

Chapter 2

Cognitive Development, Learning and Drug Use

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Use of Cannabis in Adolescence—Epidemiology and Risk Factors

For young adolescents, drugs are usually dichotomously classified as “hard drugs” and “soft drugs”. The former category comprises drugs that are known to induce physical and psychological dependence and to pose high risks to the physical and mental health of users. Opiates are perhaps the prototypical example of this category. Soft drugs, which are typically used for recreational purposes, are contrariwise considered by youths as less liable to induce dependency (physical dependence, in particular) and as not posing a significant risk to the users’ health. The most typical and generalized example of a “soft drug” is *cannabis*.

The belief in the innocuous nature of *cannabis* causes many youths to deny their use of the drug when asked about their drug habits in the clinical setting; to many youths, the concept of “drug use” is restricted to the so-called synthetic drugs. Instead, the use of *cannabis* is considered an allegedly innocuous behavior that differs little from the use of other substances with various degrees of psychoactive effects (e.g., caffeine and nicotine).

Such beliefs have led *cannabis* to quickly become the most widely used illegal drug among adolescents. For instance, in the United States, following several

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periods of fluctuation in the use of *cannabis* between 1970 and 2008, consumption increased significantly in 2010. Its prevalence was estimated to be 30.4% among adolescents attending the 8th, 10th and 12th grades, with daily consumption levels of 1.2%, 3.3% and 6.1%, respectively [1].

Contrary the extent of its use and the belief in the innocuous nature of *cannabis*, recent concerns have arisen concerning the possibility that continuous exposure to *cannabis* may cause significant psychological damage to adolescents' neurologic and cognitive development during a crucial stage of their psychological development.

There is some evidence that the generalized use of *cannabis* in adolescence represents a significant risk factor for the incidence and persistence of psychotic symptoms. One of the latest studies in this area followed up German youths over 10 years and confirmed that the use of *cannabis* effectively preceded the appearance of psychotic symptoms, even among individuals with no signs of psychotic disorders whatsoever. Thus, the study concluded that *cannabis* represents a significant risk factor for the persistence of such symptoms [2].

Recent evidence also points to the association between continuous use of *cannabis* and the high risk of developing several mood disorders, particularly bipolar and major depressive disorders [3].

Curiously, in a study that followed Australian youths for a 10-year period, even sporadic use of *cannabis* by adolescents was associated with several indicators of psychosocial maladjustment, such as school failure and future use of alcohol and illegal drugs [4].

The mechanisms underlying the psychological and neurobiological development characteristic of adolescence might make adolescents particularly at risk for the use of psychoactive substances such as *cannabis*.

Adolescence is characterized by significant neurobiological maturation processes. With respect to gray matter, the increase in cortical density that takes place before puberty undergoes remarkable reduction in the frontal, temporal and parietal lobes, although the pattern of progression is peculiar to each brain lobe (for instance, the gray matter density reaches its maximum in the frontal lobe at approximately 11 years of age, whereas gray matter density continues to increase in the temporal lobe until 14 years old) [5]. In contrast to the synaptic pruning that results in the reduction of the cortical density, white matter myelination and coherence exhibit significant increases. Of particular interest is the fact that the last areas to attain maturation are the prefrontal regions [6].

The neurobiological development that occurs in adolescence is associated with the maturation of several cognitive functions that are crucial for the future psychological adjustment of youths. Indeed, the structural development of the prefrontal cortex creates the conditions required for greater and more efficient communication with the remainder cortical and subcortical structures, thus endowing adolescents with greater efficiency in decision-making, planning, working memory, meta-cognition, behavior regulation and emotional control [7]. For these reasons, adolescence is typically essential for the maturation of the higher cognitive processes that are crucial for psychological adjustment in adulthood. The possible implications of use of *cannabis* in the development of several psychopathological disorders may be

due to an interference with the full process of neurocognitive development. Indeed, one of the hypotheses put forward to account for the pathophysiology of schizophrenia points to a reduced efficiency of the mesocortical dopaminergic system for inhibiting the mesolimbic system. The dopaminergic system, particularly in the prefrontal area, undergoes significant reorganization during adolescence. Thus, any process liable to interfere with the maturation of the mesocortical system might significantly increase the risk of psychotic disorders.

To summarize, *cannabis* is the drug most widely used by adolescents. The use of *cannabis* by adolescents has been identified as a remarkable risk factor for future disorders, particularly psychotic disorders but also affective ones. The neurocognitive changes occurring in adolescence may make this stage of life particularly vulnerable to the use of *cannabis*. Therefore, one of the most immediate effects of *cannabis* may be altered higher cognitive functions, which undergo maturation in adolescence, and a large number of psychiatric disorders may be direct consequences of these alterations.

Next, we analyze the maturation of the endocannabinoid (eCB) system and its implication for cognitive processes. Finally, in the last section of this chapter, we discuss the effects of *cannabis* on cognitive processes in adolescents.

Endocannabinoid System

The eCB system comprises several lipid neuromodulators and their receptors, which participate in various neurophysiological functions, including the processing of pain, memory and mood. At least two cannabinoid receptors (CB), which belong to the seven-transmembrane domain G protein-coupled receptor family, have been characterized: CB1 and CB2 [8, 9]. CB1 is the most abundant CB in the mammal brain and is expressed at high levels in the basal ganglia, hippocampus, cerebellum and cortex [10, 11]. Most of the effects of cannabinoid drugs on the central nervous system (CNS) are mediated by the receptor CB1 [12]. CB2 is mainly located in peripheral sites, particularly in the hematopoietic system [9]. The identification of these receptors followed the discovery of endogenous cannabinoid ligands, among which anandamide and 2-arachidonoylglycerol (2-AG) are the most relevant [13, 14].

eCBs, unlike the classical neurotransmitters, are not stored but are instead released by postsynaptic neurons due to their location in the axon terminals and retrogradely diffuse across the synaptic cleft to stimulate the CB1 receptors on the presynaptic neurons. Activation of CB1 transiently reduces the neurotransmitter release in the presynaptic terminals [15]. Retrograde inhibition of the synaptic transmission was described in GABAergic and glutamatergic synapses throughout the brain, including the neocortex. These findings suggest that eCBs represent a generalized mechanism of synaptic regulation.

In addition, eCB signaling occurs under response [16] and is synapse-specific; eCBs are synthesized from lipid precursors derived from the cell membrane; thus, they are only released when they are required. Together, those features make the eCB system a protective physiological mechanism against excessive stimulation of

the receptors to various neurotransmitters, which can easily occur in critical periods of development.

As mentioned previously, adolescence is one of such vulnerable periods of development in which the GABAergic and glutamatergic systems are undergoing remarkable development, particularly in the prefrontal area. The synaptic remodeling that occurs in adolescence is of paramount importance in the refinement of those circuits [17].

Electrophysiological studies indicate that synaptic remodeling is stimulated by neural activity in the form of electrical impulses, which are usually dependent on Ca^{2+} influx. In the presence of eCBs, the intracellular Ca^{2+} level determines the reinforcement or pruning of specific synapses, and the number and quality of such connections are determinant for the improvement of various neural networks [18]. To avoid the excitotoxicity associated with excessive Ca^{2+} influx through the postsynaptic channels in periods of system maturation, synapses should be able to control the amount of glutamate released from the presynaptic terminals. Due to its retrograde action on the GABAergic and glutamatergic synapses, the eCB system plays a crucial role in the regulation of glutamate homeostasis [15, 18, 19].

The use of exogenous cannabinoids in critical periods of development, when the associated processes are particularly intense, might interfere with the regulatory role of the eCB system in GABAergic and glutamatergic neurotransmission [20]. The main psychoactive component of *cannabis* is delta-9-tetrahydrocannabinol (THC), one of the exogenous cannabinoids most widely used by adolescents. THC acts by binding to the presynaptic CB1 receptors in the CNS.

The possible mechanisms of action of *cannabis* include reduction of the activity (loss of binding sites) and desensitization (no longer coupled to G proteins) of the CB1 receptors. These phenomena are consistently observed following chronic administration of synthetic cannabinoids and THC [21]. Thus, exposure to *cannabis*, THC in particular, in adolescence is hypothesized to impair the refining of the neural circuits in the prefrontal cortex (PFC). The dose, the developmental window and the duration of exposure determine the severity and cortical localization of the effects.

Studies in animal models also demonstrate that the PFC dopaminergic system may undergo substantial reorganization during adolescence [22]. Indeed, the dopamine concentration in the PFC decreases after the adolescence peak [23], which occurs concomitant with the improvement in the dopaminergic innervation of the prefrontal pyramidal neurons [24]. In addition, the density of the dopaminergic afferent fibers to the PFC increases during adolescence [25], which differs from other subcortical areas that project to the PFC, such as the striatum, in which the synthesis and turnover of dopamine are lower in adolescence compared to adulthood [23]. The change in the dopamine balance between the PFC and the mesolimbic subcortical structures likely results from the significant pruning of axons that project to the neocortex [26].

The use of exogenous cannabinoids during the abovementioned processes might lead to atypical development of neural circuits in the PFC. The functional implications of such atypical development include aberrant physiological communication

between the PFC and other cortical and subcortical structures, mainly as a result of anomalous dopamine and GABA transmission.

The majority of the aforementioned evidence is based on animal studies, typically rodents. In rodents, the eCB system in the prefrontal areas also seems to continue to develop throughout the course of adolescence, which is attended by a dramatic reduction in the cannabinoid binding capacity until the beginning of adulthood [27]. These studies suggest a parallel with cannabinoid use in humans, which also results in cognitive and neurofunctional alterations, as described in the following section.

Neurocognitive Effects of *Cannabis* Use

As stated above, adolescence is characterized by continuous neuronal maturation, which causes increased neurodevelopmental vulnerability to the adverse effects of exposure to exogenous cannabinoids.

This evidence notwithstanding, the neurocognitive effects of *cannabis* following different periods of abstinence have been more widely investigated in adults. The results of these studies are consistent with respect to the association between the chronic use of *cannabis* and acute negative effects on the learning and memory skills, processing speed, executive functioning, decision-making, attention and working memory. However, evidence for the long-term persistence of those neurocognitive deficits is less conclusive.

Significantly fewer studies have been conducted on the acute and chronic effects of use of *cannabis* in adolescence despite the considerable preclinical evidence demonstrating persistent adverse effects following exposure to exogenous cannabinoids in adolescence and that the use of *cannabis* often begins in this period of development.

Neuropsychological studies conducted with adolescents demonstrate acute effects following the use of *cannabis* on measurements of overall intelligence, processing speed, working memory, attention, learning and verbal memory, as well as in executive functions such as planning and sequencing, as well as increased number of perseveration errors [28–30]. A study on long-term effects (after 1 month of supervised abstinence) demonstrated a subtle persistence of neurocognitive deficits relative to the attention skills, processing speed, verbal learning and memory [30, 31]. The results of longitudinal studies are consistent with acute studies and reported a cumulative effect over time, with particularly notably effects on attention skills, processing speed and short- and long-term memory [32, 33].

Overall, neuropsychological studies provide evidence for acute and chronic neurocognitive effects following exposure to exogenous cannabinoids in adolescence. These effects exhibit differential expression according to the age at which use started. Onset of *cannabis* use before age 16–17 years old is a strong predictor of impairment of the attention skills [34] and reduction of verbal IQ [31].

Several studies demonstrate parallel evidence that the deleterious effects of *cannabis* on neurocognition are attended by changes in brain structure and function. The results of structural magnetic resonance imaging (MRI) are inconsistent in the

detection of global or regional changes in adults [35, 36]; however, MRI studies conducted with adolescents clearly demonstrate significant neurobiological and neurofunctional effects following the use of *cannabis*. Wilson et al. [37] reported that the onset of *cannabis* use in adolescence was associated with a reduction in the gray matter percentage and an increase in the white matter percentage after normalization by the total intracranial volume. The volumetric change in white matter is consistent with alterations in the integrity and structure of several of its bundles, including changes in the fractional anisotropy and mean diffusivity of the corpus callosum [38], fronto-parietal [39] and fronto-temporal circuits [40].

Functional alterations of these circuits have also been documented by studies using functional MRI and include abnormalities in the patterns of frontal, temporal and parietal activation among adolescent *cannabis* users (both acute effects and effects following different periods of abstinence) with respect to visual attention [41], inhibitory processing [42], and verbal [43] and spatial [44] working memory tasks.

Some studies have reported a connection between structural and functional aspects in verbal memory tasks, particularly, a bilateral reduction of the hippocampal formation volume in individuals who made frequent use of *cannabis* [45]. Moreover, unlike the control group, a positive association between volume and performance in verbal memory tasks was not observed in the group of *cannabis* users. More specifically, studies that performed functional neuroimaging during the performance of verbal and spatial working memory tasks reported increased activation in a brain network that included the parietal cortex, hippocampus, and anterior cingulate cortex in conjunction with a reduction of the BOLD response in the dorsolateral PFC and occipital lobe. The PFC was differentially activated following recent *cannabis* use (compared with the abstinence condition). In particular, an increased brain response was observed in the PFC, right superior parietal cortex, and bilateral insula [46]. These findings indicate different acute and chronic effects of cannabis use on the brain function of adolescents, suggesting that recent *cannabis* users require greater recruitment of the brain areas underlying the working memory circuits, whereas the abstinent adolescents exhibit mechanisms of brain reorganization and plasticity, particularly in the PFC. The pattern of increased cortical activation seems to be specific to the type of cognitive task under assessment. In attention tasks (inhibitory processing), a marked BOLD response was observed in the parietal lobe in conjunction with activation of the dorsolateral PFC.

The changes observed in the brain areas responsible for the various neurocognitive tasks (visual attention, inhibitory processing, verbal and spatial working memory), such as the frontal lobe, hippocampus, basal ganglia and striatum, might be related to the fact that these brain regions are rich in cannabinoid receptors and thus more susceptible to the action of THC. Finally, the magnitude of these changes seems to correlate with early exposure to exogenous cannabinoids in adolescence [43].

To summarize, the results of functional studies seem to reflect changes in the neural circuits associated with specific cognitive domains in adolescent *cannabis* users. An impact on the brain structure as well as consistent short-term changes in neurocognitive functioning have been observed. Together, those studies point to the presence of neurotoxic and functional effects following exposure to *cannabis* in

adolescence, with long-lasting and persistent impact on the prefrontal and parietal neuronal networks.

Indeed, as mentioned above, the concentration of CB1 receptors increases during adolescence in some brain areas, such as the PFC. Thus, the use of exogenous cannabinoids affects the maturation processes (for instance, reduction of the activity and desensitization of the CB1 receptors via synaptic regulation) that occur during the course of adolescence, with functional implications for the synaptic plasticity that underlies learning and memory processes. Together, these studies indicate that frequent use of *cannabis* in adolescence exerts a negative influence on neuromaturation and on corresponding alterations in neurocognitive functioning.

Conclusion

The study of the neurobiological, cognitive and behavioral effects of *cannabis* use is complex due to the large number of variables that must be methodologically taken into consideration. Indeed, comparison among studies is difficult due to the varying levels of exposure to *cannabis*, polydrug use, and the substantial comorbidity with psychiatric disorders, which hinder attempts to establish whether the impact of *cannabis* on neurocognitive functioning is exclusively due to the use of *cannabis*.

In addition, limitations relative to the recruitment of volunteers (treatment/follow up versus non-treatment), the distinction between acute or subacute effects, the abstinence syndromes, the definition of frequent versus sporadic users, the assessment of the influence of social and educational opportunities, and premorbid cognitive function further increase the complexity inherent to the study of the effects of *cannabis* use.

Future studies must take these variables into consideration to provide a more thorough understanding of the adverse effects of exposure to exogenous cannabinoids by means of multimodal and translational integrated approaches using neuroimaging and neurocognitive techniques as well as animal models. This approach will also allow a holistic view of the phenomenon, as well as a critical analysis of the possible therapeutic implications of the use of *cannabis*.

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