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Cannabis Use in Adolescence: A Review of Neuroimaging Findings

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ABSTRACT

Objective: Shifting policies and widespread acceptance of cannabis for medical and/or recreational purposes have fueled worries of increased cannabis initiation and use in adolescents. In particular, the adolescent period is thought to be associated with an increased susceptibility to the potential harms of repeated cannabis use, due to being a critical period for neuromaturational events in the brain. This review investigates the neuroimaging evidence of brain harms attributable to adolescent cannabis use. **Methods:** PubMed and Scopus searches were conducted for empirical articles that examined neuroimaging effects in both adolescent cannabis users and adult user studies that explored the effect of age at cannabis use onset on the brain. **Results:** We found 43 studies that examined brain effect (structural and functional magnetic resonance imaging) in adolescent cannabis users and 20 that examined the link between onset age of cannabis use and brain effects in adult users. Studies on adolescent cannabis users relative to nonusers mainly implicate frontal and parietal regions and associated brain activation in relation to inhibitory control, reward, and memory. However, studies in adults are more mixed, many of which did not observe an effect of onset age of cannabis use on brain imaging metrics. **Conclusions:** While there is some evidence of compromised frontoparietal structure and function in adolescent cannabis use, it remains unclear whether the observed effects are specifically attributable to adolescent onset of use or general cannabis use–related factors such as depressive symptoms. The relative contribution of adolescent onset of cannabis use and use chronicity will have to be more comprehensively examined in prospective, longitudinal studies with more rigorous measures of cannabis use (dosage, exposure, dependence, constituent compounds such as the relative cannabinoid levels).

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Introduction

Cannabis is not only a widely used substance of abuse worldwide, it remains the second most preferred substance of initiation in adolescents behind alcohol, with over a third of final year high school students in America having reported using cannabis (Johnston et al., 2019). Past-year prevalence of cannabis use has also been found to be significantly higher in 15- to 16-year-olds relative to the general population worldwide (United Nations Office on Drugs and Crime, 2018). Further, recently shifting attitude toward cannabis alongside a global move toward legalization of cannabis for medical and/or recreational purposes prompts worries of increasing adolescent cannabis use (Hopfer, 2014). Despite the increasingly recognized therapeutic benefit of cannabinoid compounds for a range of neurological conditions and mental health needs (Chye, Christensen, Solowij, & Yücel, 2019; Hurd, 2017; Lattanzi, Brigo, Trinka, Zaccara, & Cagnetti, 2018), the potential psychosocial and brain harms that accompany adolescent cannabis use remain a public health concern.

The adolescent period is defined as the transitional period from childhood to adulthood roughly associated with the age of 10 to 19 years, although the precise age range of adolescence is ill defined (Brenhouse & Andersen, 2011). It is accompanied by a number of behavioral and social changes, such as increased peer-directed social interactions and greater risk taking, that assist in adolescents attaining independence from the family unit (Crews, He, & Hodge, 2007; Spear, 2000). Initiation of cannabis use during this period may be symptomatic of such increased exploration and novelty-seeking (Chen & Kandel, 1995; Crews et al., 2007). Indeed, over half of cannabis use begins in adolescence (Degenhardt et al., 2008). Worryingly,

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the adolescent period is also thought to be the period of greatest vulnerability to substance use–related problems (Chambers, Taylor, & Potenza, 2003). Adolescent cannabis users (i.e., those who begun before age 15) are also more likely to persist use and experience greater use-related problems later in life, compared to late-onset users (Anthony & Petronis, 1995; DeWit, Offord, & Wong, 1997). A majority of admissions to treatment facilities for cannabis use–related problems (almost 30%) also occur between the age of 12 to 17, highlighting the potential danger of early cannabis use (Substance Abuse and Mental Health Services Administration, 2018).

The adolescent period is also accompanied by important neurodevelopmental events that drive behavioral changes and cognitive maturation (Brenhouse & Andersen, 2011). Neuromaturational changes during adolescence largely relate to increased functional specialization, whereby synapses that are overproduced in the brain during prenatal and early postnatal periods are eliminated during the transition to adulthood (Selemon, 2013). This massive synapse loss (termed "synaptic pruning") and reduction in synaptic connectivity and density occur across widespread cortical and subcortical regions that guide complex brain function including goal planning, reasoning, and impulse control (Crews et al., 2007; Gogtay et al., 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004). It is proposed that the maturation across corticolimbic networks, in particular an increase in inhibitory connections across frontal and limbic regions, drives a shift from more impulse-driven behavior typified by the adolescence period to more regulated behavior (Spear, 2000; Viveros, Marco, & File, 2005). Worryingly, external insults such as exposure to substances of abuse (e.g., cannabis) during this critical neurodevelopmental period may interfere with normal maturational events, presenting an elevated risk of cognitive problems later in life (Jacobus & Tapert, 2013, 2014; Lubman, Cheetham, & Yücel, 2014; Solowij, Lorenzetti, & Lubman, 2012).

The endocannabinoid system in adolescence

The particular vulnerability of the adolescent brain to cannabis exposure may be partly related to the developmental trend of the endogenous cannabinoid system (ECS) in the brain. The ECS consists of cannabinoid receptors that not only direct the effect of cannabis in the brain but are crucially involved in neural development throughout postnatal and adolescent periods (Dow-Edwards & Silva, 2017). In particular, the cannabinoid 1 receptor (CB1R) is widely distributed across the brain, but also heavily concentrated in striatal, limbic, and cortical regions that direct the cognitive and emotive function that continue to develop into adulthood (Pertwee & Ross, 2002; Westlake, Hewlett, Bonner, Matsuda, & Herkenham, 1994). Rodent studies have shown that CB1R levels as well as endogenous cannabinoid levels increase across development, peaking in early adolescence before decreasing to adult levels, particularly across corticolimbic regions involved in reward and cognition (i.e., prefrontal cortex and nucleus accumbens; Belue, Howlett, Westlake, & Hutchings, 1995; Ellgren et al., 2008). These dynamic changes in the ECS during adolescence are understood to modulate critical maturational processes involving synaptic pruning and plasticity (Meyer, Lee, & Gee, 2018). Perturbation of ECS signaling by cannabis administration during this period may be particularly deleterious, as it may impede the normal maturational process of corticolimbic circuits and their ascribed function (Meyer et al., 2018). Indeed, rat studies demonstrate that the desensitization and downregulation of cannabinoid receptors in response to chronic cannabinoid exposure differ in magnitude in adolescents compared to adults (Burston, Wiley, Craig, Selley, & Sim-Selley, 2010; Dalton & Zavitsanou, 2010). While adolescent rats found cannabis to be less aversive than adult rats, they exhibited greater alteration to protein expression in the hippocampus and greater cognitive impairment (learning and memory) in response to chronic cannabis administration, as compared to adult rats, reflecting increased susceptibility to the potential harms of repeated cannabis use (Cha, White, Kuhn, Wilson, & Swartzwelder, 2006; Quinn et al., 2008; Schneider & Koch, 2003).

Cognitive function in adolescent cannabis use

A number of studies have reported deficits in cognitive functioning related to adolescent cannabis use that persist into adulthood. Deficits in working memory (Dougherty et al., 2013; Hanson et al., 2010; Harvey, Sellman, Porter, & Frampton, 2007), learning (Hanson et al., 2010; Harvey et al., 2007; Solowij et al., 2011), and attention function (Huestegge, Radach, Kunert, & Heller, 2002; Jacobsen, Mencl, Westerveld, & Pugh, 2004; Medina, Nagel, Park, McQueeny, & Tapert, 2007) are most frequently discussed, while decline in verbal IQ (VIQ; Jackson et al., 2015; Pope et al., 2003) and increased impulsivity (Churchwell, Lopez-Larson, & Yurgelun-Todd,

2010; Lopez-Larson, Rogowska, & Yurgelun-Todd, 2015) have also been implicated in adolescent cannabis users compared to nonusers. Most recently, a systematic review on cognitive function in adolescent and young adult cannabis users suggests that while cognitive impairment may exist across the mentioned domains, the observed effect sizes were small and did not vary systematically with age at onset of cannabis use, raising the question as to whether adolescent relative to adult cannabis use poses a heightened risk for poorer outcomes (Scott et al., 2018).

IQ (specifically VIQ) has been thought to decline at a greater rate in adolescent-onset cannabis users relative to late-onset users and nonusers (Meier et al., 2012; Pope et al., 2003). Early-onset cannabis users (i.e., those who began use before age 17) were found to have poorer VIQ than those who commenced cannabis use during adulthood (Pope et al., 2003). This same study also found that adult-onset users' VIQ did not differ from controls. However, it is difficult to determine whether IQ decline is due to cannabis use or a common predisposing factor (Meier et al., 2012, 2018). Longitudinal studies investigating cannabis use in adolescent twin pairs found that while cannabis users had lower IQ than nonusers, cannabis-using twins did not show a significant decline in IQ when compared to their nonusing twin (Jackson et al., 2015). It is suggested that early-onset users may have had a lower cognitive capacity before commencing cannabis use, or perhaps a limited education in cannabis-using adolescents resulted in a failure to acquire appropriate verbal skills as measured by VIQ (Pope et al., 2003). Further, differences in IQ between cannabis users and nonusers may in fact be a result of other confounding factors such as other substance (i.e., cigarette) use, mental health factors, and early-life behavioral factors, rather than cannabis use itself (Mokrysz et al., 2016).

Poorer cognitive function has also been associated with adolescent onset of cannabis use (Becker et al., 2018; Solowij et al., 2011). Adults who commence cannabis use prior to 16 years of age show deficits in visual scanning, sustained attention, and working memory tasks compared to late-onset users and nonusers (Ehrenreich et al., 1999; Jacobsen et al., 2004). In one study, early age at onset impaired reaction times during a visual scanning task, even after accounting for cumulative cannabis use (Ehrenreich et al., 1999). However, the observed effect of adolescent cannabis use may be small and not necessarily dependent on onset age of use (Scott et al., 2018). Cognitive deficits may not necessarily be apparent in adolescent-onset cannabis users despite cannabis-related effects on the brain. Some studies suggest that altered recruitment strategy and neural responding may compensate for cognitive function, raising the question of whether there are brain structural or functional differences attributable to adolescent onset of cannabis use (Schweinsburg et al., 2008). Specifically, it is vital to understand the relationship between cannabis onset age (i.e., adolescent vs. adult) and brain outcomes in order to guide policies around the legality of recreational and medicinal cannabis use among minors and adolescents.

While a number of reviews have demonstrated brain structural or functional effects in cannabis use (Bloomfield et al., 2019; Lorenzetti et al., 2016; Lorenzetti, Chye, Silva, Solowij, & Roberts, 2019), they have yet to examine the neuroimaging evidence (both structural and functional) that is specifically attributable to adolescent onset of cannabis use across adolescents and adults. Furthermore, many systematic reviews and meta-analyses to date have focused on specific modality (e.g., structural magnetic resonance imaging [MRI; Lorenzetti et al., 2019] or task-based functional MRI (fMRI) [Blest-Hopley, Giampietro, & Bhattacharyya, 2018]), regions (e.g., cerebellum; Blithikioti et al., 2019), or population (e.g., abstinent adolescent cannabis users; Blest-Hopley, Giampietro, & Bhattacharyya, 2019) when exploring cannabis-related brain effects, which restricts broader inferences on the more abstract question of whether adolescent onset of cannabis use may be related to general brain imaging outcomes, both in adolescents and later in life. This narrative review investigates the neuroimaging (structural, functional, spectroscopy) evidence attributable to adolescent cannabis use. This includes evidence in adolescent cannabis users relative to nonusers, as well as evidence of association with onset age of use in adult cannabis users, with the intent to infer on brain effects specifically attributable to onset age of use. While some of the cited reviews (Bloomfield et al., 2019; Lorenzetti et al., 2016) have touched on the association between cannabis onset age and brain effects, this association is not the focus of the aforementioned reviews. Such null findings (i.e., a lack of association with onset age; Arnone et al., 2008; Cousijn et al., 2012; Mata et al., 2010) are not generally reported by these reviews, limiting the inclusivity of inferences.

Methods

Literature search was conducted across PubMed and Scopus on January 15, 2019, with the following search

terms - ((adolescen*) AND (cannabis* OR marijuana) AND (mri OR neuroimag*)). Further inclusion criteria included (a) peer-reviewed; (b) human studies; and (c) written in English. We also excluded nonempirical works (e.g., review articles and case studies) or studies that investigated samples with polysubstance use (apart from alcohol and tobacco use given the prevalence of both substances in the general population) or comorbid psychopathologies apart from cannabis use disorder.

Results

The initial search yielded 297 results from PubMed and 244 results from Scopus. After removal of duplicates and title screening to remove reviews, case studies, non-human studies, and non-neuroimaging studies, 115 articles remained. Of these, detailed screening was conducted to only include studies designed to interrogate (a) cannabis use-related neuroimaging effect in adolescent (i.e., average age < 20 years) users or (b) association of neuroimaging effect with cannabis onset age in adult users and (c) those that are not designed to examine polysubstance use. One study (Subramaniam et al., 2018) was excluded as it consists of the same sample with overlapping findings as another study (Lopez-Larson et al., 2015), while another was excluded due to high levels of psychopathology in the sample (Bellis et al., 2013). This resulted in 43 studies that examined brain effect in adolescent cannabis users (Tables 1 and 2) and 20 that examined the link between onset age of cannabis use and brain effects in adult users (Tables 3 and 4).

Brain structure in adolescent cannabis users

A number of cross-sectional structural imaging (sMRI) studies have examined brain effects in adolescent cannabis users relative to nonusers (Ashtari et al., 2011; Churchwell et al., 2010; Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Kumra et al., 2012; Lopez-Larson et al., 2011; McQueeny et al., 2011; Medina, Nagel, & Tapert, 2010; Medina et al., 2009, 2007; Scott et al., 2019; Weiland et al., 2015). These studies detailing cortical alterations in adolescent cannabis users when compared to their nonusing peers include reduced volume and surface area across parietal (i.e., superior parietal) and frontal (i.e., medial and lateral orbitofrontal [OFC], rostral middle frontal) brain regions (Churchwell et al., 2010; Kumra et al., 2012) and reduced thickness across frontal (i.e., superior frontal, right caudal middle frontal) regions and bilateral insula (Lopez-Larson et al., 2011), but increased volume and thickness of the cerebellum and left entorhinal cortex, respectively (Jacobus et al., 2014; Medina et al., 2010). Another study found that adolescent cannabis users had smaller bilateral hippocampi relative to nonusers, even after 6 months of abstinence (Ashtari et al., 2011). This study further found hippocampal volume to be positively associated with verbal learning performance in nonusers, but not in cannabis users, suggesting altered structure–function relationship in adolescent cannabis users (Ashtari et al., 2011). Earlier onset age of cannabis use was also found to be associated with smaller medial OFC volume and thicker inferior temporal, lateral OFC, anterior cingulate cortex (ACC), and superior frontal regions (Churchwell et al., 2010; Jacobus et al., 2014; Lopez-Larson et al., 2011). However, not all studies have found similar effects. Two studies have found no cortical or subcortical volume difference in cannabis-using adolescents relative to nonusers (Medina et al., 2009; Weiland et al., 2015), and one study has even found an opposite pattern of thicker cortex across widespread regions, including the frontal and parietal cortices, in adolescent cannabis users relative to nonusers (Jacobus et al., 2015). Indeed, out of the four studies that examined hippocampus volume in adolescent cannabis users relative to nonusers (Ashtari et al., 2011; Kumra et al., 2012; Medina et al., 2007; Weiland et al., 2015), only one found hippocampal volume to be reduced in adolescent cannabis users relative to nonusers (Ashtari et al., 2011). Similarly in the cortical regions, of the two most studied regions—the anterior cingulate and OFC (n studies $= 8$ and 9, respectively)—only one (Jacobus et al., 2014) and three (Cheetham et al., 2012; Churchwell et al., 2010; Jacobus et al., 2014) studies, respectively, found an effect of adolescent cannabis use in these regions.

A number of longitudinal structural imaging studies have either attempted to understand brain structure associated with later (follow up $= 4$–5 years) cannabis use in adolescents (Cheetham et al., 2012; Jacobus et al., 2016) or alternately attempted to uncover change in brain structure across time (duration $= 1.5$ years; Epstein & Kumra, 2015a). These studies separately implicate reduced rostral middle frontal thickness and reduced medial and lateral OFC volume at baseline to predict initiation of cannabis use in adolescents (Cheetham et al., 2012; Jacobus et al., 2016). One other study further suggests that adolescent cannabis use is associated with attenuated thickness loss in the inferior frontal (i.e., pars opercularis) and parietal (i.e., supramarginal, inferior

Table 1. Cross-Sectional Neuroimaging Studies on Adolescent Cannabis Use.

			Sample									
			Controls		Cannabis users			Controlled/ matched			Results	
Modality	Cognitive domain	Study	*n* (males)	Age (*SD*)	*n* (males)	Age (*SD*)	Onset age (*SD*)	AIc	Nic	ROI	Controls < cannabis users	Controls > cannabis users	Association with early-onset age
Cross-sectional													
Structural MRI		(Medina et al., 2007)[a]	16 (11)	18.0 (0.9)	16 (12)	18.0 (0.7)	14.6 (1.7)	Yes	No	**Volume** - Hippocampus - Total WM	–	–	–
		(Medina et al., 2009)[a]	16 (10)	18.0 (0.9)	16 (12)	18.0 (0.7)	14.6 (1.7)	Yes	No	**Volume** - Prefrontal (i.e., superior frontal, middle frontal, inferior frontal, OFC, anterior cingulate)	–	–	–
		(Churchwell et al., 2010)	18 (12)	17.2 (0.8)	18 (16)	17.7 (0.9)	14.9 (0.3)	No	No	**Volume** - Medial OFC - Lateral OFC	–	- R medial OFC	↓ B medial OFC
		(Medina et al., 2010)[a]	16 (10)	18.0 (0.9)	16 (12)	18.0 (0.7)	14.6 (1.7)	Yes	No	**Volume** - Cerebellum	- Cerebellum (posterior inferior vermal)	–	–
		(Ashtari et al., 2011)[b]	14 (14)	18.5 (1.4)	14 (14)	19.3 (0.8)	13.1 (1.6)	No	No	**Volume** - Amygdala - Hippocampus	–	- B hippocampus	No effect
		(Lopez-Larson et al., 2011)	18 (12)	17.3 (0.8)	18 (17)	17.8 (1.0)	15.9 (0.9)	No	No	**Thickness** - Whole brain	- B lingual - R superior temporal - R superior parietal - R inferior parietal - L paracentral	- B insula - B superior frontal - R caudal middle frontal	↑ R superior frontal
		(McQueeny et al., 2011)	47 (36)	17.7 (0.9)	35 (27)	18.0 (0.9)	14.2	Yes	Yes	**Volume** - Amygdala	- R amygdala (only in females)	–	–
		(Kumra et al., 2012)	51 (25)	16.2 (2.3)	16 (8)	16.6 (1.7)	13.0 (2.0)	No	No	**Volume** - Superior frontal - Middle frontal - Inferior frontal - Lateral OFC - Medial OFC - Superior parietal - Inferior parietal - Postcentral - Supramarginal - Precuneus - Superior temporal - Anterior cingulate - Caudate - Hippocampus - Thalamus	–	- L superior parietal - L rostral middle frontal	–
		(Weiland et al., 2015)	50 (36)	16.8 (1.0)	50 (41)	16.7 (1.1)	n.r.	Yes	Yes	**Volume** - Accumbens - Amygdala - Hippocampus - Cerebellum - Total brain (GM, WM)	–	–	–
		(Scott et al., 2019)	634 (254)	17.0 (2.1)	109 (54) occasional users + 38 (27) frequent users	18.2 (1.9)[c]	15.1 (1.8)	No	No	**Volume, thickness, GM density** - Whole brain	–	**Thickness** - L frontal (frequent users vs. controls only)	–
Diffusion tensor imaging		(Ashtari et al., 2009)[b]	14 (14)	18.5 (1.4)	14 (14)	19.03 (0.8)	13.1 (1.6)	No	No	**FA, AD, RD, MD, trace** - Whole brain	**RD, trace** - B posterior internal capsule - L middle temporal - R superior temporal	**FA, AD** - B posterior internal capsule - L middle temporal - R superior temporal	No effect
		(Yücel et al., 2010)	8 (2)	19.7 (2.7)	11 (7)	19.4 (1.9)	15.0 (1.6)	Yes	Yes	**FA** - Whole brain	–	- R SLF - B hippocampus	–
		(Epstein et al., 2014)	55 (27)	16.5 (2.6)	31 (22)	17.6 (2.4)	n.r.	No	No	**FA** - Cingulum - Corticospinal tract - IFOF - ILF - SLF - Uncinate fasciculus	–	- L IFOF	–

(*Continued*)

Table 1. Continued.

			Sample										
			Controls		Cannabis users			Controlled/ matched			Results		
Modality	Cognitive domain	Study	*n* (males)	Age (*SD*)	*n* (males)	Age (*SD*)	Onset age (*SD*)	AIc	Nic	ROI	Controls < cannabis users	Controls > cannabis users	Association with early-onset age
Magnetic resonance spectroscopy		(Prescot et al., 2011)	17 (8)	16.2 (2.1)	17 (15)	17.8 (1.1)[c]	15 (1.5)	No	No	**Aspartate, choline, creatine, glutamate, Ins, NAA** - Anterior cingulate	–	- Creatine, glutamate, Ins, NAA	–
		(Prescot et al., 2013)	16 (7)	16.0 (2.2)	13 (11)	17.9 (1.0)[c]	15.2 (1.4)	No	No	**Creatine, GABA, glutamate, Ins, NAA** - Anterior cingulate	–	- Creatine, GABA, glutamate, Ins, NAA	–
		(Bitter et al., 2014)	15 (6)	18.4 (2.0)	13 (8)	19.2 (1.1)	n.r.	No	No	**NAA** - L inferior frontal	–	–	–
Functional MRI	Rest	(Lopez-Larson et al., 2015)	31 (24)	17.2 (1.4)	43 (40)	18 (1.2)[c]	14.7 (1.4)	Yes	Yes	- Seed = OFC	**Connectivity** - R OFC and L anterior and middle cingulate - R OFC and R medial, middle, and superior frontal R OFC and L precentral - L OFC and R middle frontal - L OFC and R anterior and middle cingulate	**Connectivity** - R OFC and R superior parietal	↑ connectivity - R OFC and B superior frontal, B precentral, B supplementary motor, and L paracentral
	Reward	(Jager et al., 2012)[a]	24 (24)	16.8 (1.3)	21 (21)	17.2 (1.0)	13.2 (2.3)	No	No	- Caudate - Putamen	**Activity** - L caudate	–	↑ activity - R caudate
		(Acheson et al., 2015)	14 (11)	17.3 (1.3)	14 (11)	17.6 (1.0)	n.r.	No	No	- Whole brain	**Activity** - B middle frontal - B caudate - B claustrum - R posterior cingulate - R anterior cingulate - L insula - cerebellum (declive) **Connectivity** - R and L claustrum - L insula and posterior cingulate - Anterior cingulate and L claustrum	**Connectivity** - Anterior and posterior cingulate - Anterior cingulate and R claustrum - R medial frontal and posterior cingulate - R claustrum and L insula	–
		(Karoly et al., 2015)	38 (24)	15.8 (1.2)	14 (11)	15.8 (1.4)	12.9 (1.9)	Yes	Yes	- Seed = accumbens	–	–	–
	Memory	(Jacobsen et al., 2004)[b]	7 (2)	16.8 (1.4)	7 (3)	17.4 (1.0)	13.8 (1.9)	No	No	- Hippocampus	–	–	–
		(Padula et al., 2007)[a]	17 (12)	17.9 (1.2)	17 (14)	18.1 (0.8)	n.r.	Yes	No	- Whole brain	**Activity** - R claustrum - R putamen - R caudate - R thalamus - R pallidum - R insula - R postcentral - B precuneus - B superior parietal	–	–
		(Schweinsburg et al., 2008)[a]	17 (12)	17.9 (1.0)	15 (11)	18.1 (0.7)	14.1 (1,6)	No	No	- Whole brain	**Activity** -R superior parietal	**Activity** - R middle frontal	↓ activity - superior and inferior occipital
		(Jager et al., 2010)[a]	24 (24)	16.8 (1.3)	21 (21)	17.2 (1.0)	13.2 (2.3)	Yes	Yes	- Whole brain	**Activity** - L inferior frontal - L precentral - anterior cingulate - L superior parietal	–	–
		(Schweinsburg et al., 2010)	18 (11)	17.3 (0.8)	13 (9) recent users + 13 (9) abstinent[a] users	17.3 (0.7)	n.r.	Yes	Yes	- Whole brain	–	–	–
		(Schweinsburg et al., 2011)	22 (16)	17.6 (0.8)	8 (4)	18.1 (0.9)	14.5 (2.5)	Yes	Yes	- Whole brain	**Activity** - B superior frontal - B middle frontal - R inferior frontal	**Activity** - B cuenus - B lingual	–

Response inhibition	(Tapert et al., 2007)[a]	17 (12)	17.9 (1.0)	16 (12)	18.1 (0.7)	14.0 (1.6)	Yes	Yes	- Whole brain	**Activity** - R inferior frontal - R insula - R superior frontal - R middle frontal - R superior parietal - R inferior parietal - R precuneus	–	–
	(Behan et al., 2014)	18 (17)	16.1 (0.4)	17 (16)	16.5 (0.2)	13.0 (0.2)	Yes	Yes	- Whole brain	**Connectivity** - B parietal and cerebellum	–	–
Attention	(Abdullaev et al., 2010)	14 (10)	19.7 (1.4)	14 (10)	19.5 (0.8)	14.7	Yes	No	- Whole brain	**Activity** - B parietal - R lateral prefrontal - Supplementary motor	–	–
Motor: finger tapping	(Lopez-Larson et al., 2012)	24 (17)	18.0 (1.9)	24 (22)	18.2 (0.7)	15.3 (1.4)	No	No	- Motor - Premotor - Cingulate - Cerebellum	–	**Activity** - R cingulate - Cerebellum	–
Emotional face viewing	(Spechler et al., 2015)	70 (41)	14.6 (0.7)	70 (50) cannabis experimenter	14.8 (0.4)	13.6 (0.9)	Yes	Yes	- Whole brain	**Activity** - B amygdala - R temporal-parietal junction, B superior and middle frontal - differ between face conditions in controls but not cannabis experimenters	–	–

Note. AIc = alcohol use; Nic = nicotine use; MRI = magnetic resonance imaging; ROI = region of interest; R = right; L = left; B = bilateral; OFC = orbitofrontal cortex; GM = gray matter; WM = white matter; FA = fractional anisotropy; AD = axial diffusivity; MD = mean diffusivity; RD = radial diffusivity; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; GABA = γ-amino butyric acid; Ins = myo-inositol; NAA = N- acetyl aspartate; n.r. = not reported.

[a]After 28+ days abstinence.

[b]After 6–10 months abstinence.

[c]Significant difference in age between controls and cannabis users.

Table 2. Longitudinal Neuroimaging Studies on Adolescent Cannabis Use.

			Sample								Results		
			Controls		Cannabis users			Controlled/ matched					
Modality	Cognitive domain	Study	*n* (males)	Age (*SD*)	*n* (males)	Age (*SD*)	Onset age (*SD*)	Alc	Nic	ROI	Controls < cannabis users	Controls > cannabis users	Association with early onset age
Longitudinal													
Structural MRI		(Cheetham et al., 2011)	93 (50)	12.5–16.5 (0.5)	28 (12)	12.4–16.4 (0.6)	14.8 (0.9)	Yes	Yes	**Volume** - OFC - Anterior cingulate - Amygdala - Hippocampus	–	**Preinitiation** - R lateral OFC	–
		(Jacobus et al., 2014)[a,b]	30 (22)	17.4–17.5 (0.8)	24 (17)	17.7–17.8 (0.7)	15.4 (0.9)	Yes	No	**Thickness** - Whole brain	**Baseline** - L caudal anterior cingulate - L entorhinal - L lingual - L pericalcarine **After 28 days' abstinence** - L entorhinal	–	↓L inferior temporal, L middle temporal, L pars orbitalis, R lateral OFC, R pars triangularis, R rostral anterior cingulate
		(Epstein & Kumra, 2015a)	34 (16)	16.5 (2.1)	17 (9)	16.6 (1.6)	n.r.	Yes	Yes	**Thickness** - Superior frontal - Inferior frontal - Inferior parietal - Supramarginal - Superior temporal	**Follow-up** - L inferior frontal, L supramarginal, L inferior parietal attenuated thickness loss in cannabis users relative to controls	–	–
		(Jacobus et al., 2015)[b]	38 (29)	17.7–0.8 (1.0)	30 (19)	18.2–21.2 (0.8)	15.3 (2.0)	Yes	No	**Thickness** - Whole brain	**Baseline and follow-up** - B precentral - B postcentral - R superior parietal - R supramarginal - R precuneus - R transverse - L frontal pole temporal - L pericalcarine **Follow-up** - B paracentral - R inferior parietal - L pars opercularis - L superior frontal - L supramarginal	–	↑ R entorhinal
		(Jacobus et al., 2016)[b]	23 (13)	13.4–18.7 (0.8)	23 (13)	13.9–19.5 (0.8)	15.7 (1.7)	No	No	**Thickness** - Whole brain	–	**Preinitiation** - R rostral middle frontal	–
Diffusion tensor imaging		(Bava et al., 2013)	51 (37)	17.9–19.3 (1.1)	41 (26)	18.4–19.8 (1.2)[c]	n.r.	No	No	**FA, AD, MD, RD** - Whole brain	**Follow-up** **AD** - L posterior corona radiata **MD** - R thalamic radiation **RD** - R SLF - R superior temporal	**Follow-up** **FA** - Splenium of the corpus callosum - R prefrontal thalamic fibers - R posterior corona radiata	–
		(Becker et al., 2015)	23 (16)	19.2–21.4 (2.3)	23 (16)	19.5–21.7 (0.7)	15.4 (1.2)	Yes	Yes	**FA, RD** - Whole brain	**Baseline** **FA** - R genu and forcep minor of CC **Change across time point** **FA** - L anterior CC - posterior thalamus	**Baseline** **RD** - R genu and forcep minor of CC **Change across time point** **FA** - B SLF - L parietal operculum	No effect

											RD - R corticospinal tract - Posterior cingulum	- L superior frontal **RD** - L corticospinal tract	
		(Epstein & Kumra, 2015b)	29 (13)	16.5–18.0 (2.2)	19 (11)	16.6–18.1 (1.5)	n.r.	Yes	Yes	**FA** - Cingulum - Corticospical tract - IFOF - ILF - SLF - Uncinate fasciculus	**Change across time point** **FA** - L ILF	–	–
Arterial spin labeling		(Jacobus et al., 2012)[a]	23 (19)	17.5–17.6 (0.8)	23 (17)	17.7–17.8 (0.7)	n.r.	Yes	Yes	**Cerebral blood flow** - Whole brain	**Baseline** - R precuenus **After 28 days' abstinence** - No difference	**Baseline** - L superior temporal - L middle temporal - L insula - L medial frontal - L supramarginal **After 28 days' abstinence** - No difference	–
Functional MRI	Rest	(Camchong et al., 2017)	43 (23)	15.9–17.4 (2.9)	22 (14)	17.0–18.6 (2.0)	13.0 (2.2)	Yes	Yes	- Seed–anterior cingulate	**Change across time point** **Connectivity** - Caudal anterior cingulate and L inferior/ medial frontal	**Change across time point** **Connectivity** - Caudal anterior cingulate and L superior frontal	–
	Memory	(Tervo-Clemmens et al., 2019)	63 (29)	12.8–15.7 (0.4)	22 (12)	12.7–15.6 (0.3)	13.7 (1.3)	Yes	No	- Whole brain	**Preinitiation** **Activity** - L inferior parietal - L middle frontal	**Preinitiation** **Activity** - L lingual - L lateral occipital **Follow-up** - R cuneus	–
Structural MRI and functional MRI	Response inhibition	(Spechler et al., 2018)	1,216 (538)	14.5 (0.4)	365 (207) ever used cannabis	14.5 (0.5)	n.r.	No	No	- Whole brain	**Preinitiation** **Volume** - R medial frontal (males) - R presupplemental motor (females) **Activity** - L inferior temporal (males) - R presupplemental motor (females)	**Preinitiation** **Volume** - R OFC (female)	–

Note. Alc = alcohol use; Nic = nicotine use; MRI = magnetic resonance imaging; ROI = region of interest; R = right; L = left; B = bilateral, OFC = orbitofrontal cortex; GM = gray matter; WM = white matter; FA = fractional anisotropy; AD = axial diffusivity; MD = mean diffusivity; RD = radial diffusivity; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; CC = corpus callosum; n.r. = not reported.

[a]After 28+ days abstinence.

[b]Cannabis and alcohol users.

[c]Significant difference in age between controls and cannabis users.

Table 3. Neuroimaging Studies of Adult Cannabis Users, Comparing Early- Vs. Late-Onset Users.

			Sample										
			Early-onset cannabis users		Late-onset cannabis users			Controlled/matched			Results		
Modality	Cognitive domain	Study	*n* (males)	Age (*SD*)	*n* (males)	Age (*SD*)	Cutoff age	Alc	Nic	ROI	Early- < late-onset users	Early- > late-onset users	Association with early onset age
Early- vs. late-onset users													
Structural MRI		(Wilson et al., 2000)	29 (13)	29.5 (6.5)	28 (19)	33.2 (7.8)	< 17/≥ 17	No	No	**Volume** - Whole brain (frontal, temporal, parietal, occipital, cingulate, insula)	- Whole brain GM	- Whole brain WM	–
		(Battistella et al., 2014)	13 (13) occasional users + 16 (16) regular users	~ 24	9 (9) occasional users + 9 (9) regular users	~ 24	< 18/≥ 18	Yes	No	**Volume** - Whole brain	- L parahippocampal - R temporal pole (only in occasional users)	–	–
		(Filbey et al., 2015)	20 (11)	32.5 (8.0)	22 (16)	30.3 (7.2)	< 16/≥ 16	Yes	No	**Thickness, GM-WM contrast, local gyrification index** - Whole brain	–		↑ thickness, GM-WM contrast–B rostral middle frontal, R medial OFC, R lingual ↓ gyrification index–L inferior parietal
		(Chye, Suo et al., 2019)	50 (30)	29.2 (10.1)	86 (60)	27.7 (10.5)	< 17/≥ 17	Yes	Yes	**Thickness, surface area, gyrification index** - Whole brain	–	–	–
Diffusion tensor imaging		(Gruber et al., 2014)	11	23.2 (5.9)	14	23.2 (5.9)	< 16/≥ 16	Yes	Yes	**FA** - Genu of CC - Corona radiata -Internal capsule - External capsule	–	–	↓ FA–B genu of CC
Functional MRI	Memory	(Becker et al., 2010)	26 (19)	21.0 (2.8)	17 (15)	24.5 (3.4)	< 16/≥ 16	No	No	- Whole brain	–	**Activity** - L superior parietal	↑ activity–B superior frontal, B inferior frontal, L middle frontal, L superior temporal, L insula, L precuneus, L superior parietal, R paracentral, and L putamen
	Response inhibition	(Sagar et al., 2015)	24 (21)	23.7 (7.3)	26 (21)	24.3 (6.8)	< 16/≥ 16	Yes	Yes	- Whole brain	–	**Activity** - L anterior cingulate	

Note. Alc = alcohol use; Nic = nicotine use; MRI = magnetic resonance imaging; ROI = region of interest; R = right; L = left; B = bilateral; OFC = orbitofrontal cortex; GM = gray matter; WM = white matter; FA = fractional anisotropy; CC = corpus callosum.

Table 4. Neuroimaging Studies of Adult Cannabis Users, Associating Neuroimaging Measures with Onset of Age of Use.

			Sample								
			Controls		Cannabis users			Controlled			
Modality	Cognitive domain	Study	*n* (males)	Age (*SD*)	*n* (males)	Age (*SD*)	Onset age (*SD*)	Alc	Nic	ROI	Results Association with early onset age
Association with onset age											
Structural MRI		(Mata et al., 2010)	44 (25)	25.8 (5.8)	30 (23)	25.7 (5.0)	17.3 (3.9)	Yes	Yes	**Thickness, curvature** - Whole brain	No effect
		(Cousijn et al., 2011)	42 (26)	21.9 (2.4)	33 (21)	21.3 (2.4)	18.8 (2.3)	No	No	**Volume** - OFC - Anterior cingulate - Striatum (accumbens, caudate, putamen) - Amygdala - Hippocampus - Cerebellum	No effect
		(Orr et al., 2016)	393 (157)	22–35	464 (220) recreational users	22–35	> 50% of users first use at 15–20 years	Yes	Yes	**Volume** - Medial OFC - Lateral OFC - Caudal anterior cingulate - Caudal middle frontal - Inferior frontal - Rostral middle frontal - Superior frontal - Frontal pole - Accumbens - Amygdala - Hippocampus - Thalamus - Cerebellum **Shape** - Accumbens - Amygdala - Hippocampus	↑ R accumbens outward deflection
		(Koenders et al., 2017)	23 (13)	21.8–25.1 (2.6)	21 (14)	20.6–24.2 (2.4)	14.4 (1.5)	Yes	No	**Volume** - Hippocampus	No effect
		(Burggren et al., 2018)a	26 (14)	67.7 (7.1)	24 (16)	65.4 (7.2)	17.7 (4.2)	Yes	Yes	**Thickness** - Parahippocampal - Perirhinal - Entorhinal - Fusiform - Hippocampus	No effect
		(Levar et al., 2018)	22 (10)	21.6 (1.9)	19 (8)	20.6 (2.5)	16.2 (1.7)	Yes	No	**Thickness** - Medial OFC - Lateral OFC - Fusiform - Entorhinal - Temporal pole	↓ L entorhinal
Diffusion tensor imaging		(Arnone et al., 2008)	11 (11)	23.4 (2.9)	11 (11)	25.0 (3.0)	15.3 (2.8)	No	No	**FA, MD** - CC	No effect
		(Gruber et al., 2011)	15 (14)	25.2 (8.4)	15 (14)	25.0 (8.7)	14.9 (2.5)	No	No	**FA, trace** - Genu of the CC - Frontal - Splenium	↑ FA, ↓ trace–L frontal and R genu of CC
		(Zalesky et al., 2012)	33 (14)	31.5 (12)	59 (28)	33.4 (10.9)	16.7 (3.3)	Yes	Yes	**AD, RD** - R fimbria - Commissural fibers	↓ RD, AD–commissural fiber
		(Jakabek et al., 2016)	20 (8)	30 (10.6)	56 (24)	32.3 (10.8)	15.1 (2.3)	Yes	Yes	**FA, AD, RD** - Whole brain	↑ AD–R cingulate
		(Orr et al., 2016)	393 (157)	22–35	464 (220) recreational users	22–35	> 50% of users first use at 15–20 years	Yes	Yes	**FA, AD, MD, RD** - Whole brain	↓ FA, ↑ RD in SLF, ILF, forcep major and forcep minor

(*Continued*)

Table 4. Continued.

Modality	Cognitive domain	Study	Sample					Controlled		ROI	Results Association with early onset age
			Controls		Cannabis users						
			n (males)	Age (*SD*)	*n* (males)	Age (*SD*)	Onset age (*SD*)	Alc	Nic		
		(Levar et al., 2018)	22 (10)	21.6 (1.9)	19 (8)	20.6 (2.5)	16.2 (1.7)	Yes	No	**FA, AD, MD, RD, fiber bundle length** - Uncinate fasciculus	No effect
Functional MRI	Memory	(Tervo-Clemmens et al., 2018)	15 (2)	28.2 (0.7)	46 (18)	28.2 (0.7)	15.1 (2.3)	Yes	Yes	- Whole brain	↓ activity–R posterior parietal
	Inhibitory control	(Filbey & Yezhuvath, 2013)	–	–	74 (55)	24.2 (7.2)	17.4 (2.6)	Yes	Yes	- Seed–B basal ganglia, R frontal, B substantia nigra/ subthalamic nucleus, B orbital, B pre-supplementary motor, precentral gyrus, B parietal, B medial orbital	↓ connectivity–R frontal and precentral ↑ connectivity–R frontal and substantia nigra
	Attention	(Chang et al., 2006)	19 (11)	30.6 (1.8)	12 (9) active users + 12 (6) abstinent users	28.8 (2.8)	15.1 (0.8)	No	No	- Whole brain	↓ activity–R middle frontal ↑ activity–cerebellum

Note. Alc = alcohol use; Nic = nicotine use; MRI = magnetic resonance imaging; ROI = region of interest; R = right; L = left; B = bilateral; OFC = orbitofrontal cortex; FA = fractional anisotropy; AD = axial diffusivity; MD = mean diffusivity; RD = radial diffusivity; CC = corpus callosum.
[a]Abstinent for an average of 30 years.

parietal) regions relative to nonuse (Epstein & Kumra, 2015a). One final longitudinal study in which adolescent cannabis and alcohol users were followed over a 3-year period found consistently thicker frontal (i.e., precentral, paracentral, pars opercularis, frontal pole, and superior frontal), parietal (i.e., superior parietal, inferior parietal, supramarginal, postcentral, and percuneus), temporal (i.e., transverse temporal), and occipital (i.e., pericalcarine) regions in adolescent cannabis and alcohol users relative to nonusers (Jacobus et al., 2015).

In relation to gender differences, two studies have found female adolescent cannabis users to have a larger right amygdala and larger prefrontal (i.e., middle, inferior, and superior frontal, OFC, anterior cingulate) cortex relative to nonusing females, whereas male cannabis users had smaller prefrontal cortex relative to nonusing males and did not differ in amygdala volume (McQueeny et al., 2011; Medina et al., 2009). Yet another study suggests that predictive factor of cannabis initiation in adolescence is sex-specific. They showed that in males, left inferior temporal activity during stop signal task and larger right medial prefrontal cortex volume at age 14 predicted cannabis use by age 16; whereas in females, greater right pre-supplementary motor area volume and activity and lower right OFC volume predicted cannabis use (Spechler et al., 2018). However, in this study, cannabis initiation was defined as having ever used cannabis and did not necessarily reflect the use level of regular cannabis users.

There is also evidence of deficits in white matter integrity in adolescent cannabis users compared to their nonusing counterparts. Studies have generally examined fractional anisotropy (FA) values from diffusion tensor images (DTI) as a proxy for white matter integrity, either across the whole brain (Ashtari, Cervellione, Cottone, Ardekani, & Kumra, 2009; Bava, Jacobus, Thayer, & Tapert, 2013; Becker, Collins, Lim, Muetzel, & Luciana, 2015; Yücel et al., 2010) or in specific fiber bundles (i.e., cingulum, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and the corticospinal tract; Epstein, Cullen, Mueller, Lee, & Kumra, 2014; Epstein & Kumra, 2015b). Poorer white matter integrity has been observed in the inferior fronto-occipital fasciculus, thalamic radiations, corona radiata, corpus callosum, superior longitudinal fasciculus, and bilateral hippocampus of adolescent cannabis users relative to their nonusing peers (Epstein et al., 2014; Yücel et al., 2010). A study on adolescent cannabis users who have been abstinent for 6 months further suggests compromised

white matter integrity at the posterior internal capsule, middle temporal gyrus, and superior temporal gyrus (Ashtari et al., 2009). However, cannabis users in one study that found poorer white matter integrity in the superior and inferior longitudinal fasciculus, prefrontal and posterior thalamic radiation, superior temporal gyrus, and corona radiata were also heavy alcohol users, which confounds findings (Bava et al., 2013). Of the aforementioned tracts and white matter bundles, the most consistently implicated are the superior longitudinal fasciculus (3 out of 6 studies; Bava et al., 2013; Yücel et al., 2010), the superior temporal gyrus (2 out of 4 studies; Ashtari et al., 2009; Bava et al., 2013), and the corpus callosum (2 out of 4 studies; Bava et al., 2013; Becker et al., 2015). In particular in longitudinal studies that followed adolescent cannabis users over 1 to 2 years, decline in FA in the inferior longitudinal fasciculus and reduced growth of FA in the superior longitudinal fasciculus was observed (Becker et al., 2015; Epstein & Kumra, 2015b).

Brain structure in adult cannabis users—association with onset age

The potential effect of adolescent onset of cannabis use has also been investigated in adult users by attempting to dissociate neuroalterations by onset age. An early structural imaging study suggests that cannabis users who began using cannabis before 17 years of age, versus those who started at 17 or older, had smaller brain and gray matter volume but larger white matter volume and higher cerebral blood flow (Wilson et al., 2000). Following that, another study on occasional cannabis users found that those who began use before age 18 had smaller left parahippocampal gyrus and right temporal pole relative to occasional late users (Battistella et al., 2014). However, this pattern did not emerge in regular users, with smaller gray matter volume in regular users occurring irrespective of onset age, suggesting that brain structural differences may occur with either heavy cannabis use irrespective of onset age or in early occasional use (Battistella et al., 2014). This finding of brain structural difference by onset age is yet poorly substantiated, as a number of other studies suggest cortical morphology (thickness, surface area, gray/white matter ratio, and gyrification) does not differ by cannabis onset (Chye, Suo et al., 2019; Filbey, McQueeny, DeWitt, & Mishra, 2015; Mata et al., 2010). One of the studies did find a divergent correlation pattern in the frontal (i.e., rostral middle frontal, medial OFC) and parietal (i.e., inferior parietal) brain regions, with increasing quantity and duration of cannabis use associated with thicker cortex, increased gray/white matter ratio and decreased gyrification in early-onset (before age 16) users, but thinner cortex, reduced gray/white matter ratio, and increased gyrification in late-onset (age 16 and older) users (Filbey et al., 2015). One study found a relationship of thicker left entorhinal cortex with later onset age of cannabis use (Levar, Francis, Smith, Ho, & Gilman, 2018), but a number of others did not find any cortical (OFC, cingulate, cerebellum, medial temporal) or subcortical (striatum, amygdala, hippocampus) volumes correlated with onset age (Burggren et al., 2018; Cousijn et al., 2012; Koenders et al., 2017). The effect of cannabis onset age on brain structure may be subtler, as demonstrated by one study that found subtle shape differences associated with onset age (greater outward deflection in later onset) of the nucleus accumbens, despite comparable volumes in recreational cannabis users (Orr, Paschall, & Banich, 2016).

Examination of white matter integrity in relation to cannabis onset age has also suggested that earlier onset was correlated with poorer white matter integrity in the left frontal region, the bilateral genu of the corpus callosum, the superior and inferior longitudinal fasciculus, the cingulate gyrus, the fimbria of the hippocampus, and the forceps major and minor (Gruber, Dahlgren, Sagar, Gönenç, & Lukas, 2014; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011; Jakabek, Yücel, Lorenzetti, & Solowij, 2016; Orr et al., 2016; Zalesky et al., 2012). Lower white matter integrity was further associated with higher impulsivity as measured by the Barratt Impulsivity Scale (BIS-11; Gruber et al., 2014). However, when splitting cannabis user groups into those who started use before 16 years and those who started at 16 or older, this study did not find any significant group difference in the corpus collosum, corona radiata, or internal and external capsule. Yet other studies have found no diffusion abnormalities in the corpus callosum or uncinate fasciculus associated with onset age (Arnone et al., 2008; Levar et al., 2018).

In sum, when comparing adolescent cannabis users to nonusers, many but not all studies have demonstrated altered (either reduced or increased) volume, surface area, or thickness across frontal or parietal regions. Some studies have further implicated the cerebellum, insula, and cingulate cortex. In contrast to findings in adolescent users, studies in adult users have not been able to consistently find an association between age at onset of cannabis use and structural alterations (Burggren et al., 2018; Cousijn et al., 2012;

Mata et al., 2010; Orr et al., 2016). The regions implicated in adult studies have also been different, with findings confined to temporal regions including the parahippocampal (Battistella et al., 2014) and entorhinal cortex (Levar et al., 2018). White matter findings in both adolescent and adult cannabis users are more consistent, showing compromised white matter integrity across major tracks, particularly the longitudinal fasciculus (Bava et al., 2013; Becker et al., 2015; Epstein & Kumra, 2015b; Orr et al., 2016; Yücel et al., 2010) related to early onset of cannabis use.

Brain function in adolescent cannabis users

Resting state functional imaging studies mostly implicate OFC connectivity alteration in adolescent cannabis use. One resting state fMRI study, seeded at the right and left OFC, demonstrated greater functional connectivity among bilateral OFC, anterior and middle cingulate, and medial frontal regions in adolescent cannabis users relative to nonusers, but reduced connectivity between the right OFC and right superior parietal region (Lopez-Larson et al., 2015). A further longitudinal study over an 18-month period further demonstrated that nonusing adolescents show an increased functional connectivity between caudal cingulate and frontal regions at rest, while cannabis-using adolescents do not, implicating cannabis use in the maturation of cortical function during adolescence (Camchong, Lim, & Kumra, 2017). This study also found lower caudal cingulate–OFC connectivity at baseline predictive of greater amount of cannabis use, poorer IQ, and cognitive function (i.e., slower reaction time during an attention task) at follow-up (Camchong et al., 2017). However, analysis for this study was seeded to the anterior cingulate and was thus unable to infer on other regions not functionally connected to the cingulate. Other implicated regions also include the cerebellum and parietal region, with one study showing greater functional connectivity between parietal regions and cerebellum at rest to be positively associated with recent cannabis use in adolescent cannabis users (Behan et al., 2014).

A number of task-based functional imaging studies have also attempted to glean differences in adolescent cannabis use related to reward, memory, and executive functioning tasks. Reward processing has typically been implicated in substance use (Volkow, Fowler, & Wang, 2003), with developmental changes in reward system—involving the striatum—during adolescence thought to play a role in the development and maintenance of substance dependence (Galvan, 2010; Volkow & Morales, 2015). One study that attempted to delineate the reward neurocircuitry in adolescent cannabis users relative to nonusers during anticipation of a monetary reward found neither a performance difference nor any activation difference in their predetermined region of interest (ROI) of the nucleus accumbens (i.e., ventral striatum; Karoly et al., 2015). However, hyperactivity in the caudate has been implicated in frequent cannabis-using adolescent boys during anticipation of monetary reward and even in an unrewarded trial (Jager, Block, Luijten, & Ramsey, 2013). Caudate activation was associated with an earlier onset age of cannabis use and thought to reflect a hypersensitive motivational system that persists even in the event of unrewarded trials. Other studies also found greater neural response to gambling outcomes (both wins and losses) in the middle frontal region, anterior and posterior cingulate, caudate, and insula, but attenuated connectivity between the anterior and posterior cingulate and between the OFC and cingulate regions, in adolescent cannabis users compared to nonusers (Acheson et al., 2015).

Another implicated cognitive domain in cannabis use is memory function (Broyd, van Hell, Beale, Yücel, & Solowij, 2016). However, studies on verbal, pictorial, and spatial learning tasks have mostly distinguished no memory performance difference between adolescent cannabis users and nonusers (Jager, Block, Luijten, & Ramsey, 2010; Padula, Schweinsburg, & Tapert, 2007; Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011; Schweinsburg et al., 2008, 2010). While one study did not find any activation difference associated with verbal encoding (Schweinsburg et al., 2011), a number of others found either reduced or increased frontal (i.e., inferior, superior, and middle frontal, anterior cingulate) activity (Jager et al., 2010; Schweinsburg et al., 2008, 2010), reduced occipital activity (Schweinsburg et al., 2008), and increased basal ganglia (i.e., caudate, putamen, globus pallidus), thalamus, precuneus, postcentral, and superior parietal activity in adolescent cannabis users relative to nonusers during working memory tasks (Padula et al., 2007), suggesting some form of compensatory activation. One pilot study of seven adolescent cannabis users who had been abstinent for at least 10 months did find impaired auditory working memory performance (accuracy) and higher activation at the hippocampus compared to nonusers, but the small sample size limits generalization (Jacobsen et al., 2004). Finally, a longitudinal study suggested functional difference in adolescents to be predictive of cannabis initiation, demonstrating increased

frontoparietal (i.e., inferior parietal, middle frontal, pre-supplementary motor) activation, decreased visual association region (i.e., precuneus, lateral occipital) activation, and poorer performance during a visuo-spatial working memory task at 13 years old to be predictive of cannabis initiation by age 15 (Tervo-Clemmens et al., 2019).

Attention, decision making, and inhibitory control have all also been implicated in adolescent cannabis use. Adolescent cannabis users have shown greater right frontal, bilateral parietal, and supplementary motor cortex activation during an attention network task and poorer task performance (longer reaction time and more errors; Abdullaev, Posner, Nunnally, & Dishion, 2010). Inhibitory control, as assessed by a Go/No-Go task, has been alternately demonstrated to be comparable (Tapert et al., 2007) or poorer (i.e., lower number of successful inhibition; Behan et al., 2014) in adolescent cannabis users relative to nonusers. Yet both studies suggest heightened task-associated activation patterns across frontal, parietal, and cerebellar regions in adolescent cannabis users relative to nonusers (Behan et al., 2014; Tapert et al., 2007). Furthermore, earlier onset of use was associated with less inhibitory response in the right anterior superior frontal gyrus (Tapert et al., 2007). However, Behan et al. (2014) caution that their imaging result found was likely task-independent, as it persisted even at rest. Adolescent cannabis users may also process emotive stimuli differently than nonusers. One study suggests hypersensitivity to threat signals in adolescent cannabis users, as evidenced by greater amygdala reactivity to angry faces during an affective face processing task (Spechler et al., 2015). Meanwhile, nonusing adolescents show greater activation of the right temporal-parietal junction and bilateral superior and middle frontal regions when viewing neutral faces relative to angry faces, but this was not apparent in cannabis-using adolescents (Spechler et al., 2015).

More broadly, an arterial spin labeling technique has been used to show that adolescent cannabis users have reduced cerebral blood flow across all four cortical regions (left superior and middle temporal, left insula, left and right medial frontal, and left supramarginal) at baseline, but not after 4 weeks of abstinence (Jacobus et al., 2012). Proton magnetic resonance spectroscopy studies have also been carried out to examine neurochemical differences in adolescent cannabis users relative to nonusers. These studies have focused on either the anterior cingulate (Prescot, Locatelli, Renshaw, & Yurgelun-Todd, 2011; Prescot, Renshaw, & Yurgelun-Todd, 2013) or the inferior frontal cortex (Bitter et al., 2014) as regions of interest. Within the anterior cingulate, lower n-acetyl-aspartate (a marker of neuronal integrity), gamma-Aminobutyric acid (GABA), glutamate, creatine, and myo-inositol (neurotransmitters and metabolites involved in signal transduction and brain function) levels were found in cannabis users relative to nonusers (Prescot et al., 2011, 2013). Meanwhile, no spectroscopy difference was found in the inferior frontal cortex (Bitter et al., 2014).

Importantly, structural and functional differences may predate cannabis initiation, as demonstrated by one study showing that smaller OFC volumes in adolescents predicted initiation of cannabis use by age 16 (Cheetham et al., 2012).

Brain function in adult cannabis users—association with onset age

Functional imaging studies that explored association with onset age in adult cannabis users have been limited in numbers ($n = 5$ studies) in comparison to studies within adolescent cannabis user groups. These studies have mostly examined activation in relation to memory (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010; Tervo-Clemmens et al., 2018), attention (Chang, Yakupov, Cloak, & Ernst, 2006), and inhibitory control (Filbey & Yezhuvath, 2013; Sagar et al., 2015). One study on verbal working memory showed increased left superior parietal activation in early-onset users (before age 16) relative to late-onset users despite similar performance (Becker et al., 2010). Regression analysis further illustrated earlier onset age to be associated with greater superior parietal and putamen activity during the working memory task (Becker et al., 2010). The authors suggest that suboptimal cortical efficiency in early-onset users may be driving this observed difference. Contradictorily, in another spatial working memory study, earlier onset of cannabis use not only was associated with slower reaction time but also reduced encoding related activation at the posterior parietal cortex instead. This effect was present for both current cannabis users and "experimenters" (who have used cannabis irregularly and not within the last year), which the authors suggest to be a function of cannabis onset and not of recent or regular cannabis use (Tervo-Clemmens et al., 2018).

In relation to inhibitory control, when cannabis users were divided into early-onset (before age 16) and late-onset users, early-onset users exhibited poorer performance relative to nonusers and late-

onset users and showed greater activation around the left anterior cingulate during a modified Stroop Color Word Test (Sagar et al., 2015). However, this study adopted separate single group comparisons in controls and early and late cannabis users separately, instead of comparing across groups, making inference less reliable. Another study found age at onset to be positively correlated with frontal-precentral gyrus network and negatively correlated with the frontal–substantia nigra network (Filbey & Yezhuvath, 2013). Yet another found no association between brain activity and onset age (Hester, Nestor, & Garavan, 2009). The differing findings make it difficult to infer on inhibitory control function in early-onset cannabis use. Meanwhile, only one study examined visual attention in relation to onset age in adult cannabis users, and it found earlier onset to be associated with reduced right prefrontal activity involved in attentional function and increased cerebellar activity (Chang et al., 2006). The authors also observed an interaction effect between onset age and cumulative cannabis exposure, detailing that while decline in cerebellar activity was associated with greater cannabis exposure, this decline was steeper in early-onset users than late-onset users (Chang et al., 2006).

Discussion

Overall, the reviewed neuroimaging studies have largely pointed toward brain structural and functional differences in adolescent cannabis use. Structural imaging studies found widespread alteration (both increase and decrease) in cortical thickness and volume, largely in frontal (i.e., OFC) and parietal regions in adolescent cannabis users relative to nonusers (Churchwell et al., 2010; Jacobus et al., 2014; Kumra et al., 2012; Lopez-Larson et al., 2011), although not all studies have found similar effects (Jacobus et al., 2015; Medina et al., 2009; Weiland et al., 2015). These implicated regions are mainly involved in higher-order cognitive function, such as working memory and cognitive control, that undergo significant neuromaturation across the adolescent period (Bunge & Wright, 2007). Compromised white matter integrity has also been implicated in adolescent cannabis use, mostly in major tracts including the superior and inferior longitudinal fasciculus that connects the main lobes of the brain (Bava et al., 2013; Epstein et al., 2014; Yücel et al., 2010).

Studies investigating effects in adolescent cannabis users relative to nonusers are unable to inform on whether the observed structural alterations may be associated with cannabis use in general or specifically adolescent cannabis use. As such, a number of studies in adult cannabis users have segregated users by the age of which they began regular use, to attempt to understand the differences associated with early versus late onset of use (Battistella et al., 2014; Chye, Suo et al., 2019; Filbey et al., 2015; Gruber et al., 2014; Wilson et al., 2000), finding some indication of reduced parahippocampal and temporal pole volume related to early onset of use (Battistella et al., 2014). However, many studies point toward a lack of structural difference between early- and late-onset cannabis users (Chye, Suo et al., 2019; Filbey et al., 2015). While this lack of effect may be related to the arbitrary nature for specifying age cutoff (ranging from ages 16 to 18) when segregating early- versus late-onset users, it is relevant to note that most studies in adult cannabis users that attempt to correlate brain metrics with onset age of use have similarly failed to find effects (Burggren et al., 2018; Cousijn et al., 2012; Koenders et al., 2017; Mata et al., 2010). The effect of adolescent onset of use may be subtle in comparison to the effect of general cannabis use. This idea is substantiated by a study that found brain structural effect (i.e., smaller gray matter volume) to emerge with both heavy cannabis use irrespective of onset age or in early-onset occasional use (Battistella et al., 2014). There is likely an interactive effect of onset age and chronicity of cannabis exposure (Chang et al., 2006) that necessitates substantiation from larger, well-controlled longitudinal studies.

Resting state functional imaging studies suggest functional connectivity perturbation between OFC and cingulate regions to frontal, parietal, and cerebellar regions in adolescent cannabis users relative to nonusers (Behan et al., 2014; Camchong et al., 2017; Lopez-Larson et al., 2015). Despite this, two of these studies were ROI-based, seeded to the OFC and anterior cingulate, which prevents inference on connectivity across other regions (Camchong et al., 2017; Lopez-Larson et al., 2015). Meanwhile, there is a lack of fMRI studies in adults comparing brain function at rest and cannabis onset age. Task fMRI findings in adolescent cannabis users have been comparatively more consistent then structural MRI findings. Studies consistently implicate increased activity in caudate (Acheson et al., 2015; Jager et al., 2013; Padula et al., 2007), frontal (Abdullaev et al., 2010; Acheson et al., 2015; Jager et al., 2010; Padula et al., 2007; Schweinsburg et al., 2011; Tervo-Clemmens et al., 2019), insula (Acheson et al., 2015; Padula et al., 2007), and parietal (Abdullaev et al., 2010; Behan

et al., 2014; Schweinsburg et al., 2008; Tervo-Clemmens et al., 2019) regions, common across reward, memory, response inhibition, attention, and decision-making tasks. This is in spite of task performance being comparable across adolescent cannabis users versus nonusers (Jager et al., 2010; Karoly et al., 2015; Padula et al., 2007; Schweinsburg et al., 2008, 2010, 2011), with a heightened task-associated activation pattern being attributed to compensatory brain activation due to the increased demand in adolescent cannabis users (Schweinsburg et al., 2010, 2011). Findings were also echoed in adult studies, demonstrating brain activity associated with attention, memory, and response inhibition to be greater in early-onset users in frontal and parietal regions (Becker et al., 2010; Chang et al., 2006; Sagar et al., 2015). However, one study did find reduced parietal effect related to early onset of cannabis use during a memory task (Tervo-Clemmens et al., 2018). The small number of studies examining brain function related to early onset of cannabis use in adults limits inference on whether the observed functional difference in adolescent users extends to later life and is related to onset age rather than use.

The differing findings in adolescent studies may be related to adolescence stages (i.e., early vs. late adolescence period). The examined adolescent studies have samples that range in average age from 13 to 19, which may have confounded findings. For example, one study found that adolescent cannabis users with an average age of 16 years show thinner cortex in the parietal regions, compared to their nonusing peers (Kumra et al., 2012). Meanwhile, another two studies on adolescent cannabis users with an average age of 18 years show thicker cortex in the parietal region instead (Jacobus et al., 2015; Lopez-Larson et al., 2011). This inference is supported by a longitudinal study that found adolescent cannabis users to show an attenuated loss of cortical thickness across the adolescent period, including in the parietal regions, whereas nonusing controls show cortical thinning from 13 to 19 years old (Epstein & Kumra, 2015a). As such, adolescent cannabis users may exhibit thinner cortices early in adolescence or preinitiation of cannabis use, but thicker cortices later in adolescence, relative to nonusers. However, this notion has yet to be verified in a large, well-controlled, longitudinal study of adolescent cannabis users. Other longitudinal studies that implicate altered structure and function, mainly in the frontoparietal network, and frontal and OFC volume in preceding and predicting onset of cannabis use (Cheetham et al., 2012; Spechler et al., 2018; Tervo-Clemmens et al., 2019) further confound cause and effect in determining the trajectory of brain changes in cannabis use across the adolescent period.

Last, a range of confounding factors including gender differences (McQueeny et al., 2011; Medina et al., 2009), mental health (i.e., depressive and anxiety symptoms; McQueeny et al., 2011; Medina et al., 2007), and other substance (i.e., alcohol) use (Bava et al., 2013), that have all been found to have an influence on brain effect in the reviewed studies, further complicates interpretation of findings related to adolescent cannabis use. It is relevant to note that in most of the reviewed studies (35 out of 63), alcohol and/or nicotine use have not been matched (between groups) or controlled for in statistical analyses. Given the effect that both alcohol and nicotine use may have on the brain (Mackey et al., 2019), it is vital for future studies to more thoroughly account or control for other substance use in examining cannabis-related effects.

In sum, while some evidence implicates frontoparietal structure and function in adolescent cannabis use, it remains unclear whether the observed effects are specifically attributable to early onset of use or whether they are related to preexisting differences, chronicity of use, or other confounding factors. Studies that examine brain effect in adult cannabis use suggest minimal structural alteration attributable to adolescent onset of use, whereas evidence on functional alteration is limited in numbers. Further confounding factors including other substance use (e.g., alcohol, nicotine) also prevents an informed understanding on the harms associated with early onset of cannabis use. The relative contribution of each factor, and the interaction between cannabis onset age and chronicity of use, will have to be more comprehensively examined in prospective, longitudinal studies such as the Adolescent Brain Cognitive Development (ABCD) study (https://abcdstudy.org)—a large-scale, multisite initiative in tracking and understanding a range of biological and behavioral determinants of neurodevelopmental trajectory from adolescence into adulthood.

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References

Padula, C. B., Schweinsburg, A. D., & Tapert, S. F. (2007). Spatial working memory performance and fMRI activation interactions in abstinent adolescent marijuana users. *Psychology of Addictive Behaviors*, *21*(4), 478–487. doi:10.1037/0893-164X.21.4.478

Abdullaev, Y., Posner, M. I., Nunnally, R., & Dishion, T. J. (2010). Functional MRI evidence for inefficient attentional control in adolescent chronic cannabis abuse. *Behavioural Brain Research*, *215*(1), 45–57. doi:10.1016/j.bbr.2010.06.023

Acheson, A., Ray, K. L., Hines, C. S., Li, K., Dawes, M. A., Mathias, C. W., … Laird, A. R. (2015). Functional activation and effective connectivity differences in adolescent marijuana users performing a simulated gambling task. *Journal of Addiction*, *2015*, 1–11. doi:10.1155/2015/783106

Anthony, J. C., & Petronis, K. R. (1995). Early-onset drug use and risk of later drug problems. *Drug and Alcohol Dependence*, *40*(1), 9–15.

Arnone, D., Barrick, T. R., Chengappa, S., Mackay, C. E., Clark, C. A., & Abou-Saleh, M. T. (2008). Corpus callosum damage in heavy marijuana use: Preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. *NeuroImage*, *41*(3), 1067–1074. doi:10.1016/j.neuroimage.2008.02.064

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K. L., Roofeh, D., Cook, P., … Kumra, S. (2011). Medial temporal structures and memory functions in adolescents with heavy cannabis use. *Journal of Psychiatric Research*, *45*(8), 1055–1066. doi:10.1016/j.jpsychires.2011.01.004

Ashtari, M., Cervellione, K., Cottone, J., Ardekani, B. A., & Kumra, S. (2009). Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *Journal of Psychiatric Research*, *43*(3), 189–204. doi:10.1016/j.jpsychires.2008.12.002

Battistella, G., Fornari, E., Annoni, J.-M., Chtioui, H., Dao, K., Fabritius, M., … Giroud, C. (2014). Long-term effects of cannabis on brain structure. *Neuropsychopharmacology*, *39*(9), 2041–2048. doi:10.1038/npp.2014.67

Bava, S., Jacobus, J., Thayer, R. E., & Tapert, S. F. (2013). Longitudinal changes in white matter integrity among adolescent substance users. *Alcoholism: Clinical and Experimental Research*, *37*(Suppl. 1), E181–189. doi:10.1111/j.1530-0277.2012.01920.x

Becker, B., Wagner, D., Gouzoulis-Mayfrank, E., Spuentrup, E., & Daumann, J. (2010). The impact of early-onset cannabis use on functional brain correlates of working memory. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(6), 837–845. doi:10.1016/j.pnpbp.2010.03.032

Becker, M. P., Collins, P. F., Lim, K. O., Muetzel, R. L., & Luciana, M. (2015). Longitudinal changes in white matter microstructure after heavy cannabis use. *Developmental Cognitive Neuroscience*, *16*(5), 23–35. doi:10.1016/j.dcn.2015.10.004

Becker, M. P., Collins, P. F., Schultz, A., Urošević, S., Luciana, M., Becker, M. P., … Luciana, M. (2018). Longitudinal changes in cognition in young adult cannabis users. *Journal of Clinical and Experimental Neuropsychology*, *40*(6), 529–543. doi:10.1080/13803395.2017.1385729

Behan, B., Connolly, C. G., Datwani, S., Doucet, M., Ivanovic, J., Morioka, R., … Garavan, H. (2014). Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. *Neuropharmacology*, *84*, 131–137. doi:10.1016/j.neuropharm.2013.05.027

Bellis, M. D., De Wang, L., Bergman, S. R., Yaxley, R. H., Hooper, S. R., & Huettel, S. A. (2013). Neural mechanisms of risky decision-making and reward response in adolescent onset cannabis use disorder. *Drug and Alcohol Dependence*, *133*(1), 134–145. doi:10.1016/j.drugalcdep.2013.05.020

Belue, R. C., Howlett, A. C., Westlake, T. M., & Hutchings, D. E. (1995). The ontogeny of cannabinoid receptors in the brain of postnatal and aging rats. *Neurotoxicology and Teratology*, *17*(1), 25–30. doi:10.1016/0892-0362(94)00053-G

Bitter, S. M., Weber, W. A., Chu, W., Adler, C. M., Eliassen, J. C., Strakowski, S. M., & Delbello, M. P. (2014). N-acetyl aspartate levels in adolescents with bipolar and/or cannabis use disorders. *Journal of Dual Diagnosis*, *10*(1), 39–43. doi:10.1080/15504263.2013.869077

Blest-Hopley, G., Giampietro, V., & Bhattacharyya, S. (2018). Residual effects of cannabis use in adolescent and adult brains — A meta-analysis of fMRI studies. *Neuroscience and Biobehavioral Reviews*, *88*, 26–41. doi:10.1016/j.neubiorev.2018.03.008

Blest-Hopley, G., Giampietro, V., & Bhattacharyya, S. (2019). Regular cannabis use is associated with altered activation of central executive and default mode networks even after prolonged abstinence in adolescent users: Results from a complementary meta-analysis. *Neuroscience and Biobehavioral Reviews*, *96*, 45–55. doi:10.1016/j.neubiorev.2018.10.026

Blithikioti, C., Miquel, L., Batalla, A., Rubio, B., Maffei, G., Herreros, I., … Balcells-Oliveró, M. (in press). Cerebellar alterations in cannabis users: A systematic review. *Addiction Biology*, 1–17. doi:10.1111/adb.12714

Bloomfield, M. A. P., Hindocha, C., Green, S. F., Wall, M. B., Lees, R., Petrilli, K., … Freeman, T. P. (2019). The neuropsychopharmacology of cannabis: A review of human imaging studies. *Pharmacology and Therapeutics*, *195*, 132–161. doi:10.1016/j.pharmthera.2018.10.006

Brenhouse, H. C., & Andersen, S. L. (2011). Developmental trajectories during adolescence in males and females: A cross-species understanding of underlying brain changes. *Neuroscience and Biobehavioral Reviews*, *35*(8), 1687–1703. doi:10.1016/j.neubiorev.2011.04.013

Broyd, S. J., van Hell, H. H., Beale, C., Yücel, M., & Solowij, N. (2016). Acute and chronic effects of cannabinoids on human cognition—a systematic review. *Biological Psychiatry*, *79*(7), 557–567. doi:10.1016/j.biopsych.2015.12.002

Bunge, S. A., & Wright, S. B. (2007). Neurodevelopmental changes in working memory and cognitive control. *Current Opinion in Neurobiology*, *17*(2), 243–250. doi:10.1016/j.conb.2007.02.005

Burggren, A. C., Siddarth, P., Mahmood, Z., London, E. D., Harrison, T. M., Merrill, D. A., … Bookheimer, S. Y. (2018). Subregional hippocampal thickness abnormalities in older adults with a history of heavy cannabis use. *Cannabis and Cannabinoid Research*, *3*(1), 242–251. doi:10.1089/can.2018.0035

Burston, J. J., Wiley, J. L., Craig, A. A., Selley, D. E., & Sim-Selley, L. J. (2010). Regional enhancement of cannabinoid CB1 receptor desensitization in female adolescent rats following repeated delta-tetrahydrocannabinol exposure. *British Journal of Pharmacology*, *161*(1), 103–112. doi:10.1111/j.1476-5381.2010.00870.x

Camchong, J., Lim, K. O., & Kumra, S. (2017). Adverse effects of cannabis on adolescent brain development: A longitudinal study. *Cerebral Cortex*, 27, 1922–1930. doi:10.1093/cercor/bhw015

Cha, Y. M., White, A. M., Kuhn, C. M., Wilson, W. A., & Swartzwelder, H. S. (2006). Differential effects of delta 9 -THC on learning in adolescent and adult rats. *Pharmacology Biochemistry and Behavior*, *83*(3), 448–455. doi:10.1016/j.pbb.2006.03.006

Chambers, R. A., Taylor, J. R., & Potenza, M. N. (2003). Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *American Journal of Psychiatry*, *160*(6), 1041–1052. doi:10.1176/appi.ajp.160.6.1041

Chang, L., Yakupov, R., Cloak, C., & Ernst, T. (2006). Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. *Brain*, *129*(5), 1096–1112. doi:10.1093/brain/awl064

Cheetham, A., Allen, N. B., Whittle, S., Simmons, J. G., Yücel, M., & Lubman, D. I. (2012). Orbitofrontal volumes in early adolescence predict initiation of cannabis use: A 4-year longitudinal and prospective study. *Biological Psychiatry*, *71*(8), 684–692. doi:10.1016/j.biopsych.2011.10.029

Chen, K., & Kandel, D. B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. *American Journal of Public Health*, *85*(1), 41–48. doi:10.2105/AJPH.85.1.41

Churchwell, J. C., Lopez-Larson, M. P., & Yurgelun-Todd, D. A. (2010). Altered frontal cortical volume and decision making in adolescent cannabis users. *Frontiers in Psychology*, *1*, 1–8. doi:10.3389/fpsyg.2010.00225

Chye, Y., Christensen, E., Solowij, N., & Yücel, M. (2019). The endocannabinoid system and cannabidiol's promise for the treatment of substance use disorder. *Frontiers in Psychiatry*, *10*, 63–61. doi:10.3389/fpsyt.2019.00063

Chye, Y., Suo, C., Lorenzetti, V., Batalla, A., Cousijn, J., Goudriaan, A. E., … Yücel, M. (2019). Cortical surface morphology in long-term cannabis users: A multi-site MRI study. *European Neuropsychopharmacology*, *29*(2), 257–265. doi:10.1016/j.euroneuro.2018.11.1110

Cousijn, J., Wiers, R. W., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2012). Grey matter alterations associated with cannabis use: Results of a VBM study in heavy cannabis users and healthy controls. *NeuroImage*, *59*(4), 3845–3851. doi:10.1016/j.neuroimage.2011.09.046

Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: A critical period of vulnerability for addiction. *Pharmacology Biochemistry and Behavior*, *86*(2), 189–199. doi:10.1016/j.pbb.2006.12.001

Dalton, V. S., & Zavitsanou, K. (2010). Cannabinoid effects on CB1 receptor density in the adolescent brain: An autoradiographic study using the synthetic cannabinoid HU210. *Synapse*, *64*(11), 845–854. doi:10.1002/syn.20801

Degenhardt, L., Chiu, W.-T., Sampson, N., Kessler, R. C., Anthony, J. C., Angermeyer, M., … Wells, J. E. (2008). Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO World Mental Health Surveys. *PLoS Medicine*, *5*(7), 1053–1067. doi:10.1371/journal.pmed.0050141

DeWit, D. J., Offord, D. R., & Wong, M. (1997). Patterns of onset and cessation of drug use over the early part of the life course. *Health Education and Behavior*, *24*(6), 746–758. doi:10.1177/109019819702400609

Dougherty, D. M., Mathias, C. W., Dawes, M. A., Furr, R. M., Charles, N. E., Liguori, A., … Acheson, A. (2013). Impulsivity, attention, memory, and decision-making among adolescent marijuana users. *Psychopharmacology*, *226*(2), 307–319. doi:10.1007/s00213-012-2908-5

Dow-Edwards, D., & Silva, L. (2017). Endocannabinoids in brain plasticity: Cortical maturation, HPA axis function and behavior. *Brain Research*, *1654*(2017), 157–164. doi:10.1016/j.brainres.2016.08.037

Ehrenreich, H., Kunert, H. J., Moeller, M. R., Poser, W., Schilling, L., Gigerenzer, G., … Rinn, T. (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology*, *142*(3), 295–301. doi:10.1007/s002130050892

Ellgren, M., Artmann, A., Tkalych, O., Gupta, A., Hansen, H. S., Hansen, S. H., … Hurd, Y. L. (2008). Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *European Neuropsychopharmacology*, *18*(11), 826–834. doi:10.1016/j.euroneuro.2008.06.009

Epstein, K. A., & Kumra, S. (2015a). Altered cortical maturation in adolescent cannabis users with and without schizophrenia. *Schizophrenia Research*, *162*(1–3), 143–152. doi:10.1016/j.schres.2014.11.029

Epstein, K. A., & Kumra, S. (2015b). White matter fractional anisotropy over two time points in early onset schizophrenia and adolescent cannabis use disorder: A naturalistic diffusion tensor imaging study. *Psychiatry Research: Neuroimaging*, *232*(1), 34–41. doi:10.1016/j.pscychresns.2014.10.010

Epstein, K. A., Cullen, K., Mueller, B., Lee, S., & Kumra, S. (2014). White matter abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(3), 362–372. doi:10.1016/j.jaac.2013.12.007

Filbey, F. M., & Yezhuvath, U. (2013). Functional connectivity in inhibitory control networks and severity of

cannabis use disorder. *The American Journal of Drug and Alcohol Abuse*, *39*(6), 382–391. doi:10.3109/00952990.2013.841710

Filbey, F. M., McQueeny, T., DeWitt, S. J., & Mishra, V. (2015). Preliminary findings demonstrating latent effects of early adolescent marijuana use onset on cortical architecture. *Developmental Cognitive Neuroscience*, *16*, 16–22. doi:10.1016/j.dcn.2015.10.001

Galvan, A. (2010). Adolescent development of the reward system. *Frontiers in Human Neuroscience*, *4*, 1–9. doi:10.3389/neuro.09.006.2010

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., … Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(21), 8174–8179. doi:10.1073/pnas.0402680101

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gönenç, A., & Lukas, S. E. (2014). Worth the wait: Effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology*, *231*(8), 1455–1465. doi:10.1007/s00213-013-3326-z

Gruber, S. A., Silveri, M. M., Dahlgren, M. K., & Yurgelun-Todd, D. A. (2011). Why so impulsive? White matter alterations are associated with impulsivity in chronic marijuana smokers. *Experimental and Clinical Psychopharmacology*, *19*(3), 231–242. doi:10.1037/a0023034

Hanson, K. L., Winward, J. L., Schweinsburg, A. D., Lisdahl, K., Brown, S. A., & Tapert, S. F. (2010). Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addictive Behaviors*, *35*(11), 970–976. doi:10.1016/j.addbeh.2010.06.012

Harvey, M. A., Sellman, J. D., Porter, R. J., & Frampton, C. M. (2007). The relationship between non-acute adolescent cannabis use and cognition. *Drug and Alcohol Review*, *26*(3), 309–319. doi:10.1080/09595230701247772

Hester, R., Nestor, L., & Garavan, H. (2009). Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology*, *34*(11), 2450–2458. doi:10.1038/npp.2009.67

Hopfer, C. (2014). Implications of marijuana legalization for adolescent substance use. *Substance Abuse*, *35*(4), 331–335. doi:10.1080/08897077.2014.943386

Huestegge, L., Radach, R., Kunert, H. J., & Heller, D. (2002). Visual search in long-term cannabis users with early age of onset. *Progress in Brain Research*, *140*, 377–394. doi:10.1016/S0079-6123(02)40064-7

Hurd, Y. L. (2017). Cannabidiol: Swinging the marijuana pendulum from 'weed' to medication to treat the opioid epidemic. *Trends in Neurosciences*, *40*(3), 124–127. doi:10.1016/j.tins.2016.12.006

Jackson, N. J., Isen, J. D., Khoddam, R., Irons, D., Tuvblad, C., Iacono, W. G., … Baker, L. A. (2015). Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies. *Proceedings of the National Academy of Sciences*, *113*(5), E500–E508. doi:10.1073/pnas.1516648113

Jacobsen, L. K., Mencl, W. E., Westerveld, M., & Pugh, K. R. (2004). Impact of cannabis use on brain function in adolescents. *Annals of the New York Academy of Sciences*, *1021*(1), 384–390. doi:10.1196/annals.1308.053

Jacobus, J., & Tapert, S. F. (2013). Neurotoxic effects of alcohol in adolescence. *Annual Review of Clinical Psychology*, *9*(1), 703–721. doi:10.1146/annurev-clinpsy-050212-185610

Jacobus, J., & Tapert, S. F. (2014). Effects of cannabis on the adolescent brain. *Current Pharmaceutical Design*, *20*(13), 2186–2193. doi:10.2174/13816128113199990426

Jacobus, J., Castro, N., Squeglia, L. M., Meloy, M. J., Brumback, T., Huestis, M. A., & Tapert, S. F. (2016). Adolescent cortical thickness pre- and post marijuana and alcohol initiation. *Neurotoxicology and Teratology*, *57*, 20–29. doi:10.1016/j.ntt.2016.09.005

Jacobus, J., Goldenberg, D., Wierenga, C. E., Tolentino, N. J., Liu, T. T., & Tapert, S. F. (2012). Altered cerebral blood flow and neurocognitive correlates in adolescent cannabis users. *Psychopharmacology*, *222*(4), 675–684. doi:10.1007/s00213-012-2674-4

Jacobus, J., Squeglia, L. M., Meruelo, A. D., Castro, N., Brumback, T., Giedd, J. N., & Tapert, S. F. (2015). Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood. *Developmental Cognitive Neuroscience*, *16*, 101–109. doi:10.1016/j.dcn.2015.04.006

Jacobus, J., Squeglia, L. M., Sorg, S. F., Nguyen-Louie, T. T., & Tapert, S. F. (2014). Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence. *Journal of Studies on Alcohol and Drugs*, *75*(5), 729–743. doi:10.15288/jsad.2014.75.729

Jager, G., Block, R. I., Luijten, M., & Ramsey, N. F. (2010). Cannabis use and memory brain function in adolescent boys: A cross-sectional multicenter functional magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(6), 561–572. doi:10.1016/j.jaac.2010.02.001

Jager, G., Block, R. I., Luijten, M., & Ramsey, N. F. (2013). Tentative evidence for striatal hyperactivity in adolescent cannabis-using boys: A cross-sectional multicenter fMRI study. *Journal of Psychoactive Drugs*, *45*(2), 156–167. doi:10.1080/02791072.2013.785837

Jakabek, D., Yücel, M., Lorenzetti, V., & Solowij, N. (2016). An MRI study of white matter tract integrity in regular cannabis users: Effects of cannabis use and age. *Psychopharmacology*, *233*(19–20), 3627–3637. doi:10.1007/s00213-016-4398-3

Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2019). *Monitoring the Future: National survey results on drug use 1975-2018*. 2018 Overview: Key findings on adolescent drug use.

Karoly, H. C., Bryan, A. D., Weiland, B. J., Mayer, A., Dodd, A., & Ewing, S. W. F. (2015). Does incentive-elicited nucleus accumbens activation differ by substance of abuse? An examination with adolescents. *Developmental Cognitive Neuroscience*, *16*, 5–15. doi:10.1016/j.dcn.2015.05.005

Koenders, L., Lorenzetti, V., de Haan, L., Suo, C., Vingerhoets, W. A. M., van den Brink, W., … Cousijn, J. (2017). Longitudinal study of hippocampal volumes in

heavy cannabis users. *Journal of Psychopharmacology*, *31*(8), 1027–1034. doi:10.1177/0269881117718380

Kumra, S., Robinson, P., Tambyraja, R., Jensen, D., Schimunek, C., Houri, A., … Lim, K. (2012). Parietal lobe volume deficits in adolescents with schizophrenia and adolescents with cannabis use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(2), 171–180. doi:10.1016/j.jaac.2011.11.001

Lattanzi, S., Brigo, F., Trinka, E., Zaccara, G., Cagnetti, C., Del Giovane, C., & Silvestrini, M. (2018). Efficacy and safety of cannabidiol in epilepsy: A systematic review and meta-analysis. *Drugs*, *78*(17), 1791–1804. doi:10.1007/s40265-018-0992-5

Levar, N., Francis, A. N., Smith, M. J., Ho, W. C., & Gilman, J. M. (2018). Verbal memory performance and reduced cortical thickness of brain regions along the uncinate fasciculus in young adult cannabis users. *Cannabis and Cannabinoid Research*, *3*(1), 56–65. doi:10.1089/can.2017.0030

Lopez-Larson, M. P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J. B., Terry, J., & Yurgelun-Todd, D. A. (2011). Altered prefrontal and insular cortical thickness in adolescent marijuana users. *Behavioural Brain Research*, *220*(1), 164–172. doi:10.1016/j.bbr.2011.02.001

Lopez-Larson, M. P., Rogowska, J., & Yurgelun-Todd, D. A. (2015). Aberrant orbitofrontal connectivity in marijuana smoking adolescents. *Developmental Cognitive Neuroscience*, *16*, 54–62. doi:10.1016/j.dcn.2015.08.002

Lopez-Larson, M. P., Rogowska, J., Bogorodzki, P., Bueler, C. E., McGlade, E. C., & Yurgelun-Todd, D. A. (2012). Cortico-cerebellar abnormalities in adolescents with heavy marijuana use. *Psychiatry Research*, *202*(3), 224–232. doi:10.1016/j.pscychresns.2011.11.005

Lorenzetti, V., Alonso-Lana, S., Youssef, G. J., Verdejo-Garcia, A., Suo, C., Cousijne, J., … Solowij, N. (2016). Adolescent cannabis use: What is the evidence for functional brain alteration? *Current Pharmaceutical Design*, *22*(42), 6353–6365. doi:10.2174/1381612822666160805155922

Lorenzetti, V., Chye, Y., Silva, P., Solowij, N., & Roberts, C. A. (2019). Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(1), 59–71. doi:10.1007/s00406-019-00979-1

Lubman, D. I., Cheetham, A., & Yücel, M. (2014). Cannabis and adolescent brain development. *Pharmacology and Therapeutics*, *148*, 1–16. doi:10.1016/j.pharmthera.2014.11.009

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Development*, *75*(5), 1357–1372. doi:10.1111/j.1467-8624.2004.00745.x

Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., … Garavan, H. (2019). Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. *American Journal of Psychiatry*, *176*(2), 119–128. doi:10.1176/appi.ajp.2018.17040415

Mata, I., Perez-Iglesias, R., Roiz-Santiañez, R., Tordesillas-Gutierrez, D., Pazos, A., Gutierrez, A., … Crespo-Facorro, B. (2010). Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use. *Brain Research*, *1317*, 297–304. doi:10.1016/j.brainres.2009.12.069

McQueeny, T., Padula, C. B., Price, J., Lisdahl, K., Logan, P., & Tapert, S. F. (2011). Gender effects on amygdala morphometry in adolescent marijuana users. *Behavioural Brain Research*, *224*(1), 128–134. doi:10.1016/j.bbr.2011.05.031

Medina, K. L., McQueeny, T., Nagel, B. J., Hanson, K. L., Yang, T. T., & Tapert, S. F. (2009). Prefrontal cortex morphometry in abstinent adolescent marijuana users: Subtle gender effects. *Addiction Biology*, *14*(4), 457–468. doi:10.1111/j.1369-1600.2009.00166.x

Medina, K. L., Nagel, B. J., & Tapert, S. F. (2010). Abnormal cerebellar morphometry in abstinent adolescent marijuana users. *Psychiatry Research*, *182*(2), 152–159. doi:10.1016/j.pscychresns.2009.12.004

Medina, K. L., Nagel, B. J., Park, A., McQueeny, T., & Tapert, S. F. (2007). Depressive symptoms in adolescents: Associations with white matter volume and marijuana use. *Journal of Child Psychology and Psychiatry*, *48*(6), 592–600. doi:10.1111/j.1469-7610.2007.01728.x

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., … Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences*, *109*(40), E2657–E2664. doi:10.1073/pnas.1206820109

Meier, M. H., Caspi, A., Danese, A., Fisher, H. L., Houts, R., Arseneault, L., & Moffitt, T. E. (2018). Associations between adolescent cannabis use and neuropsychological decline: A longitudinal co-twin control study. *Addiction*, *113*(2), 257–265. doi:10.1111/add.13946

Meyer, H. C., Lee, F. S., & Gee, D. G. (2018). The role of the endocannabinoid system and genetic variation in adolescent brain development. *Neuropsychopharmacology*, *43*(1), 21–33. doi:10.1038/npp.2017.143

Mokrysz, C., Landy, R., Gage, S., Munafò, M., Roiser, J., & Curran, H. (2016). Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *Journal of Psychopharmacology*, *30*(2), 159–168. doi:10.1177/0269881115622241

Orr, J. M., Paschall, C. J., & Banich, M. T. (2016). Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. *NeuroImage: Clinical*, *12*, 47–56. doi:10.1016/j.nicl.2016.06.006

Pertwee, R. G., & Ross, R. A. (2002). Cannabinoid receptors and their ligands. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *66*(2–3), 101–121. doi:10.1054/plef.2001.0341

Pope, H. G., Gruber, A. J., Hudson, J. I., Cohane, G., Huestis, M. A., & Yurgelun-Todd, D. A. (2003). Early-onset cannabis use and cognitive deficits: What is the nature of the association? *Drug and Alcohol Dependence*, *69*(3), 303–310. doi:10.1016/S0376-8716(02)00334-4

Prescot, A. P., Locatelli, A. E., Renshaw, P. F., & Yurgelun-Todd, D. A. (2011). Neurochemical alterations in adolescent chronic marijuana smokers: A proton MRS study. *NeuroImage*, *57*(1), 69–75. doi:10.1016/j.neuroimage.2011.02.044

Prescot, A. P., Renshaw, P. F., & Yurgelun-Todd, D. A. (2013). γ-Amino butyric acid and glutamate abnormalities in adolescent chronic marijuana smokers. *Drug and Alcohol Dependence*, *129*(3), 232–239. doi:10.1016/j.drugalcdep.2013.02.028

Quinn, H. R., Matsumoto, I., Callaghan, P. D., Long, L. E., Arnold, J. C., Gunasekaran, N., … McGregor, I. S. (2008). Adolescent rats find repeated Δ9-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*, *33*(5), 1113–1126. doi:10.1038/sj.npp.1301475

Sagar, K. A., Dahlgren, M. K., Gönenç, A., Racine, M. T., Dreman, M. W., & Gruber, S. A. (2015). The impact of initiation: Early onset marijuana smokers demonstrate altered Stroop performance and brain activation. *Developmental Cognitive Neuroscience*, *16*, 84–92. doi:10.1016/j.dcn.2015.03.003

Schneider, M., & Koch, M. (2003). Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology*, *28*(10), 1760–1769. doi:10.1038/sj.npp.1300225

Schweinsburg, A. D., Nagel, B. J., Schweinsburg, B. C., Park, A., Theilmann, R. J., & Tapert, S. F. (2008). Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Research: Neuroimaging*, *163*(1), 40–51. doi:10.1016/j.pscychresns.2007.04.018

Schweinsburg, A. D., Schweinsburg, B. C., Medina, K. L., Mcqueeny, T., Brown, S. A., & Tapert, S. F. (2010). The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users. *Journal of Psychoactive Drugs*, *42*(3), 401–412. doi:10.1080/02791072.2010.10400703

Schweinsburg, A. D., Schweinsburg, B. C., Nagel, B. J., Eyler, L. T., & Tapert, S. F. (2011). Neural correlates of verbal learning in adolescent alcohol and marijuana users. *Addiction*, *106*(3), 564–573. doi:10.1111/j.1360-0443.2010.03197.x

Scott, J. C., Rosen, A. F. G., Moore, T. M., Roalf, D. R., Satterthwaite, T. D., Calkins, M. E., … Gur, R. C. (2019). Cannabis use in youth is associated with limited alterations in brain structure. *Neuropsychopharmacology*, *44*(8), 1362–1369. doi:10.1038/s41386-019-0347-2

Scott, J. C., Slomiak, S. T., Jones, J. D., Rosen, A. F. G., Moore, T. M., & Gur, R. C. (2018). Association of cannabis with cognitive functioning in adolescents and young adults. *JAMA Psychiatry*, *75*(6), 585–595. doi:10.1001/jamapsychiatry.2018.0335

Selemon, L. D. (2013). A role for synaptic plasticity in the adolescent development of executive function. *Translational Psychiatry*, *3*(3), e238. doi:10.1038/tp.2013.7

Solowij, N., Jones, K. A., Rozman, M. E., Davis, S. M., Ciarrochi, J., Heaven, P. C. L., … Yücel, M. (2011). Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology*, *216*(1), 131–144. doi:10.1007/s00213-011-2203-x

Solowij, N., Yucel, M., Lorenzetti, V., & Lubman, D. (2012). *Does cannabis cause lasting brain damage?* In D. Castle, R. M. Murray & D. Cyril. D'Souza (Eds.), Marijuana and Madness (pp. 103–113). Cambridge: Cambridge University Press.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, *24*(4), 417–463. doi:10.1016/S0149-7634(00)00014-2

Spechler, P. A., Allgaier, N., Chaarani, B., Whelan, R., Watts, R., Orr, C. … the IMAGEN Consortium. (in press). The initiation of cannabis use in adolescence is predicted by sex-specific psychosocial and neurobiological features. *European Journal of Neuroscience*, 1–11. doi:10.1111/ejn.13989

Spechler, P. A., Orr, C. A., Chaarani, B., Kan, K.-J., Mackey, S., & Morton, A. (2015). Cannabis use in early adolescence: Evidence of amygdala hypersensitivity to signals of threat. *Developmental Cognitive Neuroscience*, *16*, 63–70. doi:10.1016/j.dcn.2015.08.007

Subramaniam, P., Rogowska, J., DiMuzio, J., Lopez-Larson, M., Mcglade, E., & Yurgelun-Todd, D. A. (2018). Orbitofrontal connectivity is associated with depression and anxiety in marijuana-using adolescents. *Journal of Affective Disorders*, *239*, 234–241. doi:10.1016/j.jad.2018.07.002

Substance Abuse and Mental Health Services Administration, C. for B. H. S. and Q. (2018). Treatment episode data set (TEDS): 2016. *Admissions to and discharges from publicly funded substance use treatment*, doi:10.3886/ICPSR24280.v6

Tapert, S. F., Schweinsburg, A. D., Drummond, S. P. A., Paulus, M. P., Brown, S. A., Yang, T. T., & Frank, L. R. (2007). Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology*, *194*(2), 173–183. doi:10.1007/s00213-007-0823-y

Tervo-Clemmens, B., Simmonds, D., Calabro, F. J., Day, N. L., Richardson, G. A., & Luna, B. (2018). Adolescent cannabis use and brain systems supporting adult working memory encoding, maintenance, and retrieval. *NeuroImage*, *169*, 496–509. doi:10.1016/j.neuroimage.2017.12.041

Tervo-Clemmens, B., Simmonds, D., Calabro, F. J., Montez, D. F., Lekht, J. A., Day, N. L., … Luna, B. (2019). Early cannabis use and neurocognitive risk: A prospective functional neuroimaging study. *Biological Psychiatry*, *3*(8), 713–725. doi:10.1016/j.bpsc.2018.05.004

United Nations Office on Drugs and Crime. (2018). *World drug report 2018*. New York, NY: United Nations publication. Sales No. E.18.XI.9.

Viveros, M. P., Marco, E. M., & File, S. E. (2005). Endocannabinoid system and stress and anxiety responses. *Pharmacology Biochemistry and Behavior*, *81*(2), 331–342. doi:10.1016/j.pbb.2005.01.029

Volkow, N. D., & Morales, M. (2015). The brain on drugs: From reward to addiction. *Cell*, *162*(4), 712–725. doi:10.1016/j.cell.2015.07.046

Volkow, N. D., Fowler, J. S., & Wang, G.-J. (2003). The addicted brain: Insights from imaging studies. *Journal of Clinical Investigation*, *111*(10), 1444–1451. doi:10.1172/JCI200318533

Weiland, B. J., Thayer, R. E., Depue, B. E., Sabbineni, A., Bryan, A. D., & Hutchison, K. E. (2015). Daily marijuana use is not associated with brain morphometric

measures in adolescents or adults. *The Journal of Neuroscience*, *35*(4), 1505–1512. doi:10.1523/JNEUROSCI.2946-14.2015

Westlake, T. M., Howlett, A. C., Bonner, T. I., Matsuda, L. A., & Herkenham, M. (1994). Cannabinoid receptor binding and messenger RNA expression in human brain: An in vitro receptor autoradiography and in situ hybridization histochemistry study of normal aged and Alzheimer's brains. *Neuroscience*, *63*(3), 637–652. doi:10.1016/0306-4522(94)90511-8

Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R. E., & Provenzale, J. (2000). Brain morphological changes and early marijuana use: A magnetic resonance and positron emission tomography study. *Journal of Addictive Diseases*, *19*(1), 1–21. doi:10.1300/j069v19n01_01

Yücel, M., Zalesky, A., Takagi, M. J., Bora, E., Fornito, A., Ditchfield, M., … Lubman, D. I. (2010). White-matter abnormalities in adolescents with long-term inhalant and cannabis use: A diffusion magnetic resonance imaging study. *Journal of Psychiatry and Neuroscience*, *35*(6), 409–412. doi:10.1503/jpn.090177

Zalesky, A., Solowij, N., Yucel, M., Lubman, D. I., Takagi, M., Harding, I. H., … Seal, M. (2012). Effect of long-term cannabis use on axonal fibre connectivity. *Brain*, *135*(7), 2245–2255. doi:10.1093/brain/aws136