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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.

Contents

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

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cannabinoids (including THC), is needed to reconcile these discrepant findings.

Age of exposure appears to be a critical factor in determining the effects of cannabinoids on the brain. On the whole, there is limited evidence from animal studies that cannabinoids are neurotoxic to the adult central nervous system, however adverse effects have been observed following acute or short-term exposure during prenatal, neonatal, and adolescent periods (Downer & Campbell, 2010). For example, neonatal exposure in rodents has been associated with cortical cell death, while the same effect is not present in adult animals (Downer et al., 2007). A single dose of THC has also been found to result in greater impairment in spatial and non-spatial learning in adolescent compared to adult rats (Cha et al., 2006). Prenatal and neonatal exposure has also been found to alter the development of the major neurotransmitter systems of the brain, suggesting that early exposure may have long-lasting effects on the functions of these systems (Kumar et al., 1990; Molina-Holgado et al., 1996). In a study examining the effects of cannabinoids on the mesolimbic dopamine system, sub-chronic (3-day) treatment was found to produce a residual cross-tolerance to morphine, amphetamine, and cocaine amongst rats exposed during adolescence, but not amongst rats exposed during adulthood (Pistis et al., 2004). This differential finding supports the notion that the adolescent brain is uniquely vulnerable to neuronal adaptations following cannabinoid exposure, and suggests that these changes may also affect later responses to drugs of abuse.

It is also important to differentiate between THC and other cannabinoids, particularly cannabidiol, which accounts for up to 40% of the active component of *C. sativa* (Campos et al., 2012). While acute administration of THC has been found to increase anxiety in rodents (e.g., Schramm-Sapyta et al., 2007), numerous studies have found that cannabidiol exerts anxiolytic-like effects (e.g., Moreira et al., 2006; Campos & Guimarães, 2008; Resstel et al., 2009). Similarly, while THC has been found to induce psychotic-like effects in rodent models of schizophrenia (e.g., Malone & Taylor, 2006), cannabidiol has been shown to act as an antipsychotic (e.g., Zuardi et al., 1991; Moreira & Guimarães, 2005), with a profile similar to that of atypical antipsychotic drugs (see review by Zuardi et al., 2006). More recently, it has also been demonstrated that cannabidiol can induce antidepressant-like effects (Zanelati et al., 2010; Reus et al., 2011). When administered at appropriate doses, cannabidiol has been found to attenuate some of the effects of THC (e.g., Vann et al., 2008; Malone et al., 2009), although potentiation has also been observed (see review by Arnold et al., 2012). An important implication of this research is that studies examining the effects of THC in isolation (particularly those examining the impact of THC on cultured neurons) may not be representative of the effects of *C. sativa* as a whole (which in addition to cannabidiol, contains a range of other phytocannabinoids that may exert different psychological effects; El-Alfy et al., 2010).

In regard to cognitive effects, numerous studies have found that acute administration of cannabinoids impairs memory, learning, and attention in adult rodents and nonhuman primates (see reviews by Sullivan, 2000; Lichtman et al., 2002; Egerton et al., 2006). In particular, cannabinoids appear to have disruptive effects on short-term working memory. In rats, cannabinoids have been found to impair working memory during maze-based tasks (Lichtman et al., 1995; Ferrari et al., 1999) and delayed match to sample tasks, which require the animal to discriminate between stimuli separated by a delay (Heyser et al., 1993; Miyamoto et al., 1995). These effects have been found even at low doses; for example, a single administration of an ultra-low dose of THC (0.001–0.002 mg/kg) has been shown to result in long-term impairment in spatial learning, strategy, and working memory in mice (Tselnicker et al., 2007; Amal et al., 2010). The finding that these impairments are observable at doses too low to elicit other effects (such as motor effects) has led to the suggestion that cannabinoids may have a selective impact on memory (Ranganathan & D'Souza, 2006). To this end, rats acutely exposed to cannabinoids have been found to demonstrate altered neural activity and chemistry in a number of brain regions, including the hippocampus and prefrontal cortex, which in turn are thought to underlie disruptions in learning, memory and other cognitive processes (Campbell et al., 1986; Sullivan, 2000; Freedland et al., 2002; Lichtman et al., 2002; Whitlow et al., 2002; Egerton et al., 2006).

3. Effects of chronic exposure in animals

The neuroprotective effects of cannabinoids have been widely studied in animal models (see reviews by Guzmán et al., 2001; Sarne & Mechoulam, 2005; Galve-Roperh et al., 2008; Sarne et al., 2011). Short- to medium-term treatment with high doses of cannabinoids and THC (e.g., between 1 and 30 mg/kg for 3–25 days) have been found to prevent cell death following brain injury (e.g., Fernández-López et al., 2010, 2012; Perez et al., 2013) and exposure to neurotoxic stimuli (e.g., Lastres-Becker et al., 2005; Shen et al., 2011), while there is a large body of evidence indicating that chronic cannabinoid treatment can have immunosuppressive and anti-inflammatory properties (see reviews by Walter & Stella, 2004; Klein, 2005). Cannabinoids have also been found to promote neurogenesis, particularly in the hippocampus, which may underlie its anxiolytic and antidepressant-like effects (Jiang et al., 2005; Campos et al., 2013). At the same time, studies of longer-term cannabinoid administration to rats and primates (e.g., 1–3 months), which have included very high doses (e.g., up to 60 mg/kg; Scallet et al., 1987), have demonstrated adverse effects in the hippocampus (Heath et al., 1980; Scallet et al., 1987; Landfield et al., 1988; Lawston et al., 2000), amygdala (Heath et al., 1980), and cerebral cortex (Harper et al., 1977). These effects, which in many cases have been found to be dose-dependent, include shrinkage of neural cell nuclei and bodies, as well as reductions in synapse numbers, pyramidal cell density, and dendritic length. Dosage, age at exposure, and duration of exposure appear to be crucial factors in determining these adverse effects (Scallet, 1991).

Compared to the literature on acute effects, relatively few animal studies have examined the consequences of prolonged cannabinoid exposure on memory and other cognitive processes, including whether impairments remain following abstinence. In adult and late adolescent rats treated for 14–15 consecutive days, impairments have been found in short-term memory and working memory (Hill et al., 2004; Abush & Akirav, 2012), as well as attention (Verrico et al., 2004), although some of these effects appear to be reversible after short periods of abstinence (i.e., 5–10 days; Hill et al., 2004; Abush & Akirav, 2012). Impairments in learning and working memory have also been reported in rats treated with THC for a longer period (90 days of exposure), although recovery of function may require a more extended period of abstinence (30 days; Nakamura et al., 1991), and may vary according to the specific behavioural task used (Stiglick & Kalant, 1985).

There is growing evidence from the animal literature that more persistent and severe effects occur following adolescent exposure. A series of early studies by Stiglick and Kalant found that while immature rats treated with THC over a 3 or 6 month period showed learning impairments and increased locomotor activity even after an extended period of abstinence (1–3 months; Stiglick & Kalant, 1982a,b), these residual effects were not present in mature rats treated for a comparable period (Stiglick & Kalant, 1985). More recent research comparing adult and adolescent rats have found differential responses to cannabis exposure during adolescence, including greater and more persistent deficits in learning and memory (O'Shea et al., 2004; Quinn et al., 2008; Renard et al., 2013), as well as greater alterations in hippocampal protein expression (which may account for adolescent-specific memory effects; Quinn et al., 2008). In addition to cognitive deficits, chronic cannabinoid exposure during adolescence has been found to lead to more severe and lasting behavioural disturbances than exposure during adulthood. These includes disruptions in social behaviour and play (Schneider et al., 2008) as well as a greater number of depressive-like behaviours, including a transition from active to passive coping (as measured by the forced swim test) and a reduced motivation to seek rewarding

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stimuli (as measured by the sucrose preference test; Bambico et al., 2010). Together, these studies support the notion that the developing brain may be particularly sensitive to chronic cannabinoid exposure.

Further evidence for this hypothesis has come from prospective studies examining the consequences of adolescent exposure, which have demonstrated adverse effects that persist into adulthood. Of particular interest in this regard are a small number of experimental studies that have examined the long-term effects of adolescent cannabinoid exposure on psychosis- and depression-related behaviours in adult rodents, by using behavioural paradigms developed as a means of modelling psychotic and depressive symptoms in animals. These studies have found that rats exposed to cannabinoid agonists during adolescence show cognitive deficits (particularly in object recognition and working memory; O'Shea et al., 2004, 2006; Schneider & Koch, 2007; Quinn et al., 2008; Realini et al., 2011; Abush & Akirav, 2012; Gleason et al., 2012), impairments in prepulse inhibition (Wegener & Koch, 2009; Llorente-Berzal et al., 2011; Gleason et al., 2012), and increases in locomotor activity (Wegener & Koch, 2009), which is consistent with the notion that chronic cannabinoid exposure during adolescence may elicit a constellation of behaviours that closely resemble the symptoms of psychosis (Rubino & Parolaro, 2013).

Other findings have included long-lasting impacts on emotional reactivity and social behaviour that appear to be consistent with a depressive phenotype. These include passivity in response to acute stress and reduced consumption of palatable food (Rubino et al., 2008; Bambico et al., 2010; Realini et al., 2011), as well as a reduction in the expression of sexual motivation in females (Chadwick et al., 2011; Brook et al., 2013; Minney & López, 2013). Studies have also found long-lasting impairments in social behaviour, which could reflect an anxiogenic effect (e.g., O'Shea et al., 2004, 2006), although findings regarding other anxiety-related behaviours have been mixed and may depend on the behavioural task used (see review by Rubino et al., 2012).

Interestingly, there is evidence from animal studies that early cannabis exposure may interact with existing risk factors, or concurrent environmental stressors, to increase adverse outcomes in adulthood. For example, Schneider and Koch (2007) found that adolescent cannabinoid exposure intensified the memory impairments associated with a neonatal prefrontal cortical lesion in adult rats. Similarly, Klug and van den Buuse (2012) examined the effects of both chronic young adult cannabinoid exposure and maternal separation and found that a combination of these conditions resulted in more pronounced anxiety-related behaviour in male rats than either condition alone. The combination of cannabinoid exposure and maternal separation also resulted in a significant decrease in sucrose preference in male rats, which was not present independently. These findings are broadly consistent with the 'two-hit' hypothesis of schizophrenia, in which an initial genetic defect or developmental abnormality (the first hit) is followed by an environmental insult (the second hit) that act synergistically to trigger disease onset (Bayer et al., 1999). Although not all studies examining this hypothesis have found additive effects (Llorente-Berzal et al., 2011; Klug & Van Den Buuse, 2013), these findings nonetheless highlight the importance of considering other variables when evaluating the impact of adolescent cannabis use. This is of particular relevance to human research, given that early cannabis use frequently occurs in conjunction with other risky behaviours and/or adverse experiences that may have similar additive or interactive effects on later mental health (e.g., DuRant et al., 1999; Harley et al., 2010; Primack et al., 2012; Wang et al., 2014).

4. Effects of acute exposure in adult humans

Acute exposure to cannabis has been found to affect a wide range of central nervous system functions in humans (Zuurman et al., 2009), with variable subjective effects including perceptual distortions, euphoria and relaxation, and increased sensory perception, as well as unwanted effects such as anxiety, dizziness, and hunger (Green et al., 2003). A review of studies examining brain function during acute cannabis intoxication identified increased regional cerebral blood flow (rCBF) throughout the cortex, particularly in frontal, limbic, paralimbic, and cerebellar regions (Quickfall & Crockford, 2006). Most studies have found these increases to be positively correlated with subjective feelings of intoxication (Gonzalez, 2007). Both positive and negative psychological consequences have also been observed in human studies, which is likely due in part to the differential effects of cannabidiol and THC. For example, as in animal models, acute THC exposure in humans can increase anxiety and induce unpleasant cognitive and perceptual experiences (Carlini, 2004), while cannabidiol has anxiolytic effects (Zuardi et al., 1993; Bergamaschi et al., 2011), and may act as an antipsychotic (Zuardi et al., 2006). Human studies have also provided evidence that cannabidiol can block the adverse effects of THC (Zuardi et al., 1982), although it has been suggested that studies providing evidence for this effect may have limited relevance to the typical usage patterns of recreational cannabis users (Niesink & van Laar, 2013).

In regard to the neuroprotective effects found in the animal literature, data from human studies is scarce. In vitro, cannabinoids have been found to protect against neurotoxicity in human microglial cells (Klegeris et al., 2003), astrocytes (Sheng et al., 2005), and dopaminergic neurons (Hu et al., 2013), potentially by inhibiting the production of inflammatory mediators. Amongst healthy controls with no recent cannabis use or history of cannabis use disorder, a single dose of THC (0.0286 mg/kg) has been found to increase blood serum levels of brain-derived neurotrophic factor (BDNF), which is a crucial regulator of synaptic plasticity and has been associated with reductions in anxiety and depression (D'Souza et al., 2009). However, the same study found no effects of THC on BDNF amongst light cannabis users. Light cannabis users also demonstrated lower BDNF levels at baseline, suggesting that chronic cannabis exposure may suppress BDNF release rather than promote it.

Acute administration of cannabinoids has been consistently found to impair a range of cognitive processes including short-term and working memory, attention, learning, and executive functions (see reviews by Ranganathan & D'souza, 2006; Solowij & Pesa, 2012). Some of the most robust effects have been found in studies examining short-term episodic and working memory, where cannabinoids have been found to impair encoding, consolidation, and retrieval of both verbal and non-verbal information (Wilson et al., 1994; D'Souza et al., 2004; Ilan et al., 2004; Lane et al., 2005). Impaired performance has also been consistently found on tasks assessing attentional processes, including sustained, selective, focussed, and divided attention (Ilan et al., 2004; O'Leary et al., 2007; Ramaekers et al., 2009). A somewhat smaller number of studies have found altered inhibitory and decision-making processes following acute intoxication, although findings have not always been consistent across tasks (Hart et al., 2001; McDonald et al., 2003; Ramaekers et al., 2006; Ramaekers et al., 2009). Intravenous THC administration has also been found to induce transitory positive and negative schizophrenia-like symptoms in healthy individuals (D'Souza et al., 2004; Morrison et al., 2009). It is important to note however, that a systematic review of studies examining the effects of acute administration of cannabis or THC found inconsistent effects across a wide range of domains (Zuurman et al., 2009). The authors concluded that while memory and attention effects showed some dose–response relationships, these were inconsistent across various types of tests, and only heart rate and subjective effects could currently be considered reliable biomarkers of cannabis intoxication.

5. Effects of chronic exposure in adult humans

Studies of currently abstinent ex-users have found persistent effects of heavy use on brain function and cognition. In contrast to the increases in rCBF that have been reported following acute exposure, abstinent heavy users have been found to demonstrate lower rCBF in the prefrontal and orbitofrontal cortices (Lundqvist et al., 2001; Sevy et al., 2008), striatum (Sevy et al., 2008), cerebellum (Volkow et al., 1996; Block

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et al., 2000) and temporal lobes (Amen & Waugh, 1998), as well as globally (Tunving et al., 1986; Mathew et al., 1989). However, not all studies have consistently demonstrated effects in these regions, with a small number reporting *increased* activity (Herning et al., 2005; Sneider et al., 2008) or no effects (Mathew et al., 1986). Abstinent users have been found to demonstrate altered patterns of brain activation during cognitive tasks when compared to healthy controls, which in many studies has been observed despite no differences in task performance (Gonzalez, 2007; Martin-Santos et al., 2010; Batalla et al., 2013).

It is unclear however, how long these effects persist following abstinence. Studies assessing rCBF have differed markedly in regard to when they acquire imaging data (ranging from 12 h to 542 days following cessation; Batalla et al., 2013), which introduces the possibility that some effects may be due to the residual effects of recent use, or withdrawal, rather than reflecting persistent changes. In this regard, it is worth noting that there is evidence that initial decreases in activity may precede normalisation of function in some regions after a prolonged period of abstinence (e.g., 2–4 weeks; Sneider et al., 2008; Tunving et al., 1986). Similarly, while Schreiner and Dunn (2012) identified a range of residual neurocognitive deficits present in abstinent users, when they excluded studies that tested participants prior to 25 days of abstinence from their analyses, no significant residual effects were evident on any aspect of neurocognitive performance. As cognitive impairment is often measured within 12–48 h of last use (Solowij & Pesa, 2012), these findings raise the possibility that the effects of chronic exposure observed in humans following relatively brief periods of abstinence may not reflect lasting impairment. Indeed, it has been suggested that the long-term effects of cannabis exposure on cognition, if present, may be subtle and not clinically disabling for the majority of people (Pope et al., 2001). Moreover, lasting impairment following sustained abstinence could also relate to differences between using and non-using groups that predate use (Pope et al., 2003). Overall, very few studies have been designed to determine whether cognitive (and brain) functioning recovers following sustained abstinence, and further research has been called for in order to establish the extent and time course of recovery following cessation (Solowij & Pesa, 2012). These simple questions are of major importance and have been seriously under-investigated given the prevalence of cannabis use worldwide.

The contribution of pre-existing risk factors is also an important issue to consider when examining the consequences of chronic cannabis exposure in adulthood, particularly in relation to psychosis. Across numerous studies, deficits in the domains of attention, memory, and executive function have been likened to the cognitive endophenotypes proposed as vulnerability markers for schizophrenia (Solowij & Michie, 2007). As characteristics that reflect the actions of predisposing genes (Gottesman & Gould, 2003), endophenotypes of schizophrenia have been proposed to include abnormalities in the automatic processing of auditory stimuli (including prepulse inhibition), impaired response inhibition, and deficits in attention, working memory and other executive functions (Solowij & Michie, 2007). Given the similarity between the cognitive impairments associated with cannabis use and those associated with schizophrenia, it has been suggested that long term exposure might be associated with schizophrenia-like sequelae in some individuals (Solowij et al., 2012b). However, it is important to note that pre-existing vulnerabilities play a role in determining who is at risk, with numerous studies demonstrating psychosis liability to be associated with both earlier onset of cannabis use and greater sensitivity to its adverse effects (Henquet et al., 2008). As studies have not always adequately controlled for pre-existing risk factors when examining the association between cannabis use and psychosis (McLaren et al., 2010), it is uncertain whether cannabis use can precipitate schizophrenia in non-vulnerable individuals.

At the same time, there is sufficient evidence to warrant continued investigation of this issue. For example, Yücel et al. (2012) reported that a subgroup of patients with first episode psychosis, who had used cannabis heavily since adolescence, did not display the typical cognitive profile of individuals with schizophrenia. A positive association between psychotic symptoms and cumulative cannabis exposure has also been demonstrated in individuals with no history of psychotic disorder (Yücel et al., 2008), suggesting that pre-existing psychosis vulnerability may not be a necessary requirement for symptoms amongst heavy cannabis users. While not providing conclusive evidence for a causal relationship between cannabis use and later psychosis in otherwise healthy individuals, these studies nonetheless suggest that this possibility should not be discounted.

Although structural findings from human imaging studies are not as robust as those from animal studies, a recent review concluded that there is evidence of structural brain abnormalities in the medial temporal, prefrontal, and cerebellar regions amongst heavy users (Lorenzetti et al., 2013). While findings for many regions were mixed, there is growing evidence that adult users demonstrate reductions in hippocampal volumes (Fig. 1), with two studies reporting an association between volume reduction in the hippocampus and cumulative lifetime cannabis exposure (Yücel et al., 2006; Yücel et al., 2008). Parahippocampal alterations have also been reported amongst high frequency users (but were not found in samples that had less exposure to cannabis; Matochik et al., 2005; Tzilos et al., 2005; Jager et al., 2007). In addition, a more recent study examining hippocampal shape alterations in cannabis users with and without schizophrenia found that abnormalities in hippocampal morphology (specifically, deflations across the hippocampus with an anterior predisposition) were associated with cannabis use patterns as well as symptoms of psychosis (Solowij et al., 2013). These findings point towards a potential association between greater exposure to cannabis and morphological alterations in hippocampal and parahippocampal regions, however given the paucity of research in this area and the mixed findings from existing studies (see Lorenzetti et al., 2013), further research is needed to clarify the association between cannabis use and hippocampal structural alterations in humans.

In addition to structural MRI studies, a small number of studies have used Diffusion Tensor Imaging (DTI) to assess white matter integrity in adult cannabis users. DTI involves mapping the diffusion of water molecules in brain tissue and is used to examine white matter microstructure and patterns of anatomical connectivity. To date, investigations using DTI techniques to examine the impact of cannabis exposure have been limited in number, and are frequently complicated by the presence of other substance use (see reviews by Batalla et al., 2013; Cookey et al., 2014). However, their findings have generally supported the notion that heavy cannabis use in adults is associated with impairments in the

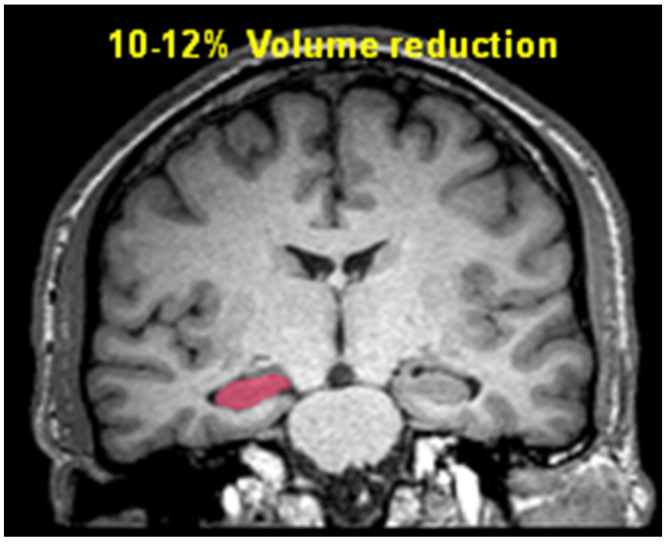

Fig. 1. Average reduction in hippocampal volumes found amongst heavy, long-term adult cannabis users. Cumulative cannabis exposure over a 10-year period was inversely correlated with volumes of the left hippocampus (Yücel et al., 2008).

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structural integrity and coherence of white matter tracts, including those within frontal regions (Gruber & Yurgelun-Todd, 2005; Gruber et al., 2011), the hippocampus (Zalesky et al., 2012), and the corpus callosum (Arnone et al., 2008; Zalesky et al., 2012; Gruber et al., 2014). Of interest, three of these studies have provided cross-sectional data supporting a relationship between poorer white matter integrity and an earlier onset of cannabis use (Gruber et al., 2011; Zalesky et al., 2012; Gruber et al., 2014). For example, Zalesky and colleagues reported impaired axonal fibre connectivity in the right fimbria of the hippocampus, splenium of the corpus callosum, and commissural fibres (Zalesky et al., 2012; see Fig. 2), with impaired connectivity in the fimbria and commissural fibres found to be positively correlated with age of onset of regular use, even after duration of regular use was controlled for. This finding provides evidence that exposure during adolescence may be more harmful than during adulthood. More broadly, it is consistent with studies in adults demonstrating that an earlier age of onset is associated with greater cognitive impairment and more pronounced morphological alterations (Jacobus et al., 2009a; Lorenzetti et al., 2013).

6. Effects of exposure during prenatal and adolescent periods

Studies examining the effects of cannabis exposure in utero and during adolescence have provided evidence that the brain is more vulnerable during these crucial neurodevelopmental periods. Cannabis exposure in utero impairs central nervous system development (Downer & Campbell, 2010) and has been associated with cognitive and behavioural deficits (Derauf et al., 2009; Wu et al., 2011; Huizink, 2014). While not comparable to animal research discussed earlier providing evidence for reorganisation of neurotransmitter systems and cortical cell death, findings in humans include subtle impairments in executive functions, including learning and memory (Fried & Watkinson, 1990; Richardson et al., 2002; Goldschmidt et al., 2004, 2008) and attention (Leech et al., 1999; Goldschmidt et al., 2000; Fried & Watkinson, 2001; Noland et al., 2005), as well as increased impulsivity and externalising behaviour problems (Fried et al., 1998; Goldschmidt et al., 2000; Richardson et al., 2002; Day et al., 2011). Although results have been variable depending on factors such as timing of exposure and age of offspring at assessment, these findings suggest that prenatal exposure may interfere with the normal trajectories and mechanisms of brain maturation (Wu et al., 2011). The relatively selective impact of prenatal cannabis exposure on higher cognitive functions has been proposed to indicate disruption of prefrontal cortical development specifically (Derauf et al., 2009). However, it is also important to note that research into prenatal cannabis exposure in humans has been somewhat limited in comparison to the extensive literature on the teratogenic effects of prenatal exposure to nicotine and alcohol (see reviews by Huizink & Mulder, 2006; Ginzel et al., 2007; Bruin et al., 2010; Lebel et al., 2011), both of which have been associated with severe and long-lasting effects on neurocognitive and behavioural development. Further prospective research is needed to clarify the magnitude of the long-term effects associated with prenatal cannabis exposure (Huizink, 2014), particularly given the range of potentially confounding variables associated with cannabis use during pregnancy (which include tobacco and alcohol use along with numerous demographic, social, and psychological characteristics; el Marroun et al., 2008).

While few studies have documented alterations in brain structure as a consequence of prenatal exposure, one study (Rivkin et al., 2008) reported volumetric changes (including reduced cortical grey matter) in children aged 10–14 who were exposed to cannabis during pregnancy. In addition, a DTI study of children who had been prenatally exposed to both cannabis and cocaine found they had greater alterations in frontal white matter integrity than children who had been exposed to cocaine alone (Warner et al., 2006).

Studies conducted with adolescent cannabis users have provided evidence that heavy or regular use is associated with a range of cognitive deficits, including impairments in attention (Tapert et al., 2002; Harvey et al., 2007; Medina et al., 2007a), learning and memory (Schwartz et al., 1989; Millsaps et al., 1994; Harvey et al., 2007; Medina et al., 2007a) and response perseveration (Lane et al., 2007). While these findings are consistent with the adult literature, there is some evidence that they may be more likely to persist with abstinence (Jacobus et al., 2009a). For example, after 3–4 weeks of abstinence, adolescent cannabis users have been found to demonstrate deficits in memory, attention, planning, and psychomotor speed when compared with non-using adolescents (Millsaps et al., 1994; Medina et al., 2007a; Hanson et al., 2010). However, other studies have provided evidence that while persisting somewhat longer than in adults, cognitive impairments fully recover following more prolonged periods of abstinence (Schwartz et al., 1989; Fried et al., 2005).

Studies examining age of onset of regular or heavy use provide evidence that adolescence is a period of increased vulnerability to the adverse effects of regular cannabis exposure. Earlier onset users have been found to show greater impairment in a range of cognitive domains, including learning and memory (Pope et al., 2003; Solowij et al., 2011a), decision-making (Solowij et al., 2012a), as well as attention and other executive functions (Fontes et al., 2011; Gruber et al., 2012). It is important to note however, that many studies examining age of onset have been retrospective and cross-sectional, and therefore cannot rule out the possibility of confounding effects (Lisdahl et al., 2013).

Of interest in this regard is a recent large-scale longitudinal study by Meier et al. (2012) that followed 1037 participants from birth to adulthood, assessing neuropsychological functioning at multiple time points between the ages of 7 and 13 years (prior to the onset of regular cannabis use) and again at age 38. They found that adolescents who reported either weekly cannabis use or were diagnosed with cannabis dependence prior to the age of 18, showed greater neuropsychological decline over the course of the study than those who were diagnosed with cannabis dependence in adulthood. Moreover, amongst adolescent-onset (but not adult-onset) persistent heavy users, these impairments remained evident even following one or more years of abstinence. These results are consistent with cross-sectional findings in adult populations (e.g., Pope et al., 2003), but eliminate the possibility of premorbid deficits accounting for the subsequent decline in neuropsychological functioning, and suggest that sustained abstinence may not be sufficient for recovery of cognitive functions if exposure has occurred during adolescence. However, it has subsequently been argued that the association between early cannabis use and decline in cognitive functions observed by Meier and colleagues could have been confounded by other variables, including socio-economic status (Rogeberg, 2013) and personality (Daly, 2013). Given these potential limitations, it may be premature to infer causality from their findings alone.

An earlier age of onset has also been associated with greater cognitive impairments even when the total duration of use is relatively short (Solowij et al., 2011a). In a prospective study examining the impact of adolescent cannabis and alcohol use on verbal learning and memory, Solowij and colleagues found that adolescents who had used cannabis for an average of 2.4 years showed greater impairment in these domains than matched groups of alcohol users and non-substance-using controls. These findings point towards an impairment in learning and memory that is not attributable to the concurrent use of alcohol or other drugs, and appears to be comparable in magnitude to the deficits found in long-term adult users (Solowij et al., 2002), yet emerges after less than three years of use during adolescence. An earlier age of onset of regular cannabis use was associated with poorer performance, even when quantity and frequency of use were controlled for, suggesting that early use may have a detrimental effect on cognitive function regardless of the extent of exposure (Solowij et al., 2011a).

Many of the confounding risk factors that have been identified in the adult literature, including psychosis vulnerability, are also important factors to consider within adolescent populations. In a longitudinal study of 1037 participants studied from birth to age 26, Caspi et al. (2005) found that the influence of adolescent cannabis use on adult

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psychosis was moderated by genetic factors, whereby only those that carried a variant of the catechol-O-methyltransferase (COMT) gene showed increased risk of disorder. Early cannabis use has also been shown to interact with environmental factors to increase the risk of psychosis, including childhood trauma (Houston et al., 2008; Harley et al., 2010), as well as growing up in an urban (as opposed to rural) area (Kuepper et al., 2011). In a recent study by Alemany et al. (2014), a three-way interaction between cannabis use, childhood abuse and COMT genotypes was found, whereby variability in the COMT gene only influenced psychosis amongst individuals who reported childhood abuse. Although age of onset of cannabis use was not assessed in this study, it points towards a highly complex relationship between cannabis use and adverse psychological outcomes that is unlikely to be easily resolved.

There is evidence that cannabis use during adolescence may have neuroanatomical consequences. A small number of structural imaging studies have found abnormalities amongst adolescent users, including smaller whole brain and cortical grey matter volumes (Wilson et al., 2000), altered prefrontal and insular cortical thickness (Lopez-Larson et al., 2011), smaller right medial OFC volumes (Churchwell et al., 2010), smaller hippocampal volumes (Ashtari et al., 2011), greater left > right hippocampal asymmetry (Medina et al., 2007c), larger right amygdala volumes (in females; McQueeny et al., 2011) and both smaller (in females) and larger (in males) prefrontal cortical volumes (Medina et al., 2009). The finding that heavy use in adolescence is associated with a reduction in prefrontal volumes, in conjunction with evidence from adult studies that an earlier age of onset is associated with greater alterations in prefrontal regions, suggests that the prefrontal cortex may be particularly vulnerable to the effects of early cannabis exposure. In contrast, while smaller hippocampal volumes have been associated with heavier use, they have less consistently been associated with age of onset, suggesting that they may be more affected by duration and intensity of exposure rather than early use specifically (Lorenzetti et al., 2013). In this regard, it is interesting to note that smaller volumes of the orbitofrontal cortex have been found to predict the onset of cannabis use in adolescence, suggesting that a reduction in prefrontal volumes amongst heavy users could also be due, it part, to factors that pre-date substance use (Cheetham et al., 2012). However, the same study found no reduction in hippocampal volumes amongst adolescents who went on to use cannabis, consistent with the notion that structural differences in this region are likely to be related to adverse effects associated with ongoing heavy use.

As in the adult literature, studies are increasingly utilising DTI as a means of examining white matter microstructure in adolescent cannabis users. With the exception of an early study that reported no white matter differences between regular cannabis users and controls (DeLisi et al., 2006), this research has generally found alterations in white matter integrity amongst heavy adolescent users (although findings have again been confounded by concurrent use of other substances; Baker et al., 2013). For example, Yücel et al. (2010) examined white matter integrity in 11 cannabis-using adolescents, 11 inhalant-using adolescents, and 8 matched controls, and found reduced fractional anisotropy in the fasciculus adjacent to the right hippocampus in cannabis users compared to controls. Similarly, Ashtari et al. (2009) recruited 14 young adult males in residential cannabis treatment who had a history of heavy cannabis use throughout adolescence (5 also reported alcohol abuse) and found reduced fractional anisotropy, increased radial diffusivity, and increased trace values in fronto-temporal regions in comparison to control participants. While the authors suggest that these findings may be indicative of an interruption in the myelination process, alcohol use was not controlled for, meaning the findings could represent a combination of cannabis and alcohol effects. More recent research has also found poorer white matter integrity amongst adolescents who use cannabis in conjunction with alcohol or other drugs, when compared to controls with minimal substance use histories (Jacobus et al., 2009b; Clark et al., 2012; Bava et al., 2013; Jacobus et al., 2013a), as well as adolescents who report heavy drinking without concurrent other substance use (Jacobus et al., 2013b).

7. Role of the endocannabinoid system in brain development: associations with schizophrenia, depression, and memory and learning deficits

Adolescence is a critical stage in human development that is characterised by substantial changes in physical, psychological and social domains. This includes the ability to perform complex cognitive tasks and regulate affect and behaviour in order to achieve long-term goals (Spear, 2000; Steinberg, 2005). These changes are underpinned by the remodelling of brain regions involved in cognitive, emotional, motivational, and sensorimotor systems. In particular, this involves extensive pruning of cortical synapses (leading to a reduction in cortical grey matter) and increased myelination (Giedd et al., 1999; Paus, 2005). Cortical grey matter volume tends to follow an 'inverted U' shaped developmental trajectory during this period. Maximal volumes are reached earliest in primary sensorimotor areas and latest in the medial and lateral regions responsible for higher-order cognitive functions (cortical maturation within medial and lateral regions continues into late adolescence; Giedd et al., 2009). It is believed that disjunctions between these developing brain systems make adolescence a period of particular vulnerability (Spear, 2000; Steinberg, 2005).

Research over the past decade has identified that the endocannabinoid system plays a crucial role in the neurodevelopmental processes occurring during this period. The endocannabinoid system consists of two G-protein-coupled cannabinoid receptors (CB1 and CB2), endocannabinoid ligands (endocannabinoids; primarily anandamide [AEA] and 2-aeachidonoyl ethanolamide [2-AG]), and the enzymes responsible for synthesis and degradation (De Petrocellis & Di Marzo, 2009). The CB1 receptor is one of the most widely expressed G-protein-coupled receptors in the brain and is thought to mediate most of the CNS effects of cannabinoid drugs, while the CB2 receptor is more abundant in peripheral tissues, particularly immune tissues (Svíženská et al., 2008). CB1 receptors in the brain are predominantly located presynaptically, where activation by endocannabinoids can inhibit transmission in both GABA-ergic and glutaminergic synapses (Freund et al., 2003). The endocannabinoid system thus plays an important role in regulating the balance between inhibitory and excitatory neuronal activity. Indeed, CB1-mediated inhibition of glutaminergic neurotransmission and control of glutamate-induced excitotoxicity is believed to be the primary mechanism by which cannabinoids can exert neuroprotective effects (Marsicano et al., 2003).

Cannabinoid receptors and endogenous cannabinoids emerge early in the developing brain, and are involved in a wide range of processes during embryonic and prenatal neural development, including proliferation and differentiation of progenitor cells, glial cell formation, neuronal migration, and axonal pathfinding (Fride, 2008; Harkany et al., 2008; Díaz-Alonso et al., 2012). In addition to being critically involved in neural development during prenatal and early post-natal life, there is growing evidence that the endocannabinoid system continues to undergo functional development during adolescence, and may also play a role in regulating neurogenesis into adulthood (Galve-Roperh et al., 2007; Malone et al., 2010; Galve-Roperh, 2012). The CB1 receptor is expressed at high levels throughout the cerebral cortex, hippocampus, basal ganglia, and cerebellum (Herkenham et al., 1990), with many of these regions undergoing substantial remodelling during adolescence. Although the role of the endocannabinoid system in adolescent neurodevelopment is not yet fully understood, there is emerging evidence of a correlation between CB1 density in a certain region and its particular critical period (see review by Bossong & Niesink, 2010).

As exogenous cannabinoids affect the function of the endocannabinoid system, it has been suggested that cannabis exposure during adolescence might disrupt this system at a critical stage of development and lead to residual effects that increase the risk of

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psychopathology (Bossong & Niesink, 2010; Downer & Campbell, 2010; Malone et al., 2010; Caballero & Tseng, 2012). In support of this hypothesis, there is evidence that alterations in the endocannabinoid system are associated with a number of mental disorders, including schizophrenia and depression (Galve-Roperh et al., 2009; Parolaro et al., 2010; Ferretjans et al., 2012). Amongst individuals with schizophrenia, alterations in CB1 binding have been found in frontal regions, including the prefrontal cortex and anterior cingulate cortex, as well as in the ventral striatum (Dean et al., 2001; Zavitsanou et al., 2004; Newell et al., 2006; Eggan et al., 2010; Wong et al., 2010; Ceccarini et al., 2013), with some evidence that increased receptor binding may increase with positive symptom severity and decrease with negative symptom severity (Wong et al., 2010; Ceccarini et al., 2013). Studies of schizophrenia have also shown genetic variations in the components of the endocannabinoid system and changes in endocannabinoid levels in CSF and blood, although findings have not always been consistent across studies (Ferretjans et al., 2012). In studies of depression, CB1 receptor binding has been found to be altered postmortem in the prefrontal cortex, anterior cingulate cortex, and ventral striatum (Hungund et al., 2004; Vinod et al., 2005; Koethe et al., 2007; Vinod et al., 2010), while genetic variation in CB1 receptor function appears to influence risk for depression (Juhasz et al., 2009; Monteleone et al., 2010) as well as antidepressant treatment response (Domschke et al., 2008). These findings are consistent with two lines of animal research that have demonstrated alterations in the endocannabinoid system following chronic stress exposure and development of a depressive phenotype following stable impairment of CB1 receptors, respectively (see Parolaro et al., 2010).

Disruption of the endocannabinoid system may also explain the deficits in memory and learning that have been found following adolescent cannabis exposure, as there is considerable evidence that the endocannabinoid system is involved in these processes (Sullivan, 2000; Marsicano & Lafenêtre, 2009). The hippocampus, which is strongly implicated in memory and learning, has a high density of CB1 receptors (Herkenham et al., 1990), and the integrity of the endocannabinoid system within this region appears to underlie a range of processes including memory acquisition, consolidation, and retrieval (De Oliveira Alvares et al., 2008; Atsak et al., 2012; Morena & Campolongo, 2014). Accordingly, numerous studies have found that exogenous cannabinoid administration interferes with performance on hippocampal-dependent tasks (Lichtman et al., 1995; Yim et al., 2008). As cannabinoid agonists inhibit release of GABA and glutamate within the hippocampus, it has been suggested that long-term cannabis use may inhibit the synaptic changes that are required for the formation and consolidation of memories (Sullivan, 2000).

Conversely, neurodevelopmental abnormalities in the endocannabinoid system could influence the impact of later cannabis use on the brain, making some individuals more vulnerable to adverse effects. This is consistent with the 'two-hit' hypothesis described earlier (Bayer et al., 1999). Indeed, Viveros et al. (2012) propose that the endocannabinoid system may be of particular interest in this model of psychiatric disorder, given its role in neural development and plasticity. They note that the first 'hit' that disrupts the endocannabinoid system can be either endogenous (e.g., a genetic mutation of the ABH12 enzyme, which degrades endocannabinoids), or exogenous (e.g., prolonged exposure to a stressful environment), impacting the development of the endocannabinoid system and increasing vulnerability to the negative effects of cannabis. Research examining the effects of maternal deprivation, one of the most frequently studied animal models of early life stress, has provided support for this hypothesis. In rodents, maternal deprivation in the first 9–10 days of life has been found to affect hippocampal expression of CB1 and CB2 receptors and their ligands (i.e., 2-AG), as well as the enzymes responsible for synthesising and degrading these (Suárez et al., 2009, 2010), suggesting that neurodevelopmental stress can alter the development of the endocannabinoid system. Although these studies did not examine the effects of subsequent cannabis exposure, other research discussed earlier within this review supports the notion that maternal deprivation (along with other pre-existing risk factors) can increase vulnerability to the adverse effects of cannabis (Schneider & Koch, 2007; Klug & van den Buuse, 2012, 2013).

While the model described by Viveros et al. (2012) relies primarily on evidence from animal models, alterations in the development of the endocannabinoid system could also influence the outcomes that

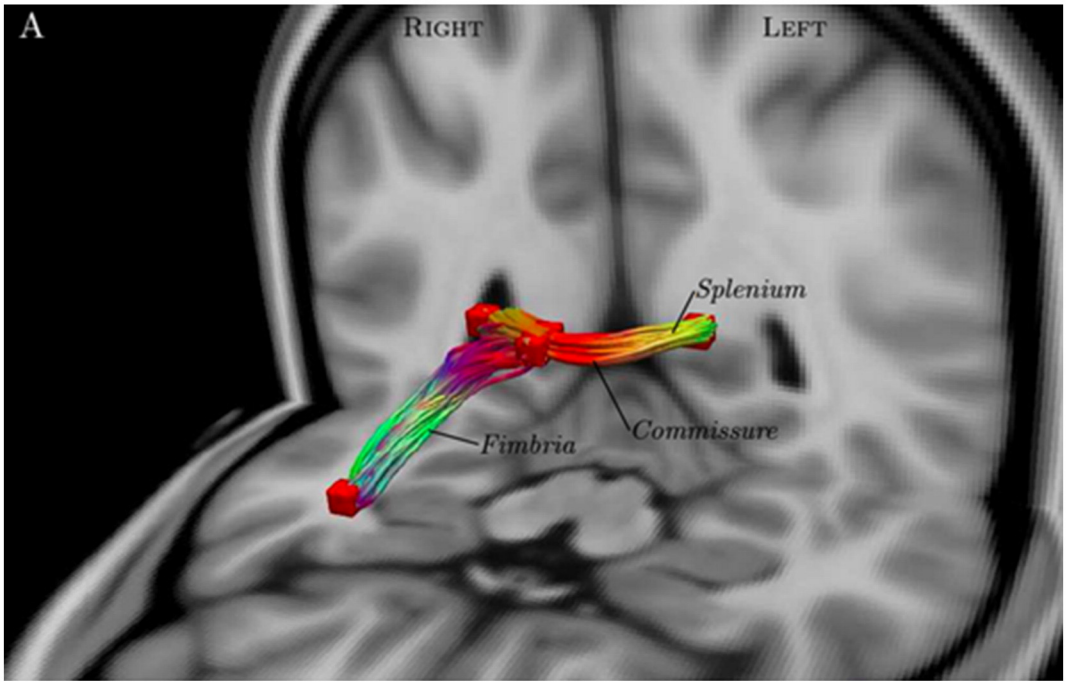

Fig. 2. Impaired axonal fibre connectivity in cannabis users compared to non-users. Voxels interconnected by fewer streamlines (3D curves following the trajectory of specific fibre bundles) are coloured red and the corresponding streamlines via which they are interconnected are coloured such that: left–right is red, superior–inferior is blue and anterior–posterior is green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Reprinted from Zalesky et al. (2012).

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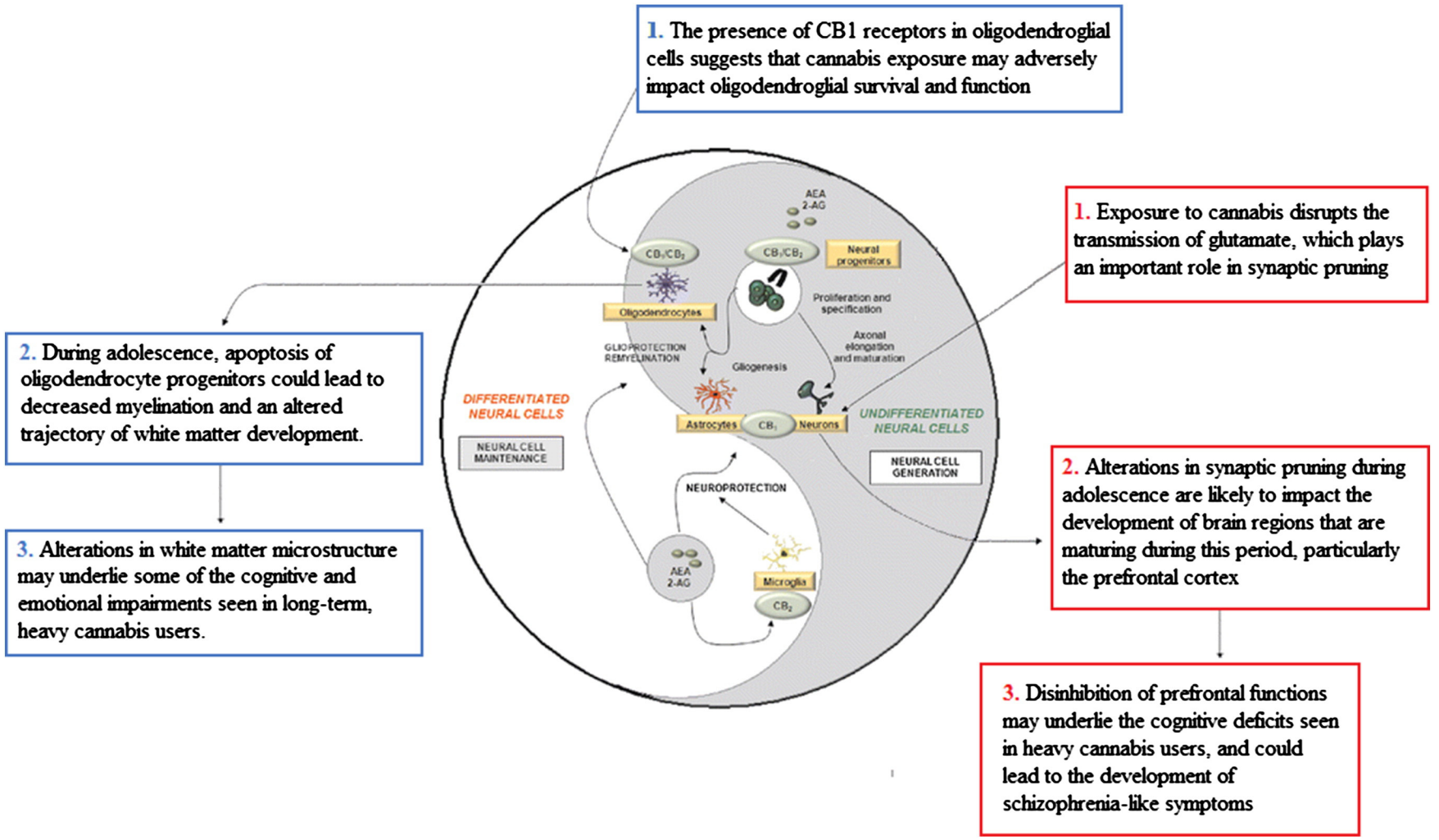

Fig. 3. Potential impact of cannabis use on adolescent brain development. The endocannabinoid system regulates the generation and specification of neural cells during prenatal and early post-natal stages of brain development (grey yang side) as well as regulating neural cell maintenance and neuroprotection in the mature brain (white ying side). In the developing brain, CB1 receptors are involved in neuronal migration and axonal pathfinding, as well as the generation of glial cells, including astrocytes and oligodendrocytes. We have proposed two potential mechanisms by which prolonged cannabis exposure during adolescence might disrupt the functions of the endocannabinoid system and alter brain development: (i) by interfering with processes of synaptic pruning (red pathway); and (ii) by altering the development of white matter (blue pathway). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) Adapted from Galve-Roperh et al. (2009).

have been associated with heavy cannabis use in humans. For example, the endocannabinoid system has been proposed to play a role in the pathogenesis of schizophrenia (although, as noted earlier, the evidence to support this hypothesis has been mixed; Ferretjans et al., 2012), while two recent studies have provided evidence that variation in the CNRI gene moderates the effect of stressful life events on depressive symptoms (Juhasz et al., 2009; Agrawal et al., 2012). While a detailed discussion of the interaction between multiple risk factors is beyond the scope of this review, these studies provide insight into how processes associated with the development of the endocannabinoid system may impact variability in risk *within* adolescent populations, as well as making the developing brain vulnerable to the effects of cannabis more generally.

8. Potential mechanisms by which cannabis use might impact brain development

The precise mechanism(s) by which cannabis use may impact adolescent brain development are not yet fully understood. However, there is evidence that the endocannabinoid system is involved in synaptic pruning and white matter development, two processes thought to be critical to the normative remodelling of brain regions during adolescence (Giedd et al., 1999; Paus, 2005). Accordingly, it is possible that exposure during critical stages of development could disrupt these processes and lead to adverse emotional and cognitive outcomes (Fig. 3).

The endocannabinoid system has been implicated in the inhibition of glutamate release (Freund et al., 2003), and exogenous cannabinoid exposure has been found to disrupt glutamate transmission (Szabo & Schlicker, 2005), with long-lasting interference in this neurotransmitter system found following administration during both prenatal (Mereu et al., 2003; Antonelli et al., 2005; Castaldo et al., 2007) and adolescent (Gleason et al., 2012) periods. As glutamate transmission plays an important role in regulating brain maturational processes, including synaptic pruning (Segal et al., 2000; Lujan et al., 2005; Catania et al., 2007), Bossong and Niesink (2010) have suggested that adolescent cannabis use could interfere with endocannabinoid-mediated control over glutamate transmission, leading to alterations in synaptic pruning and a disruption of prefrontal development. In turn, this would result in an overall disinhibition of prefrontal cortical function that underlies many of the cognitive deficits associated with long-term cannabis use and, depending on dose and timing, could also contribute to the development of psychosis or schizophrenia (Bossong & Niesink, 2010; Caballero & Tseng, 2012).

The endocannabinoid system is also believed to be involved in white matter development, with growing evidence that this process may be particularly susceptible to cannabis exposure. CB1 receptor expression is abundant in white matter areas during neural development, but diminishes during adulthood (Fig. 4), suggesting that a transient developmental period exists in which white matter structures are particularly sensitive (Romero et al., 1997; Berrendero et al., 1998). Studies have since found CB1 receptors in oligodendrocytes (Molina-Holgado et al., 2002), supporting a role for the endocannabinoid system in the processes associated with these cells during development, including the formation of myelin (Arévalo-Martín et al., 2007). As prolonged exposure to cannabis during adolescence can lead to downregulation of cannabinoid receptors (Dalton & Zavitsanou, 2010), it has been suggested that oligodendrocyte survival and function could be impacted during this period, leading to decreased myelination and an altered trajectory of white matter development (Solowij et al., 2011b). In line with this hypothesis, chronic cannabinoid exposure has been associated with altered expression of the myelin basic protein gene and myelin proteolipid protein (Kittler et al., 2000; Grigorenko et al., 2002), which are major components of the myelin sheath of oligodendrocytes (Hartman et al., 1982). More recent research has found evidence that this effect is present more than 2 weeks after the last exposure, but only in rats exposed during adolescence (Quinn et al., 2008), consistent with the notion that this may be a critical period in regard to the impact of cannabinoids on white matter development.

9. Conclusion

While epidemiological and clinical studies have consistently linked cannabis use with psychiatric illness and cognitive impairment, the mechanisms that underlie these associations are still not well understood. Research from both the animal and human literature appears to support the notion that adolescence is a period of particular risk, with exposure during this stage of development potentially resulting in more severe and persistent adverse effects than exposure during adulthood. Given the importance of the endocannabinoid system in human brain development, it is plausible that prolonged use during adolescence results in a disruption in the normative neuromaturational processes that occur during this period. In turn, this could result in long-lasting changes to brain structure and function that underlie many of the adverse cognitive and emotional outcomes associated with heavy use.

In this review, we identify synaptic pruning and white matter development as two key processes that may be adversely impacted by cannabis exposure during adolescence. Alterations in synaptic pruning and/or white matter microstructure have been associated with both schizophrenia and depression (Feinberg, 1983; Keshavan et al., 1994;

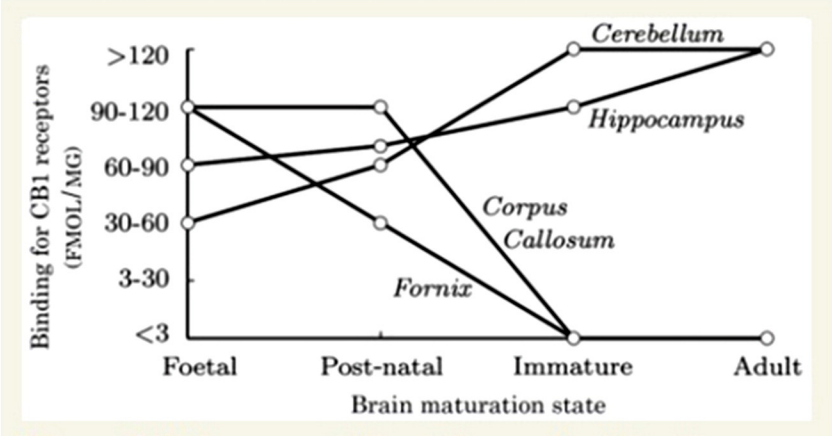

Fig. 4. Unlike neuronal tissue, white matter structures show a decrease in CB1 receptor expression as the brain matures. Consequentially, it has been suggested that axonal microstructure may be particularly sensitive to cannabis exposure during critical periods of development.
Data extracted from Romero et al. (1997) and reprinted from Zalesky et al. (2012).

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Hulvershorn et al., 2011; Tham et al., 2011), and there is evidence that heavy cannabis use may speed up or worsen these changes amongst affected individuals (Medina et al., 2007b; Solowij et al., 2011b). However to date, there have been few studies that have prospectively examined associations between adolescent cannabis exposure, altered trajectories of brain development, and psychiatric or cognitive impairment in adulthood. In the animal literature, a small number of studies appear to support the hypothesis that altered processes of brain development are responsible for the adult consequences of adolescent cannabis exposure, however further research is needed in order to understand the specific mechanism(s) that underlie these findings, in addition to their relevance to the outcomes associated with heavy use in humans.

While inconsistencies remain regarding the impact of cannabis use in adulthood, there is now sufficient evidence to consider the possibility that prolonged exposure during adolescence is harmful. The potential influence of cannabis use on brain development has important policy implications, as it underscores the need for prevention programmes that specifically focus on delaying the onset of cannabis experimentation. Together with early intervention programmes that aim to reduce the prevalence of regular or harmful use amongst young people, efforts to delay onset or minimise exposure during this period of development may be of particular importance in reducing long-term harm.

Conflicts of interest

"The authors declare that there are no conflicts of interest."

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