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Developmental exposure to cannabis compromises dopamine system function and behavior

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With the expanding legalization and decriminalization, cannabis price has decreased, and its use increased along with the content of its main ingredient, THC. Although prevalence rates for its consumption during adolescence appear unchanged, the use of more potent cannabis and the availability of powerful synthetic cannabinoids have enhanced the health risks associated with its use. The prevalence of cannabis consumption during pregnancy has also risen because of its availability/acceptability and the misconception that cannabis is safe. Evidence shows that cannabis use during development is associated with cognitive deficits and increased risks of mental illnesses. Particularly, exposure to cannabis *in utero* or during adolescence derails the normal development of the dopamine system and produces aberrant behaviors. In this review, we discuss the long-term impact of THC exposure during development on behaviors related to mesolimbic dopamine system function, and we highlight areas of research that deserve more investigation in the future.

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Introduction

Prevalence rates of mental illness have increased over the years, with the peak age of onset being decreased and up to 35% of psychiatric disorders being diagnosed before the age of 14 years [1]. The interplay between biological and environmental factors may contribute to this alarming rise of mental illness in children and adolescents. Particularly, as conceptualized in the theory of developmental origins of health and disease [2], the interaction between inherited predispositions and insults from the environment derail the normal maturation of brain circuits leading to long-lasting psychiatric vulnerability. Therefore, preventive and early intervention strategies in children, adolescents, and women at childbearing age may be key in reducing the burden of mental disorders.

A large body of research suggests that cannabis exposure is likely one of the environmental factors that significantly compromise neurodevelopment. Notably, changes in sociopolitical attitudes toward cannabis have led to its legalization and decriminalization in several countries. This is associated with a reduction of the stigma about cannabis use and the misperception that, being natural, cannabis is safe [3] and does not produce persistent adverse effects on the brain. Importantly, while the use of alcohol and tobacco during pregnancy has decreased, largely due to the increased public awareness of their negative consequences on the fetus, cannabis use has increased over the past decade [4,5]. Accordingly, cannabis is sometimes considered a therapeutic option for pregnant women to alleviate nausea or anxiety that often characterize this period [6,7]. One might, therefore, speculate that cannabis use in adolescents and women at childbearing ages might contribute to the increases in the prevalence of mental disorders.

Both psychotropic and detrimental effects of cannabis vary among individuals, and, within the same subject, they may differ depending on the fluctuations of hormonal and endocannabinoid states [8–10]. In addition, extensive clinical research underscores that certain developmental stages, such as adolescence, are time windows of high susceptibility to cannabis adverse effects on brain function and behavior [11–13]. For example, cannabis use by adolescents results in persistent alterations in the functioning of neuromodulatory systems, thereby contributing to an increased risk of developing mental disorders at some point during their lifetime [14]. Particularly, there is clear evidence that adolescent cannabis use is associated with a greater risk of schizophrenia [15] and that this risk is proportional to THC concentrations [16].

Dopamine plays a pivotal role in the regulation of numerous behavioral processes such as attention,

aggressiveness, reward-motivated behaviors, cognition, and mood. During neurodevelopment, dopamine participates in a wide range of processes, especially those related to the differentiation and maturation of forebrain structures [17,18]. Importantly, the dopamine system strongly interacts with the endogenous cannabinoid system in the basal ganglia in both physiological and pathological conditions [19]. Therefore, studying the impact of prenatal and adolescent exposure to cannabis on these systems is critical to understanding how these insults can increase the vulnerability to developing psychiatric disorders.

The aim of this review is to discuss how cannabis use may alter the developmental trajectory of the dopamine system, thereby contributing to the early onset of neuropsychiatric disorders in life (i.e. differential susceptibility). We also explore how cannabis exposure, by interfering with endocannabinoid regulation of dopamine signaling, might promote maladaptive behaviors and influence individual vulnerability to different psychopathological conditions, from infancy to adulthood.

Dopamine and endocannabinoid interaction during neurodevelopment: it takes two to tango

Dopamine and endocannabinoids are ancient evolutionary conserved signaling molecules serving as fundamental and basic regulators of physiological functions and needs [20] already operating at early stages of mammalian development [21,22]. A detailed description of their composition and regulation is beyond the scope of this review and could be found elsewhere [23,24]. Dopamine neurons are highly heterogeneous based on the expression of their specific molecular markers, wiring patterns, and functions [23]. Different programs instruct the time-specific development of dopamine neuron diversity in terms of their anatomical location, projection area, electrophysiological properties, and molecular profiles [23]. Thus, environmental stimuli and experiences may alter dopamine developmental trajectories (e.g. mesocorticolimbic pathway across adolescence) [18,25], thereby producing inappropriate wiring and functional consequences later in life.

Endocannabinoids are involved in developmental processes, spanning from fate determination to axonal pathfinding and the establishment of appropriate connectivity, and they continue to influence neurodevelopment throughout adolescence [21,22,24]. Of note, the endocannabinoid system exhibits sexual dimorphism mirroring bidirectional interactions between these lipids and gonadal hormones [26], which could contribute to the increased male vulnerability to neuropsychiatric disorders [27]. Endocannabinoid levels are abundant in the midbrain, where they regulate dopamine cell activity in homo- or heterosynaptic fashions [28], and contribute to the rewarding/teaching signal encoded by these neurons [29]. Of note, our current knowledge on endocannabinoid actions on dopamine cell activity and plasticity might be biased by the evidence mainly collected in males (but see Ref. [30]). Importantly, whereas sex hormones transiently regulate the density of type 1 cannabinoid receptors (CB1R) in many brain regions, no sex dichotomy is found in CB1R expression and function in the ventral tegmental area (VTA) [31]. Metaplastic changes in the molecular architecture of the endocannabinoid system at inhibitory synapses on dopamine cells already take place before puberty onset in rodent models of neuropsychiatric disorders [20,32], thus suggesting that the interactions between these two systems during development can produce complex consequences requiring further mechanistic studies.

Prenatal cannabis exposure and impairments of dopamine system functions

Several longitudinal studies in humans demonstrate that prenatal cannabis exposure (PCE) is a predictive risk factor for adverse outcomes [33,34], such as attention/impulsivity deficits, psychotic-like experiences, and/or externalizing/internalizing traits. A general consensus exists about the long-term detrimental effects of PCE on the progeny, although some authors question the relevance of cognitive effects on overall mental well-being [35]. Importantly, the data on which Torres and colleagues drew their conclusions [35] are likely influenced by the inherent variability of human studies, including genetic, cultural, economic, environmental, and drug-related factors (e.g. mild vs heavy consumption). In addition, one could argue [36,37] that the lack of evidence for an association between PCE and cognitive deficits should not be considered evidence of the absence of deleterious PCE effects, and, therefore, it cannot the be used to support the notion that cannabis use is safe during pregnancy. Finally, the clinical significance of PCE individuals displaying minor cognitive deficits might result in major health problems and societal burden when the population exposed to prenatal cannabis is large.

PCE animal models have complemented epidemiological studies and provided insights into potential underpinnings and the range of aberrant offspring outcomes following different types of PCE [38]. In addition, preclinical studies have provided evidence for sex differences in physiology and behavior throughout development and across the lifespan [21]. Different experimental PCE designs have also helped evaluate the effects of the timing of exposure in the animal model and the comparable time in humans. In fact, in rodents, the human equivalent of the first trimester — in terms of brain development — extends until the end of the second embryonic week, while the third-trimester

equivalent occurs during the first postnatal week [39]. Hence, specific PCE experimental designs can allow distinguishing the effects of perturbing endocannabinoid signaling during these discrete developmental stages.

Different animal models have consistently demonstrated the negative and long-lasting impact of PCE on the dopamine system. Aberrant dopamine signaling and dysregulation of cortical functions might explain many of the effects observed in human studies. In the VTA, PCE-dependent alterations in excitation-to-inhibition balance, dopamine neuronal activity, and dopamine D2 receptor sensitivity have been described along with changes in expression of the genes encoding these receptors in the target regions [40–42]. These findings might help explain the deficits in cognition, attention, and impulsivity observed in the progeny of mothers who consumed cannabis during pregnancy [33,34]. Perinatal exposure to THC or other cannabinoid agonists has also been associated with detrimental changes in plasticity, excitability, and function in target regions such as the prefrontal cortex (PFC) [43,44]. In addition, PCE produces alterations in synaptic plasticity and in gene transcription and epigenetic regulation in another dopamine target region that is the nucleus accumbens, which can underpin its lasting effects on behavior [40]. Importantly, PCE impact is often limited to the male progeny: only PCE males exhibit increased sensitivity and motivation for natural rewards, altered stress reactivity, and a decreased hedonic state in adulthood. Hurd and colleagues [45] have shown that the upregulation of Kmt2a mRNA levels associated with a decreased hedonic state and increased stress reactivity partially overlap with those obtained in patients diagnosed with major depressive disorder. This study suggests that PCE can produce effects such as repressive transcriptional processes within the striatum that may predispose to major depression. Other preclinical evidence corroborates this study and shows that PCE induces sex-dependent behavioral and neurobiological deficits in the offspring [41]. In particular, male offspring appear particularly sensitive to the harmful effects of PCE, whereas females do not significantly differ from controls in behavior and/or in cellular and synaptic function. Although the underlying mechanisms 'protecting' females from PCE detrimental effects remain elusive, this sex specificity aligns with other preclinical studies showing that female sex may be a protective factor against intrauterine environmental insults and, therefore, against neuropsychiatric disorders of developmental origin [46]. Importantly, gender differences in the deleterious effects of PCE have also been shown in humans [47,48]. Particularly, a recent linkage-cohort study involving more than 200 000 mother–offspring pairs has shown that PCE increases the risks of autism spectrum disorder, with this effect being stronger in the male progeny [48].

Adolescent cannabis exposure and impairments of dopamine system functions and behaviors

Adolescence is a period during which several structural and functional changes occur in the brain and, consequently, is a time window of high vulnerability to cannabis actions. For example, a study comparing adolescents (18–20 years old) and adults (30–40 years old), who were not frequent cannabis users, found that behavioral and cognitive effects of oral cannabis, but not the intoxicating effects, were more pronounced in adolescents compared to adults [49]. In addition, cannabis use during adolescence has long been associated with long-lasting impairments in a broad spectrum of cognitive and executive functions (e.g. sustained attention, working memory, problem-solving, and decision-making), and its use early in adolescence escalates the risk of developing diverse severe mental disorders (e.g. depression and psychosis) as well as cannabis use disorder (CUD) [14].

Animal models have helped shed light on the mechanisms underlying the effects of adolescent cannabis exposure on brain and behavior [50]. This has led to the discovery of the important role played by the endogenous cannabinoid system during brain maturation [21] and to the evidence that exogenous cannabinoids such as THC interfere with the endogenous cannabinoid system and contribute to derail neurotransmitter signaling, including the dopamine system [51,52]. In particular, both systems exhibit spatially and temporally dynamic changes throughout development, especially during the transition from adolescence to adulthood. This might help explain the heightened susceptibility of the adolescent brain to insults ('hits') such as exposure to cannabis [21]. Among the brain regions undergoing major refinement during adolescence, the PFC is pivotal for modulating higher cognitive abilities, emotional processes, social skills, and adaptive behaviors [53]. Because both dopamine and endocannabinoid systems actively participate in PFC functional maturation [54], it is expected that any interference with this signaling might result in psychopathological phenotypes later in life. In fact, in rodents, adolescent exposure to cannabinoids disinhibits PFC network function [55] with consequent hyperactivity of subcortical dopaminergic activity accompanying a range of cognitive and affective phenotypes resembling those observed in psychiatric diseases, such as schizophrenia [56]. These effects are associated with changes in subcortical regions, namely a hyperdopaminergic activity within the VTA, where dopamine neurons originate [56].

Alongside the emergence of psychotic episodes [57,58], clinical studies also strongly indicate the association between chronic or acute high-dose consumption of cannabis derivatives during adolescence and the development of adverse psychosocial outcomes (e.g. major depression, suicidal ideation, and aggression), as well as

IQ scores and cognitive function [59,60]. In addition, cannabis use during adolescence is associated with an increased risk of developing addiction to cannabis itself and most drugs of abuse [61,62]. Of note, mental health outcomes have been shown to deteriorate in the US and Canada with cannabis legalization [63,64]. Preclinical studies have confirmed these negative effects of exposure to cannabis during adolescence on emotionality, cognition, and risks of addiction and have helped elucidate the underlying neurobiological mechanisms [61,62,65]. Recently, a translational study has provided important new insights into the neurobiological and behavioral consequences of adolescent cannabis exposure [66]. Ferland and coworkers found that exposure to high dose of THC during adolescence produced long-lasting similar deficits in decision-making, which were finely analyzed by computational modeling techniques, in both the rat and human version of the Iowa Gambling Task. Notably, THC produced long-lasting impairments in decision-making, impulse control, and cognitive responses that were attributed to cell-specific and laminar-specific alterations in type 1 cannabinoid (CB1) receptor density, astrocyte transcripts, and morphology within the PFC–basolateral amygdala circuit [66]. Not only this type of translational study might provide critical information about cannabis-induced behavioral and neurobiological dysfunctions but also insights into potential therapeutic strategies.

Concluding remarks and future directions

Cannabis use has deleterious effects on brain development that may increase future risks of developing mental illnesses. While the results from an analysis of the literature appear consistent, several aspects deserve further investigation and, therefore, considered for future research.

An important neglected aspect in preclinical studies is the effect of cannabis exposure on sleep. Although sleep is key for neurodevelopment and mental health [67], and human studies demonstrate an association between cannabis use during adolescence and poor sleep outcomes [68], animal studies are surprisingly lacking. Dopamine neurons, especially those originating within the VTA, have been shown to be involved in sleep regulation [69], with their malfunction being associated with and predictive of future mental illness [70]. Hence, one might speculate that PCE by disturbing sleep in a long-lasting manner [46] may as well contribute to increasing the risk of mental illnesses [71].

While several longitudinal studies have provided critical information about the effects of both prenatal and adolescent exposure to cannabis, a better identification of the dynamic interplay between the exposure to cannabis and social determinants of health is needed. Detailed information, and possibly toxicological measures of the frequency of cannabis use by adolescents, will be critical to better quantify and interpret the specific effects of cannabis exposure.

Preclinical studies investigating and comparing the effects of different routes of cannabis administration are also warranted to deepen our understanding on manifestations of cannabinoid-mediated effects during adolescence and on pregnancy outcomes. Importantly, cannabis is mostly smoked or ingested by humans, and more preclinical investigations are required to qualitatively and quantitatively determine the effects of these routes of administration on developmental and behavioral trajectories on these segments of population (i.e. adolescents and PCE progeny). The development of new models to allow studying the specific consequence of cannabis administration by these routes [72] and [73] is critical to address these questions.

Notably and worrisomely, THC concentrations in cannabis derivatives have steadily risen over the past few decades, thus increasing the likelihood of fetal exposure to higher doses of THC and of more marked detrimental effects on the progeny. This concern extends to animal studies investigating the effects of different doses of cannabis during adolescence to determine the specific risks associated with these uses. Additionally, preclinical studies should inform about the effects of cannabidiol, another major phytocannabinoid marketed as a dietary supplement and apparently devoid of psychotropic actions. This is relevant since cannabidiol could also contribute to neurodevelopmental sequelae of cannabis use, and it is considered for use during pregnancy. In this regard, the first toxicological preclinical studies show sex-specific detrimental effects at early developmental ages, which might be predictive of adult psychopathology [74]. Given the popularity of synthetic cannabinoids ('spice drugs'), which are often more potent than natural cannabinoids, animal models should also be developed to investigate on the effects of these novel psychoactive substances.

Lastly, more translational studies [45,66], investigating human and rodent behavior with similar behavioral tasks aided by computational modeling, are needed to decipher molecular mechanisms underlying the long-lasting deleterious effects of cannabis during vulnerable neurodevelopmental periods. Collectively, this knowledge will be critical to inform the general public, health providers, and decision-makers of the risks associated with cannabis exposure during developmental periods of vulnerability to help reduce the risks of developing mental health problems.

Declaration of Competing Interest

Dr. Solinas and I declare no conflict of interest.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest.

1. •• Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, Il Shin J, Kirkbride JB, Jones P, Kim JH, *et al.*: **Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies**. *Mol Psychiatry* 2022, **27**:281-295.
This meta-analysis clearly shows that the prevalence of mental disorders has increased, while the age of onset has decreased in the last few decades. These alarming rates are likely due to environmental and life changes, and cannabis use may be one of the contributing factors.

2. Mandy M, Nyirenda M: **Developmental Origins of Health and Disease: the relevance to developing nations**. *Int Health* 2018, **10**:66-70.

3. Chambers J, Keyhani S, Ling PM, Hoggatt KJ, Hasin D, Nguyen N, Woods A, Ryder A, Cohen BE: **Perceptions of safety of daily cannabis vs tobacco smoking and secondhand smoke exposure, 2017-2021**. *JAMA Netw Open* 2023, **6**:e2328691.

4. Agrawal A, Grucza RA, Rogers CE: **Public health implications of rising marijuana use in pregnancy in an age of increasing legalization — reply**. *JAMA Pediatr* 2019, **173**:95-96.

5. Hayes S, Delker E, Bandoli G: **The prevalence of cannabis use reported among pregnant individuals in the United States is increasing, 2002-2020**. *J Perinatol* 2023, **43**:387-389.

6. O'Connor M: **Medicinal cannabis in pregnancy — panacea or noxious weed?** *J Law Med* 2018, **25**:634-646.

7. Volkow ND, Compton WM, Wargo EM: **The risks of marijuana use during pregnancy**. *JAMA* 2017, **317**:129-130.

8. Meyer HC, Lee FS, Gee DG: **The role of the endocannabinoid system and genetic variation in adolescent brain development**. *Neuropsychopharmacology* 2018, **43**:21-33.

9. Dow-Edwards D, Silva L: **Endocannabinoids in brain plasticity: cortical maturation, HPA axis function and behavior**. *Brain Res* 2017, **1654**:157-164.

10. Gee DG, Fetcho RN, Jing D, Li A, Glatt CE, Drysdale AT, Cohen AO, Dellarco DV, Yang RR, Dale AM, *et al.*: **Individual differences in frontolimbic circuitry and anxiety emerge with adolescent changes in endocannabinoid signaling across species**. *Proc Natl Acad Sci USA* 2016, **113**:4500-4505.

11. Dahl RE: **Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address**. *Ann N Y Acad Sci* 2004, **1021**:1-22.

12. Fuhrmann D, Knoll LJ, Blakemore SJ: **Adolescence as a sensitive period of brain development**. *Trends Cogn Sci* 2015, **19**:558-566.

13. Yang S, Tseng KY: **Maturation of corticolimbic functional connectivity during sensitive periods of brain development**. *Curr Top Behav Neurosci* 2022, **53**:37-53.

14. •• Ferland JN, Hurd YL: **Deconstructing the neurobiology of cannabis use disorder**. *Nat Neurosci* 2020, **23**:600-610.
This review clearly summarizes the neurobiological mechanisms involved in CUD.

15. Tandon R, Nasrallah H, Akbarian S, Carpenter WT Jr., DeLisi LE, Gaebel W, Green MF, Gur RE, Heckers S, Kane JM, *et al.*: **The schizophrenia syndrome, circa 2024: what we know and how that informs its nature**. *Schizophr Res* 2024, **264**:1-28.

16. Murray RM, Hall W: **Will legalization and commercialization of cannabis use increase the incidence and prevalence of psychosis?** *JAMA Psychiatry* 2020, **77**:777-778.

17. Vosberg DE, Leyton M, Flores C: **The Netrin-1/DCC guidance system: dopamine pathway maturation and psychiatric disorders emerging in adolescence**. *Mol Psychiatry* 2020, **25**:297-307.

18. Reynolds LM, Flores C: **Mesocorticolimbic dopamine pathways across adolescence: diversity in development**. *Front Neural Circuits* 2021, **15**:735625.

19. Garcia C, Palomo-Garo C, Gomez-Galvez Y, Fernandez-Ruiz J: **Cannabinoid-dopamine interactions in the physiology and physiopathology of the basal ganglia**. *Br J Pharmacol* 2016, **173**:2069-2079.

20. Sagheddu C, Muntoni AL, Pistis M, Melis M: **Endocannabinoid signaling in motivation, reward, and addiction: influences on mesocorticolimbic dopamine function**. *Int Rev Neurobiol* 2015, **125**:257-302.

21. •• Bara A, Ferland JN, Rompala G, Szutorisz H, Hurd YL: **Cannabis and synaptic reprogramming of the developing brain**. *Nat Rev Neurosci* 2021, **22**:423-438.
This review summarizes the state-of-the-art knowledge about neurobiological underpinnings for the negative long-lasting effects of cannabis.

22. Peters KZ, Naneix F: **The role of dopamine and endocannabinoid systems in prefrontal cortex development: adolescence as a critical period**. *Front Neural Circuits* 2022, **16**:939235.

23. Garritsen O, van Battum EY, Grossouw LM, Pasterkamp RJ: **Development, wiring and function of dopamine neuron subtypes**. *Nat Rev Neurosci* 2023, **24**:134-152.

24. Harkany T, Cinquina V: **Physiological rules of endocannabinoid action during fetal and neonatal brain development**. *Cannabis Cannabinoid Res* 2021, **6**:381-388.

25. Larsen B, Luna B: **Adolescence as a neurobiological critical period for the development of higher-order cognition**. *Neurosci Biobehav Rev* 2018, **94**:179-195.

26. Simone JJ, Green MR, McCormick CM: **Endocannabinoid system contributions to sex-specific adolescent neurodevelopment**. *Prog Neuropsychopharmacol Biol Psychiatry* 2022, **113**:110438.

27. McCarthy MM: **Sex differences in the developing brain as a source of inherent risk**. *Dialogues Clin Neurosci* 2016, **18**:361-372.

28. Melis M, Pistis M: **Hub and switches: endocannabinoid signalling in midbrain dopamine neurons**. *Philos Trans R Soc Lond B Biol Sci* 2012, **367**:3276-3285.

29. Lujan MA, Covey DP, Young-Morrison R, Zhang L, Kim A, Morgado F, Patel S, Bass CE, Paladini C, Cheer JF: **Mobilization of endocannabinoids by midbrain dopamine neurons is required for the encoding of reward prediction**. *Nat Commun* 2023, **14**:7545.

30. Melis M, De Felice M, Lecca S, Fattore L, Pistis M: **Sex-specific tonic 2-arachidonoylglycerol signaling at inhibitory inputs onto dopamine neurons of Lister Hooded rats**. *Front Integr Neurosci* 2013, **7**:93.

31. Castelli MP, Fadda P, Casu A, Spano MS, Casti A, Fratta W, Fattore L: **Male and female rats differ in brain cannabinoid CB1 receptor density and function and in behavioural traits predisposing to drug addiction: effect of ovarian hormones**. *Curr Pharm Des* 2013,.

32. Serra V, Aroni S, Bortolato M, Frau R, Melis M: **Endocannabinoid-dependent decrease of GABAergic transmission on dopaminergic neurons is associated with susceptibility to**

cocaine stimulant effects in pre-adolescent male MAOA hypomorphic mice exposed to early life stress. *Neuropharmacology* 2023, **233**:109548.

33. Corsi DJ, Donelle J, Sucha E, Hawken S, Hsu H, El-Chaar D, Bisnaire L, Fell D, Wen SW, Walker M: **Maternal cannabis use in pregnancy and child neurodevelopmental outcomes**. *Nat Med* 2020, **26**:1536-1540.

34. Solmi M, De Toffol M, Kim JY, Choi MJ, Stubbs B, Thompson T, Firth J, Miola A, Croatto G, Baggio F, *et al.*: **Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies**. *BMJ* 2023, **382**:e072348.

35. Torres CA, Medina-Kirchner C, O'Malley KY, Hart CL: **Totality of the evidence suggests prenatal cannabis exposure does not lead to cognitive impairments: a systematic and critical review**. *Front Psychol* 2020, **11**:816.

36. Chaput KH, Lebel C, McMorris CA: **Commentary: totality of the evidence suggests prenatal cannabis exposure does not lead to cognitive impairments: a systematic and critical review**. *Front Psychol* 2020, **11**:1891.

37. Testai FD, Gorelick PB, Aparicio HJ, Filbey FM, Gonzalez R, Gottesman RF, Melis M, Piano MR, Rubino T, Song SY, *et al.*: **Use of marijuana: effect on brain health: a scientific statement from the American Heart Association**. *Stroke* 2022, **53**:e176-e187.

38. Mackie K: **Preclinical models of neruodevelopmental cannabinoid exposure**. In: *Cannabis and the Developing Brain*. Edited by Melis M, Manzoni O. vol Chapter 1, Academic Press; 2022:1-11.

39. Clancy B, Darlington RB, Finlay BL: **Translating developmental time across mammalian species**. *Neuroscience* 2001, **105**:7-17.

40. DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P, Dow-Edwards D, Hurd YL: **Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring**. *Biol Psychiatry* 2011, **70**:763-769.

41. Hurd YL, Manzoni OJ, Pletnikov MV, Lee FS, Bhattacharyya S, Melis M: **Cannabis and the developing brain: insights into its long-lasting effects**. *J Neurosci* 2019, **39**:8250-8258.

42. • Frau R, Miczán V, Traccis F, Aroni S, Pongor CI, Saba P, Serra V, Sagheddu C, Fanni S, Congiu M, *et al.*: **Prenatal THC produces a hyperdopaminergic phenotype rescued by pregnenolone**. *Nat Neurosci* 2019, **22**:11.
This study is the first one describing how maternal exposure to THC alters mesolimbic dopamine system function, thereby leading to an at-risk phenotype for psychosis, which can be reverted by pregnenolone.

43. Bara A, Manduca A, Bernabeu A, Borsoi M, Serviado M, Lassalle O, Murphy MN, Wager-Miller J, Mackie K, Pelissier-Alicot AL, *et al.*: **Sex-dependent effects of in utero cannabinoid exposure on cortical function**. *Elife* 2018, **7**.

44. Scheyer AF, Borsoi M, Pelissier-Alicot AL, Manzoni OJJ: **Perinatal THC exposure via lactation induces lasting alterations to social behavior and prefrontal cortex function in rats at adulthood**. *Neuropsychopharmacology* 2020, **45**:1826-1833.

45. Ellis RJ, Bara A, Vargas CA, Frick AL, Loh E, Landry J, Uzamere TO, Callens JE, Martin Q, Rajarajan P, *et al.*: **Prenatal delta(9)-tetrahydrocannabinol exposure in males leads to motivational disturbances related to striatal epigenetic dysregulation**. *Biol Psychiatry* 2022, **92**:127-138.

46. Nashed MG, Hardy DB, Laviolette SR: **Prenatal cannabinoid exposure: emerging evidence of physiological and neuropsychiatric abnormalities**. *Front Psychiatry* 2020, **11**:624275.

47. Traccis F, Frau R, Melis M: **Gender differences in the outcome of offspring prenatally exposed to drugs of abuse**. *Front Behav Neurosci* 2020, **14**:72.

48. Tadesse AW, Ayano G, Dachew BA, Betts K, Alati R: **Exposure to maternal cannabis use disorder and risk of autism spectrum disorder in offspring: a data linkage cohort study**. *Psychiatry Res* 2024, **337**:115971.

49. Murray CH, Huang Z, Lee R, de Wit H: **Adolescents are more sensitive than adults to acute behavioral and cognitive effects of THC**. *Neuropsychopharmacology* 2022, **47**:1331-1338.

50. Peters KZ, Cheer JF, Tonini R: **Modulating the neuromodulators: dopamine, serotonin, and the endocannabinoid system**. *Trends Neurosci* 2021, **44**:464-477.

51. Melis M, Pistis P: **Endocannabinoid signaling in midbrain dopamine neurons: more than physiology?** *Curr Neuropharmacol* 2007, **5**:268-277.

52. Ellgren M, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, Devi LA, Hurd YL: **Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects**. *Eur Neuropsychopharmacol* 2008, **18**:826-834.

53. Friedman NP, Robbins TW: **The role of prefrontal cortex in cognitive control and executive function**. *Neuropsychopharmacology* 2022, **47**:72-89.

54. Bernabeu A, Bara A, Murphy Green MN, Manduca A, Wager-Miller J, Borsoi M, Lassalle O, Pelissier-Alicot AL, Chavis P, Mackie K, *et al.*: **Sexually dimorphic adolescent trajectories of prefrontal endocannabinoid synaptic plasticity equalize in adulthood, reflected by endocannabinoid system gene expression**. *Cannabis Cannabinoid Res* 2023, **8**:749-767.

55. Miller ML, Chadwick B, Dickstein DL, Purushothaman I, Egervari G, Rahman T, Tessereau C, Hof PR, Roussos P, Shen L, *et al.*: **Adolescent exposure to Delta(9)-tetrahydrocannabinol alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons**. *Mol Psychiatry* 2019, **24**:588-600.

56. Renard J, Rushlow WJ, Laviolette SR: **Effects of adolescent THC exposure on the prefrontal GABAergic system: implications for schizophrenia-related psychopathology**. *Front Psychiatry* 2018, **9**:281.

57. Hjorthoj C, Compton W, Starzer M, Nordholm D, Einstein E, Erlangsen A, Nordentoft M, Volkow ND, Han B: **Association between cannabis use disorder and schizophrenia stronger in young males than in females**. *Psychol Med* 2023, **53**:7322-7328.

58. Ganesh S, D'Souza DC: **Cannabis and psychosis: recent epidemiological findings continuing the "causality debate"**. *Am J Psychiatry* 2022, **179**:8-10.

59. Sultan RS, Zhang AW, Olfson M, Kwizera MH, Levin FR: **Nondisordered cannabis use among US adolescents**. *JAMA Netw Open* 2023, **6**:e2311294.

60. Camchong J, Lim KO, Kumra S: **Adverse effects of cannabis on adolescent brain development: a longitudinal study**. *Cereb Cortex* 2017, **27**:1922-1930.

61. Realini N, Rubino T, Parolaro D: **Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids**. *Pharmacol Res* 2009, **60**:132-138.

62. Stringfield SJ, Torregrossa MM: **Disentangling the lasting effects of adolescent cannabinoid exposure**. *Prog Neuropsychopharmacol Biol Psychiatry* 2021, **104**:110067.

63. Reece AS, Hulse GK: **Co-occurrence across time and space of drug- and cannabinoid- exposure and adverse mental health outcomes in the National Survey of Drug Use and Health: combined geotemporospatial and causal inference analysis**. *BMC Public Health* 2020, **20**:1655.

64. Hall W, Stjepanovic D, Dawson D, Leung J: **The implementation and public health impacts of cannabis legalization in Canada: a systematic review**. *Addiction* 2023, **118**:2062-2072.

65. Zuo Y, Iemolo A, Montilla-Perez P, Li HR, Yang X, Telese F: **Chronic adolescent exposure to cannabis in mice leads to sex-biased changes in gene expression networks across brain regions**. *Neuropsychopharmacology* 2022, **47**:2071-2080.

66. •• Ferland JN, Ellis RJ, Betts G, Silveira MM, de Firmino JB, Winstanley CA, Hurd YL: **Long-term outcomes of adolescent THC exposure on translational cognitive measures in adulthood in an animal model and computational assessment of human data**. *JAMA Psychiatry* 2023, **80**:66-76.

This article is an exceptional example of how combining preclinical and clinical models with modern computational approaches can provide deep insights into the underlying mechanisms accounting for the negative effects of adolescent exposure to cannabis.

67. Tarokh L, Saletin JM, Carskadon MA: **Sleep in adolescence: physiology, cognition and mental health**. *Neurosci Biobehav Rev* 2016, **70**:182-188.

68. Tuvel AL, Winiger EA, Ross JM: **A review of the effects of adolescent cannabis use on physical health**. *Psychiatr Clin North Am* 2023, **46**:719-739.

69. Monti JM, Monti D: **The involvement of dopamine in the modulation of sleep and waking**. *Sleep Med Rev* 2007, **11**:113-133.

70. Lopez-Mucino LA, Garcia-Garcia F, Cueto-Escobedo J, Acosta-Hernandez M, Venebra-Munoz A, Rodriguez-Alba JC: **Sleep loss and addiction**. *Neurosci Biobehav Rev* 2022, **141**:104832.

71. Freeman D, Sheaves B, Waite F, Harvey AG, Harrison PJ: **Sleep disturbance and psychiatric disorders**. *Lancet Psychiatry* 2020, **7**:628-637.

72. Freels TG, Baxter-Potter LN, Lugo JM, Glodosky NC, Wright HR, Baglot SL, Petrie GN, Yu Z, Clowers BH, Cuttler C, *et al.*: **Vaporized cannabis extracts have reinforcing properties and support conditioned drug-seeking behavior in rats**. *J Neurosci* 2020, **40**:1897-1908.

73. Jenkins BW, Buckhalter S, Perreault ML, Khokhar JY: **Cannabis vapor exposure alters neural circuit oscillatory activity in a neurodevelopmental model of schizophrenia: exploring the differential impact of cannabis constituents**. *Schizophr Bull Open* 2022, **3**:sgab052.

74. Iezzi D, Caceres-Rodriguez A, Chavis P, Manzoni OJJ: **In utero exposure to cannabidiol disrupts select early-life behaviors in a sex-specific manner**. *Transl Psychiatry* 2022, **12**:501.