Adolescent exposure to cannabis as a risk factor for psychiatric disorders

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J Psychopharmacol 2012 26: 177 originally published online 18 July 2011
DOI: 10.1177/0269881111405362

Review

Adolescent exposure to cannabis as a risk factor for psychiatric disorders

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Journal of Psychopharmacology
26(1) 177–188

DOI: 10.1177/0269881111405362
jop.sagepub.com

Abstract

Adolescence represents a critical period for brain development and the endocannabinoid system plays a crucial role in the regulation of neuronal refinement during this period. Cannabis is the most consumed drug among adolescent people and its heavy use may affect maturational refinement by disrupting the regulatory role of the endocannabinoid system. In animals, adolescent cannabinoid exposure has been reported to cause long-term impairment in specific components of learning and memory and to differentially affect emotional reactivity with milder effects on anxiety behaviour and more pronounced effects on depression-like behaviour. Moreover, adolescent exposure to cannabinoids might represent a risk factor for developing psychotic-like symptoms at adulthood. Also epidemiological studies suggest that heavy adolescent cannabis use may increase the risk of cognitive abnormalities, psychotic illness, mood disorders and other illicit substance use later in life. In conclusion, the available data point to the hypothesis that heavy cannabis use in adolescence could increase the risk of developing psychiatric disorders, especially in people who already have a vulnerability to develop a psychiatric syndrome. Only few papers have investigated the neurobiological substrates of this vulnerability, thus further studies are needed to clarify the molecular mechanisms underlying the effect of cannabis on the adolescent brain.

Keywords

Adolescence, cannabinoids, cannabis, cognition, emotionality, endocannabinoid system, gateway, psychiatric disorders, psychosis

The endocannabinoid system

The term 'endocannabinoid system' refers to a neuromodulatory system present both in the brain and periphery comprising the receptors, their intrinsic lipid ligands, and associated proteins (transporters, biosynthetic and degradative enzymes). To date The International Union of Basic and Clinical Pharmacology has identified two types of cannabinoid receptors, named CB1 and CB2 based on the order of their discovery (Matsuda et al., 1990; Munro et al., 1993), both belonging to the superfamily of G protein coupled receptors.

The cannabinoid CB1 receptor is a presynaptic receptor widely expressed throughout the brain with high density in the striatum, hippocampus, and cerebellum, and moderate to low densities in the amygdala, midbrain and cerebral cortex (Glass and Felder, 1997; Herkenham et al., 1991). Its activation inhibits neurotransmitter release from the axon terminals and it is widely accepted that most of the CNS effects of cannabinoid drugs are mediated by CB1 receptors. The cannabinoid CB1 receptor is also present at lower density in peripheral tissues, including liver, adipocytes, exocrine pancreas, gastrointestinal tract, skeletal muscle and circulating immune cells (Matias et al., 2006).

CB2 receptors were cloned a few years later (Munro et al., 1993) and whilst they were thought to be predominately located in immune cells in tissues such as the spleen and liver, there are recent papers showing that cannabinoid CB2 receptors may also be expressed in neurons (Brusco et al., 2008; Gong et al., 2006; Van Sickle et al., 2005). The CB1 receptor activation through both Gi/o proteins inhibits adenylyl cyclase activity, activates potassium channels and inhibits voltage-gated calcium channels, while the CB2 receptor is known only to couple to Gi proteins (Howlett, 2002).

The presence of endogenous ligands for the cannabinoid receptor (endocannabinoids) was demonstrated soon after the characterization of the receptors. The two main endogenous ligands of cannabinoid receptors are anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Stella et al., 1997; Sugiura et al., 1995). Both are arachidonic acid derivatives produced from phospholipid precursors postsynaptically through activity-dependent activation of specific phospholipase enzymes (Piomelli, 2003). Later on, N-arachidonoyl dopamine (NADA) was also identified as

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endocannabinoid followed by N- arachidonoyl-glycerol ether and O-arachidonoyl ethanolamine (De Petrocellis and Di Marzo, 2009).

The endogenous ligands do not share the same biosynthetic or metabolic pathways, indicating distinct mechanisms of regulation. Different pathways can produce AEA from the phospholipid precursors N-arachidonoyl-phosphatidylethanolamine, the most direct of which (that is, direct conversion) is catalysed by an N-acyl-phosphatidylethanolamine selective phosphodiesterase.

2-AG is mainly synthesized through activation of phospholipase C and the subsequent production of diacylglycerol, which is rapidly converted to 2-AG by diacylglycerol lipase. Concerning metabolism, after its re-uptake, AEA is hydrolysed by the enzyme fatty acid amide hydrolase (FAAH), generating arachidonic acid and ethanolamine, while 2-AG is primarily metabolized by monoacylglycerol lipase (MAG lipase), which results in the formation of arachidonic acid and glycerol (Di Marzo and Petrosino, 2007). Both AEA and 2-AG, possibly under conditions in which the activity of MAGL or FAAH is suppressed, might become substrate for cyclooxigenase 2 and give rise to the corresponding hydroperoxy derivatives (Rouzer and Marnett, 2008).

Apart from their well known binding to CB1 and CB2 receptors, endocannabinoids may also bind to other receptors: for example AEA may activate intracellularly the potential vanilloid receptor type 1 (TRPV1) (Ross, 2003). Moreover, other putative endocannabinoid receptors are the 'orphan' G protein coupled receptor GPR55 (Ryberg et al., 2007) and the peroxisome proliferator activated receptor (PPAR) (O'Sullivan, 2007).

However, CB1 and CB2 receptors are certainly the most studied molecular targets for AEA and 2-AG, which activate them with different affinity: AEA has the highest affinity in both cases, whereas 2-AG has the highest efficacy in both cases (McPartland et al., 2007).

Importantly, the endocannabinoid signalling acts differently from most neurotransmitter systems. Specifically, endocannabinoids are released 'on demand' by post-synaptic cells, function as retrograde signals and traverse back across the synapse, where they bind pre-synaptically located CB1 receptors and reduce synaptic transmitter release (Freund et al., 2003). On this basis, the endocannabinoid system can be considered one of the major players in regulating the activity state of various neurotransmitters, participating in synaptic plasticity.

Endocannabinoid system and adolescent brain maturation

In the last 10 years a series of elegant papers highlighted the significant role of the endocannabinoid system during neural development, through modulation of neurogenesis, neuronal differentiation, axon pathfinding and development of some transmitter systems (for a review see Galve-Roperh et al., 2009).

In contrast to earlier beliefs, brain development continues through both childhood and adolescence, the developmental period during which the body and brain emerge from an immature state to adulthood (Spear, 2000; Steinberg and Morris, 2001).

Adolescence is characterized by a development shift from producing a large number of neurons to creating efficient neuronal pathways. This aim is reached through a process of synaptic refinement, by which some connections between brain cells are pruned and eliminated, whereas 'useful' neurons, synapses and dendrites are preserved for the adult brain (Cohen-Cory, 2002; Katz and Shatz, 1996; Luna, 2009; Whitford et al., 2007). Presumably, this means that synapses relevant for survival and optimal function flourish, whereas connections that are not being used vanish (for a review see Bossong et al., 2010). Moreover, white matter increases; functional magnetic resonance imaging (fMRI) studies showing greater correlation across disparate regions on certain tasks (Giedd et al., 1999). Inverted U grey matter changes may reflect the brain's increasing refinement for specialization and these processes appear to be strongly influenced by external stimuli (Giedd et al., 1999). Thus, environmental insults, such as cannabis consumption, can disturb the fine neural refinement that takes place in adolescence, making this period particularly vulnerable.

Research on the involvement of the endocannabinoid system in adolescent brain development is very scarce. Considering the neuromodulatory role of the endocannabinoid system and its strategic position on GABAergic and glutamatergic synapses, it can be suggested that this system could be involved in the process of maturational refinement of neuronal networks.

This hypothesis is indirectly reinforced by data emphasizing the dynamic nature of the endocannabinoid system in the adolescent brain.

A recent study in rats showed clear developmental fluctuations of the endocannabinoid levels throughout adolescence in the nucleus accumbens and prefrontal cortex, brain regions involved in reward, motivation and cognition (Ellgren et al., 2008). The most profound alteration was the constant increase of AEA levels in the prefrontal cortex, which were almost three times higher in late than in early adolescence. On the contrary, a decrease in 2-AG concentrations were observed in the prefrontal cortex and in the nucleus accumbens in the later phase of adolescence. Similarly, Wenger et al. (2002) found that the AEA levels peak during puberty and then decline during adulthood in the hypothalamus of female rats. In addition, CB1 receptors may vary in the prefrontal cortex and nucleus accumbens core during adolescence, but these alterations appear to be less marked than for endocannabinoids (Ellgren et al., 2008). Similarly, Rodriguez de Fonseca et al. (1993) demonstrated a transient increase in CB1 expression in early adolescence that declines at adulthood. In humans (Mato et al., 2003) autoradiographic levels of CB1 receptors seem to increase progressively from early postnatal stages to adulthood in region such as frontal cortex, striatum and hippocampus. More recently, Eggan et al. (2010) examined the CB1 receptor immunoreactivity (CB1R-IR) and mRNA (CB1mRNA) expression in the dorsolateral prefrontal cortex (DLPFC) of monkeys. CB1R-IR axon density significantly decreased in layers 1 and 2 during the first postnatal year, but significantly increased in layer 4, especially during adolescence. In contrast, CB1mRNA levels

were highest one week postnatal, declined over the next two months, and then remained unchanged into adulthood. The postnatal refinements in the laminar distribution of CB1R-IR axons suggest that CB1 receptors may be relevant for the development of cognitive functions reliant on the DLPFC.

Further studies are needed to better clarify the ontogenic changes in the endocannabinoid system during adolescence and their functional relevance for brain maturation; however, it is clear that during this period this system is dynamic, with peak levels of both ligands and receptors in specific brain areas. In this regard, genetic deletion of CB1 receptor gene might represent a useful tool to clarify the role of the endocannabinoid system in neurodevelopment. Through this approach it was demonstrated that the endocannabinoid system has a major impact on the pre- and post-synaptic availability of mu opioid receptors (Lane et al., 2010), GABAergic receptors (Uriguen et al., 2011) and serotonergic signalling (Aso et al., 2009).

Concluding, we can hypothesize that the endocannabinoid system signalling continues to exert an important role in the neuronal refinement typical of this period. Thus, its strong stimulation through exogenous cannabinoids, such as tetrahydrocannabinol (THC), can disrupt the regulatory role of the endocannabinoid system, producing long lasting consequences for adult brain function.

Adolescent cannabis use and neuropsychiatric disorders

Nearly 160 million people world-wide used cannabis in 2005 (UNODC, 2007), and more than half of the first users in the USA were under the age of 18 (SAHMSA, 2007). This high prevalence of cannabis use among adolescent people has been reported in many countries (for a review see Hall and Degenhardt, 2007) and despite this, the scientific community is still debating on the existence of a clear relationship between early cannabis use and risk to develop psychiatric disorders.

On one hand, the great variability in human studies in regard to culture, social and economic background and education level of the subjects makes it difficult to establish causal links between adolescent marijuana consumption and presence of psychiatric illnesses, altered affective outcomes and drug dependence in adulthood. For example, studies examining the link between cannabis consumption and the risk to develop psychiatric diseases in adulthood need to differentiate the contributions of current use and total lifetime cannabis exposure from any purported effect on neurodevelopment as well as variations in the concentration of THC and other cannabinoids, such as cannabidiol in different cannabis strains (Morgan et al., 2010), admixture with tobacco and confounding effects of other substances (i.e. alcohol and nicotine). One strategy to evaluate directly the relationship between prior cannabis experience and adult altered responses independent of cultural, social and moral factors is represented by the use of experimental animal models. Studies in animals would provide more reliable data but the difficulty here is selecting an experimental model really resembling the human psychiatric illness. In fact, the models currently available suffer several limitations and often represent only certain aspects of the pathologies, making it difficult to translate the findings to the human condition. Moreover careful investigation should be made of the effect of adolescent cannabinoid exposure in vulnerable people, i.e. people with genetic vulnerability (for example, the polymorphism in COMT gene for psychosis) or already suffering from environmental and social adversities. Indeed, for psychosis, it appears that cannabis use interacts with other risk factors, such as genetic vulnerability and other environmental factors, e.g. obstetric insults and various social adversities, to contribute toward psychosis onset (Barkus and Murray, 2010). This aspect will not be easily solved by means of animal studies, and further and specifically addressed clinical studies are needed.

These considerations apart, in this review we will summarize the most recent literature on the relationship between adolescent exposure to cannabinoids and increased risk for certain neuropsychiatric diseases, taking into account both human and animals studies, and we will try to delineate the most likely picture arising from the presented findings.

Animal studies

Despite the increasing use of cannabis among adolescents, not many experimental studies have dealt with long-lasting effects induced by chronic cannabinoid treatment during adolescence. The few studies available have sometimes produced conflicting results, mostly due to differences in experimental parameters such as rat strain, cannabinoid agonist used, and dosing regimen, thus complicating the comparison of data.

The existing literature points to the presence of subtle changes in the adult brain circuits after heavy cannabis consumption in adolescence.

Four main issues are addressed: long-term effects of adolescent cannabinoid exposure on cognition, emotional reactivity, psychotic-like behaviour, and vulnerability to drug abuse.

Cognition. The most remarkable and consistent part of the data regards cognitive deficit. When recognition memory was tested through the novel object recognition test, most papers reported impairments after chronic cannabinoid treatment during adolescence that were evident from 15 days to 30 days after discontinuing the treatment (O'Shea et al., 2004, 2006; Quinn et al., 2008; Realini et al., 2010; Schneider and Koch, 2003). These impairments were present in both males and females, were induced by both the natural and synthetic cannabinoid compounds, and did not occur when the treatment was performed at adulthood. The only discrepant finding was by Higuera-Matas et al. (2009), who reported no significant effect of chronic CP55,940 during adolescence on recognition memory in both male and female adult rats. However, it is worth noting that they tested animals after a longer withdrawal period, i.e. 59 days, and maybe at this interval of time the long-lasting behavioural changes were recovered. If this is true, the effect of adolescent cannabis exposure on cognition might be considered as long-lasting

and not irreversible, a feature really relevant at epidemiological level. Further studies are needed to make this point clearer.

Spatial learning assessed through the Morris water maze was not affected by adolescent exposure to natural or synthetic cannabinoids in both male or female rats (Cha et al., 2006, 2007; Higuera-Matas et al., 2009). However, spatial working memory in the radial maze was impaired in both genders (Rubino et al., 2009a, 2009b).

As a general conclusion, the cognitive deficit appears to be task-specific, thus suggesting impairments in specific components of learning and memory rather than widespread effects: in particular, it appears that whenever the working memory component is involved in the test performance, we observe a deficit. With regard to the possible cellular mechanism underlying the cognitive impairment induced by adolescent exposure to cannabinoids, very few works addressed this issue. Quinn et al. (2008) reported that the impairment they observed in object recognition memory in adult male rats after adolescent exposure can be linked to changes in hippocampal proteins. Specifically they found alterations in proteins involved in regulating oxidative stress/mitochondrial functioning and cytoarchitecture. In our work, we found that both male and female rats showed spatial working memory deficits; however, intriguingly, the brain regions where the likely molecular underpinnings have been observed were different: the hippocampus for males and the prefrontal cortex for females. In fact in adult female rats exposed to THC in adolescence the memory impairment was correlated to a significant decrease in synaptophysin and PSD95 proteins in the prefrontal cortex and, as demonstrated by proteomic analysis of the synaptosomes from the same brain area, to the presence of less active synapses characterized by reduced ability in maintaining normal synaptic efficiency (Rubino et al., 2009a). In adult male rats pre-exposed to THC during adolescence the spatial working memory deficit was instead related to a significant decrease in the astroglial marker GFAP as well as in pre- and post-synaptic protein expression (VAMP2, PSD95) and NMDA receptor levels in the hippocampus. These animals also exhibited lower total dendritic length and number as well as reduced spine density in the hippocampal dentate gyrus (Rubino et al., 2009b), suggesting that THC pre-treated rats may establish fewer synaptic contacts and/or less efficient synaptic connections throughout the hippocampus. These data join others already present in the literature providing substantial evidence that for some tasks males and females may use differing neural paths to reach the same behavioural end point (for a review see Andreano and Cahill, 2009).

Emotionality. Adolescent exposure to cannabinoids also appears to alter emotional reactivity in adulthood. Contrasting data were reported regarding anxiety when the elevated plus maze test was used. In fact while some authors reported no changes in the anxiety profile of animals pre-treated with cannabinoid compounds during adolescence (Bambico et al., 2010; Higuera-Matas et al., 2009; Mateos et al., 2010; Rubino et al., 2008), others described an anxiolytic effect (Biscaia et al., 2003; Wegener and Koch, 2009). On the contrary, when the social interaction test was performed, all the authors found an impairment in social behaviours after adolescent exposure to cannabinoids (Leweke and Schneider, 2010; O'Shea et al., 2004, 2006; Realini et al., 2010). Since a reduction in social interaction has been considered an anxiogenic behaviour in rodent (File and Hyde, 1978), it appears that depending on the test used, cannabinoids may differently affect anxiety-like behaviour in rodents, showing no changes in the anxiety profile, being anxiolytic or even anxiogenic.

However, since alterations in social activity in the social interaction test do not correlate well with performance in other animal tests of anxiety, such as the elevated plus maze and open field (Berton et al., 1997), it may be suggested that the reduction in social behaviour observed in the social interaction test might reflect other, distinct psychological domains that could be relevant to other psychopathological disorders such as depression (Pardon et al., 2002; Tõnissaar et al., 2008). In line with social behaviour, when another aspect of anxiety, the hyponeophagia, was considered, cannabinoid exposure during adolescence did evoke an anxiety-like suppression of appetitive drive in a novel environment (Bambico et al., 2010). This complex picture likely suggests that the effect of adolescent exposure to cannabinoids on anxiety behaviour is different depending on the specific component of anxiety considered in the various tests and this could be due to the different neuroanatomical and molecular correlates involved.

In addition to reduced social behaviour, two other features of depression-like reactivity in animals are behavioural despair (measured in the forced swim test) and anhedonia (assessed as sucrose preference or palatable food consumption). Both symptoms were present after adolescent exposure to both synthetic or natural cannabinoids (Bambico et al., 2010; Realini et al., 2010; Rubino et al., 2008), suggesting the presence of a depressive phenotype in adult animals after adolescent exposure to cannabinoids.

The behavioural picture that characterizes the depressive phenotype was paralleled by the presence of biochemical parameters linked to depression, such as decreased CREB activation in the prefrontal cortex and hippocampus, increased CREB activation and dynorphin levels in the nucleus accumbens, decreased neurogenesis in the dentate gyrus of the hippocampus, likely triggered by a long-lasting impairment of the CB1 receptor signalling in the VTA, amygdala and nucleus accumbens (Rubino et al., 2008; Realini et al., 2010). Moreover, Bambico et al. (2010) suggested that depression-like behaviours in adulthood may be instigated by serotonergic hypoactivity and noradrenergic hyperactivity, as demonstrated by electrophysiological recordings revealing attenuated activity of the serotonergic dorsal raphe neurons, and hyperactivity of noradrenergic neurons in the locus coeruleus of adult animals pre-exposed to cannabinoids during adolescence.

As already seen for cognitive impairments, the depressive phenotype did not develop when the chronic cannabinoid administration was performed in older animals (Bambico et al., 2010; Realini et al., 2010), thus suggesting the existence of an age-dependent vulnerability of the brain to enduring adverse effects of cannabinoids.

Psychosis. Experimental studies dealing with long-lasting effects of adolescent cannabinoid exposure on psychosis-related behaviours in adult rodents are very scarce. Obviously, it is impossible to model schizophrenia in its entirety since schizophrenia represents a complex disorder with a very heterogeneous presentation of a variety of symptoms that can affect all areas of psychological functioning. Patients typically experience to a variable extent a combination of symptoms, often divided into positive (e.g. hallucinations, delusions, thought disorganizations), negative (e.g. loss of motivation, affective blunting, alogia, social withdrawal, reduced hedonic capacity) and cognitive ones (e.g. deficits in attention, memory and executive functions).

Early attempts to develop models that mimic the entirety of the diagnostic syndromes in schizophrenia have evolved into more appropriate efforts to model and study specific symptoms. Current animal models are designed to test specific causative or mechanistic hypotheses regarding schizophrenia. Pharmacological models generally have some predictive or construct validity and are based on increasing activity of neurotransmitters considered to be involved in schizophrenia, such as dopamine and glutamate. Since life events have been proposed to be a cause of schizophrenia, neurodevelopmental models have also been used to reproduce some core symptoms of the disease. Finally, epidemiological studies provide considerable evidence for the genetic contribution to the aetiology of schizophrenia. However, numerous linkage and association studies with candidate genes for schizophrenia have excluded the possibility that schizophrenia is related to a single gene mutation: transmission is now thought more likely to involve multiple susceptible loci (for reviews see Marcotte et al., 2001; Nestler and Hyman, 2010; Rapoport et al., 2005).

Since long-lasting effects of adolescent exposure to cannabinoids on the cognitive dimension and emotional reactivity have already been discussed above, we will focus our attention on the positive symptoms. While the positive symptoms of schizophrenia, such as auditory hallucinations and delusions, are uniquely human, the literature on animal models of this symptom has focused on two main categories of behaviour: locomotor hyperactivity and disruptions of prepulse inhibition (PPI). PPI is considered a measure of 'sensorimotor gating' and is reduced in schizophrenia patients (Braff et al., 2001; Perry et al., 2001). The cross-species nature of startle and PPI facilitates the use of animal models of gating deficits, therefore measures of sensorimotor gating are among the most widely studied physiological markers used in experimental studies of schizophrenia (Geyer, 2008). Only two papers have addressed the effect of chronic pubertal cannabinoid exposure on sensorimotor gating at adulthood and report a long-lasting PPI deficit (Schneider and Koch, 2003; Wegener and Koch, 2009).

The concept of testing for locomotor hyperactivity in animal models as a symptom of psychosis is based upon the premises that enhanced dopaminergic activity in rodents leads to enhanced motor activity (Geyer, 2008) and changes in dopaminergic activity, and although they are unlikely to be the primary cause of positive symptoms of schizophrenia, may be involved in varying degrees of symptomatology (Van den Buuse, 2010). Therefore locomotor hyperactivity, either at baseline or after treatment with psychoactive drugs, such as amphetamine or phencyclidine, has become widely used as a behavioural tool to investigate psychosis-like behaviours. As for PPI, few papers extensively investigated basal locomotor activity in adult animals pre-exposed to cannabinoids during adolescence and they reported confounding results: some of them showed no significant alterations in the open field recordings (Biscaia et al., 2003; Rubino et al., 2008), while others stated the presence of locomotor hyperactivity (Wegener and Koch, 2009). This last paper also investigated Fos immunoreactivity in selected brain regions of pubertal cannabinoid and vehicle treated rats after acute dopaminergic drugs such as apomorphine and haloperidol and found altered brain responsiveness depending on the rat's drug history. So far, no published paper dealt with the consequence of cannabinoid adolescent exposure on psychoactive drug-induced locomotor activation.

Regardless of the paucity of papers, the available data appear to support the hypothesis that adolescent exposure to cannabinoids might represent a risk factor for developing psychotic-like symptoms at adulthood. This conclusion seems to be more credible when the two-hit hypothesis of schizophrenia is taken into account. In this hypothesis, genetic or environmental factors disrupt early central nervous system development, producing long-term vulnerability to a 'second hit' that then may lead to the onset of schizophrenic symptoms. Accordingly, a combination of neonatal prefrontocortical lesion with chronic pubertal cannabinoid administration has been shown to lead to greater impairments in various forms of social behaviour (Schneider et al., 2005), as well as object recognition memory (Schneider and Koch, 2007), thus suggesting that pubertal cannabinoid administration in vulnerable individuals might act as a risk factor for inducing enhanced behavioural disturbances. Another recent study in line with the two-hit hypothesis demonstrated that adolescent exposure to THC worsened the cognitive impairment in the object recognition test induced by chronic intermittent administration of phencyclidine (PCP), an animal model of schizophrenia-like cognitive deficit (Vigano et al., 2009). At biochemical level this was supported by a more pronounced desensitization of CB1 receptors in the prefrontal cortex of THC + PCP treated rats and a more severe reduction of anandamide in this same cerebral area (Vigano et al., 2009). However, when a genetic factor was considered, as in COMT ko mice or neuregulin 1 heterozygous mice, increased or decreased sensitivity to THC has been described, often in contrast with the human data (Boucher et al., 2007; Long et al., 2010; O'Tuathaigh et al., 2010).

Gateway hypothesis. Finally, regarding the hypothesis that adolescent exposure to cannabinoids might induce subsequent use of other addictive drugs, the so-called 'gateway hypothesis', no conclusive findings are available. Contrasting results have been found for psychostimulant drugs. Increased acquisition of cocaine self-administration was reported restricted to adult female rats pretreated with cannabinoids in adolescence (Higuera-Matas et al., 2008), and this might be due to up-regulated dopamine transporter (DAT) in the caudate putamen (Higuera-Matas et al., 2010). In fact, male rats

that did not present alteration in cocaine self-administration neither showed changes in DAT levels (Higuera-Matas et al., 2008, 2010). In contrast, adolescent exposure to synthetic or natural cannabinoids did not alter dopaminergic or behavioural responses to amphetamine (Ellgren et al., 2004). However, more recently, Rodriguez-Arias et al. (2010) reported increased reinforcing effects of MDMA in mice exposed to cannabinoids during adolescence. In line with this, Pistis et al. (2004) demonstrated that an enduring form of neuronal adaptation occurs in DA neurons after subchronic cannabinoid treatment during adolescence, affecting subsequent responses to drugs of abuse. More consistent data have been reported on adolescent cannabinoid exposure and opiate dependence: male rats presented significant increases in the acquisition of both morphine and heroin self-administration, and this might be due to cannabinoid-induced alterations in limbic mu opioid receptor system (Biscaia et al., 2008; Ellgren et al., 2008). However, female rats appear to be unaffected by the same treatment (Biscaia et al., 2008). In this same work the authors demonstrated that the effect in male rats is only evident when the demands required by the schedule of reinforcements are low. More recently Morel et al. (2009) confirmed the facilitating role of adolescent THC in adult opioid consumption: they demonstrated that chronic dronabinol in adolescence increased the sensitivity to morphine conditioning in the place preference paradigm. Interestingly, adolescent dronabinol had opposite effects when injected in maternally deprived rats: in these animals it prevented the occurrence of morphine place preference (Morel et al., 2009). This last finding might point toward the self-medication use of cannabis in subgroups of individuals subjected to an early adverse environment.

Human studies

Marijuana continues to be the most popular illicit drug among young people and cannabis use among the population has been accompanied in the last years by a decrease in the age of first use (Monshouwer et al., 2005).

Clearly, most of the individuals who use cannabis do not report an adverse reaction to it, but a minority of heavy users will develop problems. A growing body of evidence suggest that the heavy use of cannabis, mainly during adolescence, may have adverse psychosocial consequences such as increased risks of cognitive abnormalities, psychotic illness, depression and increased risks of other illicit substance use (for a review see Di Forti et al., 2007).

Cognition. Cannabis use during adulthood has known effects on cognition. Acute cannabis intoxication has been associated with transient and reversible decrements in attention, memory, executive functions and time estimation (for a review see Solowij and Pesa, 2010).

However, adult research may not generalize to adolescents. Thus far, the current literature suggests that adolescents are more vulnerable to the effects of cannabis use. Within several hours of intake, regular marijuana use in human adolescents or young adults negatively affects learning, memory, attention, and spatial working memory (Fried et al., 2005; Harvey et al., 2007; Medina et al., 2007a). As previously reported for psychosis and depression, the effects of cannabis on cognition appear to be associated with heavier and more recent use (Fried et al., 2005). Cannabis use before the age of 16 years worsened the performance in a task requiring focused attention (Ehrenreich et al., 1999). Similarly, another study demonstrated that the initiation of cannabis before, but not after, the age of 17 years was associated with lower verbal IQ scores (Pope et al., 2003). On the other hand, studies that have not made a distinction between the initiation of cannabis use in adolescence or in adult life have failed to show any persistent cognitive impairment (Pope et al., 2001).

The cognitive impairment during acute cannabis intoxication has been largely demonstrated but the extent to which such deficits persist throughout the abstinence is still debated (for a review see Solowij et al., 2002).

While the adult literature suggests that marijuana users may improve to the same level as controls with sustained abstinence (Pope et al., 2002), the adolescence research to date suggests continued impairment after a month of non-use (Medina et al., 2007b). In a recent study, Hanson et al. (2010) examined cognitive functions among adolescent cannabis users over three weeks of abstinence. Cannabis users performed worse than controls on measures of verbal learning and verbal working memory after approximately three days of abstinence but they performed similarly to controls after two and three weeks without substance use. However, adolescent cannabis users showed attention deficits that persisted throughout the three weeks of abstinence.

The precise mechanism by which cannabis impairs cognition remains unknown although structural abnormalities such as reduced hippocampal volumes have been related to exposure to cannabis in long-term heavy cannabis users (Yücel et al., 2008) and cannabis use may interfere with cortical metabolism in regions implicated in the execution of memory tasks (Eldreth et al., 2004). Recent studies demonstrated a close association between chronic adolescent cannabis exposure and anatomical and functional consequences in the brain such as hippocampal asymmetry (Medina et al., 2007a), aberrant activation patterns in different brain regions (Schweinsburg et al., 2008a) and altered white matter microstructure (Bava et al., 2009). Interestingly, in some functional imaging studies, adolescent cannabis users demonstrated aberrant patterns of activation despite similar performance to non-users (Padula et al., 2007; Schweinsburg et al., 2008b) and, more recently, Medina et al. (2010) demonstrated that adolescent cannabis users had significantly larger inferior posterior vermis volume than controls and this was associated with poorer executive functioning. This frontocerebellar dysfunction was still evident following one month of abstinence, suggesting that even once cognitive deficits are no longer detectable, brain function may remain affected.

Depression. Despite the numerous findings concerning the impact of adolescent cannabis use on cognition and psychotic disorders, associations with non-psychotic disorders have received less attention. Evidence for a link between rising rates of cannabis use and depression among young

people in many countries has grown (Degenhardt et al., 2003).

A study conducted between 1992 and 1998 in the Australian state of Victoria suggested the existence of a relationship between chronic daily cannabis use and depression in both adolescents and adults and this association was more common in young females than in males (Patton et al., 2002). In particular, cannabis use in girls under the age of 15 years significantly raised the risk of subsequent suicidal ideation or attempt in the following 15 years (Wilcox and Anthony, 2004). Research in a representative sample of Australians aged 13–17 years found that those who had used cannabis were three times more likely than those who had never used cannabis to meet criteria for depression (Rey et al., 2002). Fergusson et al. (2002) found that adolescents who had used cannabis 10 or more times by the age of 15–16 years were more likely to also meet criteria for a mood disorder at that age. At age 20–21 years, 30% of those who were using cannabis at least weekly met criteria for depression (Fergusson et al., 2003). Van Laar et al. (2007) in another longitudinal study reported that cannabis use increased the risk for depressive disorders (unipolar and bipolar) without affecting the occurrence of anxiety disorders. Moreover the elevated risk was observed for frequent abusers only (with weekly or daily use). Accordingly, Hayatbakhsh et al. (2007) demonstrated that those who had an onset of cannabis use before age 15 and used it frequently were more likely to report symptoms of anxiety and depression in early adulthood. This observation was still significant when confounding factors were taken into account. More recently, Lee et al. (2008) found a strong association between heavy cannabis use and moderate–severe depressive symptoms in an Indigenous Arnhem Land community sample, with rates of depression higher in females than in males. From these longitudinal studies it appears that early onset and regular cannabis use represents an increased risk of later depression.

On the contrary, de Graaf et al. (2010) evaluating the causal association that links early-age onset (age < 17 years) cannabis use with later onset risk of depression on subjects from 17 countries, found that the overall association was modest and showed no sex difference. This apparent discrepancy might be due to the lack of differentiation between heavy and occasional cannabis use in this study. In fact, it is important to consider the level of cannabis use. It has been most typical to examine the pattern of comorbidity between the heavy cannabis use and other mental health problems, most probably because it is at higher levels of use that we might expect to see associations with other problems.

Psychosis. A large intake of cannabis during adolescence triggers acute psychotic episodes and may worsen outcomes in established psychosis. Different longitudinal studies have confirmed this and demonstrated also that the risk was greater in subjects with a positive family history for psychosis (D'Souza et al., 2009; Henquet et al., 2005a; Le Bec et al., 2009). In a study involving young German individuals aged 14–24 years, it has been demonstrated that cannabis use at baseline increased the incidence of psychotic symptoms at a 4-year follow-up (Henquet et al., 2005b). These results were confirmed also by Ferdinand et al. (2005) in a 14-year follow-up study of 4–16 year olds from the Dutch population, indicating that cannabis use predicted future psychotic symptoms in individuals who did not have such symptoms before they began using cannabis. In the same line McGrath et al. (2010), using a sibling pair analysis nested within a prospective birth cohort, demonstrated that early cannabis use is associated with psychosis-related outcomes in young adults. The use of sibling pair analysis provides the opportunity to control for a range of unmeasured potential confounding variables, thus making the results more compelling. Interestingly, the inverse relationship has also been demonstrated: that is, the presence of psychotic symptoms in those who had never used cannabis predicted future cannabis use (for a review see Dekker et al., 2009).

This association between cannabis consumption and subsequent psychotic illness appears to be highly dependent on the age when drug use begins. For example, in a New Zealand study initiation by the age of 18 years doubled, whereas initiation by 15 years quadrupled, the odds of subsequent psychotic disorders at follow-up at the age of 26 years (Arseneault et al., 2002). Moreover, cannabis use at a younger age relates to an earlier onset of psychotic symptoms (Dragt et al., 2010; Sugranyes et al., 2009). The reasons underlying the greater effect observed in those who begin cannabis use early in adolescence is still unclear. However, as previously mentioned in this review significant changes in the brain occur during adolescence and drugs of abuse affect brain circuits involved in reward, decision making, attention, learning and memory, and behavioral control, all of which are still maturing into early adulthood, and cannabis use in this period may lead to alterations in neurobiology that increase psychosis risk.

It has long been recognized that cannabis consumption acutely causes a transient psychotic episode in some healthy individuals and cannabinoids can exacerbate symptoms in individuals with an established psychotic disorder; moreover cannabinoids can exacerbate, trigger relapse, and have negative consequences on the course of the illness symptoms (D'Souza et al., 2009). Of course, not all cannabis users develop psychosis, indicating that cannabis use interacts with other known and unknown factors, such as genetic vulnerability (i.e. the COMT Val108Met polymorphism) and other environmental factors, finally leading to psychosis onset (Caspi et al., 2005; Dominguez et al., 2010; Fergusson et al., 2006a; Henquet et al., 2008, 2009; Semple et al., 2005). Further studies are needed to characterize the factors underlying individual vulnerability to cannabis-induced psychosis. Moreover, the role of the endocannabinoid system in neural development and in the modulation of neurotransmitter systems during adolescence should be better investigated to understand the mechanisms contributing to the enhanced vulnerability to psychosis observed in adolescent cannabis users.

Gateway hypothesis. Epidemiological data indicate that chronic heavy cannabis use might be associated with an increased risk of using, abusing or becoming dependent on other illicit drugs. In line with this, cannabis use among adolescents may act as a 'gateway drug', facilitating the later use

during adulthood of other, non-marijuana, drugs (Fergusson et al., 2006b). However, it is difficult to demonstrate the causal link between cannabis consumption and later heavier drug use since other variables, such as the environment or genetic factors, may influence adolescents' tendency of using both marijuana and hard drugs. In a study by Wagner and Anthony (2002) the relationship between cannabis consumption and later hard drug abuse does not involve a causal connection but mostly depends upon the contextual variables. Another study demonstrated that, compared with non-users, adolescent cannabis users have a major probability of later use of other illicit drugs and this relationship is mediated primarily by common shared environmental factors (Lessem et al., 2006). Lynskey et al. (2003), using data from twin pairs to control both household and genetic influences, found that both monozygotic and dizygotic individual twins who had used cannabis before age 17 were more likely than their non-using co-twins to use hard drugs thereafter. In contrast, Cleveland and Wiebe (2008) demonstrated that earlier cannabis consumption among monozygotic twin pairs did not predict later hard drug use differences, suggesting that the 'gateway effect' might be influenced by genetic factors. More recently, a study by Degenhardt et al. (2010), using epidemiological survey carried out in 17 countries worldwide, provided evidence that although a clear dose–response relationship exists between cannabis use and later drug abuse, whereby regular users were most likely to have adverse outcomes during young adulthood, occasional adolescence-onset cannabis use that persists into young adulthood is clearly related to increased risks of subsequent consumption of other illicit drugs (Degenhardt et al., 2010). Disagreement remains about the reasons why such associations persist, but researchers have proposed biochemical explanations that suggest that early-onset drug use might affect the maturing adolescent brain, increasing the adolescents' propensity to use other drugs (Hall and Lynskey, 2005). For example, cannabis, by altering the opioid system in the brain, may lead to a change in hedonic processing that promotes subsequent opioid use (Ellgren et al., 2007).

Conclusions

Although drug abuse and addiction can happen at any time during a person's life, drug use typically starts in adolescence, a period when the first signs of mental illness commonly appear. It is therefore not surprising that comorbid disorders can already be seen among youth. Thus, understanding the long-term impact of early drug exposure is a critical area of comorbidity research. General population studies have been consistent in showing that the younger people are when they first use drugs, the more likely they are to progress from experimental usage to dependence or abuse. In general, early cannabis use during adolescence seems to be closely related to an increased probability of later psychiatric problems and there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychiatric illness later in life. The neurobiological substrate of the adolescent vulnerability is still largely unknown and experimental studies need to elucidate the cellular and molecular mechanism underlying these effects. However, the few data available seem to suggest that heavy adolescent exposure to cannabinoids is able to modify neuronal connectivity in specific brain areas that is still present long after the end of the treatment. This peculiar feature is not present when the exposure is performed on adult animals.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

References

Andreano JM and Cahill L (2009) Sex influences on the neurobiology of learning and memory. *Learn Mem* 16: 248–266.

Arseneault L, Cannon M, Poulton R, Murray R, Caspi A and Moffitt TE (2002) Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 325: 1212–1213.

Aso E, Renoir T, Mengod G, Ledent C, Hamon M, Maldonado R, et al. (2009) Lack of CB1 receptor activity impairs serotonergic negative feedback. *J Neurochem* 109: 935–944.

Bambico FR, Nguyen NT, Katz N and Gobbi G (2010) Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission. *Neurobiol Dis* 37: 641–655.

Barkus E and Murray RM (2010) Substance use in adolescence and psychosis: clarifying the relationship. *Annu Rev Clin Psychol* 6: 365–389.

Bava S, Jacobus J, Mahmood O, Yang TT and Tapert SF (2009) Neurocognitive correlates of white matter quality in adolescent substance users. *Brain Cogn* 72: 347–354.

Berton O, Ramos A, Chaouloff F and Mormde P (1997) Behavioral reactivity to social and nonsocial stimulations: a multivariate analysis of six inbred rat strains. *Behav Genet* 27: 155–166.

Biscaia M, Marín S, Fernández B, Marco EM, Rubio M, Guaza C, et al. (2003) Chronic treatment with CP 55,940 during the periadolescent period differentially affects the behavioural responses of male and female rats in adulthood. *Psychopharmacology (Berl)* 170: 301–308.

Biscaia M, Fernández B, Higuera-Matas A, Miguéns M, Viveros MP, García-Lecumberri C, et al. (2008) Sex-dependent effects of periadolescent exposure to the cannabinoid agonist CP-55,940 on morphine self-administration behaviour and the endogenous opioid system. *Neuropharmacology* 54: 863–873.

Bossong MG and Niesink RJM (2010) Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Prog Neurobiol* 92: 370–385.

Boucher AA, Arnold JC, Duffy L, Schofield PR, Micheau J and Karl T (2007) Heterozygous neuregulin 1 mice are more sensitive to the behavioural effects of Delta9-tetrahydrocannabinol. *Psychopharmacology (Berl)* 192: 325–336.

Braff DL, Geyer MA and Swerdlow NR (2001) Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology (Berl)* 156: 234–258.

Brusco A, Tagliaferro PA, Saez T and Onaivi ES (2008) Ultrastructural localization of neuronal brain CB2 cannabinoid receptors. *Ann NY Acad Sci* 1139: 450–457.

Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, et al. (2005) Moderation of the effect of adolescent onset cannabis use on adult psychosis by a functional

polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene x environment interaction. *Biol Psychiatry* 57: 1117–1127.

Cha YM, White AM, Kuhn CM, Wilson WA and Swartzwelder HS (2006) Differential effects of delta9-THC on learning in adolescent and adult rats. *Pharmacol Biochem Behav* 83: 448–455.

Cha YM, Jones KH, Kuhn CM, Wilson WA and Swartzwelder HS (2007) Sex differences in the effects of delta9-tetrahydrocannabinol on spatial learning in adolescent and adult rats. *Behav Pharmacol* 18: 563–569.

Cleveland HH and Wiebe RP (2008) Understanding the association between adolescent marijuana use and later serious drug use: gateway effect or developmental trajectory? *Dev Psychopathol* 20: 615–632.

Cohen-Cory S (2002) The developing synapse: construction and modulation of synaptic structures and circuits. *Science* 298: 770–776.

Degenhardt L, Hall W and Lynskey M (2003) Exploring the association between cannabis use and depression. *Addiction* 98: 1493–1504.

Degenhardt L, Dierker L, Chiu WT, Medina-Mora ME, Neumark Y, Sampson N, et al. (2010) Evaluating the drug use 'gateway' theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. *Drug Alcohol Depend* 108: 84–97.

de Graaf R, Radovanovic M, van Laar M, Fairman B, Degenhardt L, Aguilar-Gaxiola S, et al. (2010) Early cannabis use and estimated risk of later onset of depression spells: Epidemiologic evidence from the population-based World Health Organization World Mental Health Survey Initiative. *Am J Epidemiol* 172: 149–159.

Dekker N, Linszen DH and De Haan L (2009) Reasons for cannabis use and effects of cannabis use as reported by patients with psychotic disorders. *Psychopathology* 42: 350–360.

De Petrocellis L and Di Marzo V (2009) An introduction to the endocannabinoid system: from the early to the latest concepts. *Best Pract Res Clin Endocrinol Metab* 23: 1–15.

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258: 1946–1949.

Di Forti M, Morrison PD, Butt A and Murray RM (2007) Cannabis use and psychiatric and cognitive disorders: the chicken or the egg? *Curr Opin Psychiatry* 20: 228–234.

Di Marzo V and Petrosino S (2007) Endocannabinoids and the regulation of their levels in health and disease. *Curr Opin Lipidol* 18: 129–140.

Dominguez MD, Saka MC, Lieb R, Wittchen HU and van Os J (2010) Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. *Am J Psychiatry* 167: 1075–1082.

Dragt S, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, de Haan L, et al. (2010) Age of onset of cannabis use is associated with age of onset of high-risk symptoms for psychosis. *Can J Psychiatry* 55: 165–171.

D'Souza DC, Sewell RA and Ranganathan M (2009) Cannabis and psychosis/schizophrenia: human studies. *Eur Arch Psychiatry Clin Neurosci* 259: 413–431.

Eggan SM, Mizoguchi Y, Stoyak SR and Lewis DA (2010) Development of cannabinoid 1 receptor protein and messenger RNA in monkey dorsolateral prefrontal cortex. *Cereb Cortex* 20: 1164–1174.

Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, et al. (1999) Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology (Berl)* 142: 295–301.

Eldreth DA, Matochik JA, Cadet JL and Bolla KI (2004) Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *Neuroimage* 23: 914–920.

Ellgren M, Hurd YL and Franck J (2004) Amphetamine effects on dopamine levels and behavior following cannabinoid exposure during adolescence. *Eur J Pharmacol* 497: 205–213.

Ellgren M, Spano SM and Hurd YL (2007) Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. *Neuropsychopharmacology* 32: 607–615.

Ellgren M, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, et al. (2008) Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *Eur Neuropsychopharmacol* 18: 826–834.

Ferdinand RF, van der Ende J, Bongers I, Selten JP, Huizink A and Verhulst FC (2005) Cannabis–psychosis pathway independent of other types of psychopathology. *Schizophr Res* 79: 289–295.

Fergusson DM, Horwood LJ and Swain-Campbell N (2002) Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* 97: 1123–1135.

Fergusson DM, Horwood LJ, Lynskey MT and Madden PA (2003) Early reactions to cannabis predict later dependence. *Arch Gen Psychiatry* 60: 1033–1039.

Fergusson DM, Poulton R, Smith PF and Boden JM (2006a) Cannabis and psychosis. *BMJ* 332: 172–175.

Fergusson DM, Boden JM and Horwood LJ (2006b) Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction* 101: 556–566.

File SE and Hyde JR (1978) Can social interaction be used to measure anxiety? *Br J Pharmacol* 62: 19–24.

Freund TF, Katona I and Piomelli D (2003) Role of endogenous cannabinoids in synaptic signaling. *Physiol Rev* 83: 1017–1066.

Fried PA, Watkinson B and Gray R (2005) Neurocognitive consequences of marihuana – a comparison with predrug performance. *Neurotoxicol Teratol* 27: 231–239.

Galve-Roperh I, Palazuelos J, Aguado T and Guzmán M (2009) The endocannabinoid system and the regulation of neural development: potential implications in psychiatric disorders. *Eur Arch Psychiatry Clin Neurosci* 259: 371–382.

Geyer MA (2008) Developing translational animal models for symptoms of schizophrenia or bipolar mania. *Neurotox Res* 14: 71–78.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. (1999) Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2: 861–863.

Glass M and Felder CC (1997) Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. *J Neurosci* 17: 5327–5333.

Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, et al. (2006) Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res* 1071: 10–23.

Hall W and Degenhardt L (2007) Prevalence and correlates of cannabis use in developed and developing countries. *Curr Opin Psychiatry* 20: 393–397.

Hall WD and Lynskey M (2005) Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. *Drug Alcohol Rev* 24: 39–48.

Hanson KL, Winward JL, Schweinsburg AD, Medina KL, Brown SA and Tapert SF (2010) Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addict Behav* 35: 970–976.

Harvey MA, Sellman JD, Porter RJ and Frampton CM (2007) The relationship between non-acute adolescent cannabis use and cognition. *Drug Alcohol Rev* 26: 309–319.

Hayatbakhsh MR, Najman JM, Jamrozik K, Mamun AA, Alati R and Bor W (2007) Cannabis and anxiety and depression in young adults: a large prospective study. *J Am Acad Child Adolesc Psychiatry* 46: 408–417.

Henquet C, Murray R, Linszen D and van Os J (2005a) The environment and schizophrenia: the role of cannabis use. *Schizophr Bull* 31: 608–612.

Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, et al. (2005b) Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* 330: 11.

Henquet C, Di Forti M, Morrison P, Kuepper R and Murray RM (2008) Gene-environment interplay between cannabis and psychosis. *Schizophr Bull* 34: 1111–1121.

Henquet C, Rosa A, Delespaul P, Papiol S, Fananás L, van Os J, et al. (2009) COMT ValMet moderation of cannabis-induced psychosis: a momentary assessment study of 'switching on' hallucinations in the flow of daily life. *Acta Psychiatr Scand* 119: 156–160.

Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR and Rice KC (1991) Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci* 11: 563–583.

Higuera-Matas A, Soto-Montenegro ML, del Olmo N, Miguéns M, Torres I, Vaquero JJ, et al. (2008) Augmented acquisition of cocaine self-administration and altered brain glucose metabolism in adult female but not male rats exposed to a cannabinoid agonist during adolescence. *Neuropsychopharmacology* 33: 806–813.

Higuera-Matas A, Botreau F, Miguéns M, Del Olmo N, Borcel E, Pérez-Alvarez L, et al. (2009) Chronic periadolescent cannabinoid treatment enhances adult hippocampal PSA-NCAM expression in male Wistar rats but only has marginal effects on anxiety, learning and memory. *Pharmacol Biochem Behav* 93: 482–490.

Higuera-Matas A, Botreau F, Del Olmo N, Miguéns M, Olías O, Montoya GL, et al. (2010) Periadolescent exposure to cannabinoids alters the striatal and hippocampal dopaminergic system in the adult rat brain. *Eur Neuropsychopharmacol* 20: 895–906.

Howlett AC (2002) The cannabinoid receptors. *Prostaglandins Other Lipid Mediat* 68–69: 619–631.

Katz LC and Shatz CJ (1996) Synaptic activity and the construction of cortical circuits. *Science* 274: 1133–1138.

Lane DA, Chan J and Lupica CR, The cannabinoid receptors Pickel VM (2010) Cannabinoid-1 receptor gene deletion has a compartment-specific affect on the dendritic and axonal availability of μ-opioid receptors and on dopamine axons in the mouse nucleus accumbens. *Synapse* 64: 886–897.

Le Bec PY, Fatséas M, Denis C, Lavie E and Auriacombe M (2009) Cannabis and psychosis: search of a causal link through a critical and systematic review. *Encephale* 35: 377–385.

Lee KS, Clough AR, Jaragba MJ, Conigrave KM and Patton GC (2008) Heavy cannabis use and depressive symptoms in three Aboriginal communities in Arnhem Land, Northern Territory. *Med J Aust* 188: 605–608.

Lessem JM, Hopfer CJ, Haberstick BC, Timberlake D, Ehringer MA, Smolen A, et al. (2006) Relationship between adolescent marijuana use and young adult illicit drug use. *Behav Genet* 36: 498–506.

Leweke FM and Schneider M (2010) Chronic pubertal cannabinoid treatment as a behavioural model for aspects of schizophrenia: effects of the atypical antipsychotic quetiapine. *Int J Neuropsychopharmacol* 3: 1–9.

Long LE, Chesworth R, Arnold JC and Karl T (2010) A follow-up study: acute behavioural effects of Delta(9)-THC in female heterozygous neuregulin 1 transmembrane domain mutant mice. *Psychopharmacology (Berl)* 211: 277–289.

Luna B (2009) Developmental changes in cognitive control through adolescence. *Adv Child Dev Behav* 37: 233–278.

Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PA, Nelson EC, et al. (2003) Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA* 289: 427–433.

Marcotte ER, Pearson DM and Srivastava LK (2001) Animal models of schizophrenia: a critical review. *J Psychiatry Neurosci* 26: 395–410.

Mateos B, Borcel E, Loriga R, Luesu W, Bini V, Llorente R, et al. (2010) Adolescent exposure to nicotine and/or the cannabinoid agonist CP 55,940 induces gender-dependent long-lasting memory impairments and changes in brain nicotinic and CB1 cannabinoid receptors. *J Psychopharmacol* 25: 1676–1690.

Matias I, Bisogno T and di Marzo V (2006) Endogenous cannabinoids in the brain and peripheral tissues: regulation of their levels and control of food intake. *Int J Obes (Lond)* 1: S7–S12.

Mato S, Del Olmo E and Pazos A (2003) Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. *Eur J Neurosci* 17: 1747–1754.

Matsuda LA, Lolait SJ, Brownstein MJ, Young AC and Bonner TI (1990) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346: 561–564.

McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, et al. (2010) Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Arch Gen Psychiatry* 67: 440–447.

McPartland JM, Glass M and Pertwee RG (2007) Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *Br J Pharmacol* 152: 583–593.

Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ and Tapert SF (2007a) Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol* 29: 141–152.

Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ and Tapert SF (2007b) Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc* 13: 807–820.

Medina KL, Nagel BJ and Tapert SF (2010) Abnormal cerebellar morphometry in abstinent adolescent marijuana users. *Psychiatry Res* 30: 152–159.

Monshouwer K, Smit F, de Graaf R, van Os J and Vollebergh W (2005) First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction* 100: 963–970.

Morel LJ, Giros B and Daugé V (2009) Adolescent exposure to chronic delta-9-tetrahydrocannabinol blocks opiate dependence in maternally deprived rats. *Neuropsychopharmacology* 34: 2469–2476.

Morgan CJ, Schafer G, Freeman TP and Curran HV (2010) Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *Br J Psychiatry* 197: 285–290.

Munro S, Thomas KL and Abu-Shaar M (1993) Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365: 61–65.

Nestler EJ and Hyman SE (2010) Animal models of neuropsychiatric disorders. *Nat Neurosci* 13: 1161–1169.

O'Shea M, Singh ME, McGregor IS and Mallet PE (2004) Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. *J Psychopharmacol* 18: 502–508.

O'Shea M, McGregor IS and Mallet PE (2006) Repeated cannabinoid exposure during perinatal, adolescent or early adult ages produces similar longlasting deficits in object recognition and reduced social interaction in rats. *J Psychopharmacol* 20: 611–621.

O'Sullivan SE (2007) Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol* 152: 576–582.

O'Tuathaigh CM, Hryniewiecka M, Behan A, Tighe O, Coughlan C, Desbonnet L, et al. (2010) Chronic adolescent exposure to Δ-9-tetrahydrocannabinol in COMT mutant mice: impact on psychosis-related and other phenotypes. *Neuropsychopharmacology* 35: 2262–2273.

Padula CB, Schweinsburg AD and Tapert SF (2007) Spatial working memory performance and fMRI activation interaction in abstinent adolescent marijuana users. *Psychol Addict Behav* 21: 478–487.

Pardon MC, Gould GG, Garcia A, Phillips L, Cook MC, Miller SA, et al. (2002) Stress reactivity of the brain noradrenergic system in three rat strains differing in their neuroendocrine and behavioral responses to stress: implications for susceptibility to stress-related neuropsychiatric disorders. *Neuroscience* 115: 229–242.

Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M and Hall W (2002) Cannabis use and mental health in young people: cohort study. *BMJ* 325: 1195–1198.

Perry W, Minassian A, Feifel D and Braff DL (2001) Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. *Biol Psychiatry* 50: 418–424.

Piomelli D (2003) The molecular logic of endocannabinoid signalling. *Nat Rev Neurosci* 4: 873–884.

Pistis M, Perra S, Pillolla G, Melis M, Muntoni AL and Gessa GL (2004) Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. *Biol Psychiatry* 56: 86–94.

Pope HG Jr, Gruber AJ and Yurgelun-Todd D (2001) Residual neuropsychologic effects of cannabis. *Curr Psychiatry Rep* 3: 507–512.

Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA and Yurgelun-Todd D (2002) Cognitive measures in long-term cannabis users. *J Clin Pharmacol* 42: 41S–47S.

Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA and Yurgelun-Todd D (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? *and* 69: 303–310.

Quinn HR, Matsumoto I, Callaghan PD, Long LE, Arnold JC, Gunasekaran N, et al. (2008) Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology* 33: 1113–1126.

Rapoport JL, Addington AM, Frangou S and Psych MRC (2005) The neurodevelopmental model of schizophrenia. *Mol Psychiatry* 10: 434–449.

Realini N, Vigano D, Guidali C, Zamberletti E, Rubino T and Parolaro D (2010) Chronic URB597 treatment at adulthood reverted most depressive-like symptoms induced by adolescent exposure to THC in female rats. *Neuropharmacology* 60: 235–243.

Rey JM, Sawyer MG, Raphael B, Patton GC and Lynskey M (2002) Mental health of teenagers who use cannabis. Results of an Australian survey. *Br J Psychiatry* 180: 216–221.

Rodríguez-Arias M, Manzanedo C, Roger-Sánchez C, Do Couto BR, Aguilar MA and Miñarro J (2010) Effect of adolescent exposure to WIN 55212-2 on the acquisition and reinstatement of MDMA-induced conditioned place preference. *Prog Neuropsychopharmacol Biol Psychiatry* 34: 166–171.

Rodríguez de Fonseca F, Ramos JA, Bonnin A and Fernández-Ruiz JJ (1993) Presence of cannabinoid binding sites in the brain from early postnatal ages. *Neuroreport* 4: 135–138.

Ross RA (2003) Anandamide and vanilloid TRPV1 receptors. *Br J Pharmacol* 140: 790–801.

Rouzer CA and Marnett LJ (2008) Non-redundant functions of cyclooxygenases: oxygenation of endocannabinoids. *J Biol Chem* 283: 8065–8069.

Rubino T, Vigano D, Realini N, Guidali C, Braida D, Capurro V, et al. (2008) Chronic delta 9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates. *Neuropsychopharmacology* 33: 2760–2771.

Rubino T, Realini N, Braida D, Alberio T, Capurro V, Viganò D, et al. (2009a) The depressive phenotype induced in adult female rats by adolescent exposure to THC is associated with cognitive impairment and altered neuroplasticity in the prefrontal cortex. *Neurotox Res* 15: 291–302.

Rubino T, Realini N, Braida D, Guidi S, Capurro V, Viganò D, et al. (2009b) Changes in hippocampal morphology and neuroplasticity induced by adolescent THC treatment are associated with cognitive impairment in adulthood. *Hippocampus* 19: 763–772.

Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson NO, Leonova J, et al. (2007) The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 152: 1092–1101.

SAMHSA (2007) *Results from the 2006 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07-4293). Rockville, MD.

Schneider M and 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: 1760–1769.

Schneider M and Koch M (2007) The effect of chronic peripubertal cannabinoid treatment on deficient object recognition memory in rats after neonatal mPFC lesion. *Eur Neuropsychopharmacol* 17: 180–186.

Schneider M, Drews E and Koch M (2005) Behavioral effects in adult rats of chronic prepubertal treatment with the cannabinoid receptor agonist WIN 55,212-2. *Behav Pharmacol* 16: 447–454.

Schweinsburg AD, Brown SA and Tapert SF (2008a) The influence of marijuana use on neurocognitive functioning in adolescents. *Curr Drug Abuse Rev* 1: 99–111.

Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ and Tapert SF (2008b) Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Res* 163: 40–51.

Semple DM, McIntosh AM and Lawrie SM (2005) Cannabis as a risk factor for psychosis: systematic review. *J Psychopharmacol* 19: 187–194.

Solowij N and Pesa N (2010) Cognitive abnormalities and cannabis use. *Rev Bras Psiquiatr* 32: 31–40.

Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, et al.; Marijuana Treatment Project Research Group (2002) Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 287: 1123–1131.

Spear L (2000) Modeling adolescent development and alcohol use in animals. *Alcohol Res Health* 24: 115–123.

Steinberg L and Morris AS (2001) Adolescent development. *Annu Rev Psychol* 52: 83–110.

Stella N, Schweitzer P and Piomelli D (1997) A second endogenous cannabinoid that modulates long-term potentiation. *Nature* 388: 773–778.

Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. (1995) 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* 215: 89–97.

Sugranyes G, Flamarique I, Parellada E, Baeza I, Goti J, Fernandez-Egea E, et al. (2009) Cannabis use and age of diagnosis of schizophrenia. *Eur Psychiatry* 24: 282–286.

Tõnissaar M, Herm L, Eller M, Kõiv K, Rinken A and Harro J (2008) Rats with high or low sociability are differently affected by chronic variable stress. *Neuroscience* 152: 867–876.

UNODC (United Nations Office on Drug and Crime) (2007) *UNODC World Drug Report*. Retrieved from http://www.unodc.org/unodc/en/data-and-analysis/WDR-2007.html (accessed January 2011).

Uriguen L, García-Gutiérrez MS and Manzanares J (2011) Decreased GABAA and GABAB receptor functional activity in cannabinoid CB1 receptor knockout mice. *J Psychopharmacol* 25: 105–110.

Van den Buuse M (2010) Modeling the positive symptoms of schizophrenia in genetically modified mice: pharmacology and methodology aspects. *Schizophr Bull* 36: 246–270.

Van Laar M, van Dorsselaer S, Monshouwer K and de Graaf R (2007) Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction* 102: 1251–1260.

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* 310: 329–332.

Vigano D, Guidali C, Petrosino S, Realini N, Rubino T, Di Marzo V, et al. (2009) Involvement of the endocannabinoid system in phencyclidine-induced cognitive deficits modelling schizophrenia. *Int J Neuropsychopharmacol* 12: 599–614.

Wagner FA and Anthony JC (2002) Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *Am J Epidemiol* 15: 918–925.

Wegener N and Koch M (2009) Behavioural disturbances and altered Fos protein expression in adult rats after chronic pubertal cannabinoid treatment. *Brain Res* 1253: 81–91.

Wenger T, Gerendai I, Fezza F, González S, Bisogno T, Fernandez-Ruiz J, et al. (2002) The hypothalamic levels of the endocannabinoid, anandamide, peak immediately before the onset of puberty in female rats. *Life Sci* 70: 1407–1414.

Whitford TJ, Rennie CJ, Grieve SM, Clark CR, Gordon E and Williams LM (2007) Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology. *Hum Brain Mapp* 28: 228–237.

Wilcox HC and Anthony JC (2004) The development of suicide ideation and attempts: an epidemiologic study of first graders followed into young adulthood. *Drug Alcohol Depend* 7: S53–S67.

Yücel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, et al. (2008) Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 65: 694–701.