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Cannabis and adolescent brain development

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ABSTRACT

Heavy cannabis use has been frequently associated with increased rates of mental illness and cognitive impairment, particularly amongst adolescent users. However, the neurobiological processes that underlie these associations are still not well understood. In this review, we discuss the findings of studies examining the acute and chronic effects of cannabis use on the brain, with a particular focus on the impact of commencing use during adolescence. Accumulating evidence from both animal and human studies suggests that regular heavy use during this period is associated with more severe and persistent negative outcomes than use during adulthood, suggesting that the adolescent brain may be particularly vulnerable to the effects of cannabis exposure. As the endocannabinoid system plays an important role in brain development, it is plausible that prolonged use during adolescence results in a disruption in the normative neuromaturational processes that occur during this period. We identify synaptic pruning and white matter development as two processes that may be adversely impacted by cannabis exposure during adolescence. Potentially, alterations in these processes may underlie the cognitive and emotional deficits that have been associated with regular use commencing during adolescence.

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1. Introduction

Increases in the popularity of cannabis over the past 50 years, particularly amongst adolescents and young adults, has seen increased attention placed on its potential harms and benefits (Hall & Pacula, 2003; Volkow et al., 2014). Although cannabinoids possess a range of neuroprotective properties, there is nonetheless sufficient evidence to suggest that Δ9-tetrahydrocannabinol (THC), the main psychoactive component of *Cannabis sativa*, can have adverse effects on mental health (Sarne & Mechoulam, 2005; Sarne et al., 2011; Niesink & van Laar, 2013). In particular, studies have demonstrated that adolescent cannabis users appear to be at heightened risk for a range of adverse psychological outcomes, including psychotic symptoms and neurocognitive impairments (Jacobus et al., 2009a; Malone et al., 2010; Van Winkel &

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Kuepper, 2014). Establishing the mechanisms that underlie vulnerability within this population is likely to have important implications for our understanding of the psychological harms associated with regular cannabis use.

Reviews of the epidemiological and clinical literature have provided a complicated picture of the relationship between cannabis use and mental health. Epidemiological studies have found that heavy cannabis users experience a greater number of psychotic symptoms and elevated rates of depression and anxiety when compared to infrequent or non-users (Degenhardt et al., 2003; Moore et al., 2007; Crippa et al., 2009; McLaren et al., 2010; Richardson, 2010), while clinical studies have demonstrated impairments in learning and memory that persist beyond the period of acute intoxication (Solowij & Battisti, 2008). Deficits in a wide range of other executive functions have also been reported (Crean et al., 2011), including decision-making (e.g., Churchwell et al., 2010; Solowij et al., 2012a), processing speed (e.g., Fried et al., 2005), and attention (e.g., Solowij et al., 2002), with some studies demonstrating dose–response effects in which the heaviest users display the greatest deficits (e.g., Bolla et al., 2002; Gruber et al., 2011). In addition, reviews of longitudinal studies suggest that heavy cannabis use increases risk for later psychosis (Moore et al., 2007; McLaren et al., 2010; Large et al., 2011) and, to a lesser extent, depression (Moore et al., 2007; Lev-Ran et al., 2013).

Despite these findings, the issue of causality is far from resolved. Indeed, many clinical and epidemiological studies have failed to adequately control for confounding factors (such as other substance use, comorbid mental health conditions, or sociodemographic characteristics), or have reported non-significant or attenuated findings once these factors have been included in the analysis (see reviews by Moore et al., 2007; Hall & Degenhardt, 2009; McLaren et al., 2010). As such, it remains unclear whether heavy cannabis use can induce psychotic disorders that would not have otherwise occurred (McLaren et al., 2010). If this association was indeed causal, it would be expected that the incidence of schizophrenia would have increased as the use of cannabis has become more prevalent, but supporting evidence has so far been mixed (Degenhardt et al., 2003; Boydell et al., 2006; Ajdacic-Gross et al., 2007; Hickman et al., 2007).

There are also unresolved questions regarding the impact of cannabis use on human brain structure and function, including whether heavy cannabis use can induce neurobiological changes that account for the psychological and cognitive effects observed in heavy users. While animal models have provided evidence that some cannabinoids can exert neuroprotective and neurogenic effects (Sarne & Mechoulam, 2005; Sarne et al., 2011), there is less evidence from the human literature that cannabinoids, particularly THC, possesses the same properties. Indeed, a recent review by Lorenzetti et al. (2014) investigating the structural consequences of cannabis use concluded that although many brain regions appear unaffected or not reliably implicated, there is growing evidence that heavy use is associated with structural alterations in medial temporal regions (e.g., Matochik et al., 2005; Yücel et al., 2008; Ashtari et al., 2011; Demirakca et al., 2011). However, the same review noted that there has been insufficient research to determine whether reliable associations exist between brain morphology and psychopathology in heavy cannabis users. Similar conclusions have been drawn regarding the consequences of heavy use on brain function. While studies have demonstrated various functional differences between users and controls on tasks assessing cognitive and emotional processes, these have often occurred in the absence of significant differences in task performance and their relevance to psychiatric disorders and other outcomes is not well understood (see review by Batalla et al., 2013).

Despite these inconsistencies, a number of studies have nonetheless provided robust findings that point towards the existence of vulnerable subgroups (Van Winkel & Kuepper, 2014). Adolescence is a period of particular interest in this regard. Adolescent cannabis users have been found to be at elevated risk for adverse outcomes, including more persistent cognitive impairments (see review by Jacobus et al., 2009a), and increased risk of psychotic symptoms (Arseneault et al., 2002; Fergusson et al., 2003; Stefanis et al., 2004). Indeed, the most consistent evidence for an association between cannabis use and psychosis relates to studies that focus on adolescent exposure (Van Winkel & Kuepper, 2014). Although regular cannabis use in adolescence may not always be harmful (as individual risk will be influenced by many of the same confounding variables that have been identified in studies of adults), such studies suggest that adolescence may be a critical period in regard to increased risk of adverse outcomes. More specifically, it has been proposed that cannabis use may be more harmful during adolescence due to the critical involvement of the endocannabinoid system in brain development (Galve-Roperh et al., 2009; Downer & Campbell, 2010), and the potentially disruptive impact of exogenous cannabinoid exposure on associated processes, such as white matter development (Solowij et al., 2011b) and synaptic pruning (Bossong & Niesink, 2010). Studies examining the structural consequences of adolescent cannabis exposure, while limited in number, appear to support the notion that early use can have adverse effects on brain morphology in some individuals (see reviews by Baker et al., 2013; Batalla et al., 2013).

The aim of the current review is to consolidate findings from a broad literature examining the impact of cannabis use on the brain. As many of the negative effects of regular cannabis use appear to be moderated by whether exposure commences during adolescence, it is important to consider these effects within the context of the unique neurobiological changes and associated confounds that occur during this period of development. More specifically, we contextualise the effects of cannabis use on the endocannabinoid system as it relates to the neuromaturational changes that occur during adolescence. In doing so, we consider a wide range of studies from both the animal and human literature that provide a complex picture of the potential harms and benefits that have been associated with cannabis use. We consider the impact of adolescent cannabis use on the endocannabinoid system, placing particular emphasis on the findings of structural imaging studies that have examined whether heavy cannabis use is associated with gross morphological changes or alterations in white matter microstructure. Ultimately, understanding how adolescent cannabis use might impact processes of brain development will not only contribute to our understanding of vulnerability, but may also help clarify some of the inconsistencies and contradictions in the wider literature on cannabis use and mental health.

2. Effects of acute exposure in animals

The impact of acute cannabinoid exposure on the brain depends on a range of factors, including age, exposure duration, dose, and cell type (Downer & Campbell, 2010). It has been proposed that cannabinoids exert differential effects depending on the dose that is administered, with high doses (between 1 and 10 mg/kg) offering neuroprotection and low doses inducing mild damage to the brain (Sarne & Mechoulam, 2005). However, other research has demonstrated that chronic low doses can protect against the impact of ageing on neurogenesis, loss of cognitive function, and inflammation (Marchalant et al., 2008, 2009a,b). Indeed, there is evidence that acute administration of cannabinoids and THC can protect against brain injury (Nagayama et al., 1999; Van der Stelt et al., 2001) (Panikashvili et al., 2001; Mauler et al., 2003; Panikashvili et al., 2006; Alvarez et al., 2008; Lafuente et al., 2011), and reduce neuroinflammation (Walter & Stella, 2004; Elliott et al., 2011), and may provide preconditioning effects at ultra-low doses (Assaf et al., 2011; Fishbein et al., 2012). Other studies however, have found that both high and low doses of THC applied directly to cultured cortical neurons can cause cellular changes characteristic of apoptosis (Campbell, 2001; Downer et al., 2001), and it has been suggested that THC may have greater potential for adverse effects than other cannabinoids (Sarne & Mechoulam, 2005). Further research examining dose effects in vitro versus in vivo, as well as potential differences between different