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From Genes to Behavior: The Role of DAT1, DRD4, and COMT in Addictive Behaviors and Epigenetic-Psychological Interactions

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Narrative Review

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Abstract

Background: The dopaminergic reward system plays a key role in susceptibility to addictions, while genetic and epigenetic variability within the DAT1, DRD4, and COMT genes may shape psychological mechanisms related to impulsivity, anxiety, and personality traits.

Methods: This narrative review synthesizes findings from four original studies (2024-2025) involving individuals with substance and behavioral addictions, as well as control groups. The analysis focused on genotype × clinical status interactions, DAT1 promoter methylation, and psychological profiles assessed with standardized questionnaires (STAI, NEO-FFI).

Results: Single polymorphisms only occasionally distinguished addicted individuals from controls; when present, these main effects were modest relative to interactions. Significant effects emerged in gene-trait interactions and epigenetic associations: DRD4 exon 3 VNTR showed group × genotype effects for trait anxiety and neuroticism; COMT rs4680 was associated with increased anxiety in addicted individuals, with additional group × genotype interactions for lower conscientiousness; and higher DAT1 promoter methylation related to lower neuroticism and higher conscientiousness. Addicted individuals, particularly psychostimulant users, exhibited a psychological profile marked by higher anxiety and neuroticism and lower conscientiousness, agreeableness, and extraversion, with increased openness to experience.

Conclusions: The findings highlight that vulnerability to addiction reflects a complex interplay between genetic, epigenetic, and psychological factors. Rather than direct effects of single polymorphisms, gene-epigenome interactions and personality traits appear central. This integrated perspective underscores the importance of combining biological and psychological data and suggests that such markers may serve as dynamic indicators for personalized addiction medicine.

Keywords: Dopamine; Reward system; Addictions; Genetics; Epigenetics; Personality.

Introduction

Dopamine plays a crucial role in the regulation of human behavior- it influences motivation, emotions, learning, concentration, and the experience of pleasure [1,2]. In neurobiology, the mesolimbic reward system is of central importance to these processes, encompassing, among others, the Ventral Tegmental Area (VTA), nucleus accumbens, and prefrontal cortex. This system is responsible for the sensation of satisfaction and the formation of so-called "pleasure memory," which motivates the repetition of reward-related behaviors [3].

Addictions-both to psychoactive substances and behavioral ones - are currently recognized as one of the major public health challenges, generating high social and medical costs. At their core lie dysfunctions of the reward system. The intake of psychoactive substances or engagement in addictive behaviors (e.g., gambling) leads to increased dopamine release, giving the brain a sense of reward [4,5]. Research has shown that addicted individuals often display lower dopamine levels in the central nervous system or reduced sensitivity of dopamine receptors. This results in a state in which ordinary stimuli no longer bring satisfaction, and the brain requires stronger stimulation to achieve pleasure. Consequently, a vicious cycle of reward and tolerance emerges, in which addictive behaviors are repeated to maintain neurochemical balance [1,6].

Genetic and epigenetic studies indicate that susceptibility to addiction development may be modulated by elements of the reward system [7-10]. Of particular importance are genes affecting dopaminergic neurotransmission, such as DAT1 (dopamine transporter), COMT (catechol-O-methyltransferase), and DRD4 (dopamine receptor D4). Their polymorphisms and epigenetic modifications may influence impulsivity, personality traits, and vulnerability to addictions, especially through interactions with psychological and environmental factors [7-10].

The aim of this article is to provide a synthetic overview of the authors' research findings from the past two years, in the context of the literature on the role of dopamine, reward mechanisms, and genetic and epigenetic factors in addictions, with particular emphasis on the DAT1, DRD4, and COMT genes [7-10]. Understanding these mechanisms has not only theoretical but also clinical significance, as it points to potential directions for therapeutic interventions that support addiction treatment and reduce the risk of relapse.

Material and methods

This article is a narrative review. The starting point was the findings of four studies by the authors published in 2024-2025 (covering populations with substance and behavioral addictions, as well as control groups) - see Table 1 [7-10]. The results of these studies were summarized and then compared with the relevant literature.

The selection of supplementary literature was purposive. Sources were identified through citation chasing/snowballing from the reference lists of the four primary studies, as well as through the authors' expertise and familiarity with the subject.

No formal systematic database searches were conducted, nor were predefined language or publication date restrictions applied. Only peer-reviewed or accepted-for-publication works were included; one study (DRD4 Ex3) is accepted and in press, therefore we cite the preprint DOI pending the final bibliographic details. Studies focusing on DAT1 promoter methylation, DAT1 VNTR polymorphisms, DRD4 exon 3 VNTR, and COMT rs4680 in the context of impulsivity, personality traits, and psychological functioning in addicted individuals were considered eligible. Purely descriptive publications (e.g., single case reports) and studies lacking thematic relevance were excluded.

Information extraction involved collecting sample sizes, group definitions, psychometric tools used (e.g., NEO-FFI, STAI, BIS-11), as well as reported statistics (e.g., OR, χ^2, F, p-values) and key effects from the original works. No meta-analysis or re-analysis of primary data was conducted; results are presented as reported by the original authors.

The synthesis was qualitative and organized by marker (DAT1 - methylation; DAT1 - VNTR; DRD4 - VNTR; COMT) and phenotype (psychological profile). Interpretative content, potential biological mechanisms, and limitations are discussed in the Discussion section.

Since this work is a review based on published data, approval from a bioethics committee was not required [Table 1].

Results

Analysis of Candidate Genes of the Reward System

DAT1 - promoter methylation [7]

The methylation level of 33 CpG sites in the DAT1 promoter was examined in a group of individuals addicted to psychostimulants (n = 226) and controls (n = 290). Differences were observed at specific sites: lower methylation in addicts at sites 1, 9, and 14, and higher methylation at sites 32 and 33. In odds ratio analyses, significant effects were found for island 1 (OR = 1.99), 9 (OR

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Table 1: Status of Key Original Studies Underpinning This Review.

No.	First Author and Year	Main Gene /Study Topic	Publication Status	Journal	Impact Factor	DOI
1	Recław et al., 2024	Methylation DAT1	Published	International Journal Molecular Sciences	4,9	https://doi.org/10.3390/ijms25010532
2	Recław et al., 2025	DAT1 VNTR	Published	Biomedicines	3,9	https://doi.org/10.3390/biomedicines13081852
3	Boroń et al., 2024	DRD4 VNTR	Accepted for Publication	Psychiatria Polska	1,1	https://doi.org/10.21203/rs.3.rs-4409644/v1
4	Recław et al., 2024	COMT rs4680	Published	Genes	2,8	https://doi.org/10.3390/genes15030299

= 1.48), 14 (OR = 1.87), 32 (OR = 0.64), and 33 (OR = 0.47); overall methylation did not differ between groups.

In correlation analyses within the addicted group, total methylation level was negatively correlated with NEO-FFI Neuroticism ($r = -0.154$, $p = 0.020$) and positively correlated with Openness ($r = 0.148$, $p = 0.026$) and Conscientiousness ($r = 0.137$, $p = 0.040$).

DAT1 - VNTR [8]

In a study of 128 men with behavioral addictions and 200 controls, no differences in DAT1 genotype frequencies were observed between groups. However, a significant group × genotype interaction was found for attentional impulsivity (BIS-AI): individuals with behavioral addictions and the 9/9 genotype obtained the highest BIS-AI scores ($F_{2,322} = 5.48$; $p = 0.0046$). No significant interactions were observed for motor or non-planning impulsivity.

DRD4 - Ex 3 VNTR [9]

In a study (accepted for publication in Psychiatria Polska) including 107 men with behavioural and amphetamine addiction and 200 healthy controls, the exon 3 VNTR polymorphism of the DRD4 gene was analysed. Genotype distributions differed between groups (s/s more frequent; s/l and l/l less frequent in the addicted group; $\chi^2 = 9.914$; $p = 0.0070$), and allele frequencies also differed (s allele more frequent; l allele less frequent in the addicted group; $\chi^2 = 11.190$; $p = 0.0008$). Factorial analyses showed significant group × genotype interactions for STAI-trait ($F_{2,301} = 4.85$; $p = 0.0084$; $\eta^2 = 0.031$) and for NEO-FFI Neuroticism ($F_{2,301} = 3.38$; $p = 0.0354$; $\eta^2 = 0.022$), indicating that the phenotypic expression of DRD4 Ex3 variants was contingent on clinical status. No significant interactions were observed for STAI-state or the remaining NEO-FFI domains.

COMT - rs4680 [10]

In a sample of 107 men with gambling disorder and/or amphetamine dependence and 200 controls, a difference was noted in the distribution of COMT rs4680 genotypes ($\chi^2 = 6.681$; $p = 0.03543$). In group comparisons, individuals with gambling disorder and/or amphetamine dependence showed higher scores on STAI-trait (6.98 vs. 5.33; $p = 0.0019$), STAI-state (5.60 vs. 4.77; $p < 0.0001$), and Neuroticism (6.58 vs. 4.76; $p < 0.0001$), as well as lower Agreeableness scores (4.28 vs. 5.54; $p < 0.0001$). In 2×3 analyses, significant group (addicted/control) × rs4680 interactions were found for STAI-trait ($F_{2,301} = 3.39$; $p = 0.0351$; $\eta^2 = 0.022$), STAI-state ($F_{2,301} = 3.41$; $p = 0.0343$; $\eta^2 = 0.022$), and Conscientiousness ($F_{2,300} = 6.47$; $p = 0.0018$; $\eta^2 = 0.041$).

Analysis of the Psychological Profile of Addicted Individuals

DAT1 - promoter methylation [7]

NEO-FFI (group comparison): individuals with psychostimulant dependence showed higher Neuroticism (6.58 vs. 4.61; $p < 0.00001$) and Openness (5.01 vs. 4.50; $p = 0.0045$), and lower Extraversion (5.84 vs. 6.36; $p = 0.0076$), Agreeableness (4.28 vs. 5.59; $p < 0.00001$), and Conscientiousness (5.60 vs. 6.10; $p = 0.0173$).

DAT1 - VNTR [8]

Impulsivity (BIS-11): compared with controls, individuals with behavioral addictions had higher BIS-11 total scores (73.23 ± 12.00 vs. 67.98 ± 10.16; $p = 0.0001$), as well as higher BIS-AI (attentional; $p = 0.0001$) and BIS-MI (motor; $p = 0.0001$); BIS-NI (non-planning) showed no significant difference.

Genotype × group interaction (BIS-AI): a significant DAT1 × group status interaction was found for BIS-AI ($F_{2,322} = 5.48$; $p = 0.0046$); within the addicted subgroup, the highest BIS-AI scores were observed in 9/9 carriers (post hoc: 9/9 > 9/10, 10/10).

DRD4 - Ex 3 VNTR [9]

Anxiety (STAI) and personality (NEO-FFI): significant group × genotype interactions were found for STAI-trait ($F_{2,301} = 4.85$; $p = 0.0084$; $\eta^2 = 0.031$) and for Neuroticism ($F_{2,301} = 3.38$; $p = 0.0354$; $\eta^2 = 0.022$). Post hoc comparisons indicated higher STAI-trait and Neuroticism scores in addicted individuals for specific DRD4 Ex3 genotypes (notably s/s; also s/l) relative to controls, whereas no

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significant interaction emerged for STAI-state or other NEO-FFI scales.

COMT - rs4680 [10]

STAI and NEO-FFI (group comparison): individuals with gambling disorder and/or amphetamine dependence had higher STAI-trait (6.98 vs. 5.33; $p = 0.0019$) and STAI-state (5.60 vs. 4.77; $p < 0.0001$), higher Neuroticism (6.58 vs. 4.76; $p < 0.0001$), and lower Agreeableness (4.28 vs. 5.54; $p < 0.0001$); no significant differences were observed in the remaining scales. Interactions (2 × 3 ANOVA): significant group × rs4680 interactions were found for STAI-trait ($F_{2,301} = 3.39$; $p = 0.0351$), STAI-state ($F_{2,301} = 3.41$; $p = 0.0343$), and Conscientiousness ($F_{2,300} = 6.47$; $p = 0.0018$).

Summary: Overall, the results indicate that different variants of genes associated with the dopaminergic system modulate impulsivity, anxiety, and personality traits in addicted individuals, with effects being specific to the type of polymorphism.

Discussion

In a series of our own studies [7-10], it was demonstrated that genetic and epigenetic markers of the dopaminergic system modulate both psychological traits and susceptibility to addictive behaviors. The findings clearly indicate that differences in genotype frequencies alone (DAT1, DRD4, COMT) do not distinguish addicted individuals from controls; rather, significant effects emerge in genotype × clinical status interactions and associations with psychological profiles. An example is the DAT1 VNTR, where 9/9 carriers in the addicted group exhibited higher attentional impulsivity, or the DRD4 polymorphism, in which specific genotypes were linked to elevated trait anxiety and neuroticism in addicted individuals. Likewise, COMT rs4680 revealed its role only when considered alongside psychological measures - genotypic variants were associated with increased anxiety and reduced conscientiousness in addicted individuals, but not in controls. Complementing these results are epigenetic data: specific differences in DAT1 promoter methylation in addicted individuals point to potential mechanisms of dopamine transporter regulation that may modulate reward sensitivity and susceptibility to impulsive behaviors.

An integrated interpretation of these findings supports the concept that addictions result from a dynamic interaction of biological and psychological factors rather than from single gene polymorphisms [11-13]. DAT1, DRD4, and COMT - through their roles in dopaminergic transmission - affect different domains of functioning: from emotion regulation (e.g., anxiety, neuroticism), through cognitive control, to various dimensions of impulsivity. Epigenetic regulation of DAT1 further demonstrates that environmental factors, such as exposure to psychoactive substances, can induce lasting changes in gene expression and shape a personality profile conducive to the development of addiction. In clinical practice, this means that genes and their modifications are not diagnostic markers per se but indicators of susceptibility, which, in combination with specific personality traits, may increase the risk of maintaining addictive behaviors and relapse [14-16].

At the psychological level, individuals with substance and behavioral addictions exhibited traits conducive to the development and maintenance of addictive behaviors. In our studies [7-10], higher levels of anxiety - both as a state and trait (STAI) - were noted, along with elevated neuroticism and greater openness to experience. At the same time, addicted individuals scored lower on agreeableness, conscientiousness, and extraversion (NEO-FFI). This personality profile reflects a combination of heightened emotional reactivity and reduced cognitive self-control, which may facilitate the escalation of compulsive behaviors and sustain the cycle of addiction. Notably, elevated openness to experience was also observed, which may contribute to greater novelty seeking and experimentation with psychoactive substances. In the context of addiction, this heightened openness could interact with impulsivity and reduced self-control, reinforcing vulnerability to risk-taking behaviors. Our findings are consistent with previous observations linking high neuroticism, impulsivity, and low levels of traits associated with cognitive control to increased vulnerability to addictions [17-21].

At the biological level, the results indicate that dopaminergic system genes modulate different stages of neurotransmission in ways specific to addicted populations. DAT1, as the main dopamine transporter, is responsible for reuptake of the neurotransmitter from the synaptic cleft. In our study, differences in DAT1 promoter methylation were site-specific rather than global: addicted individuals exhibited a distinct CpG pattern, and correlation analyses indicated that higher methylation was associated with lower neuroticism and higher conscientiousness. This pattern suggests that reduced methylation may weaken psychological self-control and contribute to vulnerability, whereas higher methylation could play a protective role. Although we lacked expression or protein-level data - a significant limitation - these associations point to potential mechanisms linking epigenetic regulation of DAT1 with both dopaminergic tone and personality traits. In this sense, DAT1 methylation may serve as an 'epigenetic

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memory' of environmental exposure [23], but its functional implications require further investigation.

COMT, the key enzyme degrading dopamine in the prefrontal cortex, remains a candidate for explaining the balance between cognitive control and emotional reactivity. In our sample, the rs4680 polymorphism was linked to higher anxiety in addicted individuals, and significant group × genotype interactions emerged for both anxiety (STAI-trait and STAI-state) and conscientiousness. These effects indicate that the phenotypic expression of COMT variability depends on clinical status rather than reflecting a simple main effect of genotype - hypothetically pointing to a biological mechanism underlying heightened neuroticism and deficits in self-control in addicted individuals [24,25]. In the case of DRD4, longer VNTR alleles in exon 3 modify receptor signaling and have been repeatedly associated with novelty seeking and impulsivity. In our study, however, the effect did not manifest as differences in impulsivity, but rather as group × genotype interactions for trait anxiety and neuroticism, suggesting that the clinical context may "unlock" the phenotypic expression of these variants [26,27]. Overall, the findings suggest not a direct determination of addiction by biological differences but rather their role in modulating dopaminergic sensitivity and adaptive capacity. Combined with specific personality profiles, this may substantially increase the risk of addiction onset and persistence, although the underlying functional mechanisms still require confirmation.

From an epigenetic perspective, observations concerning DAT1 promoter methylation are particularly noteworthy. Addictions are a classic example of disorders in which environmental factors - such as psychoactive substance use, stress, deprivation, or sleep disturbances - affect the dopaminergic system, leading to lasting changes in gene regulation. The literature highlights that DNA methylation may serve as a "molecular trace" of experience [28-30]; in addicted individuals, reduced methylation has been correlated with higher neuroticism and lower self-control [7,31]. These findings may suggest that disturbances in dopaminergic regulation are reinforced by epigenetic changes linked to personality traits. However, it must be emphasized that these are correlational data, and in our material neither gene expression nor protein levels were assessed, limiting the ability to draw direct functional conclusions.

Importantly, epigenetic modifications, although consolidated under chronic exposure to psychoactive substances, are not necessarily irreversible. Preclinical data indicate that methylation of genes associated with the dopaminergic system can be modified by pharmacological interventions (e.g., DNA methyltransferase inhibitors), as well as by non-pharmacological factors such as physical activity, diet, or environmental stimulation [32-34]. Clinical studies, though still limited, suggest that lifestyle-related factors, including stress reduction techniques, emotional regulation practices, and mindfulness-based interventions, may be associated with changes in the methylation of genes involved in dopaminergic neurotransmission, underscoring the plasticity of these mechanisms [35-37]. From this perspective, epigenetics may serve as a potential link between treatment and biological processes - indicating that effective addiction therapy may not only reduce symptoms but also partially reverse adverse "molecular traces" within the reward system. Such a perspective opens the way toward the development of biomarkers for therapeutic response and personalized interventions.

From a clinical perspective, the question arises whether epigenetic indicators - such as DAT1 promoter methylation - may in the future serve as dynamic biomarkers of susceptibility to addictions or of treatment response. Current evidence suggests this possibility, as epigenetic modifications are plastic and may undergo partial normalization with abstinence or therapy [38,39]. However, at present they should be regarded only as candidate biomarkers rather than validated clinical tools. Further studies are needed to integrate methylation analyses with measures of gene expression, neural functioning, and therapeutic outcomes.

In contrast to genetic studies, which identify relatively stable differences in DNA sequence, epigenetic analyses provide insight into the organism's dynamic response to the environment [40,41]. DAT1, DRD4, and COMT polymorphisms rarely function as unequivocally predictive markers of addiction - their effects become apparent primarily in interaction with psychological or clinical factors. Epigenetics adds an additional dimension of plasticity: methylation modifications may both consolidate the effects of chronic exposure (e.g., to psychoactive substances) and undergo partial normalization with abstinence or treatment [42,43]. This implies that genetic factors represent a "substrate of susceptibility," whereas epigenetic mechanisms act as a "risk modulator" that responds to individual experiences. Integrating these perspectives brings us closer to understanding the clinical heterogeneity of addictions and explains why some individuals with a given genotype develop addiction, while others - despite carrying the risk variant - remain resilient.

The findings align with established theoretical models of addiction, particularly the allostatic model and the dual-process model. According to the allostatic

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framework, chronic substance use leads to a shift in the neurobiological set point: on one hand, there is a reduction in baseline dopaminergic tone, while on the other, there is heightened reactivity to substance-related cues [44-47]. Epigenetic changes in the DAT1 gene may constitute a molecular mechanism underlying this process, consolidating adaptations associated with chronic use. The dual-process model, in turn, emphasizes the interplay between automatic impulses and cognitive control - our results suggest that COMT and DRD4 polymorphisms modulate precisely these two domains: the emotional-motivational (anxiety, neuroticism) and the control dimension. Incorporating genetic and epigenetic data into these models provides a more comprehensive explanation of addiction heterogeneity and individual differences in vulnerability [44-47].

It is also important to highlight the heterogeneity of addictions, both biological and psychological. The mechanisms described for the dopaminergic system may manifest differently depending on the type of substance or the nature of the addiction. For example, in alcoholism, COMT variants associated with emotional regulation may play a greater role, whereas in behavioral addictions, such as gambling, epigenetic mechanisms modulating reward system sensitivity appear more prominent [48-51]. These differences may explain why some polymorphisms exert an effect only in specific clinical groups and why the psychological profile of individuals with substance dependence does not always overlap with that of individuals with behavioral addictions. Understanding this heterogeneity is essential for developing vulnerability models that account for risk and resilience pathways characteristic of specific types of addictions [52-54].

Future research directions underscore the need for longitudinal designs to determine whether the observed genetic, epigenetic, and psychological differences are causes or consequences of addiction. Particularly promising are multi-omic approaches that integrate genetics, epigenetics, transcriptomics, neuroimaging, and psychometrics [55,56]. Such strategies will enable mapping the networks of relationships between gene variants, epigenetic regulation, brain function, and behavior, bringing us closer to building coherent models of vulnerability and resilience to addiction.

From a clinical standpoint, the most important conclusion is that neither single genetic variants nor isolated psychological indicators can be treated as standalone diagnostic markers. Their value becomes evident only within an integrated framework that combines biological and psychological information into coherent “risk profiles” [57-59]. Epigenetic indicators, such as DAT1 promoter methylation, may additionally serve as dynamic biomarkers - reflecting treatment efficacy and relapse susceptibility. Ultimately, the integration of genetic, epigenetic, and psychological markers opens the way toward personalized addiction medicine, in which therapeutic interventions are tailored not only to clinical symptoms but also to the biological and personality profile of the patient [50].

Limitation

This article is a narrative review, which constitutes the first limitation. The starting point was the results of four studies conducted by the authors over the past two years, involving populations with substance-related and behavioral addictions as well as control groups. These findings were synthesized and contrasted with the broader literature. The selection of additional references followed a purposive sampling strategy, with sources identified mainly through citation chasing/snowballing and the expert judgment of the authors. While this approach allowed the inclusion of the most thematically relevant studies, it also limits the ability to capture the full spectrum of research available in the field.

A second limitation concerns the methodological heterogeneity of psychological assessment. Across the individual studies, different psychometric instruments were applied (e.g., NEO-FFI, STAI, BIS-11), which complicates direct comparisons between analyses. Although all of these questionnaires address essential aspects of personality and psychological functioning, the lack of a uniform test battery may introduce additional variability and limit the extent of data integration.

It should also be emphasized that detailed limitations regarding sample characteristics, methods, and interpretation were discussed in the original research articles. For the purposes of this review, only the key issues common to the entire body of data need to be highlighted: the absence of gene expression or protein-level analyses, which restricts the ability to link genetic and epigenetic findings to functional biological consequences, and the focus on selected dopaminergic polymorphisms at the expense of a broader genomic context. This means that the presented findings should be considered as a fragment of a larger puzzle rather than a complete picture of the biological underpinnings of addiction.

Conclusion

The presented findings should be considered as a fragment of a larger puzzle rather than a complete picture of the biological underpinnings of addiction. Taken together, the results suggest that genetic and epigenetic variability

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in dopaminergic system genes - particularly DRD4, COMT, and DAT1 - influences vulnerability to addictions primarily through interactions with psychological traits such as anxiety, conscientiousness, and openness to experience, rather than through direct effects of single polymorphisms. This integrated perspective highlights the importance of combining biological and psychological data in the study of addiction and supports the view that gene-epigenome interplay may provide biomarkers relevant for personalized psychiatry.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy concerns.

Conflicts of Interest: The authors declare no conflicts of interest.

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