Short communication

Marijuana and its effects in Brain

Abstract: *Cannabis sativa* (hemp) plant is the source of cannabis-based products which comes from any part of the plant such as seeds, stems and flowering tops. The products of this plant are used for recreational purpose. It can also be used to sooth the pain and other medical conditions. Not all products of this plant is mind altering but some of them posses the psychotic effect. The active ingredient of the plant is called as cannabinoids. Almost 120 active chemicals are present in cannabis. According to the scientific reports these cannabis can be used to chronic pain in adults, nausea and vomiting resulting from chemotherapy treatment, some symptoms of multiple sclerosis (MS).These cannabis can be ingested in various forms such as smoking, taking it as supplements, topical treatment, eating either raw or with candies, can be added in tea as a brew. This chapter will address the effect of these cannabis in human brain and its mechanisms of action.

Keywords: cannabinoids, Cannabenoid receptors, dopaminergic neuron, endocannabinoids, Δ9-tetrahydrocannabinol (THC)

INTRODUCTION

Delta-9-tetrahydrocannabinol (THC) is a cannabinoid molecule in marijuana from *Cannabis sativa* (hemp) plant. In rats exposed to THC from gestational day 15 to postnatal day 9, with THC at a daily dose (5 *per os*) has caused subtle neurofunctional deficits (Campolongo et al., 2007). THC, can also affect the rodent ontogeny process, especially on dopaminergic neuron development and enkephalinergic neuron. Cannabenoid receptors (CB1) are seen during prenatal development and there are higher chances of these receptors to be transferred from mother to the offspring through placenta in both human and rodents (Dalterio, 1986). Young pregnant women tend to abuse this drug, in western culture. In 2014, approximately 183 million people used marijunana and in 2016, 22 million people abused cannabis (United Nations Office on Drugs and Crime. World drug report.2015.; The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016).During active brain development, cannabenoid receptors are expressed in high level in areas such as hippocampus, amygdala, and prefrontal cortex (PFC). The age of exposure to cannabis affects the prenatal, perinatal and adolescent periods of life (Hurd *et al.,* 2019). In rats, THC pretreated animals has shown worse performance with a defect in spatial working memory when tested in radial arm maze (Rubino *et al.,* 2009). This clearly indicates that in experimental models, adolescent chronic exposure in rats to THC has serious impact on learning and memory. In adolescent rats exposed to THC, it caused defects in synaptic plasticity in hippocampus (Le et al.,, 2022). Endocannabinoid system is a neuromodulatory network in brain plays a major role in cognitive and physiological process. Heavy marijuana use alters the brain tissue analysed by Voxel-based morphometry (Matochik et al., 2005).

Δ^9-tetrahydrocannabinol is the primary chemical binds with cannabinoid receptors. Anandamide (N-arachidonoylethanolamine) and 2-arachidonoyl glycerol (2-AG) in animals are the main endocannabinoids. CB1 and CB2 receptors, mediate the binding of phyto as well as endocannabinoids. Inside the brain those areas with higher cognitive functions , motor control regions, hindbrain regions express high level of CB1 receptors (Glass et al., 1997). Regular cannabis usage affects various functions of the brain such as working memory, attention, and cognitive control processing (Kim et al., 2019). Functional MRI has shown there is an interaction between recreational cannabis use and cognitive function (Sagar et al., 2018). Adult chronic cannabis users have reduced attention, cognitive control, poor memory, improper decision-making, motor performance and affective processing **(**Chang et al., 2006; Jager et al., 2006; Kanayama et al., 2004; Bechara et al., 2000; Nestor et al., 2009; Vaidya et al., 2012; Wesley et al., 2010; King et al., 2011; Gruber et al., 2009). A metanalysis on CANN+ patients with CANN- has revealed several cognitive dysfunctions when tested in premorbid IQ, current IQ, verbal learning, verbal working memory, motor inhibition (Bogaty et al., 2018). CBD induces alterations in brain activity in both the healthy volunteers and people with psychiatric disorder (Batalla *et al.,* 2021). Genetic variations also impact the use of cannabis , in subjects wit h Val *COMT* allele there was a reduced functions of working memory, verbal and visual memory . The *CNR1*, *AKT1*, *DBH* and *5-HTT/SLC6A4* genes may also be involved in modulating the neurological effects of cannabis use. All these genes are also known to be linked with schizophrenia (Cosker *et al.,* 2018). 'psychotomimetic' effects of Δ9-tetrahydrocannabinol (THC)- haloperidol and their combination was investigated in a double-blind, placebo-controlled, partial three-way crossover ascending dose study in 35 healthy, male mild cannabis users. THC significantly decreased many 'psychotomimetic' effects of CNS (Liem-Moolenaar et al., 2010). Schizophrenia-like psychosis is reported from heavy use of cannabis

as per the recent findings. In a study conducted in twenty two adult males it was found that THC can induce acute psychotic reaction in psychiatrically well individuals (Morrison et al., 2019). Executive function and inhibitory motor control are also affected by high potency marijuana (Ramaekers et al., 2006). And MRI study has revealed that orbitofrontal gyri volume was singnificantly lower in marijuana users followed by orbitofrontal cortex and forceps minor innervations was higher (Filbey et al., 2014)..

Apart from natural source from cannabis plant this also is produced synthetically in names such as spice, K2 or Kronic being widely misused . Although cannabis is used in various treatments still its danger can not be overlooked. Consuming delta-9-tetrahydrocannabinol (THC) has lot of effects on synaptic plasticity as a short term change and neuronal structural alternations as the long term change and it affects the endocannabinoid system Exposure to THC at the early life leads to the alternations in neural connectivity in areas such as cognition and behaviour. Marijuna use not only affects the brain but it also effects the sympathetic nervous system, that controls blood pressure, platelet activation, and electrophysiological effects. During periods of aactive neuronal development, cannabinoid receptors are highly expressed in areas that control cognitive and behaviour. Animal studies have shown that exocannbenoids can damage the processes that control cognition and behaviour (Testai et al., 2022).

Marijuana is smoked and enters blood stream through lungs , if taken orally through digestive system it enters the blood. Though blood it reaches brain where it binds with cannebinoid receptors causing alterations. From childhood if it is taken then through midlife it causes neuropsychological decline (Meier et al., 2012). In adolescent period if marijuana is used it leads to long term effects on the how the neural connections are made within the brain (NIH,

2019). These changes in the neural network can impact attention, memory, and learning. THC cause “high” feeling in people. Cannnabinoid hypermesis syndrome are characterised by vomiting. Nausea and dehydration (Gali et al., 2012). The other names of cannabis are pot, weed and ganja that is the most widely used recreational drug globally. USA and Canada has delegailised this drug that increasing the usage in teen population (Thomas et al., 2014; Wolff and Jouanjus, 2017). Ischemic stroke can occur in individuals who chronically use marijuana (Thanvi and Treadwell 2009). Cerebral infract is another effects of cannabinoids noted through inhalation and combustion (Garret et al., 1977; Wolff and Jouanjus, 2017). CB-1 receptor agonist WIN 55,212-2 is a synthetic cannabis upon injection in Adult male Sprague–Dawley rats for 22 days it caused significant hippocampal morphological alternations (Lawston et al., 2000). Early cannabis exposure causes psychotic like experience in adolescents (Dennisoff et al., 2022). THC alters the inhibitory interneurons in cerebellum (Ma et al., 2009). Mariunana smoking can increase stroke , a case study who used marijunana regular end up with having the stroke in occipital lobe , the subject is also positive for heterozygous for factor V Leiden associated with thrombosis (Marinella et al., 2001; Mateo et al., 2006). THC can impact prenatal life which is a time for normal signalling pathways and also it affects the adolescence time by altering the brain maturation. Though marijuana is said to be harmless our understanding on its effects in brain has revealed the presence of exiting evidence on abnormal changes in brain and behaviour, so this dug must carefully be used by pregnant mothers and adolescents. In USA marijuana use is higher and approximately 3 in 10 patients express marijunana use disorder (Hasin et al., 2015)..

References

1. Campolongo P, Trezza V, Cassano T, et al. Perinatal exposure to delta-9-tetrahydrocannabinol causes enduring cognitive deficits associated with alteration of cortical gene expression and neurotransmission in rats. *Addict Biol*. 2007;12(3-4):485-495. doi:10.1111/j.1369-1600.2007.00074.x
2. Dalterio SL (1986) Cannabinoid exposure: effects on development. *Neurobehav Toxicol Teratol* 8 :345 –352.
3. United Nations Office on Drugs and Crime. World drug report.2015. Accessed February 10, 2021. https://www.unodc.org/unodc/en/index.html
4. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.**Lancet Psychiatry**. 2018; 5:987–1012. doi: 10.1016/S2215-0366(18)30337-7
5. 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. doi: 10.1523/JNEUROSCI.1165-19.2019
6. Rubino T, Realini N, Braida D, et al. Changes in hippocampal morphology and neuroplasticity induced by adolescent THC treatment are associated with cognitive impairment in adulthood. *Hippocampus*. 2009;19(8):763-772. doi:10.1002/hipo.20554
7. Le A, Quintanilla J, Mani MA, Piomelli D, Lynch G, Gall CM. Persistent sexually dimorphic effects of adolescent THC exposure on hippocampal synaptic plasticity and episodic memory in rodents. Neurobiology of Disease, Volume 162, January 2022, 105565
8. Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study

in the fetal, neonatal and adult human brain. *Neuroscience*. 1997;77:299–318. doi: 10.1016/S0306-4522(96)00428-9.

9. Kim D-J, Schnakenberg Martin AM, Shin Y-W, Jo HJ, Cheng H, Newman SD, Sporns O, Hetrick WP, Calkins E, O'Donnell BF. Aberrant structural-functional coupling in adult cannabis users. *Hum Brain Mapp*. 2019;40:252–61. doi: 10.1002/hbm.v40.1.

10. Sagar KA, Gruber SA. Interactions between recreational cannabis use and cognitive function: lessons from functional magnetic resonance imaging. *Ann. N Y Acad Sci*. 2018. doi: 10.1111/nyas.13990.

11. Chang L, Yakupov R, Cloak C, Ernst T. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. *Brain J Neurol*. 2006;129:1096–112. doi: 10.1093/brain/awl064.

12. Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. *Psychopharmacology (Berl.)*. 2006;185:358–68. doi: 10.1007/s00213-005-0298-7.

13. Jager G, Van Hell HH, De Win MML, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Effects of frequent cannabis use on hippocampal activity during an associative memory task. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2007;17:289–97. doi: 10.1016/j.euroneuro.2006.10.003.

14. Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA. Spatial working memory in heavy cannabis users: a functional magnetic resonance

imaging study. *Psychopharmacology (Berl.)*. 2004;176:239–47. doi: 10.1007/s00213-004-1885-8

15. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain J Neurol*. 2000;123:2189–202. doi: 10.1093/brain/123.11.2189.
16. Nestor L, Hester R, Garavan H. Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *NeuroImage*. 2010;49:1133–43. doi: 10.1016/j.neuroimage.2009.07.022.
17. Vaidya JG, Block RI, O'Leary DS, Ponto LB, Ghoneim MM, Bechara A. Effects of chronic marijuana use on brain activity during monetary decision-making. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2012;37:618–29. doi: 10.1038/npp.2011.227.
18. Wesley MJ, Hanlon CA, Porrino LJ. Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. *Psychiatry Res*. 2011;191:51–59. doi: 10.1016/j.pscychresns.2010.10.002.
19. King GR, Ernst T, Deng W, Stenger A, Gonzales RMK, Nakama H, Chang L. Altered brain activation during visuomotor integration in chronic active cannabis users: relationship to cortisol levels. *J Neurosci Off J Soc Neurosci*. 2011;31:17923–31. doi: 10.1523/JNEUROSCI.4148-11.2011.
20. Gruber SA, Rogowska J, Yurgelun-Todd DA. Altered affective response in marijuana smokers: an FMRI study. *Drug Alcohol Depend*. 2009;105:139–53. doi: 10.1016/j.drugalcdep.2009.05.022.

21. Bogaty SER, Lee RSC,Hickie IB and Hermens DF. Meta-analysis of neurocognition in young psychosis patients with current cannabis use. Journal of Psychiatric Research, Volume 99, April 2018, Pages 22-32.

22. Batalla A, Bos J, Postma A and Bossong AG. The Impact of Cannabidiol on Human Brain Function: A Systematic Review. Front. Pharmacol., 21 January 2021 Sec.Neuropharmacology https://doi.org/10.3389/fphar.2020.61818

23. Coskera E, Schwitzerab T, Ramozcd N, Ligierae F,Lalannef L, Gorwoodcdg P, SchwanabhiV.Laprévoteabh. The effect of interactions between genetics and cannabis use on neurocognition. A review. Progress in Neuro-Psychopharmacology and Biological Psychiatry. Volume 82, 2 March 2018, Pages 95-106.

24. Liem-Moolenaar M, te Beek ET, de Kam ML, Franson KL, Kahn RS, Hijman R , Touw D, Joop M A van Gerven Central nervous system effects of haloperidol on THC in healthy male volunteers . Journal of Psychopharmacology. . 2010 Nov;24(11):1697-708.

25. P. D. Morrison, V. Zois, D. A. McKeown, T. D. Lee, D. W. Holt, J. F. Powell, S. Kapur and R. M. Murray. The acute effects of synthetic intravenous Δ9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychological Medicine, 2019, Volume 39 Issue 10

26. Ramaekers JG, Kauert G, van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR. High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2006;31:2296–303. doi: 10.1038/sj.npp.1301068.

27. Filbey FM , Sina Aslan, Vince D. Calhoun, Jeffrey S. Spence, Eswar Damaraju, Arvind Caprihan, and Judith Segall. Long-term

effects of marijuana use on the brain. PNAS . November 10, 2014, 111 (47) 16913-16918

28. Testai FD, Gorelick PB, Aparicio HJ, Filbey FM, Gonzalez R, Gottesman RF, Melis M, Piano MR, Rubino T, Song SY; on behalf of the American Heart Association Stroke Brain Health Science Subcommittee of the Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Use of marijuana: effect on brain health: a scientific statement from the American Heart Association. *Stroke.* 2022;53:e176–e187. doi: 10.1161/STR.0000000000000396.
29. Meier, M.H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R.S., ...& Moffitt, T.E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences, 109(40), 2657-2664.*
30. National institute on Drug Abuse. (2019). *Marijuana.*
31. National institute on Drug Abuse. (2019). How does marijuana produce its effects?
32. National institute on Drug Abuse. (2019). What are marijuana's long-term effects on the brain?
33. Galli, J.A., Sawaya, R.A., & Friedenberg, F.K. (2012). Cannabinoid Hyperemesis Syndrome. *Current Drug Abuse Reviews, 4(4), 241-249.*
34. Thomas, G., Kloner, R. A., Rezkalla, S. (2014). Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am. J. Cardiol.* 113, 187–190. doi: 10.1016/j.amjcard.2013.09.042

35. Wolff, V., Jouanjus, E. (2017). Strokes are possible complications of cannabinoids use. *Epilepsy Behav.* 70, 355–363. doi: 10.1016/j.yebeh.2017.01.031

36. Thanvi, B. R., Treadwell, S. D. (2009). Cannabis and stroke: is there a link? *Postgrad Med. J.* 85, 80–83. doi: 10.1136/pgmj.2008.070425

37. Garrett, C. P., Braithwaite, R. A., Teale, J. D. (1977). Unusual case of tetrahydrocannabinol intoxication confirmed by radioimmunoassay. *Br. Med. J.* 2, 166. doi: 10.1136/bmj.2.6080.166

38. Lawston J, Alice Borella, John K Robinson, Patricia M Whitaker -Azmitia. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. Brain Research, Volume 877, Issue 2, 22 September 2000, Pages 407-410

39. Denissoff A, Mustonen A, Jouko Miettunen, Anni-EmiliaAlakokkare, JuhaVeijola, James G.Scott, Musa B.Sami, SoljaNiemelä. Trajectories of adolescent psychotic-like experiences and early cannabis exposure: Results from a Finnish Birth Cohort Study. Schizophrenia Research, Volume 246, August 2022, Pages 95-102

40. Ma YL, Weston SE, Whalley BJ, Stephens GJ. The phytocannabinoid Δ^9-tetrahydrocannabivarin modulates inhibitory neurotransmission in the cerebellum

41. Marinella, M. A. (2001). Stroke after marijuana smoking in a teenager with factor V Leiden mutation. *South Med. J.* 94, 1217–1218.

42. Mateo, I., Infante, J., Gomez Beldarrain, M., Garcia-Monco, J. C. (2006). Cannabis and cerebrovascular disease. *Neurologia* 21, 204–208.

43. Matochik, J. A., Eldreth, D. A., Cadet, J. L., Bolla, K. I. (2005). Altered brain tissue composition in heavy marijuana users. *Drug Alcohol Depend.* 77, 23–30. doi: 10.1016/j.drugalcdep.2004.06.011

44. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. *JAMA Psychiatry*. 2015;72(12):1235-1242.