An Update on the Behavioral and Neurobiological Effects of Cannabis Use in Adolescents: A Translational Perspective

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The convergence of early initiation, increasing product potency, and widespread availability has reshaped the contemporary cannabis landscape, heightening concerns about its impact on adolescent mental health. Translational research combining longitudinal human neuroimaging and animal models provides compelling evidence that cannabis use—particularly with high-tetrahydrocannabinol (THC) products and frequent use—can disrupt adolescent brain development and behavior. This vulnerability is especially relevant to trajectories leading to psychosis, schizophrenia, and cannabis use disorder, while also elevating risks for anxiety and depression. Although not all adolescents who use cannabis will experience adverse outcomes, a susceptible subset may face lasting consequences. These risks underscore the urgent need for targeted public education and innovative clinical research to mitigate cannabis-associated harms. Encouragingly, emerging neurobiological findings suggest that not all cannabis-induced brain changes persist into adulthood. Epigenetic mechanisms implicated in the long-term effects of THC exposure further indicate that some neural and behavioral alterations may be reversible. Given the high plasticity of the adolescent brain, this evidence points to a critical window for prevention and early intervention strategies capable of altering the course of cannabis-related psychopathology and supporting more resilient developmental outcomes.

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Adolescence, the period of transition from childhood to adulthood, is characterized by an increase in novelty seeking, risk-taking behavior, and emotional and cognitive growth (1). It is also a critical developmental stage of vulnerability for the emergence of psychiatric disorders (2), including the initiation of substance use. This is significant, as most adults with substance use disorders initiate use during adolescence, leading to lifelong consequences. Substances like alcohol and tobacco, which often have their onset of use during adolescence, are well recognized to have a long-standing public health burden, yet cannabis, which is also recognized as a "starter drug," is one that has often been perceived as safe or even beneficial. Many adolescents and young adults consider cannabis as "healthier" than alcohol, a tool to manage anxiety, or a natural remedy for stress and problems with sleep. Cannabis is depicted as benign or therapeutic, and for many youths, experimentation with cannabis is seen as a rite of passage rather than a risky drug. However, today's adolescents face unique risks compared to previous generations who experimented with cannabis—namely, initiation of use at earlier ages, higher-potency and concentrated products, a plethora of cannabis and cannabinoid products, numerous delivery methods, and reduced stigma—that make this drug more accessible and appealing especially to adolescents and young adults.

The dramatic sociopolitical changes in recent years have markedly reshaped the landscape of cannabis consumption not only among teens, but across all age groups. The decriminalization and legalization of cannabis throughout the United States and globally have spurred the emergence of a multibillion dollar industry in the United States alone, which depends heavily on public consumption and new users. Cannabis, once viewed through the lens of criminality or counterculture, is now fully embedded in mainstream markets, with reduced public stigma. This shift is also reflected in its consumption. Today, more individuals report daily or near-daily cannabis use than alcohol consumption (3). This change is related in part to the destigmatization of cannabis and to the fact that it is associated with lower direct mortality as compared to alcohol and tobacco, which are still responsible for substantial morbidity and mortality in society. However, this narrative belies a more complex reality, since cannabis is not benign and has become increasingly implicated in psychiatric disturbances, especially among vulnerable youths.

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What makes today's context regarding cannabis particularly disconcerting, especially in relation to adolescent brain development, is the convergence of potent, highly accessible cannabis products and an environment that normalizes and even encourages use, all promoting a "simple" and "natural" drug. This runs counter to current facts. Cannabis is a complex plant containing over 500 chemicals, at least 120 of which are cannabinoids, about whose biological effects our knowledge remains limited (4). Delta-9-tetrahydrocannabinol (Δ^9-THC) is the main psychoactive component of cannabis, which mediates the drug's euphorigenic or "high" effects and its psychiatric risk. In contrast to previous decades, when the concentration of Δ^9-THC was 2%–4% in the dried herbal flower most frequently consumed, the concentrations now range from 10% to 20% (5), and beyond 50% for resin (6), a form typically used for consumption through vaporization and dabbing, with certain products containing Δ^9-THC concentrations over 90% (7). Even in licensed dispensaries, the Δ^9-THC concentration is consistently >15% for both medicinal and recreational products, some having over 60% (8). All these potent products have been developed to produce a faster and more intense "high." Clearly, the diversity and strength of available products—concentrates, edibles, vape cartridges—have transformed cannabis into a substance of markedly different potency (i.e., the concentration of Δ^9-THC) and pharmacology than just a generation ago. The diversity of products being consumed has also evolved through companies manipulating federal loopholes of Δ^9-THC products, which are still federally illegal, in order to attract new users with the creation of THC "light" products such as Δ^8-THC. Such products are chemically derived from hemp cannabis plant (<0.3% THC), which is instead rich in cannabidiol (CBD), a nonintoxicating cannabinoid. However, the THC "light" products are still intoxicating and significantly impact the brain (9). Moreover, the process of making such semisynthetic products, as well as the creation of new purely synthetic Δ^9-THC products, depend on the use of chemicals that can be toxic, particularly to the developing brain.

The marked change in the sociopolitical cannabis landscape and cannabis consumption has led to increased research attention being given to the potential health impact of this drug. Although cannabis research still lags behind that of alcohol and tobacco, research into cannabis and its effects has exploded over the past two decades. One area of particular focus is the impact of cannabis on the developing brain. This article provides a general overview of the behavioral and biological consequences of adolescent cannabis use, drawing on recent human and animal research studies to illuminate what we know, what remains uncertain, and what the future may hold.

THE ENDOCANNABINOID SYSTEM AND ADOLESCENT BRAIN DEVELOPMENT

Understanding how cannabis interacts with the developing brain requires insight into the neurobiological system it targets: the endocannabinoid system (ECS). The ECS is a major modulatory system with wide impact on numerous biological processes maintaining homeostatic balance. During adolescence, the ECS plays a crucial role in orchestrating brain maturation, particularly in corticolimbic neural circuits underlying cognition, motivation, reward, emotion, and stress regulation (10). The ECS comprises cannabinoid receptors (primarily CB1R and CB2R) that typically inhibit transmitter release. It also includes endogenous retrograde signaling ligands that travel *backward* (from the postsynaptic neuron to the presynaptic cell) to regulate neurotransmitter release. The primary ECS ligands studied to date are anandamide and 2-arachidonoylglycerol, which are a part of a large and complex lipid system and are tightly regulated by enzymes responsible for their synthesis and degradation, including fatty acid amide hydrolase and monoacylglycerol lipase (11). In recent years, the ECS concept has been expanded into what is now called the "endocannabinoidome," which includes over 100 related fatty acid–derived mediators, dozens of associated receptors (including orphan receptors such as the G protein–coupled receptor 55, the transient receptor potential cation channel subfamily V member 1, and peroxisome proliferator-activated receptors), and numerous anabolic and catabolic enzymes (12). The full endocannabinoidome is still poorly characterized, including the complex ontological development of its various components, so below I focus on the primary ECS.

The components of the ECS dynamically change during the lifespan, and levels of the endocannabinoid (eCB) ligands and CB1R, the most abundant G protein–coupled receptor in the brain, peak during adolescence (10, 13). Noted sex differences in synaptic function mediated by the CB1R also peak around adolescence. For example, while other forms of plasticity, like long-term potentiation, are already mature in both sexes by adolescence, eCB-mediated long-term depression (LTD), a major form of synaptic plasticity, is expressed early in females but only appears at puberty in males (14). Moreover, these sex differences in eCB-mediated LTD appear to be particular to the prefrontal cortex (PFC), a brain region that plays a significant role in executive function (14). Given the critical role of the ECS in regulating synaptic function and its broad expression throughout the brain, it is evident that THC has the potential to affect numerous neurobiological processes and neural circuits relevant to psychiatric risk. Several neurobiological processes of particular relevance during adolescent development that are modulated by the ECS and peak during this phase include synaptic pruning and myelination, which are essential for refinement of neural circuits and maturation of the brain. The ECS is also essential for the normal maturation of subcortical structures such as the ventral striatum and amygdala, influencing the development of reward and emotional processes (15) as well as playing an intricate role in stress response (16).

THE TRAJECTORY OF ADOLESCENT CANNABIS USE

Significant debates continue regarding whether cannabis use during adolescence impacts brain development in ways that

might have lasting effects relative to psychiatric risk. Understandably, much of the debate stems from the numerous uncontrollable factors inherent in human studies—for example, genetics, environment, family history—as well as to the fact that most studies were underpowered. As a result, it has been challenging to disentangle brain signatures ascribed to the direct consequence of cannabis exposure compared to that existing before the onset of cannabis use. Longitudinal neuroimaging consortium studies have been instrumental in addressing certain "chicken-and-egg" debates by being able to study the same individual before and after the onset of substance use. Most of the recent data available to address these questions are from landmark prospective longitudinal neuroimaging studies from the IMAGEN consortium, launched in 2008 in Europe to track a cohort of ~2,000 teens from age 14, and the Adolescent Brain Cognitive Development (ABCD) study, launched in 2016 in the United States to track the development of ~11,000 youths from ages 9–10 to determine various factors, including drug use, in relationship to brain and behavioral health. Despite differences in the age of recruitment for these studies as well as differences in cannabis products between Europe and the United States, certain consistent findings are emerging that suggest that adolescent cannabis use is associated with structural and functional brain changes, as well as increased risk for behavioral and mental health problems.

Animal models are also an important strategy to track longitudinal and causal effects regarding the direct exposure to cannabis and cannabinoids. There are nevertheless certain limitations. For instance, preclinical models normally examine the effects of Δ^9-THC, not cannabis, and routes of administration or exposure and amounts of total exposure normally seen in humans are not fully replicated. Additionally, animal models do not mirror most psychiatric disorders, especially psychosis-related disorders, but they have provided important insights regarding specific phenotypes relevant to psychiatric conditions. Despite the various caveats, several behavioral and biological outcomes show convergence between animal models and human studies that together are important to consider regarding the potential consequences of adolescent cannabis and cannabinoid exposure.

Adolescent Cannabis Use, Cerebral Cortex, and Cognition

One observation that has been debated for years regarding potential consequences of adolescent cannabis use relates to its effects on cortical thickness. It was rightly posited that the results might be confounded by preexisting differences before teens ever used a drug. Data from the longitudinal IMAGEN study demonstrated that despite no preexisting differences in brain structure among early teens (~14 years old), those engaging in cannabis use after that time showed reduced cortical thickness 5 years later, especially in the PFC, a brain region critical for executive functioning (17). Specifically, cannabis users exhibited accelerated age-related cortical thinning—remodeling of the cortex that normally occurs during adolescence and into young adulthood—with the degree of PFC thinning having a dose-dependent relationship to cannabis use. Moreover, the pattern of cannabis-related thinning also significantly overlapped with the cortical density of CB1R based on in vivo positron emission tomography maps (17). The association between cannabis use and cerebral cortical thickness also remained later in life (~22 years of age), even when controlling for recent cannabis use (17). Altered cortical thickness was also causally demonstrated in rodent studies, with adolescent Δ^9-THC exposure leading to reduced structural complexity of pyramidal cortical cells in the medial PFC and accelerated pruning into young adulthood, along with marked perturbation in the expression of dendritic and synaptic plasticity-related genes (18). Other preclinical studies confirm such findings. This includes a recent translational investigation in which human homologs of genes that were differentially expressed as a consequence of adolescent THC exposure in a rodent model correlated with cannabis-related variations in cortical thickness in human adolescents (19). Such genes were coexpressed in astrocytes, microglia, and a specific type of pyramidal cells that are enriched for dendrite-related genes. Collectively, accumulating data suggest that THC use during adolescence may influence cortical thickness by impacting glutamatergic synapses and dendritic arborization. Moreover, the reprogramming of the transcriptome of the pyramidal cells that were structurally changed as a consequence of adolescent THC exposure were characterized by marked developmental network disturbances for epigenetic regulators showing a striking enhanced coexpression of chromatin- and dendrite-related genes (18). These and other findings align with accumulating evidence in humans and animal models of significant epigenetic contributions to the long-lasting developmental effects of cannabis (20). The fact that epigenetic mechanisms are reversible also suggests that some of the effects seen with adolescent cannabis or THC exposure are not deterministic for lifelong negative health.

Other considerations of prefrontal cortical function and cognitive development relevant to adolescent cannabis exposure relate to decision making and impulse control, behaviors often compromised in teens. Cortical thinning evident in the right PFC of teens with cannabis use was associated with attentional impulsiveness at their 5-year follow-up (17). Our recent translational study (21) also demonstrates that similar to human chronic users, with cannabis exposure initiated during adolescence, young adult rats exposed to high-dose THC (comparable to ~15% products today) during adolescence exhibit increased risky decision making and impulsive behavior. Dose was a key factor since the cognitive effects were not evident in animals exposed during adolescence to low-dose THC (comparable to ~4% products). Moreover, in the high-dose THC animals, the CB1R was altered in a layer- and cell-specific manner—reduced in layer 2/3 GABAergic cells in the prelimbic cortex but increased on glutamatergic terminals—which would

be expected to reduce excitatory output overall from the PFC (21).

Many considerations remain to be addressed regarding the neuroanatomical patterns observed in teens and emerging adults, including whether apparent subregional effects of cannabis relate to the developmental timing of drug exposure. For instance, in evaluating the IMAGEN longitudinal data at ~10 years after baseline assessment, associations between adolescent cannabis initiation prior to age 19 and cortical thickness change were primarily evident in dorso- and ventrolateral portions of the PFC (22). In contrast, cannabis initiation that occurred between ages 19 and 22 was associated with thickness change in temporal and cortical midline areas. Whether specific cortical and subcortical regions are more susceptible to cannabis-induced perturbation due to dynamic changes specifically occurring in that region during distinct developmental windows remains an open question. Additionally, while certain cortical alterations seen in teens with cannabis use are evident into early adulthood, not all structural changes persist into adulthood, suggesting that some effects may be transient rather than enduring.

Behavioral outcomes appear partly congruent with neurobehavioral findings. Given the role of the PFC in executive functioning, it is not surprising that studies report that adolescents who use cannabis tend not only to have changes in PFC structure and connectivity, but also reduced cognitive performance, particularly in measures of memory and attention, as well as educational underachievement. However, meta-analysis of studies focused on adolescents and young adults note only small cognitive effects, likely due to multiple confounding variables, with the most significant impairments associated with heavy and/or frequent cannabis use (9). The proliferation of concentrated cannabis products and today's daily and near-daily use of cannabis underscore the need for research to provide definitive answers.

Relevance to Psychosis and Schizophrenia

Of the broad array of adverse outcomes implicated in cannabis use during adolescence, the association with increased psychosis and schizophrenia risk has been most robust, but controversial. Debates regarding causality relate to the potential genetic contribution to this association given the increased risk for schizophrenia among individuals with a genetic predisposition (23). There is, nevertheless, a growing consensus that early onset and frequent use of high-potency cannabis are linked to an elevated risk for psychotic symptoms and schizophrenia (24). Even accounting for genetics, recent data highlight that it is high-potency cannabis that accounts for the worse effects on psychosis. This was evident in a multicenter study across Europe in which the strongest predictors of whether an individual would have a psychotic disorder or not were daily use of cannabis and use of high-potency cannabis (25). A question that is naturally raised is whether psychosis risk decreases on stopping the use of cannabis. While the risk of psychotic disorder appears to decline with time following cannabis cessation, this appears to depend on the cannabis potency and duration of abstinence. Former users who had stopped use within the past 1–4 weeks had the highest risk for psychotic disorder, with the risk declining over weeks. However, it took 37 weeks or more of abstinence for the risk level to recede to that of individuals who never used cannabis. Moreover, frequent users of high-potency types of cannabis still maintained an elevated risk compared to never users even after abstaining for 3–4 years (26).

Schizophrenia and psychosis-related disorders are difficult to replicate in preclinical animal studies, but specific schizophrenia-like phenotypes have been studied in which confounding issues like genetics can be controlled. A recent meta-analysis of rodent studies revealed a strong association between adolescent exposure to THC, and synthetic CB1R agonists, and impaired schizophrenia-related behavioral phenotypes (27). These behaviors spanned broad schizophrenia-like behavioral alterations, including cognitive deficits (e.g., working memory, novel object recognition, novel object location recognition, social novelty preference), sensorimotor gating (prepulse inhibition), and changes similar to negative symptoms of schizophrenia (e.g., reduced social motivation, and sucrose preference). These effects were also persistent even after long-term abstinence, again consistent with the protracted effects of adolescent cannabis use, especially with high-potency THC.

Cannabis Use Disorder Trajectory

As the potency of any psychoactive substance increases, so does its potential for abuse and ultimately the development of a substance use disorder. This is no different for cannabis, as evidenced by the increased risk of addiction as the use of high-potency THC increases (7). Adolescent cannabis use is a critical window for the subsequent development of cannabis use disorder (CUD) (28). Teen use is associated with approximately two to three times the risk of developing a CUD compared to using cannabis during adulthood, irrespective of the intensity of use (29). Similar to other conditions, individual differences are important to consider since not everyone develops a CUD upon consuming cannabis. Several key predictors are now recognized to increase the risk of developing CUD and related psychopathologies. These include adverse childhood experiences of trauma, abuse, and household dysfunction; prenatal cannabis exposure; biological sex, such that males tend to initiate earlier—although the sex gap is closing—and females show faster progression to CUD; stress; early age at onset of use; high frequency of use; and high-potency THC (28).

Adolescence is also a sensitive window for the increased association observed between CUD and schizophrenia. This link has become more apparent due to recent changes in the growing prevalence of cannabis in countries with previously low cannabis use. For example, in Denmark, the increased incidence of cannabis-induced psychosis paralleled the

increases in the potency of cannabis, and it was predicted that a large proportion of such individuals would develop schizophrenia (24). Indeed, the proportion of cases of schizophrenia associated with CUD increased three- to fourfold during the past two decades in Denmark (30). This dramatic change also highlighted age and biological sex for this risk. For individuals 16–20 years old, the association between CUD and schizophrenia was approximately two times as high for males compared with females. For individuals 21–25 years old, the association was approximately 50% higher for males than females. However, there were no differences between males and females for those >26 years old. Thus, young men appear more vulnerable with their trajectory to CUD and schizophrenia starting with the onset of cannabis use as teens. The significant attributable risk of CUD was estimated to be one in five to develop schizophrenia, emphasizing the critical mental health impact of the increasing prevalence and use of high-potency cannabis by teens and young adults.

While significant attention needs to be given to adolescents regarding developing CUD, it is critical to understand the significant impact of even nondisordered cannabis use, a condition that is at least four times more common than CUD and whose frequency is expected to grow. Accumulating data show that teens who use cannabis but do not meet criteria for a clinical CUD diagnosis still show cognitive deficits and low academic performance (2). The significant impact seen with nondisordered cannabis use most likely relates to the high-potency and increased frequency of cannabis being consumed today, even for some individuals who do not meet a CUD diagnosis.

Adolescent Cannabis and Anxiety/Stress/ Emotional Regulation

Similar to adults, one reason teens cite for using cannabis is to help in managing anxiety and stress, although most data show that the use of cannabis, especially with high-potency THC, exacerbates these conditions. A systematic review and meta-analysis that examined the prospective associations between adolescent cannabis use and subsequent anxiety outcomes reported a significant positive association between adolescent cannabis use and later anxiety symptoms and disorders (31). Teens who reported cannabis use were more likely to develop a subsequent anxiety disorder in later adolescence or adulthood. This was a robust finding that remained after controlling for various factors such as comorbid substance use, parental psychiatric disorders, and baseline emotional and behavioral problems. Additionally, among boys from a community sample (32), increase in weekly cannabis use and continuing cannabis use throughout adolescence predicted, in a dose-dependent fashion, symptoms of anxiety and depression 10 years later. Our rodent model of adolescent THC exposure in males (33) also showed that high-dose, but not low-dose, THC leads to protracted elevated levels of corticosterone, increased sensitivity to a stressor (overnight social isolation) and reduced social interaction later in life. The heightened stress reactivity evident with high-dose adolescent THC in combination with a subsequent stress was also characterized by a marked reorganization of the transcriptome within the basolateral amygdala, a brain region central to stress and emotional regulation. In addition to perturbation of stress-related genes, adult rodents with high-dose adolescent THC and stress experience also showed a unique recruitment of astrocyte-specific genes related to synaptic homeostasis, which was also reflected structurally with decreased astrocytic processes and branching (33). Altered amygdala function was also evident in other preclinical studies, such as in adolescent THC in mice exposed to stress (34). This experience resulted in impaired cued fear extinction in adulthood, with resistance to fear extinction associated with decreased neuronal activity in the basolateral amygdala.

Despite the central role of the amygdala in anxiety and stress and the strong role of the ECS in mediating such phenotypes, the human literature is mixed regarding cannabis-induced changes in the amygdala as a consequence of adolescent use. A meta-analysis of studies focused on young adults reported nonsignificant amygdala volume differences between young cannabis users and nonusers, even after accounting for age and cannabis use level (35). A recent study of a subsample of the ABCD data also found no significant association between cannabis use and amygdala volume in early adolescence (36). However, cannabis use was linked to increased depressive symptoms, particularly in those individuals with smaller amygdala volumes. Long-lasting depressive- and anxiety-like phenotypes have been observed in adult rats with escalating THC doses during adolescence (37). While various preclinical studies report on protracted alterations in limbic brain regions, these findings are difficult to reconcile with the human in vivo neurobiological results. This is evident especially in functional neuroimaging studies examining the consequences of adolescent cannabis use, where the results have been quite mixed. A recent meta-analysis suggests that adolescent cannabis use is associated with altered brain activity not only in relation to executive control, but also in emotion processing and reward processing (38). However, alterations may vary based on sex, CUD severity, psychiatric comorbidity, and duration of abstinence.

CHALLENGES AND KNOWLEDGE GAPS

The potency and diversity of modern cannabis products introduce new risks and challenges since we lack rigorous data on these newer products, delivery methods, and semisynthetic derivatives. Filling that gap of knowledge any time soon in relation to adolescent use will be challenging. Longitudinal human studies typically require at least 5 years to assess developmental and psychiatric trajectories. Preclinical animal studies must therefore evolve to examine higher-potency THC exposures and focus on translationally relevant behavioral phenotypes. These models are essential

for elucidating the molecular and cellular mechanisms by which cannabis exposure during adolescence alters brain development.

Another challenge is cannabis education. First, it is important to distinguish high-potency products from low-potency products that have historically been termed "cannabis" or "marijuana." Terminology matters in being able to obtain relevant data and to understand the clinical consequences of the various cannabis and cannabinoid products being consumed. The effects of cannabinoids other than THC on the adolescent brain, as well as non-cannabinoid chemicals in cannabis, are still unknown and constitute another major gap. Studying the interaction among the hundreds of chemicals in cannabis presents a formidable and impossible challenge due to the sheer number of potential combinations. Still, targeted studies on the most used cannabinoids and formulations are essential to advance the field.

Clinicians face substantial challenges in treating CUD, the number of which are expected to increase as the growth of concentrated cannabis products continue. While psychosocial interventions remain critical, there are no U.S. Food and Drug Administration–approved pharmacotherapies for CUD, either for adolescents or adults. Moreover, the challenge is to develop medications that would be suitable and safe for the developing brain. For example, small clinical trials showed promise that *N*-acetylcysteine, an antioxidant and pro-cystine supplement, might be a strategy to reduce cannabis use in adolescents with CUD (39). An animal model also demonstrated that *N*-acetylcysteine prevents THC-induced increase in anxiety- and depressive-like phenotypes as a consequence of adolescent exposure in male rats (37). However, in the clinical trial, *N*-acetylcysteine only appears effective if paired with contingency management behavioral intervention (39). These findings raise important questions about whether behavioral interventions should always be integrated into research and treatment efforts targeting adolescents.

CONCLUSIONS

The convergence of early initiation, high-potency products, and widespread availability of today's cannabis landscape has created an environment ripe for mental health challenges. Translational research spanning human neuroimaging and animal models affirms that cannabis can alter adolescent brain development and behavior. While not every teen who uses cannabis will experience negative outcomes, a subset may face lasting consequences, especially those now consuming high-potency THC products. Efforts are urgently needed in education and clinical research innovation to mitigate cannabis-associated risks. There is also hope. Neurobiological evidence showing that epigenetic mechanisms underlie long-term effects of cannabis/THC suggests that some of the neural and behavioral effects are most likely reversible. Indeed, not all neurobiological perturbation observed in teens with cannabis use is maintained into adulthood, and along with the plasticity of the adolescent brain, there is a window of opportunity for prevention and early intervention to change the trajectory of cannabis-related psychopathologies.

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