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

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

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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.
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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. If 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;

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

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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. 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 (McCrory 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 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. 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; 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 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).

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 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).

According with a recent 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 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).

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 (Hosseinifard 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 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 pint out to a diminished white matter integrity as a neurobiological marker of attachment in substance use disorder.

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 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 cannab* OR methamphetamine* OR heroin* OR stimulant* OR tobacco OR cigarette* OR ecstasy.

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 have 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**.

- 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 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).

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 (Arnau et al., 2008), greater emotion-regulation (Kober, 2014, Karimi et al., 2019, Zdanklewicz-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).

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 aethiopathogenic 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., 2016Kim 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 Zdanklewicz-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

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, serotoninergic 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 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 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 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 glucorticoids 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 *rs242938*A allele) in the *CRHR1* 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 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 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 (Dannlowski 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 (*CHRNB2)*, 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., 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 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 that 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 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 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 hydroxymethilation 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).

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 out 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/serotoninergic 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 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 dopaminercic activity, have been found to be related to neglect and poor parenting perception (Gerra et al., 2009a). In another study focused on the serotoninergic 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 psycho-stimulants and that this mechanism may underlie increased vulnerability for drug use (Oswald et al., 2014).

These preliminary findings suggest that dopaminergic/serotoninergic 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).

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 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 μ, κ and δ 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 β-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., 2011).

We found only one recent study (Groh et al. 2020) that evaluated the interrelationship between the serum level of β-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 β-endorphin, suggesting that reduced endogenous opioid peptides could have a role in the altered in 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 (Dannlowski 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 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 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 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 $GABA_A$ 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).

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" 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, 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 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 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 tried to delineate a hypothetical model, which is currently only partially empirically validated, to describe 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 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).

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 2**).

- Figure 2 approximately here -

4.3. Limitation and future directions

We highlight that, despite our specific focus on attachment, the majority of the studies investigating the relation between early parent-child experiences and SUD did not include only measurement strictly related to attachment. We extended our research to adverse parent-child experiences, which are known to have a potential effect on attachment, because although longitudinal data reveal a moderate degree of stability in attachment patterns from infancy to adulthood, there may be discontinuities in attachment pattern depending on life circumstances (Mikulincer e Shaver, 2016; Fraley et al., 2020). In fact, attachment trajectories are more uneven and less predictable in children whose early experiences include adversity and maltreatment (Prior & Glaser, 2006).

Secondarily, it is worth noting, that all epigenetic studies focused on DNA methylation. However multiple regulatory epigenetic elements in conjunction seem to orchestrate gene expression and regulation, including non-coding RNAs and chromatin modifications. 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 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.

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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-environmental 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 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

Tables.

Table 1. Studies on the genetic factors associated with attachment and Substance Use Disorder

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
Monoamines								
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

			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
Hypothalamic-Pituitary-Adrenal axis								

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 polymorfisms	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
Opioids								
Cimino et al., 2020	Italy	150	Children, aged 8-9	- (general psychopathology)	μ-opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Copeland et al., 2011	USA	226	Children, aged 9-17	Any substances	μ-opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Noto et al., 2020	Japan	725	Healthy adults, aged 18-35	- (personality traits)	μ-opioid receptor gene: A118G single nucleotide polymorphism	Parenting	-	Cross-sectional
Oxytocin								
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
Others								
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

			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 β2 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
Monamines								
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

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
Hypothalamic-Pituitary-Adrenal axis								
Tyrka et al., 2016	USA	340	Adults, aged 18–65	Any substance	Glucocorticoid receptor gene (NR3C1): methylation of exon 1_F of the promoter region	ACEs	Dexamethasone/ corticotropin releasing hormone test	Cross-sectional
Opioids								
NONE								
Oxytocin								
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
Monoamines								
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

			Disorder and healthy controls, aged 20-36		adrenocorticotropic 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
Hypothalamic-Pituitary-Adrenal axis								
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 adrenocorticotropic 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, adrenocorticotropic 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 adrenocorticotropic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional

Gerra et al. 2014	Italy	30	Male patients with Opioid Use Disorder, aged 22-35	Opioid	Serum adrenocorticotropic 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 adrenocorticotropic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotropic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides α-melanocyte stimulating hormone (MSH) and β-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

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
Opioids								
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotropic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides α-melanocyte stimulating hormone (MSH) and β-endorphin (END)	ACEs	Treatment with diamorphine	Cross-sectional
Oxytocin								
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

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

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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. 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 (McCrory 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 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 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).

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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 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 thisAccording 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. Wwe 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 experiences. In this review, instead, we will focus specifically on parental attachmentand 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 (Hosseinifard 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 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 pint out to a diminished white matter integrity as a neurobiological marker of attachment in substance use disorder.

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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 cannab* OR methamphetamine* OR heroin* OR stimulant* OR tobacco OR cigarette* OR ecstasy.

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**.

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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).

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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 (Arnau et al., 2008), greater emotion-regulation (Kober, 2014, Karimi et al., 2019, Zdanklewicz-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).

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 aethiopathogenic 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., 2016Kim 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 Zdanklewicz-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

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, serotoninergic 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 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 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 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 glucorticoids 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 *rs242938*A allele) in the *CRHR1* 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 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 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 (Dannlowski 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 (*CHRNB2)*, 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.,

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 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 that 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 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

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 hydroxymethilation 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).

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 out 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/serotoninergic 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 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 dopaminercic activity, have been found to be related to neglect and poor parenting perception (Gerra et al., 2009a). In another study focused on the serotoninergic 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 psycho-stimulants and that this mechanism may underlie increased vulnerability for drug use (Oswald et al., 2014).

These preliminary findings suggest that dopaminergic/serotoninergic 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).

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 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 μ, κ and δ 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 β-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., 2011).

We found only one recent study (Groh et al. 2020) that evaluated the interrelationship between the serum level of β-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 β-endorphin, suggesting that reduced endogenous opioid peptides could have a role in the altered in 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 (Dannlowski 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 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 an 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 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 $GABA_A$ 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).

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, 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 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 identifiedproposed pathways are not likely acting in isolation, but they may beare 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 tried to delineate a hypothetical model, which is currently only partially empirically validated, to describe 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 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).

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 2~~1~~**).

- Figure ~~1~~2 approximately here -

4.3. Limitation and future directions

~~Among the limitation of our review~~W~~ w~~e 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,~~W~~ w~~e extended our research to adverse parent-child experiences, which are known to have a potential effect on attachment, because a~~. Even because, a~~lthough 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, i~~I~~t is worth noting, ~~as potential limitation on our findings,~~ that all epigenetic studies focused ~~only~~ on DNA methylation.~~, h~~ However multiple regulatory epigenetic elements in conjunction seem to orchestrate gene expression and regulation, including non-coding RNAs and chromatin modifications.

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 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.

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.

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Figure Captions

Figure 1. PRISMA Flow diagram

Figure ~~1~~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-environmental 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

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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

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

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Tables.

Table 1. Studies on the genetic factors associated with attachment and Substance Use Disorder

Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
Monoamines								
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

			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
Hypothalamic-Pituitary-Adrenal axis								

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 polymorfisms	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
Opioids								
Cimino et al., 2020	Italy	150	Children, aged 8-9	- (general psychopathology)	μ-opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Copeland et al., 2011	USA	226	Children, aged 9-17	Any substances	μ-opioid receptor gene: A118G single nucleotide polymorphism	Attachment	-	Cross-sectional
Noto et al., 2020	Japan	725	Healthy adults, aged 18-35	- (personality traits)	μ-opioid receptor gene: A118G single nucleotide polymorphism	Parenting	-	Cross-sectional
Oxytocin								
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
Others								
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

			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 β2 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
Monamines								
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

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
Hypothalamic-Pituitary-Adrenal axis								
Tyrka et al., 2016	USA	340	Adults, aged 18–65	Any substance	Glucocorticoid receptor gene (NR3C1): methylation of exon 1_F of the promoter region	ACEs	Dexamethasone/ corticotropin releasing hormone test	Cross-sectional
Opioids								
NONE								
Oxytocin								
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

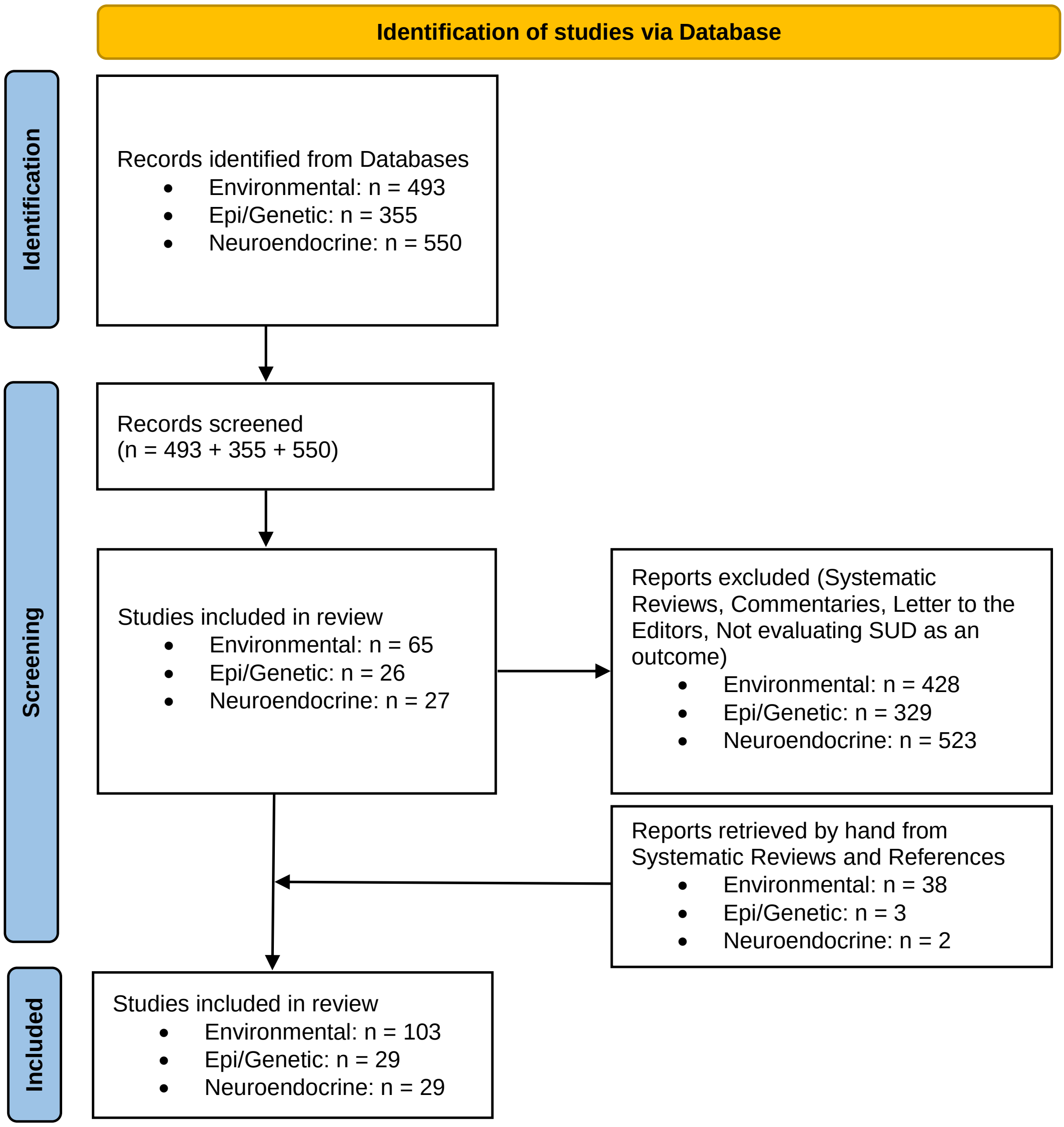
Reference	Country	Sample size	Population	Substance	Gene/Hormone	Attachment measure (direct/indirect)	Task/intervention	Type
Monoamines								
Berglund et al., 2013	Sweden	18	Male patients with Alcohol Use Disorder, aged 35-55	Alcohol	Serum prolactine reactivity	ACEs	Prolactin response to a selective 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

			Disorder and healthy controls, aged 20-36		adrenocorticotropic 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
Hypothalamic-Pituitary-Adrenal axis								
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 adrenocorticotropic 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, adrenocorticotropic 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 adrenocorticotropic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional

Gerra et al. 2014	Italy	30	Male patients with Opioid Use Disorder, aged 22-35	Opioid	Serum adrenocorticotropic 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 adrenocorticotropic hormone (ACTH) and cortisol	ACEs	-	Cross-sectional
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotropic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides α-melanocyte stimulating hormone (MSH) and β-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

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
Opioids								
Groh et al. 2019	Germany	15	Patients with Opioid Use Disorder, aged 18-45	Opioid	Serum adrenocorticotropic hormone (ACTH) and cortisol reactivity; proopiomelanocortin peptides α-melanocyte stimulating hormone (MSH) and β-endorphin (END)	ACEs	Treatment with diamorphine	Cross-sectional
Oxytocin								
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 1


Identification of studies via Database
Identification
Records identified from Databases
• Environmental: n = 493
• Epi/Genetic: n = 355
• Neuroendocrine: n = 550
Screening
Records screened
(n = 493 + 355 + 550)
Studies included in review
• Environmental: n = 65
• Epi/Genetic: n = 26
• Neuroendocrine: n = 27
Reports excluded (Systematic Reviews, Commentaries, Letter to the Editors, Not evaluating SUD as an outcome)
• Environmental: n = 428
• Epi/Genetic: n = 329
• Neuroendocrine: n = 523
Reports retrieved by hand from Systematic Reviews and References
• Environmental: n = 38
• Epi/Genetic: n = 3
• Neuroendocrine: n = 2
Included
Studies included in review
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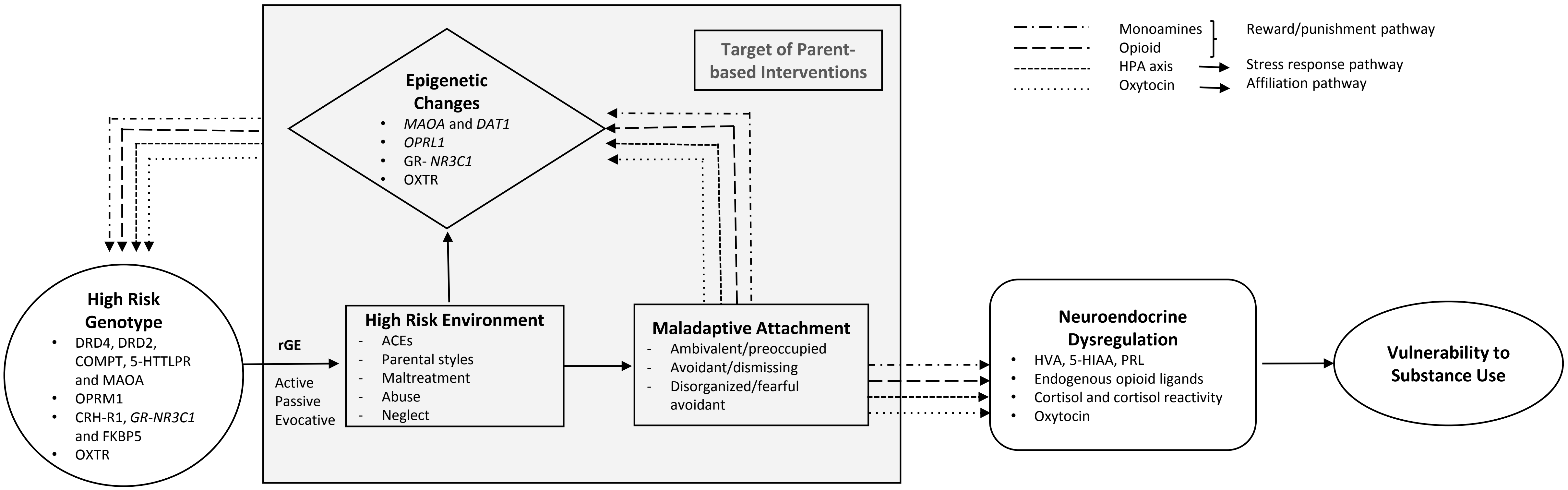
• Epi/Genetic: n = 29
• Neuroendocrine: n = 29

Figure 2


Monoamines
Opioid
Reward/punishment pathway
HPA axis
Stress response pathway
Oxytocin
Affiliation pathway
Target of Parent-based Interventions
Epigenetic Changes
MAOA and DAT1
OPRL1
GR- NR3C1
OXTR
High Risk Genotype
DRD4, DRD2, COMPT, 5-HTTLPR and MAOA
OPRM1
CRH-R1, GR-NR3C1 and FKBP5
OXTR
rGE
Active
Passive
Evocative
High Risk Environment
ACEs
Parental styles
Maltreatment
Abuse
Neglect
Maladaptive Attachment
Ambivalent/preoccupied
Avoidant/dismissing
Disorganized/fearful avoidant
Neuroendocrine Dysregulation
HVA, 5-HIAA, PRL
Endogenous opioid ligands
Cortisol and cortisol reactivity
Oxytocin
Vulnerability to Substance Use