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Inflammatory and epigenetic alterations associated with attention deficits in adolescents with cocaine base paste addiction

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ABSTRACT

Cocaine base paste (CBP) is an intermediate product in the process of obtaining cocaine (COC), known for its low cost, high toxicity, and poor quality. Its use became widespread in Argentina during the socioeconomic crisis of 2001–2002 and is more prevalent among individuals under 25 and those from low socioeconomic backgrounds. This pilot study aimed to characterize inflammatory and epigenetic mechanisms involved in CBP and COC addiction, and their relationship to attention deficits. We analyzed adolescents with CBP dependence (n = 25), COC dependence (n = 22), and non-dependent controls (CTR, n = 25). Gene expression analysis revealed decreased levels of NF-κB and TNF-α in both drug-dependent groups. The CBP group also showed reduced expression of DNMT1 and DNMT3A, while only DNMT1 was decreased in the COC group. These changes were consistent with lower global DNA methylation levels in both groups compared to controls. We observed that DNMT1 expression was related to top-down attention. While higher DNMT1 levels were associated with better attention performance in the CTR and COC groups, the CBP group showed the opposite pattern. These findings support the presence of distinct molecular adaptations in CBP and COC abusers and may help identify potential targets linked to cognitive deficits in addiction.

1. Introduction

The United Nations Office on Drugs and Crime (UNODC) World Drug Report 2024 highlights a moderate but steady increase in global drug use over the past decade. In 2022, an estimated 292 million people worldwide had used drugs in the previous 12 months, marking a 20 % rise compared to previous years (United Nation-Office on Drugs and Crime, 2024). Cocaine, the most widely used stimulant in the Americas, has seen a significant global increase over the past two decades. The number of cocaine users grew from 17.4 million in 2012 to 23.5 million in 2022, accounting for 0.5 % of the global population aged 15 to 64 (United Nation-Office on Drugs and Crime, 2024). In Latin America, cocaine use extends beyond its pure salt form (cocaine hydrochloride, COC), which is typically inhaled, but also includes various smokable cocaine products. These smokable products, derived from the coca leaf, emerge as byproducts of the cocaine production process (Castaño, 2000) and undergo chemical processing that lowers their melting points, enabling volatilization through heat (Cortés Amador Ernesto and Pien Metaal, 2020). One of the most common forms is Pasta base or cocaine base paste (CBP), a collective name given to several different forms of

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smokable cocaine. CBP's composition varies across regions, with widespread adulteration—nearly 60 % of analyzed samples contained additives such as caffeine, phenacetin, and lidocaine, reaching over 80 % in Argentina and Uruguay (Cortés Amador Ernesto and Pien Metaal, 2020; Secretaría de Políticas Integrales sobre Drogas de la Nación Argentina, 2017). In Latin America, the consumption of CBP is widespread (Castaño, 2000). Due to its easy availability and low cost, it is the substance most widely used among adolescents in vulnerable sectors of society (Cortés Amador Ernesto and Pien Metaal, 2020). In Argentina, the annual prevalence of COC abuse is estimated at 1.5 %. For CBP, although the annual prevalence in the general population is less than 1 %, this number almost triples within the population under 25 years old. If we consider the socially/economically vulnerable areas of the population, it reaches 10 % (Hugo, 2006; Secretaría de Políticas Integrales sobre Drogas de la Nación Argentina, 2017; SEDRONAR, 2017). So, the abusive consumption of CBP affects doubly vulnerable "young" and "socially relegated sectors" populations.

As with cocaine, CBP abuse affects physical, organic, and psychological health. Its rapid pulmonary absorption produces intense but short-lived effects, leading to brief euphoria followed by anxiety, craving, and potential psychosis (Castaño, 2000). Prolonged use can result in severe weight loss, respiratory problems, neurological damage, and social isolation (Brasesco et al., 2010).

Research on the behavioral and neurological effects of CBP abuse is limited. In rodents, CBP exposure has been linked to anxiety-like behavior, memory impairments, and increased locomotor activity with repeated use (Berardino et al., 2019; Prieto et al., 2015). In human studies, adolescents with CBP dependence exhibited deficits in executive functions, sustained attention, and cognitive flexibility, correlating with reduced caudate volume (Aragón-Daud et al., 2024; de la Fuente et al., 2021). Additionally, CBP consumers exhibited lower empathy levels, which were associated with decreased gray matter volume in brain regions related to social cognition (Baez et al., 2021). Neuroimaging studies also revealed reduced prefrontal cortex activity in CBP consumers (Ferrando et al., 2009). At the molecular level, studies in animal models have demonstrated that chronic CBP exposure, followed by abstinence, results in changes in the expression of immediate-early genes (IEGs) in the nucleus accumbens (NAc) and prefrontal cortex (PFC), which are implicated in addiction-related neural adaptations (Berardino et al., 2019). Additionally, differential expression of genes involved in synaptic signaling and neuroplasticity (Drd1a, Gria1, Cnr1) has been linked to locomotor sensitization, a hallmark of repeated drug exposure (Prieto et al., 2020). However, no studies have yet demonstrated molecular changes associated with CBP abuse in humans.

Recent research has focused on immune system dysfunction and chronic inflammation, which have been linked to the pathophysiology of substance abuse (Lacagnina et al., 2017). NF-κB is a key regulator of the innate immune response, promoting the expression of proinflammatory cytokines such as IL-1β and TNF-α. These mediators contribute to the activation of central and peripheral inflammation, inducing neurobiological processes related to addiction and neurological disorders (Escobar et al., 2023a; Nennig and Schank, 2017).

More recently, the epigenetic modulation of gene expression, particularly DNA methylation (DNAm), has emerged as a key factor in the development of addiction (Walker and Nestler, 2018). Global and site-specific changes in DNA methylation have been observed in addiction, with studies showing that cocaine, but not morphine, reduces global DNA methylation in the prefrontal cortex (PFC) (Lax and Szyf, 2018; Tian et al., 2012a). DNA methylation is regulated by DNA methyltransferases (DNMTs) and Ten-Eleven Translocation (TET) proteins, which work together to maintain genomic stability and regulate methylation patterns (Moore et al., 2012). In the PFC, DNMT3b mRNA and protein levels were found to be downregulated, leading to hypomethylation in response to cocaine addiction (Tian et al., 2012a).

Considering the multifactorial nature of drug addiction, this pilot and exploratory study aims to characterize the inflammatory and epigenetic mechanisms associated with CBP drug abuse, and to examine their relationship with attention-related cognitive domains. Additionally, it seeks to compare these alterations with those observed in adolescents with COC abuse, a form of consumption with a well-established clinical profile and extensive literature. Although both substances are highly addictive, they differ in route of administration, composition (notably, CBP contains multiple adulterants), and clinical-behavioral impact (de la Fuente et al., 2019; Secretaría de Programación para la Prevención de la Drogadicción y la Lucha Contra el Narcotráfico (SEDRONAR), 2015). Including both a control group and a COC group allows for a more comprehensive analysis of the specific effects of CBP. We hypothesize that CBP and COC abuse induces changes in gene expression, specifically in inflammatory pathways and DNA methylation machinery, through epigenetic mechanisms, which can exert lasting effects on cognitive processes such as attention. To test this hypothesis, blood and saliva samples were collected from adolescents with a history of CBP or COC abuse, as well as from non-abusing controls.

2. Materials and methods

2.1. Participants

The study included 49 participants: 15 with CBP dependence, 17 with COC dependence (both meeting DSM-IV criteria), and 17 controls (CTR). This study analyzed a random subsample of the cohort reported by De la Fuente et al. (Aragón-Daud et al., 2024; de la Fuente et al., 2021), selected based on the availability of both blood and saliva samples, resulting in a sample size comparable to previous studies (Gan et al., 1998; Halpern et al., 2003; Moreira et al., 2016a). Group classification was based on the primary substance leading to treatment, determined by a neuropsychiatric interview on lifetime substance use (Supplementary Table 1) and the MINI-Plus (Supplementary Table 2), with final consensus by three addiction-specialist psychiatrists.

Participants had at least one year of drug abuse and between three and eighteen months of abstinence. Most met the criteria for polysubstance abuse. None had a history of neurological disease or Axis I disorders (Supplementary Table 3). Participants on psychiatric medication were included only if doses were below established thresholds or if they had discontinued treatment at least one month prior (Supplementary Table 4) with only three participants meeting these criteria. Groups showed no significant differences in gender or handedness and were matched for age, education, and socioeconomic status (SES) (Supplementary Table 5). All participants provided written informed consent following the Declaration of Helsinki. The study was approved by the ethics committee at Favaloro University, adhering to international guidelines for human medical research (N°609/16, record 554). Fig. 1 illustrates the protocol followed for each participant.

2.2. Biological sample collection and nucleic acid extraction

Unstimulated saliva and blood samples were collected from each participant. Blood was stored in Tempus™ tubes for RNA stabilization, and all samples were kept at −80 °C until processing. DNA was extracted from 5 ml of saliva using the PureLink Genomic Kit (Thermo Fisher), and RNA from blood using the Tempus Spin RNA Isolation Kit (Applied Biosystems), following the manufacturers' protocols.

2.3. Quantitative real-time PCR (qPCR)

cDNA was synthesized from 1000 ng of RNA using M-MLV Reverse Transcriptase. qPCR was performed using SYBR Green on a StepOnePlus system (Applied Biosystems), with T-Plus DNA Polymerase (INBIO HIGHWAY). Primers are listed in Supplementary Table 6.

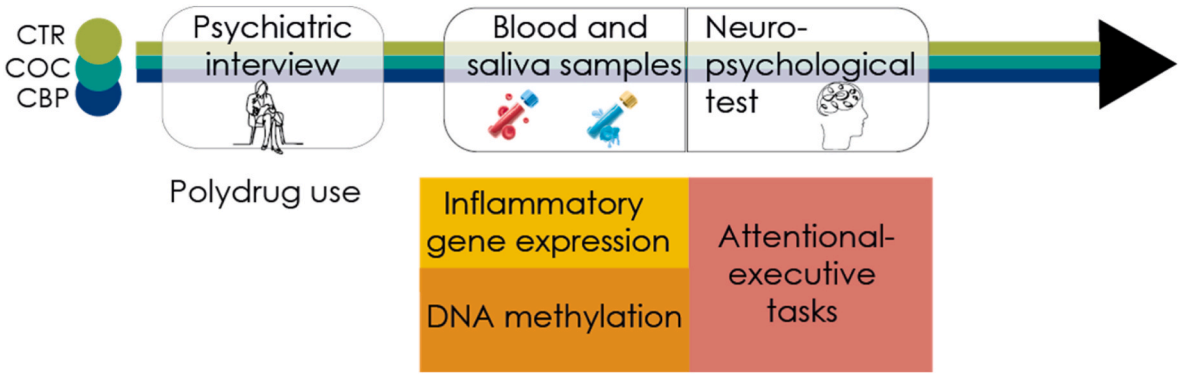

Fig. 1. Representative diagram of the study's experimental design. Based on the psychiatric interview regarding substance abuse, participants were divided into three groups: CTR (n = 17), COC (n = 17), and CBP (n = 15). Biological samples were then collected to analyze inflammatory response and DNA methylation, followed by a neuropsychological assessment to measure attention.

2.4. Global DNA methylation analysis using dot blot assay

Global DNA methylation analysis was performed using the methodology described by Alberca et al. (2024) A description of the procedure is provided in the Supplementary Material.

2.5. Cognitive assessment

We reanalyzed data from Aragón-Daud et al. (2024) (Aragón-Daud et al., 2024), confirming previous attention findings. Our goal was to correlate these results with changes in gene expression and DNA methylation. Participants completed an attentional-executive neuropsychological battery. Bottom-up processes were evaluated using the Trail Making Test A (TMT-A) (Reitan, 1985, 1993), Trail 1 and Distractor List of the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1941), Forward Digit Span (Wechsler, 1999), and Forward Corsi Block-Tapping Test (Corsi, 1972). Top-down processes were assessed with the Backwards Digit Span (Wechsler, 1999), Backwards Corsi Block-Tapping Test (Corsi, 1972), Symbol-Digit Modality (Smith, 1973), Trail Making Test B (TMT-B) (Reitan, 1993), Letter and Number Sequencing Test (LNST) (Wechsler, 1999), and the Stroop Test (Stroop, 1935). A full description of the tasks is provided in (Aragón-Daud et al., 2024) and in the supplementary material.

2.6. Statistical analysis

Statistical analyses were conducted in R (v3.6.0) with a significant threshold of $p < 0.05$. Group differences were assessed using the Kruskal-Wallis test, followed by Wilcoxon pairwise comparisons with the Holm correction for multiple comparisons when significant, effect sizes (η^2) were calculated for each test and interpreted as small ($\eta^2 < 0.01$), medium ($\eta^2 \approx 0.06$), or large ($\eta^2 \geq 0.14$). Only significant results are shown in figures, marked with asterisks. The analysis of DNA methylation and the models used to explore associations between attention parameters and gene expression are described in detail in the supplementary material. Model fit was assessed using R^2, and effect sizes were estimated with partial η^2, which reflects the unique contribution of each factor while controlling for others.

3. Results

3.1. Inflammatory gene expression changes

Peripheral inflammatory markers play a crucial role in understanding the pathophysiology of drug-related conditions (Piechota et al., 2010). Inflammatory processes are involved in several neuropsychiatric disorders, including substance abuse (Bauer and Teixeira, 2019). To explore this, we analyzed NF-kB, TNFα, IL-6, and IL-1β gene expression in blood samples from all groups. NF-kB expression was significantly reduced in both CBP and COC groups compared to CTR (Fig. 2A) (group effect: $H = 23.13$, $p < 0.001$, $\eta^2 = 0.459$; post hoc comparison: CTR vs. CBP ***$p < 0.001$; CTR vs. COC ***$p < 0.001$; COC vs. CBP $p = 0.1$). TNFα showed a similar decrease (Fig. 2B) (group effect: $H = 16.97$, $p < 0.001$, $\eta^2 = 0.325$; post hoc comparison: CTR vs. CBP ***$p < 0.001$; CTR vs. COC ***$p < 0.001$; COC vs. CBP $p = 0.4475$). IL-6 showed only a trend (Fig. 2C) (group effect: $H = 5.29$, $p = 0.070$, $\eta^2 = 0.072$; post hoc comparison: CTR vs. CBP $p = 0.236$; CTR vs. COC 1.000; COC vs. CBP $p = 0.064$), and no significant differences were found for IL1b (Fig. 2D) (group effect: $H = 3.91$, $p = 0.141$, $\eta^2 = 0.042$; post hoc comparison: CTR vs. CBP $p = 0.24$; CTR vs. COC 0.20; COC vs. CBP $p = 0.98$). These results suggest a reduced inflammatory response, particularly in NF-kB and TNFα, in CBP and COC dependence.

3.2. Changes in global DNA methylation and methylation machinery

Clinical and epidemiological studies suggest that global DNA methylation changes may be associated with addiction development (Anier et al., 2018). To assess this, 5-methylcytosine (5-mC) was detected in saliva DNA using a dot blot assay with a specific 5-mC antibody. Fig. 3A and B show images of the standard curve and representative samples. Global DNA methylation was significantly reduced in CBP and COC groups compared to CTR (Fig. 3C) (GLM with gamma distribution; group: $\chi^2 = 8.5897$, $p = 0.01364$; $R^{2\ \text{McFadden}} = 0.150$). Group showed a moderate effect size ($\eta^2 \approx 0.15$), based on deviance-derived estimates. Post hoc comparison: CTR vs. CBP *$p = 0.04$; CTR vs. COC *$p = 0.04$).

To investigate whether methylation-related genes are altered by CBP and COC dependence, we examined the expression of TET1, TET2, TET3, DNMT1, and DNMT3B. No group differences were found in TET1, TET2, or TET3 expression (Fig. 3D, E and F) (TET1: group effect: $H = 0.734$, $p = 0.693$, $\eta^2 = 0.028$ | TET2: group effect: $H = 0.30$, $p = 0.861$, $\eta^2 = 0.037$; | TET3: group effect: $H = 1.95$, $p = 0.377$, $\eta^2 = 0.001$). In contrast, DNMT1 was significantly reduced in both CBP and COC groups versus CTR (Fig. 3G) (group effect: $H = 12.55$, $p = 0.002$, $\eta^2 = 0.223$; post hoc comparison: CTR vs. CBP **$p = 0.0048$; CTR vs. COC **$p = 0.0030$; COC vs. CBP $p = 0.7790$). DNMT3A expression decreased only in CBP vs. CTR (Fig. 3H) (group effect: $H = 7.190$, $p = 0.027$, $\eta^2 = 0.113$; post hoc comparison: CTR vs. CBP *$p = 0.0075$; CTR vs. COC $p = 0.2660$; COC vs. CBP $p = 0.4984$)

3.3. Attention and its relationship with inflammatory response

Recent studies show that adolescents using CBP present deficits in attention, executive functions, and memory (de la Fuente et al., 2021).

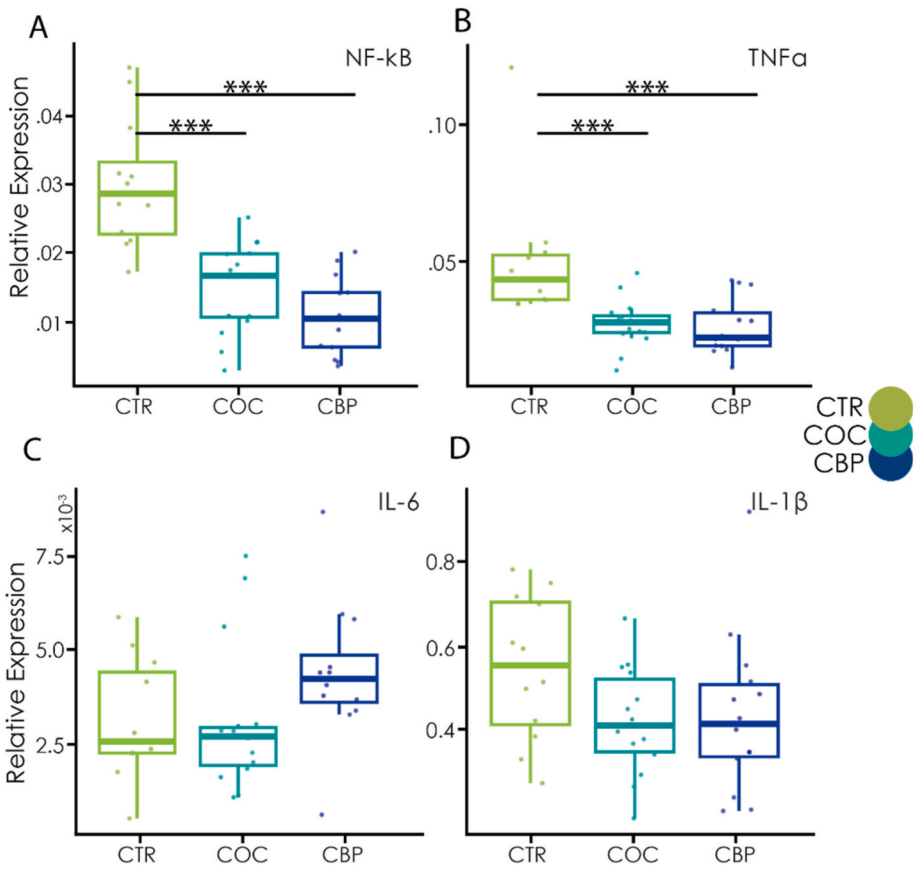

Fig. 2. Gene expression associated with the inflammatory response. Gene expression was measured using quantitative PCR (qPCR) on blood samples from the CTR, COC, and CBP groups. Expression levels were normalized to the reference genes HPRT and GAPDH. (A) NF-κB: A Kruskal-Wallis test ($p < 0.0001$) followed by a Wilcoxon-Mann-Whitney post hoc test revealed a significant reduction in expression in both the COC and CBP groups compared to the CTR group. (B) TNFα: Kruskal-Wallis ($p < 0.001$) followed by the Wilcoxon-Mann-Whitney post hoc test showed a significant reduction in expression in both the COC and CBP groups compared to the CTR group. (C) IL-6: Kruskal-Wallis analysis revealed a trend toward significant differences ($p = 0.07$). (D) IL-1β: Kruskal-Wallis analysis showed no significant differences ($p = 0.1414$). Group differences were assessed using the Kruskal-Wallis test, and pairwise comparisons were conducted using the Wilcoxon-Mann-Whitney test with the Holm correction method for p-values. Data are expressed as mean ± SEM. Asterisks on bar graphs indicate significant post hoc comparisons.

Attention was assessed in two domains: bottom-up (sustained and selective) and top-down (alternating and divided, linked to executive function) (Pratt et al., 2011). Prior findings reported deficits in both domains for CBP abuse, and mainly top-down for COC abuse [10]. Our analysis confirmed the previously published results in our sample (Fig. 4A–C). (General attention: group effect: $H = 22.11$, $p < 0.001$, $\eta^2 = 0.437$; post hoc comparison: CTR vs. CBP ***p = 0.00031; CTR vs. COC p = 0.95659; COC vs. CBP ***p = 5.7e-06 | Topdown: group effect: $H = 15.63$, $p < 0.001$, $\eta^2 = 0.296$; post hoc comparison: CTR vs. CBP ***p = 0.00026; CTR vs. COC p = 0.06599; COC vs. CBP p = 0.03862. | Bottomup: group effect: $H = 6.913$, $p = 0.0031$, $\eta^2 = 0.107$; post hoc comparison: CTR vs. CBP *p = 0.038; CTR vs. COC p = 0.957; COC vs. CBP p = 0.087).

To explore associations between inflammatory markers and attentional domains (global, top-down, bottom-up), we performed linear models. NF-kB showed a significant effect ($R2 = 0.326$) on general attention ($F(1,35) = 5.44$, $p = 0.025$, η^2 partial $= 0.233$) and a group effect ($F(2,35) = 5.31$, $p = 0.009$, η^2 partial $= 0.135$), with no interaction NF-kB:Group ($F(2,35) = 0.42$, $p = 0.661$, η^2 partial $= 0.023$) (Fig. 4D). For top-down attention ($R^2 = 0.381$), NF-kB ($F(1,34) = 12{,}17$, $p = 0.001$; η^2 partial $= 0.264$) and group ($F(1,34) = 3.55$, $p = 0.038$; η^2 partial $= 0.173$) had significant effects but not their interaction ($F(1,34) = 0.82$, $p = 0.448$; η^2 partial $= 0.046$) (Fig. 4E). No effects were found for bottom-up attention (Fig. 4F).

Regarding TNFα, general attention ($R^2 = 0.356$) was influenced by TNFα ($F(1,33) = 4.87$, $p = 0.034$; η^2 partial $= 0.129$) and group ($F(2,33) = 5.74$, $p = 0.007$, η^2 partial $= 0.258$), without interaction TNFa:Group ($F(2,33) = 0.93$, $p = 0.401$, η^2 partial $= 0.054$) (Fig. 4G). In top-down attention ($R^2 = 0.352$), both TNFα ($F(1,32) = 7.96$, $p = 0.008$, η^2 partial $= 0.199$) and group showed significant effects; ($F(2,32) = 4.35$, $p = 0.021$, η^2 partial $= 0.214$), with no interaction ($F(2,32) = 0.33$, $p = 0.71$, η^2 partial $= 0.020$) (Fig. 4H). No effects were observed in bottom-up attention (Fig. 4I). IL-6 and IL-1β showed no significant effects in any attentional domain.

These results indicate that both NF-kB and TNFa exert a global effect on general attention and top-down attention. However, the absence of a significant interaction between groups and genes suggests that the influence of NF-κB and TNF-α on attention may not be equally robust across all groups.

3.4. Attention and its relationship with epigenetic machinery

Subsequently, we examined associations between attentional performance and methylation-related gene expression. For general attention ($R^2 = 0.354$), DNMT1 showed a trend toward significance ($F(1,34) = 3.00$, $p = 0.092$, η^2 partial $= 0.081$), with a significant group effect ($F(2,34) = 7.57$, $p = 0.002$, η^2 partial $= 0.308$), but no interaction DNMT1:Group ($F(2,34) = 0.23$, $p = 0.795$, η^2 partial $= 0.013$) (Fig. 4J). Remarkably, in top-down attention ($R^2 = 0.496$), DNMT1 had significant effect ($F(1,33) = 8.85$, $p = 0.005$, η^2 partial $= 0.212$) and group had significant effects ($F(2,33) = 7.81$, $p = 0.0027$, η^2 partial $= 0.322$), along with a significant interaction DNMT1:Group ($F(2,33) = 4.02$, $p = 0.027$,

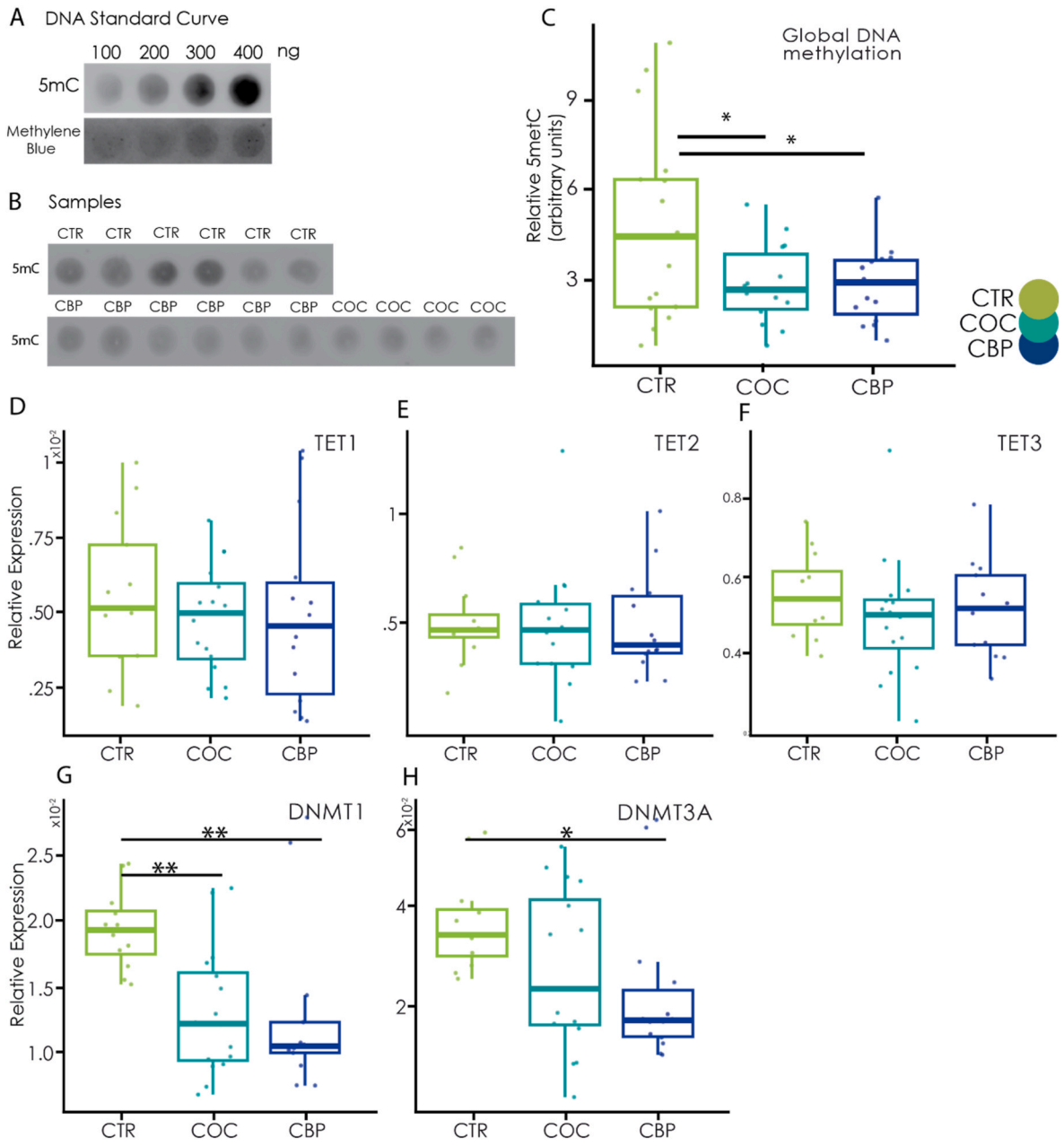

Fig. 3. Measurement of global DNA methylation and gene expression related to DNA methylation machinery. Global DNA methylation levels were assessed using the DotBlot technique on saliva DNA samples from the CTR, COC, and CBP groups, employing a specific 5 mC antibody. (A and B) Representative DotBlot membranes images showing the standard curve and samples in duplicate, respectively. (C) Relative quantification of global DNA methylation levels was performed using a generalized linear model (GLM) with a gamma distribution ($p = 0.01364$). Post hoc comparisons revealed significant differences: CTR vs. CBP *$p = 0.04$; CTR vs. COC *$p = 0.04$. Gene expression was measured using quantitative PCR (qPCR) on blood samples from the CTR, COC, and CBP groups, with expression levels normalized to the reference genes HPRT and GAPDH. (D) TET1: Kruskal-Wallis analysis showed no significant differences ($p = 0.6929$). (E) TET2: Kruskal-Wallis analysis showed no significant differences ($p = 0.8612$). (F) TET3: Kruskal-Wallis analysis showed no significant differences ($p = 0.3774$). (G) DNMT1: Kruskal-Wallis analysis ($p = 0.0021$), followed by the Wilcoxon-Mann-Whitney post hoc test, indicated a significant reduction in expression in both the COC and CBP groups compared to the CTR group. (H) DNMT3A: Kruskal-Wallis analysis ($p = 0.02746$), followed by the Wilcoxon-Mann-Whitney post hoc test, revealed a significant reduction in expression in the CBP group compared to the CTR group. Data are expressed as mean ± SEM. Asterisks in bar graphs indicate significant post hoc comparisons.

η^2 partial = 0.196) (Fig. 4K), suggesting DNMT1's impact varies by group. Slope analysis showed a positive association in CTR (78.2, 95 % CI [−26.75, 183.2]) and COC (63.2, 95 % CI [4.67, 121.8]), and a negative one in CBP (−29.1, 95 % CI [75.48, 17.3]); only COC vs. CBP reached significance (estimate = 92.3, p = 0.044). No effects were found in bottom-up attention (Fig. 4L).

For DNMT3A and general attention ($R^2 = 0.33$), a significant group effect was observed ($F(2,35) = 7.43$, $p = 0.002$, η^2 partial = 0.298), with no impact of DNMT3A ($F(1,35) = 1.70$, $p = 0.201$, η^2 partial = 0.046) or interaction ($F(2,35) = 0.34$, p = 0.715, η^2 partial = 0.019) (Fig. 4M).

Similarly to what was observed with DNMT1 and top-down attention ($R^2 = 0.448$), both DNMT3A ($F(1,34) = 6.87$, $p = 0.013$, η^2 partial = 0.168) and group ($F(2,34) = 7.45$, $p = 0.002$, η^2 partial = 0.305) showed significant effects, and a trend toward interaction was found ($F(2,34) = 2.93$, $p = 0.067$, η^2 partial = 0.147) (Fig. 4N). Slope analysis showed positive trends in CTR (15.7, 95 % CI [−18.53, 50.0]) and COC (20.4, 95

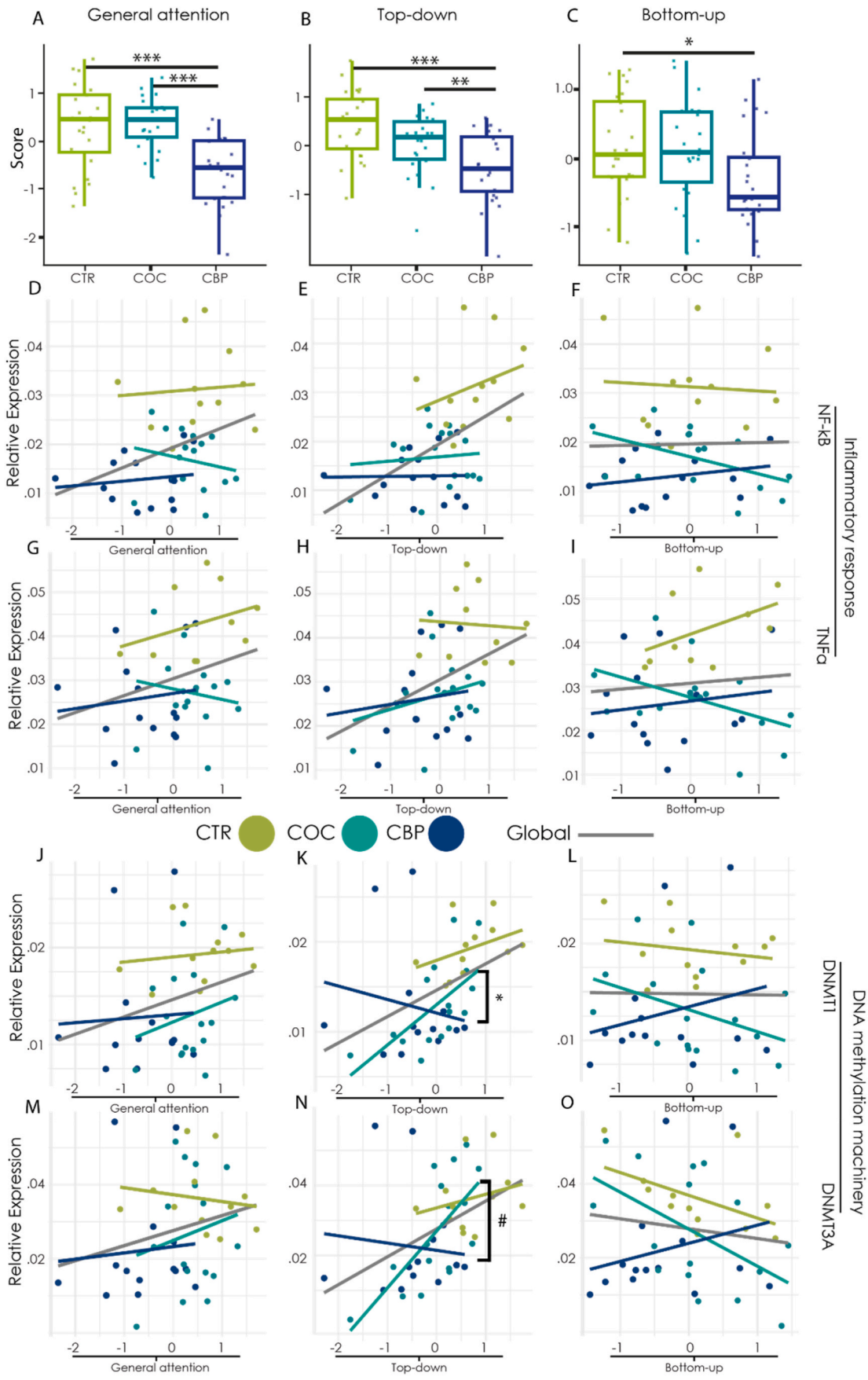

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Fig. 4. Association between attention test performance and genes related to inflammatory response and DNA methylation machinery. (A) A general attention score analysis, using the Kruskal-Wallis test (p = 1.582e-05), followed by the Wilcoxon-Mann-Whitney post hoc test, revealed a significant reduction in the CBP group compared to both the CTR and COC groups. (B) Top-down attention relies on internal cognitive processes, focusing on alternating and divided attention, and links closely to executive function. Kruskal-Wallis analysis (p = 0.02746), followed by the Wilcoxon-Mann-Whitney post hoc test, revealed a significant reduction in the CBP group compared to both the CTR and COC groups. (C) The bottom-up domain involves sustained and selective attention driven by external stimuli. A Kruskal-Wallis analysis (p = 0.03154), followed by a Wilcoxon-Mann-Whitney post hoc test, revealed a significant reduction in the CBP group compared to the CTR group. (D–O). Linear models were used to analyze the relationship between gene expression and attentional performance across groups. ANOVA was employed to assess the significance of factors and their interactions, followed by Wilcoxon-Mann-Whitney post hoc tests for pairwise comparisons, with Holm's correction applied for multiple comparisons. (D) Significant effect of NF-kB on general attention (p = 0.034), significant group effect (p = 0.0072), and no significant effect of the NF-kB: Group interaction were observed (p = 0.6615). (E) Significant effect of NF-kB on top-down attention (p = 0.0014), significant group effect (p = 0.0397), and no significant interaction of NF-kB: group were found. (F) No significant effect of NF-kB on bottom-up attention was observed. (G) Significant effect of TNFa on general attention (p = 0.0343), significant effect of the group (p = 0.007), and no significant TNFa: Group interaction were found (p = 0.4009). (H) Significant effects of TNFa on top-down attention (p = 0.0081), significant effect of the group (p = 0.021), and no significant TNFa: group interaction were found (p = 0.71). (I) No significant effect of TNFa on bottom-up attention was observed. (J) Significant effect of DNMT1 on general attention (p = 0.0922), significant effect of the group (p = 0.0019), and no significant effect of DNMT1:Group interaction (p = 0.7948) were found. (K) Significant effect of DNMT1 on top-down attention (p = 0.0054), significant effect of the group (p = 0.0017), and significant DNMT1:Group interaction were found (p = 0.0273). Asterisks indicate significant differences in the slopes between the CBP and COC groups. (L) No significant effect of DNMT1 on bottom-up attention was observed. (M) No significant effect of DNMT3A on general attention (p = 0.2012), significant effect of the group (p = 0.0020), and no significant effect of the interaction DNMT3A: group were observed (p = 0.7154). (N) Significant effect of DNMT3A on top-down attention (p = 0.0130), significant effect of the group (p = 0.0021), and a trend toward DNMT3A: group (p = 0.0672) were observed. Numerals indicate a trend toward significant differences in the slopes between the CBP and COC groups. (O) No significant effect of DNMT3A on bottom-up attention was observed.

% CI [1.07, 39.8]), and a negative one in CBP (−11.6, 95 % CI [−31.40, 8.3]). Pairwise comparisons revealed no significant differences between CTR and COC (p = 0.9681) or CTR and CBP (p = 0.3521), but a near-significant difference between COC and CBP (p = 0.0632), suggesting an opposite relationship between DNMT3A and top-down attention. No effects were found for bottom-up attention (Fig. 4O). TET1, TET2, TET3, and global methylation levels showed no significant impact across attention domains.

These results highlight that the expression of DNMT1 and DNMT3A, along with group differences, significantly influences top-down attention. The opposing patterns observed across groups suggest group-specific molecular mechanisms underlying attentional control.

4. Discussion

This pilot exploratory study examined the potential impact of CBP and COC consumption in adolescents. We found reduced expression of inflammatory markers (NF-κB and TNF-α) and DNA methylation-related enzymes (DNMT1 and DNMT3A), along with decreased global DNA methylation levels in drug-abusing grops. Notably, DNMT1 expression was differentially associated with attentional performance across groups. CBP abuse is particularly relevant from a public health perspective because it typically occurs in contexts of high social vulnerability, primarily due to its low cost and easy availability (Pedro Cófreces et al., 2024). Moreover, CBP differs from COC not only in its socioeconomic context of use but also in its pharmacological properties, as it is usually smoked, allowing for a rapid onset of action, and contains a variety of toxic adulterants that may exacerbate its harmful effects (Raverta Cristina, Chasin Alice M, Boris Duffau, Barboza Fanny, Scorza Cecilia, Sosa Graciela, Cejana Passos, Castillo Albaro, Arce César, Suarez Hector, Cumsille Francisco, Ahumada Graciela, Hynes Marya, Demarco Maria, 2016). To our knowledge, this is the first study in our region conducted in humans that examines these effects using an interdisciplinary approach, allowing for a comprehensive analysis of the affected processes.

Inflammation is increasingly recognized as a central player in the biological consequences of drug addiction (Escobar et al., 2023b). Clinical and preclinical work has shown that cocaine use dysregulates immunity, elevating proinflammatory cytokines while suppressing anti-inflammatory ones (Bravo et al., 2023; Moreira et al., 2016b). However, human data remains scarce and sometimes conflicting. Contrary to many reports of heightened proinflammatory markers in active cocaine users, we observed reduced TNF-α and NF-κB expression in adolescents of both CBP and COC groups.

This discrepancy appears to depend on the timing of sample collection relative to drug exposure. Abstinence triggers immune responses that may contribute to withdrawal symptoms and relapse (Re et al., 2022). However, the findings regarding the immune profile during abstinence are not consistent across studies (Bravo et al., 2023). Some research reports an increase in proinflammatory cytokines such as TNF-α, IL-6, and IL-18 shortly after drug cessation, particularly in methamphetamine users. At the same time, other studies have shown reduced levels of these cytokines during detoxification (Luo et al., 2022; Re et al., 2022). For example, Levandowski et al. found that TNF-α levels initially fell below baseline and then normalized over the detoxification period (Levandowski et al., 2016). In our cohort, abstinent for 4–14 months, we similarly detected persistently reduced TNF-α, suggesting ongoing immune regulation. Moreover, the downregulation of NF-κB, a key regulator of inflammatory gene expression, points to altered peripheral signaling during prolonged abstinence.

All measurements were made in peripheral blood, and although peripheral markers may mirror neuroinflammation, the precise link between systemic and central immune responses in psychostimulant addiction remains undefined (Li et al., 2024). It has been proposed that peripheral inflammation can disrupt blood–brain barrier integrity by modulating adhesion molecules and increasing permeability [46, 47], thereby facilitating the entry of cytokines and immune cells into the CNS and amplifying neuroinflammatory cascades (Turkheimer et al., 2021).

In this scenario, mapping the cytokine profile at each stage of exposure, withdrawal, and relapse, and understanding the interplay between the peripheral and central components of the immune system seems crucial to identify new biomarkers.

In the CBP group, we observed reduced global DNA methylation and significantly lower expression of DNMT1 and DNMT3A. In contrast, the COC group showed only a decrease in DNMT1 expression. These findings align with previous studies showing that addiction involves global and gene-specific methylation changes (Lax and Szyf, 2018). In animal models, DNA methylation in the nucleus accumbens plays a key role in maintaining drug-associated memories and relapse risk. For instance, manipulating DNMT activity long after cocaine exposure altered cocaine-seeking behavior (Massart et al., 2015). Our results suggest that the hypomethylation observed during abstinence in CBP users may reflect an adaptive mechanism aimed at reversing drug-induced gene network changes, possibly contributing to reduced craving and restoration of homeostasis (Vaillancourt et al., 2017).

Cocaine abuse has been shown to reduce global methylation and DNMT3b expression in the prefrontal cortex, effects associated with its rewarding impact (Tian et al., 2012b). Similarly, we observed a hypomethylation pattern in saliva from CBP abusers, suggesting that peripheral samples may reflect central epigenetic changes. Although the

extent to which peripheral methylation mirrors brain patterns remains debated, studies have shown higher correlations between saliva and brain ($r = 0.90$) compared to blood or buccal samples (Nishitani et al., 2023; Smith et al., 2015), supporting the use of saliva in neuroepigenetic research. Given the variability in methylation changes across substances, tissues, and contexts, further studies are needed to understand better the underlying mechanisms in both CBP and COC abusers.

As previously reported (Aragón-Daud et al., 2024; de la Fuente et al., 2021), both CBP and COC users show reduced general attention. Notably, CBP abusers display deficits in both top-down and bottom-up attention, while COC abusers show impairments only in top-down attention. A key contribution of this study is the association of these behavioral impairments with changes in gene expression related to inflammation and DNA methylation.

We found that attention performance differed between groups in terms of NF-κB and TNFα expression, although the interaction between group and gene expression was not statistically significant. Nonetheless, scatter plots suggest a trend: control participants exhibit higher NF-κB and TNFα expression, along with better attention, whereas CBP and COC abusers display reduced expression and poorer performance. This pattern suggests a potential connection between inflammatory gene expression and attention that may not be fully captured by statistical analysis. NF-κB, beyond its immune role, is also involved in key neuroplastic processes such as synaptogenesis, spine formation, and neuronal differentiation (Boersma et al., 2011; Imielski et al., 2012; Russo et al., 2009). These functions are crucial for learning, memory, and neuroadaptations induced by drugs, stress, and environmental stimuli (Nennig and Schank, 2017).

Regarding epigenetic regulation, we found a significant interaction between group and DNMT1 expression for top-down attention, with a similar trend for DNMT3A. Although both the CBP and COC groups show reduced DNMT1 expression and decreased global DNA methylation compared to controls, the relationship between gene expression and attentional performance differs across groups. In the COC and CTR groups, higher DNMT1 expression is associated with improved attention performance, suggesting a functional role in top-down attentional control. Conversely, the CBP group exhibits the opposite pattern, where increased DNMT1 expression is associated with poorer performance. This divergence may reflect a dysregulation of DNMT1 in CBP abusers, possibly due to a more disrupted epigenetic environment or other group-specific molecular alterations. While DNMT1 maintains DNA methylation during replication, potentially explaining the reduced global methylation seen in both groups, DNMT3A and DNMT3B are primarily responsible for de novo methylation (Cui and Xu, 2018).

Although studies directly linking DNMTs to attention in substance use are lacking, evidence from attention deficit hyperactivity disorder (ADHD) research suggests an association between DNA methylation and attention. For instance, ADHD patients show lower global methylation levels in blood samples (Müller et al., 2022), and altered methylation at specific loci has been associated with poorer attention performance in 9-year-old children (Li et al., 2021). In neurons, DNMT1 and DNMT3A are expressed post-mitotically, and their deletion in forebrain excitatory neurons reduces hippocampal synaptic plasticity, leading to learning and memory impairment (Feng et al., 2010), which supports their role in cognitive functions.

This study has several limitations that should be taken into account when interpreting the findings. First, DNA methylation and gene expression were assessed in peripheral tissues, saliva, and blood, respectively, which may not fully capture molecular changes occurring in the brain. Second, DNA methylation was measured globally, without locus-specific resolution, limiting the ability to identify gene- or region-specific epigenetic alterations. Finally, the relatively small sample size reduces statistical power and may limit the generalizability of the results. Future studies with larger cohorts and more precise, site-specific molecular analyses are needed to validate and extend these findings.

In conclusion, this pilot study reveals altered expression of inflammatory markers and DNA methylation-related enzymes in adolescents with CBP and COC abuse, alongside reduced global DNA methylation. The differential expression of DNMT1, particularly its divergent association with top-down attention across groups, highlights the potential cognitive relevance of epigenetic regulation in substance use. These findings support the hypothesis that changes in the expression of inflammatory factors may be mediated by alterations in DNA methylation. However, further experimental studies are needed to clarify the causal links and underlying mechanisms.

CRediT authorship contribution statement

Silvina V. Sonzogni: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Laura A. de la fuente:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Camila Mimura:** Formal analysis, Methodology. **Agustina Aragon-Daud:** Formal analysis, Methodology. **Sofía Schurmann Vignaga:** Formal analysis, Methodology. **Daiana Vota:** Methodology. **Facundo Manes:** Investigation, Methodology, Resources. **Marcelo Cetkovich:** Conceptualization, Formal analysis, Investigation, Methodology. **Teresa Torralva:** Conceptualization, Investigation, Methodology, Resources. **Agustin Ibañez:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Eduardo T. Cánepa:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to assist with English grammar during the preparation of this manuscript. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare no competing interests. M. Cetkovich reports having received speaker honoraria from Gador, Lundbeck, Abbott, Pfizer, Baliarda, Roemmers, TEVA, Janssen, and Grunenthal in the last three years. The other authors declare no conflicts of interest.

Appendix A. Supplementary data

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