HHS Public Access

Author manuscript

Curr Addict Rep. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Curr Addict Rep. 2016 June 1; 3(2): 182–188. doi:10.1007/s40429-016-0101-3.

Comorbid Cannabis and Tobacco Use in Adolescents and Adults

Punitha Subramaniam, BS[a,b], **Erin McGlade, PhD**[b,c,d], and **Deborah Yurgelun-Todd, PhD**[a,b,c,d]

[a]Interdepartmental Program in Neuroscience, University of Utah, Salt Lake City, UT, USA

[b]Diagnostic Neuroimaging, University of Utah, Salt Lake City, UT USA

[c]Department of Psychiatry, University of Utah, Salt Lake City, UT

[d]George E. Whalen Department of Veterans Affairs Medical Center, VA VISN 19 Mental Illness Research, Education and Clinical Center (MIRREC), Salt Lake City, UT, USA

Abstract

The prevalence of comorbid cannabis and tobacco use has been increasing among adolescents and adults and has been shown to be associated with a range of changes or deficits in physical, psychological and behavioral outcomes. Moreover, comorbid use has been shown to have a differential effect on the structure and function of the brain, especially as it relates to the reward circuitry and learning and memory. This interaction might be mediated by the involvement of the endocannabinoid system and alterations in dopamine signaling in regions associated with reward and cognitive functioning. While current findings demonstrate a differential effect of comorbid use on neurobiological and behavioral correlates compared with single substance use, additional studies are needed controlling for potential psychiatric comorbidities, age of onset of use and use of other substances. Understanding the neurobiological mechanisms associated with comorbid cannabis and tobacco use will be important in developing successful treatment outcomes in the future.

Keywords

Cannabis; Tobacco; Endocannabinoid system; Neuroimaging

Corresponding Author: Punitha Subramaniam, The Brain Institute, University of Utah, 383 Colorow Dr, Salt Lake City, UT 84108, USA, punitha.subramaniam@utah.edu, 801-587-2511.
Dr. Erin McGlade, The Brain Institute, University of Utah, 383 Colorow Drive, Salt Lake City UT 84108, USA, erin.mcglade@hsc.utah.edu
Dr. Deborah Yurgelun-Todd, The Brain Institute, University of Utah, 383 Colorow Drive, Salt Lake City, UT 84108, USA, Deborah.Yurgelun-Todd@hsc.utah.edu

Conflict of Interest

Punitha Subramaniam, Erin McGlade, and Deborah Yurgelun-Todd declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Introduction

Two of the most commonly used substances worldwide include cannabis/marijuana and tobacco/nicotine. Many individuals use both of these substances often in conjunction with one another. Specifically, in addition to the close proximal use of cannabis and tobacco, a significant number of cannabis users report ingesting cannabis and tobacco simultaneously [1, 2]. Thus, while specific effects may be associated with the different methods of administration of cannabis and tobacco, this distinction has not been addressed by a majority of the literature studying cannabis and tobacco use. Therefore, in this review, comorbid use of cannabis and tobacco will encompass independent co-occurring use (co-use) of both substances as well as simultaneous use, unless otherwise specified.

According to the 2013 National Survey on Drug Use and Health (NSDUH), the frequency of marijuana use in individuals aged 12 and older has significantly increased in the past decade (2002–2013) with approximately 5.7 million individuals reporting daily or almost daily use in the past year. On the other hand, approximately 66.9 million individuals aged 12 and older reported past month use of tobacco products. This indicates that both marijuana and tobacco use is an important area of public health concern [3]. In recent years, an increase in comorbid use patterns of cannabis and tobacco has been observed in both adolescent and adult cohorts. Recent studies have indicated that 78.3% of past month adult cannabis users reported past month tobacco use with an increasing trend of comorbidity observed among both males and females of different age ranges and most racial/ethnic groups[4, 5]. Similarly, among adolescents and young adults, cannabis and tobacco have been one of the most common comorbid substances used worldwide[6]. These findings highlight the importance of examining the effects of comorbid cannabis and tobacco use as well as the independent effects that may be associated with cannabis and tobacco use.

Cannabis and tobacco have both been regarded as gateway drugs, although this remains a point of ongoing debate. The gateway hypothesis posits that initial use of substances such as tobacco and cannabis will lead to the use of other drugs such as cocaine and heroin[7, 8]. It is commonly reported that tobacco along with alcohol is primarily the first substance used, which has been identified as leading to the progression of cannabis use and subsequently other drugs[9]. However, the reverse has also been shown, whereby cannabis use precedes the use of tobacco products and other substances[10, 11]. Based on a systematic review by Ramo and colleagues, (2012), studies examining the relationship between cannabis and tobacco use have noted that initiation and escalation of tobacco smoking was associated with an increased probability of marijuana use[6]. Additionally, individuals who started smoking tobacco at an earlier age were two times more likely to develop a marijuana use disorder compared to nonsmoking individuals[6]. Similarly, marijuana use has been shown as a potential risk factor for the subsequent initiation of tobacco smoking as well as for the advancement to nicotine dependence[11, 12]. These observations suggest a complex interaction between cannabis and tobacco use that may have been overlooked in previous studies that needs to be explored further.

Comorbid use of cannabis and tobacco has been associated with changes or impairments in physical, psychological, behavioral and mental health as well as across social domains.

Individuals with comorbid use of both substances were more inclined to report antisocial behaviors and meet criteria for psychiatric disorders including anxiety disorders, bipolar disorder, and personality disorders. They were also more likely to drop out of school earlier, drive under the influence of alcohol and be involved in partner violence[13]. In a study assessing adiposity in males and females, a significant interaction was observed with cannabis use and cigarette smoking in males. Participants who smoked 15 cigarettes per day, evidenced an inverted "U" shaped association between cannabis use levels per week and change in body mass index and waist circumference measures. In contrast, non-cigarette smoking participants evidenced a "U"-shaped association. This interaction was not significant in females, indicating the presence of a gender effect in this association[14]. Additionally, a significant association between increased frequency of cigarette use, marijuana use and depression has been observed in males[15]. In a longitudinal study that was conducted examining the relationship between cannabis and cigarette use and psychotic experiences, it was observed that cannabis and cigarette use was independently associated with a 3.2 and 4.2 fold increase in psychotic experiences[16]. However, after adjusting for cigarette use and cannabis use, correspondingly, the probability of psychotic experiences was attenuated by 50% and 30%. These findings suggest that the relationship between cannabis and cigarette use and psychotic experiences might be confounded by other factors. However, of the 48 participants who reported only cannabis use, only 3 reported that they did not mix cannabis with tobacco which again highlights the importance of understanding the interaction between comorbid cannabis and tobacco use[16]. In addition to these behavioral and socio-cultural observations, recent studies have focused on examining the neurobiological correlates that are associated with comorbid cannabis and tobacco use. A summary of key studies reviewed is provided in Table 1.

Interaction between Endocannabinoid System and Nicotine Addiction

A range of factors have been identified to elucidate the relationship between cannabis and tobacco use, including shared genetic risks predisposing individuals to the use of both substances as well as environmental, behavioral and social cues that are associated with co-use and/or simultaneous use of cannabis and tobacco[17, 18]. Furthermore, both cannabis and tobacco have a common route of administration via inhalation/smoking that may condition individuals to progress to the use of cannabis when they have been smoking tobacco or vice versa[19]. The involvement of the endocannabinoid system in relation to nicotine addiction is another important factor that needs to be taken into consideration in understanding comorbid use.

The endocannabinoid system consists of cannabinoid receptors and endogenous ligands that are present throughout the central nervous system and peripheral regions. Two of the commonly identified cannabinoid receptors are cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). Although other cannabinoid receptors have been identified, their function has not been well characterized[20]. The CB1 receptor is one of the most abundant G-protein coupled receptors in the brain and is found in high concentrations in the hippocampus, cerebellum and prefrontal cortex (PFC) among other regions[21]. In addition to being found in the brain, CB1 receptors are also found in peripheral regions such as the liver, gut and adipose tissue[22]. Conversely, CB2 receptors primarily have been found in

immune cells although recent studies have identified CB2 receptor expression in regions such as the hippocampus and cerebellum as well as other central nervous system regions albeit at lower levels compared to CB1 receptors[21]. Anandamide and 2-arachidonoylglycerol (2-AG) are endogenous cannabinoid ligands that bind to the receptors to exert modulatory effects in the central nervous system and peripheral regions. In the brain, the endocannabinoid system acts as a retrograde messenger system by inhibiting the release of different excitatory and inhibitory neurotransmitters. These, in turn, modulate the release of other neurotransmitters including dopamine, which plays a critical role in controlling reward mechanisms in the brain and is a key player in addiction related behavior[23]. Δ^9-tetrahydrocannabinol (THC), which is the key psychoactive compound in cannabis, exerts its effects by binding to CB1 receptors in the brain and in recent years, numerous studies have demonstrated that the endocannabinoid system is also involved in modulating addictive behavior associated with other substances including nicotine[24, 25]. It has been suggested that nicotine acts on the endocannabinoid system by triggering the release of anandamide and 2-AG in the mesolimbic reward circuitry involving the ventral tegmental area (VTA) and nucleus accumbens (NAcc)[25]. An increase in the levels of endogenous cannabinoids can lead to the presynaptic inhibition of neurotransmitters such as γ-amino butyric acid (GABA), which may subsequently lead to an increase in dopamine levels that enhances the rewarding effects of nicotine. This perspective has been supported Gonzalez and colleagues who demonstrated an increase in anandamide levels in limbic regions following chronic administration of nicotine in rats [26]. Additionally, it has been observed that increases in dopamine levels in the NAcc following nicotine administration as well as other substances were inhibited when the CB1 receptor was blocked using an antagonist, rimonabant [27]. However, various other factors might be involved in mediating the interaction between the endocannbinoid system and tobacco use and thus, further studies are needed to obtain a better understanding of the underlying mechanisms that might be involved in relation to comorbid cannabis and tobacco use.

Preclinical studies have also demonstrated an association between cannabis and nicotine at a pharmacological and behavioral level. In one particular study, co-administration of nicotine and THC was found to significantly intensify acute responses such as hypolocomotion, hypothermia and antinociception that were observed when only THC was administered[28]. In addition, a significant association was observed between the co-administration of sub-threshold doses of THC and nicotine and rewarding effects assessed using a conditioned place paradigm. No significant rewarding effects were observed when either of the drugs was administered independently at the sub-threshold dosage[28]. The authors suggested that this observation could have been due to an additive effect of nicotine and THC on the mesolimbic dopaminergic circuit. In line with this, Valjent and colleagues also demonstrated increased c-fos expression, a marker of neuronal activity, in limbic and cortical regions that are highly innervated with dopaminergic inputs following co-administration of THC and nicotine[28]. Using the conditioned place paradigm, Castane and colleagues (2002), reported observing rewarding effects in wild-type mice following the administration of nicotine at various doses. However, these effects were not present in CB1 receptor knockout mice indicating the potential involvement of the endocannabinoid system in modulating addictive responses associated with nicotine use[29]. In support of this, administration of the CB1

receptor antagonist, rimonabant, has been shown to mitigate the rewarding effects of nicotine. Furthermore, Panillo and colleagues, (2013) demonstrated that rats with a history of THC exposure were more inclined to self-administer nicotine compared to control rats suggesting that prior cannabis exposure might prime the reward circuitry by manipulating the endocannabinoid system leading to increased susceptibility toward nicotine use and addiction[30]. These studies indicate a potential priming effect associated with nicotine and THC which leads to an enhancement of rewarding effects and other behavioral responses that are associated with comorbid cannabis and tobacco use. Additionally, a priming effect might lead to increased susceptibility to the initiation and dependence of comorbid use of both substances. While there is strong evidence linking the endocannabinoid system and nicotine addiction, it is important to note that the endocannabinoid system also has been implicated in addiction to alcohol and other drugs such as opioids and psychostimulants[24, 31]. However, due to the high rates of comorbidity associated with cannabis and tobacco, the involvement of CB1 receptors in facilitating reward related behaviors associated with nicotine should be examined. Results from these investigations will be important for developing treatment options targeting the endocannabinoid sytem in relation to addictive behaviors.

Neural Correlates of Cannabis and Tobacco Use

Numerous studies have sought to determine the neural correlates that are associated with cannabis and tobacco use independently; however, the number of studies assessing the neurobiological and related behavioral implications of comorbid cannabis and tobacco use have been lacking, especially in an adolescent cohort. Previous human studies have relied heavily on neuroimaging techniques, which have demonstrated that cannabis use is associated with structural and functional alterations in brain regions that are abundant in CB1 receptors such as the hippocampus, amygdala, PFC and cerebellum[32, 33]. Additionally, these alterations have been correlated with impairments in various cognitive functions such as learning and memory, decision-making, and inhibitory processing among others[34–36]. Similarly, in tobacco users, studies have consistently shown changes in structural and functional measures associated with cigarette smoking in regions of the brain that also have been implicated with cannabis use such as the PFC, thalamus, temporal and occipital regions and the cerebellum[37]. However, recent neuroimaging studies have yielded results pointing towards a differential effect associated with *comorbid* cannabis and tobacco use [38, 39]. For example, Wetherill and colleagues (2015) examined gray matter volume in cannabis and tobacco alone and comorbid cannabis and tobacco users as well as in healthy controls. The investigators observed that smaller gray matter volume was observed in the thalamus of both the cannabis only and comorbid users whereas gray matter volume in the left cerebellum was smaller in the tobacco only and comorbid users. In addition, compared to healthy controls, greater gray matter volume was observed in the left putamen in the cannabis, tobacco and comorbid group[38]. These findings are suggestive of an independent effect of cannabis and tobacco use as well as comorbid use on gray matter volume in specific regions of the brain. The above mentioned study is one of the first to compare structural differences associated with independent cannabis and tobacco use and comorbid cannabis and tobacco use in an adult population and thus further studies will need

to be conducted in order to obtain a more comprehensive picture regarding potential structural changes that might be correlated with cannabis and tobacco use.

In addition to assessing structural changes, neuroimaging investigations have applied resting state functional imaging approaches to understand brain changes potentially associated with substance use. Wetherill and colleagues (2015) examined default mode network (DMN) connectivity using resting-state functional magnetic resonance imaging (rs-fMRI) techniques with the posterior cingulate cortex (PCC) as a seed region in cannabis only, tobacco only, cannabis and tobacco users as well as healthy controls. Comparisons between the three substance using groups showed no significant differences in DMN connectivity. However, when compared to healthy controls, the cannabis group showed lower connectivity strength between the PCC and the temporal, medial prefrontal cortex (mPFC), cerebellar and parahippocampal regions as well as enhanced connectivity between the PCC and right anterior insula which was positively correlated with years of cannabis use. Tobacco users showed lower connectivity between the PCC and temporal, mPFC (ventral ACC and medial orbitofrontal cortex (mOFC)) and cerebellar (crus I/II) regions and enhanced PCC-cerebellar (bilateral lobule VIIIB) and PCC-mPFC (bilateral frontal poles) connectivity. Cannabis and tobacco users only showed lower PCC-temporal cortex connectivity[40]. The authors proposed that the observed alterations in DMN connectivity were related to addiction more generally and as such might represent an underlying neurobiological vulnerability associated with substance use.

A notable number of studies assessing comorbid cannabis and tobacco use have focused on regions of the brain and factors that are involved in reward processing, a functional system that has previously been shown to play an important role in addiction related behavior[41]. For example, in a high-resolution positron emission tomography (PET) study, Leroy and colleagues found that the tobacco only and cannabis and tobacco users had significantly lower dopamine transporter (DAT) binding in the caudate and putamen compared to non-smoking controls[42]. Further analysis in this study found that the signal estimate of DAT availability also was reduced in the ventral striatum, *VTA*, substantia nigra, white and gray matter of the cingulate gyrus as well as several thalamic nuclei in the tobacco only and comorbid groups. However, it is important to note that a cannabis only group was not included for comparison and any possible specificity associated with pure cannabis use versus cannabis and tobacco use was not examined.

Karoly and colleagues studied an adolescent cohort, using functional magnetic resonance imaging (fMRI) in conjunction with the monetary incentive delay (MID) task to evaluate reward processing. They observed that the tobacco only using group demonstrated reduced activation in the left and right NAcc during anticipation of reward compared to the alcohol only, healthy controls and polysubstance using groups. No significant differences were observed in the cannabis only and polysubstance-using groups suggesting that the tobacco only using group was particularly susceptible to reward related activity[43]. Using a similar MID task-dependent fMRI paradigm, Jansma and colleagues (2013) pharmacologically manipulated the endocannabinoid system via THC administration to evaluate reward-processing activity in the NAcc and caudate putamen in nicotine addicted subjects and healthy controls. Following the administration of THC, nicotine addicted subjects exhibited

a significant reduction in activity during anticipation of reward in the NAcc and caudate putamen indicating an interaction between the endocannabinoid system and nicotine use[44]. Despite assessing similar reward processing activity, comparison of the observed results in these studies needs to be done with caution due to the difference in experimental design and subject cohorts examined.

The effects of substance use on the central nervous system have also been studied using cognitive approaches. Cannabis use has primarily been shown to lead to impairments in cognitive functioning whereas acute tobacco use has been postulated to enhance cognitive functions[45, 46]. It has been suggested that one of the reason for increased prevalence of comorbid cannabis and tobacco use is due to the opposing effects exerted by the substances and that tobacco is used to mask the impairments that are associated with cannabis use[47]. For instance, in a study assessing episodic memory in cannabis and tobacco users, deficits in episodic memory were observed in cannabis users with intermittent tobacco use whereas no significant impairments were observed in cannabis users with consistent tobacco use[48]. Similarly, in a study by Jacobsen and colleagues, (2007), cannabis users with at least 60 episodes of cannabis use exhibited deficits in recalling learned words after a 25 minute delay compared to users with less than 40 lifetime episodes of cannabis use during abstinence from smoking conditions whereas in the smoking condition, no significant deficits were observed[49]. The investigators also assessed working memory using an auditory n-back task during an fMRI imaging session. They found that relative to the cannabis users with 40 lifetime episodes of use, those with 60 episodes of cannabis use showed decreased performance accuracy with increasing working memory load in the n-back task independent of smoking condition and that increased task-related activation was observed in posterior cortical regions during high verbal working memory load during the abstinence condition [49]. This suggests that tobacco use might attenuate memory impairments that are associated with cannabis use. However, in a study assessing the relationship between memory and structural changes in the hippocampus, a region that plays an important role in learning and memory processes, a unique relationship was observed between changes in hippocampal volume and memory scores between healthy controls and comorbid cannabis and tobacco users. Specifically, in the healthy control group, a positive trend relating larger hippocampi volume and greater memory scores was observed whereas in the comorbid group, an inverse relationship was observed – smaller hippocampi volume was associated with better memory[39]. It is important to note that while significantly smaller hippocampus volumes were observed for the marijuana only using group and marijuana and nicotine using group, memory performance was reported to be the most impaired in the comorbid group implying a potential interaction at a behavioral level between the two substances.

Conclusion

In summary, comorbid cannabis and tobacco use has been shown to be associated with a range of changes or deficits in physical, psychological and behavioral outcomes. Moreover, comorbid use has been shown to have a differential effect on the structure and function of the brain, especially as it relates to the reward circuitry and learning and memory. This interaction might be mediated by the involvement of the endocannabinoid system and alterations in dopamine signaling in regions associated with reward and cognitive

functioning. However, there is still a paucity of research in this area and thus, more studies will need to be conducted to obtain a more comprehensive picture regarding the combined effects of cannabis and tobacco on the brain and the mechanisms involved. In addition to expanding on and replicating the studies that have been completed to date, future studies should focus on addressing and controlling for other potential comorbidities that are often present in substance use disorders. These include but are not limited to depression, anxiety and schizophrenia[50]. Moreover, future studies also should include data regarding comorbid use of alcohol, which is commonly used along with cannabis and tobacco and has demonstrated neurobiological effect[51]. Furthermore, it is critically important to conduct studies in adolescent cohorts, especially since adolescence is a period of time during which critical neurodevelopmental maturation takes place. Consequently, the adolescent brain may respond differently to the effects of substances such as cannabis and tobacco, when compared with effects observed in adult onset users[52]. Ultimately, gaining a better understanding regarding the association between comorbid cannabis and tobacco use as well the interaction of the neurobiological correlates will provide us with the ability to improve treatment as well as preventive measures for cannabis and tobacco co-use.

References

Papers of particular interest, published recently, have been highlighted as:

*Of importance

1. Akre C, et al. Cannabis and tobacco use: where are the boundaries? A qualitative study on cannabis consumption modes among adolescents. Health Educ Res. 2010; 25(1):74–82. [PubMed: 19515745]
2. Barrett SP, Darredeau C, Pihl RO. Patterns of simultaneous polysubstance use in drug using university students. Hum Psychopharmacol. 2006; 21(4):255–63. [PubMed: 16783813]
3. Substance Abuse and Mental Health Administraton. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Administration; 2014. NSDUH Series H-48, HHS Publication No. (SMA) 14-4863
4. Schauer GL, et al. Assessing the overlap between tobacco and marijuana: Trends in patterns of co-use of tobacco and marijuana in adults from 2003–2012. Addict Behav. 2015; 49:26–32. [PubMed: 26036666]
5. Schauer GL, et al. Differences in Tobacco Product Use Among Past Month Adult Marijuana Users and Nonusers: Findings From the 2003–2012 National Survey on Drug Use and Health. Nicotine Tob Res. 2015
6*. Ramo DE, Liu H, Prochaska JJ. Tobacco and marijuana use among adolescents and young adults: a systematic review of their co-use. Clin Psychol Rev. 2012; 32(2):105–21. This article provides a comprehensive review on the epidemiology and patterns of comorbid cannabis and tobacco use, predictors and consequences of use as well as associations with mental health issues in adolescents and young adults. Prevention and treatment options addressing comorbid use is also discussed. [PubMed: 22245559]
7. Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction. 2006; 101(4):556–69. [PubMed: 16548935]
8. Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. Am J Epidemiol. 2002; 155(10):918–25. [PubMed: 11994231]
9. Kandel D, Kandel E. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatr. 2015; 104(2):130–7. [PubMed: 25377988]

10. Becker J, et al. Cannabis use and other predictors of the onset of daily cigarette use in young men: what matters most? Results from a longitudinal study. BMC Public Health. 2015; 15:843. [PubMed: 26330150]
11. Patton GC, et al. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. Addiction. 2005; 100(10):1518–25. [PubMed: 16185213]
12. Rubinstein ML, Rait MA, Prochaska JJ. Frequent marijuana use is associated with greater nicotine addiction in adolescent smokers. Drug Alcohol Depend. 2014; 141:159–62. [PubMed: 24928480]
13. Peters EN, et al. Psychiatric, psychosocial, and physical health correlates of co-occurring cannabis use disorders and nicotine dependence. Drug Alcohol Depend. 2014; 134:228–34. [PubMed: 24183498]
14. Dube E, et al. Cigarette smoking may modify the association between cannabis use and adiposity in males. Pharmacol Biochem Behav. 2015; 135:121–7. [PubMed: 26026899]
15. Crane NA, Langenecker SA, Mermelstein RJ. Gender differences in the associations among marijuana use, cigarette use, and symptoms of depression during adolescence and young adulthood. Addict Behav. 2015; 49:33–9. [PubMed: 26036667]
16. Gage SH, et al. Associations of cannabis and cigarette use with psychotic experiences at age 18: findings from the Avon Longitudinal Study of Parents and Children. Psychol Med. 2014; 44(16): 3435–44. [PubMed: 25066001]
17. Agrawal A, et al. Mechanisms underlying the lifetime co-occurrence of tobacco and cannabis use in adolescent and young adult twins. Drug Alcohol Depend. 2010; 108(1–2):49–55. [PubMed: 20047801]
18. Agrawal A, Budney AJ, Lynskey MT. The co-occurring use and misuse of cannabis and tobacco: a review. Addiction. 2012; 107(7):1221–33. [PubMed: 22300456]
19. Agrawal A, Lynskey MT. Tobacco and cannabis co-occurrence: does route of administration matter? Drug Alcohol Depend. 2009; 99(1–3):240–7. [PubMed: 18926646]
20. Mackie K. Cannabinoid receptors: where they are and what they do. J Neuroendocrinol. 2008; 20(Suppl 1):10–4. [PubMed: 18426493]
21. Svizenska I, Dubovy P, Sulcova A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures–a short review. Pharmacol Biochem Behav. 2008; 90(4):501–11. [PubMed: 18584858]
22. Despres JP. The endocannabinoid system: a new target for the regulation of energy balance and metabolism. Crit Pathw Cardiol. 2007; 6(2):46–50. [PubMed: 17667864]
23. Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annu Rev Psychol. 2013; 64:21–47. [PubMed: 22804774]
24. Maldonado R, Valverde O, Berrendero F. Involvement of the endocannabinoid system in drug addiction. Trends Neurosci. 2006; 29(4):225–32. [PubMed: 16483675]
25. Scherma M, et al. The endocannabinoid system: a new molecular target for the treatment of tobacco addiction. CNS Neurol Disord Drug Targets. 2008; 7(5):468–81. [PubMed: 19128204]
26. Gonzalez S, et al. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res. 2002; 954(1):73–81. [PubMed: 12393235]
27. Cheer JF, et al. Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J Neurosci. 2007; 27(4):791–5. [PubMed: 17251418]
28. Valjent E, et al. Behavioural and biochemical evidence for interactions between Delta 9-tetrahydrocannabinol and nicotine. Br J Pharmacol. 2002; 135(2):564–78. [PubMed: 11815392]
29. Castane A, et al. Lack of CB1 cannabinoid receptors modifies nicotine behavioural responses, but not nicotine abstinence. Neuropharmacology. 2002; 43(5):857–67. [PubMed: 12384171]
30. Panlilio LV, et al. Prior exposure to THC increases the addictive effects of nicotine in rats. Neuropsychopharmacology. 2013; 38(7):1198–208. [PubMed: 23314220]
31. Pava MJ, Woodward JJ. A review of the interactions between alcohol and the endocannabinoid system: implications for alcohol dependence and future directions for research. Alcohol. 2012; 46(3):185–204. [PubMed: 22459871]

32. Rocchetti M, et al. Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users. Psychiatry Clin Neurosci. 2013; 67(7):483–92. [PubMed: 24118193]
33. Batalla A, et al. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PLoS One. 2013; 8(2):e55821. [PubMed: 23390554]
34. Sneider JT, et al. A preliminary study of functional brain activation among marijuana users during performance of a virtual water maze task. J Addict. 2013; 2013:461029. [PubMed: 23951549]
35. Gruber SA, Yurgelun-Todd DA. Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. Brain Res Cogn Brain Res. 2005; 23(1):107–18. [PubMed: 15795138]
36. Churchwell JC, Lopez-Larson M, Yurgelun-Todd DA. Altered frontal cortical volume and decision making in adolescent cannabis users. Front Psychol. 2010; 1:225. [PubMed: 21833280]
37. Jasinska AJ, et al. Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. Neuropharmacology. 2014; 84:111–22. [PubMed: 23474015]
38*. Wetherill RR, et al. Cannabis, Cigarettes, and Their Co-Occurring Use: Disentangling Differences in Gray Matter Volume. Int J Neuropsychopharmacol. 2015; 18(10) This article is one of the first studies to examine structural brain differences in association with cannabis and tobacco use alone and in combination. This study revealed a specific relationship between alterations in gray matter volume in specific regions with cannabis and/or tobacco use.
39*. Filbey FM, et al. Combined effects of marijuana and nicotine on memory performance and hippocampal volume. Behav Brain Res. 2015; 293:46–53. This study highlights a unique relationship between hippocampal volume and memory in comorbid marijuana and nicotine users as compared to healthy control. [PubMed: 26187691]
40*. Wetherill RR, et al. Cannabis, cigarettes, and their co-occurring use: Disentangling differences in default mode network functional connectivity. Drug Alcohol Depend. 2015; 153:116–23. An article examining alterations in default mode network connectivity and its association with cannabis and/or tobacco use. Suggests that alterations in this network might be related to addiction in general rather than specific substances. [PubMed: 26094186]
41. Gardner EL. Addiction and brain reward and antireward pathways. Adv Psychosom Med. 2011; 30:22–60. [PubMed: 21508625]
42. Leroy C, et al. Striatal and extrastriatal dopamine transporter in cannabis and tobacco addiction: a high-resolution PET study. Addict Biol. 2012; 17(6):981–90. [PubMed: 21812871]
43. Karoly HC, et al. Does incentive-elicited nucleus accumbens activation differ by substance of abuse? An examination with adolescents. Dev Cogn Neurosci. 2015
44. Jansma JM, et al. THC reduces the anticipatory nucleus accumbens response to reward in subjects with a nicotine addiction. Transl Psychiatry. 2013; 3:e234. [PubMed: 23443360]
45. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med. 2011; 5(1):1–8. [PubMed: 21321675]
46. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology (Berl). 2010; 210(4):453–69. [PubMed: 20414766]
47. Rabin RA, George TP. A review of co-morbid tobacco and cannabis use disorders: possible mechanisms to explain high rates of co-use. Am J Addict. 2015; 24(2):105–16. [PubMed: 25662704]
48. Schuster RM, et al. Tobacco may mask poorer episodic memory among young adult cannabis users. Neuropsychology. 2015; 29(5):759–66. [PubMed: 25558879]
49. Jacobsen LK, et al. Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. Biol Psychiatry. 2007; 61(1):31–40. [PubMed: 16631130]
50. Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. Am J Psychiatry. 2005; 162(8):1483–93. [PubMed: 16055769]
51. Oscar-Berman M, Marinkovic K. Alcohol: effects on neurobehavioral functions and the brain. Neuropsychol Rev. 2007; 17(3):239–57. [PubMed: 17874302]

52. Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Ann N Y Acad Sci. 2004; 1021:1–22. [PubMed: 15251869]

Table 1

Summary of studies examining the relationship between cannabis and tobacco use

Author (Year)	Study Population	Design	Key Findings
Filbey et al., (2015)	▪ 36 MJ, 19 Tob, 19 MJ+Tob, 16 HC ▪ Age range: 18–50	▪ Cognitive/MRI	▪ Smaller hippocampal volumes in all MJ using groups. ▪ Inverse relationship between memory and hippocampal volume was noted in comorbid users whereas in HC's a positive correlation was observed.
Wetherill et al., (2015)	▪ 19 MJ, 24 Tob, 23 MJ+Tob, 21 HC ▪ Age range: 20–57	▪ Resting state fMRI	▪ Comorbid users demonstrated reduced connectivity between the PCC and temporal cortex. MJ and Tob were independently associated with differential connectivity patterns between the PCC, mPFC and cerebellar and parahippocampal regions.
Wetherill et al., (2015)	▪ 19 MJ, 21 Tob, 21 MJ+Tob, 21 HC ▪ Mean age range: 28–34	▪ Structural MRI	▪ Comorbid users demonstrated larger gray matter volume in the left putamen. Smaller thalamus gray matter volume was observed in all MJ groups and smaller gray matter in the left cerebellum was observed in all Tob groups.
Leroy et al., (2011)	▪ 14 Tob, 13 MJ+Tob, 11 HC ▪ Mean age range: 25.9–30.2	▪ PET – HRRT/MRI	▪ DAT binding and availability was significantly reduced in comorbid and Tob users in striatal regions. DAT availability was also reduced in extrastriatal regions in both substance-using groups.
Karoly et al., (2015)	▪ 14 MJ, 34 Tob, 17 MJ+Tob, 12 Alcohol, 17 MJ+Tob +Alcohol, 38 HC ▪ Age range: 14–18	▪ Task-dependent fMRI: MID	▪ The Tob using group demonstrated decreased activation to reward anticipation in the bilateral NAcc compared to all other substance using groups except MJ.
Crane et (2015)	▪ Baseline: n = 1108; Age range: 15–16 ▪ At 6 years: n= 1064; Age range: 21–22	▪ Longitudinal study	▪ Higher frequency of cigarette use was related al., to increased frequency of MJ use, which was significantly correlated, with increased symptoms of depression, especially in males.
Schuster et al., (2015)	▪ 64 MJ	▪ Cognitive	▪ Higher levels of past year MJ use were associated

Author (Year)	Study Population	Design	Key Findings
	▪ Mean age: 20.81		with poorer episodic memory among sporadic Tob users but not among consistent Tob users.
Jansma et al., (2013)	▪ 10 NAD, 11 HC ▪ Mean age range: 21.2–25.6	▪ Pharmacological fMRI Task – MID	▪ THC administration was found to significantly reduce activity in the nucleus accumbens and caudate putamen during the reward anticipation phase in NAD subjects.
Rubinstein et al., (2014)	▪ 165 participants ▪ Age range: 13–17	▪ General linear model analysis of MJ use and NAD	▪ Frequency of MJ use was positively correlated with nicotine addiction across all measures of dependence
Bonn-Miller et al., (2011)	▪ 39 Tob, 34 MJ, 82 MJ+Tob, 67 HC ▪ Mean age: 22.43	▪ Clinical	▪ The tobacco-only group reported significantly higher negative affectivity with regard to anxiety and depressive symptoms compared to the other 3 groups. ▪ The combined user group also reported greater anxiety symptoms than the MJ only group and non-users.
Dube et al., (2015)	▪ 271 male, 319 female ▪ Age range: 17–24	▪ Clinical	▪ A “U” shaped association was observed between cannabis use and change in adiposity in male and female non-smokers. ▪ An inverted “U” shape association between cannabis use and change in adiposity was observed in male smokers.
Gage et al., (2014)	▪ 1756 participants ▪ Age: ~18	▪ Clinical	▪ Both MJ and Tob use were similarly associated with psychotic experiences although a majority of MJ users also reported Tob use.

MJ = Marijuana/Cannabis; Tob = Tobacco/Nicotine; HC = Healthy Control; MRI – Magnetic Resonance Imaging; fMRI – functional MRI; MID – Monetary Incentive Delay; THC – Δ^9-tetrahydrocannabinol; PET-HRRT – Positron Emission Tomography – High Resolution Research Tomograph; DAT – Dopamine transporter; NAD – Nicotine addiction; PCC – posterior cingulate cortex; mPFC – medial prefrontal cortex; NAcc – Nucleus accumbens