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REVIEW ARTICLE

The effects of cocaine exposure in adolescence: Behavioural effects and neuroplastic mechanisms in experimental models

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Drug addiction is a devastating disorder with a huge economic and social burden for modern society. Although an individual may slip into drug abuse throughout his/her life, adolescents are at higher risk, but, so far, only a few studies have attempted to elucidate the underlying cellular and molecular bases of such vulnerability. Indeed, preclinical evidence indicates that psychostimulants and adolescence interact and contribute to promoting a dysfunctional brain. In this review, we have focused our attention primarily on changes in neuroplasticity brought about by cocaine, taking into account that there is much less evidence from exposure to cocaine in adolescence, compared with that from adults. This review clearly shows that exposure to cocaine during adolescence, acute or chronic, as well as contingent or non-contingent, confers a vulnerable endophenotype, primarily, by causing changes in neuroplasticity. Given the close relationship between drug abuse and psychiatric disorders, we also discuss the translational implications providing an interpretative framework for clinical studies involving addictive as well as affective or psychotic behaviours.

KEYWORDS
adolescence, cocaine, neuroplasticity, nucleus accumbens, prefrontal cortex

1 | INTRODUCTION

Following the rearrangements occurring in the brain prenatally, such as the correct innervation patterns guided by neurotrophic factors together with physiological arborisation and branching (Sidman & Rakic, 1973), remodelling occurs also in the adolescent brain such as overshooting of synapses together with pruning and myelination, all of which lead to structural and activity changes that dynamically affect the homeostasis of the brain (Andersen, 2003) and contribute to defining its adult topography (Figure 1). Adolescence is indeed a period of remarkable modifications both in body and behaviours that may influence the transition into adulthood. It is critical to consider

Abbreviations: ADHD, attention deficit hyperactivity disorder; Arc/Arg3.1, activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1; Arg kinase, adhesion-regulated non-receptor tyrosine kinase; BDNF, brain-derived neurotrophic factor; DAT, dopamine transporter; F-actin, filamentous actin; FGF-2, fibroblast growth factor 2; FKBP51, FK506 binding protein 5; G-actin, globular actin; NAc, nucleus accumbens; NOR test, novel object recognition test; p190RhoGAP, Rho GTPase-activating protein; PFC/mPFC/oPFC, prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex; PND, post-natal day; PSD-95, postsynaptic density protein 95, scaffolding protein; Rho, Ras homologous gene; ROCK, Rho-associated protein kinase; Src1, steroid receptor coactivator-1; Ube3a, ubiquitin-protein ligase E3A; VTA, ventral tegmental area.

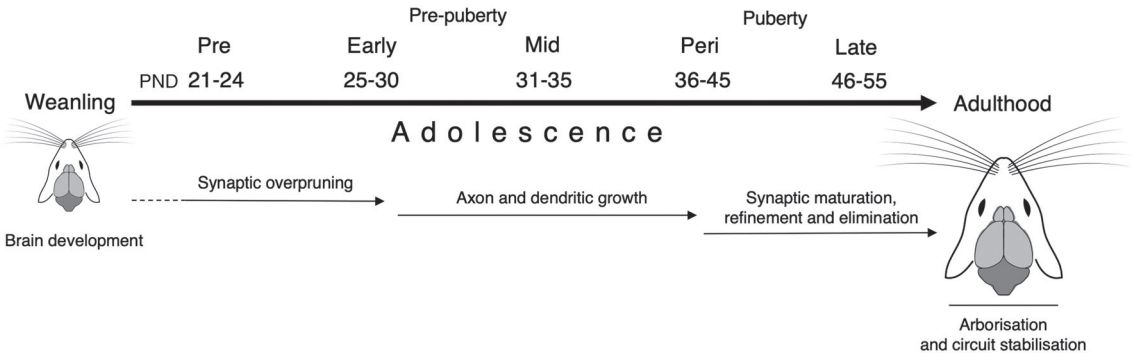

FIGURE 1 Schematic representation of timeline developmental stages and structural brain maturation during rat adolescence (PND, post-natal day)

that, in terms of ontogeny, each brain region exhibits a unique profile, with some developing earlier and some later and those brain regions that develop later and are still maturing during adolescence, are highly sensitive to any deviation from the normal developmental trajectory (Andersen, 2003). Adolescence, as a concept, incorporates several dynamics (social, environmental) that dictate inter-individual variability. It is indeed a delicate period for determining future behaviours in humans. Thus, abnormalities that impair the maturational trajectory of the adolescent brain result in an increasing incidence of neuropsychiatric disorders including, among others, substance abuse, depression, psychoses, anxiety (Moss et al., 2014; Paus et al., 2008; Rutherford et al., 2010).

Among the risk factors that may interfere with correct brain development, exposure to drugs of abuse plays a crucial role. Indeed, it is during this time of life that people more likely first experiment with drugs of abuse. The importance of adolescent drug use for both individuals and society is clear. Indeed, we can divide risks into immediate- (overdose, violent behaviour) and long-term risks (adverse consequence to the different organs of the body, including the brain, as well as abuse liability in adulthood, school dropout, social issues). Adolescents favour physical over cognitive activities, they are more likely to indulge in risky behaviours with peers such as drug-taking, they are more prone to the rewarding effects of drugs of abuse and feel less their adverse effects and, also, they suffer to a lesser extent from the unpleasant effects of abstinence (Casey et al., 2008; Doremus-Fitzwater & Spear, 2007; Spear, 2000). Such harmful alignment of susceptibilities may favour an overuse of drugs. These proclivities well explain why the use of rewarding drugs becomes normative in adolescence and why adolescents respond to such drugs in a significantly different way from adults. Intriguingly, the features mentioned above of human adolescents are shared by adolescent rodents (rats or mice), emphasising that adolescence is indeed an evolutionary phase, maintained through different species, and further pointing to animal models as a unique means to gather knowledge on the transition between adolescence and adulthood in terms of drug abuse.

In this review, we will focus on the preclinical data available for **cocaine** exposure during adolescence. Cocaine is a psychostimulant drug, characterised by harmful and addictive properties (Nutt et al., 2007), which is widely used throughout the world causing huge economic and social burdens. Although people are often focused on the rewarding properties of cocaine, exposure to the psychostimulant can also imperil health due to a series of adverse events other than its addictiveness, suggesting a wider impact of cocaine exposure on human health that can also be extended to adolescents. Epidemiological data are controversial, as some indicate that cocaine use has declined among adolescents in this century, but still prevalent in this age group (Schneider et al., 2018; Schulenberg et al., 2018) and some claim that cocaine use is instead rising (Johnson et al., 2015; Schneider et al., 2018). The European Drug Report 2020 indicates that in the European Union around 4.3 million people (1.3%) aged 15–64 (among them 2.4% aged 15–34) have used cocaine in the last year (EMCDDA, 2020). In the United States, the 2018 National Survey of Drug Use and Health (NSDUH) indicates that 0.4% of adolescents aged 12 to 17, 5.8% of young adults aged 18 to 25 and 1.6% of adults aged 26 or older used cocaine in the past year (SAMHSA, 2019). An estimated 79.6% of adolescents perceived great risk from weekly cocaine use, compared with 82.6% of young adults and 87.9% of adults aged 26 or older (SAMHSA, 2019). Based on these data, it appears that cocaine is still widely abused among adolescents and young adults and, therefore, we need to develop critical information not only on how cocaine acts but also on its deleterious consequences. To this end, preclinical models are crucial to understanding how exposure to drugs of abuse during adolescence, affecting the refinement of brain networks, may cause long-lasting impairments. A still debated issue relies on the possibility that exposure to drugs of abuse, impinging on the fine-tuning of brain circuits that normally occurs during brain development, may indeed reprogram the developmental trajectory, through aberrant rearrangements in structure and function, thus influencing the way the brain copes with external, challenging events that may occur later in life, leading to enduring consequences. This consideration goes beyond the concept that developmental exposure to drugs of abuse may influence only addiction later in life (Kuhn et al., 2013) and highlights the notion that interfering with an immature brain is a dynamic process that may lead to disparate outcomes. For instance,

people seeking a cure for stimulant dependence often display depressive symptoms (McKetin et al., 2011) whereas long-term abstinence from heavy psychostimulant use may unmask or worsen depression-like symptoms, albeit psychostimulants are known to induce initial mood elevation (McGregor et al., 2005). It is important to note that the feature of mood-raising could be, paradoxically, counterproductive as the subjects could abuse stimulants to raise the tone of their mood, depressed because of the abstinence. Similarly, people can show psychotic symptoms that do not always vanish after interrupting the stimulant use (Farrell et al., 2019).

We will start by providing an overview of the neuroplastic changes deriving from a single exposure to cocaine during adolescence. This aims at showing that even a single exposure to cocaine is sufficient to alter homeostasis in an adolescent brain. Then, we will review evidence showing that repeated exposure to cocaine during adolescence results in long-term, persistent neuroadaptive changes. Next, we will review cocaine-induced sensitisation in adolescent rats, an effect that may definitely influence drug abuse later in life, contributing to long-term alterations in behaviour. We will then focus our attention on anxiety-like behaviours and cognitive deficit following single or repeated exposure to cocaine during adolescence. This is critical because such altered behaviours may represent a drug-induced endophenotype, common to different mental disorders, but also a predictive feature for treatment response. We will then conclude the review by providing an interpretation and discussion of the main findings available.

2 | SINGLE EXPOSURE OF ADOLESCENT RATS TO COCAINE

2.1 | Effects of adolescent cocaine on neuroplasticity: The role of trophic factors

Concerning psychostimulants, evidence exists that a single injection of cocaine is sufficient to increase extracellular levels of **dopamine** more in adolescents than adults (Walker & Kuhn, 2008). This finding suggests that the still incomplete maturation of the dopamine system (Volz et al., 2009; Walker et al., 2010) may contribute to explain the heightened behavioural and dopaminergic responses observed during adolescence. Studies on the first exposure to psychostimulants are important as the same neural substrates contributing to the acute reinforcing properties of drugs are involved also following repeated treatment leading to the negative emotional states that are intimately linked to drug withdrawal.

Among the factors that may contribute to such heightened sensitivity to drugs of abuse, aberrant expression of trophic factors may play a pivotal role (McGinty et al., 2010; Thomas et al., 2008). Neurotrophic factors are critical for brain development processes including proliferation, migration, differentiation, and survival (Reichardt, 2006). Additionally, they also participate in synaptogenesis, myelination, neuroprotection, and neuroplasticity (Molteni et al., 2001). Among these neurotrophic factors, basic **fibroblast growth factor (FGF-2)** is expressed in the developing brain (Gomez-Pinilla et al., 1994) and is sensitive to early-in-life manipulations (Fumagalli et al., 2005) or to neurotoxicants (Slotkin et al., 2007; Slotkin et al., 2008). We found that a single injection of cocaine during adolescence caused regional differences in the FGF-2 expression pattern, with up-regulation in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) and reduction in the hippocampus, highlighting a precise brain region-dependent profile (Giannotti et al., 2015). Besides, we found that the first injection of cocaine primed the response to a second exposure, in terms of FGF-2 expression. This observation is extremely intriguing in view of the fact that exposure to cocaine during adolescence may influence the response to a subsequent event later in life (e.g., subsequent exposure to cocaine or stress), an effect that goes beyond the alteration of the trophic response. Using this simple approach, we can conclude that the system responds to the first exposure to the psychostimulant by promoting a trophic, neuroprotective response in mPFC and NAc (Giannotti et al., 2015) that may represent a form of homeostatic adaptation to the increased neuronal activity brought about by cocaine, whereas the response to the second injection could be interpreted as a neuronal and cell responsiveness adaptation, which is a function of the first injection. An intriguing observation that comes from this study relies on the reduced expression of FGF-2 observed in the hippocampus, which may represent the first step of defective hippocampal neurogenesis (Fares et al., 2019; Woodbury & Ikezu, 2014; Zechel et al., 2010) that, notably, plays a critical role in relapse-related events (Deschaux et al., 2014). This suggests that even a single exposure to cocaine during adolescence may influence addiction-related events later in life. Additionally, the diminution of hippocampal FGF-2 expression may characterise the emotional response following a single dose of cocaine, contributing to the related anxiety phenotype (Kohtz et al., 2010). Indeed, FGF-2 overexpression early in life rescues an anxiety phenotype in rats that were classified as low responders to novelty (Turner et al., 2011) whereas the silencing of the FGF-2 gene causes an anxiety-like behaviour (Eren-Kocak et al., 2011). Moreover, the reduction of FGF-2 expression lasts for at least 7 days, highlighting the enduring nature of a single developmental injection. This observation is intriguing because FGF-2 is involved in depression (Evans et al., 2004; Riva et al., 2005) and its expression is regulated by antidepressants (Bachis et al., 2008; Maragnoli et al., 2004). Further, a single administration of cocaine during adolescence is sufficient to determine anhedonia in a group of emotionally vulnerable rats, whereas other rats appear resilient (Caffino, Mottarlini, & Fumagalli, 2020). Notably, such distinction into two different populations of rats appears to be dictated by opposing modulation of the neurotrophin, **brain-derived neurotrophic factor (BDNF)**, both at central and peripheral levels, further pointing to modulation of trophic factors-related processes as critical for the response of the adolescent brain to cocaine (Caffino, Mottarlini, & Fumagalli, 2020). This finding allows us to speculate that a single injection of cocaine during brain development might trigger depressive-like states in rodents.

2.2 | Effects of adolescent cocaine on neuroplasticity: Structural remodelling

Besides changes in the expression of trophic factors, a single injection of cocaine leads to structural rearrangements that may account for maladaptive responses to environmental challenges and sustaining drug-taking and drug-seeking behaviours (Toda et al., 2006). We have recently demonstrated that a single cocaine injection during adolescence alters actin dynamics, causing morphological changes in dendritic spines (Caffino, Giannotti, Mottarlini, et al., 2017). We found that a single cocaine treatment during adolescence alters the balance between globular (G-) and filamentous (F-) actin, in the NAc and mPFC. Notably, such changes of accumbal actin dynamics are comparable to those shown by Toda and coworkers following repeated exposure to cocaine (Toda et al., 2006), suggesting that the remodelling observed following a single exposure to cocaine during adolescence might represent an initial step that leads to changes in functional synapses, an effect that may sustain addictive behaviours (Shen et al., 2009; Toda et al., 2006). The exposure to the second injection of cocaine revealed different adaptations that strictly depend upon the brain region considered. Thus, in the mPFC, the effect of the first injection waned after the second exposure to cocaine, presumably indicating that the first injection had reached a maximum effect whereas, in the NAc the second injection normalised the increased F-actin/G-actin ratio elicited by the first injection suggesting that the cytoskeleton is still capable of mounting an adaptive response to the psychostimulant. From these data, it appears that the cortical cytoskeleton is more vulnerable when re-exposed to cocaine presumably because, at variance from the NAc, which matures earlier, the mPFC is still developing during adolescence and, perhaps, more sensitive to psychostimulant interference.

We then performed a more in-depth analysis of dendritic spines (Caffino et al., 2018) and found that a single injection of cocaine during adolescence reduced the density of dendritic spines in the mPFC while increasing the immature protrusions known as filopodia. This morphological investigation revealed that the effects of developmental cocaine are subtle but highly dynamic. Whereas spine length was not altered, the head of active spines was enlarged, an effect restricted to mushroom-shaped dendritic spines, that is, the most active type of dendritic spines (Caffino et al., 2018). Rearrangements of dendritic spines are paralleled by a reorganisation of the **glutamate** synapse, characterised by reduced expression of the main **NMDA and AMPA receptor** subunits and their respective scaffolding proteins. Interestingly, we also found reduced expression of the integral glutamatergic protein PSD-95 and the cytoskeletal protein Arc/Arg3.1, known to be sensitive to cocaine exposure (Fosnaugh et al., 1995; Fumagalli et al., 2006; Fumagalli, Franchi, et al., 2009). The peculiarity of these findings derives from the evidence that such changes were restricted to the postsynaptic density, with no effects in the homogenate, implying that cocaine does not affect the synthesis of these glutamate determinants but, rather, their synaptic retention, suggesting a functional effect of these cocaine-induced glutamatergic modifications. Further, the evidence that adult rats exposed to the same experimental paradigm did not exhibit such glutamate adjustments suggests that it is the interference, by cocaine, with the correct developmental brain trajectory of the glutamate synapse that causes such outcomes.

To sum up (Figure 2), a single injection of cocaine during adolescence is sufficient to promote brain alterations that persist at least for 7 days after the injection. Also, a single injection of cocaine during brain development has a metaplastic effect, as the first injection is able to prime the response to a further drug exposure. Further, as the

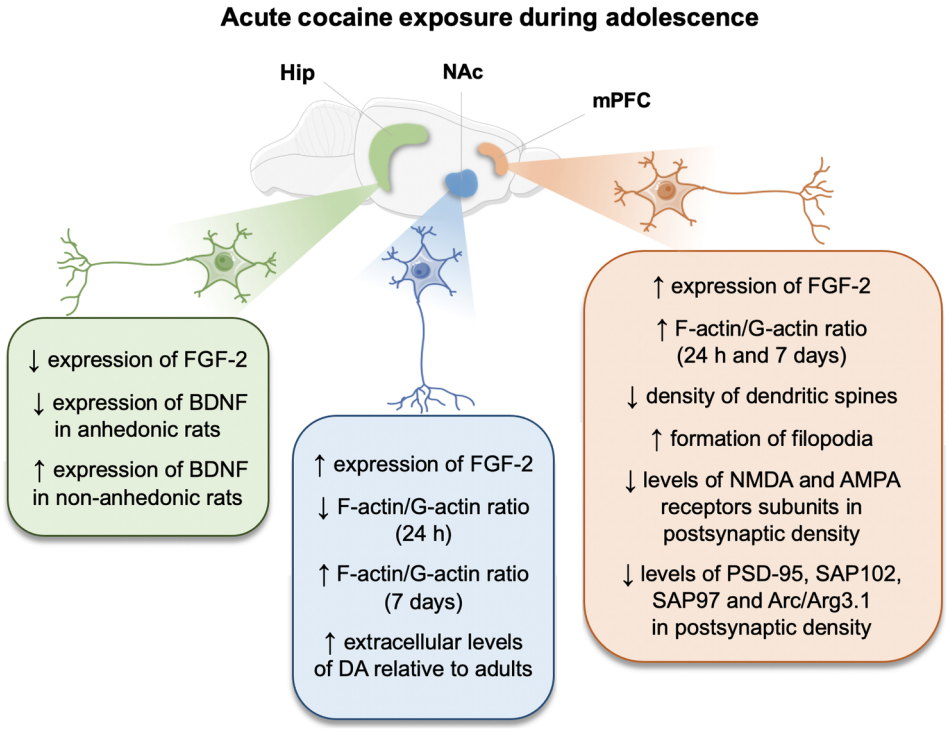

FIGURE 2 Molecular correlates of acute cocaine exposure during adolescence: Effects in the medial prefrontal cortex (mPFC), hippocampus (Hip) and nucleus accumbens (NAc). BDNF, brain-derived neurotrophic factor; FGF-2, fibroblast growth factor 2; F-actin, filamentous actin; G-actin, globular actin; DA, dopamine; h, hours

same single injection of cocaine in adulthood does not cause the same changes 7 days later, this indicates that such vulnerability is engendered by exposures occurring during brain development. Further, understanding the neuroadaptive changes set in motion by the first drug exposure during adolescence may also allow predictions about the sensitivity of these motivational systems occurring following repeated exposure to drugs. In fact, it has been demonstrated that, in rodents, a single exposure to cocaine may initiate a cascade of neurophysiological events that resemble long-term potentiation, leading to a long-lasting increase of synaptic strength (Ungless et al., 2001). It would be extremely difficult and potentially not practical to study humans immediately after their first exposure to cocaine because the obvious bias severely limits the inferences that could be drawn. However, this consideration does not diminish the importance of such an approach.

3 | REPEATED EXPOSURE OF ADOLESCENT RATS TO COCAINE

Although even a single exposure to cocaine may affect brain development, prolonged exposure to the psychostimulant may indeed lead to more detrimental effects.

Similar to humans, Wong and coworkers have shown that, relative to adults (post-natal day [PND] 88), adolescent rats exposed to different protocols of cocaine self-administration at PND 42 show a greater intake of cocaine, acquire cocaine self-administration more rapidly, exhibit escalation of cocaine intake and work harder for the drug (Wong et al., 2013). Moreover, it has been demonstrated that this heightened susceptibility to cocaine addiction is associated with increased electrophysiological properties of VTA dopamine neurons.

3.1 | Effects of adolescent cocaine on neuroplasticity: The role of trophic factors

Developmental exposure to cocaine increased both FGF-2 and BDNF expression in the mPFC following long-term, but not short-term, withdrawal (Figure 3) (Giannotti et al., 2013, 2014, 2016). This confirms the enduring effects of early exposure to the psychostimulant and corroborates the effects of withdrawal on brain homeostasis. Lack of changes in the expression of these proteins after short-term withdrawal indicates that their expression progressively increased during withdrawal, suggesting that both FGF-2 and BDNF might participate in the so-called 'incubation of craving' (Lu et al., 2004; Pickens et al., 2011; Verheij et al., 2016), that is, a process involving adaptations in the corticolimbic reward system that develops over time. A similar increase was found in the hippocampus of PND 80 rats exposed to cocaine during adolescence (Zhu et al., 2016). The increase of BDNF expression after long-term withdrawal, together with dysregulation of BDNF downstream pathway, is extremely relevant as it has been observed in the brain of cocaine addicts (Alvaro-Bartolome et al., 2011). McGinty et al. (2010) showed a reduction of the neurotrophin expression following short-, but not long-, term abstinence after repeated exposure to cocaine in adulthood, suggesting that developmental cocaine exposure influences the profile of BDNF expression differently from adult exposure. Such differences are further strengthened by the evidence that cocaine exposure during brain development engages, primarily, the **PI3 kinase** pathway in the mPFC (Giannotti et al., 2014) whereas, in adulthood, MAP kinase is principally recruited in the PFC (Whitfield et al., 2011). This suggests that the timing of exposure to the same compound may dictate the preferential intracellular pathways activated by the neurotrophin BDNF. It is important to note that the ablation of the **dopamine transporter (DAT)**, the major target of cocaine, leads to enduring effects on the

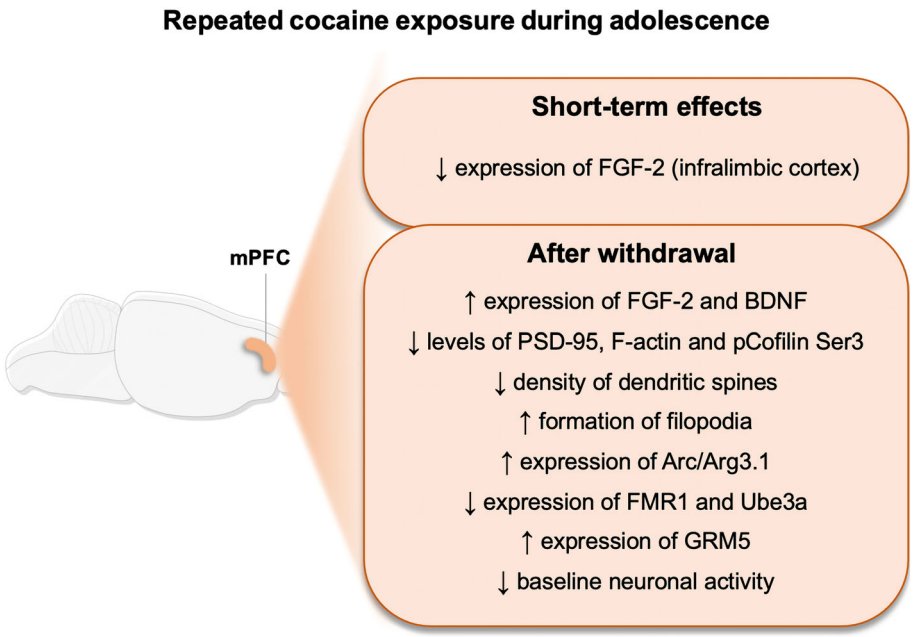

FIGURE 3 Molecular correlates of repeated cocaine exposure during adolescence in the mPFC. $mGlu_5$ receptor, metabotropic glutamate receptor; FMR1, fragile X mental retardation gene

neurotrophin, both in mice (Fumagalli et al., 2003) and rats (Leo et al., 2018), further supporting a tight linkage between the DAT, dopamine and BDNF.

A critical consideration on the functional significance of developmental exposure to cocaine relies on the evidence that long-term exposure to cocaine during adolescence may influence not only baseline levels of neuroplastic proteins but, also, their response to a challenging situation. For instance, adolescent exposure to cocaine self-administration renders rats highly responsive to the subsequent effects of stress even after a prolonged drug-free period. In rodents, adolescent-onset of cocaine use showed greater stress-induced reinstatement of cocaine seeking when compared to rats with adult-onset of cocaine use, suggesting that experiencing cocaine during adolescence increased the risk of relapse later in life (Wong & Marinelli, 2016).

Moreover, in terms of FGF-2, we found that the response to acute stress resulted in a significant down-regulation of the trophic factor expression in the mPFC of rats repeatedly exposed to cocaine during adolescence (Giannotti et al., 2013), an effect that is opposite to that normally observed following acute stress (Fumagalli, Calabrese, Luoni, Bolis, et al., 2012; Fumagalli, Calabrese, Luoni, Shahid, et al., 2012). These results suggest reduced cellular responsiveness to an adverse event after prolonged cocaine exposure and further point to this brain region, which is still maturing during adolescence, as a brain structure uniquely sensitive to cocaine exposure (Giannotti et al., 2013). It would be interesting to investigate whether the repeated exposure to a demanding event, such as chronic stress, would be able to offset the neurotrophic response following acute cocaine administration during adolescence, as we have previously shown in adult rats (Fumagalli, Caffino, et al., 2009).

3.2 | Effects of adolescent cocaine on neuroplasticity: The glutamate synapse

The long-term exposure to cocaine during brain development also dynamically altered the homeostasis of the glutamate synapse in the mPFC. We found that short-term withdrawal (3 days) from prolonged cocaine exposure during adolescence reduced baseline mPFC neuronal activity. This is intriguing because reduced cortical activity creates a hyperactive state that, in the presence of an appropriate stimulus (i.e., stress), may induce drug-seeking (Goldstein & Volkow, 2011; Jentsch & Taylor, 1999). Exposure to stress of rats treated with cocaine during adolescence reorganised the glutamate synapse as shown by increased release and reduced reuptake of glutamate together with enhanced postsynaptic responsiveness of the obligatory subunit of the NMDA receptor, **GluN1**, which led to hyperresponsive spines (Caffino, Calabrese, et al., 2015). It is possible that such sensitisation to acute stress provides the ground for the increased sensitivity to stress observed in cocaine users (Fox et al., 2008; Sinha et al., 2003). Further, the formation of a hypersensitive glutamatergic synapse in the mPFC may help to explain the negative emotional state observed in animal models of cocaine abuse (Koob, 2008) and, also, contribute to the depression-like symptoms observed during the initial phase of cocaine withdrawal in humans (Gawin, 1991).

Short-term withdrawal following repeated exposure to cocaine led also to structural rearrangements, which are known to be critical for addiction. We found, for instance, altered spine dynamics as shown by reduced expression of PSD-95, cofilin, and F-actin (Caffino, Giannotti, et al., 2015). Confocal imaging confirmed expression data showing reduced density and altered morphology together with the formation of non-functional, inactive spines (i.e., filopodia) (Caffino, Giannotti, et al., 2015). The impaired reorganisation of the mPFC appears to occur through the coordinated dysregulation of the actions of the **glucocorticoid receptor**, its co-chaperone **FKBP51**, that normally retains the receptor in the cytoplasm and the protein Src1 that participates in the activation of the transcriptional activity of glucocorticoid receptors (Caffino, Giannotti, et al., 2015). These findings may hold several implications. First, the alteration of glucocorticoid receptor responsiveness may contribute to the negative emotional state observed in humans during early periods of abstinence (Koob, 2013). Further, because it is known that increased glucocorticoid receptor activity impairs cognition, also through changes in dendritic spine morphology (Finsterwald & Alberini, 2014; Gourley, Swanson, et al., 2012; Swanson et al., 2013), the glucocorticoid receptor-dependent alteration in structural remodelling following developmental exposure to cocaine may negatively influence the normal functioning of cortical synapses, leading to altered learning and memory (Robinson & Kolb, 2004). It is possible that the combination of a hyperactive glucocorticoid receptor system and impaired structural rearrangements of the mPFC may synergise and heighten the sensitivity to the addictive properties of cocaine (Chambers et al., 2003).

Structural remodelling occurs also at longer points of drug withdrawal indicating the enduring consequence set in motion by developmental cocaine exposure. Repeated exposure to cocaine during adolescence altered the expression and the mechanisms of synthesis of Arc/Arg3.1 (Caffino et al., 2014), an effector, immediate early, gene critical for cytoskeletal plasticity and known to be engaged in structural synaptic plasticity (Bramham et al., 2008) as well as in the action of cocaine (Fosnaugh et al., 1995; Fumagalli, Franchi, et al., 2009; Hearing et al., 2008). Arc/Arg3.1 expression was significantly increased in the mPFC of rats at adulthood, through the alteration of finely tuned mechanisms that, under physiological conditions, regulate its synthesis involving, for instance, the ubiquitin-protein ligase E3A and the metabotropic glutamate $mGlu_5$ receptor (Caffino et al., 2014). Exposure to cocaine during development causes longer-lasting effects on the expression of this effector protein as the effects of adult exposure to cocaine wane already after 2 weeks (Fumagalli et al., 2006), again suggesting that exposure to cocaine while the mPFC is still maturing causes persistent alterations.

Interestingly, 24 h after the last exposure, we exposed adolescent rats to the so-called Novel Object Recognition (NOR) test to investigate whether developmental exposure to cocaine had altered their cognitive performance. We found that cocaine-treated rats spent more time exploring the novel object than saline-treated rats,

suggesting improved memory. After exposure to such a test, the expression of Arc/Arg3.1 was differently modulated in the two subregions of the mPFC. In fact, we found that, in the infralimbic cortex, Arc/Arg3.1 expression was increased only in cocaine-, but not saline-, treated rats suggesting that, under physiological conditions, the infralimbic cortex is not recruited to perform such a test whereas it is unusually engaged in rats exposed to cocaine during adolescence (Caffino, Giannotti, Racagni, & Fumagalli, 2017). Conversely, in the prelimbic cortex, the NOR test increased Arc/Arg3.1 expression in both experimental groups, suggesting that this subregion of the cortex is usually activated during this task and not influenced by cocaine. This suggests that exposure to cocaine during brain development has triggered an abnormal activation of the infralimbic cortex to the NOR test. Intriguingly, we also found that the changes in Arc/Arg3.1 expression are paralleled by changes in the structural protein PSD-95, a protein critically involved in the remodelling of the glutamate synapse (Caffino, Giannotti, Racagni, & Fumagalli, 2017).

3.3 | Cocaine-induced sensitisation in adolescent rats

It is known that repeated injections of cocaine can induce a progressive and enduring augmentation of its motor stimulant effect: this phenomenon is known as behavioural sensitisation. This mechanism is also known to play a critical role in the process of craving (Covington & Miczek, 2001) and it is therefore linked with addiction and long-lasting plastic changes in the brain. Because adolescence is a crucial period for the transition from hedonic to compulsive use of cocaine, several researchers have focused on the possibility that developmental exposure to cocaine might induce, as observed during adulthood, sensitisation to cocaine exposure. Repeated exposure to cocaine during adolescence (5-week-old rats) causes increased locomotor responses at withdrawal days 3, 14, and 60 with the higher sensitised response at the longer time point (Brandon et al., 2001). Similarly, Marin et al. (2008) have shown that a cocaine exposure from PND 30 to PND 34 and a subsequent challenge at PND 37 (i.e., still adolescent), PND 64 (i.e., early adulthood) or PND 94 (full adulthood) resulted in cocaine sensitisation at PND 37 and PND 64 but not at PND 94 (Marin et al., 2008). These results suggest that the drug sensitisation induced by developmental exposure to cocaine lasted into early adulthood, but waned in adulthood, that is, 2 months after the end of developmental exposure (Marin et al., 2008). Laviola et al. (1995) performed the cocaine treatment slightly before Marin et al., and challenged the rat with a further, single injection of cocaine 2 days later. These authors found increased sensitisation in adolescent rats, with a more pronounced effect in females (Laviola et al., 1995). Exposing animals to chronic self-administration during adolescence or adulthood, Frantz et al. (2007) found that adolescent rats exhibited cocaine sensitisation at a higher dose of cocaine challenge, implying that they were less sensitive to drug sensitisation than adults (Frantz et al., 2007). At variance from other authors, Ujike and associates showed that chronic exposure to cocaine before PND 21 did not result in cocaine sensitisation in adulthood suggesting that adaptive mechanisms may have come into play to protect against sensitisation effects (Ujike et al., 1995). Rowson et al. (2018) assessed the effects of cocaine exposure during adolescence or adulthood in female rats pre-exposed to chronic stress. The authors found that only adolescent rats developed sensitisation to cocaine exposure, a behaviour that was independent of previous stress history. This study is interesting because it is one of the few that uses female rats but also because it demonstrates that female adolescent rats appear to be more sensitive when compared to adult rats in terms of cocaine-induced sensitisation (Rowson et al., 2018). However, a thorough examination of the effects set in motion by developmental exposure to cocaine in female rats is mandatory. The above mentioned studies on cocaine-induced sensitisation are indeed heterogeneous in terms of results. Such discrepancies may be due to several factors, alone or in combination. For instance, it is possible that the modality of cocaine exposure (contingent vs. non-contingent), the developmental time of exposure (early vs. late adolescence), or the time of analysis (a short or long period after the last drug exposure) may indeed influence cocaine-induced sensitisation in adolescent rats.

It has also been shown that adolescent exposure to cocaine can lead to cross-sensitisation in adulthood. In fact, Shanks and associates have shown that cocaine (but also other psychostimulants such as **amphetamine** and **methylphenidate**) are able to induce cross-sensitisation to **methamphetamine** in adulthood, further suggesting that developmental cocaine exposure has a wide effect on drug abuse later in life (Shanks et al., 2015).

3.4 | Anxiety-like behaviours following long-term exposure to cocaine during adolescence

Withdrawal from long-term cocaine exposure indeed affects the emotional behaviour in rodents, thus mimicking very closely human behaviour (Coffey et al., 2000; Gawin & Kleber, 1986; Satel et al., 1991). In addition, it has been demonstrated that targeting anxiety symptoms mitigates the risk of cocaine reinstatement (Buffalari et al., 2012), suggesting that anxiety is intimately linked to drug addiction. Valzachi et al. (2013) exposed animals to cocaine from PND 30 to PND 37 and found increased anxiety behaviours in the elevated plus-maze, together with increased sensitisation, in PND 47 rats (Valzachi et al., 2013). In another paper, Alves and associates employed a binge cocaine paradigm (15 mg kg^{-1} cocaine injection, three times daily) between PND 35 and PND 50 and examined anxiety in the elevated plus-maze in early adulthood. Under these conditions, adolescent-treated rats did not show anxiety-like behaviours (Alves et al., 2014). Santucci and Madeira (2008) exposed PND 30 rats to cocaine assessing anxiety levels with an elevated zero maze followed by a second assessment performed 4 weeks thereafter. These authors found an anxiogenic effect that lasted as long as 12 weeks after the cessation of treatment, that is, an effect that persisted way into adulthood (Santucci & Madeira, 2008), presumably related to drug withdrawal. The same group also showed that an anxiogenic-like response

emerged even after a shorter withdrawal of 10 days (Santucci & Rosario, 2010) using a similar behavioural test. Conversely, Estelles et al. (2007) exposed adolescent mice to a binge paradigm similar to Alves et al., and found an anxiolytic effect in the elevated plus-maze, an effect that may be due to the fact that mice were exposed to cocaine at a younger age (PND 26 vs. PND 35) (Estelles et al., 2007). At variance from these results, Zhu et al. (2018) have shown that rats exposed to cocaine during adolescence exhibited higher anxiety-like behaviour in adulthood, measured by the elevated plus-maze test. These authors also showed that drug-induced, long-lasting, anxiety-like behaviours in adulthood were paralleled by a reduction of both synaptic and dendrite spine densities in pyramidal neurons of mPFC (Zhu et al., 2016, 2018). Notably, the same group has recently published the evidence that developmental exposure to cocaine heightened GABAergic neurotransmission in the prelimbic cortex thus reducing the neuronal activity of pyramidal neurons in this part of the cortex, a mechanism that may sustain anxiety- and depression-like-behaviours observed in adulthood (Shi et al., 2019).

A further interesting observation was provided by Garcia-Cabrerizo and Garcia-Fuster (2018) who demonstrated that adolescent exposure to cocaine (PNDs 33–39) enhanced negative state (anhedonia-like behavioural despair) only following cocaine re-exposure in adulthood: this is an important notion in the sense that preventing contact with drug abuse in adulthood might prevent the manifestation of the negative emotional state (Garcia-Cabrerizo & Garcia-Fuster, 2018). The discrepancy between these different lines of evidence may be ascribed to potential confounding factors such as different paradigms of cocaine exposure or different ages in which the elevated plus-maze test was performed. This consideration suggests that (1) different windows of vulnerability may exist during adolescence with respect to anxiety symptoms and (2) duration of withdrawal following the last exposure may represent a crucial determinant for the investigation of the anxiety-like phenotypes. Further, the anxiolytic effect set in motion by exposure to cocaine during adolescence observed in some of the papers mentioned above may indicate that a reduced cautious behaviour may promote drug-taking later in life.

3.5 | Repeated exposure to cocaine during adolescence: Effects on cognition

In adult humans, alterations of cognitive functions following chronic cocaine exposure, such as short- or long-term memory processes or attention have been widely demonstrated (Ardila et al., 1991; Bolla et al., 2003; Rosselli et al., 2001; Rosselli & Ardila, 1996); however, little is known on after adolescent cocaine use. It is known that adolescence is a period of life characterised by structural rearrangements that are primarily characterised by synaptic reorganisation and pruning of dendritic spines. Notably, cocaine is one of the most potent regulators of spine density and morphology in rodents, even after a single exposure (Caffino et al., 2018). In addition, repeated exposure to cocaine during this extremely sensitive period has been shown to reduce spine density in the rat mPFC (Caffino, Giannotti, et al., 2015; Gourley, Olevska, et al., 2012; Zhu et al., 2018). Such changes, which mostly affect the PFC, are likely to impact cognitive tasks (Kantak, 2020). The orbitofrontal cortex (oPFC) is a critical substrate implicated in cognitive sensitivity to psychostimulants, it is responsible for the outcomes of decision-making behaviours in cocaine addiction (Lucantonio et al., 2012) and it is known to be dysfunctional in cocaine addicts (Volkow & Fowler, 2000). At molecular level, the Arg kinase is a cytoskeletal regulatory protein that plays a critical role in maintaining dendritic spines stability, acting through p190RhoGAP on **Rho-kinase** functioning. Gourley et al. (2009) have elegantly shown that dendritic arbours are destabilised at PND 31 in the oPFC of Arg-knockout mice (Gourley et al., 2009), an effect that results in reversal learning task deficits, a readout of reduced cognitive flexibility. Such deficits were significantly exacerbated by low-dose of cocaine, revealing a strong inflexibility of Arg-knockout mice in coping with changes of circumstances in the reversal learning task (Gourley et al., 2009). Interestingly, DePoy and associates found that inhibition of Rho-kinase in the oPFC replicates the neurobehavioural defects observed in cocaine-treated mice (DePoy et al., 2013) suggesting a potential mechanism of cocaine-induced vulnerability.

Goal-directed and decision-making behaviours are highly evolved behaviours that require coordination of all cognitive functions, such as learning and memory processes, and are mainly regulated by the prelimbic cortex subregion of the mPFC. These goal-oriented and decision-related processes depend on actions that might, or might not, be reinforced. Interestingly, BDNF overexpression in the prelimbic cortex contributes to reducing the ability to discriminate between actions that are more or less, likely to be reinforced (Gourley, Olevska, et al., 2012) whereas prelimbic cortex-targeted BDNF knockdown enhances the capability to differentiate among actions, reinforced or not, allowing goal-directed decisions to be made (Hinton et al., 2014). On the other hand, sub-chronic cocaine exposure in early-adolescent wild-type animals increases BDNF expression in the mature prelimbic cortex, thus reinforcing habit-like behaviours and vulnerability to cocaine seeking (Lu et al., 2010; McGinty et al., 2010). Notably, the goal-directed effect induced by BDNF silencing in wild-type animals is not effective in mice with a history of cocaine exposure during adolescence (PNDs 31–35). Indeed, BDNF-deficient mice exposed to cocaine were insensitive to modifications in the response outcomes (Hinton et al., 2014), strengthening their inability to discriminate between actions, reinforced or not. Other studies have examined the executive functions following chronic exposure to cocaine in adolescence. In fact, exposure to high doses of cocaine starting from PND 30 for 14 days altered perseveration, impulsive choice, and general reinforcement processes further pinpointing adolescence as a period extremely sensitive to pharmacological insults (Pope et al., 2016).

Based on the lines of evidence provided above, it appears that interference, by cocaine, with the maturational profile of cognition-modulating proteins leads to neurocognitive impairment. As for other domains, the deleterious effects of adolescent cocaine taking are inherently linked to the drug dose, route of administration, and

frequency of use. However, for drugs of abuse, the length of withdrawal may play a major role as the deriving negative emotional state may impinge on cocaine-induced cognitive deterioration further worsening the pathological outcome. Accordingly, Santucci and Rabidou (2011) have shown that exposure of PND 30 rats to cocaine (10 or 20 mg kg^{-1}) for 8 days induces cognitive impairments in early adulthood (Santucci & Rabidou, 2011). In this experiment, the authors tested the animals for the acquisition of a two-choice object discrimination task. In this test, cocaine-treated rats acquired the discrimination behaviour much later at both doses. Interestingly, LeBlanc-Duchin and Taukulis (2007) showed that chronic adolescent exposure to the psychostimulant methylphenidate (starting at PND 35) yields prolonged impairment of memory for objects as well (LeBlanc-Duchin & Taukulis, 2007). We have contributed to strengthening the role of withdrawal in cognitive-related deficits showing that exposure of PND 28 rats to cocaine for 2 weeks and subsequent exposure to the NOR test at different times of withdrawal may have a different effect on memory processes (Mottarlini et al., 2020). In fact, after 2 weeks of withdrawal the ability of cocaine-withdrawn rats to recognise the novel object was severely impaired whereas when during early withdrawal, memory was improved (unpublished observation), an effect that may be due to the fact that the rodent behavioural response may rely more on the expectancy that rats may have of being exposed to the psychostimulant, an effect that may drive their behaviour towards the novel object (Burton et al., 2018). Interestingly, adult rats exposed to the same treatment paradigm were not cognitively impaired, further suggesting the resilience of adult rats and the vulnerability of adolescent rats to the effects brought about by cocaine.

4 | DISCUSSION

Indeed, normal development of the CNS depends upon a series of complex and dynamic mechanisms. It is therefore likely that exposure to psychostimulants during adolescence could be detrimental.

A crucial issue when assessing the effects of developmental exposure to cocaine is how to weigh them, as they heavily depend upon the timing of exposure, the stage of assessment and the brain region of interest. The timing of the insult is critical because it is highly possible that the earlier the exposure to cocaine the greater the effect on the neuronal network of the developing brain. Because, often, a too-broad definition of adolescence is given, sometimes including the juvenile period, it is difficult to precisely relate a given period of adolescence in rats with that in humans. To this end, PND 28 is generally considered the earliest age of adolescence (Figure 1) (Gulley & Juraska, 2013). Further, this issue can be even more complicated if earlier-in-life adversities occur that may influence the response of the adolescent brain to the cocaine insult. In fact, early-in-life adversities may alter the plasticity of the reward circuitry thus conferring susceptibility to psychopathologies (Birnie et al., 2020), although it is not that easy to disentangle events occurring before adulthood from the causal role of early adversities. Previous work has shown that early-life stress (i.e., repeated maternal separation) enhanced the acquisition of cocaine self-administration (Moffett et al., 2007), increased the motivational salience for cues that were previously paired with cocaine (Viola et al., 2016), induced higher locomotor response to cocaine (Kikusui et al., 2005), increased vulnerability to drug abuse (Alves et al., 2020) and anticipated adolescence negative behavioural outcomes associated with drug use normally seen during adulthood (Bis-Humbert et al., 2020). Further, Lo Iacono and associates have shown that traumatic childhood may sensitise to cocaine, both in mice and humans, through the dysregulation of the brain and peripheral immune responses (Lo Iacono et al., 2018). Thus, it appears that detailed knowledge is critical, albeit still lacking in-depth, on how early adversities may influence the use of drugs during adolescence suggesting that, perhaps, drug abuse in adolescence is tightly linked to the modulation of stress response in young people. There is a real possibility that adolescents consume drugs to be able to cope with stress within a developmental timeframe. These findings appear to be of translational value, as humans exposed to childhood maltreatment displayed enhanced anticipatory responses to drug cues (Elton et al., 2015) and more severe effects of withdrawal during cocaine abstinence (Francke et al., 2013).

Another crucial topic relates to the stage of assessment of the effects caused by cocaine. Ideally, the molecular response to a given treatment during neurodevelopment should be examined over a detailed temporal course. It has been shown in this review that the psychostimulant stimulus is able to cause behavioural and neuroplastic changes at time points that rule out the possibility that traces of cocaine still exist in the brain, suggesting that drug withdrawal interacts with cocaine exposure to cause such effects. These observations highlight the notion that drugs of abuse promote their deleterious effects in the developing brain not only when they are present but also in their absence. It is important to note that the stage of assessments of developmental exposure to cocaine may influence the duration of the resulting effects on the brain. So far, it is still not clear whether such effects vanish as abstinence persists.

Last, but not least, the effects of developmental exposure to drugs of abuse also depend upon the brain region examined. Based on the existing data, the major target of exposure to cocaine during brain development is indeed the PFC, an observation that is consonant with its maturational timetable (Andersen, 2003). It is, thus, possible to hypothesise that, during adolescence, exposure to cocaine has stronger effects on the PFC which, being still immature, has not yet developed defensive mechanisms to oppose to these insults.

The analysis of the effects brought about by only a single exposure to psychostimulants during brain development has allowed us to bring further support to the theory that adolescence is a period of extreme sensitivity to drugs of abuse. We have shown that a single exposure to cocaine during brain maturation reproduces the depressive-like signs (Caffino, Mottarlini, & Fumagalli, 2020) that are usually observed following repeated exposure to drugs of abuse or chronic stress in adulthood (Kompagne et al., 2008; Markou & Koob, 1991; Scheggi et al., 2011; Willner et al., 1997): accordingly, it is tempting to speculate that adolescence extends the pro-depressive

effects of a single injection of cocaine, as they last for at least 7 days. These results also suggest that even a single exposure to cocaine may contribute to psychopathology by altering developmental trajectories. In psychiatry, in fact, it is not yet known whether single or multiple episodes (for instance single or repeated stressful events) are needed to cause the development of a pathological phenotype. Our data on a single cocaine treatment suggest that a single episode is sufficient to promote the manifestation of a psychopathological endophenotype, although we cannot rule out that repeated psychostimulant exposure may identify a more severe psychopathological trait, perhaps even longer-lasting. In this regard, the preclinical investigation of the effects of exposure to cocaine during adolescence, be it single or chronic, may help to identify markers of vulnerability and to predict potential long-term outcomes, thus indicating that higher liability to cocaine-induced psychopathology may originate following developmental exposure. However, we have to take into account that the developing brain, when exposed to cocaine, may exhibit vulnerability but also resilience, as previously mentioned in this review (Caffino, Mottarlini, Mingardi, et al., 2020), thus opposing the derailment of the processes that characterise vulnerability. This would be consistent with the hypothesis formulated by Andersen and associates who suggested that brain development can represent not only a point of vulnerability but also a window of opportunity (Andersen, 2003). Indeed, this hypothesis would suggest that interfering with pharmacological or other types of manipulations early after the adolescent insult may sculpt the immature brain into a specific direction. For instance, the prolonged exposure to the stimulant methylphenidate, a drug widely used for the treatment of attention deficit hyperactivity disorder (ADHD), before puberty, rather than after puberty, influenced the response to a cocaine injection after a long withdrawal period (Andersen et al., 2002) and increased vulnerability to cocaine self-administration in adulthood (Brandon et al., 2001) via alterations of VTA dopamine neuronal activity (Brandon et al., 2003), further stressing the notion that the phase of development during which the treatment occurs is crucial for the overall outcome. In addition, it has to be taken into account the concept that traits that predispose individuals to depression-like conditions could also predispose them to cocaine use. Because preventative approaches to limit the burden of cocaine exposure in adolescents are currently not available, the identification of endophenotypes caused by adolescent cocaine exposures (i.e., neurobehavioural and cognitive deficits) might be instrumental to test pharmacological strategies during early phases of psychiatric disorders manifesting at later time points.

Another critical issue regarding developmental exposure to drugs of abuse relies on whether it induces abuse liability, that is, whether such exposure may lead to increased use in adulthood. Preclinical data indicate that adolescent priming may indeed favour consumption during adulthood. These results show that developmental exposure to cocaine influences the incubation of cocaine craving and drug-seeking in adulthood. However, other studies did not confirm these results showing, instead, that incubation of cocaine craving is mitigated in rats that self-administered cocaine during adolescence (Li et al., 2018; Li & Frantz, 2009). In particular, it has been hypothesised that developmental exposure to drugs of abuse may undermine the correct formation of adaptive mechanisms that are required for a correct response to rewarding stimuli in adulthood, suggesting that drug abuse in adulthood might be subjected to a sort of early-life programming. We have recently contributed to this field showing that adolescent exposure to cocaine may enhance the rewarding threshold necessary to drive conditioned place preference in adulthood, presumably predisposing adolescent-exposed rats to higher consumption of cocaine when adult (Caffino et al., 2021). However, this issue is still under debate.

Cocaine exposure during adolescence also affects the cognitive domain. This is a critical consideration that links developmental exposure to psychostimulants again with psychiatric traits. The focus on cognitive alterations is indeed crucial because, as observed for several psychiatric disorders, a cognitive deficit can persist even after significant improvement of typical psychiatric symptoms (i.e., psychotic and depressive symptoms). This is compatible with the evidence that rats exposed to cocaine during adolescence, but not during adulthood, do exhibit cognitive impairment following 2 weeks after the last drug exposure (Mottarlini et al., 2020). It is interesting to note that different adverse conditions occurring early in life (i.e., prenatal stress, maternal separation; developmental exposure to drugs of abuse) seem to cause similar cognitive dysfunctions suggesting that deficits in cognition may indeed represent an endophenotype of several mental illnesses and it may also represent a predictive feature for the functional outcome and treatment response in several of these disorders (Addington & Barbato, 2012; Andreou & Bozikas, 2013).

Overall, exposure to cocaine during adolescence represents a deviation from a normal developmental trajectory that confers enduring, (mal)adaptive effects to the developing brain, likely to lead to a predisposition to addiction and/or psychopathological traits later in life. Alteration of several domains (i.e., mood, cognition, not necessarily linked) as a consequence of adolescent cocaine exposure may constitute independent pathologies inside cocaine addiction. Indeed, the use of animal models is imperative in this regard, as changes occurring during adolescence are evolutionarily conserved and strongly maintained among various species (Spear, 2016). To this end, increasing effort must be put into dissecting the neurobiological impact that characterises the exposure to drugs of abuse during adolescence. Further preclinical studies need to closely address which specific cell types, if any, suffer from cocaine exposure, primarily in the mPFC, during a critical time window of development. In addition, more work is needed to establish a time course of the effects of cocaine, which may allow identifying a hazard classification of the different phases of brain development.

4.1 | Concluding remarks

The data discussed in this review clearly demonstrate that developmental exposure to cocaine evokes profound behavioural changes as well as multifaceted and regionally selective molecular and synaptic adaptations in the expression of key markers of neuroplasticity

TABLE 1 Summary of behavioral and neurochemical changes induced by acute and/or repeated exposure of adolescent rats to cocaine

Age of cocaine exposure (experimental model)	Dose/route	Species/ sex	Neurochemical changes	Behavioural changes	References
Acute exposure of adolescent rats to cocaine					
PND 35; PND 36; PNDs 35 and 36; PND 42; PNDs 35 and 42 *mPFC and NAc dissected 2 h after the second injection at PND 36 or 42*	20 mg kg^{-1} at PND 35; i.p. 10 mg kg^{-1} at PND 36/42; i.p.	Sprague Dawley rats; male	*mPFC at PND 36* ↑ F-actin/G-actin ratio after one injection at PND 35 or 36 *mPFC at PND 42* ↑ F-actin/G-actin ratio after one injection at PND 35 or 42 *NAc at PND 36* ↓ F-actin/G-actin ratio after one injection at PND 35 or 36 *NAc at PND 42* ↑ F-actin/G-actin ratio after one injection at PND 35 ↓ F-actin/G-actin ratio after one injection at PND 42	–	Caffino, Giannotti, Mottarlini, et al. (2017)
PND 35 *mPFC dissected at PND 42*	20 mg kg^{-1}; i.p.	Sprague Dawley rats; male	*mPFC at PND 42* ↓ total spine density ↑ formation of filipodia ↑ spines head width ↓ NMDA receptor subunit (GluN1, GluN2A and GluN2B) protein levels in the postsynaptic density ↓ AMPA receptor subunit (GluA1 and GluA2) protein levels in the postsynaptic density ↓ PSD-95, SAP97, SAP102, Arc/Arg3.1 protein levels in the postsynaptic density	–	Caffino et al. (2018)
PNDs 35 and 42 *Hip dissected 3 h after sucrose preference test*	20 mg kg^{-1}; i.p.	Sprague Dawley rats; male	*Hip at PND 42* ↓ total BDNF, BDNF exon I, IV and VI mRNA levels in anhedonic rats ↑ total BDNF and ↓ BDNF exon VI mRNA levels in non-anhedonic rats ↓ mBDNF protein levels in the homogenate and postsynaptic density in anhedonic rats ↑ mBDNF protein level in non-anhedonic rats in the homogenate ↓ pTrkB Tyr706 and TrkB protein levels in the postsynaptic density in anhedonic rats ↓ pAkt S_{473}/Akt and pERK2 $T_{185/187}$/ERK2 protein levels in anhedonic rats	*Sucrose preference test at PND 42:* - Population of anhedonic rats - Population of non-anhedonic rats	Caffino, Mottarlini, and Fumagalli (2020)

(Continues)

TABLE 1 (Continued)

Age of cocaine exposure (experimental model)	Dose/route	Species/ sex	Neurochemical changes	Behavioural changes	References
			↓ nucleus/cytosol glucocorticoid receptor protein levels in anhedonic and non-anhedonic rats		
PND 35; PND 36; PNDs 35 and 36; PND 42; PNDs 35 and 42 *mPFC, FCx, Hip, NAc dissected 2 h after the second injection at PND 36 or 42*	20 mg kg^{-1} at PND 35; i.p. 10 mg kg^{-1} at PND 36/42; i.p.	Sprague Dawley rats; male	*mPFC at PND 42* ↑ FGF-2 mRNA level after one injection at PND 35 *NAc at PND 36* ↑ FGF-2 mRNA level after one injection at PND 35 or 36 *NAc at PND 42* ↑ FGF-2 mRNA level after one injection at PND 42 ↑ FGF-2 mRNA level after two injections at PNDs 35 and 42 *Hip at PND 36* ↓ FGF-2 mRNA level after one injection at PND 35 or 36 *Hip at PND 42* ↓ FGF-2 mRNA level after one injection at PND 35	–	Giannotti et al. (2015)
PND 28	15 mg kg^{-1}; i.p.	Sprague Dawley rats; male	*Caudate and NAc core at PND 28* ↑ dopamine overflow compared to adult rats (PND 65)	–	Walker and Kuhn (2008)
Repeated exposure of adolescent rats to cocaine					
PNDs 35–50	15 mg kg^{-1}; i.p. (3 × day)	Wistar rats; male	*Amg at PND 60* ↓ DA level ↓ DAT mRNA level *VTA/SN at PND 60* ↑ TH mRNA and protein levels	↓ time spend in the central platform in the EPM after 10 days of withdrawal ↓ frequency of flight behaviour and ↑ social investigation in the R/I after 10 days of withdrawal	Alves et al. (2014)
PNDs 28–32	15 mg kg^{-1}; i.p.	Sprague Dawley rats; male	–	↑ locomotor responses after 3, 14 and 60 days of withdrawal (COC challenge with 7.5 mg kg^{-1})	Brandon et al. (2001)
PNDs 28–42 *mPFC dissected at PNDs 45 and 90*	20 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*mPFC at PND 45* ↑ Arc/Arg3.1 mRNA levels *mPFC at PND 90* ↑ Arc/Arg3.1 protein levels in the homogenate and nuclear fraction ↑ GRM5 mRNA level ↓ FMR1, Ube3a and Gria1 mRNA levels	–	Caffino et al. (2014)

TABLE 1 (Continued)

Age of cocaine exposure (experimental model)	Dose/route	Species/ sex	Neurochemical changes	Behavioural changes	References
			↓ GluA1 protein level		
PNDs 28–42 *mPFC dissected 15 min after stress (5-min swim stress)* *at PND 45*	20 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*mPFC at PND 45* ↓ EAAT1, EAAT2 and glial glutamate exchanger mRNA levels in stressed rats ↑ GS mRNA level in stressed rats ↑ vGLUT1 mRNA level in stressed rats ↓ vGAT mRNA level in non-stressed and stressed rats ↓ GAD67 mRNA level in stressed rats ↑ pGluN1/GluN1 and pPak1/Pak1 protein levels in stressed rats ↑ Cdc42 mRNA level in stressed rats ↓ Arc protein level in non-stressed rats ↑ Arc protein level in stressed rats	↑ immobility time during swim stress at PND 45	Caffino, Calabrese, et al. (2015)
PNDs 28–42 *mPFC dissected at PNDs 45 and 90*	20 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*mPFC at PND 45* ↓ total spine density ↑ formation of filipodia ↑ Nr3c1 and Src1 mRNA levels ↑ GR protein levels in the cytosolic and nuclear fraction ↑ nuclear/cytosolic ratio of GR protein levels ↑ pGR S232 protein level ↓ FKBP51 protein level ↓ CaD mRNA level ↓ PSD95, F-actin and pCofilin S3 protein levels	–	Caffino, Giannotti, et al. (2015)
PNDs 28–42 *IF and PL dissected from rats exposed/not exposed to NOR test* *at PND 43*	20 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*IL at PND 43* ↓ Arc/Arg3.1 mRNA levels in rats not exposed to NOR ↓ Arc/Arg3.1 protein levels in rats not exposed to NOR in the postsynaptic density ↓ PSD-95 protein levels in rats not exposed to NOR in the postsynaptic density	↑ discrimination index in the NOR test	Caffino, Giannotti, Racagni, and Fumagalli (2017)
PNDs 33–39	15 mg kg^{-1}; i.p.	Sprague Dawley rats; male	*dSTR at PND 71* ↓ c-Fos activation after COC challenge (15 mg kg^{-1})	↓ sucrose preference at PND 77 after COC challenge at PND 71 (15 mg kg^{-1})	Garcia-Cabrerizo and Garcia-Fuster (2018)
PNDs 28–42	20 mg kg^{-1}; s.c.	Sprague Dawley	*mPFC at PND 45* ↓ FGF-2 mRNA level in stressed rats	–	Giannotti et al. (2013)

(Continues)

TABLE 1 (Continued)

Age of cocaine exposure (experimental model)	Dose/route	Species/ sex	Neurochemical changes	Behavioural changes	References
mPFC, Hip, NAc and STR dissected 15 min after stress (5-min swim stress) at PNDs 45 and 90		rats; male	*mPFC at PND 90* ↑ FGF-2 mRNA level in non-stressed rats		
PNDs 28–42 *mPFC dissected at PNDs 45 and 90*	20 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*mPFC at PND 90* ↑ total BDNF and BDNF exon IV mRNA levels ↑CaRF and NF-kB (transcription factors involved in the regulation of BDNF exon IV expression) mRNA levels ↑ proBDNF and mBDNF protein levels ↑ tPA mRNA level ↓ let7-d, miR-124 and miR-132 levels ↑ trkB, pAkt, pmTOR, pS6K and Arc protein levels in the crude synaptosomal fraction ↓ AMPA receptor subunit (GluA) protein levels in the crude synaptosomal fraction	–	Giannotti et al. (2014)
PNDs 28–42 *IL, PL, dHip, vHip, NAc core, NAc shell, cAmy, VTA dissected at PND 43*	20 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*IL, NAc core, cAmy, vHip and VTA at PND 43* ↓ FGF-2 mRNA levels	–	Giannotti et al. (2016)
PNDs 32–35	10 or 20 mg kg^{-1}; i.p.	Sprague Dawley rats; male and female	–	↑ locomotor responses after 2 days of withdrawal (COC challenge with 10 mg kg^{-1})	Laviola et al. (1995)
PNDs 30–34 *mPFC and NAc dissected at PNDs 37, 64 and 94*	10 mg kg^{-1}; i.p. (2 × day)	Wistar rats; male	*mPFC at PND 37* ↑ GluR1 protein level	↑ locomotor responses after 3 and 30 days of withdrawal (COC challenge with 10 mg kg^{-1})	Marin et al. (2008)
PNDs 28–42 *PrhC dissected from rats exposed/not exposed to NOR test at PND 56*	5 mg kg^{-1}; s.c.	Sprague Dawley rats; male	*PrhC at PND 56* ↑ mBDNF protein level in non-tested rats in the homogenate ↓ mBDNF protein level in tested rats versus non-tested in the homogenate ↓ mBDNF protein level in non-tested rats in the postsynaptic density ↓ TrkB protein level in non-tested rats in the homogenate ↓ pERK2/ERK2 protein level in tested rats versus non-tested in the homogenate ↑ BDNF mRNA level in non-tested rats	↓ discrimination index in the NOR after 14 days of withdrawal	Mottarlini et al. (2020)

TABLE 1 (Continued)

Age of cocaine exposure (experimental model)	Dose/route	Species/ sex	Neurochemical changes	Behavioural changes	References
			↓BDNF mRNA level in tested rats versus non-tested ↑ Arc/Arg3.1 mRNA level in non-tested rats ↓ Arc/Arg3.1 mRNA level in tested rats versus non-tested ↓ Arc/Arg3.1 protein levels in tested rats versus non-tested in the homogenate ↓ PSD-95 protein level in tested rats versus non-tested in the homogenate		
PNDs 30–38	10 mg kg^{-1}; s.c.	Sprague Dawley rats; male	–	↑ anxiety-like behaviour in the EZM after 55–60 and 83–91 days of withdrawal	Santucci and Madeira (2008)
PNDs 30–38	10 or 20 mg kg^{-1}; s.c.	Long-Evans rats; male	–	↑ anxiety-like behaviour in the EZM after 10–11 of withdrawal	Santucci and Rosario (2010)
PNDs 21–25; PNDs 28–32	15 mg kg^{-1}; i.p. (2 × day)	Sprague Dawley rats; male and female	–	↑ activity and stereotypy after 21 days of withdrawal (COC challenge with 15 mg kg^{-1})	Ujike et al. (1995)
Self-administration from PNDs 41–43 For 7 or 10 days	0.6 or 1.2 mg kg^{-1} inf^{-1}; *i.v.*	Sprague Dawley rats; male	–	↑ stress-induced (electric footshock, corticosterone or yohimbine) re-instatement of cocaine seeking compared to rats with adult-onset of cocaine use	Wong and Marinelli (2016)
PNDs 28–42	15 mg kg^{-1}; i.p.	Sprague Dawley rats; male	*dHip and vHip at PND 80* ↑ percentage of abnormal neurons ↓ activity of superoxide dismutase (SOD) ↑ synapsin I and synaptophysin protein levels ↑ GFAP and S-100β protein levels ↑ CAS3, CAS8, Bcl-2 and BAX protein levels ↑ IL-6, IL-1β and TNFα protein levels ↑ BDNF and ΔFOSB protein levels ↓ p-CREB-1 protein level	↑ anxiety-like behaviour in the EPM after 10–11 of withdrawal at PND 80	Zhu et al. (2016)

(Continues)

TABLE 1 (Continued)

Age of cocaine exposure (experimental model)	Dose/route	Species/sex	Neurochemical changes	Behavioural changes	References
PNDs 28–42	15 mg kg^{-1}; i.p.	Sprague Dawley rats; male	*mPFC at PND 77* ↓ synaptic density ↓ dendritic spine density ↓ synapsin I and PSD-95 protein levels	↑crossing and rearing number in the OFT at PND 75 ↑ anxiety-like behaviour in the EPM after 10–11 of withdrawal at PND 76	Zhu et al. (2018)

Abbreviations: AMPA, receptor: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Arc/Arg3.1, activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1; BDNF, brain-derived neurotrophic factor; CaD, Caldesmon; cAmy, central nucleus of amygdala; CaRF, calcium responsive factor; CAS3, caspase-3; CAS8, caspase-3; Cdc42, cell division cycle 42; COC, cocaine; CREB, cAMP-response element binding protein; DA, dopamine; DAT, dopamine transporter; dHip, dorsal hippocampus; dSTR, dorsal striatum; EAAT1/2, excitatory amino acid transporter 1/2; EPM, elevated plus-maze; ERK2, mitogen-activated protein kinase 1; EZM, elevated zero maze; FCx, frontal cortex; FGF-2, fibroblast growth factor 2; FKBP51, FK506 binding protein 5; FMR1, fragile X mental retardation gene; F-actin, filamentous actin; GAD67, glutamate decarboxylase 67; GFAP, glial fibrillary acidic protein; GR, glucocorticoid receptor; GRM5, metabotropic glutamate receptor 5; GS, glutamine synthetase; GluN1/2A/2B, glutamate NMDA receptor 1/2A/2B subunit; Hip, hippocampus; IL, infralimbic (subregion of the medial prefrontal cortex); IL-6, interleukin 6; i.p., intraperitoneal; mBDNF, mature form of brain-derived neurotrophic factor; mPFC, medial prefrontal cortex; NF-kB, nuclear factor B; NMDA receptor, N-methyl-D-aspartate receptor; NOR, novel object recognition; OFT, open field test; Pak1, p21-activated kinase 1; PL, prelimbic (subregion of the medial prefrontal cortex); PND, post-natal day; PSD-95, postsynaptic density protein 95; PthC, perirhinal cortex; R/I, resident–intruder paradigm; SAP102, synapse-associated protein 102; SAP97, postsynaptic density protein 97; s.c., subcutaneous; SN, substantia nigra; Src-1, steroid receptor coactivator-1; TH, tyrosine hydroxylase; TNFα, tumour necrosis factor α; tPA, tissue plasminogen activator; TrkB, tropomyosin receptor kinase B; Ube3a, ubiquitin-protein ligase E3A; vGAT, vesicular gamma-aminobutyric acid (GABA) transporter; vGLUT1, vesicular glutamate transporter; vHip, ventral hippocampus; VTA, ventral tegmental area.

(Table 1). It appears, indeed, that psychostimulants and adolescence interact and contribute to promoting a dysfunctional brain by converging on a set of protein abnormalities that may contribute to shaping both the behavioural and neuroplastic effects, reinforcing the notion of adolescence as a period of life uniquely sensitive to the exposure to drugs of abuse. Similar treatments do not produce the same effects in the adult animal, thus strongly pointing to adolescence as a window of extreme vulnerability to the deleterious effects of cocaine. It is not likely that cocaine-induced changes in neuroplasticity can cause overt disorders but, rather, minute alterations that may impair, at least in part, brain homeostasis and neuroplasticity, thus providing the ground for different psychiatric comorbidities. The several lines of evidence shown here converge on a cohesive picture that points to neuroplastic changes and structural remodelling as the main effects set in motion by cocaine exposure during adolescence.

4.2 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to Pharmacology (http://www.guidetopharmacology.org), and are permanently archived in the Concise Guide to Pharmacology 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Kelly et al., 2019; Alexander, Mathie et al., 2019).

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CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to the work herein described.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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