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Interaction of Cannabis Use and Aging: From Molecule to Mind

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Abstract

Given the aging Baby Boomer generation, changes in cannabis legislation, and the growing acknowledgment of cannabis for its therapeutic potential, it is predicted that cannabis use in the older population will escalate. It is, therefore, important to determine the interaction between the effects of cannabis and aging. The aim of this report is to describe the link between cannabis use and the aging brain. Our review of the literature found few and inconsistent empirical studies that directly address the impact of cannabis use on the aging brain. However, research focused on long-term cannabis use points toward cumulative effects on multimodal systems in the brain that are similarly affected during aging. Specifically, the effects of cannabis and aging converge on overlapping networks in the endocannabinoid, opioid, and dopamine systems that may affect functional decline particularly in the hippocampus and prefrontal cortex, which are critical areas for memory and executive functioning. To conclude, despite the limited current knowledge on the potential interactive effects between cannabis and aging, evidence from the literature suggests that cannabis and aging effects are concurrently present across several neurotransmitter systems. There is a great need for future research to directly test the interactions between cannabis and aging.

Keywords

Cannabis; aging; cannabis use; delta-9-tetrahydrocannabiol; endocannabinoid system

Introduction

Prevalence of cannabis use in older populations

Cannabis is one of the most commonly abused substances in the United States (Substance Abuse and Mental Health Services Administration, 2016), with increasing prevalence of use due to legalization and decreasing perception of harm (Carliner, Brown, Sarvet, & Hasin, 2017; Compton, Han, Jones, Blanco, & Hughes, 2016; Hasin, 2018). Between 2002 and 2014, cannabis use among adolescents remained fairly constant (Carliner et al., 2017), while use among adults over the age of 18 years increased consistently (Carliner et al., 2017; Han et al., 2017; Pacek, Mauro, & Martins, 2015). The National Survey on Drug Use and Health showed that between 2003 and 2014, the rate of past-year cannabis use rose from 2.95% to

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9.08% among the 50- to 64-year-old age group and from 0.15% to 2.04% among those older than 65 years (Substance Abuse and Mental Health Services Administration, 2016; Salas-Wright et al., 2017). This indicates a liberalization of cannabis use in the current older-adult population (i.e., 50 years or older), referred to as the Baby Boomer generation (born between 1946 and 1965; Black & Joseph, 2014). In this report, we define “older adults” as individuals 50 years or older (Lloyd & Striley, 2018). Based on the trend of decreased perceived harm from cannabis use among older adults (Carliner et al., 2017), the prevalence of medicinal and recreational cannabis use is expected to keep increasing.

Similar to other age groups, cannabis use is also associated with vulnerability toward comorbid neuropsychiatric and substance use disorders in older adults (Choi, DiNitto, & Marti, 2016; Choi, DiNitto, Marti, & Choi, 2016; Han et al., 2017). Wu and Blazer (2014) posit that substance use disorder has become one of the most common psychiatric conditions found in this population. The prevalence of cannabis use disorder is rising in the general population, which increased to 2.9% (2012–2013) from 1.5% in 2001–2002 (Hasin et al., 2015). The number of older users affected with cannabis use disorder appears to increase with the rate of cannabis use in older adults. For example, cannabis abuse and dependence based on *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria have increased from 0.4% to 1.3% in middle-aged to older adults (45–64 years) and 0.1% to 0.3% in those older than 65 years from 2001–2002 to 2012–2013 (Hasin et al., 2015). Kaskie, Ayyagari, Milavetz, Shane, and Arora (2017) noted that the increase of cannabis use in older adults is attributable to both medicinal and recreational uses that are difficult to distinguish, and Arora et al. (2019) found that older adults are currently more accepting about the use of medicinal cannabis. Of the older cannabis using population, peak age of first onset of use onset is 18–20, suggesting that potential effects in this population are predominantly from chronic or long-term use (Choi et al., 2016). This implies that despite the general changes in the perception of cannabis use, the cumulative effect of more than 30 years of regular cannabis use may be predominant in current older adults, compared to that of older adults who report a relatively recent onset of use. This indicates the need for determining the effects of long-term cannabis use on aging. Considering the trend of increasing cannabis use in older adults, it is essential to provide a prospective insight on the interaction between cannabis use and the aging process.

Cannabis mechanisms

The primary psychoactive ingredient in cannabis is delta-9-tetrahydrocannabinol (THC). Of the cannabinoids, THC is most widely associated with the negative effects of cannabis (Bhattacharyya et al., 2010), such as increased anxiety (Crippa et al., 2009), psychotic symptoms (D’Souza et al., 2004), increased impulsivity (McDonald, Schleifer, Richards, & de Wit, 2003), loss of learning capability (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003), motor control (Ramaekers et al., 2006), and substance use disorder (Hurd, Michaelides, Miller, & Jutras-Aswad, 2014; Stopponi et al., 2014). More recently, there is growing recognition that THC also provides therapeutic benefits that includes neuroprotection against oxidative stress (Hampson, Grimaldi, Axelrod, & Wink, 1998) and from the accumulation of amyloid-β peptides related to Alzheimer’s disease (Cao et al., 2014). THC acts as a partial agonist at two known endocannabinoid system receptors,

cannabinoid receptors 1 and 2 (CB1R, CB2R) and is a comparable affinity analog of the endogenous agonists anandamide (AEA) and 2-arachidonyl glycerol (2-AG; Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Felder & Glass, 1998; Paronis, Nikas, Shukla, & Makriyannis, 2012; Pertwee, 2008). Although its biochemical affinity is lower, THC also acts on the opioid system as an allosteric modulator (Kathmann, Flau, Redmer, Tränkle, & Schlicker, 2006; Pertwee, 2008). Thus, cannabis use directly modulates both the endocannabinoid and opioid systems. THC also indirectly modulates multiple other neurotransmitter systems, such as dopamine, serotonin, acetylcholine, and norepinephrine (Al-Hasani & Bruchas, 2011; Castillo, Younts, Chavez, & Hashimotodani, 2012), which may be due to CB1Rs being one of the most common G-protein-coupled receptors in the brain (Lovinger & Mathur, 2016). Endocannabinoids regulate the activity of the aforementioned neurotransmitters in the neocortex, limbic regions, basal ganglia, and cerebellum (Fride, 2005; Pazos, Nunez, Benito, Tolon, & Romero, 2005), which are disrupted by exogenous cannabinoids such as THC (Mato et al., 2004).

Aging mechanisms

Aging processes increase vulnerability toward some neurodegenerative disorders (Baker & Petersen, 2018; Mattson & Magnus, 2006). Fundamental age-related changes in the central nervous system (CNS) include cellular degradations due to reductions in energy metabolism (Camandola & Mattson, 2017) and accumulated oxidative damages (Peters, 2006; Sohal & Weindruch, 1996). Aging affects multiple neurotransmitter systems including the endocannabinoid, opioid, and dopamine systems. In the endocannabinoid system, animal studies show that CB1R density and its binding decrease particularly in the basal ganglia of aged rats, and the activity of messenger RNA expressing CB1R concurrently degrades (Romero et al., 1998; Berrendero et al., 1998). Further, the G-protein coupling of CB1R in limbic forebrain may decrease in older mice (Wang, Liu, Harvey-White, Zimmer, & Kunos, 2003). Evidence from humans, on the other hand, indicate that the CB1R density in the basal ganglia and hippocampus increases due to aging in females (Van Laere et al., 2008). However, there was not enough evidence exists to verify genetic and molecular level changes in CB1R. The activity of the opioid system also declines due to aging, as studies using rodents have found decreased levels of endogenous opiates and opioid receptor density and binding with aging (Agnati et al., 1986; Gambert, Garthwaite, Pontzer, & Hagen, 1980; Hess, Joseph, & Roth, 1981; Nagahara, Gill, Nicolle, & Gallagher, 1996; Petkov, Petkov, & Stancheva, 1988). These age-related changes in the endocannabinoid and opioid systems may be related to these systems' roles in defense mechanisms against stress factors and the management of adaptive responses such as fear and anxiety (Lutz, Marsicano, Maldonado, and Hillard (2015); Colasanti, Rabiner, Lingford-Hughes, and Nutt (2011)). Similar to the endocannabinoid and opioid systems, the dopamine system also deteriorates with aging in terms of concentration of receptors (Bäckman et al., 2011; De Keyser, Ebinger, & Vauquelin, 1990; Seeman et al., 1987), receptor binding level (Backman et al., 2000), and density of transporters (Ishibashi et al., 2009; Volkow et al., 1994).

At the systems level, neural and synaptic plasticity are significantly affected by normal aging. The process of neurogenesis occurs adult linearly with increasing age (Gage, 2002; Kuhn, Dickinson-Anson, & Gage, 1996; Manganas et al., 2007), especially in the

hippocampus (Gage, 2002; Manganas et al., 2007)—a region rich in endocannabinoids and CB1R (Glass, Dragunow, & Faull, 1997). Simultaneously, synaptogenesis also slows down due to aging (Luebke, Chang, Moore, & Rosene, 2004; Peters, Sethares, & Luebke, 2008; Petralia, Mattson, & Yao, 2014). At the tissue level, gray and white matter in the brain are significantly affected by aging, particularly in the hippocampus and frontal cortex (Fjell et al., 2009, 2014; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). Reduction in hippocampal volume is found to correlate with memory impairment in normal aging (Persson et al., 2012). Age-dependent degeneration in prefrontal gray and white matter have been associated with disruptions in executive function, such as attention and working memory (Gold, Powell, Xuan, Jicha, & Smith, 2010; Gopher and Koriat, 1999; Grady, 2012; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006).

Taken together, cannabis and aging effects are concurrently present across several neurotransmitter systems, but especially in the hippocampus and prefrontal cortex, which are critical in the interaction between aging and cannabis use.

The current literature on the effects of cannabis use in aging

To date, empirical studies regarding the effect of cannabis use in older adults are sparse. Thayer (2018) provided the most comprehensive report on the topic, highlighting significant structural and functional loss in individuals older than 60 years of age with a history of regular cannabis use defined once or more per week for at least the last year. The authors found that older cannabis users showed gray matter decline in the frontal pole and precentral cortex and reductions in performance on tasks utilize executive function that correlated with years of regular use. On the other hand, Auer et al. (2016) based on a large cohort (N = 3,385) followed for over 25 years, has shown that verbal memory, which relates closely to the hippocampus (Dolan & Fletcher, 1997), is more affected by prolonged cannabis use in older adults than executive function, which is subserved by the prefrontal cortex (Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2016). Burggren et al. (2018) studied former heavy users aged 57 to 75 years old with a history of cannabis abuse during adolescence (20 days per month during adolescence that declined to 1–2 uses per month after age 35, with the length of abstinence averaging at 29.9 ± 6.0 years). The authors reported significant reduction of gray matter in hippocampal subregions (cornu ammonis 1, 2, and 3 and dentate gyrus) that corresponded with memory impairment, showing that the effect of cannabis use during youth can persist and alter brain function in later life. Animal studies, however, have found opposing effects of cannabis in hippocampal volume and memory loss. For example, it was found that chronic (defined as 28 days of use) but low-dose exposure (3 mg/kg or lower) of THC increased the number of synapses in hippocampus and facilitated memory and learning functions in mature to older (12 and 18 months old) mice (Bilkei-Gorzo et al., 2017) and that a single injection of ultra-low-dose THC (0.002 mg/kg) to elderly mice (24 months old) achieves the same functional improvement (Sarne, Toledano, Rachmany, Sasson, & Doron, 2018). The difference between human and animal studies may be due to the potency of THC being examined, where higher doses may have led to the effects described in the human literature. Studies are needed to clarify the dose-dependent effects of THC in humans. Bilkei-Gorzo (2012) has an extensive review that highlighted the importance of the interaction between molecular and cellular processes of aging and changes

in the endocannabinoid system, but studies on chronic cannabis use and its interaction with aging effects have not been abundant since. In sum, a prospective review on the limited knowledge of the interaction between cannabis use and aging and the mismatch between preclinical and clinical studies is necessary.

Given the scarce empirical studies on the effects of cannabis in the aging population in humans, this review will try to integrate the separate effects of aging and cannabis use. The following sections will discuss these effects at the microscopic level (endocannabinoid and opioid and indirectly via dopamine, serotonin, acetylcholine, and norepinephrine systems) and at the macroscopic level (brain structures, networks, and behaviors).

Molecular level interactive effects of cannabis use and aging

The endocannabinoid system

The primary psychoactive ingredient of cannabis, THC, targets the endocannabinoid system. As Pertwee (2008) has extensively reviewed, the two known main functions of the endocannabinoid system are (1) regulatory inhibition of various neurotransmitters (i.e., dopamine, serotonin, acetylcholine, and norepinephrine) and (2) modulation of the immune system, as in inflammatory responses. Two known neuronal receptors in this system are CB1Rs, which are ubiquitous in the CNS, and CB2Rs, which are predominantly in peripheral immune cells (Pertwee, 2008). Throughout this review, we will describe the larger literature on the effects of chronic use of cannabis in the CNS via CB1R (Pertwee, 2006), although CB2R changes will be discussed in the section “Effects beyond THC and CB1Rs.”

Chronic cannabis use (see Tables 1 and 2 for study-specific definitions of chronic cannabis use) is known to affect the endocannabinoid system at the molecular level, inducing changes in endocannabinoids, cannabinoid receptors, and degrading enzymes. In general, the activity of the endocannabinoid system seems to be downregulated and the CB1Rs desensitized by long-term cannabis use (Gonzalez, Cebeira, & Fernandez-Ruiz, 2005). In the same vein, CB1R density has been consistently documented to decrease in animals and humans (Ceccarini et al., 2015; D’Souza et al., 2016; De Fonseca, Gorriti, Fernandez-Ruiz, Palomo, & Ramos, 1994; Villares, 2007), especially in neocortical regions, anterior cingulate cortex, hippocampus, and parahippocampus (Hirvonen et al., 2012). Martini et al. (2007) provided molecular evidence using cultured human cells that both internally and externally derived cannabinoids can downregulate CB1Rs. In human subjects, endogenous CB1R agonists show differential changes following frequent cannabis use, where AEA decreases and 2-AG increases in cerebrospinal fluid (Morgan et al., 2013). The level of endocannabinoid-degrading enzymes seems to diminish with frequent use of cannabis (Boileau et al., 2016). Boileau, et al. (2016) indicated that the fatty acid amide hydrolase, the enzyme that degrades AEA, is lower in chronic cannabis users than non-users (average duration of regular use = 17.5 ± 10.8 years). In sum, cannabis-dependent alterations at the molecular level in the endocannabinoid system are prominent in CB1Rs.

Some animal studies indicate age-related degenerative changes in CB1Rs that are similar to those induced by chronic use of cannabis in humans. In normal aging rodents, the mRNA level of CB1R seems to decrease in the hippocampus (Berrendero et al., 1998), as well as its

expression in the prefrontal and other cortices (Heng, Beverley, Steiner, & Tseng, 2011). The binding level of CB1Rs also seems to decrease in the basal ganglia (Romero et al., 1998), cerebellum, and cerebral cortex (Berrendero et al., 1998). Results on the density of CB1R are regionally specific, showing increases in the dentate gyrus of the hippocampus (Berrendero et al., 1998) and temporal cortex (Liu, Bilkey, Darlington, & Smith, 2003). However, some studies reported no distinct changes in CB1R densities in older mice (Wang et al., 2003). In humans with no history of cannabis use, Van Laere et al. (2008) showed that the concentration of CB1R across widespread brain regions seems to increase, although genetic and molecular-level changes that require invasive observations are currently unknown. Thus, changes of CB1R concentration in older adults, increases in counterbalance the decrease caused by chronic cannabis use. Nevertheless, it is probably the case that while the density of CB1Rs is at least intact or increasing during aging, there are molecular or genetic downregulations underlying CB1Rs (Bilkei-Gorzo, 2012), and future studies are required to quantify in vivo age-related effects in CB1Rs.

It is important to note that cannabis-dependent alterations and age-related deterioration may have a bidirectional interaction. This is demonstrated in animal studies showing differential CB1R effects across age groups. Using mice that genetically lack CB1Rs, a quadratic relationship between CB1R signaling and age was found such that 2-month-old animals without CB1Rs showed higher learning and memory performance compared to those with CB1Rs, while 5-month-old animals without CB1Rs showed performance indistinguishable to those with CB1Rs and 12-month-old animals showed worse cognitive performance relative to those with CB1Rs (Albayram et al., 2011; Albayram, Bilkei-Gorzo, & Zimmer, 2012). Neuronal loss in the hippocampus, which underlies memory function, was also noted in the 12-month-old animals (Driscoll et al., 2006; Golomb et al., 1996). Bilkei-Gorzo et al. (2012) suggested that age-related deterioration in cognition is accelerated in those without CB1Rs. This interaction between endocannabinoid system function and aging implies potential detrimental effects of cannabis use that can accelerate age-related decline, particularly as it relates to cognition.

There are two age-related factors that may modulate the effects of cannabis: regional specificity of CB1R changes and age by sex interaction of CB1Rs. Although the downregulation of CB1Rs is consistently found in chronic users, the change differs between brain regions (Ceccarini et al., 2015; Hirvonen et al., 2012). Using postmortem human brains that were cannabis-positive, Villares (2007) showed that the mRNA expression is reduced in the basal ganglia and hippocampal regions. For in vivo human brains, decreases in CB1R density were more prominent in neocortical regions, anterior cingulate cortex, and hippocampus (Ceccarini et al., 2015; Hirvonen et al., 2012; Villares, 2007). Concurrently, abstinence from cannabis use normalized downregulation, but the recovery was faster in the basal ganglia and slower in the hippocampus (Hirvonen et al., 2012). This indicates that the slower molecular adaptation of CB1Rs to THC in hippocampus suggests that it is more susceptible to molecular degeneration associated with cannabis use. This is further supported by a meta-analysis across 14 studies showing significant volumetric reduction of the hippocampus in cannabis users (Rocchetti et al., 2013). Berrendero et al. (1998) noted the age-related reduction of mRNA levels in hippocampal CB1R. Thus, the endocannabinoid system in the hippocampus is especially vulnerable to both age- and cannabis-related

neurodegeneration, suggesting that the effect of chronic cannabis use present in older adults may lead to deeper memory dysfunction.

The density of CB1Rs also depends on an age by sex interaction (Cha, Jones, Kuhn, Wilson, & Swartzwelder, 2007). It is widely reported that males use cannabis more frequently and in higher doses than females (Cuttler, Mischley, & Sexton, 2016) even in the older adult population (Choi, DiNitto, & Marti, 2016). While males appear to have denser concentrations of CB1Rs than females during earlier adulthood (18–45 years), CB1R concentrations remain unchanged in later adulthood in frontal and parietal cortices for males (45–70 years), whereas the concentration in females increase throughout brain regions across the life-span and eventually surpasses that of males (Van Laere et al., 2008). This suggests that normal aging can render the endocannabinoid system more vulnerable toward the effects of cannabis in males. Thus, future studies should take sex into account when determining the interaction between cannabis and aging on the endocannabinoid system.

The opioid system

THC acts as an allosteric agonist of opioid receptors (Kathmann et al., 2006; Pertwee, 2008) whose influence underlies hedonic response (Berridge & Robinson, 1998; Le Merrer, Becker, Befort, & Kieffer, 2009). Studies using aging rodents showed that the opioid system degrades in receptor density and binding of opioid receptors in the hippocampus (Amenta, Zaccheo, & Collier, 1991; Hess et al., 1981; Nagahara et al., 1996). The opioid system also significantly interacts with the dopamine system. For example, opioid agonists applied to the nigrostriatal pathway seems to increase dopamine metabolism (Wood, 1983), and dopamine agonists may briefly facilitate the activity of mRNA that expresses the opioid receptor (Azaryan, Clock, & Cox, 1996).

The endocannabinoid system interacts with the opioid system via CB1R and μ-opioid receptors that are localized in the striatum (Lopez-Moreno, Lopez-Jimenez, Gorriti, & de Fonseca, 2010; Pickel, Chan, Kash, Rodriguez, & MacKie, 2004) and lead to common functional outcomes. For instance, agonists for both receptors produce anti-nociceptive and sedative effects and drug-related rewards (Corchero, Manzanares, & Fuentes, 2004; Maldonado & Valverde, 2003). CB1R agonists have been found to attenuate the opioid signals induced via activating μ-opioid receptors, and vice versa; thus, activating two receptors simultaneously may reduce signals from both (Rios, Gomes, & Devi, 2006). Similarly, CB1R antagonists seem to mimic the inhibitory functions of μ-opioid antagonists (Schoffelmeer, Hogenboom, Wardeh, & De Vries, 2006). Using morphine-dependent rats (μ-opioid agonist), Navarro et al. (2001) found that a CB1R antagonist can cause behaviors that resemble opiate withdrawal symptoms, canceling the effect of opioid agonists in a similar way as opioid antagonists. A later study using rats showed that a CB1R agonist and antagonist can induce differential effects on morphine dependence; a CB1R agonist may counteract behavioral dependence toward supra-threshold morphine, while a CB1R antagonist may facilitate dependence toward subthreshold morphine (Ahmad, Lauzon, de Jaeger, & Laviolette, 2013). Owing to allosteric interactions, an antagonist to either of the two systems can modulate dependence on the other. Indeed, Singh, Verty, McGregor, and Mallet (2004) showed that a CB1R antagonist can attenuate morphine-related rewards in

morphine-dependent rats. In De Vries, Homberg, Binnekade, Raaso, and Schoffelmeer (2003), the authors also showed that a CB1R antagonist can be used to prevent the reinstatement of behavioral dependence toward opiates in rats after an extinction period of heroin (opioid agonist). However, in human cannabis users, the usage dose may affect the consequences, as Haney (2007) showed that an opioid antagonist reduces the intoxicating effect of low THC dose (20 mg) but not high dose (40 mg) for users (21–45 years old without comorbid drug dependence). In short, the endocannabinoid and opioid receptors interact as if they are cross-compatible systems that can be modulated by each other's ligands (Cooper and Haney, 2009).

In addition to mediating response to substances, the endocannabinoid and opioid systems share a fundamental common ground in modulating stress response, which is also associated with age-related alterations. The internal process dealing with external stress is the stress response that is centrally modulated by the hypothalamic-pituitary-adrenal (HPA) axis (Kandel, Schwartz, & Jessell, 2000). It activates in response to an acute external stress by releasing cortisol from the adrenal cortex that provides a negative feedback upon the hypothalamus to inhibit the activity of the HPA axis (Kandel et al., 2000). The activity of the endocannabinoid and opioid systems both increase in response to external stress (Mansi, Laforest, & Drolet, 2000; Patel, Roelke, Rademacher, & Hillard, 2005). Endocannabinoid agonists modulate the activity of the HPA axis to adjust the magnitude of the short- and long-term stress response (Hill & Tasker, 2012; Morena, Patel, Bains, & Hill, 2016). The opioid system also acts to diminish the stress response and normalize its physical and mental impacts (Drolet et al., 2001; Ribeiro, Kennedy, Smith, Stohler, & Zubieta, 2005). Because enhanced activation of the HPA axis is a risk factor for cannabis and opiate dependence (George, Le Moal, & Koob, 2012; Goeders, 2003), functional loss in the endocannabinoid and opioid systems may predispose one toward dependence.

While the activity of the HPA axis may vary in aging (Lupien et al., 1996), the level of stress response significantly correlates with structural and functional neurodegeneration related to aging, such that the stronger response to stress, the greater the hippocampal atrophy and corresponding memory loss (Issa, Rowe, Gauthier, & Meaney, 1990; Lupien et al., 1998; Lupien, McEwen, Gunnar, & Heim, 2009). Thus, an increase in the stress response may result in accelerated cognitive aging via alterations in the functionality of endocannabinoid and opioid systems. Because THC acts on both the endocannabinoid and opioid systems, long-term effects of cannabis use may exacerbate age-dependent disruptions in the stress response. Chronic cannabis users have been reported to show a blunted response toward external stress with regard to subjective stress ratings and cortisol levels (Cuttler et al., 2017). However, it appears that the stress-relieving effects of THC may be present for a brief period of time (Mayer, Matar, Kaplan, Zohar, & Cohen, 2014) and that higher doses of THC (12.5 mg) are not effective for this purpose and only disrupt cognitive functions (Childs, Lutz, & de Wit, 2017). It has been shown that the level of cannabis use correlates with lower amygdala activity in response to aversive stimuli (Cornelius, Aizenstein, & Hariri, 2010), which reflects attenuation of fear response (Phelps et al., 2001). Chronic cannabis users have also shown reduced sensitivity to aversive stimuli and negative affect (Somaini et al., 2012). These findings demonstrate that cannabis' modulatory effect on stress response wanes in those with longer duration of use and/or with higher THC potency, which may suggest

disruptions in the modulation of stress response following greater cannabis use. Indeed, chronic cannabis users show an increased level of cortisol at baseline (King et al., 2011) and an attenuated cortisol increase (Ranganathan et al., 2009), providing evidence for a compromise in the modulation of the stress response, which may be related to a reduction of the "on-demand" recruitment or mitigation of stress response in the users. In regard to aging, this can lead to amplified abnormalities especially in the hippocampus and its related functions, which increase vulnerability toward age-related degenerations and disorders (i.e., Alzheimer's disease). Importantly, alterations in the hippocampus can drive further hyperactivity in the HPA axis because the hippocampus also exerts inhibitory modulation on the hypothalamus (Pedersen, Wan, & Mattson, 2001). This can impose a cycle in older adults that may be more difficult to resolve.

The endocannabinoid and opioid systems also share endogenous pain analgesic effects (Bushlin, Rozenfeld, & Devi, 2010). Specifically, similar to opioid agonist's anti-nociceptive effect (Fields, Heinricher, & Mason, 1991), THC shows comparable analgesic effect in animals (Buxbaum, 1972) and in human patients with chronic pain (Ware et al., 2010). Further, agonists of these two systems appear to exacerbate each other's analgesic effect in rodents (Cichewicz, Martin, Smith, & Welch, 1999; Cichewicz & McCarthy, 2003), although results in humans are not as clear (Nielsen et al., 2017). CB1Rs are found in the periaqueductal gray, a midbrain region involved in pain modulation via opioid receptors (Basbaum & Fields, 1984). A significant proportion of CB1R and μ-opioid receptors are co-localized (Wilson-Poe, Morgan, Aicher, & Hegarty, 2012). Applying cannabinoid agonists to the periaqueductal gray created an analgesic effect in rats (Finn et al., 2003; Lichtman, Cook, & Martin, 1996; Wilson-Poe, Pocius, Herschbach, & Morgan, 2013). Injecting high-dose THC (at least 4 mg/kg) subcutaneously to mice amplified the effect of morphine and, importantly, the synergistic effect was canceled by adding a CB1R antagonist (Smith, Cichewicz, Martin, & Welch, 1998). Similarly, κ- and δ-opioid receptor antagonists attenuated the synergistic effect of THC and morphine in mice (Pugh, Smith, Dombrowski, & Welch, 1996). Together, these indicate that the cross-compatibility between two systems can exert similar analgesic outcomes. Cannabinoid agonists alone were also effective in reducing chronic neuropathic pain (Guindon, Desroches, Dani, & Beaulieu, 2007; Liang, Huang, & Hsu, 2007). Many older adults with chronic pain are prescribed opioids (Chau, Walker, Pai, & Cho, 2008), and medicinal use of cannabis appears to help reduce the dose of prescribed opiates in practice (Abuhasira, Schleider, Mechoulam, & Novack, 2018). Cross-sectional data showed that cannabis use was effective in pain relief (on average, 70% magnitude of pain relieved; Degenhardt et al., 2015). Longitudinal studies are needed to examine the duration of these effects.

The dopamine system

Dopamine is the primary neurotransmitter involved in reward response and substance use disorder (Berke and Hyman, 2000), and its signal encodes reward and motivation to achieve the reward (Wise, 2009). Endocannabinoids partially interact with the dopamine system in processes related to the development of substance use disorders, as Maldonado, Valverde, and Berrendero (2006) explain with well-illustrated, deeper discussions. The endocannabinoid system is at the balance between inhibition and excitation of the

dopamine-releasing neurons, but external application of cannabis seems to consequently increase dopamine due to depolarization-induced suppression of inhibition that attenuates inhibitory GABAergic inputs onto the ventral tegmental area (Lupica & Riegel, 2005; Maldonado et al., 2006), the origin of the dopamine reward pathway. THC also facilitates dopamine signals from the nucleus accumbens, a part of the mesolimbic reward pathway (Chen et al., 1990). On the other hand, the excitatory glutamatergic inputs that increase the release of dopamine are also simultaneously weakened by cannabinoids (Melis et al., 2004; Robbe, Alonso, Duchamp, Bockaert, & Manzoni, 2001), and these effects balance the concentration of dopamine and the reward signal, illustrated in Maldonado et al. (2006). In chronic cannabis users, this balance is compromised because the sensitivity of the glutamatergic and GABAergic synapses that modulate the dopamine signal decreases (Hoffman, Oz, Caulder, & Lupica, 2003), as well as dopamine synthesis (Bloomfield, Morgan, Kapur, Curran, & Howes, 2014). It appears that the effect of cannabis use is crucial to these long-term alterations in the dopamine system, because some of the impacts may be alleviated using cannabinoid antagonists (Diana, Melis, Muntoni, & Gessa, 1998; Lupica & Riegel, 2005).

Normal aging also significantly alters the dopamine system (Luine, Bowling, & Hearns, 1990). Dopamine receptors continuously decrease in binding level and density with aging (Backman et al., 2000; Bäckman et al., 2011; Mukherjee et al., 2002; Seeman et al., 1987), and dopamine transporters also decrease (Ishibashi et al., 2009; Volkow et al., 1994). However, the level of dopamine synthesis appears to be maintained in the older population (Karrer, Josef, Mata, Morris, & Samanez-Larkin, 2017) or even upregulated (Nandhagopal et al., 2011). Dreher, Meyer-Lindenberg, Kohn, and Berman (2008) showed that the reward-related blood-oxygen-level-dependent signal increases with lower basal level of dopamine in older individuals, in contrast with the young. The authors explained that this may be due to alterations of prefrontal modulation upon striatal dopamine regions. The increase of dopamine synthesis in older adults, therefore, may reduce the reward-induced activation. However, it was found that the higher level of synthesis in older adults is not significantly beneficial for cognitive functions associated with dopamine (Berry et al., 2016).

In sum, the associations between basal dopamine signals and endogenous synthesis of dopamine in cannabis users differ between younger and older individuals. In the older population, the reduction of dopamine synthesis due to cannabis use (Bloomfield et al., 2014) may be counterbalanced with the adaptive changes in the aging dopamine system. Although Dreher et al. (2008) and Berry et al. (2016) noted that the higher basal level of dopamine may not be beneficial for older adults, no expectations can be made on the changes of dopamine functions in older cannabis users due to the lack of previous studies. Further studies are required to discuss the trajectory of dopamine activity and the behaviors in older cannabis users to clarify the consequences in molecular and behavioral levels.

The serotonin system

Endocannabinoid receptors are highly expressed in the dorsal raphe nucleus where serotonin originates (Haring, Marsicano, Lutz, & Monory, 2007) and in the prefrontal cortex that regulates the activity of serotonin neurons in the dorsal raphe nucleus (Jankowski & Sesack,

2004). Cannabinoids modulate serotonin terminals via quadratic relationship, such that the repeated use of lower-dose (WIN 55,212-2 of 0.2 mg/kg) cannabinoids appears to enhance the activity of serotonin neurons, but a higher dose (WIN 55,212-2 of 2.0 mg/kg) decreases it (Bambico, Katz, Debonnel, & Gobbi, 2007). In normal aging, the serotonin system shows reduced receptor binding and losses in related functions, such as sleep and its quality (Meltzer et al., 1998).

Serotonin activity is associated with depressive disorders (Blier & de Montigny, 1999; Levinson, 2006), and cannabis use has been related to the increased risk toward the development of depression (Degenhardt, Hall, & Lynskey, 2003). For example, Hill, Sun, Tse, and Gorzalka (2006) showed that chronic cannabinoid treatment altered the activity of serotonin receptors in a manner similar to that reported in depression. The pathological effect of depression appears to resemble, and even accelerate, molecular and behavioral aging (Wolkowitz, Epel, Reus, & Mellon, 2010). Within cannabis users (> 50 years) who have major depressive episodes, their frequency of cannabis use showed a positive correlation with the odds of suicidal thoughts (Choi, DiNitto, Marti et al., 2016). Together, these findings indicate that older cannabis users may have disruptions in the serotonin system due to the effects of cannabis, which can lead to an increase in the vulnerability toward major depressive disorders or deeper symptoms within depression (i.e., suicidal ideation).

The acetylcholine system

The endocannabinoid and the acetylcholine systems closely interact with each other, as extensively reviewed in Oz, Al Kury, Keun-Hang, Mahgoub, and Galadari (2014). Endocannabinoids can bidirectionally modulate the release of acetylcholine (Degroot & Nomikos, 2007). The CB1R antagonist seems to increase the release of acetylcholine in the hippocampus (Degroot et al., 2006). An acute application of a CB1R agonist may also increase the release of acetylcholine (Acquas, Pisanu, Marrocu, & Di Chiara, 2000) via modulating μ-opioid and D1 dopamine receptors (Pisanu, Acquas, Fenu, & Di Chiara, 2006). In rats, this effect was found to be biphasic with a higher dose (5 mg/kg) of a CB1R agonist inhibiting acetylcholine projections from the hippocampus but facilitating with lower-dose (0.5 mg/kg) CB1R agonists (Tzavara, Wade, & Nomikos, 2003), and the inhibition of acetylcholine release due to higher-dose THC does not diminish after chronic administration (Tzavara et al., 2003). This suggests that the chronic use of cannabis has prolonged influences in reducing the acetylcholine signals in the brain (Carta, Nava, & Gessa, 1998).

In aging humans, the nucleus basalis of Meynert, a predominant origin of acetylcholine innervations, shows significant cell loss (Szenborn, 1993), which leads to the reduction of the activity in the acetylcholine system correlating with age-related cognitive impairments, particularly memory functions (Schliebs & Arendt, 2011). Studies testing spatial memory in rodents suggest that memory impairments due to cannabis use appear to be attributable to the hypo-activity of the acetylcholine system (i.e., the reduction of acetylcholine concentration; Mishima, Egashira, Matsumoto, Iwasaki, & Fujiwara, 2002; Nava, Carta, Battasi, & Gessa, 2000; Nava, Carta, Colombo, & Gessa, 2001; Varvel, Hamm, Martin, &

Lichtman, 2001). Applying a CB1R agonist caused memory impairments in rodents, and the deficit was normalized after using an acetylcholinesterase inhibitor (Goonawardena, Robinson, Hampson, & Riedel, 2010; Mishima et al., 2002). The effect on the acetylcholine system may be more important for memory impairments due to cannabis use than the direct alterations in CB1R signals, because Robinson et al. (2010) showed that the negative impact of WIN 55,212-2 (a CB1R agonist) upon memory is reversed by acetylcholinesterase inhibitors in rodents, but not CB1R blockers. In humans, Theunissen et al. (2015) found that applying an acetylcholinesterase inhibitor attenuates verbal memory impairment following the acute use of cannabis in occasional cannabis users. Further, a recent pilot study showed an improving trend of attention functions in humans with cannabis abuse/dependence defined in the DSM-IV, using an acetylcholinesterase inhibitor (Sugarman, De Aquino, Poling, & Sofuoglu, 2019). This suggests that some of the memory impairments due to cannabis use may be modulated by the functionality of the acetylcholine system in humans. Thus, chronic use of cannabis may accelerate the cognitive functional loss in older adults at a faster pace than in typical aging. To note, cannabis use is found to be highly comorbid with tobacco use (Goodwin et al., 2018), and the effect of cannabis use seems to interact with that of tobacco use in verbal learning and memory functions (Schuster, Crane, Mermelstein, & Gonzalez, 2015). Since nicotine contains the nicotinic acetylcholine receptor agonist, studies are needed to disentangle the interactive effects between cannabis and nicotine use in older humans.

The norepinephrine system

Norepinephrine is a neurotransmitter predominantly involved in the arousal and activity of the sympathetic nervous system, in addition to stress response, attention, and memory functions (Berridge & Waterhouse, 2003; Sara, 2009). Its innervations mainly originate from the locus coeruleus in the brainstem (Kandel et al., 2000). The endocannabinoid and the norepinephrine systems functionally interact with each other; the direct application of the cannabinoid to rats seems to disinhibit and consequently increase the activity of norepinephrine neurons (Muntoni et al., 2006) and increase the release of norepinephrine in the frontal cortex (Oropeza, Page, & Van Bockstaele, 2005). Further, endocannabinoid neurons are co-localized with norepinephrine neurons within the nucleus accumbens, nucleus tractus solitarius (Carvalho, Mackie, & Van Bockstaele, 2010), frontal cortex (Page, Oropeza, & Van Bockstaele, 2008), and locus coeruleus (Scavone, Mackie, & Van Bockstaele, 2010). In healthy older adults, norepinephrine level appears to decline in the basal forebrain and cortex, but not significantly in the hippocampus (Luine et al., 1990). In the human locus coeruleus (aged 49–98 years), however, the absolute number of neurons does not seem to decrease due to aging (Ohm, Busch, & Bohl, 1997). In male rats, while basal levels of norepinephrine in plasma remains unchanged, an increase in levels in response to external stress seems to be significantly higher in the older than younger adult rats (Mabry, Gold, & McCarty, 1995). In humans, the responsivity of the norepinephrine system toward external application of epinephrine agonists or antagonists appears to increase in normal aging (Peskind et al., 1995).

The endocannabinoid and norepinephrine systems interact in relation to stress response via the HPA axis (Gorzalka, Hill, & Hillard, 2008; Hill & McEwen, 2010; Hill et al., 2010;

Morilak et al., 2005), as reported in a more extensive review on this topic and well-documented by Scavone, Sterling, and Van Bockstaele (2013). Chronic application of a CB1R agonist (CP-55,940, 1 mg/kg for rats) is known to alter the baseline activity of the HPA axis (Corchero, Fuentes, & Manzanares, 1999), and the effect may be attenuated by norepinephrine antagonists (the effect of HU-210 of 0.1 mg/kg reduced by prazosin of 1 mg/kg or propranolol 2.5 mg/kg (McLaughlin, Hill, & Gorzalka, 2009). Interestingly, administering a CB1R agonist increased the transient release of norepinephrine, but prevented the release of norepinephrine in response to external stress (Reyes et al., 2012), indicating that cannabinoid intake can bidirectionally modulate the activity of the norepinephrine system. This is in line with changes found in chronic cannabis users, which show disrupted HPA axis function, so that it is hyperactive during baseline, yet shows attenuated dynamic response (i.e., reduction in on-demand responsivity). However, the age-related increase of responsivity to external stress in the norepinephrine system seems to be the opposite compared to the changes in chronic cannabis users. Thus, chronic cannabis use in older adults may have some counterbalancing effect in the norepinephrine system.

In terms of cognitive functions, the norepinephrine system is important in memory processing (Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006; Murchison et al., 2004; Przybyslawski, Roullet, & Sara, 1999; Tully & Bolshakov, 2010). Using older rats (22–25 months old), Luo et al. (2015) found that downregulation of norepinephrine levels in the hippocampus correlates with impaired emotional memory due to aging, which is recovered by supplementing norepinephrine. Similarly, Mei et al. (2015) showed that the depletion of norepinephrine can impair spatial memory in younger rats (3 months old) to the level of the older rats (30 months old). Additionally, memory impairment in the older rats was improved by applying exogenous norepinephrine. This indicates that the regulation of norepinephrine has important implications in memory functions of older adults, and its application may be protective against characteristic memory loss due to aging. Based on the fact that cannabis appears to increase circulating norepinephrine levels and reduce on-demand levels, studies are needed to determine how cannabis may lead to improvements in memory in older adults.

Summary

Although chronic cannabis use primarily affects the endocannabinoid system, its impact can be widespread across multiple neurotransmitter systems owing to the ubiquity of CB1Rs. Furthermore, presynaptic CB1Rs closely interact with other neurotransmitter systems by modulating the level of neurochemical signaling. This section described six neurotransmitter systems that are affected by both aging and cannabis use. The literature describes differential relationships, such as counteracting in the density of receptors (i.e., endocannabinoid) or level of synthesis (i.e., dopamine), or biphasic changes (i.e., norepinephrine). In addition, the interactive effects of cannabis and other neurotransmitter systems on cognitive functions, particularly memory, vary. For example, cannabis use induces a decrease in acetylcholine levels that leads to memory impairment, while cannabis upregulates the basal level of norepinephrine that leads to memory improvement. In sum, cannabis affects multiple neurotransmitter systems such that chronic use can potentially decrease the flexibility of neurotransmitter regulation.

Interactive effects of cannabis use and aging on neural and synaptic plasticity

The endocannabinoid system has fundamental functions in the mediation of neurogenesis and synaptic plasticity especially in the hippocampus (Harkany, Mackie, & Doherty, 2008; Heifets & Castillo, 2009; Mulder et al., 2008), as reviewed by Heifets and Castillo (2009). Neurogenesis, particularly in the hippocampus, plays a role in encoding new information and forgetting past memories (Akers et al., 2014). The mechanism of neurogenesis involves the activity of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF; Conner et al., 2009; Park & Poo, 2013; Rossi et al., 2006) and its interactions with the endocannabinoid system (Ferreira, Ribeiro, Rodrigues, Sebastiao, & Xapelli, 2018; Luongo, Maione, & Di Marzo, 2014; Keimpema, Hökfelt, Harkany, & Doherty 2014). The endocannabinoid signal appears to be functionally similar and temporally concurrent with that produced by the BDNF system. During neurogenesis, BDNF facilitates intracellular production of endocannabinoids and the expression of cannabinoid receptors (Lemtiri-Chlieh & Levine, 2010; Maison, Walker, Walsh, Williams, & Doherty, 2009). The initiated endocannabinoid signals may control growth, migration, and targeting of neuronal cells along with BDNF signaling (Berghuis et al., 2005; Mulder et al., 2008) and the survival of neurons (Galve-Roperh, Aguado, Palazuelos, & Guzman, 2008). Thus, activation of the endocannabinoid system is critical in the general process of neurogenesis (Aguado et al., 2005) and synaptogenesis (Berghuis et al., 2007).

The effect of external THC administration on neurogenesis seems to depend on two major factors: chronicity of administration and dose. Acute application (5 or 10 mg/kg) of THC increases the intracellular signaling of phosphorylated cAMP response element binding protein (CREB) that is associated with neurogenesis in the rats' granule cell layer of the cerebellum (Casu et al., 2005), but repeated/chronic use of a low-dose CB1R agonist (i.e., THC) appears to increase the same signal in the nucleus accumbens (1.5 mg/kg of THC for 7 days), the hippocampus (0.1 mg/kg of HU 210 for 10 days), and the prefrontal cortex (2.0 mg/kg of THC every 48 hours for 21 days) of rats (Butovsky et al., 2005; ElBatsh, Moklas, Marsden, & Kendall, 2012; Jiang et al., 2005). Finally, studies using rodents' brains show that while low-dose THC (3 mg/kg for 28 days) was found beneficial for neurogenesis (Bilkei-Gorzo et al., 2017), a higher dose or increasing doses seem to be ineffective (increasing from 20 to 80 mg/kg for 3 weeks; Kochman, dos Santos, Fornal, & Jacobs, 2006) or even produce impairments in hippocampal synaptogenesis (10 mg/kg for 7 days; Fan, Yang, Zhang, & Chen, 2010). The translation of the aforementioned results using animals to the case of humans, however, requires caution because of not only the systematic differences but also that animal studies lack the qualitative analyses on complex changes in cognitive functions after applying THC. Prenderville, Kelly, and Downer (2015) introduced more relevant examples in this area. Calabrese and Rubio-Casillas (2018) and Sarne, Asaf, Fishbein, Gafni, and Keren (2011) provided comprehensive perspectives on how chronicity and dose can render differential effects in cellular and functional levels.

The endocannabinoid system is an important mediator of synaptic plasticity in the brain. As mentioned earlier, endocannabinoids are ubiquitous retrograde ligands, which release upon

postsynaptic excitation, then reduce the presynaptic release of various neurotransmitters, thereby modulating short-term synaptic plasticity (Alger, 2002; Katona and Freund, 2012; Pertwee, 2008). Further, endocannabinoids are involved in prolonged synaptic plasticity largely via long-term depression (LTD) by inhibiting presynaptic glutamatergic signaling shortly after it was received in the postsynaptic neuron (Ghosh, Reuveni, Zidan, Lamprecht, & Barkai, 2018; Heifets & Castillo, 2009). The endocannabinoid system is also implicated in modulating long-term potentiation (LTP) induced by a fast train of presynaptic excitatory signals. This modulation can be primed by external cannabinoids. Upon administration, the resulting cannabinoid signals may exert retrograde inhibition upon excitatory synapses to reduce LTP (Davies, Pertwee, & Riedel, 2002) or selectively facilitate the synaptic LTP by inhibiting synapses that oppose the excitatory connections (Chevaleyre, Takahashi, & Castillo, 2006). In the hippocampus, studies using mice showed that not having CB1R relates to higher capability to strengthen synaptic connections and form new memories (Bohme, Laville, Ledent, Parmentier, & Imperato, 1999) and being protective against neuronal damages due to ethanol (Subbanna, Shivakumar, Psychoyos, Xie, & Basavarajappa, 2013). Slanina, Roberto, and Schweitzer (2005) also showed that blocking CB1R enhances LTP by lowering activation thresholds using rat hippocampal slices. Thus, endocannabinoid signaling may have a double-edge effect in neural and synaptic plasticity by both increasing neurogenesis but also disrupting synaptic transmission.

The processes of neurogenesis and synaptogenesis are intact in older adults (Burke & Barnes, 2006), albeit downregulated (Kuhn et al., 1996; Luebke et al., 2004; Manganas et al., 2007; Martin-Pena et al., 2006; Olariu, Cleaver, & Cameron, 2007; Peters et al., 2008; Petralia et al., 2014). Activity of BDNF, an important factor for the two processes, is significantly affected in normal aging. While the decrease of BDNF concentration is restricted to the midbrain, the expression of BDNF receptors that initiates the signals is reduced in widespread areas, as discovered in rats (Croll, Ip, Lindsay, & Wiegand, 1998). In rats' hippocampus, levels of BDNF mRNA appear to be stable in normal aging (Lapchak et al., 1993), and Katoh-Semba and colleagues showed that the level of BDNF in hippocampus is upregulated in older rats and mice (Katoh-Semba, Semba, Takeuchi, & Kato, 1998). It is noteworthy that not all subdivisions of the hippocampus undergo age-related neuronal loss (West, 1993). While physiological properties of the healthy older adults' hippocampus are largely preserved (Burke & Barnes, 2006; Lister & Barnes, 2009), changes in synapses were more prominent. The excitatory postsynaptic field potential in the perforant path of the hippocampus seems to decrease in amplitude in older rats (Barnes & McNaughton, 1980); therefore, the number of synapses appears to be reduced by normal aging (Geinisman, de Toledo-Morrell, Morrell, Persina, & Rossi, 1992). In terms of synaptic plasticity, normal aging contributes to a lower threshold for LTD while causing the reversal of LTP to be easier, thus increasing the ratio of LTD over LTP in the hippocampus (Norris, Korol, & Foster, 1996). Further, the threshold for inducing LTP in the hippocampus increases, making LTP more difficult to happen (Barnes, Rao, & Houston, 2000), leading to reductions in encoding and consolidation efficiency and deletion of past memories in the older population. Indeed, behaviorally, the tendency to develop more LTD is associated with impaired memory functions (Foster & Kumar, 2007).

In normal aging, the most important age-related neurodegeneration may influence generation and maintenance of hippocampal cell synapses versus neurogenesis. It has been widely reported that to overcome this loss in hippocampal function, compensatory mechanisms through the recruitment of prefrontal regions are utilized in older adults (Bartsch & Wulff, 2015; Dennis, Daselaar, & Cabeza, 2007; Gutchess et al., 2005; Miller et al., 2008; Persson et al., 2006). However, this compensation does not seem as efficacious as relying on hippocampal activity for memory encoding (Miller et al., 2008; Persson et al., 2006). This suggests that maximizing the synaptic plasticity in the hippocampus during memory processing can be beneficial for older adults to attenuate potential functional decline.

Recent studies using old rodents reported that long-term low-dose exposure to THC (3 mg/kg for 28 days) enhances the synaptogenesis and the level of dendritic spine density in hippocampal neurons of 12- to 18-month-old mice (Bilkei-Gorzo et al., 2017), and even a single injection of the low-dose THC (0.002 mg/kg) may normalize memory and learning impairment of 24-month-old mice (Sarne et al., 2018). The mechanism of action in the above-mentioned benefits in synaptogenesis is dependent on the agonistic effect of endocannabinoid upon BDNF signaling (Berghuis et al., 2005; Mulder et al., 2008). However, D'Souza, Pittman, Perry, and Simen (2009) found lower baseline BDNF without an expected BDNF increase following THC administration in human cannabis users diagnosed with cannabis abuse disorder. On the other hand, Angelucci and colleagues did not find the reduction of BDNF in cannabis-dependent users, but reported that the NGF decreased in concentration (Angelucci et al., 2008). Regular use of high-dose THC (10 mg/kg for 7 days), which is more in line with typical human levels of consumption, also seems to reduce intracellular signals and synaptic currents gated by glutamatergic receptors, consequently decreasing the hippocampal LTP in rodents (Fan et al., 2010; Hoffman, Oz, Yang, Lichtman, & Lupica, 2007). From these, it can be presumed that older cannabis users may have reduced neuronal and synaptic plasticity due to altered baseline capability for synaptogenesis and that further use of cannabis in a controlled dose might not be beneficial due to potential tolerance in both endocannabinoid and BDNF systems.

To summarize, neurogenesis and synaptogenesis are cellular processes important in the preservation of brain function. Synaptogenesis degrades with age and leads to the loss of memory functions. The literature demonstrates an important regulatory role of endocannabinoid signaling in memory function such that downregulation of the endocannabinoid system caused by chronic cannabis use can impair memory similar to aging. On the other hand, low-dose THC aids hippocampal synaptogenesis in rodents.

Effects of cannabis use and aging on brain structures, networks, and behaviors

Macroscopic effects of normal aging have been extensively documented using behavioral tasks coupled with neuroimaging techniques that can observe brain structures and networks associated with specific functions. Two of the most distinct structural changes in the brain as a result of aging relate to the hippocampus and the prefrontal cortex. Notably, brain regions,

networks, and functions predominantly altered by normal aging overlap with those affected by chronic cannabis use (Broyd, van Hell, Beale, Yucel, & Solowij, 2016) because these regions are rich with cannabinoid receptors (Lorenzetti, Solowij, & Yucel, 2016).

As already mentioned in detail in the above sections, gray matter loss in the hippocampus is one of the primary degenerations associated with normal aging (Driscoll et al., 2006), with its degenerative pace increasing with age (Raz, Rodrigue, Head, Kennedy, & Acker, 2004). Hippocampal decline is directly related to deficits in learning and memory (Driscoll et al., 2006), as described above. Gray and white matter in the prefrontal cortex seem to be highly susceptible to age-related degenerations (Allen, Bruss, Brown, & Damasio, 2005; Gunning-Dixon et al., 2009; Raz et al., 1997; Salat, Kaye, & Janowsky, 1999; Salat, Kaye, & Janowsky, 2001). Among brain networks, the prefrontal cortex and frontoparietal network develop later in life, with the frontoparietal network being more susceptible toward degeneration with increasing age (Douaud et al., 2014; Zhang et al., 2014). Prefrontal cortex and frontoparietal network functions, such as executive function (Miller & Cohen, 2001), most vulnerable to normal aging (Buckner, 2004; Grady, 2008; Salthouse, 2009). Executive function includes performance in external tasks, inhibition, attention, cognitive flexibility, and working memory (Braun et al., 2015; McNab et al., 2008; Miller and Cohen, 2001; Schulze et al., 2011). The integrity of frontoparietal network fibers are critical in tasks related to control and cognitive flexibility, which also deteriorate with aging (Fjell et al., 2016; Gallen, Turner, Adnan, & D'Esposito, 2016; Gold et al., 2010).

In terms of the effects of cannabis on brain structure, although some cross-sectional studies found no difference in chronic cannabis users (Koenders et al., 2017; Matochik, Eldreth, Cadet, & Bolla, 2005; Tzilos et al., 2005), the majority of studies report that hippocampal volume is reduced in both chronic and light users (Chye et al., 2017; Cousijn et al., 2012; Demirakca et al., 2011; Orr, Paschall, & Banich, 2016; Yücel et al., 2008). White matter connected to the hippocampus also show decreases in heavy cannabis users (Zalesky et al., 2012). Significant memory deficits were found in chronic cannabis users (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Solowij and Battisti, 2008), with memory loss being one of the most robust functional findings in both acute and chronic cannabis users (Broyd et al., 2016). Cannabis users may compensate for memory impairments by recruiting parahippocampal activity during memory encoding. This tendency was found greater in higher-frequency cannabis users than lower-frequency users (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010). A recent study in older adults with a history of long-term cannabis use added that while most parts of the hippocampus exhibit gray matter loss, neocortical regions surrounding the hippocampus (i.e., entorhinal, perirhinal, and parahippocampal cortices) do not (Burggren et al., 2018). Thus, it appears that the initial compensatory mechanism for the hippocampal decline due to cannabis use involves para-hippocampal regions that are relatively preserved.

Chronic cannabis users have also demonstrated gray matter loss in the orbitofrontal cortex (Arnone et al., 2008; Filbey et al., 2014; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011). They also show white matter degenerations in frontal regions (Brumback, Castro, Jacobus, & Tapert, 2016), but these results are less consistent. Jakabek, Yücel, Lorenzetti, and Solowij (2016) have shown that the cannabis-related changes in the integrity of white matter

may be complicated by the aging effect, so that the diffusivity within white matter increases toward different directions due to cannabis use and aging. This partly explains the inconsistency of the results on white matter changes due to chronic cannabis use. Cannabis users show disruptions in the frontoparietal functional network (Chang, Yakupov, Cloak, & Ernst, 2006). Resting-state functional connectivity in prefrontal regions was found to be hyperactive in cannabis users (Filbey et al., 2014; Filbey & Yezhuvath, 2013). During behavioral tasks, cannabis users have shown hyperconnectivity in the frontoparietal network (Harding et al., 2012), with decreased network activation during a visuomotor task, suggesting that the functional connectivity changes may imply compensatory recruitment to maintain task performance.

These studies show that cannabis-related macroscopic changes in gray matter and functional networks are concordant with age-related structural and functional alterations. Thus, it is likely that chronic cannabis use coupled with normal aging may increase vulnerability toward degenerative disorders. In addition, prefrontal degeneration in older adult users due to aging (Fjell et al., 2016) could lead to a greater imbalance between prefrontal cognitive control and reward response. In the Impaired Response Inhibition and Salience Attribution model, prefrontal dysfunction could lead to exaggerated craving-related attention (i.e., biased attention) that is unmatched by prefrontal cognitive control (Goldstein and Volkow, 2011). This imbalance has been noted as a key mechanism behind substance use disorders, including cannabis use disorder (Volkow, Wang, Fowler, Tomasi, & Telang, 2011; Zehra et al., 2019). Some effective treatment strategies in cannabis use disorder, such as cognitive behavioral therapy and contingency management (Sherman & McRae-Clark, 2016), are indeed dependent on prefrontal cortical functions, such as executive function (Mohlman & Gorman, 2005; Takeuchi et al., 2013). Although a longitudinal study on middle-age to older adults has shown that the integrity of executive function may not necessarily decrease due to the length of cannabis use (Auer et al., 2016), aging may still have a detrimental effect (Fjell et al., 2016). Due to these aging effects on prefrontal cortical functions, response to treatment in older chronic cannabis users may be more challenging.

Finally, it is noteworthy that the functional loss in the hippocampus in older adults induces an alternative mechanism in memory processing, recruiting prefrontal neurons, and establishing the new functional connectivity between the hippocampus and prefrontal cortex (Bartsch & Wulff, 2015; Dennis et al., 2007; Gutchess et al., 2005; Miller et al., 2008; Persson et al., 2006). This compensation in chronic cannabis users, however, may be less efficient, because both the prefrontal cortex and hippocampus experience faster degeneration than in healthy older adults. In other words, chronic cannabis use in older adults may reduce the capacity of functional scaffolding (Park & Reuter-Lorenz, 2009) that can aid in sustaining memory performance.

Cannabis use in age-related neurodegenerative diseases

Dementia is one of the most prevalent age-related neurodegenerative disorders. In 2010, 4.7% of those 60 years or older worldwide were diagnosed with dementia (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012). Alzheimer’s disease is the most common form of dementia, populating around 70% of dementia cases (Reitz, Brayne, & Mayeux, 2011).

Some of its behavioral symptoms include progressive loss of episodic memory, difficulties in daily life and learning process, and psychological aspects such as depression (Amieva et al., 2008).

There has been an extensive amount of studies on the cause and treatment for Alzheimer's disease, although a clear understanding has not yet been fully determined. The molecular-level pathology of Alzheimer's disease has been identified by an increase in specific molecules in the brain (i.e., neurofibrillary tangles and amyloid-beta plaques; Alzheimer, 1911; Jack et al., 2016). Kinney, Bemiller, Murtishaw, Leisgang, and Lamb (2018) also noted that the prolonged inflammatory responses in the brain may be also an important underlying mechanism of the onset of Alzheimer's disease. Chronic neuroinflammation relates to the neuronal damages characteristic to Alzheimer's disease (Akiyama et al., 2000; Heneka et al., 2015). In particular, a distinctive cellular feature in Alzheimer's disease is hippocampal cell loss (Apostolova et al., 2006; Fjell et al., 2014), which correlates with memory impairment in healthy older adults (Golomb et al., 1993; Golomb et al., 1996).

Medicinal use of cannabis may be effective in alleviating neuroinflammation found in Alzheimer's disease. Using low-dose synthetic cannabinoid for a short period of time (WIN 55,212-2 0.01 mg, 7 days) prevented inflammatory responses in rodents' brains affected by Alzheimer's disease (Ramirez, Blazquez, Gomez del Pulgar, Guzman, & de Ceballos, 2005). Low-dose administration of synthetic cannabinoid for a longer time (JWH-133 0.2 mg/kg, 4 months) was also effective in reducing neuroinflammatory responses (Martin-Moreno et al., 2012). Importantly, using naturally available THC and cannabidiol (CBD) together showed efficacy in preserving memory functions in mouse model of Alzheimer's disease. A single application of an ultra-low dose (0.002 mg/kg) of THC was also found to be protective against artificially induced inflammatory responses in mice (Fishbein-Kaminietsky, Gafni, & Sarne, 2014). Such benefits of cannabinoids may be due to its antioxidative effects (Bonnet & Marchalant, 2015; Carracedo et al., 2004).

Cannabis also showed therapeutic effects in reversing functional and structural damages in the hippocampus. Again, low-dose administration (0.1 mg/kg) of synthetic cannabinoids for a short time (10 days) was found to promote neurogenesis in the hippocampus (Jiang et al., 2005). Both acute (7 days) and chronic (21 days) applications of low-dose (1.5 mg/kg) THC was also reported to facilitate steps in neurogenesis (Suliman, Taib, Moklas, & Basir, 2018). The similar treatment using THC (3 mg/kg) for a longer time (28 days) reversed age-related deficits in learning and memory as well as enhancing synaptogenesis in the hippocampus (Bilkei-Gorzo et al., 2017). Even using a single injection of ultra-low-dose THC (0.002 mg/kg) in mice was capable of increasing tissue volume of the posterior hippocampus, which is involved in spatial memory and learning functions (Sarne et al., 2018). Despite the discrepancies in dosage, these findings suggest that repeated use of controlled low-dose cannabinoids, synthetic or natural, might provide a preventive effect on the pathologies of Alzheimer's disease, particularly in regard to reducing neuroinflammatory responses and facilitating hippocampal neurogenesis (Marchalant, Baranger, Wenk, Khrestchatisky, & Rivera, 2012). It is noteworthy that all of these findings were in rodents and potential contributions of the individual cannabinoids (e.g., THC, CBD) and their entourage effects in human subjects are yet to be elucidated.

Parkinson's disease is another prevalent neurodegenerative disorder, occurring in 1% of adults older than 60 years of age (Erkkinen, Kim, & Geschwind, 2018). It is characterized as significant loss in dopamine cells with pronounced deficits in motor functions, and the most severe loss of neurons occurs in the substantia nigra, where dopamine projections targeting upper motor system originate (Alexander, DeLong, & Strick, 1986; Ross et al., 2004). Although the degeneration in the dopamine system is not enough to fully explain the pathology (Lang & Obeso, 2004), supplementing the precursor of dopamine (L-DOPA) or dopamine agonist alleviates some of the symptoms (Cools, 2006; Hornykiewicz, 1974). Thus, treatment of Parkinson's disease has been focused on replenishing dopamine signals in the brain and enhance the associated functions, particularly those that are motor-related.

Because THC increases dopamine release in the striatum, it is worth considering its therapeutic potential in Parkinson's disease (Bloomfield, Ashok, Volkow, & Howes, 2016; Bossong et al., 2009; Stokes et al., 2010). In a rat model, daily administration of THC for a medium length of time (3 mg/kg for 2 weeks) was found to reduce the pace of dopamine cell death (Lastres-Becker, Molina-Holgado, Ramos, Mechoulam, & Fernandez-Ruiz, 2005). Garcia-Arencibia et al. (2007) found in rats that a synthetic cannabinoid reversed the loss of dopamine signals (HU-308, 5 mg/kg). Further, in a human cell culture model, a single injection of THC (0.01 mM) was found to result in neuroprotective effects to cells against toxins that induce Parkinson's disease via upregulating CB1R (Carroll, Zeissler, Hanemann, & Zajicek, 2012). Animal models using marmosets (van Vliet, Vanwersch, Jongsma, Olivier, & Philippens, 2008) and drosophila (Jimenez-Del-Rio, Daza-Restrepo, & Velez-Pardo, 2008) further indicated that cannabinoid agonists may recover motor functions in Parkinson's disease.

Despite the neuroprotective effect of THC or the other cannabinoids in Parkinson's disease, it is essential to note that most of the previous studies were regarding acute damages that induce Parkinsonian symptoms and target the dopamine system only. A real-life model of Parkinson's disease takes lifelong accumulated damages and compensations in multiple systems (Dauer & Przedborski, 2003). Furthermore, an important risk to note is that dopamine therapy for Parkinson's disease increases susceptibility toward development of impulse control disorder, which is a behavioral addiction that relates to pathological gambling or compulsive behaviors reported in Parkinson's disease patients (Weintraub et al., 2010). Impulse control disorder shares pathophysiological features with substance use disorder, especially in the loss of sensitivity in reward pathways (Brewer & Potenza, 2008). This may occur because of an imbalance in Parkinson's disease patients' functions of the ventral striatum, which underlies reward processing, and the dorsal striatum that underlies motor control due to dopamine agonist "flooding" of the reward pathway (Voon, Mehta, & Hallett, 2011). It is reported that chronic use of THC upregulates BDNF in ventral tegmental area and nucleus accumbens, which may result in enhanced reward response (Butovsky et al., 2005). Thus, the application of cannabinoids for treating the human model of Parkinson's disease shows great promise, although more research is needed.

This section focused on Alzheimer's disease and Parkinson's disease given their high prevalence rate (Erkkinen et al., 2018). In the United States, around 9.74% of the older adults aged older than 70 years have Alzheimer's disease (Plassman et al., 2007), and

around 1% to 2% of those older than 65 years have Parkinson's disease (Kowal, Dall, Chakrabarti, Storm, & Jain, 2013). Because of their prevalence, there is greater literature on these two diseases relative to other neurodegenerative diseases. FTD is another form of dementia common in those younger than the age of 60 (Ratnavalli, Brayne, Dawson, & Hodges, 2002; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). There are two studies on its potential treatment via activating CB2R in peripheral nervous system on transgenic mice that show characteristics of FTD (Espejo-Porras et al., 2015, 2019). They found that the mouse model of the disorder shows increased concentration of CB2R in the spinal cord. However, further studies are needed to confirm that modulating CB2R will be effective to mitigate changes in CNS. Cannabinoids have also been tested to treat some symptoms of Lewy body dementia. Cannabidiol (CBD) may be effective in reducing psychotic symptoms in Lewy body dementia (Zuardi et al., 2009), as well as alleviating ischemic, perfusion-related damages in vascular dementia (Roman, 2003). Mechanisms for these effects may be due to alleviation of autophagy and inflammatory responses induced by neurovascular damages that can then exert neuroprotective effects (Wang et al., 2018).

Effects beyond THC and CB1Rs

Given that the majority of the literature has described the effects of THC, we largely focused on the effects of THC and the activation of CB1R in older cannabis users. However, THC is not the only compound in cannabis that has known effects on the brain. There is also emerging literature on CBD, an allosteric antagonist of CB1R and CB2R with lower binding affinity than THC that exhibits no psychoactive properties (Pertwee, 2008). CBD may counterbalance some of the undesired effects of THC (Hermann & Schneider, 2012). Thus, CBD may have a potential use in reversing THC-induced damages in older adults, along with other therapeutic benefits. At the molecular level, despite its relatively lower affinity to cannabinoid receptors, CBD is known to significantly antagonize the effect of THC (Pertwee, 2008). For example, cannabis users who predominantly have residual THC seem to show higher psychotic symptoms that resemble schizophrenia (Morgan and Curran, 2008), while those with more CBD show less cognitive impairment (Morgan, Schafer, Freeman, & Curran, 2010). In addition, chronic THC administration was shown to induce hippocampal atrophy and cognitive loss, while CBD showed a protective effect against hippocampal degeneration (Demirakca et al., 2011; Lorenzetti et al., 2016; Yücel et al., 2016). CBD and THC have "entourage effects" such that pretreating CBD before THC can increase the remaining concentration of THC by attenuating its metabolism in the brain (Klein et al., 2011). However, when the behavioral effect was measured per separate use of THC or CBD, a single administration of THC was found to facilitate anxiety, intoxication, and positive psychotic effects compared to CBD (Fusar-Poli et al., 2009; Winton-Brown et al., 2011). In addition, CBD shows the opposite activity patterns during various cognitive tasks in comparison to THC (Bhattacharyya et al., 2010).

As reviewed above, preclinical studies show that a controlled use of THC may enhance neuroprotection and functional compensation in the hippocampus, but CBD alone can exert therapeutic effects, as reviewed in Chye, Christensen, Solowij, and Yücel (2019). CBD was found to reduce the inflammatory responses, protect against cell death (Castillo, Tolón, Fernández-Ruiz, Romero, & Martinez-Orgado, 2010; El-Remessy et al., 2006), and prevent

hippocampal neurodegeneration (Schiavon et al., 2014). CBD even appears to reverse neurodegenerations in hippocampus caused by chronic cannabis use, which may be useful to alleviate the accumulated damages of cannabis use in older adults (Beale et al., 2018). This evidence suggests that the presence of CBD is a beneficial complement to THC, which can increase the therapeutic effects and reduce undesired psychoactive effects and cognitive deficits in older adults. However, a longitudinal study in older adults should be performed controlling the dose of cannabis with a consistent ratio of CBD over THC to clarify the medicinal benefits cannabis can provide.

It is also noteworthy that the chemical composition of cannabis has changed over time, with different strains containing higher THC levels. Cascini, Aiello, and Di Tanna (2012) reviewed studies worldwide and found the mean percentage of THC included in consumed cannabis has risen from 0.93% in 1970 to 9.75% in 2010. ElSohly et al. (2016) further noted that in recent years, from 2009 to 2014, the average potency of consumed THC is an increasing trend (9.75%–11.84%), whereas the trend of CBD is decreasing (0.39%–0.15%) in the United States. Higher-potency cannabis has been associated with greater negative impact on users' behaviors (Volkow, Baler, Compton, & Weiss, 2014). Thus, the effects of long-term use in older adults may differ from those in younger adults simply due to the fact that younger adults may have had access to higher-potency THC longer than older adults. The varied potency of THC and other cannabinoid levels in cannabis over the last few decades is important to consider when extrapolating differences between younger and older adults, as well as when determining the effects of long-term use in older individuals.

Unlike CB1R that is prominent in the CNS, CB2R is an endocannabinoid receptor type found mostly in the peripheral nervous system and immune cells (Pertwee, 2006; Pertwee, 2008). Although its role is not as well-documented as CB1Rs, some of the important therapeutic effects of cannabis appear to involve changes in the neuroimmune system (Aso et al., 2015; Martin-Moreno et al., 2012; Ramirez et al., 2005), where CB2R signaling is important. As one ages, oxidative stress accumulates over time and attacks the mitochondrial function that processes metabolism so that the neurons in older populations have less energy efficiency and are more susceptible to further damages (Lu et al., 2004). In this regard, the neuroimmune activity represented as microglial activity also increases in normal aging (Schuitemaker et al., 2012). Neuroinflammation is not significantly increased in normal aging (Suridjan et al., 2014), but those with neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease (Heneka et al., 2015; Hirsch & Hunot, 2009), show distinct neuroinflammatory responses in regions associated with corresponding functional loss (Ownby, 2010).

The neurodegenerative diseases associated with aging are attributable to changes in the mitochondrial DNA (Wilkins & Swerdlow, 2016). They can further lead to accumulation of damaged mitochondria or cell death, both of which can trigger inflammatory responses that link to neurodegenerative diseases (Green, Galluzzi, & Kroemer, 2011). CB2R is expressed in glial cells in the CNS and is thought to modulate inflammatory response (Ashton & Glass, 2007). For instance, the activation of CB2R seems to prevent glial activation and increase cytokines and chemokines associated with inflammation (Chung et al., 2016). Thus, external modulation of CB2R activity may help reduce the neuroinflammatory responses that lead to

cell damage. CB2R agonists were further found to be protective to ischemic damages in neurons (Choi et al., 2013; Fujii et al., 2014) and degeneration in white matter fibers (Arévalo-Martín et al., 2008). Further, activating CB2R may increase the cell proliferation in the brain (Galve-Roperh et al., 2013). Palazuelos et al. (2006) and Palazuelos, Ortega, Diaz-Alonso, Guzman, and Galve-Roperh (2012) showed that applying CB2R agonists can increase the hippocampal cell proliferation. In sum, administration of CBD may reduce neuroinflammation by binding to the peripheral CB2R in immune cells (Turcotte, Blanchet, Laviolette, & Flamand, 2016) or aid the neurogenesis in the CNS. CB2R agonists, including CBD, may be effective for targeting age-related neurodegeneration.

Summary and conclusions

The challenge in the literature is in determining the specific effects of cannabis from specific effects of aging. To date, there have been few empirical studies that have addressed this question. The study by Burggren et al. (2018) compared older individuals who formerly used cannabis (length of abstinence averaging at 29.9 ± 6.0 years) against age-matched individuals who never used cannabis to disentangle the effects of cannabis from aging. Their findings showed reductions in gray matter of hippocampal subregions in former chronic users compared to the non-using older adults. Such hippocampal reductions have also been reported in younger chronic cannabis users, suggesting that this effect is present in chronic cannabis users independent of aging effects (Chye et al., 2017; Cousijn et al., 2012; Yücel et al., 2008, 2016). Nevertheless, there is paucity of studies that compare longer- (onset in younger age) and shorter-duration (onset in older age, i.e., older than 50 years) cannabis use among the older population that could further address unique effects of cannabis use in older adults. Current findings from existing human studies show that prefrontal structure and function are vulnerable to the effects of aging and those of hippocampus are susceptible to degenerations due to both aging and cannabis use. We identified preclinical studies, however, that demonstrated a protective effect in hippocampal structure and potential procognitive results owing to long-term use of low-dose cannabis in the aging brain. Together, this indicates that there are complex consequences of chronic cannabis use that interact with the different aspects of aging, which cannot be fully addressed by animal models. Future studies should target older cannabis users with shorter and longer duration of regular use, using multimodal approaches to identify the interaction of cannabis use and aging in micro- and macroscopic viewpoints. A longitudinal design for shorter- and longer-span effect of cannabis use may also be beneficial.

Our examination of the concordant effects of the aging process and cannabis use suggests that effects of chronic use of cannabis and aging have complex interactions in molecular/cellular level. The main effects of both aging and cannabis use seem to compromise the structure and function of the hippocampus, thus cannabis use may accelerate age-related degenerations in the hippocampus. Nevertheless, it may indirectly lead to the functional states more vulnerable to cannabis-related problems in older adults. The ubiquity of endocannabinoid receptors in the brain and their regulatory roles upon various neurotransmitters as well as essential cell functions of neurons can further result in global changes in brain structures and behaviors. Interestingly, these diffused effects lends the use

of a cannabinoid marker for age-related changes in multiple systems clinically useful for understanding the general changes in the older adult's brain.

Despite its widely reported harms in chronic use for humans, cannabis has also been shown to alleviate functional loss in aging under controlled usage. Preclinical studies indicate that if used in a healthy population and with a restricted low dose, cannabis may be neuroprotective and aid in maintaining neurogenesis in older adults. Further, the controlled use of cannabis may be selectively beneficial for alleviating chronic pain disorders in place of opioid medications. Taken together, the therapeutic benefits of cannabinoids hold promise, especially if the benefits of cannabis use outweigh the risks (e.g., increased probability of experiencing substance use disorder). Further investigations are essential on this cost–benefit ratio that includes determination of the effect of low-dose cannabis should be performed using healthy human subjects to extend the preclinical outcomes to clinical uses.

While beyond the scope of this review, it is important to note the high comorbidity of cannabis use with other substances, such as alcohol and nicotine (Degenhardt, Hall, & Lynskey, 2001; Goodwin et al., 2018). Subbaraman and Kerr (2015) analyzed the 2005 and 2010 National Alcohol Surveys and showed that 60% to 70% of cannabis users also use alcohol. For many of the human studies reviewed in this manuscript, co-use of other substances, including alcohol and nicotine use, were not controlled for (i.e., exclusionary criterion or covaried in analyses). Thus, any unique versus combined contributions of cannabis in aging is not known given differential effects of isolated versus combined cannabis use reported in the literature (Filbey, Gohel, Prashad, & Biswal, 2018; Filbey, McQueeny, Kadamangudi, Bice, & Ketcherside, 2015; Hartman & Huestis, 2013). Future studies should take into account other substance use when determining the specific effects of cannabinoids in aging.

To conclude, we summarized the previous literature on the effect of cannabis use and normal aging, respectively, and aimed to provide the integrative viewpoint on these two factors. Future empirical studies on the effects of cannabis use on the aging brain are critical. These studies could include (1) determining the difference between acute and chronic effects of cannabis use in normal aging; (2) pinpointing the risks and benefits of cannabis in the aging population; (3) optimizing the dose for therapeutic benefits (particularly in those with neurodegenerative and chronic pain disorders); and (4) identifying the modulatory factors that affect the interaction of cannabis use and aging effect (e.g., cognitive reserve and gender).

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Table 1.

Profiles of cannabis users from the studies cited in Section “Interactive effects of cannabis use and aging on neural and synaptic plasticity.”

References	Human/ animal	Duration	Onset of first use	Current age	Definition of chronic use	Exclusion criteria for comorbidities
Ceccarini et al., 2015	Human	10.2 ± 4.6 years	15.8 ± 2.5 years	26.0 ± 4.1 years	Using at least once a month for at least 4 years	Subjects with a recent history of alcohol abuse according to the guidelines of >5 alcoholic units/day in the past 30 days were excluded
D’Souza et al., 2016	Human		16.0 ± 1.8 years	26.2 ± 5.7 years	Regular cannabis use for 2 years with ≥ 21 days of use, ≥ 30 joints or equivalent used in the past 30 days, ≥ 120 days of use in the past 6 months, and meeting DSM-IV cannabis dependence criteria	Subjects were excluded for a DSM-IV criteria diagnosis of nicotine dependence and an alcohol abuse diagnosis by the guidelines of ≥ 4 drinks on any single day and ≥ 14 drinks per week
De Fonseca et al., 1994	Rats	7 days		Adult (> 3 months)	Received a daily intraperitoneal injection of (6.4 mg/kg)	N/A
Villares, 2007	Human,	postmortem		< 12 years	24.0 ± 4.5	Users must have met WHO-DSM-IV criteria and confirmed by retrospective family history review
N/A Boileau et al., 2016	Human	17.5 ± 10.8 years	16.1 ± 3.9 years	33 ± 10 years	N/A	For the positron emission tomography scan, users were excluded if they had a blood alcohol concentration > 0 on the testing day or if nicotine was used within 12 hours of testing
Morgan et al., 2013	Human	6.5 ± 2.9 (heavy), 4.7 ± 3.3 (light)		22.1 ± 2.4 years including controls and heavy/light users	People using cannabis > 10 times in a month were classified as heavy users and < 10 times as light users	No significant group differences in the number of regular alcohol users or level of use.
Hirvonen et al., 2012	Human	12.0 ± 7.0 years	15.0 ± 3.0 years	28.0 ± 8.0 years	Males using cannabis daily without seeking treatment	Levels of alcohol and nicotine were used as covariates
Cuttler, Mischley, and Sexton, 2016	Human			33.6 ± 13.2 years	Used cannabis in the past 90 days	N/A
Cuttler et al., 2017	Human			Stressed: 26.1 ± 1.4 (Mean ± SE) years Not stressed: 25.1 ± 1.9 years (Mean ± SE)	Using cannabis on a daily or near daily basis (defined as using cannabis a minimum of 3–4 days per week) for at least 1 year	People who used alcohol 4 or more days per week were excluded. No control for tobacco use
Somaini et al., 2012	Human	8.8 ± 3.1 years		24.1 ± 2.7 years	Used cannabis 2–3 times a day for at least 3 years without any abstinence period	Previous consumption of excessive alcohol excluded
King et al., 2011	Human	5.9 years (Mean)	15.2 years (Mean)	21.7 years (Mean)	Using cannabis 6 – 7 days a week for at least 1 year	Levels of alcohol and nicotine were confirmed to be not significantly different between groups
Ranganathan et al., 2009	Human			28.3 ± 10.2 years	Positive urine toxicological test for cannabis at screening, and at least 10 exposures to cannabis within the past month	Excluded for recent abuse of (3 months) or dependence on (1 year) alcohol but not nicotine

References	Human/ animal	Duration	Onset of first use	Current age	Definition of chronic use	Exclusion criteria for comorbidities
Hoffman et al., 2003	Rats	7 days		2 – 4 weeks	Received a daily intraperitoneal injection of WIN 55,212-2 (10 mg/kg) or THC (10 mg/kg)	N/A
Bloomfield et al., 2014	Human	4.9 ± 2.0 years, weekly use	15.5 ± 1.6 years	20.4 ± 1.3 years	Using at least weekly for > 1 year	No use of drugs other than cannabis, tobacco, alcohol, and caffeine within 1 week before positron emission tomography scan
Carta, Nava, and Gessa, 1998	Rats	7 days		Age not specified, weight 225–250 g	Received intraperitoneal injection of THC twice a day (2.5, 5, 7.5 mg/kg) for 7 days	N/A
Bilkei-Gorzo et al., 2017	Mice	28 days		2, 12, and 18 months	Received intraperitoneal injection of THC of 3 mg/kg daily	N/A
Kochman et al., 2006	Mice	21 days		Adult, weight 20–25 g	Received oral doses of THC from 20 to 80 mg/kg	N/A
Fan et al., 2010	Mice	7 days		6–9 weeks	Received intraperitoneal injection of THC of 10 mg/kg daily	N/A
D'Souza et al., 2009	Human			22.7 ± 2.8 years	Light users: (1) a positive urine toxicological test for cannabis, (2) ≥ 10 exposures to cannabis in the past month, (3) ≥ 100 lifetime cannabis exposures, and (4) current DSM-IV cannabis abuse disorder	Users with recent diagnosis of alcohol abuse (3 months) or dependence (1 year) excluded, nicotine dependence allowed but only 1 current tobacco smoker present in users group
Angelucci et al., 2008	Human	10.7 ± 5.2 years	16.5 ± 2.7 years	27.3 ± 5.6 years	Diagnosed as cannabis-dependent according to DSM-IV	Cannabis users with a history of alcohol abuse or dependence excluded, no specific conditions on nicotine use
Hoffman et al., 2007	Rats	7 days		Young, 2 – 4 weeks	Received intraperitoneal injection of THC of 10 mg/kg daily	N/A

Note. Years or months are shown in mean ± standard deviation unless specified. Numbers that are not specified explicitly are left blank in the table. All numbers are rounded to one decimal place even the original manuscript reported otherwise.

DSM-IV = Fourth version of the *Diagnostic and Statistical Manual of Mental Disorders*; THC = delta-9-tetrahydrocannabinol; WHO = World Health Organization; N/A: not applicable.

Table 2.

Profiles of cannabis users from some of the studies cited in Section "Effects of cannabis use and aging on brain structures, networks, and behaviors."

References	Duration	Onset of first use	Onset of regular use	Current age	Definition of chronic use	Exclusion criteria for comorbidities
Koenders et al., 2017		14.4 ± 1.5 years	16.2 ± 2.3 years	20.6 ± 2.2 years	Used more than 10 days per month for at least 2 and did not seek treatment for cannabis use problems	Included measures of alcohol use (Alcohol Use Disorder Identification Test) and nicotine dependence using the Fagerström Tolerance Questionnaire (Fagerström & Schneider, 1989) but did not exclude subjects for comorbidity
Matochik et al., 2005	7.5 ± 5.5 years	15.7 ± 2.5 years		25.4 ± 5.0 years	Currently used four or more times per week for a minimum of 2 years	Subjects were excluded for a past or current DSM-IV criteria diagnosis of dependence or abuse of any substance except for marijuana
Tzilos et al., 2005	22.6 ± 5.7 years	16.0 ± 4.1 years		38.1 ± 6.2 years	Had at least 5,000 lifetime cannabis uses	Subjects were excluded for a history of alcohol abuse or dependence according to DSM-IV
Chye et al., 2017			16.5 ± 3.4 years	30.4 ± 10.0 years	Used cannabis regularly (at least twice a month) for at least 2 years, and the Severity of Dependence Scale ≥ 4	The levels of alcohol and nicotine use were used as covariates
Cousijn et al., 2012	2.5 ± 1.9 years		18.8 ± 2.3 years	21.3 ± 2.4 years	Used cannabis 10 or more days during the last month, at least 240 days during the last 2 years, without a history or current seeking of treatment	Excluded subjects with Alcohol Use Disorder Identification Test score higher than 10, smoke more than 20 cigarettes a day, or a positive urine screen for alcohol (Saunders et al., 1993)
Demirakca et al., 2011	5.4 years			19–25 years	5.4 years in an average daily dose of 0.27 g	The levels of alcohol and nicotine use were used as covariates
Orr, Paschall, and Banich, 2016		52 users younger than 15, 170 users 15–17, 151 users 18–20, 93 users older than 20 years			Users stratified into 174 (1–5), 63 (6–10), 94 (11–100), 60 (101–999), 75 users (1000+ times) ranging from light to heavy uses	The levels of alcohol and nicotine use were used as covariates
Yücel et al., 2008	19.7 ± 7.3 years		20.1 ± 6.9 years	39.8 ± 8.9 years	Selected users based on durations	The levels of alcohol and nicotine were confirmed to be not different between groups, although significantly more cannabis users do use nicotine compared to controls
Zalesky et al., 2012	15.6 ± 9.5 years		16.7 ± 3.3 years	33.4 ± 10.9 years	Used at least twice a month for a minimum of 3 years	The levels of alcohol and nicotine use were used as covariates
Bolla et al., 2002	4.8 ± 3.1 years			22.4 ± 4.9 years	Users stratified into 7 (light, 2–14), 8 (middle, 18–70), 7 users (heavy, 78–117 joints per week)	Alcohol consumption of fewer than 14 alcoholic drinks per week, no considerations for nicotine use
Becker et al., 2010	51.3 ± 37.8 months	15.1 ± 2.0 years		22.5 ± 3.5 years	Minimum lifetime cannabis usage of 10 g	Subjects were excluded for a history of alcohol abuse according to DSM-IV, and the level of nicotine use was confirmed to be not different between groups
Burggren et al., 2018	11.3 ± 13.0 years		17.7 ± 4.2 years	65.4 ± 7.2 years	Cannabis exposure during adolescence (used at least 20 days/month, initiating use before age	Smoking and light alcohol use allowed (< 14 drinks/week for men, < 7 drinks/week for women)

References	Duration	Onset of first use	Onset of regular use	Current age	Definition of chronic use	Exclusion criteria for comorbidities
					20) and continuing for at least 1 year with no more than 1 to 2 uses/month after age 35)	
Arnone et al., 2008	107.9 ± 42.3 months	15.3 ± 2.8 years		25.0 ± 3.0 years	Smoked cannabis daily (≥ 2 years)	Subjects consuming ≥ 21 units of alcohol/week were also excluded, no considerations for nicotine use
Filbey et al., 2014	9.4 ± 8.1 years	18.3 ± 3.2 years		25.0 ± 8.4 years	Cannabis group defined as currently using cannabis regularly (at least four times per week) over the last 6 months	The levels of alcohol and nicotine use were used as covariates
Gruber et al., 2011	10.1 ± 9.7 years	14.9 ± 2.5 years		25.0 ± 8.7 years	Used at least 3,000 joints in their lifetime, diagnosed as cannabis abuse disorder according to DSM-IV	No subjects met diagnostic criteria for current or previous alcohol abuse or dependence
Jakabek et al., 2016	15.5 ± 9.7 years	15.1 ± 2.3 years	16.3 ± 2.6 years	32.3 ± 10.8 years	Minimum use of twice a month for at least 3 years	The levels of alcohol and nicotine use were used as covariates
Chang et al., 2006				27.9 ± 3.1 years	Used cannabis at least 5 days per week for a minimum of 2 years	Subjects were excluded for a current use or history of alcohol abuse in DSM-IV, but not nicotine. 3 controls, 5 THC abstinent, and 5 THC active subjects smoked nicotine cigarettes daily
Filbey and Yezhuvath, 2013	5.5 ± 5.5 years	17.3 ± 2.5 years		23.7 ± 6.5 years	Regular cannabis use of at least 4 uses per week for at least 6 months prior, diagnosed as cannabis dependent according to DSM-IV	The levels of alcohol and nicotine use were used as covariates
Harding et al., 2012	Median of 20 years (ranging 10–38)		Median of 16 years (ranging 12 – 25)	36.5 ± 8.8 years	Used on a daily or near-daily basis for no fewer than 10 years	The levels of alcohol and nicotine use were used as covariates

Note. Years or months are shown in mean ± standard deviation unless specified. Numbers that are not specified explicitly are left blank in the table. All numbers are rounded to one decimal place even the original manuscript reported otherwise.

DSM-IV = Fourth version of the *Diagnostic and Statistical Manual of Mental Disorders*; THC = delta-9-tetrahydrocannabinol.