Susceptibility to Psychiatric Diseases After Cannabis Abuse in Adolescence: Animal Models

Tiziana Rubino and Daniela Parolaro

Abstract Epidemiological evidence suggests that adolescent exposure to delta-9-tetrahydrocanabinol, the psychoactive component of *Cannabis*, confers an increased risk for developing psychiatric disorders later in life. However, epidemiological studies have a correlative nature and are limited by ethical problems which can be circumvented by animal models.

After a preliminary section describing the dynamic changes that occur in the endocannabinoid system during adolescence, in the following sections, the more relevant animal data on the long-lasting consequences of adolescent exposure to cannabinoids is reported. Behavioral evidence in terms of impairment in cognition, vulnerability to mood disorders, schizophrenia, and subsequent drug abuse as well as the underlying neurobiological aspects are summarized.

The arising picture seems to support the hypothesis that adolescent exposure to cannabinoids might represent a risk factor for the development of psychiatric-like symptoms in adulthood since the external stimulation of the endocannabinoid system can profoundly alter its physiological role, thus triggering alterations in the maturational events occurring in the adolescent brain.

Quantifying the relative adverse and beneficial effects of cannabis and its constituent cannabinoids is becoming a priority particularly considering that several countries are legalizing its use. Although it is still a matter of debate, there is evidence suggesting that chronic adolescent marijuana exposure may be associated with a higher risk for neuropsychiatric diseases, including schizophrenia (Rubino and Parolaro 2015; Renard et al. 2014). During adolescence, the endocannabinoid system is highly active, driving the central nervous system maturation. Thus,

T. Rubino
Department of Biotechnology and Life Sciences, University of Insubria, via Manara 7, 21052 Busto Arsizio, VA, Italy

D. Parolaro (✉)
Department of Biotechnology and Life Sciences, University of Insubria, via Manara 7, 21052 Busto Arsizio, VA, Italy

Fondazione Zardi Gori, via Curtatone 25, 20100 Milano, Italy
e-mail: daniela.parolaro@uninsubria.it

M. Melis (ed.), *Endocannabinoids and Lipid Mediators in Brain Functions*,
DOI 10.1007/978-3-319-57371-7_9

adolescent exposure to exogenous cannabinoids might interfere with normal cortical maturation, causing neurobiological changes that impair brain function. This chapter will describe the behavioral and cellular evidence of enhanced susceptibility to neuropsychiatric disorders after cannabinoid abuse in adolescence obtained using validated animal models. Moreover, a preliminary description of the maturational processes occurring in the endocannabinoid system during adolescence will be provided.

1 The Endocannabinoid System in Adolescence

Several physical, neural, and behavioral changes occur simultaneously during adolescence. Indeed, the brain of adolescents is subjected to extensive synaptic and neurochemical remodeling in areas involved in emotions, learning, decision-making, and reward-motivated behaviors. These complex changes may make the human brain more vulnerable, and transient imbalances, primarily among developmental trajectories of corticolimbic structures, can leave an individual susceptible to mental illness. The endocannabinoid system (eCB) is a lipid signaling system consisting of specific receptors (cannabinoid CB1 and CB2 receptors), endogenous ligands (mainly anandamide and 2-arachidonoylglycerol), and a battery of enzymes responsible for the synthesis and degradation of these ligands. The eCB system plays a major role in neurodevelopmental processes which are particularly active during adolescence, and several studies have highlighted its active and dynamic nature during this age.

Rodriguez de Fonseca et al. (1993) showed that CB1 receptor (CB1R) binding in the rat brain is highest just prior to the onset of adolescence (postnatal day (PND) 25–29), followed by a general linear reduction to adult levels within limbic, striatal, and cortical structures. Accordingly, recent findings from different laboratories demonstrated that prefrontal cortex (PFC) CB1R expression in male rats declines in pre- to early adolescence with a region-specific rate (Ellgren et al. 2008; Heng et al. 2011). Indeed there is a gradual decline of the CB1R expression in limbic/associative regions, whereas major changes in sensorimotor regions are not evident until mid- to late adolescence, with the functionality of these receptors following the same developmental pattern (Heng et al. 2011). Accordingly, Rubino et al. (2015) showed that in female rodents, CB1Rs increase from mid- to late adolescence (PND 60) and decline by adulthood (PND 75; Rubino et al. 2015). The efficacy of CB1 receptor coupling with G proteins through adolescence does not show significant alteration, at least in the PFC, implying that CB1Rs seem to be more efficient during adolescence (Rubino et al. 2015). Recently, an interesting paper was published by Schneider et al. (2015) in which the introduction of a gain-of-function mutation in the gene that encodes for the CB1R generated rats with sustaining features of adolescent behavior in adulthood. Indeed, adult mutant rats exhibited typical high risk/novelty seeking, increased peer interaction, enhanced impulsivity, and augmented reward sensitivity for drug and nondrug reward when

compared to wild-type littermates. Partial inhibition of CB1R activity normalized mutant rats' behavior.

These observations in adult mutant rats together with the above cited reports on enhanced CB1R signaling in adolescence highlight that the activity state and functionality of the CB1R are critical for mediating adolescent behavior. Interestingly no differences were observed between the genotypes for the two main endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG).

The picture regarding changes in the level of the two main endocannabinoids, AEA and 2-AG, during adolescence is still at the beginning, and the few data available are somewhat divergent, probably for the difference in the strain and sex of the used animals.

In male rats, a continuous increase in PFC AEA levels throughout the adolescent period was reported, anandamide being almost three times higher in later adolescence. However, 2-arachidonoylglycerol concentrations in the same brain area were highest very early in adolescence (PND 29), decreased by PND 38, and increased again in late adolescence (PND 50; Ellgren et al. 2008). Similarly, Rubino et al. (2015), in the PFC of female rats, observed that AEA levels increased from mid- to late adolescence and then decreased into adulthood, while 2-AG levels first decreased and subsequently increased. Interestingly, despite these dynamic changes, the activity of the two degrading enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, did not show any variation throughout the developmental window, suggesting a more likely involvement of the synthetic enzymes in regulating endocannabinoid levels.

Concerning other brain areas, it was reported that hypothalamic AEA content in female rats increases immediately preceding vaginal opening (as a physical marker of pubertal onset; Wenger et al. 2002), whereas in male rats the pattern of the AEA adolescent fluctuation in the amygdala, hippocampus, and hypothalamus (PND 25–70) was similar as in the PFC (Lee et al. 2013). Moreover, two other related N-acylethanolamines hydrolyzed by FAAH, oleoylethanolamine and palmitoylethanolamine, exhibit the same temporal-specific pattern as AEA, indicating that the corticolimbic AEA fluctuations are at least partly due to corresponding changes in FAAH activity (Lee et al. 2013).

Concluding the eCB system during adolescence shows a high instability and participates actively to the final brain's refinement that occur in this period. External stimulation of this system can profoundly alter its physiological role triggering altered brain maturation.

2 Behavioral Consequences of Cannabinoid Abuse in Adolescence

2.1 Emotional Aspects

Chronic administration of cannabinoid compounds in adolescent animals has been reported to lead to altered emotional reactivity later in life.

The picture emerging from studies evaluating the effect on anxiety behavior is quite complex, since different results have been obtained depending on the specific component of anxiety under study and the tests used to monitor it. The most difficult interpretation regards data on general anxiety, monitored in the elevated plus maze test or the open field test. Indeed, adult animals that were exposed to cannabinoids during adolescence have been reported to exhibit no changes in their behavior (Rubino et al. 2008; Higuera-Matas et al. 2009; Bambico et al. 2010; O'Tuathaigh et al. 2010; Mateos et al. 2011; Bortolato et al. 2014; Cadoni et al. 2015), an anxiolytic-like response (Biscaia et al. 2003; Wegener and Koch 2009; Cadoni et al. 2015), or even anxiety (Llorente-Berzal et al. 2013; Stopponi et al. 2014; O'Tuathaigh et al. 2010; Abboussi et al. 2015; but see also Renard et al. 2016 who used the light–dark box test). This lack of consistency might be due to differences in several experimental parameters such as the cannabinoid compound used (synthetic versus natural), the precise developmental period of exposure, and the strain of animals used. For example, it is well known that synthetic cannabinoids are full CB1 receptor agonists, whereas the natural ingredient of *Cannabis*, delta-9 tetrahydrocannabinol (THC), is a partial agonist. This could greatly affect the adaptive changes occurring in the brain in response to chronic exposure. Also the strain of animals used in the experimentation could play a fundamental role in the response to cannabinoid treatment, due to a possible different genetic background. This is the case, for example, in Cadoni's study (Cadoni et al. 2015), where it was reported an anxiolytic-like effect in adult Lewis rats exposed to THC during adolescence and no changes in anxiety behavior in the Fisher344 ones. In the same line, O'Tuathaigh et al. (2010) reported that only mice KO for the catechol-O-methyltransferase (COMT) gene were able to develop an anxiety-like behavior at adulthood after adolescent exposure to THC, while wild-type ones did not.

These different experimental parameters seem to play a minor role when social anxiety has been investigated. All the researchers who monitored this aspect reported a decrease in social interaction in adult rats after adolescent cannabinoid exposure. This was demonstrated with both synthetic and natural cannabinoid agonists, in male and female animals (Leweke and Schneider 2011; O'Shea et al. 2004, 2006; Quinn et al. 2008; Realini et al. 2011; Zamberletti et al. 2014; Renard et al. 2016). The only exception is the Gleason's paper (2012) performed in mice, even if a trend to a decreased social interaction might be seen after the adolescent treatment. The most likely reason for the lack of the effect in Gleason's work may reside in the fact that the behavior was monitored long after the end of the treatment (nearly 3 months later), whereas in all the other studies it was checked within

2 months. This suggests that at least some of the altered behaviors induced by the adolescent cannabinoid exposure might be normalized with time. Although reduction in social interaction has been considered an anxiogenic behavior in rodents (File and Hyde 1978), it is also well known that a significant and pervasive impairment in social functioning is associated with major depressive disorder (Hirschfeld et al. 2000). According to this view, impaired social behavior might also be a sign present in a depressive-like phenotype. Besides reduced social behavior, two other features of depression-like reactivity in animals are behavioral despair/passive coping strategy (measured in the forced swim test) and anhedonia (assessed as sucrose preference or palatable food consumption). Accumulating literature provides evidence that adolescent exposure to THC or WIN 55,212-2 induces passive coping strategy in the forced swim test and a reduction in the sucrose preference or palatable food consumption (Rubino et al. 2008; Realini et al. 2011; Bambico et al. 2010; Zamberletti et al. 2014). This suggests the presence of dysfunction in motivational processes, and, intriguingly, these effects appear to be stronger in female rats (Rubino et al. 2008). In line with this, Chadwick et al. (2011) reported that adolescent exposure to CP-55,940 decreased sexual motivation in adult female rats.

As a whole, these findings suggest the presence of altered emotional reactivity and hedonic processes after adolescent cannabinoid exposure, especially in female animals.

2.2 Cognition

Most literature on adolescent cannabinoid exposure in animal models agrees on the presence of long-lasting impairments in learning and memory.

Impairments in episodic memory tested in the classical or spatial version of the novel object recognition test or in the social recognition test have been reported after adolescent exposure to synthetic or natural cannabinoid agonists in adult rats and mice and in both sexes (Abush and Akirav 2012; O'Shea et al. 2004, 2006; Quinn et al. 2008; Realini et al. 2011; Renard et al. 2013, 2016; Schneider and Koch 2003; Zamberletti et al. 2014; Abboussi et al. 2015; Lovelace et al. 2015). Few exceptions to this rule are represented by papers where adolescent exposure was performed for very short periods of time (3 days, Cadoni et al. 2015) or where the cognitive effect was monitored much longer than in other studies after the end of the treatment (Higuera-Matas et al. 2009). The former exception might suggest that a longer period of exposure is needed to elicit the cognitive deficit, whereas the latter suggests, again, the possibility that some signs might spontaneously return to control value with time. Spatial working memory deficits have been observed after adolescent THC exposure in adult rats (Rubino et al. 2009a, b, 2015), mice (O'Tuathaigh et al. 2010), and monkeys (Verrico et al. 2014), as well as impairments in cognitive flexibility assessed through the attentional set-shifting task (Gomes et al. 2015). When other forms of memory were considered, no lasting

effects were observed. This was the case for aversive memory (Rubino et al. 2009a, b) or "pure" spatial learning in the Morris water maze (Abush and Akirav 2012; Cha et al. 2006, 2007; Higuera-Matas et al. 2009).

These data point toward a task-specific effect of adolescent cannabinoid exposure on cognition, suggesting that the exposure might more likely affect the forms of memory where both PFC and hippocampus play a role and the integrity of their interaction is needed to perform the task.

2.3 Psychosis

Epidemiological studies suggest that cannabis use during adolescence confers an increased risk for developing psychotic symptoms later in life (D'Souza et al. 2009; Evins et al. 2012).

Schizophrenia represents a complex disorder associated with various disturbances in motivational, social, emotional, and cognitive processing. Some of these features are uniquely human (i.e., hallucination and delusions) and cannot be reproduced in animals. Differently, several experimental protocols can reproduce impairment in cognition and altered emotionality present in schizophrenia, and the consequences of cannabis in adolescence on these signs has been already examined in the previous chapters. Thus, in the present chapter, only the effect of adolescent cannabis use on two other paradigms considered as valid translational models of schizophrenia will be reported: the pre-pulse inhibition of startle (PPI—a measure of sensorimotor gating, the ability of an organism to attain information and process it correctly) and drug-induced hyperactivity (Lodge and Grace 2009; Powell and Miyakawa 2006).

2.3.1 Pre-pulse Inhibition

Chronic adolescent treatment with the cannabinoid agonist WIN 55,212-2 provoked impairment in PPI in rats and mice that was still present long after the treatment withdrawal (Gleason et al. 2012; Schneider and Koch 2003; Wegener and Koch 2009). In contrast, Llorente-Berzal et al. (2011) and O'Tuathaigh et al. (2012) did not show alterations in this behavior after adolescent exposure to synthetic cannabinoid agonists (CP55940, 0.4 mg/kg, or WIN 55,212-2, 1 or 2.5 mg/kg, respectively). The reason for this discrepancy is quite difficult to find. Data for both evidence were obtained in mice and rats, using a synthetic cannabinoid agonist. The only speculation we may put forward is that the last two groups performed a longer treatment (15 or 21 days) with the same dose of agonist (thus triggering a deep state of tolerance), while the former ones performed a shorter treatment (10 days) or used an irregular protocol of injections (none, one, or two daily injections for 25 days), thus reducing the risk to develop profound tolerance. More recently, Renard et al. (2016) showed that adult rats pretreated with THC in adolescence displayed PPI

deficits at both the pre-pulse intensity levels of 76 and 80 dB compared with control rats. Interestingly the same protocols in adult rats did not affect PPI.

2.3.2 Locomotor Hyperactivity

Finally, locomotor hyperactivity in rodents may have some face validity for certain components of the positive symptoms of schizophrenia, such as psychotic agitation (Van Den Buuse 2010). However, despite its ease of quantification in rodents, very few data are available about the long-term effect of adolescent cannabinoid exposure on this behavioral sign. A significant increase in locomotor activity in the open field was observed in adult rats exposed to WIN 55,212-2 during adolescence (Wegener and Koch 2009). Differently, other groups showed no significant alterations in the open field recordings (Biscaia et al. 2003; Rubino et al. 2008), and some others found that young adult rats chronically treated with CP55,940 showed reduced baseline locomotor activity 2 weeks after the treatment's cessation (Klug and Van Den Buuse 2013). Our group recently observed that adolescent exposure to THC increased the locomotor activating effect of phencyclidine (PCP) when this was administered acutely in adulthood (Zamberletti et al. 2014). In fact, the low dose of PCP injected (2.5 mg/kg) did not induced locomotor activation in vehicle-treated animals but significantly increased locomotion in THC-treated rats. Moreover, stereotyped behaviors were observed in vehicle-treated animals following acute PCP injection, but this effect was significantly enhanced in THC-treated rats.

2.3.3 Two-Hit Hypothesis

Schizophrenia is a multifactorial disease characterized by the combined action of multiple genes of small effect size (Owen et al. 2005) and a number of environmental risk factors (McGrath et al. 2003), which causes the development of this mental disorder (Mackay-Sim et al. 2004). This is conceptualized in the "two-hit hypothesis" of schizophrenia, which predicts that genetic and environmental risk factors interactively (G × E interaction) cause the development of the disorder (Bayer et al. 1999; Caspi and Moffitt 2006).

Genetic factors may confer vulnerability to psychosis outcomes following exposure to cannabis, i.e., a gene-environment interaction. In specific, the genes encoding for COMT, neuregulin (Nrg1), brain-derived neurotrophic factor (BDNF), and disrupted in schizophrenia 1 (DISC1) have been implicated in conferring such vulnerability.

COMT

In one of the first studies that drew attention to gene × environment interactions, Caspi et al. (2005) reported that the COMT gene moderated the risk of psychotic

disorder with adolescent cannabis exposure. The enzyme COMT plays a critical role in the breakdown of dopamine (DA) in the PFC (Papaleo et al. 2008), in contrast to the striatum where DA is cleared by a transporter. The COMT gene has a common polymorphism in humans where valine (Val) is substituted for methionine at the158/108 locus, and this results in 40% higher enzymatic activity and thus more rapid degradation of DA. Lower cortical DA levels in individuals homozygous for the Val (158) polymorphism are associated with, among other things, poorer cognitive performance and inefficient pre-cortical functioning (Tunbridge et al. 2006). Accordingly, COMT knockout (KO) mice were more vulnerable than wild types (WT) to the disruptive effects of WIN55212 adolescent treatment on PPI. Moreover, acute pharmacological inhibition of COMT in mice modified acute cannabinoid effects on startle reactivity, as well as PPI. COMT KO mice also demonstrated differential effects of adolescent cannabinoid administration on sociability and anxiety-related behavior, confirming and extending earlier reports of COMT×cannabinoid effects on the expression of schizophrenia-related endophenotypes (O'Tuathaigh et al. 2012).

Neuregulin

Nrg1, a leading schizophrenia susceptibility gene, is relevant to several schizophrenia-related neurodevelopmental processes due to its involvement in axonal guidance, myelination, and GABAergic and glutamatergic neurotransmission (Mei and Xiong 2008). Heterozygous deletion of Nrg1 results in increased sensitivity of mice to schizophrenia-like symptoms induced by THC, especially under stressful conditions (Boucher et al. 2007). Long's lab team exposed adolescent WT and Nrg1 heterozygous (HET) mice to chronic THC during adolescence (Long et al. 2013). Surprisingly, Nrg1 mutants appeared less susceptible to THC-induced suppression of investigative social behaviors than control mice. However, adolescent THC exacerbated the hyperlocomotive phenotype characteristic for adult Nrg1 mutant mice (Karl et al. 2007; Long et al. 2013). Nrg1 deficiency also modulated the effects of adolescent THC on neurotransmitter systems involved in the pathophysiology of schizophrenia. Genotype-specific THC effects on CB1 expression in the substantia nigra were found: reduced CB1 level was present in Nrg1 HET drug-free mice, but its level increased in Nrg1 mice post THC challenge. Lower CB1 expression levels in the substantia nigra might be responsible for the observed decreased susceptibility of adolescent Nrg1 mutant mice. Nrg1 also conferred opposing effects of THC on serotonin 2A receptor expression in the insular cortex, and NMDA receptor binding was selectively increased in the hippocampus and cingulate cortex of Nrg1 HET mice (Long et al. 2013) (for a better mechanistic understanding of Nrg1-THC interaction on NMDA receptor expression in the hippocampus, see Spencer et al. 2013).

Concluding Nrg1 modulated the behavioral sensitivity of mice to cannabinoids during adolescence providing evidence for a role of Nrg1-cannabis interactions in schizophrenia.

BDNF

Reduced BDNF signaling has been shown in the frontal cortex and hippocampus in schizophrenia. Young BDNF HET mice and wild-type controls were chronically treated with the cannabinoid receptor agonist, CP55,940. Two weeks later, baseline PPI was lower but average startle was increased in BDNF HET compared to wild-type controls. Acute CP55,940 administration before the PPI session increased PPI only in male HET mice. In females, only small increases of PPI in all groups upon acute CP55,940 administration were observed. Acute CP55,940 administration furthermore reduced startle, and this effect was greater in HET mice irrespective of chronic CP55,940 pretreatment. Moreover, male "two-hit" mice, but not females, were hypersensitive to the effect of acute CP55,940 on sensorimotor gating. These effects may be related to a selective upregulation of CB1 receptor density in the nucleus accumbens (Klug and Van Den Buuse 2013).

DISC1

Recent research evaluated the interaction between cannabis in adolescence and another genetic risk factor, DISC1 (Brandon and Sawa 2011; Kamiya et al. 2012). Ballinger et al. (2015) demonstrated that a perturbation in DISC1 exacerbates the response to adolescent THC exposure in adult mice, such as deficits in fear-associated memory. Moreover, downregulation of the expression of CB1Rs in the PFC, hippocampus, and amygdala was induced by either expression of dominant-negative mutant of DISC1 (DN-DISC1) or adolescent THC treatment. A synergistic reduction of c-Fos expression induced by cue-dependent fear memory retrieval in DN-DISC1 with adolescent THC exposure was also found. These results suggest that alteration of CB1R-mediated signaling in DN-DISC1 mice may underlie susceptibility to detrimental effects of adolescent cannabis exposure on adult behaviors.

Environment × Environment Interaction

Some evidence has been recently accumulated highlighting the presence of environment × environment interaction in cannabis vulnerability in adolescence. Neonatal rodents subjected to prefrontal cortex lesioning showed impairment in various forms of social behavior and in object recognition memory after WIN 55,212-2 exposure in adolescence (Schneider and Koch 2007). Similarly, exposure to THC in adolescence produced a larger disruption of PPI in rats reared in social isolation (Malone and Taylor 2006), and a greater cognitive impairment was shown after THC in rats preexposed to PCP (Vigano et al. 2009). Interestingly stressful events early in life (maternal deprivation/separation) associated with adolescent exposure to natural or synthetic cannabinoids provoked different behavioral results when compared with non-stressed control animals. Indeed no effect, increased

cannabinoid-induced effect, or even decreased cannabinoid-induced effect was observed, depending on the sex of the animals and the considered behavior (Llorente-Berzal et al. 2011; Zamberletti et al. 2012; Klug and Van Den Buuse 2012). Recently, Gomes et al. (2015) showed that WIN 55212-2 administration in adolescence did not exacerbate the behavioral and electrophysiological changes (increased locomotor response to amphetamine administration and increased number of spontaneously active dopamine neurons in the ventral tegmental area) present in the methylazoxymethanol acetate (MAM) developmental disruption model of schizophrenia. WIN 55212-2 treatment attenuated the locomotor response to amphetamine in MAM rats without affecting dopamine neuron activity.

To conclude, the interaction between a previous hit (genetic or environmental) and cannabinoid exposure in adolescence warrants further investigations, and the different outcomes seem to be dependent by the considered gene profile, the nature and the time of the environmental factors, and the sex.

3 The Gateway Hypothesis

The possibility that cannabis use during adolescence increases the vulnerability to drug abuse disorders later in life, the so-called gateway hypothesis, has been heavily debated over the last decades due to contrasting results obtained with epidemiological studies. The definitive causal link between cannabis use and subsequent abuse of other illicit drugs should come from the use of experimental animal models. However, despite the use of these models, no conclusive findings are available, due to the existence of contrasting results even under these controlled conditions.

The most consistent data have been collected in studies considering cannabinoid-opioid interaction. Male, but not female, rats presented significant increases in the acquisition of both morphine and heroin self-administration after adolescent exposure to natural or synthetic cannabinoid agonists (Ellgren et al. 2007; Biscaia et al. 2008). Similarly, chronic cannabinoids in adolescence increased the sensitivity to morphine or heroin conditioned place preference (CPP) (Morel et al. 2009; Cadoni et al. 2015). Conversely, the same authors under different conditions or other authors reported that adolescent THC exposure neither affected heroin CPP (Cadoni et al. 2015) nor heroin self-administration (Stopponi et al. 2014). However Stopponi et al. (2014) found that adolescent THC pretreatment enhanced subsequent vulnerability to relapse to heroin seeking caused by yohimbine administration (as a pharmacological stressor). These discrepancies might be explained by differences in experimental parameters such as the strain of animals under investigation and the different heroin doses used for self-administration.

More contrasting results have been found regarding the interaction with psychostimulant drugs. Increased acquisition of cocaine self-administration was reported in adult female, but not male, rats pretreated with cannabinoids in

adolescence (Higuera-Matas et al. 2008). However, the locomotor activating effects of cocaine are enhanced after adolescent THC exposure (Dow-Edwards and Izenwasser 2012). Conversely, pretreatment with natural or synthetic cannabinoid agonists during early adolescence did not alter locomotor responses to amphetamine (Ellgren et al. 2004). Finally, exposure to cannabinoids during adolescence enhanced the acquisition and reinstatement of 3,4-methylenedioxymetamphetamine hydrochloride-induced CPP in mice (Rodriguez-Arias et al. 2010).

Very recently, data on cannabinoid–cannabinoid interaction have been reported (Scherma et al. 2015). These authors demonstrated that adolescent exposure to THC significantly increases WIN 55212-2 self-administration in adulthood. Indeed, THC-exposed rats acquired cannabinoid self-administration more rapidly than controls and showed higher rates of consumption when self-administration behavior reached asymptote.

In conclusion, the picture is still quite unclear regarding the role of Cannabis as a possible gateway drug to subsequent abuse of other illicit compounds. Maybe a more complex theory taking into account also influences of individual (personality traits) and environmental (substance availability, peer influence) characteristics will better describe this complex phenomenon.

4 Cellular Mechanisms Underlying Adolescent Brain Vulnerability

Despite their paucity, the available data seem to support the hypothesis that cannabis in adolescence might exert developmental interference on the eCB system. Accordingly, adolescent THC exposure in male and female rats induced lasting CB1 receptor downregulation and desensitization in different cerebral areas, females being more sensitive than males (Rubino et al. 2008, 2015; Burston et al. 2010). Moreover, in the PFC of THC-exposed female animals, the significant decrease of CB1R binding, still present in adulthood, was paralleled by a significant decrease of AEA levels (Rubino et al. 2015). Mice exposed to WIN 55,212-2 during adolescence exhibited at adulthood increased MGL and FAAH levels, suggesting increases in endocannabinoid degradation (Gleason et al. 2012). Recently, Ortega-Alvaro et al. (2015) showed that CB1R deletion induces a pre-attentional deficit and CB1 KO mice have significantly lower PPI values than WT mice. Moreover, treatment with the CB1R antagonist AM251 produces an impairment of PPI in WT mice, and typical and atypical antipsychotics did not ameliorate PPI deficit in CB1 KO mice. These data emphasize the important role of CB1R in sensorimotor gating modulation and suggest that the long-lasting downregulation of CB1R observed after cannabinoid in adolescence can play a role in the PPI impairment.

Collectively strong cannabis exposure in adolescence can profoundly affect the developmental trajectories of the different components of the eCB system such as

receptors (CB1 and CB2) and endocannabinoid levels (AEA), thus provoking its dysregulation and indirectly interfering with the final brain connectivity. These data strengthen the hypothesis that the alteration in the dynamic changes present in the eCB system during adolescence provoked by cannabis could profoundly affect the neurodevelopmental processes in which this system is involved.

For example, working memory and decision-making are refined during adolescence and require the functional maturation of the PFC. Interestingly, the eCB tone seems to play a fundamental role in some maturational processes occurring in the adolescent PFC. Indeed, adolescent THC exposure induced alterations in the maturational fluctuations of NMDA and AMPA subunits in this brain area, leading to larger amounts of gluN2B and gluA1 at adulthood (Rubino et al. 2015). Moreover, due to the fact that NMDA receptors play a critical role in regulating adolescent maturation of GABAergic networks in the PFC (Thomases et al. 2013), adolescent cannabinoid exposure might also affect the GABAergic system. Accordingly, Cass et al. (2014) showed that WIN55,212-2 exposure during early or mid-adolescence, but not later in life, caused a functional downregulation of GABAergic transmission in the PFC. Similarly, Zamberletti et al. (2014) demonstrated that adolescent THC exposure resulted in reduced GAD67 and basal GABA levels in the same brain area. These data suggest that adolescent cannabinoid exposure impacts not only the endocannabinoid system but also the glutamatergic and the GABAergic ones. These three systems are important in shaping cortical oscillations, a neural network activity in the neocortex (Uhlhaas et al. 2009) that is implicated in cognitive and sensory processing (Buzsaki and Draguhn 2004; Wang 2010). Chronic exposure to cannabinoids during adolescence permanently suppresses pharmacologically evoked cortical oscillations (Raver et al. 2013), and this effect seems to be mediated partly by CB1 receptors, but there is also some evidence of the involvement of CB2 and other non-cannabinoid receptors (Raver and Keller 2014). Moreover, the functional downregulation of GABAergic transmission in the PFC induced by adolescent cannabinoid exposure might impact the functionality of PFC excitatory descending projections. According to this hypothesis, increased ventral tegmental area (VTA) DA neuronal firing frequencies and relative proportion of spikes firing in burst have been described in adult rats chronically exposed to THC during adolescence (Renard et al. 2016). Similarly, an increased number of spontaneously active VTA dopaminergic neurons were seen in adult rats treated with WIN55,212-2 during puberty (Gomes et al. 2015). This VTA hyper-DAergic activity impacts molecular and neuronal activity parameters in the VTA DAergic output targets, such as the PFC and NAc. Indeed, an increased dopamine turnover was observed in the ventral striatum of adult rats chronically treated with WIN55,212-2 during adolescence (Bortolato et al. 2014), as well as altered amounts of D1 and D2 receptors in PFC and NAc (Higuera-Matas et al. 2010; Zamberletti et al. 2012). Consistent with this state of hyper-DAergic function in the mesocorticolimbic system, acute administration of the D3 receptor antagonists U-99194A partially restored the cognitive performances in the novel object recognition test disrupted by chronic cannabinoid exposure during adolescence (Abboussi et al. 2015).

Besides the impact on the maturation of different neurotransmitter systems, the endocannabinoid system has been recently suggested to affect the process of synaptic pruning (Rubino et al. 2015). Alterations in this event can lead to structural changes in the adult brain that might play a part in the dysfunctionality triggered by adolescent cannabinoid exposure. In male rats, adolescent exposure to WIN55,212-2 significantly decreased spine density in the nucleus accumbens immediately after treatment (Carvalho et al. 2016). More interestingly, long after the end of treatment, adolescent cannabinoid exposure has been shown to reduce spine density in the dentate gyrus of the hippocampus at adulthood, paralleled by a significant decrease in dendrite length and number (Rubino et al. 2009b) as well as a significant decrease in the basal dendritic arborization of pyramidal neurons in layer II/III of the PFC (Rubino et al. 2015).

As the brain is composed of many different cell types, including, but not limited to, neurons, it is only logical that adolescent cannabinoid exposure could also affect the functionality of other cell types besides neurons. According to this view, adolescent WIN55,212-2 treatment has been shown to induce an increase in the survival of oligodendroglia precursors in the striatum and PFC immediately after treatment (Bortolato et al. 2014). The role of this alteration in cannabinoid-induced effects is still not known, but pave the way to the increasing importance for brain function of the interaction between glial cells and neurons. More recently, Zamberletti et al. (2015) reported that adolescent THC administration induces a persistent neuroinflammatory state specifically localized within the adult PFC, characterized by increased expression of pro-inflammatory markers (TNF-α, iNOS, and COX-2), and reduction of the anti-inflammatory cytokine IL-10. Moreover, this neuroinflammatory phenotype was associated with downregulation of CB1 receptor on neuronal cells and upregulation of CB2 on microglia cells. Interestingly, blocking microglia activation with ibudilast during THC treatment significantly attenuated short-term memory impairment in adulthood. This was paralleled by the prevention of the increases in TNF-α, iNOS, and COX-2 levels as well as of the upregulation of CB2 receptors on microglia cells.

5 Conclusions

In conclusion, this review shows that cannabinoid administration in adolescence can profoundly affect the maturation of the endocannabinoid system, thus triggering important dysregulation in the final remodeling of other neurotransmitter pathways (glutamate, GABA, and dopamine). These dysfunctions represent the neurobiological substrate of the behavioral abnormalities resembling psychiatric diseases that become evident at adulthood. Moreover, recent evidence suggests that besides neuron also glial cells are affected by cannabinoid in adolescence, thus underlying the presence of a more generalized dysfunctional picture involving all the cellular elements of the central nervous system. Finally, no conclusive findings

are available for the gateway hypothesis due to the presence of limited and contrasting data mainly focused on opioids and psychostimulants.

References

Abboussi O, Said N, Fifel K, Lakehayli S, Tazi A, El Ganouni S (2015) Behavioral effects of D3 receptor inhibition and 5-HT4 receptor activation on animals undergoing chronic cannabinoid exposure during adolescence. Metab Brain Dis 31(2):321–327

Abush H, Akirav I (2012) Short- and long-term cognitive effects of chronic cannabinoids administration in late-adolescence rats. PLoS One 7:e31731

Ballinger MD, Saito A, Abazyan B, Taniguchi Y, Huang CH, Ito K, Zhu X, Segal H, Jaaro-Peled H, Sawa A, Mackie K, Pletnikov MV, Kamiya A (2015) Adolescent cannabis exposure interacts with mutant DISC1 to produce impaired adult emotional memory. Neurobiol Dis 82:176–184

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

Bayer TA, Falkai P, Maier W (1999) Genetic and non-genetic vulnerability factors in schizophrenia: the basis of the "two hit hypothesis". J Psychiatr Res 33:543–548

Biscaia M, Marin S, Fernandez B, Marco EM, Rubio M, Guaza C, Ambrosio E, Viveros MP (2003) Chronic treatment with CP 55,940 during the peri-adolescent period differentially affects the behavioural responses of male and female rats in adulthood. Psychopharmacology (Berl) 170:301–308

Biscaia M, Fernandez B, Higuera-Matas A, Miguens M, Viveros MP, Garcia-Lecumberri C, Ambrosio E (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

Bortolato M, Bini V, Frau R, Devoto P, Pardu A, Fan Y, Solbrig MV (2014) Juvenile cannabinoid treatment induces frontostriatal gliogenesis in Lewis rats. Eur Neuropsychopharmacol 24:974–985

Boucher AA, Arnold JC, Duffy L, Schofield PR, Micheau J, Karl T (2007) Heterozygous neuregulin 1 mice are more sensitive to the behavioural effects of delta9-tetrahydrocannabinol. Psychopharmacology (Berl) 192:325–336

Brandon NJ, Sawa A (2011) Linking neurodevelopmental and synaptic theories of mental illness through DISC1. Nat Rev Neurosci 12:707–722

Burston JJ, Wiley JL, Craig AA, Selley DE, Sim-Selley LJ (2010) Regional enhancement of cannabinoid CB₁ receptor desensitization in female adolescent rats following repeated delta-tetrahydrocannabinol exposure. Br J Pharmacol 161:103–112

Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926–1929

Cadoni C, Simola N, Espa E, Fenu S, Di Chiara G (2015) Strain dependence of adolescent Cannabis influence on heroin reward and mesolimbic dopamine transmission in adult Lewis and Fischer 344 rats. Addict Biol 20:132–142

Carvalho AF, Reyes BA, Ramalhosa F, Sousa N, Van Bockstaele EJ (2016) Repeated administration of a synthetic cannabinoid receptor agonist differentially affects cortical and accumbal neuronal morphology in adolescent and adult rats. Brain Struct Funct 221:407–419

Caspi A, Moffitt TE (2006) Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci 7:583–590

Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW (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

Cass DK, Flores-Barrera E, Thomases DR, Vital WF, Caballero A, Tseng KY (2014) CB1 cannabinoid receptor stimulation during adolescence impairs the maturation of GABA function in the adult rat prefrontal cortex. Mol Psychiatry 19:536–543

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

Chadwick B, Saylor AJ, Lopez HH (2011) Adolescent cannabinoid exposure attenuates adult female sexual motivation but does not alter adulthood CB1R expression or estrous cyclicity. Pharmacol Biochem Behav 100:157–164

Dow-Edwards D, Izenwasser S (2012) Pretreatment with delta9-tetrahydrocannabinol (THC) increases cocaine-stimulated activity in adolescent but not adult male rats. Pharmacol Biochem Behav 100:587–591

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

Ellgren M, Hurd YL, 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, 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, Devi LA, Hurd YL (2008) Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. Eur Neuropsychopharmacol 18:826–834

Evins AE, Green AI, Kane JM, Murray RM (2012) The effect of marijuana use on the risk for schizophrenia. J Clin Psychiatry 73:1463–1468

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

Gleason KA, Birnbaum SG, Shukla A, Ghose S (2012) Susceptibility of the adolescent brain to cannabinoids: long-term hippocampal effects and relevance to schizophrenia. Transl Psychiatry 2:e199

Gomes FV, Guimaraes FS, Grace AA (2015) Effects of pubertal cannabinoid administration on attentional set-shifting and dopaminergic hyper-responsivity in a developmental disruption model of schizophrenia. Int J Neuropsychopharmacol 18(2):1–10

Heng L, Beverley JA, Steiner H, Tseng KY (2011) Differential developmental trajectories for CB1 cannabinoid receptor expression in limbic/associative and sensorimotor cortical areas. Synapse 65:278–286

Higuera-Matas A, Soto-Montenegro ML, Del Olmo N, Miguens M, Torres I, Vaquero JJ, Sanchez J, Garcia-Lecumberri C, Desco M, Ambrosio E (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, Miguens M, Del Olmo N, Borcel E, Perez-Alvarez L, Garcia-Lecumberri C, Ambrosio E (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, García-Lecumberri C, Ambrosio E (2010) Periadolescent exposure to cannabinoids alters the striatal and hippocampal dopaminergic system in the adult rat brain. Eur Neuropsychopharmacol 20:895–906

Hirschfeld RM, Montgomery SA, Keller MB, Kasper S, Schatzberg AF, Moller HJ, Healy D, Baldwin D, Humble M, Versiani M, Montenegro R, Bourgeois M (2000) Social functioning in depression: a review. J Clin Psychiatry 61:268–275

Kamiya A, Sedlak TW, Pletnikov MV (2012) DISC1 pathway in brain development: exploring therapeutic targets for major psychiatric disorders. Front Psych 3:25

Karl T, Duffy L, Scimone A, Harvey RP, Schofield PR (2007) Altered motor activity, exploration and anxiety in heterozygous neuregulin 1 mutant mice: implications for understanding schizophrenia. Genes Brain Behav 6:677–687

Klug M, Van Den Buuse M (2012) Chronic cannabinoid treatment during young adulthood induces sex-specific behavioural deficits in maternally separated rats. Behav Brain Res 233:305–313

Klug M, Van Den Buuse M (2013) An investigation into "two hit" effects of BDNF deficiency and young-adult cannabinoid receptor stimulation on prepulse inhibition regulation and memory in mice. Front Behav Neurosci 7:149

Lee TT, Hill MN, Hillard CJ, Gorzalka BB (2013) Temporal changes in N-acylethanolamine content and metabolism throughout the peri-adolescent period. Synapse 67:4–10

Leweke FM, Schneider M (2011) Chronic pubertal cannabinoid treatment as a behavioural model for aspects of schizophrenia: effects of the atypical antipsychotic quetiapine. Int J Neuropsychopharmacol 14:43–51

Llorente-Berzal A, Fuentes S, Gagliano H, Lopez-Gallardo M, Armario A, Viveros MP, Nadal R (2011) Sex-dependent effects of maternal deprivation and adolescent cannabinoid treatment on adult rat behaviour. Addict Biol 16:624–637

Llorente-Berzal A, Puighermanal E, Burokas A, Ozaita A, Maldonado R, Marco EM, Viveros MP (2013) Sex-dependent psychoneuroendocrine effects of THC and MDMA in an animal model of adolescent drug consumption. PLoS One 8:e78386

Lodge DJ, Grace AA (2009) Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. Behav Brain Res 204:306–312

Long LE, Chesworth R, Huang XF, McGregor IS, Arnold JC, Karl T (2013) Transmembrane domain Nrg1 mutant mice show altered susceptibility to the neurobehavioural actions of repeated THC exposure in adolescence. Int J Neuropsychopharmacol 16:163–175

Lovelace JW, Corches A, Vieira PA, Hiroto AS, Mackie K, Korzus E (2015) An animal model of female adolescent cannabinoid exposure elicits a long-lasting deficit in presynaptic long-term plasticity. Neuropharmacology 99:242–255

Mackay-Sim A, Feron F, Eyles D, Burne T, McGrath J (2004) Schizophrenia, vitamin D, and brain development. Int Rev Neurobiol 59:351–380

Malone DT, Taylor DA (2006) The effect of delta9-tetrahydrocannabinol on sensorimotor gating in socially isolated rats. Behav Brain Res 166:101–109

Mateos B, Borcel E, Loriga R, Luesu W, Bini V, Llorente R, Castelli MP, Viveros MP (2011) 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 CB(1) cannabinoid receptors. J Psychopharmacol 25:1676–1690

McGrath JJ, Feron FP, Burne TH, Mackay-Sim A, Eyles DW (2003) The neurodevelopmental hypothesis of schizophrenia: a review of recent developments. Ann Med 35:86–93

Mei L, Xiong WC (2008) Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. Nat Rev Neurosci 9:437–452

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

Ortega-Alvaro A, Navarrete F, Aracil-Fernandez A, Navarro D, Berbel P, Manzanares J (2015) Differential pharmacological regulation of sensorimotor gating deficit in CB1 knockout mice and associated neurochemical and histological alterations. Neuropsychopharmacology 40:2639–2647

O'Shea M, Singh ME, McGregor IS, 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, 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'Tuathaigh CM, Hryniewiecka M, Behan A, Tighe O, Coughlan C, Desbonnet L, Cannon M, Karayiorgou M, Gogos JA, Cotter DR, Waddington JL (2010) Chronic adolescent exposure to delta-9-tetrahydrocannabinol in COMT mutant mice: impact on psychosis-related and other phenotypes. Neuropsychopharmacology 35:2262–2273

O'Tuathaigh CM, Clarke G, Walsh J, Desbonnet L, Petit E, O'Leary C, Tighe O, Clarke N, Karayiorgou M, Gogos JA, Dinan TG, Cryan JF, Waddington JL (2012) Genetic vs. pharmacological inactivation of COMT influences cannabinoid-induced expression of schizophrenia-related phenotypes. Int J Neuropsychopharmacol 15:1331–1342

Owen MJ, Craddock N, O'Donovan MC (2005) Schizophrenia: genes at last? Trends Genet 21:518–525

Papaleo F, Crawley JN, Song J, Lipska BK, Pickel J, Weinberger DR, Chen J (2008) Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. J Neurosci 28:8709–8723

Powell CM, Miyakawa T (2006) Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? Biol Psychiatry 59:1198–1207

Quinn HR, Matsumoto I, Callaghan PD, Long LE, Arnold JC, Gunasekaran N, Thompson MR, Dawson B, Mallet PE, Kashem MA, Matsuda-Matsumoto H, Iwazaki T, Mcgregor IS (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

Raver SM, Keller A (2014) Permanent suppression of cortical oscillations in mice after adolescent exposure to cannabinoids: receptor mechanisms. Neuropharmacology 86:161–173

Raver SM, Haughwout SP, Keller A (2013) Adolescent cannabinoid exposure permanently suppresses cortical oscillations in adult mice. Neuropsychopharmacology 38:2338–2347

Realini N, Vigano D, Guidali C, Zamberletti E, Rubino T, Parolaro D (2011) Chronic URB597 treatment at adulthood reverted most depressive-like symptoms induced by adolescent exposure to THC in female rats. Neuropharmacology 60:235–243

Renard J, Krebs MO, Jay TM, Le Pen G (2013) Long-term cognitive impairments induced by chronic cannabinoid exposure during adolescence in rats: a strain comparison. Psychopharmacology (Berl) 225:781–790

Renard J, Krebs MO, Le Pen G, Jay TM (2014) Long-term consequences of adolescent cannabinoid exposure in adult psychopathology. Front Neurosci 8:361

Renard J, Vitalis T, Rame M, Krebs MO, Lenkei Z, Le Pen G, Jay TM (2016) Chronic cannabinoid exposure during adolescence leads to long-term structural and functional changes in the prefrontal cortex. Eur Neuropsychopharmacol 26:55–64

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

Rodriguez-Arias M, Manzanedo C, Roger-Sanchez C, Do Couto BR, Aguilar MA, Minarro 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

Rubino T, Parolaro D (2015) The impact of exposure to cannabinoids in adolescence: insights from animal models. Biol Psychiatry 79(7):578–585

Rubino T, Vigano D, Realini N, Guidali C, Braida D, Capurro V, Castiglioni C, Cherubino F, Romualdi P, Candeletti S, Sala M, Parolaro D (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, Guidi S, Capurro V, Vigano D, Guidali C, Pinter M, Sala M, Bartesaghi R, Parolaro D (2009a) Changes in hippocampal morphology and neuroplasticity induced by adolescent THC treatment are associated with cognitive impairment in adulthood. Hippocampus 19:763–772

Rubino T, Realini N, Braida D, Alberio T, Capurro V, Vigano D, Guidali C, Sala M, Fasano M, Parolaro D (2009b) 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, Prini P, Piscitelli F, Zamberletti E, Trusel M, Melis M, Sagheddu C, Ligresti A, Tonini R, Di Marzo V, Parolaro D (2015) Adolescent exposure to THC in female rats disrupts developmental changes in the prefrontal cortex. Neurobiol Dis 73:60–69

Scherma M, Dessi C, Muntoni AL, Lecca S, Satta V, Luchicchi A, Pistis M, Panlilio LV, Fattore L, Goldberg SR, Fratta W, Fadda P (2015) Adolescent delta-tetrahydrocannabinol exposure alters WIN55,212-2 self-administration in adult rats. Neuropsychopharmacology 41(5):1416–1426

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

Schneider M, 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, Kasanetz F, Lynch DL, Friemel CM, Lassalle O, Hurst DP, Steindel F, Monory K, Schafer C, Miederer I, Leweke FM, Schreckenberger M, Lutz B, Reggio PH, Manzoni OJ, Spanagel R (2015) Enhanced functional activity of the cannabinoid type-1 receptor mediates adolescent behavior. J Neurosci 35:13975–13988

Spencer JR, Darbyshire KM, Boucher AA, Kashem MA, Long LE, McGregor IS, Karl T, Arnold JC (2013) Novel molecular changes induced by Nrg1 hypomorphism and Nrg1-cannabinoid interaction in adolescence: a hippocampal proteomic study in mice. Front Cell Neurosci 7:15

Stopponi S, Soverchia L, Ubaldi M, Cippitelli A, Serpelloni G, Ciccocioppo R (2014) Chronic THC during adolescence increases the vulnerability to stress-induced relapse to heroin seeking in adult rats. Eur Neuropsychopharmacol 24:1037–1045

Thomases DR, Cass DK, Tseng KY (2013) Periadolescent exposure to the NMDA receptor antagonist MK-801 impairs the functional maturation of local GABAergic circuits in the adult prefrontal cortex. J Neurosci 33:26–34

Tunbridge EM, Harrison PJ, Weinberger DR (2006) Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. Biol Psychiatry 60:141–151

Uhlhaas PJ, Roux F, Singer W, Haenschel C, Sireteanu R, Rodriguez E (2009) The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. Proc Natl Acad Sci USA 106:9866–9871

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

Verrico CD, Gu H, Peterson ML, Sampson AR, Lewis DA (2014) Repeated delta9-tetrahydrocannabinol exposure in adolescent monkeys: persistent effects selective for spatial working memory. Am J Psychiatry 171:416–425

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

Wang XJ (2010) Neurophysiological and computational principles of cortical rhythms in cognition. Physiol Rev 90:1195–1268

Wegener N, 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, Gonzalez S, Bisogno T, Fernandez-Ruiz J, Di Marzo V (2002) The hypothalamic levels of the endocannabinoid, anandamide, peak immediately before the onset of puberty in female rats. Life Sci 70:1407–1414

Zamberletti E, Prini P, Speziali S, Gabaglio M, Solinas M, Parolaro D, Rubino T (2012) Gender-dependent behavioral and biochemical effects of adolescent delta-9-tetrahydrocannabinol in adult maternally deprived rats. Neuroscience 204:245–257

Zamberletti E, Beggiato S, Steardo L Jr, Prini P, Antonelli T, Ferraro L, Rubino T, Parolaro D (2014) Alterations of prefrontal cortex GABAergic transmission in the complex psychotic-like phenotype induced by adolescent delta-9-tetrahydrocannabinol exposure in rats. Neurobiol Dis 63:35–47

Zamberletti E, Gabaglio M, Prini P, Rubino T, Parolaro D (2015) Cortical neuroinflammation contributes to long-term cognitive dysfunctions following adolescent delta-9-tetrahydrocannabinol treatment in female rats. Eur Neuropsychopharmacol 25:2404–2415