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The Neurocognitive Effects of Cannabis Across the Lifespan

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Abstract

Purpose of review: This review examines the neurocognitive effects of cannabis and relevant developmental factors across adolescence (age 13–21), adulthood (21–65), and older adulthood (65+).

Recent findings: Cannabis use is robustly associated with poorer neurocognitive functioning; however, studies that carefully control for confounds have often not found any evidence for impairment. Notably, the endocannabinoid system may underly how cannabis use affects neurocognitive functions, including heightened vulnerability during adolescence. In contrast, the endocannabinoid system may underlie protective neurocognitive effects of cannabis in older adults. Notably, older adults have reported sharp increases in recent cannabis use.

Summary: As legalization increases the accessibility, variety, and potency of cannabis, strong empirical evidence is needed to understand its neurocognitive effects across the lifespan. In particular, rigorous study designs are needed to investigate the neurocognitive effects of cannabis, including among vulnerable populations (adolescents, older adults) and mediating (e.g., endocannabinoid system) and moderating factors (e.g., alcohol use).

Keywords

Cannabis; Cannabinoids; Development; Lifespan; Cognitive; Neurocognitive

Introduction

Recent decades have seen profound shifts in the attitudes, legality, accessibility, and potency of cannabis products, particularly in the United States (U.S.). Based on current state-level policies and U.S. census data, approximately one in three Americans have legal access to

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Declaration of Interest

None

recreational cannabis. Further, public opinion polls suggest that most Americans support the federal legalization of cannabis [1]. Importantly, legal cannabis markets have increased the availability of a wide variety of cannabis products, including potent flower (20+% tetrahydrocannabinol [THC]), high-potency concentrates (80+% THC), and novel modes of administration (e.g., vaping, waxes/dabs). The potential public health effects of more potent cannabis products are unclear, but greater levels of cannabinoid exposure are associated with more adverse outcomes.

In addition to the potential public health risks of legal-market cannabis products, the adverse effects of cannabis may be heightened, particularly among adolescents. Adolescence is broadly marked by critical neurodevelopment in affective and cognitive substrates. Further, cannabinoids are thought to exert psychoactive effects via the endocannabinoid system, which may be uniquely susceptible to adverse effects during adolescence [2]. While the mechanisms of the neurocognitive effects of cannabis in adolescence are still being studied, much less is known about how the endocannabinoid system may be susceptible or resistant to similar effects during older adulthood. Whereas evidence is mixed about whether adolescents have increased use since legalizations, epidemiological evidence is clear that adults aged 65+ have had marked increased in cannabis use since legalization [3].

As the general public and scientific community navigate this pivotal period of increasing access to cannabis, evidence is needed to more clearly understand the public health effects of cannabis and cannabinoids across the lifespan. Thus, this review assessed empirical evidence on the neurocognitive effects of cannabis and mechanisms that may vary across the lifespan. Throughout this review, we focus on three primary components of cannabinoid system interactions. First, exogenous cannabinoids are compounds introduced into the body and typically derived from the cannabis sativa plant (e.g., THC). Second, endogenous cannabinoids are compounds produced by the body. Finally, cannabinoid receptors are a mechanism by which endogenous and exogenous cannabinoids exert their effects. This review assesses the neurocognitive effects and mechanisms of cannabis across adolescence (ages 13–21), adulthood (21–65), and older adulthood (65+).

Adolescence

Neurocognitive Effects of Cannabis in Adolescence—There are virtually no human studies examining the acute effects of cannabis in adolescence. Therefore, we focus on the short- and long-term effects of cannabis in adolescents that have been more widely studied.

Adolescent cannabis use is consistently associated with poorer neurocognitive outcomes, but a closer examination of the literature suggests that this association is nuanced. Scott and colleagues recently conducted an extensive meta-analysis on adolescent/young adult cannabis use and neurocognitive functioning. Significant effect sizes were observed for worse performance on tasks of learning (d=−0.33), executive functioning (EF)-abstraction/shifting, (d=−0.30), information processing speed (d=−0.26), delayed memory (d=−0.26), EF-inhibition (d=−0.25), EF-updating/working memory (d=−0.22), and attention (d=−0.21) [4]. Effect sizes were not significant in the domains of verbal/language, visuospatial, and motor functioning. However, across 15 studies that required cannabis abstinence for 72+ hours before assessment, there was no evidence of poorer impairments in any neurocognitive

domain. Further, an earlier age of initiation did not influence the effect sizes; however, early initiation was defined inconsistently across studies (ranging from 15–18 years old). A more recent meta-analysis of longitudinal studies examined the effects of cannabis on IQ before and following cannabis initiation. Across the literature, there were minimal decreases in IQ (d=−0.13, ~2 IQ points) among those who initiated cannabis use; however, these decreases were significant among adolescents who frequently used cannabis or met cannabis dependence criteria [5]. Although recent meta-analyses indicate that chronic or frequent cannabis use during adolescence is associated with worse neurocognitive functioning, there is an ongoing debate about whether these decreases are clinically meaningful [6]. Thus, despite a broad link between adolescent cannabis use and poorer neurocognitive functioning, these effects are minimal, may be limited to residual effects within a few days after use, and are most pronounced with heavy use.

Mechanisms of the Neurocognitive Effects of Cannabis in Adolescence—Adolescence is characterized by substantial neurodevelopment, including neuronal differentiation, synaptogenesis, and synaptic pruning to establish mature neuronal networks. The endocannabinoid system is a highly evolutionarily conserved system [7] that is fundamental to adolescent neurodevelopment and modulates the nervous system throughout adulthood [8]. For example, synapses in the endocannabinoid system modulate neurotransmitter release [9], thereby regulating neuromaturation processes [10, 11]. Two components of the endocannabinoid system may be pertinent to the neurocognitive effects of cannabis during adolescence. First, endogenous cannabinoids are made “on-demand” in a precise temporospatial manner to modulate neurodevelopment [11]. Second, the cannabinoid 1 (CB1) receptor is widely expressed in the developing brain [8, 12]. In particular, there is a high concentration of CB1 receptors in white matter areas during adolescence, and CB1 receptor density diminishes in mature neural circuits once synaptogenesis is complete [12, 13]. Notably, CB1 receptor density and endogenous cannabinoid levels peak during early adolescence [14]. Importantly, exogenous cannabinoids (e.g., THC) act on the endocannabinoid system. For example, the psychoactive effects of THC occur specifically via its binding to the CB1 receptor. As a result of the endocannabinoid system modulating neurodevelopment and mediating the psychoactive effects of THC, the adolescent brain may be uniquely vulnerable to the adverse effects of cannabis use [15, 16].

Whereas endogenous cannabinoids affect neural activity in a temporally- and spatially-specific manner, exogenous cannabinoids (e.g., THC) affect neural activity for several hours and in a non-specific manner [8]. In addition, exogenous cannabinoids are lipophilic and readily cross the blood-brain barrier [17]. Thus, cannabinoid exposure during neurodevelopment may interfere with neuronal differentiation and survival, alter neurotransmitter system development, and diminish neurocognitive functioning as a result [18]. Notably, much of what is known about the biochemical impact of exogenous cannabinoid exposure on the adolescent brain has been elucidated from animal models. Additional information can be garnered from neuroimaging studies, including associations between cannabis use in adolescents and adults (see below).

Neuroimaging studies investigating the effects of cannabis in adolescents have received immense interest [19–24]. A recent review summarized findings across three neuroimaging

meta-analyses of adolescent cannabis use [25–28]. Notably, the extant literature suggests altered brain activation among adolescents who use cannabis, compared to those who do not use cannabis, during neurocognitive tasks. However, findings are inconsistent regarding specific brain regions that differ as a function of cannabis use. For example, prefrontal regions and the insula may be affected by cannabis exposure, resulting in adverse neurocognitive effects. Further, as reviewed by Lu *et al.*, exposure to cannabinoids may alter the development of crucial neurotransmitter systems, including dopamine, serotonin, gamma-aminobutyric acid (GABA), and the opioid system [8]. Neurotransmitter system anomalies in the prefrontal cortex, in particular, may increase disinhibition and underlie the cognitive decrements associated with long-term cannabis use [18].

In addition, neuroimaging evidence implicates the endocannabinoid system in the development of neurocognitive functioning [29]. For example, CB1 receptors are highly expressed in the hippocampus, and the endocannabinoid system is broadly implicated in memory acquisition, consolidation, and retrieval [18]. As a result of chronic cannabis use activating the endocannabinoid system, neurodevelopment and neurocognitive functioning may be adversely affected. For example, exogenous cannabinoid exposure during adolescence may decrease glutamatergic neurotransmission and contribute to learning impairment [30]. Further, exogenous cannabinoid exposure is associated with altered hippocampal long-term potentiation, glutamate release, and impaired neurocognitive functioning [31]. Thus, the endocannabinoid system affects the development of neural substrates that underlie neurocognitive functioning. Consequently, cannabis use may impair neurocognitive functioning during adolescence and potentially later in life.

Summary of Cannabis Effects in Adolescence—Cannabis is associated with neurocognitive decrements in adolescence across several domains, including learning, memory, and executive functioning. However, it is unclear whether cannabis impairs long-term neurocognitive functioning or whether any impairment persists with abstention. Study designs that reinforce abstinence amongst adolescent users and examine changes post abstinence could shed light on these questions.

Some mechanisms have been identified that may explain how cannabis use reduces neurocognitive functioning. In particular, the endocannabinoid system has received substantial attention, given its roles in neurodevelopment and the psychoactive effects of THC. Peripheral endocannabinoid markers partially reflect central processes and offer a possible window into the developing brain [32]. However, it is important to consider mechanistic studies in the context of findings from large-scale studies investigating the neurocognitive effects of cannabis. Although cannabis use introduces exogenous cannabinoids that may perturb the endocannabinoid system, evidence suggests that diminished neurocognitive functioning may only occur within a few days after last use or if these perturbations are frequent and chronic.

Adulthood

Neurocognitive Effects of Cannabis in Adulthood—The acute, neurocognitive effects of cannabis use have primarily been studied in young and middle-aged adults (i.e.,

21–65). Placebo-controlled, laboratory-based cannabis administration studies consistently suggest that cannabis acutely impairs episodic and working memory, attentional processing, and executive functioning (shifting) in this age group (for review, see [33]). One of the most robust cognitive harms of cannabis use is acute memory impairment during intoxication [34–37], but regular users show minimal performance decrements [37, 38]. Similarly, cannabis acutely impairs divided attention among occasional users, but not heavy users [39]. Findings across these studies suggest that experienced cannabis users may be tolerant to the acute effects of cannabis. However, some evidence suggests a dose-response relationship on executive functioning may occur even among regular users. For example, performance on the Wisconsin Card Sorting Test is substantially impaired after 17 mg THC and less so after 13 mg THC [40]. Further, a recent study found acute effects on delayed verbal memory among tolerant high-potency concentrate users (i.e., THC ≥ 75%); however, effects were not seen in other cognitive domains [41]. Thus, tolerance may play a role in some of the acute neurocognitive effects of cannabis, but dose-response effects suggest that THC may acutely affect neurocognitive performance even among experienced users.

As with adolescents, there is a robust effect across the literature of chronic cannabis use and poorer neurocognitive functioning among middle-aged adults, but there are important caveats to these findings. In particular, cannabis use does not occur in isolation from other neurocognitive risk factors. Instead, cannabis use and adverse mental health outcomes co-occur with many environmental risk factors, including peer group deviance, familial psychopathology, family-of-origin marital instability, and lower family-of-origin socioeconomic status (SES) [42–44]. Controlling for covariates such as SES and other drug use has explained the effects of cannabis use on worse processing speed and executive functioning but not on verbal memory [43, 45]. Alternatively, family-controlled designs have provided a powerful way to control exhaustively for confounding genetic and environmental factors that make family members alike (e.g., siblings or twins). These studies have generally found that, among sibling/twin pairs, the heavier using family member does not tend to have worse neurocognitive functioning [46]. However, adverse effects have been observed for higher levels of cannabis use on delayed verbal recall [47]. Notably, the amount and duration of cannabis use and the length of abstinence are challenging to assess retrospectively, suggesting that prospective studies should be prioritized.

Mechanisms of the Neurocognitive Effects of Cannabis in Adulthood—After neuromaturation concludes in emerging adulthood, the endocannabinoid system regulates synaptic plasticity [9] and modulates neurocognitive functioning throughout adulthood [17]. Further, positron emission tomography research has found that CB1 receptors are downregulated in chronic cannabis users, indicating decreased CB1 receptor density. However, these effects are reversed by abstaining from cannabis for four weeks. Thus, the endocannabinoid system may continue to play a role in neurocognitive effects in adults.

Cerebral blood flow (CBF) is an important neurophysiological mechanism and may affect neurocognitive functioning [48]. Concerning the acute effects of THC, early neuroimaging studies of regional CBF demonstrated that acute THC administration affects brain function and increases metabolic activity, particularly in the frontal and parietal cortices [49–52]. These findings have been refined with increased spatial resolution. More recent findings

suggest that THC increases CBF in the anterior cingulate cortex, bilateral insula, medial superior frontal, and left orbital frontal cortex [53–56]. Notably, only two studies, to our knowledge, have investigated the effects of CBD on CBF [57, 58]. These studies found CBF reductions in the left hippocampal complex (hippocampus, parahippocampal gyrus, amygdala) but conflicting effects in the posterior cingulate cortex.

In the last decade, studies have examined the effects of exogenous cannabinoids on resting-state connectivity. Two studies have suggested that THC disrupts resting-state networks in the superior frontal pole, middle and inferior frontal gyri, and dorsolateral prefrontal cortex (via inhalation; [59]) and in subcortical areas that include the PFC (via oral administration; [60]). Additionally, increased frontostriatal activity has been observed following a high dose of CBD (oral, 600 mg) but not following a low dose CBD (oral, 10 mg), suggesting a dose-dependent effect [61]. However, only a few studies have examined how THC and CBD affect neural connectivity, making it difficult to draw firm conclusions. Thus, additional studies are needed to understand how cannabis use affects connectivity more clearly.

Several recent studies have used magnetic resonance spectroscopy (MRS) to investigate whether acute and chronic cannabis use is associated with changes in neurotransmitter systems. MRS allows for investigating the molecular mechanisms by which THC exerts its effects on behavior, with a focus on glutamate. Preclinical studies suggest that acute THC dose-dependently reduces synaptic glutamate and neurotransmission [62]. Measurements of subcortical glutamate/glutamine (Glx) have also shown increases after THC administration in humans, which converges with preclinical work [62, 63]. CBD appears to have similar effects on subcortical Glx but decreases Glx in the anterior cingulate cortex [64]. Notably, baseline Glx levels may moderate the degree to which changes occur after acute administration, with higher Glx levels at baseline predicting greater changes after acute THC administration [62]. Among chronic cannabis users, MRS studies suggest that glutamate metabolites are 10–15% lower in substrates related to neurocognitive functioning (e.g., anterior cingulate cortex), and some findings suggest accompanying reductions in GABA (for review, see [53]). In summary, recent findings from MRS studies suggest that it represents a key translational methodology to identify potential targets for investigating individual differences in response to varying levels of exogenous cannabinoids.

Summary of Effects in Adulthood—The extant literature suggests that THC and CBD affect memory, but these effects may vary by tolerance, dose, timing, and form of administration [41]. Specifically, cannabis use is associated with acute impairment of memory, attention, and executive functioning, as well as persistent decrements in verbal memory in middle-aged but not younger adults. In addition, adverse effects of chronic exposure on memory and learning have been observed, even in some studies that carefully control confounds. Thus, rigorously designed prospective longitudinal studies that can measure and account for confounding factors are needed, as well as carefully conducted laboratory-based studies that investigate mechanisms.

Older Adulthood

Neurocognitive Effects of Cannabis in Older Adulthood—Recent epidemiological research (i.e., the National Survey of Drug Use and Health) indicates that cannabis use increased by approximately 10-fold between 2007 and 2018 among adults over age 65 [3]. While there are numerous public health questions related to the use of cannabinoids in this population, one crucial question is how cannabinoids might impact neurocognitive functioning in older adults, who are already at risk because of their age for mild cognitive impairment and dementia. The importance of this question is underscored by the rapidly aging global population and the mortality, morbidity, and socioeconomic costs of dementia (estimated $2 trillion by 2030; [65]). Unfortunately, while there has been substantial interest in the effects of cannabis use on neurocognitive functioning in adolescents, emerging adults, and even middle-aged adults, there have been very few studies in aging adults.

Despite the dearth of existing studies, there has recently been increasing interest in the role of cannabinoids and changes in neurocognitive functioning in aging in animal and human studies [for recent reviews, see 66]. While most animal studies on THC model these effects in young animals, there are now a few studies on the effects of cannabinoids in aging animals. In one study, chronic administration of low doses of THC was shown to reverse age-related cognitive decline. These effects were associated with molecular and neuronal changes in the hippocampus [67]. Similarly, in another study, a single low dose of THC improved neurocognitive functioning [68]. These results contrast with the deleterious effect of THC in brain development and neurocognitive functioning in young animals [67]. These intriguing initial findings highlight the need for further animal studies to better model and understand the impact of cannabis on aging in humans.

There are very few studies in humans examining the neurocognitive effects of cannabis in older adults. Two longitudinal studies in adults (~50 years old) reported that cannabis was associated with improved performance on cognitive tasks, and these improvements were accompanied by changes in brain activity [69, 70]. Another study in an older sample (age 60+) suggested no differences in neurocognitive functioning, positive or negative, between long-term cannabis users and non-users. In that same study, cannabis users had greater gray matter volume in the putamen than non-using older adults [71]. More recent studies with an aging population (age 60+) found that regular cannabis users, compared to non-users, had greater gray matter density (typically associated with increased abilities) in subcortical regions such as the putamen, pallidum, and caudate [72]. Additionally, frequent cannabis use in this sample was associated with greater functional connectivity in hippocampal and cerebellar areas [73]. Finally, a recent comparison of the acute effects of cannabis on cognitive measures indicated that a group of older adults (age >55) were less sensitive to the deleterious effects of THC as compared to a group of younger adults (age < 25) [74].

Mechanistic Changes of the Neurocognitive Effects of Cannabis in Older Adulthood—A crucial question is, by what mechanism do cannabinoids affect neurocognitive functioning in the aging population? There appear to be two basic candidates that might explain the beneficial neurocognitive effects of cannabinoids in an aging population. The first mechanism is related to the endocannabinoid system, consisting of

receptors (CB1 and CB2) and endogenous ligands (2-AG and AEA). As discussed above, the endocannabinoid system plays a vital role in brain development, and CB1 receptors peak during adolescence. From adolescence through older adulthood, CB1 receptors decrease by about 50% (for review, see [75]). The loss of CB1 receptors and 2-AG in subcortical regions is associated with loss of gray matter density [76]. In contrast, increased levels of CB1 and 2-AG are associated with neurogenesis in these areas. It is unclear whether exogenous cannabinoids (e.g., THC) stimulate the endocannabinoid system in ways that enhance CB1 or 2-AG functioning, thereby delaying the neurodegeneration that coincides with aging.

A second possible mechanism is related to the effect of cannabinoids and the endocannabinoid system on neuroinflammation (for review, see Andrade et al., under review). Neuroinflammation has been implicated in aging on the loss of neurocognitive function. As we age, neuroinflammatory mediators (e.g., cytokines, chemokines, prostaglandins, free radicals) are upregulated in the brain, and these markers have been linked to age-related cognitive impairment and dementia [77–82]. For example, higher interleukin (IL)-6 levels have been associated with poorer auditory and working memory performance [83] and a general decline in neurocognitive function [84]. Furthermore, serum levels of cytokines are elevated in dementia and AD [85, 86], and IL-6 levels are negatively associated with gray matter volume [83]. Persistent neuroinflammation is also associated with Aβ plaques and neurofibrillary tangles, which signal neurodegeneration [87]. While the specific effects of the endocannabinoid system and cannabinoids still need to be carefully elucidated, the anti-inflammatory properties of cannabinoids have been widely documented [88, 89]. Cannabinoids exhibit immunomodulatory actions through several mechanisms impacting immune cell proliferation, migration, apoptosis, cell signaling, and cytokine production and release [90].

Summary of Effects in Older Adulthood—On balance, the few recent studies with humans suggest that cannabis may have long-term positive effects on brain structure and function among aging populations. Furthermore, the acute cognitive effects may be less deleterious in older adulthood. However, much remains unknown. For example, animal and human studies have primarily focused on the effects of THC. Virtually nothing is known about the effects of CBD in this population. In addition, other potential risks of cannabis may be more relevant to older adults compared to other ages (e.g., the psychomotor effects and risk of falling) and need to be more thoroughly examined. Finally, it is important to note that the age of initiation of regular use needs to be examined, as some studies have suggested that THC use in early development may have deleterious effects later in life, whereas later initiation may not [91]. Future human studies need to examine this variable more carefully.

Conclusions

While there has been a swift shift in the legality, accessibility, and potency of cannabis in the last decade, rigorous research on the public health effects of these new products has lagged [92]. Here, we reviewed the state of the scientific literature on the neurocognitive effects of cannabis across the lifespan. Among adolescents and adults, there is a link between cannabis use and poorer neurocognitive functioning. Notably, well-controlled studies of adolescents and adults have generally found little evidence of adverse neurocognitive effects.

In middle-aged adults, recent evidence suggests that neurocognitive effects occur but vary by tolerance, dose, timing, and form of administration. Finally, the empirical literature has largely overlooked the potential for neurocognitive effects of cannabis in older adults (e.g., age 65+), despite this age cohort reporting a 10-fold increase in cannabis use during the last 10–20 years. Further, the aging brain is at risk for mild cognitive impairment and dementia. Thus, there is a clear and pressing need to understand whether THC, CBD, and other cannabinoids affect neurocognitive functioning among older adults.

A review of the literature identifies at least three considerations for future research. First, evidence implicates the endocannabinoid system in the neurocognitive effects of cannabis across the lifespan, including the potential for deleterious effects in adolescents and beneficial effects in older adults. Thus, studies investigating mechanisms within the endocannabinoid system may help advance our understanding of the neurocognitive effects of cannabis across the lifespan. Second, most mechanistic studies investigating the endocannabinoid system's role have focused on adults (age 21–65). As discussed throughout, there are important developmental changes in the endocannabinoid system, highlighting the need for similar mechanistic studies in adolescents and older adults. Finally, many studies that control for other substance use or familial confounds have often yielded negligible effects of cannabis use on neurocognitive outcomes. Even among these well-controlled studies, some findings remain consistent with a causal effect among heavy users; however, it is unclear whether these effects are clinically meaningful. Thus, as cannabis legalization appears likely to continue across the U.S. and worldwide, there is a particular need for studies that apply careful controls and investigate the mechanisms of how cannabis use may affect neurocognitive functioning across the lifespan.

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Table 1.

Summary of key articles and findings on the effects of cannabis across adolescents, emerging/young adults, and older adults.

Study	Developmental Period	Study Design	Key Findings
Rubino et al., 2015 [16]	Adolescents & Emerging Adults (*M* age = 17.8 – 24.3)	Meta-analysis of neuroimaging studies of cannabis users vs. non-users	Cannabis users have altered neural activity during neurocognitive tasks.
Scott et al., 2018 [4]	Emerging Adults (*M* age = 20.6 – 20.8)	Meta-analysis, primarily of regular cannabis users	Cannabis users performed worse on learning (d=−0.33), shifting (d=−0.30), processing speed (d=−0.26), delayed memory (d=−0.26), inhibitory (d=−0.25), working memory (d=−0.22), and attention (d=−0.21). Effects do not continue after 72 hours since last use.
Bloomfield et al., 2019 [53]	Adolescents & Young Adults	Review of acute and chronic effects	Chronic cannabis users may have anomalous glutamatergic and GABAergic functioning in neurocognitive substrates, which may increase risk for neuropsychiatric problems.
Crane et al., 2013 [33]	Emerging & Young Adults	Review of acute and non-acute effects in regular users	Cannabis acutely impairs episodic and working memory, attentional processing, and executive functioning (shifting) in adults. Non-acute impairments in episodic memory are seen in adults, but level of use likely plays a role.
Broyd et al., 2016 [35]	Primarily Young Adults	Review of acute effects and chronic effects	Acute and chronic effects of cannabis on poorer verbal learning, verbal memory, attention, psychomotor functioning. Tolerance may not reduce acute neurocognitive effects of cannabis.
Di Marzo et al., 2015 [7]	Adolescents through Older Adults (primarily from animal models)	Review of the endocannabinoid system in aging and neurodegenerative disorders	CB1 receptor density decreases by 50% from adolescence through older adulthood. Endocannabinoid changes may broadly increase risk for neurodegenerative diseases.

Note. Mean ages are listed for the meta-analyses that included this information.