Growing up high: Understanding the impacts of adolescent cannabis use on mental health and brain development

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Abstract

Adolescence represents one of the most crucial periods of human brain development. This unique neurodevelopmental window involves a complex interplay of synaptic re-modelling, the establishing of cortical and sub-cortical emotional processing and cognitive neural circuits along with a greater propensity for engaging in risky behaviours and experimentation with illicit drugs. A growing body of both clinical and pre-clinical evidence has demonstrated that exposure to cannabis, and more specifically, Δ-9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, can strongly increase the likelihood of developing serious neuropsychiatric disorders in later life. Adolescent THC exposure is linked to long-term cognitive impairments, emotional dysregulation, mood disorders and increased vulnerability to schizophrenia. The interplay between adolescent THC exposure and mental health risks have been linked to a wide array of underlying neurobiological pathologies, including structural and morphological alterations in brain circuits linked to cognitive function and emotional regulation. Despite this growing body of data, there remains considerable confusion and misinformation regarding how and why adolescent cannabis use can ultimately increase these psychopathological risk factors. Nevertheless, the confluence of clinical and pre-clinical neuroscience research related to these questions is finally providing much needed insight into the relative risks and identifying useful biomarkers that may ultimately allow us to establish more reliable criteria and guidelines for safer cannabis access and help mitigate these risks to mental health.

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Introduction

What's so Special about the Adolescent Brain?

In humans and most other mammalian species, adolescence represents a critically important window for brain development. Combined with the surge in puberty-related sex hormones, critical periods of synaptic pruning and re-modelling are ongoing processes within the adolescent neocortex, allowing for the fine-tuning of synaptic communication and plasticity associated with normal cognitive development and higher-order executive control functions over adaptive behaviours.[1,2] Notably, critical regulatory pathways between higher cortical regions such as the prefrontal cortices and sub-cortical emotional processing circuits such as the mesolimbic pathway, comprising the ventral tegmental area (VTA) and nucleus accumbens (NAc) and the amygdaloid nuclei, are in the process of maturation. Indeed, these higher cortical regions are amongst the last to develop to maturity in the mammalian brain, which has critical implications for the ability (or lack thereof) of adolescents to regulate sub-cortical neural regions such as the mesolimbic system and amygdala, all of which are crucial emotional processing centres[3,4] and are known to be pathologically dysregulated in a wide array of mental health disorders, including depression, anxiety, addiction and schizophrenia. The brain's cannabinoid signaling system is found ubiquitously in the brain. However, high concentrations of central cannabinoid receptors (CB1Rs), upon which extrinsic cannabinoids such as THC act on, have been found to be localized in neural regions critical to emotional regulation and cognitive processing, including the brain regions described above 5,6, wherein they can potently modulate affective and cognitive functions associated with mood disorders, addiction and schizophrenia-related symptoms.[7-11]

Historically, Canada has consistently been a global leader in adolescent cannabis usage rates. Indeed, as recently as 2013, it was reported that Canadian adolescents (11 to 15 years) maintained the highest rates of cannabis consumption when compared to 29 similar advanced economies.[12-14] This report revealed that 28% of Canadian adolescents had consumed cannabis at least once over the past year. In addition, there is evidence for increasing frequency of usage, as a growing percentage of Canadian adolescent users (22% of boys and 10% of girls) report being daily or weekly users.[12-14] Given that legalization has only recently taken place in Canada, the ways in which changes to cannabis access may influence these rates are not yet known. Nevertheless, clear and consistent evidence both from clinical and pre-clinical

research studies has demonstrated a link between adolescent exposure to cannabis and increased vulnerability to a variety of neuropsychiatric conditions. These studies have found evidence for enduring cognitive deficits along with more severe psychiatric symptoms ranging from depression and anxiety to psychosis. Interestingly, this evidence has also revealed that adolescent cannabis exposure tends to target a specific set of brain circuits and neurochemical signaling pathways which seem to interact with the presence of pre-existing genetic markers that may render certain individuals particularly vulnerable.

The Impact of Adolescent Cannabis Exposure on Mental Health Outcomes

While the psychotropic side-effects of acute cannabis had been documented for decades in the medical literature, in 1987, Andreasson et al[15] published a watershed, large-scale retrospective clinical study showing that, in a sample of >45,000 Swedish military conscripts, increased use of cannabis during adolescence was linked to a 4-fold increase in the likelihood of being diagnosed with schizophrenia as a young adult. This association held even after accounting for confounds from other psychiatric co-morbidities and social backgrounds. Since that time, dozens of similar epidemiological studies have confirmed this correlation, not only for schizophrenia-related symptoms, but for long-term cognitive impairments as well.[16-20]

Nevertheless, the implications from these clinical studies is not as straightforward as one might assume. For example, retrospective clinical epidemiological studies cannot accurately account for how much THC an individual might have been exposed to historically, nor the psychotropic potency of cannabis strains used. In addition, retrospective self-reporting of cannabis consumption frequency may not be accurate. More importantly, correlation does not equal causation. In the absence of basic, mechanistic evidence, it is entirely possible that individuals pre-disposed to developing schizophrenia are simply more likely to seek out cannabis in the first place and that these neuropsychiatric symptoms would manifest themselves regardless of cannabis exposure.

It is important to consider that cannabis is a highly complex plant, containing over 120 distinct phytochemicals. We are only now beginning to scratch the surface in terms of understanding what each component can do physiologically and more importantly, how these different components interact to produce their psychotropic effects in the human brain. Besides THC, cannabidiol (CBD), is the largest non-psychoactive component of the plant and is relatively well-characterized both pharmacologically and in terms of its effects in the brain. More importantly, CBD has been shown to counteract many of the psychotropic, neuronal and molecular effects of THC. Accordingly, the strain of cannabis one is exposed to and its relative concentrations of THC vs. CBD, is of tremendous importance in determining psychiatric risk from cannabis exposure. For example, CBD not only mitigates many of the psychotropic and psychiatric side-effects of THC21-24, growing evidence suggests that CBD may serve as an effective anti-psychotic treatment.[25,26]

Not surprisingly, strains of cannabis with high levels of THC and relatively lower levels of CBD (e.g. sinsemilla), have been shown to be the most strongly associated with psychosis risk.[27] Research in our laboratory and others has identified the primary neurobiological mechanisms by which CBD produces its anti-psychotic effects; primarily, by counteracting dysregulation of the brain's dopamine (DA) pathway and normalizing DA activity states in the brain's mesolimbic pathway, the major brain circuit that is associated with schizophrenia-related psychoses.[23,24] In fact, CBD has been shown to acutely decrease the activity states of the brain's DA neurons and improve cognitive deficits associated with schizophrenia-like DA neuron dysregulation.[23,24] Interestingly, CBD also modulates several molecular signaling pathways in opposite directions to that of THC, demonstrating a remarkable opposing role for CBD in the etiology of THC's mental health-related side effects.

These critical distinctions between CBD and THC also have tremendous implications for public health policy concerning adolescent access to specific, high-potency strains of cannabis, and there is a clear need for evidence-based frameworks by which restrictions on sales of high-potency cannabis products to young adults should be implemented. In Canada, while there are Provincially determined age of access restrictions to the legal purchase and consumption of cannabis, policies concerning which specific products and/or potency levels should be regulated on the basis of age, are not clearly established. Thus, while there is clear neurobiological evidence for continued brain development into the mid-twenties,[28,29] the potential effects of exposure to high potency cannabis products beginning as late as 18 or 19 years of age are not understood and have been poorly studied. Nevertheless, there is a growing body of both clinical and pre-clinical research demonstrating profound alterations to normal neurodevelopmental trajectories following adolescent exposure to THC.

What Does THC do to the Developing Adolescent Brain?

Human epidemiological studies exploring the effects of adolescent cannabis exposure on later mental health trajectories are limited not only in terms of establishing causality, but also in terms of the identification of the precise brain mechanisms underlying these effects, particularly at the molecular and single-neuron levels of analysis. On the other hand, translating data from rodent studies to the human context can be challenging. For example, while adolescent cannabis use typically involves voluntary inhalation of smoked cannabis cigarettes, most rodent studies rely on systemic modes of THC administration such as intra-venous, oral of intra-peritoneal injections administered by the experimenter. Nevertheless, there is considerable congruence between clinical and pre-clinical studies that have empirically studied the neurodevelopmental and acute effects of cannabis on the brain.

As discussed previously, schizophrenia-related psychoses have been the most examined epidemiological correlate of adolescent cannabis exposure. Schizophrenia is a devastating neuropsychiatric disorder impacting ~ 1% of the global population. In industrialized countries such as Canada, rates of schizophrenia have been gradually increasing for several decades.[30,31] The symptom profile of schizophrenia is remarkably complex, making it difficult to treat and diagnose and also to model effectively in non-human experimental models. Nevertheless,

the core endophenotypes of schizophrenia are well-established and many of them can be successfully modelled in pre-clinical behavioural assays using rodents. For example, the 'positive' symptoms of schizophrenia include paranoia, hallucinations, anxiety and psychosis, all of which have been functionally linked to dysregulation of the brains mesocorticolimbic DA signaling system. Indeed, the only effective anti-psychotic medications currently available all target the brain's DA 'D2' receptor system by blocking its activation. Animal models using rodents have successfully modelled these effects of DA dysregulation by using pharmacological administration of drugs like amphetamine, which cause overactivation of the DA signaling pathway. In contrast, the 'negative' symptoms of schizophrenia involve symptoms such as social withdrawal, anhedonia, problems with filtering relevant cognitive information, emotional dysregulation, memory impairments and deficits in cognitive flexibility. Currently, there are few pharmacological treatment options that successfully target these emotional and cognitive symptoms of schizophrenia.

Rodent models of adolescent cannabis exposure have generally used chronic, escalating schedules of exposure to THC to mimic the effects of chronic cannabis use during critical periods of neurodevelopmental vulnerability. Results from these studies have been largely consistent with clinical human findings, demonstrating that exposure to THC during short windows of adolescent brain development can trigger a host of schizophrenia-like endophenotypes, including both positive and negative-like symptom clusters. For example, Renard et al.[32] reported that chronic THC exposure in rats during just 10 days of adolescent brain development induced increased anxiety, memory impairments, social withdrawal and significant deficits in cognitive filtering, lasting all the way to early adulthood. Remarkably, these effects were absent in experimental groups receiving THC during adulthood, underscoring the exquisite sensitivity of the adolescent brain to THC. Even more striking, rats exposed to THC during adolescence displayed a highly robust and persistent dysregulated state of their DA neurotransmitter system, consistent with human schizophrenia. In addition, examination of specific molecular biomarkers in the prefrontal cortical regions of these groups revealed several striking similarities to findings in human schizophrenia patients. For example, adolescent THC-exposed rats displayed massive downregulation in a signalling pathway called glycogen-synthase-kinase-3 (GSK-3), an effect that is also found in post-mortem samples of schizophrenia patient populations[33] and is linked to hyperactive signaling through the DA D2 receptor system.[34] Interestingly this same study reported strong downregulation of two other important molecular pathways, the mammalian target of rapamycin (mTOR) and p70-S-6-kinase, both of which are strongly decreased in major depression[35] , suggesting that psychiatric risk factors from long-term THC exposure may extend beyond schizophrenia-related symptoms to mood and anxiety disorders as well, as recently suggested in human clinical studies.[36]

Interestingly, pre-clinical rodent studies have also confirmed several clinical reports demonstrating that genetic biomarkers associated with the regulation of specific molecular pathways in the brain are strongly predictive of determining who is most likely to experience psychiatric side effects from adolescent cannabis use. For example, individuals who had genotypic abnormalities associated with regulation of protein kinase B (Akt), were at increased risk of neuropsychiatric symptoms following adolescent cannabis use.[37,38] Consistent with these studies, adolescent THC exposure in rodents was found to dramatically downregulate levels of Akt in the prefrontal cortex.[32] Similarly, genetic markers associated with the dopamine D2 receptor have been linked to THC-induced psychiatric risk factors,[39,40] consistent with pre-clinical findings showing strongly dysregulated DA transmission following adolescent or acute THC exposure.[32,41] These findings underscore the important point that certain genetic predispositions most likely need to be present to experience adolescent cannabis-induced psychopathology. The task for clinical and pre-clinical research is to more clearly elucidate what these biomarkers are and find appropriate prognostic tools that will allow us to identify which individuals might be at increased risk of neuropsychiatric disorders following adolescent cannabis use. In addition, determining how these genetic pre-dispositions might interact with environmental factors linked to cannabis use will provide further causal understanding of gene-environment interactions underlying adolescent cannabis use and the later development of neuropsychiatric disorders.

This brief overview of recent empirical findings demonstrating the neuropathological sequelae associated with adolescent cannabinoid exposure, highlights the ongoing progress being made in the field. However, an equally important consideration is how might these cannabinoid-induced neuropathological events be mitigated or even reversed following adolescent exposure? Can these broad molecular and neuronal adaptations be corrected or are we past the point of no return once the adolescent brain has been already exposed to high levels of THC?

Can we Reduce or Reverse the Impacts of Cannabis Exposure on the Developing Brain?

As discussed previously, given the ability of CBD to counteract many of THC's psychotropic and neurophysiological effects, one of the most important factors determining psychiatric risk from cannabis exposure relates to the potency of THC. Recently, alternative cannabis use formats such as vaping instruments and extracted, purified THC preparations such as 'shatter', have been reported to contain dramatically higher THC concentrations (e.g. ~70-95% THC in some preparations). These increasingly popular delivery formats typically contain THC in the absence of any CBD, meaning that the mitigating effects of CBD on THC-related psychotropic side-effects are completely absent. Accordingly, regulation of both the delivery formats of cannabinoids and limitations on THC concentrations will be critically important for reducing the risks of cannabis exposure during neurodevelopment, even among young people at legal age for cannabis consumption.

However, beyond the importance of THC content regulation in cannabis products, recent pre-clinical evidence has suggested that the effects of adolescent THC exposure on neuropsychiatric risk factors might be treatable and/or reversible, even after chronic exposure periods. Using a translational rodent model of adolescent THC exposure, our lab recently discovered that one of the major neuropathological effects of neurodevelopmental THC exposure involves a long-term loss of the inhibitory

neurotransmitter, γ-amino-butyric-acid (GABA), directly in the prefrontal cortex region of the brain.[42] Similar to many of the molecular adaptations following THC exposure discussed previously, this loss of GABA in the frontal cortex is one of the hallmark pathological features associated with schizophrenia.[43] Remarkably, we found that when GABA signals were restored in the frontal cortex, virtually all of the schizophrenia-like symptoms of adolescent THC exposure, including dysregulation of the DA system, was completely reversed. While it will be essential to replicate such findings in full-scale human trials, such pre-clinical data provides some compelling evidence that the long-term effects of adolescent cannabis exposure may be reversible, with appropriate pharmacological interventions.

Thus, basic neuroscience research into identifying the precise mechanisms underlying the neuropathological effects of adolescent THC exposure on the brain must be integrated with extensive clinical testing to more effectively devise methods of reducing cannabis-related risks to brain development.

Where do we go from here?

Moving forward, advancing our understanding of cannabis-related neurodevelopmental risk factors must include ongoing identification of specific biomarkers that may render specific individuals more or less susceptible to cannabis-related neurodevelopmental risks. To date, only a small handful of genetic susceptibility markers have been identified which seem to be related to a person's increased likelihood of suffering from cannabis-related psychiatric disorders. No doubt, complex psychiatric conditions such as depression, anxiety, schizophrenia and addiction are linked to a multitude of genetic susceptibility markers and it is therefore critical to round out our understanding of these specific genetic loci and the downstream molecular and neurochemical pathways they control. Beyond genetics, basic neuroscience research continues to characterize the specific effects of adolescent cannabinoid exposure on neurotransmitter pathways and neural circuits that are fundamentally altered by adolescent cannabinoid exposure. The identification of these biomarkers will allow for the development of potential interventions aimed at reversing neurodevelopmental damage induced by chronic cannabinoid exposure. More importantly, by identifying how the specific phytochemical constituents of cannabis (such as THC) are producing deleterious effects in at risk individuals, we will be better positioned to develop safer formulations, prognostic screens and delivery formats for cannabis that may mitigate many of these mental-health related risk factors.

References

1. Bossong MG, Niesink RJ (2010) Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. Prog Neurobiol. 92:370-85.
2. Chambers RA, Taylor JR, Potenza MN (2003) Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry. 160:1041-52.
3. Giedd JN, Blumenthal J, Jeffries NO, et al. (1999) Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 2:861-3.
4. Andersen SL (2003) Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci Biobehav Rev. 27:3-18.
5. Tsou K, Brown S, Sanudo-Pena MC, et al. (1998) Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 83:393-411.
6. Marsicano G, Lutz B (1999) Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 11:4213–4225.
7. Ahmad T, Sun N, Lyons D, et al. (2017) Bi-directional cannabinoid signalling in the basolateral amygdala controls rewarding and aversive emotional processing via functional regulation of the nucleus accumbens. Addict Biol. 22:1218-1231.
8. Draycott B, Loureiro M, Ahmad T, et al. (2014) Cannabinoid transmission in the prefrontal cortex bi-phasically controls emotional memory formation via functional interactions with the ventral tegmental area. J Neurosci. 34:13096-109.
9. Laviolette SR, Grace AA. (2006) Cannabinoids Potentiate Emotional Learning Plasticity in Neurons of the Medial Prefrontal Cortex through Basolateral Amygdala Inputs. J Neurosci. 26:6458-68.
10. Ahmad T, Lauzon NM, de Jaeger X, et al. (2013) Cannabinoid transmission in the prelimbic cortex bidirectionally controls opiate reward and aversion signaling through dissociable kappa versus μ-opiate receptor dependent mechanisms. J Neurosci. 33:15642-51.
11. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 35:764-74.
12. United Nations Children's Fund. Child well-being in rich countries. A comparative overview. Innocenti Report Card 11. Florence, Ital: United Nations Children's Fund; 2013.
13. Spithoff S, Kahan M (2014) Cannabis and Canadian youth: evidence, not ideology. Can Fam Physician. 60:785-7.
14. Centre for Addictions Research of BC. Cannabis use in British Columbia: patterns of use, perceptions, and public opinion as assessed in the 2004 Canadian addiction survey. Victoria, BC: Centre for Addictions Research of BC; 2006.
15. Andréasson S, Allebeck P, Engström A, et al. (1987) Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet. 2:1483-6.
16. Helle S, Ringen PA, Melle I, et al. (2016) Cannabis use is associated with 3 years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site sample (N=1119). Schizophr Res. 170:217-21.
17. Aas M, Melle I, Bettella F, et al. (2018) Psychotic patients who used cannabis frequently before illness onset have higher genetic predisposition to schizophrenia than those who did not. Psychol Med. 48:43-49.
18. Ringen PA, Nesvåg R, Helle S, Lagerberg TV, Lange EH, Løberg EM, Agartz I, Andreassen OA, Melle I. (2016) Premorbid cannabis use is associated with more symptoms and poorer functioning in schizophrenia spectrum disorder. Psychol Med. 46:3127-3136.
19. Boydell J, van Os J, Caspi A, et al. (2006) Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol Med. 36:1441-6.
20. Gobbi G, Atkin T, Zytynski T, et al. (2019) Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. JAMA Psychiatry. Feb 13. doi: 10.1001/jamapsychiatry.2018.4500. [Epub ahead of print]
21. Englund A, Morrison PD, Nottage J, et al. (2013) Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 27:19-27.
22. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 35:764-74.
23. Norris C, Loureiro M, Kramar C, et al. (2016) Cannabidiol Modulates Fear Memory Formation Through Interactions with Serotonergic Transmission in the Mesolimbic System. Neuropsychopharmacology. 41:2839-2850.

24. Renard J, Loureiro M, Rosen LG, et al. (2016) Cannabidiol Counteracts Amphetamine-Induced Neuronal and Behavioral Sensitization of the Mesolimbic Dopamine Pathway through a Novel mTOR/p70S6 Kinase Signaling Pathway. J Neurosci. 36:5160-9.
25. Leweke FM, Piomelli D, Pahlisch F, et al. (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2:e94.
26. Leweke FM, Mueller JK, Lange B, et al. (2016) Therapeutic Potential of Cannabinoids in Psychosis. Biol Psychiatry. 79:604-12.
27. Di Forti M, Marconi A, Carra E, et al. (2015) Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry. 2:233-8.
28. Ben Bashat D, Ben Sira L, Graif M, et al. (2005) Normal white matter development from infancy to adulthood: comparing diffusion tensor and high b value diffusion weighted MR images. J Magn Reson Imaging 21:503–511.
29. Lebel C, Beaulieu C (2011) Longitudinal Development of Human Brain Wiring Continues from Childhood into Adulthood. J Neurosci 31:10937-10947.
30. Dealberto MJ. (2013) Are the rates of schizophrenia unusually high in Canada? A comparison of Canadian and international data. Psychiatry Res. 209:259-65.
31. Bray I, Waraich P, Jones W, et al. (2006) Increase in schizophrenia incidence rates: findings in a Canadian cohort born 1975-1985. Soc Psychiatry Psychiatr Epidemiol. 2006 41:611-8.
32. Renard J, Rosen LG, Loureiro M, et al. (2017) Adolescent Cannabinoid Exposure Induces a Persistent Sub-Cortical Hyper-Dopaminergic State and Associated Molecular Adaptations in the Prefrontal Cortex. Cereb Cortex. 27:1297-1310.
33. Kozlovsky N, Belmaker RH, Agam G. (2001) Low GSK-3 activity in frontal cortex of schizophrenic patients. Schizophr Res. 52:101-105.
34. Sutton LP, Rushlow WJ. 2012. The dopamine D2 receptor regulates Akt and GSK-3 via Dvl-3. Int J Neuropsychopharmacol 15:965–979.
35. Jernigan CS, Goswami DB, Austin MC, et al. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 35:1774–1779.
36. Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. Journal of Affective Disorders. 2018 April 6; [Epub ahead of print].
37. Colizzi M, Iyegbe C, Powell J, et al. (2015) Interaction between DRD2 and AKT1 genetic variations on risk of psychosis in cannabis users: a case-control study. NPJ Schizophr. 1:15025.
38. Di Forti M, Iyegbe C, Sallis H, Kolliakou A, et al. (2012) Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biol Psychiatry. 72:811-6.
39. Colizzi M, Iyegbe C, Powell J, et al. (2015) Interaction Between Functional Genetic Variation of DRD2 and Cannabis Use on Risk of Psychosis. Schizophr Bull. 41:1171-82.
40. Kuepper R, Morrison PD, van Os J, et al. (2010) Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. Schizophr Res. 121:107-17.
41. Fitoussi A, Zunder J, Tan H, et al. (2018) Delta-9-tetrahydrocannabinol potentiates fear memory salience through functional modulation of mesolimbic dopaminergic activity states. Eur J Neurosci. 47:1385-1400.
42. Renard J, Szkudlarek HJ, Kramar CP, et al. (2017) Adolescent THC Exposure Causes Enduring Prefrontal Cortical Disruption of GABAergic Inhibition and Dysregulation of Sub-Cortical Dopamine Function. Sci Rep. 7:11420.
43. Lewis DA, Curley AA, Glausier JR, et al. (2012) Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35:57-67.