. Psychol. Rev.* 86, 101985. <https://doi.org/10.1016/j.cpr.2021.101985>

Englund, M. M., Kuo, S. I. C., Puig, J., & Collins, W. A. (2011). Early roots of adult competence: The significance of close relationships from infancy to early adulthood. *International journal of behavioral development*, 35(6), 490–496. <https://doi.org/10.1177/0165025411422994>

Enoch, M.A., 2012. The influence of gene-environment interactions on the development of alcoholism and drug dependence. *Curr. Psychiatry Rep.* 14, 150–158. <https://doi.org/10.1007/s11920-011-0252-9>

Estevez, A., Jauregui, P., Lopez-Gonzalez, H., 2019. Attachment and behavioral addictions in adolescents: The mediating and moderating role of coping strategies. *Scand. J. Psychol.* 60, 348–360. <https://doi.org/10.1111/sjop.12547>

Estévez, A., Jáuregui, P., Sánchez-Mareos, I., López-González, H., Griffiths, M.D., 2017. Attachment and emotion regulation in substance addictions and behavioral addictions. *J. Behav. Addict.* 6, 534–544. <https://doi.org/10.1556/2006.6.2017.086>

Fairbairn, C.E., Briley, D.A., Kang, D., Fraley, R.C., Hankin, B.L., Ariss, T., 2018. A meta-analysis of longitudinal associations between substance use and interpersonal attachment security. *Psychol. Bull.* 144, 532–555. <https://doi.org/10.1037/bul0000141>

Feinstein, A.R., 1970. The pre-therapeutic classification of co-morbidity in chronic disease. *J. Chronic Dis.* 23, 455–468. [https://doi.org/10.1016/0021-9681\(70\)90054-8](https://doi.org/10.1016/0021-9681(70)90054-8)

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Fite, P.J., Brown, S., Hossain, W., Manzardo, A., Butler, M.G., Bortolato, M., 2019. Tobacco and  
12 cannabis use in college students are predicted by sex dimorphic interactions between MAOA  
13 genotype and child abuse. *CNS Neurosci. Ther.* 25, 101–111. <https://doi.org/10.1111/ens.13002>
- 14 Flanagan, J.C., Baker, N.L., McRae-Clark, A.L., Brady, K.T., Moran-Santa Maria, M.M., 2015. Effects  
15 of adverse childhood experiences on the association between intranasal oxytocin and social stress  
16 reactivity among individuals with cocaine dependence. *Psychiatry Res.* 229, 94–100.  
17 <https://doi.org/10.1016/j.psychres.2015.07.064>
- 18 Fraley, R. C., 2019. Attachment in adulthood: Recent developments, emerging debates, and future  
19 directions. *Annual review of psychology*, 70, 401–422.
- 20 Frank, L.E., Nagel, S.K., 2017. Addiction and Moralization: the Role of the Underlying Model of  
21 Addiction. *Neuroethics* 10, 129–139. <https://doi.org/10.1007/s12152-017-9307-x>
- 22 Fuchshuber, J., Unterrainer, H.F., 2020. Childhood Trauma, Personality, and Substance Use Disorder:  
23 The Development of a Neuropsychanalytic Addiction Model. *Front. Psychiatry* 11, 1–21.  
24 <https://doi.org/10.3389/fpsyt.2020.00531>
- 25 Garcia Huidobro, D., Doty, J.L., Davis, L., Borowsky, I.W., Allen, M.L., 2018. For Whom Do Parenting  
26 Interventions to Prevent Adolescent Substance Use Work? *Prev. Sci.* 19, 570–578.  
27 <https://doi.org/10.1007/s11121-017-0853-6>
- 28 Garg, E., Chen, L., Nguyen, T.T.T., Pokhvisneva, I., Chen, L.M., Unternaehrer, E., MacIsaac, J.L.,  
29 McEwen, L.M., Mah, S.M., Gaudreau, H., Levitan, R., Moss, E., Sokolowski, M.B., Kennedy, J.L.,  
30 Steiner, M.S., Meaney, M.J., Holbrook, J.D., Silveira, P.P., Karnani, N., Kobor, M.S., O'Donnell,  
31 K.J., 2018. The early care environment and DNA methylome variation in childhood. *Dev.*  
32 *Psychopathol.* 30, 891–903. <https://doi.org/10.1017/S0954579418000627>
- 33 Gattamorta, K.A., Varela, A., McCabe, B.E., Mena, M.P., Santisteban, D.A., 2017. Psychiatric  
34 Symptoms, Parental Attachment, and Reasons for Use as Correlates of Heavy Substance Use Among  
35 Treatment Seeking Hispanic Adolescents. *Subst. Use Misuse* 52, 392–400.  
36 <https://doi.org/10.1080/10826084.2016.1229338>
- 37 Gerra, G., Angioni, L., Zaimovic, A., Moi, G., Bussandri, M., Bertacca, S., Santoro, G., Gardini, S.,  
38 Caccavari, R., Nicoli, M.A., 2004. Substance Use among High School Students: Relationships with  
39 Temperament, Personality Traits, and Parental Care Perception. *Subst. Use Misuse* 39, 345–367.  
40 <https://doi.org/10.1081/JA-120028493>
- 41 Gerra, G., Garofano, L., Santoro, G., Bosari, S., Pellegrini, C., Zaimovic, A., Moi, G., Bussandri, M.,  
42 Moi, A., Brambilla, F., Donnini, C., 2004. Association between Low Activity Serotonin Transporter  
43 Genotype and Heroin Dependence: Behavioral and Personality Correlates. *Am. J. Med. Genet.—*  
44 *Neuropsychiatr. Genet.* 126 B, 37–42. <https://doi.org/10.1002/ajmg.b.20111>
- 45 Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell'Agnello, G., Manfredini, M., Somaini, L.,  
46 Petracea, F., Caretti, V., Saracino, M.A., Raggi, M.A., Donnini, C., 2007. Homovanillic acid (HVA)  
47 plasma levels inversely correlate with attention deficit hyperactivity and childhood neglect measures  
48 in addicted patients. *J. Neural Transm.* 114, 1637–1647. <https://doi.org/10.1007/s00702-007-0793-6>
- 49 Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell'Agnello, G., Manfredini, M., Somaini, L.,  
50 Petracea, F., Caretti, V., Baroni, C., Donnini, C., 2008. Adrenocorticotrophic hormone and cortisol  
51 plasma levels directly correlate with childhood neglect and depression measures in addicted patients.  
52 *Addict. Biol.* 13, 95–104. <https://doi.org/10.1111/j.1369-1600.2007.00086.x>
- 53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell'Agnello, G., Manfredini, M., Somaini, L., Petraceca, F., Caretti, V., Raggi, M.A., Donnini, C., 2009. Childhood neglect and parental care perception in cocaine addicts: Relation with psychiatric symptoms and biological correlates. *Neurosci. Biobehav. Rev.* 33, 601–610. <https://doi.org/10.1016/j.neubiorev.2007.08.002>

Gerra, G., Manfredini, M., Somaini, L., Milano, G., Ciccocioppo, R., Donnini, C., 2016. Perceived parental care during childhood, ACTH, cortisol and nicotine dependence in the adult. *Psychiatry Res.* 245, 458–465. <https://doi.org/10.1016/j.psychres.2016.09.001>

Gerra, G., Somaini, L., Manfredini, M., Raggi, M.A., Saracino, M.A., Amore, M., Leonardi, C., Cortese, E., Donnini, C., 2014. Dysregulated responses to emotions among abstinent heroin users: Correlation with childhood neglect and addiction severity. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 48, 220–228. <https://doi.org/10.1016/j.pnpbp.2013.10.011>

Gerra, G., Zaimovic, A., Castaldini, L., Garofano, L., Manfredini, M., Somaini, L., Leonardi, C., Gerra, M.L., Donnini, C., 2010. Relevance of perceived childhood neglect, 5-HTT gene variants and hypothalamus-pituitary-adrenal axis dysregulation to substance abuse susceptibility. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 153, 715–722. <https://doi.org/10.1002/ajmg.b.31038>

Gerra, G., Zaimovic, A., Garofano, L., Ciusa, F., Moi, G., Avanzini, P., Talarico, E., Gardini, F., Brambilla, F., Manfredini, M., Donnini, C., 2007. Perceived parenting behavior in the childhood of cocaine users: Relationship with genotype and personality traits. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 144, 52–57. <https://doi.org/10.1002/ajmg.b.30388>

Gerra, M.C., Manfredini, M., Cortese, E., Antonioni, M.C., Leonardi, C., Magnelli, F., Somaini, L., Jayanthi, S., Cadet, J.L., Donnini, C., 2019. Genetic and Environmental Risk Factors for Cannabis Use: Preliminary Results for the Role of Parental Care Perception. *Subst. Use Misuse* 54, 670–680. <https://doi.org/10.1080/10826084.2018.1531430>

Ghasempour, A., Mahmoodi Aghdam, M., n.d. The Role of Depression and Attachment Styles in Predicting Students' Addiction to Cell Phones. *Addict. Heal.* 7, 192–7.

Gill, R. 2017. Addictions from an Attachment Perspective: Do Broken Bonds and Early Trauma Lead to Addictive Behavior. New York, NY: Routledge

Gorwood, P., Wohl, M., Le Strat, Y., Rouillon, F., 2007. Gene-environment interactions in addictive disorders: epidemiological and methodological aspects. *Comptes Rendus—Biol.* 330, 329–338. <https://doi.org/10.1016/j.crv.2007.02.017>

Greenberg, M.T., Siegel, J.M., Leitch, C.J., 1983. The nature and importance of attachment relationships to parents and peers during adolescence. *J. Youth Adoles.* 12, 373–386. <https://doi.org/10.1007/BF02088721>

Groh, A., Rhein, M., Roy, M., Gessner, C., Lichtinghagen, R., Heberlein, A., Hillemacher, T., Bleich, S., Walter, M., Frieling, H., 2020. Trauma Severity in Early Childhood Correlates with Stress and Satiety Hormone Levels in a Pilot Cohort Receiving Diamorphine Maintenance Treatment. *Eur. Addict. Res.* 26, 103–108. <https://doi.org/10.1159/000505293>

Grossmann, K. E., Grossmann, K., & Waters, E. (Eds.), 2005. Attachment from infancy to adulthood: The major longitudinal studies. New York: Guilford Press.

Hagan, M.J., Modecki, K., Tan, L.M., Luecken, L., Wolchik, S., Sandler, I., 2019. Binge drinking in adolescence predicts an atypical cortisol stress response in young adulthood. *Psychoneuroendocrinology*, 100, 137–144. <https://doi.org/10.1016/j.psyneuen.2018.10.002>

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

Formatted: English (United Kingdom)

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Hahn, H.C., Lahiff, M., Guterman, N.B., 2003. Acculturation and parental attachment in Asian-  
12 American adolescents' alcohol use. *J. Adoles. Health* 33, 119–129. [https://doi.org/10.1016/S1054-](https://doi.org/10.1016/S1054-139X(03)00058-2)  
13 [139X\(03\)00058-2](https://doi.org/10.1016/S1054-139X(03)00058-2)
- 14 Haile, C. N., Kosten, T. R., & Kosten, T. A., 2007. Genetics of dopamine and its contribution to cocaine  
15 addiction. *Behavior genetics*, 37(1), 119–145.
- 16 Hansson, A.C., Cippitelli, A., Sommer, W.H., Fedeli, A., Björk, K., Soverchia, L., Terasmaa, A., Massi,  
17 M., Heilig, M., Cicciocioppo, R., 2006. Variation at the rat *Cnr1* locus and sensitivity to relapse into  
18 alcohol seeking induced by environmental stress. *Proc. Natl. Acad. Sci. U. S. A.* 103, 15236–15241.  
19 <https://doi.org/10.1073/pnas.0604419103>
- 20 Hart, H., Lim, L., Mehta, M.A., Curtis, C., Xu, X., Breen, G., Simmons, A., Mirza, K., Rubia, K., 2018.  
21 Altered Functional Connectivity of Fronto-Cingulo-Striatal Circuits during Error Monitoring in  
22 Adolescents with a History of Childhood Abuse. *Front. Hum. Neurosci.* 12, 7.  
23 <https://doi.org/10.3389/fnhum.2018.00007>
- 24 Hayre, R.S., Goulter, N., Moretti, M.M., 2019. Maltreatment, attachment, and substance use in  
25 adolescence: Direct and indirect pathways. *Addict. Behav.* 90, 196–203.  
26 <https://doi.org/10.1016/j.addbeh.2018.10.049>
- 27 Heerde, J.A., Bailey, J.A., Toumbourou, J.W., Catalano, R.F., 2019. Longitudinal Associations Between  
28 the Adolescent Family Environment and Young Adult Substance Use in Australia and the United  
29 States. *Front. Psychiatry* 10, 1–10. <https://doi.org/10.3389/fpsyt.2019.00821>
- 30 Heinrichs, S.C., Koob, G.F., 2004. Corticotropin-releasing factor in brain: A role in activation, arousal,  
31 and affect regulation. *J. Pharmacol. Exp. Ther.* 311, 427–440. <https://doi.org/10.1124/jpet.103.052092>
- 32 Henden, E., Melberg, H.O., Røgeberg, O.J., 2013. Addiction: Choice or Compulsion? *Front. Psychiatry*  
33 4. <https://doi.org/10.3389/fpsyt.2013.00077>
- 34 Henry, K.L., 2008. Low Prosocial Attachment, Involvement With Drug-Using Peers, and Adolescent  
35 Drug Use: A Longitudinal Examination of Mediation Mechanisms. *Psychol. Addict. Behav.* 22,  
36 302–308. <https://doi.org/10.1037/0893-164X.22.2.302>
- 37 Henry, K.L., Oetting, E.R., Slater, M.D., 2009. The Role of Attachment to Family, School, and Peers in  
38 Adolescents' Use of Alcohol: A Longitudinal Study of Within Person and Between Persons Effects.  
39 *J. Couns. Psychol.* 56, 564–572. <https://doi.org/10.1037/a0017041>
- 40 Heyman, G.M., 2009. *Addiction: A disorder of choice.*, *Addiction: A disorder of choice.* Harvard  
41 University Press, Cambridge, MA, US.
- 42 Hines LA, Morley KI, Mackie C, Lynskey M., 2015. Genetic and Environmental Interplay in Adolescent  
43 Substance Use Disorders. *Curr Addict Rep.* 2, 122–129. <https://doi.org/10.1007/s40429-015-0049-8>
- 44 Hicks, B. M., Johnson, W., Durbin, C. E., Blonigen, D. M., Iacono, W. G., & McGue, M., 2013. Gene-  
45 environment correlation in the development of adolescent substance abuse: Selection effects of child  
46 personality and mediation via contextual risk factors. *Dev. Psychopathol.*, 25(1), 119.  
47 <https://doi.org/10.1017/S0954579412000946>
- 48 Hitchcock, P., Fried, E. I., & Frank, M. (2021). Computational Psychiatry Needs Time and Context.  
49 *Annual Review of Psychology*, 73. <https://doi.org/10.1146/annurev-psych-021621-124910>
- 50 Holmes, J., & Holmes, J., 2014. *John Bowlby and Attachment Theory* (2nd ed.). Routledge.  
51 <https://doi.org/10.4324/9781315879772>
- 52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Hood, C.O., Tomko, R.L., Baker, N.L., Tuck, B.M., Flanagan, J.C., Carpenter, M.J., Gray, K.M., Saladin,  
12 M.E., McClure, E.A., 2020. Examining sex, adverse childhood experiences, and oxytocin on  
13 neuroendocrine reactivity in smokers. *Psychoneuroendocrinology* 120, 104752.  
14 <https://doi.org/10.1016/j.psyneuen.2020.104752>
- 15 Huang, M. C., Chen, L. Y., Chang, H. M., Liang, X. Y., Chen, C. K., Cheng, W. J., Xu, K., 2018.  
16 Decreased Blood Levels of Oxytocin in Ketamine-Dependent Patients During Early Abstinence.  
17 *Front. Psychiatry* 9, 633. <https://doi.org/10.3389/fpsyt.2018.00633>
- 18 Ieick R, Lauer S, Romo L, Dupuy G, Lépine JP, Vorspan F. 2013. Dysfunctional parental styles perceived  
19 during childhood in outpatients with substance use disorders. *Psychiatry Res.* 210, 522-528.
- 20 Iglesias, E. B., Fernández del Río, E., Calafat, A., & Fernández-Hermida, J. R., 2014. Attachment and  
21 substance use in adolescence: a review of conceptual and methodological aspects. *Adicciones*, 26,  
22 77-86.
- 23 Jiang, N., Xu, J., Li, X., Wang, Y., Zhuang, L., Qin, S., 2021. Negative Parenting Affects Adolescent  
24 Internalizing Symptoms Through Alterations in Amygdala Prefrontal Circuitry: A Longitudinal Twin  
25 Study. *Biol. Psychiatry* 89, 560-569. <https://doi.org/10.1016/j.biopsych.2020.08.002>
- 26 Jiang, S., Postovit, L., Cattaneo, A., Binder, E.B., Aitchison, K.J., 2019. Epigenetic Modifications in  
27 Stress Response Genes Associated With Childhood Trauma. *Front. Psychiatry* 10.  
28 <https://doi.org/10.3389/fpsyt.2019.00808>
- 29 Joëls, M., Karst, H., DeRijk, R., de Kloet, E.R., 2008. The coming out of the brain mineralocorticoid  
30 receptor. *Trends Neurosci.* 31, 1-7. <https://doi.org/10.1016/j.tins.2007.10.005>
- 31 Jordan, S., Sack, P.M., 2009. Schutz- und Risikofaktoren [Protective factors and risk factors]. In:  
32 Thomasius, R., Schulte-Markwort, M., Küstner, U.J., and Riedesser, P., editors. *Suchtstörungen im*  
33 *Kindes- und Jugendalter. Das Handbuch: Grundlagen und Praxis.* Stuttgart, Germany: Schattauer. p.  
34 127-38.
- 35 Kanamori, M., Weissman, J., De La Rosa, M., Trepka, M.J., Rojas, P., Cano, M.A., Melton, J.,  
36 Unterberger, A., 2016. Latino Mother/Daughter Dyadic Attachment as a Mediator for Substance Use  
37 Disorder and Emotional Abuse. *J. Immigr. Minor. Heal.* 18, 896-903. [https://doi.org/10.1007/s10903-](https://doi.org/10.1007/s10903-015-0312-z)  
38 [015-0312-z](https://doi.org/10.1007/s10903-015-0312-z)
- 39 Kendler, K.S., Myers, J., Prescott, C.A., 2000. Parenting and adult mood, anxiety and substance use  
40 disorders in female twins: An epidemiological, multi-informant, retrospective study. *Psychol. Med.*  
41 30, 281-294. <https://doi.org/10.1017/S0033291799001889>
- 42 Kendler, K. S., Sundquist, K., Ohlsson, H., PalmÚr, K., Maes, H., Winkleby, M. A., & Sundquist, J.  
43 (2012). Genetic and familial environmental influences on the risk for drug abuse: a national Swedish  
44 adoption study. *Archives of general psychiatry*, 69(7), 690-697.
- 45 Kilpatrick, D.G., Koenen, K.C., Ruggiero, K.J., Acierno, R., Galea, S., Resnick, H.S., Roitzsch, J., Boyle,  
46 J., Gelemtier, J., 2007. The serotonin transporter genotype and social support and moderation of  
47 posttraumatic stress disorder and depression in hurricane-exposed adults. *Am. J. Psychiatry* 164,  
48 1693-1699. <https://doi.org/10.1176/appi.ajp.2007.06122007>
- 49 Knudsen, E.I., 2004. Sensitive periods in the development of the brain and behavior. *J. Cogn. Neurosci.*  
50 16, 1412-1425. <https://doi.org/10.1162/0898929042304796>
- 51 Kober, H., 2014. Emotion regulation in substance use disorders. In J. J. Gross (Ed.), *Handbook of*  
52 *emotion regulation.* The Guilford Press, pp 428-446.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Kogan, S.M., Cho, J., Beach, S.R.H., Smith, A.K., Nishitani, S., 2018. Oxytocin receptor gene methylation and substance use problems among young African American men. *Drug Alcohol Depend.* 192, 309–315. <https://doi.org/10.1016/j.drugaledep.2018.08.022>

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. *The Lancet. Psychiatry* 3, 760–773. [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8)

Kostelecky, K.L., 2005. Parental attachment, academic achievement, life events and their relationship to alcohol and drug use during adolescence. *J. Adoles.* 28, 665–669. <https://doi.org/10.1016/j.adolescence.2004.12.006>

Kumpfer K.L., Alvarado R., Whiteside H.O., 2003. Family based interventions for substance use and misuse prevention. *Subst Use Misuse* 38, 1759–1787. <https://doi.org/10.1081/ja-120024240>

Lachman, H.M., Papolos, D.F., Saito, T., Yu, Y.M., Szumlanski, C.L., Weinshilboum, R.M., 1996. Human catechol O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 6, 243–250. <https://doi.org/10.1097/00008571-199606000-00007>

Ladd-Aeosta, C & Fallin, MD 2016, 'The role of epigenetics in genetic and environmental epidemiology', *Epigenomics* 8, 271–283. <https://doi.org/10.2217/epi.15.102>

Laucht, M., Blomeyer, D., Buchmann, A.F., Treutlein, J., Schmidt, M.H., Esser, G., Jennen-Steinmetz, C., Rietschel, M., Zimmermann, U.S., Banaschewski, T., 2012. Catechol O-methyltransferase Val158-met genotype, parenting practices and adolescent alcohol use: Testing the differential susceptibility hypothesis. *J. Child Psychol. Psychiatry Allied Discip.* 53, 351–359. <https://doi.org/10.1111/j.1469-7610.2011.02408.x>

Lee, J.M., Bell, N.J., 2003. Individual differences in attachment-autonomy configurations: Linkages with substance use and youth competencies. *J. Adoles.* 26, 347–361. [https://doi.org/10.1016/S0140-1971\(03\)00018-6](https://doi.org/10.1016/S0140-1971(03)00018-6)

Levandowski, M.L., Viola, T.W., Prado, C.H., Wieck, A., Bauer, M.E., Brietzke, E., Grassi-Oliveira, R., 2016. Distinct behavioral and immunoendocrine parameters during crack-cocaine abstinence in women reporting childhood abuse and neglect. *Drug Alcohol Depend.* 167, 140–148. <https://doi.org/10.1016/j.drugaledep.2016.08.010>

Lewis, C. R., & Olive, M. F., 2014. Early life stress interactions with the epigenome: potential mechanisms driving vulnerability towards psychiatric illness. *Behav. Pharmacol.*, 25(5–6), 341. <https://doi.org/10.1097/FBP.0000000000000057>

Li, T., Du, J., Yu, S., Jiang, H., Fu, Y., Wang, D., Sun, H., Chen, H., Zhao, M., 2012. Pathways to Age of Onset of Heroin Use: A Structural Model Approach Exploring the Relationship of the COMT Gene, Impulsivity and Childhood Trauma. *PLoS One* 7, e48735. <https://doi.org/10.1371/journal.pone.0048735>

Lindberg, M.A., Fugett, A., Carter, J.E., 2015. Tests of the attachment and clinical issues questionnaire as it applies to alcohol dependence. *J. Addict. Med.* 9, 286–295. <https://doi.org/10.1097/ADM.0000000000000131>

Lindberg, M.A., Thomas, S.W., 2011. The attachment and clinical issues questionnaire (ACIQ): Scale development. *J. Genet. Psychol.* 172, 329–352. <https://doi.org/10.1080/00221325.2010.541382>

Liu, C., & Chung, M., 2015. Genetics and epigenetics of circadian rhythms and their potential roles in neuropsychiatric disorders. *Neuroscience bulletin*, 31(1), 141–159.

Formatted: Font color: Auto

Formatted: No underline, Font color: Auto

Field Code Changed

Formatted: No underline, Font color: Auto

Formatted: No underline, Font color: Auto

Formatted: Font color: Auto

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Love, T. M., Stohler, C. S., & Zubieta, J. K. (2009). Positron emission tomography measures of  
12 endogenous opioid neurotransmission and impulsiveness traits in humans. *Archives of general*  
13 *psychiatry*, 66(10), 1124–1134. <https://doi:10.1001/archgenpsychiatry.2009.134>
- 14 Luk, J.W., Patoek Peckham, J.A., King, K.M., 2015. Are Dimensions of Parenting Differentially Linked  
15 to Substance Use Across Caucasian and Asian American College Students? *Subst. Use Misuse* 50,  
16 1360–1369. <https://doi.org/10.3109/10826084.2015.1013134>
- 17 Lutz, P.E., Gross, J.A., Dhir, S.K., Maussion, G., Yang, J., Bramouille, A., Meaney, M.J., Turecki, G.,  
18 2018. Epigenetic Regulation of the Kappa Opioid Receptor by Child Abuse. *Biol. Psychiatry* 84, 751–  
19 761. <https://doi.org/10.1016/j.biopsych.2017.07.012>
- 20 Lyons Ruth, K., Bureau, J. F., Holmes, B., Easterbrooks, A., & Brooks, N. H., 2013. Borderline  
21 symptoms and suicidality/self injury in late adolescence: Prospectively observed relationship  
22 correlates in infancy and childhood. *Psychiatry research*, 206(2–3), 273–281.
- 23 Lyvers, M., Mayer, K., Needham, K., Thorberg, F.A., 2019. Parental bonding, adult attachment, and  
24 theory of mind: A developmental model of alexithymia and alcohol-related risk. *J. Clin. Psychol.* 75,  
25 1288–1304. <https://doi.org/10.1002/jclp.22772>
- 26 Main, M., Hesse, E., & Kaplan, N., 2005. Predictability of Attachment Behavior and Representational  
27 Processes at 1, 6, and 19 Years of Age: The Berkeley Longitudinal Study. In K. E. Grossmann, K.  
28 Grossmann, & E. Waters (Eds.), *Attachment from infancy to adulthood: The major longitudinal*  
29 *studies*. Guilford Publications, pp. 245–304.
- 30 Machin, A. J., & Dunbar, R. I., 2011. The brain opioid theory of social attachment: a review of the  
31 evidence. *Behaviour*, 148(9–10), 985–1025. <https://doi.org/10.1163/000579511X596624>
- 32 Marecau, K., Brick, L.A., Knopik, V.S., Reijneveld, S.A., 2020. Developmental Pathways from Genetic,  
33 Prenatal, Parenting and Emotional/Behavioral Risk to Cortisol Reactivity and Adolescent Substance  
34 Use: A TRAILS Study. *J. Youth Adolesce.* 49, 17–31. <https://doi.org/10.1007/s10964-019-01142-8>
- 35 Maremmani, I., Pacini, M., Popovic, D., Romano, A., Maremmani, A.G., Perugi, G., Deltito, J., Akiskal,  
36 K., Akiskal, H., 2009. Affective temperaments in heroin addiction. *J Affect Disord.* 117, 186–92.  
37 <https://doi.org/10.1016/j.jad.2009.01.007>
- 38 McCrory, E.J., Mayes, L., 2015. Understanding Addiction as a Developmental Disorder: An Argument  
39 for a Developmentally Informed Multilevel Approach. *Curr. Addict. Reports* 2, 326–330.  
40 <https://doi.org/10.1007/s40429-015-0079-2>
- 41 McLaughlin, A., Campbell, A., McColgan, M., 2016. Adolescent Substance Use in the Context of the  
42 Family: A Qualitative Study of Young People's Views on Parent-Child Attachments, Parenting Style  
43 and Parental Substance Use. *Subst. Use Misuse* 51, 1846–1855.  
44 <https://doi.org/10.1080/10826084.2016.1197941>
- 45 Meyers, J.L., Shmulewitz, D., Wall, M.M., Keyes, K.M., Aharonovich, E., Spivak, B., Weizman, A.,  
46 Frisch, A., Edenberg, H.J., Gelernter, J., Grant, B.F., Hasin, D., 2015. Childhood adversity moderates  
47 the effect of ADH1B on risk for alcohol-related phenotypes in Jewish Israeli drinkers. *Addict. Biol.*  
48 20, 205–214. <https://doi.org/10.1111/adb.12102>
- 49 Mier, D., Kirsch, P., Meyer-Lindenberg, A. 2010. Neural substrates of pleiotropic action of genetic variation  
50 in COMT: a meta-analysis. *Mol Psychiatry*. 15, 918–927.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Milaniak, I., Watson, B. & Jaffee, S.R., 2015. Gene-Environment Interplay and Substance Use: A Review of Recent Findings. *Curr Addict Rep* 2, 364–371. <https://doi.org/10.1007/s40429-015-0069-4>

Miljkovitch, R., Pierrehumbert, B., Karmaniola, A., Bader, M., Halfon, O., 2005. Assessing attachment cognitions and their associations with depression in youth with eating or drug misuse disorders. *Subst. Use Misuse* 40, 605–623. <https://doi.org/10.1081/JA-200055349>

Mollick, J.A., Kober, H., 2020. Computational models of drug use and addiction: A review. *J. Abnorm. Psychol.* 129, 544–555. <https://doi.org/10.1037/abn0000503>

Moore, L. D., Le, T., & Fan, G., 2013. DNA methylation and its basic function. *Neuropsychopharmacology*, 38(1), 23–38. <https://doi.org/10.1038/npp.2012.112>

Moran-Santa Maria MM, McRae-Clark AL, Back SE, DeSantis SM, Baker NL, Spratt EG, Simpson AN, Brady KT. 2010. Influence of cocaine dependence and early life stress on pituitary-adrenal axis responses to CRH and the Trier social stressor. *Psychoneuroendocrinology* 35, 1492–500. <https://doi.org/10.1016/j.psyneuen.2010.05.001>

Muehlhan, M., Höcker, A., Miller, R., Trautmann, S., Wiedemann, K., Lotzin, A., Barnow, S., Schäfer, I., 2020. HPA axis stress reactivity and hair cortisol concentrations in recently detoxified alcoholics and healthy controls with and without childhood maltreatment. *Addict. Biol.* 25, 1–8. <https://doi.org/10.1111/adb.12681>

Mulder, R.H., Rijlaarsdam, J., Luijk, M.P.C.M., Verhulst, F.C., Felix, J.F., Tiemeier, H., Bakermans-Kranenburg, M.J., Van Ijzendoorn, M.H., 2017. Methylation matters: FK506-binding protein-51 (FKBP5) methylation moderates the associations of FKBP5 genotype and resistant attachment with stress regulation. *Dev. Psychopathol.* 29, 491–503. <https://doi.org/10.1017/S095457941700013X>

Mikulincer, M., & Shaver, P. R. (2016). *Attachment in adulthood: Structure, dynamics, and change*. Guilford Press.

Munafò, M.R., Freimer, N.B., Ng, W., Ophoff, R., Vejjola, J., Miettunen, J., Järvelin, M.R., Taanila, A., Flint, J., 2009. 5-HTTLPR genotype and anxiety-related personality traits: A meta-analysis and new data. *Am. J. Med. Genet. Part B: Neuropsychiatr. Genet.* 150, 271–281. <https://doi.org/10.1002/ajmg.b.30808>

Musetti, A., Terrone, G., Corsano, P., Magnani, B., Salvatore, S., 2016. Exploring the link among state of mind concerning childhood attachment, attachment in close relationships, parental bonding, and psychopathological symptoms in substance users. *Front. Psychol.* 7, 1–9. <https://doi.org/10.3389/fpsyg.2016.01193>

Negriff, S., Saxbe, D.E., Trickett, P.K., 2015. Childhood maltreatment, pubertal development, HPA axis functioning, and psychosocial outcomes: An integrative biopsychosocial model. *Dev. Psychobiol.* 57, 984–993. <https://doi.org/10.1002/dev.21340>

Nelson, E.E., Panksepp, J., 1998. Brain substrates of infant-mother attachment: Contributions of opioids, oxytocin, and norepinephrine. *Neurosci. Biobehav. Rev.* 22, 437–452. [https://doi.org/10.1016/S0149-7634\(97\)00052-3](https://doi.org/10.1016/S0149-7634(97)00052-3)

Nestler, E.J., 2014. Epigenetic mechanisms of drug addiction. *Neuropharmacology* 76, 259–268. <https://doi.org/10.1016/j.neuropharm.2013.04.004>

Nestler, E.J., Luscher, C., 2019. The Molecular Basis of Drug Addiction: Linking Epigenetic to Synaptic and Circuit Mechanisms. *Neuron* 102, 48–59. <https://doi.org/10.1016/j.neuron.2019.01.016>

Formatted: English (United Kingdom)  
Formatted: English (United Kingdom)  
Formatted: English (United Kingdom)

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Neville, M. J., Johnstone, E. C., & Walton, R. T., 2004. Identification and characterization of ANKK1:  
12 a novel kinase gene closely linked to DRD2 on chromosome band 11q23. 1. *Hum. Mutat.*, 23(6), 540-  
13 545. <https://pubmed.ncbi.nlm.nih.gov/15146457/>
- 14 Niyonsenga, T., Blackson, T.C., De La Rosa, M., Rojas, P., Dillon, F., Ganapati, E.N., 2012. Social  
15 support, attachment, and chronic stress as correlates of latina mother and daughter drug use behaviors.  
16 *Am. J. Addict.* 21, 157–167. <https://doi.org/10.1111/j.1521-0391.2011.00202.x>
- 17 Noto, K., Suzuki, A., Shirata, T., Matsumoto, Y., Takahashi, N., Goto, K., Otani, K., 2020. Mu opioid  
18 receptor polymorphism moderates sensitivity to parental behaviors during characterization of  
19 personality traits. *Neuropsychiatr. Dis. Treat.* 16, 2161–2167. <https://doi.org/10.2147/NDT.S265774>
- 20 Nummenmaa, L., Manninen, S., Tuominen, L., Hirvonen, J., Kalliokoski, K.K., Nuutila, P., Jääskeläinen,  
21 I.P., Hari, R., Dunbar, R.I.M., Sams, M., 2015. Adult attachment style is associated with cerebral  $\mu$ -  
22 opioid receptor availability in humans. *Hum. Brain Mapp.* 36, 3621–3628.  
23 <https://doi.org/10.1002/hbm.22866>
- 24 Nylander, I., Todkar, A., Granholm, L., Vrettou, M., Bendre, M., Boon, W., Andershed, H., Tuvblad, C.,  
25 Nilsson, K.W., Comasco, E., 2017. Evidence for a Link Between Fkbp5/FKBP5, Early Life Social  
26 Relations and Alcohol Drinking in Young Adult Rats and Humans. *Mol. Neurobiol.* 54, 6225–6234.  
27 <https://doi.org/10.1007/s12035-016-0157-z>
- 28 Oitzl, M.S., Champagne, D.L., van der Veen, R., de Kloet, E.R., 2010. Brain development under stress:  
29 hypotheses of glucocorticoid actions revisited. *Neurosci. Biobehav. Rev.* 34, 853–66.  
30 <https://doi.org/10.1016/j.neubiorev.2009.07.006>
- 31 Olsson, C.A., Moyzis, R.K., Williamson, E., Ellis, J.A., Parkinson-Bates, M., Patton, G.C., Dwyer, T.,  
32 Romaniuk, H., Moore, E.E., 2011. Gene-environment interaction in problematic substance use:  
33 Interaction between DRD4 and insecure attachments. *Addict. Biol.* 18, 717–726.  
34 <https://doi.org/10.1111/j.1369-1600.2011.00413.x>
- 35 Ossola, P., Gerra, M.C., Gerra, M.L., Milano, G., Zatti, M., Zavan, V., Volpi, R., Marchesi, C., Donnini,  
36 C., Gerra, G., Di Gennaro, C., 2020. Alcohol use disorders among adult children of alcoholics  
37 (ACOAs): Gene-environment resilience factors. *Prog. Neuro-Psychopharmacology Biol. Psychiatry*  
38 108. <https://doi.org/10.1016/j.pnpbp.2020.110167>
- 39 Oswald, L.M., Wand, G.S., Kuwabara, H., Wong, D.F., Zhu, S., Brasic, J.R., 2014. History of childhood  
40 adversity is positively associated with ventral striatal dopamine responses to amphetamine.  
41 *Psychopharmacology (Berl)*. 231, 2417–2433. <https://doi.org/10.1007/s00213-013-3407-z>
- 42 Pappa, I., Szekeley, E., Mileva Seitz, V.R., Luijk, M.P.C.M., Bakermans-Kranenburg, M.J., van  
43 IJzendoorn, M.H., Tiemeier, H., 2015. Beyond the usual suspects: a multidimensional genetic  
44 exploration of infant attachment disorganization and security. *Attach. Hum. Dev.* 17, 288–301.  
45 <https://doi.org/10.1080/14616734.2015.1037316>
- 46 Parade, S. H., Huffhines, L., Daniels, T. E., Stroud, L. R., Nugent, N. R., & Tyrka, A. R. (2021). A  
47 systematic review of childhood maltreatment and DNA methylation: candidate gene and epigenome-  
48 wide approaches. *Translational psychiatry*, 11(1), 1–33.
- 49 Park, A., Sher, K.J., Todorov, A.A., Heath, A.C., 2011. Interaction between the DRD4 VNTR  
50 polymorphism and proximal and distal environments in alcohol dependence during emerging and  
51 young adulthood. *J. Abnorm. Psychol.* 120, 585–595. <https://doi.org/10.1037/a0022648>
- 52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Parker, G., Tupling, H., Brown, L.B., 1979. A Parental Bonding Instrument. *Br. J. Med. Psychol.* 52, 1–10. <https://doi.org/10.1111/j.2044.8341.1979.tb02487.x>
- 12  
13 Pellerone, M., Tolini, G., Polopoli, C., 2016. Parenting, identity development, internalizing symptoms, and alcohol use: A cross-sectional study in a group of Italian adolescents. *Neuropsychiatr. Dis. Treat.* 12, 1769–1778. <https://doi.org/10.2147/NDT.S106791>
- 14  
15  
16 Pettenon, M., Kessler, F.H.P., Guimarães, L.S.P., Pedroso, R.S., Hauck, S., Pechansky, F., 2014. Perceptions of parental bonding in freebase cocaine users versus non-illicit drug users. *Indian J. Med. Res.* 139, 835–840.
- 17  
18  
19 Pickard, H., 2017. Responsibility without Blame for Addiction. *Neuroethics* 10, 169–180. <https://doi.org/10.1007/s12152-016-9295-2>
- 20  
21 Pirnia, B., Khosravani, V., Maleki, F., Kalbasi, R., Pirnia, K., Malekanmehr, P., Zahiroddin, A., 2020. The role of childhood maltreatment in cortisol in the hypothalamic-pituitary-adrenal (HPA) axis in methamphetamine-dependent individuals with and without depression comorbidity and suicide attempts. *J. Affect. Disord.* 263, 274–281. <https://doi.org/10.1016/j.jad.2019.11.168>
- 22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65
- Prior, V., & Glaser, D., 2006. *Understanding attachment and attachment disorders: Theory, evidence and practice.* Jessica Kingsley Publishers.
- Plotka R., 2011. Adult Attachment Interview (AAI). In: Goldstein S., Naglieri J.A. (eds) *Encyclopedia of Child Behavior and Development.* Springer, Boston, MA. <https://doi.org/10.1007/978-0-387-79061-9-68>
- Prom Wormley, E. C., Ebejer, J., Dick, D. M., & Bowers, M. S., 2017. The genetic epidemiology of substance use disorder: a review. *Drug and alcohol dependence*, 180, 241–259.
- Riggs A.D. & Porter T.N., 1996. Overview of epigenetic mechanisms. In *Epigenetic mechanisms of gene regulation* (eds. Russo VEA, Martienssen R, Riggs AD), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 29–45.
- Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR., 2009. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA.* 301, 2462–71. <https://doi.org/10.1001/jama.2009.878>. Erratum in: *JAMA.* 2009 302, 492. PMID: 19531786; PMCID: PMC2938776.
- Robakis, T.K., Zhang, S., Rasgon, N.L., Li, T., Wang, T., Roth, M.C., Humphreys, K.L., Gotlib, I.H., Ho, M., Khechaduri, A., Watson, K., Roat Shumway, S., Budhan, V. V., Davis, K.N., Crowe, S.D., Ellie Williams, K., Urban, A.E., 2020. Epigenetic signatures of attachment insecurity and childhood adversity provide evidence for role transition in the pathogenesis of perinatal depression. *Transl. Psychiatry* 10, 1–14. <https://doi.org/10.1038/s41398-020-0703-3>
- Rovai L., Maremmani AGI, Bacciardi S., Gazzarrini D., Pallucchini A., Spera V., Perugi G., Maremmani I., 2017. Opposed Effect of Hyperthymic and Cyclothymic Temperament in Substance Use Disorder (Heroin or Alcohol Dependent Patients). *Journal of Affective Disorders.* 218: 339–345. <https://doi.org/10.1016/j.jad.2017.04.041>
- Rovaris, D.L., Mota, N.R., Bertuzzi, G.P., Aroche, A.P., Callegari Jacques, S.M., Guimarães, L.S.P., Pezzi, J.C., Viola, T.W., Bau, C.H.D., Grassi-Oliveira, R., 2015. Corticosteroid receptor genes and childhood neglect influence susceptibility to crack/cocaine addiction and response to detoxification treatment. *J. Psychiatr. Res.* 68, 83–90. <https://doi.org/10.1016/j.jpsychires.2015.06.008>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Roy, A., 2002. Self-rated childhood emotional neglect and CSF monoamine indices in abstinent cocaine-abusing adults: Possible implications for suicidal behavior. *Psychiatry Res.* 112, 69-75. [https://doi.org/10.1016/S0165-1781\(02\)00176-2](https://doi.org/10.1016/S0165-1781(02)00176-2)
- 12  
13  
14 Ruggeri, B., Nymberg, C., Vuoksima, E., Lourdusamy, A., Wong, C. P., Carvalho, F. M., ... & IMAGEN Consortium. (2015). Association of protein phosphatase PPM1G with alcohol use disorder and brain activity during behavioral control in a genome-wide methylation analysis. *American Journal of Psychiatry*, 172(6), 543-552.
- 15  
16  
17  
18 Ruggeri, B., Macare, C., Stopponi, S., Jia, T., Carvalho, F.M., Robert, G., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Büchel, C., Cattrell, A., Conrod, P.J., Desrivieres, S., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.L., Martinot, M.L.P., Nees, F., Papadopoulos-Orfanos, D., Paus, T., Poustka, L., Smolka, M.N., Vetter, N.C., Walter, H., Whelan, R., Sommer, W.H., Bakalkin, G., Cicocioppo, R., Schumann, G., 2018. Methylation of OPRL1 mediates the effect of psychosocial stress on binge drinking in adolescents. *J. Child Psychol. Psychiatry Allied Discip.* 59, 650-658. <https://doi.org/10.1111/jcpp.12843>
- 19  
20  
21  
22  
23  
24  
25 Sandler, I.N., Schoenfelder, E.N., Wolchik, S.A., MacKinnon, D.P., 2011. Long term impact of prevention programs to promote effective parenting: Lasting effects but uncertain processes. *Annu. Rev. Psychol.* 62, 299-329. <https://doi.org/10.1146/annurev.psych.121208.131619>
- 26  
27  
28 Schäfer, I., Teske, L., Schulze Thüsing, J., Homann, K., Reimer, J., Haasen, C., Hissbach, J., Wiedemann, K., 2010. Impact of childhood trauma on hypothalamus-pituitary-adrenal axis activity in alcohol-dependent patients. *Eur. Addict. Res.* 16, 108-114. <https://doi.org/10.1159/000294362>
- 29  
30  
31 Schindler, A., 2019. Attachment and Substance Use Disorders: Theoretical Models, Empirical Evidence, and Implications for Treatment. *Front. Psychiatry* 10, 1-13. <https://doi.org/10.3389/fpsyt.2019.00727>
- 32  
33  
34 Schindler, A., Bröning, S., 2015. A Review on Attachment and Adolescent Substance Abuse: Empirical Evidence and Implications for Prevention and Treatment. *Subst. Abus.* 36, 304-313. <https://doi.org/10.1080/08897077.2014.983586>
- 35  
36  
37 Schindler, A., Sack, P.M., 2015. Exploring attachment patterns in patients with comorbid borderline personality and substance use disorders. *J. Nerv. Ment. Dis.* 203, 820-826. <https://doi.org/10.1097/NMD.0000000000000377>
- 38  
39  
40 Schindler, A., Thomasius, R., Petersen, K., Sack, P.M., 2009. Heroin as an attachment substitute? Differences in attachment representations between opioid, ecstasy and cannabis abusers. *Attach. Hum. Dev.* 11, 307-330. <https://doi.org/10.1080/14616730902815009>
- 41  
42  
43 Schindler, A., Thomasius, R., Sack, P.M., Gemeinhardt, B., Küstner, U., 2007. Insecure family bases and adolescent drug abuse: A new approach to family patterns of attachment. *Attach. Hum. Dev.* 9, 111-126. <https://doi.org/10.1080/14616730701349689>
- 44  
45  
46 Schmid, B., Blomeyer, D., Treutlein, J., Zimmermann, U.S., Buchmann, A.F., Schmidt, M.H., Esser, G., Rietschel, M., Banaschewski, T., Schumann, G., Laucht, M., 2010. Interacting effects of CRHR1 gene and stressful life events on drinking initiation and progression among 19-year-olds. *Int. J. Neuropsychopharmacol.* 13, 703-714. <https://doi.org/10.1017/S1461145709990290>
- 47  
48  
49  
50 Schouts, O., Van Tol, H.H.M., 2003. The human dopamine D4 receptor repeat sequences modulate expression. *Pharmacogenomics J.* 3, 343-348. <https://doi.org/10.1038/sj.tpj.6500208>
- 51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Scragg, R., Reeder, A.I., Wong, G., Glover, M., Nosa, V., 2008. Attachment to parents, parental tobacco  
12 smoking and smoking among Year 10 students in the 2005 New Zealand national survey. *Aust. N. Z.*  
13 *J. Public Health* 32, 348–353. <https://doi.org/10.1111/j.1753-6405.2008.00253.x>
- 14 Shi, Z., Bureau, J. F., Easterbrooks, M. A., Zhao, X., & Lyons-Ruth, K., 2012. Childhood maltreatment  
15 and prospectively observed quality of early care as predictors of antisocial personality disorder  
16 features. *Infant Mental Health Journal*, 33(1), 55–69. <https://doi.org/10.1002/imhj.20295>
- 17 Sroufe LA, Carlson EA, Levy AK, Egeland B. 1999. Implications of attachment theory for  
18 developmental psychopathology. *Dev Psychopathol.* 11, 1–13.  
19 <https://doi.org/10.1017/s0954579499001923>
- 20 Sroufe, L. A., 2005. Attachment and development: A prospective, longitudinal study from birth to  
21 adulthood. *Attachment & human development*, 7(4), 349–367.  
22 <https://doi.org/10.1080/14616730500365928>
- 23 Stojakovic, A., Waleczak, M., Cieślak, P.E., Trenk, A., Sköld, J., Zajdel, J., Mirrasekhan, E., Karlsson,  
24 C., Thorsell, A., Heilig, M., Parkitna, J.R., Blasiak, T., Engblom, D., 2018. Several behavioral traits  
25 relevant for alcoholism are controlled by  $\gamma 2$  subunit containing GABAA receptors on dopamine  
26 neurons in mice. *Neuropsychopharmacology* 43, 1548–1556. <https://doi.org/10.1038/s41386-018-0022-z>
- 27  
28  
29 Strathearn, L., Mertens, C.E., Mayes, L., Rutherford, H., Rajhans, P., Xu, G., Potenza, M.N., Kim, S.,  
30 2019. Pathways Relating the Neurobiology of Attachment to Drug Addiction. *Front. Psychiatry* 10,  
31 1–15. <https://doi.org/10.3389/fpsy.2019.00737>
- 32 Su, J., Supple, A.J., Leerkes, E.M., Kuo, S.I.C., 2019. Latent trajectories of alcohol use from early  
33 adolescence to young adulthood: Interaction effects between 5-HTTLPR and parenting quality and  
34 gender differences. *Dev. Psychopathol.* 31, 457–469. <https://doi.org/10.1017/S095457941800024X>
- 35 Sun, J., Kranzler, H.R., Gelernter, J., Bi, J., 2020. A genome-wide association study of cocaine use  
36 disorder accounting for phenotypic heterogeneity and gene-environment interaction. *J. Psychiatry*  
37 *Neurosci.* 45, 34–44. <https://doi.org/10.1503/jpn.180098>
- 38 Sundar, M., Patel, D., Young, Z., & Leong, K. C., 2021. Oxytocin and Addiction: Potential Glutamatergic  
39 Mechanisms. *Int. J. Mol. Sci.*, 22(5), 2405. <https://doi.org/10.3390/ijms22052405>
- 40 Taylor-Sechafer, M., Jacobvitz, D., Steiker, L.H., 2008. Patterns of attachment organization, social  
41 connectedness, and substance use in a sample of older homeless adolescents: Preliminary findings.  
42 *Fam. Community Heal.* 31, S81–8. <https://doi.org/10.1097/01.FCH.0000304021.05632.a1>
- 43 Tops, M., Koole, S.L., Ijzerman, H., Buisman-Pijlman, F.T.A., 2014. Why social attachment and  
44 oxytocin protect against addiction and stress: Insights from the dynamics between ventral and dorsal  
45 corticostriatal systems. *Pharmacol. Biochem. Behav.* 119, 39–48.  
46 <https://doi.org/10.1016/j.pbb.2013.07.015>
- 47 Torresani, S., Favaretto, E., Zimmermann, C., 2000. Parental representations in drug-dependent patients  
48 and their parents. *Compr. Psychiatry* 41, 123–129. [https://doi.org/10.1016/S0010-440X\(00\)90145-7](https://doi.org/10.1016/S0010-440X(00)90145-7)
- 49 Tremblay, M., Baydala, L., Khan, M., Currie, C., Morley, K., Burkholder, C., Davidson, R., Stillar, A.,  
50 2020. Primary Substance Use Prevention Programs for Children and Youth: A Systematic Review.  
51 *Pediatrics* 146, e20192747. <https://doi.org/10.1542/peds.2019-2747>
- 52 Tyrka, A.R., Parade, S.H., Welch, E.S., Ridout, K.K., Price, L.H., Marsit, C., Philip, N.S., Carpenter,  
53 L.L., 2016. Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations  
54

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

with early adversity and depressive, anxiety and substance use disorders. *Transl. Psychiatry* 6, e848. <https://doi.org/10.1038/tp.2016.112>

UN General Assembly, 2016. Resolution adopted by the General Assembly on 19 April 2016. S 30/1. Our joint commitment to effectively addressing and countering the world drug problem. *Ungass* 56350, 1–27.

Unternaehrer E, Meyer AH, Burkhardt SCA, Dempster E, Staehli S, Theill N, Lieb R, Meinlschmidt G, 2015. Childhood maternal care is associated with DNA methylation of the genes for brain derived neurotrophic factor (BDNF) and oxytocin receptor (OXR) in peripheral blood cells in adult men and women. *Stress* 18, 451–461.

Unterrainer, H.F., Hiebler Ragger, M., Koschutnig, K., Fuchshuber, J., Tscheschner, S., Url, M., Wagner Skacel, J., Reininghaus, E.Z., Papousek, I., Weiss, E.M., Fink, A., 2017. Addiction as an attachment disorder: White matter impairment is linked to increased negative affective states in poly-drug use. *Front. Hum. Neurosci.* 11, 1–11. <https://doi.org/10.3389/fnhum.2017.00208>

Vaht, M., Kurrikoff, T., Laas, K., Veidebaum, T., & Harro, J. (2016). Oxytocin receptor gene variation rs53576 and alcohol abuse in a longitudinal population representative study. *Psychoneuroendocrinology*, 74, 333–341.

Van Der Vorst, H., Engels, R.C.M.E., Meeus, W., Deković, M., Vermulst, A., 2006. Parental attachment, parental control, and early development of alcohol use: A longitudinal study. *Psychol. Addict. Behav.* 20, 107–116. <https://doi.org/10.1037/0893-164X.20.2.107>

van der Zwaluw, C. S., & Engels, R. C. M. E., 2009. Gene-environment interactions and alcohol use and dependence: Current status and future challenges. *Addiction* 104, 907–914. <https://doi.org/10.1111/j.1360-0443.2009.02563.x>

Van Der Zwaluw, C.S., Engels, R.C.M.E., Vermulst, A.A., Franke, B., Buitelaar, J., Verkes, R.J., Scholte, R.H.J., 2010. Interaction between dopamine D2 receptor genotype and parental rule setting in adolescent alcohol use: Evidence for a gene-parenting interaction. *Mol. Psychiatry* 15, 727–735. <https://doi.org/10.1038/mp.2009.4>

Van Ijzendoorn, M.H., Caspers, K., Bakermans-Kranenburg, M.J., Beach, S.R.H., Philibert, R., 2010. Methylation matters: Interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. *Biol. Psychiatry* 68, 405–407. <https://doi.org/10.1016/j.biopsych.2010.05.008>

Van Tol, H. H., Wu, C. M., Guan, H. C., Ohara, K., Bunzow, J. R., Civelli, O., Kennedy, J., Seeman, P., Niznik, H. B., & Jovanovic, V. 1992. Multiple dopamine D4 receptor variants in the human population. *Nature*. 358, 149–152.

Vaske, J., Newsome, J., Wright, J.P., 2012. Interaction of serotonin transporter-linked polymorphic region and childhood neglect on criminal behavior and substance use for males and females. *Dev. Psychopathol.* 24, 181–193. <https://doi.org/10.1017/S0954579411000769>

Vink, J.M., 2016. Genetics of addiction: Future focus on gene × environment interaction? *J. Stud. Alcohol Drugs* 77, 684–687. <https://doi.org/10.15288/jsad.2016.77.684>

Vinkers, C.H., Van Gastel, W.A., Schubart, C.D., Van Eijk, K.R., Luyckx, J.J., Van Winkel, R., Joëls, M., Ophoff, R.A., Boks, M.P.M., 2013. The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the COMT Val158Met polymorphism. *Schizophr. Res.* 150, 303–311. <https://doi.org/10.1016/j.schres.2013.07.020>

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 Virkkunen, M., Eggert, M., Rawlings, R., Linnoila, M., 1996. A prospective follow-up study of alcoholic  
12 violent offenders and fire setters. *Arch. Gen. Psychiatry* 53, 523–529.  
13 <https://doi.org/10.1001/archpsyc.1996.01830060067009>
- 14 Vismara, L., Presaghi, F., Bocchia, M., Ricci, R.V., Ammaniti, M., 2019. Attachment Patterns in Subjects  
15 Diagnosed With a Substance Use Disorder: A Comparison of Patients in Outpatient Treatment and  
16 Patients in Therapeutic Communities. *Front. Psychiatry* 10, 1–12.  
17 <https://doi.org/10.3389/fpsyg.2019.00807>
- 18 Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic Advances from the Brain Disease  
19 Model of Addiction. *N. Engl. J. Med.* 374, 363–371. <https://doi.org/10.1056/nejmra1511480>.
- 20 Vrettou, M., Nilsson, K.W., Tuvblad, C., Rehn, M., Åslund, C., Andershed, A.K., Wallén-Mackenzie,  
21 Å., Andershed, H., Hodgins, S., Nylander, I., Comaseo, E., 2019. VGLUT2 rs2290045 genotype  
22 moderates environmental sensitivity to alcohol-related problems in three samples of youths. *Eur.*  
23 *Child Adolesc. Psychiatry* 28, 1329–1340. <https://doi.org/10.1007/s00787-019-01293-w>
- 24 Walsh, A., 1995. Parental attachment, drug use, and facultative sexual strategies. *Soc. Biol.* 42, 95–107.  
25 <https://doi.org/10.1080/19485565.1995.9988890>
- 26 Wang, J., Qin, W., Liu, B., Wang, D., Zhang, Y., Jiang, T., & Yu, C. (2013). Variant in OXTR gene and  
27 functional connectivity of the hypothalamus in normal subjects. *Neuroimage*, 81, 199–204.
- 28 Whitesell, M., Bachand, A., Peel, J., Brown, M., 2013. Familial, Social, and Individual Factors  
29 Contributing to Risk for Adolescent Substance Use. *J. Addict.* 2013, 1–9.  
30 <https://doi.org/10.1155/2013/579310>
- 31 Willis, A.S., Wallston, K.A., & Johnson, K.R. S., 2001. Tobacco and alcohol use among young adults:  
32 Exploring religious faith, locus of health control, and coping strategies as predictors. In T. G. Plante,  
33 & A. C. Sherman (Eds.), *Faith and health: Psychological perspectives*, Guilford Press, New York, pp.  
34 213–239.
- 35 Zaso, M.J., Goodhines, P.A., Wall, T.L., Park, A., 2019. Meta-Analysis on Associations of Alcohol  
36 Metabolism Genes with Alcohol Use Disorder in East Asians. *Alcohol Alcohol.* 54, 216–224.  
37 <https://doi.org/10.1093/alealc/agz011>
- 38 Zhai, Z.W., Kirisci, L., Tarter, R.E., Ridenour, T.A., 2014. Psychological dysregulation during  
39 adolescence mediates the association of parent-child attachment in childhood and substance use  
40 disorder in adulthood. *Am. J. Drug Alcohol Abuse* 40, 67–74.  
41 <https://doi.org/10.3109/00952990.2013.848876>
- 42 Zhang, H., Wang, F., Kranzler, H.R., Zhao, H., Gelernter, J., 2013. Profiling of childhood adversity-  
43 associated DNA methylation changes in alcoholic patients and healthy controls. *PLoS One* 8, e65648.  
44 <https://doi.org/10.1371/journal.pone.0065648>
- 45 Zhang, Y., Wang, D., Johnson, A.D., Papp, A.C., Sadée, W., 2005. Allelic expression imbalance of  
46 human mu opioid receptor (OPRM1) caused by variant A118G. *J. Biol. Chem.* 280, 32618–32624.  
47 <https://doi.org/10.1074/jbc.M504942200>
- 48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**Figure Captions**

**Figure 1.** PRISMA Flow diagram

**Figure 12.** Addiction is not a self-fulfilling prophecy.

Note, Environmental and genetic factors, alongside adverse childhood experiences, could concur to determine, through parental attachment relationships, a potential vulnerability to substance use, by way of epigenetic and neuroendocrine mechanisms. High risk genotypes could influence early environment through active, passive and evocative gene\*environment correlations (rGE). Gene-environment interplay, in turn, could activate a cascade of neuroendocrine changes in monoaminergic, HPA-axis, opioidergic and oxytocinergic systems, which ultimately determine vulnerability to addiction. Epigenetic changes induced by the early exposure to high risk environment seem to further exacerbate the burden of genetic predisposition. We hypothesized that epigenetic changes, induced by positive and caring parenting, could changes these trajectories, reducing the expression of the high risk genotypes and potentiating the expression of protective ones. ACEs: Adverse Childhood experiences; COMT: Catechol-O-Methyltransferase and the Monoamine Oxidases A genes; CRH-R1: Corticotropin-Releasing Hormone Receptor 1 gene; DAT1: Dopamine Transporter 1 gene; DRD4 and DRD2: Dopamine Receptor

Formatted: Font: Not Italic  
Formatted: Font: Not Bold, Not Italic

Formatted: Font: Not Bold, Not Italic  
Formatted: Font: Not Bold, Not Italic  
Formatted: Font: Not Bold, Not Italic  
Formatted: Font: Not Bold, Not Italic  
Formatted: Font: Not Bold, Not Italic

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

D4 and D2 genes; FKBP5: glucocorticoid receptor co-chaperone FK506-binding protein 5 gene; GR-

Formatted: Font: Not Bold, Not Italic

NR3C1: Glucocorticoid Receptor gene; 5-HIAA: Serotonin metabolite 5-hydroxyindoleacetic Acid

Formatted: Font: Not Bold, Not Italic

Formatted: Font: Not Bold, Not Italic

5-HTTLPR: Serotonin Transporter Linked Promoter Region gene; HVA: Dopamine metabolite

Formatted: Font: Not Bold, Not Italic

Homovanillic Acid; MAOA: Monoamine Oxidase A gene; OPR1: Opioid Related Nociceptin Receptor

Formatted: Font: Not Bold, Not Italic

Formatted: Font: Not Bold, Not Italic

1 gene; OPRM1: mu-Opioid Receptor 1 gene; OXTR: Oxytocin Receptor gene; PRL: prolactine

Formatted: Font: Not Bold, Not Italic

Formatted: Font: Not Bold, Not Italic

Notes: Environmental and genetic factors, alongside adverse childhood experiences, could concur to determine, through parental attachment relationships, a potential vulnerability to substance use, by way of epigenetic and neuroendocrine mechanisms. Protective genotypes or high risk genotypes could influence early environment through active, passive and evocative gene\*environment correlations (rGE). Gene environmental interplay, in turn, could activate a cascade of neuroendocrine changes in monoaminergic, HPA axis, opioidergic and oxytocinergic systems, which ultimately determine resilience or vulnerability to addiction. However, epigenetic changes, induced by positive and caring parenting could changes these trajectories, reducing the expression of the high risk genotypes and potentiating the expression of the protective ones

14  
15  
16  
17  
18  
19  
20  
21  
22  
23 **Tables.**

24  
25 **Table 1.** Studies on the genetic factors associated with attachment and Substance Use Disorder

26  
27

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
<b>Monoamines</b>								
Althaus et al., 2009	The Netherlands	65	Children with Pervasive Developmental Disorder or Attention Deficit Hyperactivity Disorder and healthy controls, aged 10-12	Potential correlation with a reward deficit syndrome	Dopamine receptor gene (DRD2) / ankyrin repeat and kinase domain containing 1 (ANKK1): Taq1 A allele polymorphism	Attachment	Electrocortical event-related potentials	Cross-sectional
Brody et al., 2014	USA	502	Youths, aged 16 through 18	Any substances	Dopamine receptor gene (DRD4): alleles with 7 or more repeats (7R+)	Parenting	Strong African American Families-Teen program	Longitudinal
Fite et al., 2018	USA	500	Adults, aged 18-25	Cannabis and tobacco	Monoamine oxidase A gene (MAO-A): upstream variable number tandem repeat (uVNRT) polymorphism	ACEs	-	Cross-sectional
Gerra et al., 2007	Italy	96	Male patients with cocaine use disorder, aged 19-25 years	Cocaine	Serotonin transporter promoter gene (5-HTTLPR)	Parenting	-	Cross-sectional
Gerra et al., 2010	Italy	187	Youths, aged 14-19	Any illicit substances	Serotonin transporter promoter gene (5-HTTLPR)	ACEs	-	Cross-sectional
Gerra et al., 2019	Italy	185	Patients with cannabis use disorder and healthy	Cannabis	Dopamine receptor gene (DRD2) / ankyrin	ACEs and parenting	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

			controls, aged 19-25		repeat and kinase domain containing 1 (ANKK1): Taq1 A allele polymorphism			
Laucht et al., 2012	Germany	285	Youths, aged 15-19	Alcohol	Catechol-O-methyltransferase (COMT) gene: Val(158)Met polymorphism	Parenting	-	Longitudinal
Li et al., 2012	China	450	Patients with opioid use disorder, aged 26-41	Heroin	Catechol-O-methyltransferase (COMT) gene: rs737866 single nucleotide polymorphism	ACEs	-	Cross-sectional
Olsson et al., 2011	Australia	839	Youths, aged 14 through 24	Nicotine, cannabis and alcohol	Dopamine receptor gene (DRD4): alleles with 7 or more repeats (7R+)	Attachment	-	Longitudinal
Ossola et al., 2021	Italy	107	Adult Children of Alcoholic Parents (ACoAs)	Alcohol	Serotonin transporter promoter gene (5-HTTLPR); dopamine receptor gene (DRD2) / ankyrin repeat and kinase domain containing 1 (ANKK1): Taq1 A allele polymorphism	ACEs	-	Cross-sectional
Park et al., 2011	USA	234	Adults, aged 18 through 34	Alcohol	Dopamine receptor gene (DRD4): 4 variable number tandem repeat (VNTR) polymorphism	ACEs	-	Longitudinal
Vaske et al., 2012	USA	2403	Youths, aged 11 through 26	Cannabis	Serotonin transporter promoter gene (5-HTTLPR)	ACEs	-	Longitudinal
Vinkers et al., 2013	The Netherlands	918	Adults, aged 18-25	Cannabis	Catechol-O-methyltransferase (COMT) gene: Val(158)Met polymorphism	ACEs	-	Cross-sectional
<b>Hypothalamic-Pituitary-Adrenal axis</b>								

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Nylander et al., 2017	Sweden	838	Male adults, aged 20-24	Alcohol	FK506-binding protein (FKBP5): rs1360780 single nucleotide polymorphism	Attachment	-	Cross-sectional
Rovaris et al., 2015	Brazil	139	Female patients with cocaine use disorder, aged 25-35	Cocaine	Mineralocorticoid (NR3C2) and glucocorticoid (NR3C1) receptor genes: rs5522 and rs6198 single nucleotide polymorphisms	ACEs	-	Cross-sectional
Schmid et al., 2010	Germany	270	Youths, aged 15 through 19	Alcohol	Corticotropin-releasing hormone receptor 1 (CRHR1): rs242938 and rs1876831 single nucleotide polymorphisms	ACEs	-	Longitudinal
<b>Opioids</b>								
Cimino et al., 2020	Italy	150	Children, aged 8-9	- (general psychopathology)	$\mu$ -opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Copeland et al., 2011	USA	226	Children, aged 9-17	Any substances	$\mu$ -opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Noto et al., 2020	Japan	725	Healthy adults, aged 18-35	- (personality traits)	$\mu$ -opioid receptor gene: A118G single nucleotide polymorphism	Parenting	-	Cross-sectional
<b>Oxytocin</b>								
Dannlowski et al., 2016	Germany	309	Healthy adults, aged 18-59	-	Oxytocin receptor gene (OXTR): rs53576 single nucleotide polymorphism of G-allele	ACEs	Facial emotions responsiveness in fMRI	Cross-sectional
<b>Others</b>								
Carey et al., 2015	USA	1,558	Patients with Opioid or Alcohol Use Disorders and	Cannabis	6 endocannabinoid (eCB) genes: anabolism (DAGLA, DAGLB, NAPEPLD),	ACEs	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

			healthy controls, aged 18-50		catabolism (MGLL, FAAH), binding (CNR1)			
Csala et al., 2015	Hungary	232	Patients with Nicotine Use Disorder, aged 38-64	Nicotine	Neural nicotinic acetylcholinergic receptors gene (nAChR): rs2072660 single nucleotide polymorphism of $\beta$ 2 subunit	Parenting	-	Cross-sectional
Vrettou et al., 2019	Sweden	3612	Youths, aged 14-22	Alcohol	Vesicular Glutamate Transporter 2 gene (VGLUT2): rs2290045 single nucleotide polymorphism	Attachment and ACEs	-	Cross-sectional
Beach et al., 2015	USA	183	Young adult, aged 17 through 22	Alcohol and nicotine	Telomere length	Parenting	-	Longitudinal
Sun et al., 2020	USA	9965	Adults, aged 25-55	Cocaine	Genome-Wide Association Study (GWAS)	ACEs	-	Cross-sectional

**Note.** ACEs= Adverse Childhood Experiences: retrospective scales on perceived maltreatment, physical/sexual abuse and neglect were included.

Attachment: includes retrospective measures of child-parents relationship, as well as direct measures of attachment in childhood

Parenting: evaluations of positive and negative parenting were included.

**Table 2.** Studies on the epigenetic mechanisms associated with attachment and Substance Use Disorder.

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
<b>Monamines</b>								
Bendre et al., 2018	Sweden	53	Male patients with Substance Use Disorders, aged 16 through 21	Alcohol	Monoamine oxidase A gene (MAO-A): methylation of the first exon and intron of the upstream variable number of tandem repeats (VNTR)	ACEs and parenting	-	Longitudinal

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

De Nardi et al., 2020	Italy	79	Youths, aged 18-34	Internet addiction	Dopamine transporter gene (DAT1): methylation of the 5'-untranslated region (UTR) variable number of tandem repeats (VNTR)	Attachment	-	Cross-sectional
<b>Hypothalamic-Pituitary-Adrenal axis</b>								
Tyrka et al., 2016	USA	340	Adults, aged 18-65	Any substance	Glucocorticoid receptor gene (NR3C1): methylation of exon 1F of the promoter region	ACEs	Dexamethasone/corticotropin releasing hormone test	Cross-sectional
<b>Opioids</b>								
NONE								
<b>Oxytocin</b>								
Kogan et al., 2018	USA	358	Adults, aged 18 through 19	Any substance	Oxytocin receptor gene (OXTR): methylation of the promoter region	ACEs	-	Longitudinal

**Table 3.** Studies on the neuroendocrine mechanisms associated with attachment and Substance Use Disorder

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
<b>Monoamines</b>								
Berglund et al., 2013	Sweden	18	Male patients with Alcohol Use Disorder, aged 35-55	Alcohol	Serum prolactine reactivity	ACEs	Prolactin response to a selective 5-HT reuptake inhibitor (citalopram)	Cross-sectional
Gerra et al. 2007	Italy	126	Patients with Opioid and Cocaine Use Disorder and healthy control, aged 22-35	Opioid and cocaine	Serum homovanillic acid	ACEs	-	Cross-sectional
Gerra et al. 2009a	Italy	94	Male patients with Cocaine Use	Cocaine	Serum homovanillic acid, prolactine.	ACEs and parenting	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

			Disorder and healthy controls, aged 20-36		adrenocorticotrophic hormone (ACTH) and cortisol			
Oswald et al., 2014	USA	28	Adults, aged 18-29	Amphetamine	Intrasyaptic dopamine release observed with the positron emission tomography (PET)	ACEs	-	Cross-sectional
Roy et al. 2002	USA	29	Male patients with Cocaine Use Disorder, aged 35-45	Cocaine	Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid	ACEs	-	Cross-sectional
Virkkunen et al. 1996	Finland	114	Male offenders with Cocaine Use Disorder, aged 18-45	Alcohol	Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid	ACEs	-	Cross-sectional
<b>Hypothalamic-Pituitary-Adrenal axis</b>								
Dawes et al. 1999	USA	297	Sons of fathers with substance abuse disorders and healthy controls, aged 10-22	Any substance	Serum testosterone, dehydrotestosterone and cortisol reactivity	ACEs	Auditory evoked potential task	Cross-sectional
Doan et al. 2014	USA	162	Children, aged 8 through 17	Any substance	Serum cortisol, epinephrine, norepinephrine	ACEs	-	Longitudinal
Flanagan et al. 2015	USA	31	Patients with Cocaine Use Disorder, aged 33-51	Cocaine	Salivary cortisol and dehydroepiandrosterone reactivity	ACEs	Intranasal oxytocin and Trier Social Stress Test (TSST)	Cross-sectional
Gerra et al. 2008	Italy	126	Patients with Opioid and Cocaine Use Disorder and healthy control, aged 22-35	Opioid and cocaine	Serum adrenocorticotrophic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional
Gerra et al. 2009a	Italy	94	Male patients with Cocaine Use Disorder and healthy controls, aged 20-36	Cocaine	Serum homovanillic acid, prolactine, adrenocorticotrophic hormone (ACTH) and cortisol	ACEs and parenting	-	Cross-sectional
Gerra et al. 2009b	Italy	187	Youths experimenters of illegal drugs and healthy controls, aged 14-19	Any illicit substance	Serum adrenocorticotrophic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Gerra et al. 2014	Italy	30	Male patients with Opioid Use Disorder, aged 22-35	Opioid	Serum adrenocorticotrophic hormone (ACTH) and cortisol reactivity	ACEs	Neutral and unpleasant pictures selected from the International Affective Picture System Self-assessment Manikin procedure	Cross-sectional
Gerra et al. 2016	Italy	100	Male patients with Nicotine Use Disorder and healthy controls, aged 20-50	Nicotine	Serum adrenocorticotrophic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotrophic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides $\alpha$ -melanocyte stimulating hormone (MSH) and $\beta$ -endorphin (END)	ACEs	Treatment with diamorphine	Cross-sectional
Hagan et al. 2019	USA	160	Adults, aged 24-28	Alcohol	Salivary cortisol reactivity	ACEs	Modified Trier Social Stress Test (TSST)	Cross-sectional
Hood et al. 2020	USA	144	Adults, aged 18-45	Nicotine	Salivary cortisol reactivity	ACEs	Intranasal oxytocin and Trier Social Stress Test (TSST)	Cross-sectional
Levandowski et al. 2016	Brazil	132	Female patients with Cocaine Use Disorder and healthy controls, aged 18-55	Cocaine	Serum cortisol and cytokines	ACEs	-	Cross-sectional
Marceau et al. 2019	The Netherlands	591	Youths, aged 16	Alcohol, nicotine and marijuana	Salivary cortisol reactivity	Parenting	Trier Social Stress Test (TSST)	Cross-sectional
Moran-Santa Maria et al. 2010	USA	85	Patients with Cocaine Use Disorder and healthy controls, aged 24-51	Cocaine	Serum ACTH and cortisol reactivity	ACEs	Corticotropin-releasing hormone (CRH) challenge and Trier Social Stress Test (TSST)	Cross-sectional
Muehlhan et al. 2018	Germany	130	Patients with Alcohol Use Disorder and healthy controls, aged 18-65	Alcohol	Salivary and serum ACTH and cortisol reactivity and hair cortisol concentrations (HCC)	ACEs	Trier Social Stress Test (TSST)	Cross-sectional
Negriff et al. 2015	USA	254	Youths, aged 10 through 18	Alcohol and cannabis	Salivary cortisol reactivity	ACEs	Trier Social Stress Test (TSST) modified for children	Longitudinal

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Pirnia et al. 2019	Iran	195	Patients with Methamphetamine Use Disorder, aged 18-35	Methamphetamine	Salivary cortisol	ACEs	-	Cross-sectional
Roy et al. 2002	USA	29	Male patients with Cocaine Use Disorder, aged 35-45	Cocaine	Urinary free cortisol (UFC)	ACEs	-	Cross-sectional
Schäfer et al. 2010	Germany	38	Patients with Alcohol Use Disorder, aged 18-65	Alcohol	Serum ACTH and cortisol	ACEs	-	Cross-sectional
<b>Opioids</b>								
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotrophic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides $\alpha$ -melanocyte stimulating hormone (MSH) and $\beta$ -endorphin (END)	ACEs	Treatment with diamorphine	Cross-sectional
<b>Oxytocin</b>								
Fuchshuber et al, 2020	United Kingdom	48	Male patients with poly-Substance Use Disorder and healthy control, aged 19-38	Any substance	Serum OT reactivity	Attachment	Adult Attachment Projective Picture System (AAP)	Cross-sectional
Gerra et al. 2017	Italy	18	Male patients with Opioid Use Disorder and healthy control, aged 21-48	Opioid	Serum OT	ACEs	-	Cross-sectional
Huang et al. 2018	Taiwan	130	Patients with Ketamine Use Disorder and healthy control, aged 18-60	Ketamine	Serum OT	ACEs	-	Cross-sectional

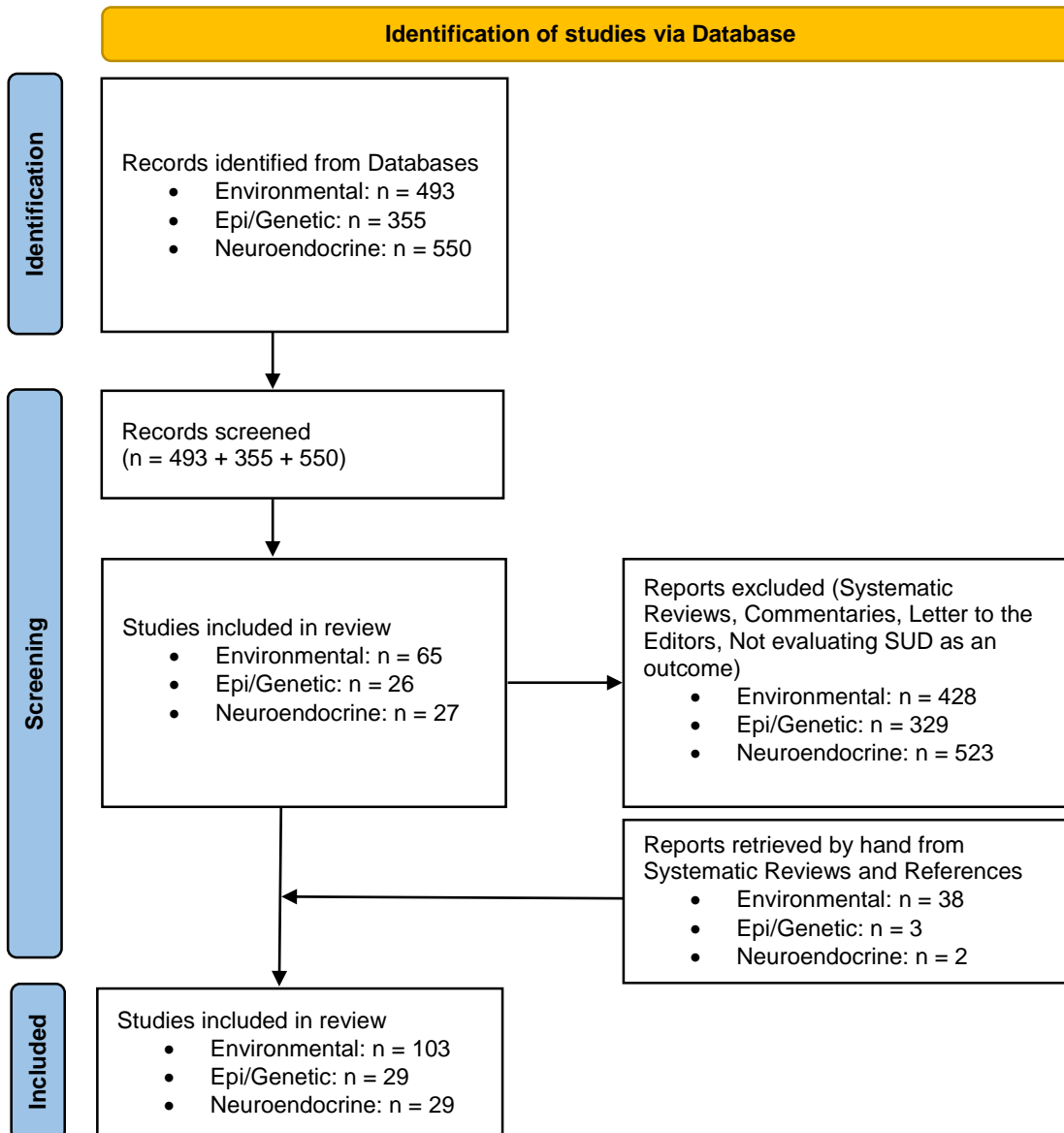


Figure 2

