Review

Vulnerability Factors for the Psychiatric and Behavioral Effects of Cannabis

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Abstract: Cogent evidence shows that cannabis plays a variable role on behavioral regulation and the pathophysiology of most psychiatric conditions. Accordingly, cannabis has been alternatively shown to exacerbate or ameliorate mental symptoms, depending on its composition and route of consumption, as well as specific individual and contextual characteristics. The vulnerability to the psychological effects of cannabis is influenced by a complex constellation of genetic and environmental factors. In the present article, we will review the current evidence on the pharmacological, individual and situational factors that have been documented to affect the behavioral and psychiatric effects of cannabinoids.

Keywords: cannabinoids; vulnerability; CB receptors

1. Introduction

Recent epidemiological surveys have ascertained that marijuana and other hemp plant (*Cannabis sativa*) products are the most widely abused illicit substances in Western countries [1], and their consumption among minors and young adults is steadily rising [2,3]. One of the most worrisome implications of this scenario lies in the role of cannabis as a risk factor for the development of several
staggering psychiatric conditions, including schizophrenia and bipolar disorder [4–9]. In striking contrast with this notion, however, several psychiatric patients are reported to use cannabis for its therapeutic properties [10–13]. Indeed, the effects of cannabis are extremely variable across different individuals, in relation to a broad array of vulnerability factors. The identification of these genetic and environmental elements is poised to become a critical goal for the enactment of preventative and therapeutic strategies for cannabis-related mental disorders; nevertheless, research on the biological underpinnings of susceptibility to cannabis is still in its preliminary stages and limited by the inadequacy of animal models to reproduce this inherently human aspect.

A promising approach to grapple with this nodal issue may be afforded by the analysis of the variations in emotional and cognitive effects of cannabinoids and their biological underpinnings. The literature on the behavioral outcomes of cannabis and related agents is fraught with apparent inconsistencies among different authors and laboratories. These discrepancies, often regarded as an important hindrance to our understanding of the psychotropic properties of cannabinoids, may prove a rich source of data to establish a theoretical framework to study the vulnerability for cannabis-induced outcomes.

2. The Endocannabinoid System

The hemp plant features about 80 terpenophenolic alkaloids, collectively named phytocannabinoids, which are known to exert a number of medicinal properties (for a comprehensive review on the topic, see [15]). In spite of such a rich variety of ingredients, most psychotropic effects of cannabis are produced by one phytocannabinoid, Δ⁹-tetrahydrocannabinol (THC) [16]. Recent findings have revealed that other components, such as cannabidiol (CBD) and cannabichromene (CBC) may play a key role in the behavioral outcomes of cannabis and in the modulation of the psychological effects of THC [17]. The potential involvement of CBD in the psychological and behavioral effects of cannabis, however, remains elusive and is beyond the scope of this manuscript; for a thorough analysis of the issue, the interested reader is referred to the recent reviews by Zuardi et al. [18], and Scuderi et al. [19].

The isolation of THC and the development of its synthetic analogs led to the identification of two G𝑖/𝑜 protein-coupled receptors, respectively termed CB₁ and CB₂ [20,21]. Anatomical studies have revealed that these receptors display a highly divergent pattern of distribution throughout the organism: CB₁ are highly abundant in the brain [22], and densely expressed in all the main regions that govern emotional and cognitive behavior, including prefrontal and cingulate cortex, amygdaloid complex, septo-hippocampal system, striatum, midbrain nuclei etc. [22–26]. Conversely, CB₂ are prevalent in the periphery, and particularly in immune cells [27]. This topographical dichotomy has been recently tempered by a number of studies documenting the presence of CB₂ receptors in several brain regions [28,29]. The ultrastructural localization of CB receptors in neurons is still partially unknown, but the bulk of evidence supports that CB₁ are mainly located in presynaptic boutons [30,31], while CB₂ have been generally detected in postsynaptic terminals [32,33]. This segregation seemingly suggests that CB₁ and CB₂ receptors may exert distinct actions in the regulation of brain functions, as well as the psychotropic effects of cannabinoids. Notably, the activation of presynaptic CB₁ receptors has been shown to inhibit the opening of voltage-operated calcium channels and reduce the release of key neurotransmitters, including γ-aminobutyric acid (GABA) and glutamate [34–38]. The characterization
of CB₁ receptors in homo- and heterodimeric organizations, however, suggests that variable arrangements of this molecule may correspond to different functional roles [25,39–42].

Both CB₁ and CB₂ receptors are endogenously activated by a number of arachidonic acid derivatives (endocannabinoids), such as anandamide (N-arachidonylethanolamine) [43] and 2-arachidonoylglycerol (2-AG) [44,45]. These two endocannabinoids are synthesized upon demand through enzymatic degradation of membrane phospholipids, and released into the synaptic space [46,47]. While 2-AG has been shown to be the main retrograde mediator in glutamatergic [48–51] and GABAergic synapses [52,53] via CB₁ activation, anandamide may act as an activity-dependent modulator of monoamine neurotransmission in several brain regions [54–56]. Several findings appear also to indicate that endocannabinoids modulate the signaling of several neuropeptides and hormones [57–63]. This highly complex network of interactions (reviewed by López-Moreno et al. [64]) is reflected in the multifaceted modulatory effects of cannabis on the regulation of brain and behavioral functions.

3. The Role of Cannabis in Behavioral Regulation and Psychiatric Disorders

3.1. Emotional and Cognitive Effects of Cannabis

In most users, inhalation or ingestion of modest amounts of cannabis increase sociability, relaxation, and creativity [65,66]; these anxiolytic and mood-enhancing properties are the main incentive to the recreational use of marijuana and other hemp products [67,68]. In contrast, a smaller contingent of individuals - particularly first-time users - experience a number of undesirable emotional effects after cannabis consumption, such as panic, phobic manifestations, dysphoria [69–77].

Notably, cannabis has been documented to induce psychotic symptoms, such as derealization, depersonalization, paranoia and auditory hallucinations [70]. In particular, these alterations are commonly manifested in two distinct nosographic entities [78]: (a) toxic psychosis, featuring euphoria, perceptual distortions, clouding of consciousness and cognitive deficits [79]; (b) functional psychosis, characterized by positive symptoms similar to those featured in schizophrenia (including bizarre and paranoid ideation), but no cognitive impairment. This disturbance is highly sensitive to antipsychotic agents and posited to reflect an underlying disorder in predisposed individuals.

Acute cannabis consumption also triggers variable cognitive dysfunctions, encompassing short-term perceptual, psychomotor, attentional and mnemonic deficits [66,80–82], (for a thorough review on the topic, see Solowij and Pesca [83]).

One of the key factors that have been shown to influence the differential responsiveness to cannabinoids is the dose of exposure. Particularly in first-time or non-habitual users, low dosages of THC or marijuana are generally conducive to euphoria, hilarity, relaxation and subtle perceptual changes; conversely, higher concentrations are known to elicit fear, agitation and psychotic manifestations, as well as attentional and mnemonic impairments [71,74,76–79,84–86].

The most stringent evidence concerning dose-dependent, bidirectional effects of cannabinoids on emotional responses comes from research in experimental rodents. Several studies have revealed that, in rats and mice, low doses of CB₁ receptor agonists attenuate anxiety-like and depression-like behaviors, and enhance locomotion and exploratory activity; in contrast, elevated concentrations of
cannabinoids are typically anxiogenic and aversive [87–96] and alter attentional processing, executive functions and working and recognition memory [97–101].

Interestingly, the behavioral impact of low doses of cannabinoids is posited to mimic the physiological effects of endocannabinoids. Accordingly, the pharmacological inhibition of reuptake and enzymatic degradation of anandamide has been shown to induce anxiolysis and antidepressant-like effects in animals [55,102–104]. Of note, endocannabinoids and low doses of cannabinoids have been found to support the encoding and retrieval of select types of memory, and to ameliorate cognitive functions in rodents [105,106]. While these findings point to the possibility that cannabinoids may exert biphasic effects also on select cognitive properties, evidence on this issue is still lacking.

Prolonged consumption of cannabis, particularly in adolescence, is generally conducive to persistent affective and cognitive sequelae in adulthood [107]. These alterations include avolition and alexithymia [71,108–110], as well as impairments in informational processing, sustained and distributed attention, spatial working memory, verbal fluency, decision making and executive functions [76,81,111–114]. Interestingly, recent studies have correlated some of these deficits to abnormalities in cortical and hippocampal metabolism [115].

In addition to dose-related factors, other determinants play a key role in the behavioral effects of cannabis. For example, the relative composition in different ingredients (and particularly CBD and CBC) is likely to exert a profound influence on the emotional outcomes of this drug, in view of the anxiolytic properties of CBD [17–19]. Furthermore, the impact of cannabis is certainly modulated by a number of vulnerability factors, such as genetic background, age, gender etc. The available evidence on the role of these critical elements will be reviewed in the following chapter.

3.2. Anxiety- Spectrum and Mood Disorders

Although cannabis abuse and dependence are frequently comorbid with affective and anxiety disorders [9,86,116–121], very few studies have been focused on the pathophysiological link between these phenomena. While cannabis does not appear to play a conclusive role in affective and anxiety disorders [72,122–124], convergent lines of evidence show that its consumption can profoundly affect the severity and the clinical presentation of their symptoms. In conformity with the high variability in emotional outcomes observed in healthy individuals, however, cannabis has been shown to exert opposite effects in different clusters of patients. A number of studies have reported that this substance can precipitate the symptoms of anxiety-spectrum, bipolar and depressive disorders, and reduce the therapeutic efficacy of benchmark agents [7,125–128]. Conversely, several patients suffering from anxiety and mood disorders use cannabis as a relaxant and for self-therapeutic purposes [7,13,129–133]. In support of this last notion, anxiety disorders have been shown to predict later cannabis use disorder [74,134,135]. Furthermore, few clinical trials in the 1980’s have shown that nabilone - a cannabinoid analog approved in United Kingdom as an antiemetic treatment – has anxiolytic effects in psychiatric patients [136–138].

However, it is important to note that, while the initial consumption of cannabis can have relaxant effects in patients suffering from anxiety and mood disorders, its chronic use could actually exacerbate the symptoms of these illnesses by dampening the functions of the endocannabinoid system.
The implication of endocannabinoid system in anxiety and depression has been also extensively shown by preclinical studies. While CB receptor ligands have been shown to induce variable effects on both anxiety- and depression-like behaviors in rodents (for reviews on this topic, see Vinod and Hungund [139], Bortolato and Piomelli [140], and Parolaro et al. [141]), blockade of anandamide reuptake and degradation elicits anxiolytic and antidepressant-like effects [55,102,104,105,142], suggesting a key role of this endocannabinoid in emotional regulation.

3.3. Psychotic Disorders

The relation between cannabis consumption and schizophrenia has been observed in many epidemiological surveys [4,143–145]. Several lines of evidence have convincingly shown that cannabis use is a risk factor for psychotic disorders [5,6,8]; in particular, longitudinal studies have documented that habitual cannabis consumption in adolescence leads to an increase in incidence of schizophrenia [122,146,147]. Indeed, cannabis consumption is frequently comorbid with first-episode schizophrenia [148].

This evidence is also supported by experimental studies, which found that cannabis products and THC can exacerbate positive and negative symptoms in schizophrenia patients [149,150]. Interestingly, administration of THC at high doses has been shown to cause endophenotypical alterations similar to those observed in schizophrenia patients, such as decrease in the P300 component of event-related potentials [151,152] and reduction of prepulse inhibition of the startle reflex [153,154].

Nevertheless, several schizophrenia patients have reported beneficial effects from cannabis consumption, such as the reduction of anxiety [10,11] and negative symptoms, such as affective flattening and anergia [155–156]. Furthermore, a small subset of psychotic patients motivate cannabis use as a self-therapeutic strategy to attenuate positive symptoms, such as auditory hallucinations and paranoia, or to countenance the side effects induced by antipsychotic medications [156–157].

Some lines of research suggest that the endocannabinoid system may exert an important modulatory role in the pathophysiology of psychosis [158]. For example, expression of CB1 receptors has been shown to be increased in prefrontal cortex, anterior and posterior cingulate cortex of schizophrenia patients [159–160]. However, this evidence has not been replicated by subsequent studies [161–162]. Anandamide levels are elevated in the CSF of first-episode schizophrenia patients [163], they have been found to be inversely correlated with psychotic symptoms [164]. Moreover, the excess of anandamide is reversed by typical antipsychotics [164], suggesting that this endocannabinoid may be instrumental for the homeostasis of dopamine neurotransmission. Interestingly, high cannabis use in first-episode schizophrenia patients has been shown to reduce anandamide levels; this down-regulation in anandamide signaling may in fact increase the risk for psychosis or precipitate its manifestations [163].

The neurobiological underpinnings of the role of endocannabinoids in schizophrenia are still largely elusive and may concern different systems, such as dopamine, glutamate and GABA, particularly in relation to their maturation during adolescence [165].

Taken together, this background supports the view that cannabinoids may play different roles in schizophrenia, probably in relation to the highly heterogenous nosological entities described by this category and potentially distinct functions of the endocannabinoid system in the pathophysiology of this disorder.
The high variability of the impact of cannabis in schizophrenia-related alterations is also reflected in the numerous discrepancies on the effects of cannabinoids in rodents tested on the prepulse inhibition of the startle, a well-validated index of sensorimotor gating [166,167].

4. Vulnerability Factors

The seemingly contradictory scenario outlined in the previous section underscores the relevance of interindividual differences in the psychological and behavioral effects of cannabis in healthy individuals, psychiatric patients and animal models. The variations in the emotional and cognitive sequelae of cannabis are likely influenced by the interaction of drug-related characteristics (frequency and duration of use, dose consumed and relative concentrations of ingredients) and vulnerability factors, both intrinsic (including genetic vulnerability, age, gender, premorbid personality traits, etc.) and extrinsic (exposure to stress, concomitant use of other drugs etc.).

4.1. Genetic Background

Although genetic components have been largely advocated as a factor of vulnerability for the emotional and cognitive effects of cannabis, research in this respect is still preliminary. McGuire and colleagues [168] found that healthy subjects with a positive family history of schizophrenia had a higher likelihood to develop hallucinations and other psychotic symptoms following cannabis consumption.

The quest for genetic determinants has indicated a potential role of some of the polymorphic variants of the CNR1 gene, encoding for CB1 receptor protein [169]. Indeed, allelic variations of this gene have been associated with alcoholism and drug use [169–172], impulsivity [173], neuroticism [174] as well as different striatal responses to social stimuli [175,176]. A particular polymorphic variant of the CNR1 gene, featuring multiple Adenine-Adenine-Thymine (AAT) repeats and deemed to regulate the transcription of CB1 receptor, has been associated with different risks for depression in Parkinson disease patients [177] and a diagnostic cluster of schizophrenia [178,179], (for contrasting results, see [180]). Additionally, other alterations of CNR1 gene may act as a protective factor for schizophrenia, or induce a better pharmacological response to atypical antipsychotics [181].

In addition to allelic variations in CNR1 gene, other polymorphic variants and genetic factors have been linked to a different vulnerability for the role of cannabis in schizophrenia [182]. In particular, several lines of evidence have indicated that the Val108Met allelic variant Catechol-O-methyltransferase (COMT), which codifies for a high-activity variant of this enzyme, is associated with a higher risk of psychosis [183], particularly in conjunction with other predisposing environmental factors, such as psychosocial stress [184]. Recent evidence has also shown that different haplotypes of neuregulin 1 gene (Nrg1) have also been implicated in the sensitivity to the effects of cannabinoids in mice [185]. Finally, cannabis dependence has been associated with the C3435T single nucleotide polymorphism (SNP) of the gene ABCB1, encoding for the membrane transporter P-glycoprotein [186]. Specifically, the 3435 CC genotype (resulting in increased P-glycoprotein expression) was more common among cannabis-dependent patients than controls. Interestingly, the same polymorphism has been shown to influence the response to antipsychotic and antidepressant treatment [187,188], potentially suggesting a role of its variants in the psychiatric outcomes of cannabis [163].
4.2. Age and Gender

Adolescence has been shown to be an important vulnerability factor for cannabis-induced sequelae. For instance, juvenile age plays a key role in the development of attentional alterations following acute cannabis use, which are not commonly observed in adult users [189,190]. In line with this concept, the impairments in sustained attention in chronic adult users have been shown to increase in severity for users that initiated cannabis consumption before 15 years of age [191]. Early onset of cannabis consumption has been associated with a higher susceptibility to psychosis [4,122]. In view of the critical role of endocannabinoids in neurodevelopmental processes [158,192], it is likely that early consumption of cannabis may interfere with critical neurodevelopmental processes occurring throughout adolescence, including synaptic sprouting and pruning [193,194], myelination, changes in neurotransmitter concentrations etc. The consequences of exposure to non-endogenous cannabinoids in such a critical period may be particularly severe if associated with other factors, such as genetic or environmental determinants, and lead to profound alterations of the circuitry underpinning specific mental disorders. The role of age would then be particularly important for schizophrenia, in consideration of its neurodevelopmental nature [195].

Interestingly, some lines of clinical investigation have documented the existence of gender differences in the vulnerability to cannabis-mediated changes, with a higher severity of anxiety-like and depression-like manifestations in females [195,196], (for a general presentation of gender-related issues in cannabis-mediated effects, see Fattore and Fratta [197]).

The contribution of age and sex characteristics to the emotional effects of cannabis has been largely bolstered by animal experimentation. As reviewed by Rubino and Parolaro [107], the available preclinical evidence supports the possibility that adolescent exposure to cannabinoids and gender differences may affect emotional and cognitive behaviors in adulthood. For example, treatment of rats with cannabinoids during juvenile stages induce reductions in social interaction, novel object recognition, sensorimotor gating, and enhance depression-like behaviors in adulthood [98,198-200].

4.3. Environmental Contingencies

The anxiogenic and hallucinogenic effects of cannabis are more frequently observed in novel and stressful settings [201–204]. Early stress (particularly from child abuse or neglect) has been shown to interact with cannabis use in determining the risk of development of schizophrenia in adolescence [123,205–207]. In particular, cogent evidence points to the critical role of gene-environment interactions in the association between cannabis and psychosis [182].

Stressful environmental situations are also known to exacerbate the anxiety and aversive reactions associated with acute administration of cannabinoids in both humans and animals [140]. Conversely, environmental enrichment has been shown to enhance the rewarding properties of CB1 agonists in rodents [103]. It is important to note that the role of environmental factors on the outcomes of cannabis may also be mediated by its influence on the motivation to consume the drug, particularly in early adolescence [208].
4.4. Other Factors

In addition to the aforementioned determinants, the vulnerability for the psychiatric sequelae of cannabis is likely to include a number of other factors, such as the premorbid personality and concurrent use of other substances. Polydrug use is a common characteristic in cannabis users [209] and may certainly influence the pathophysiological trajectory of most behavioral and psychiatric effects of this substance.

Furthermore, the impact of cannabis is certainly dependent on the specific variety of substance consumed, with respect to the concentrations and the relative composition of psychoactive ingredients; indeed, the anxiolytic and antipsychotic effects of CBD have been postulated to largely contribute to the behavioral outcomes of cannabis [86,210,211].

5. Conclusions

While epidemiological and clinical evidence suggests that early and heavy cannabis abuse may enhance the risk of developing psychotic and possibly affective disorders, most users do not develop psychiatric conditions, and some may even use cannabis for self-medication purposes. Indeed, the relationship between cannabis and mental disorders is influenced by a wide set of determinants, related to individual and environmental characteristics, as well as the level, modality and regimen of drug exposure. The convergence of these factors may induce distinct alterations of the expression of CB receptors, as well as their functional link to downstream effectors (such as other neurotransmitter systems), thereby shaping the subjective effects of cannabis, as well as its role in the pathophysiology of mental disorders. Accordingly, chronic environmental stress has been shown to predispose to some untoward effects of cannabis and to induce changes in CB₁ receptor expression in experimental animals [104,142,212,213].

On the other hand, chronic consumption of cannabis may facilitate the onset of psychiatric disorders by inducing a down-regulation of the endocannabinoid system. Most long-term sequelae of cannabis chronic consumption may not strictly result from the intrinsic behavioral effects of the drug, but mainly from the progressive neuroplastic processes enacted as a homeostatic response to the prolonged exposure to exogenous cannabinoids. Such mechanisms may lead to a progressive reduction of the synthesis and signaling of anandamide and 2-AG, as well as to a desensitization of CB receptors, possibly promoting the progression of certain psychiatric disorders.

The recent availability of a positron emission tomography (PET) tracer for in vivo brain imaging of the CB₁ receptor in humans and monkeys [214,215] affords a unique opportunity to test the specific role of this receptor in the vulnerability to the subjective responses to cannabis. Indeed, these ligands have already been employed to show gender differences in CB₁ expression of healthy probands [216], and document an association between low CB₁ receptor density and novelty-seeking personality trait [217]. These studies are paving the way for further work on a more detailed analysis of the neurobiological mechanisms by which several vulnerability factors may affect CB receptor responsiveness and influence the pathophysiology of cannabinoid-related mental disorders.
References

1. Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: National Findings; Office of Applied Studies: Rockville, MD, USA, 2009. NSDUH Series H-36, HHS Publication No. SMA 09-4434.

2. Gledhill-Hoyt, J.; Lee, H.; Strote, J.; Wechsler, H. Increased use of marijuana and other illicit drugs at US colleges in the 1990s: results of three national surveys. Addiction 2000, 95, 1655-1667.

3. Degenhardt, L.; Lynskey, M.; Hall, W. Cohort trends in the age of initiation of drug use in Australia. Aust. N.Z.J. Public. Health 2000, 24, 421-426.

4. Arseneault, L.; Cannon, M.; Witton, J.; Murray, R.M. Causal association between cannabis and psychosis: examination of the evidence. Br. J. Psychiatry 2004, 184, 110-117.

5. Smit, F.; Bolier, L.; Cuijpers, P. Cannabis use and the risk of later schizophrenia: a review. Addiction 2004, 99, 425-430.

6. Semple, D.M.; McIntosh, A.M.; Lawrie, S.M. Cannabis as a risk factor for psychosis: systematic review. J. Psychopharmacol. 2005, 19, 187-194.

7. Ashton, C.H.; Moore, P.B.; Gallagher, P.; Young, A.H. Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. J. Psychopharmacol. 2005, 19, 293-300.

8. Moore, T.H.; Zammit, S.; Lingford-Hughes, A.; Barnes, TR.; Jones, P.B.; Burke, M.; Lewis, G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007, 370, 319-328.

9. van Laar, M.; van Dorselaer, S.; Monshouwer, K.; de Graaf, R. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? Addiction 2007, 102, 1251-1260.

10. Dixon, L.; Haas, G.; Weiden, P.; Sweeney, J.; Frances, A. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. Schizophr. Bull. 1990, 16, 69-79.

11. Dixon, L.; Haas, G.; Weiden, P.J.; Sweeney, J.; Frances, A.J. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am. J. Psychiatry 1991, 148, 224-230.

12. Häfner, H. Schizophrenia and depression. Eur. Arch. Psychiatry Clin. Neurosci. 2005, 255, 157-158.

13. Arendt, M.; Rosenberg, R.; Fjordback, L.; Brandholdt, J.; Foldager, L.; Sher, L.; Munk-Jørgensen, P. Testing the self-medication hypothesis of depression and aggression in cannabis-dependent subjects. Psychol. Med. 2007, 37, 935-945.

14. El-Sohly, M.A.; Slade, D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005, 78, 539-548.

15. Izzo, A.A.; Borrelli, F.; Capasso, R.; Di Marzo, V.; Mechoulam, R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol. Sci. 2009, 30, 515-527.

16. Gaoni, Y.; Mechoulam, R. Isolation, structure and partial synthesis of an active constituent of hashish. J. Amer. Chem. Soc. 1964, 86, 1646.
17. El-Alfy, A.T.; Ivey, K.; Robinson, K.; Ahmed, S.; Radwan, M.; Slade, D.; Khan, I.; El-Sohly, M.; Ross, S. Antidepressant-like effect of Delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa. *Pharmacol. Biochem. Behav.* **2010**, *95*, 434-442.

18. Zuardi, A.W. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev. Bras. Psiquiatr.* **2008**, *30*, 271-280.

19. Scuderi, C.; Filippis, D.D.; Iuvone, T.; Blasio, A.; Steardo, A.; Esposito, G. Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders. *Phytother. Res.* **2009**, *23*, 597-602.

20. Matsuda, L.A.; Lolait, S.J.; Brownstein, M.J.; Young, A.C.; Bonner, T.I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *346*, 561-564.

21. Munro, S.; Thomas, K.L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61-65.

22. Herkenham, M.; Lynn, A.B.; Little, M.D.; Johnson, M.R.; Melvin, L.S.; de Costa, B.R.; Rice, K.C. Cannabinoid receptor localization in brain. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 1932-1936.

23. Herkenham, M.; Lynn, A.B.; Johnson, M.R.; Melvin, L.S.; de Costa, B.R.; Rice, K.C. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J. Neurosci.* **1991**, *11*, 563-583.

24. Glass, M.; Faull, R.L.M.; Dragunow, M. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study on the fetal neonatal and adult human brain. *Neuroscience* **1997**, *77*, 299-318.

25. Katona, I.; Rancz, E.A.; Acsady, L.; Ledent, C.; Mackie, K.; Hajos, N.; Freund, T.F. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. *J. Neurosci.* **2001**, *21*, 9506-9518.

26. Hajas, N.; Freund, T.F. Pharmacological separation of cannabinoid sensitive receptors on hippocampal excitatory and inhibitory fibers. *Neuropsychopharmacology* **2002**, *43*, 503-510.

27. Galiègue, S.; Mary, S.; Marchand, J.; Dussossoy, D.; Carrière, D.; Carayon, P.; Bouaboula, M.; Shire, D.; Le Fur, G.; Casellas, P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur. J. Biochem.* **1995**, *232*, 54-61.

28. Van Sickle, M.D.; Duncan, M.; Kingsley, P.J.; Mouihate, A.; Urbani, P.; Mackie, K.; Stella, N.; Makriyannis, A.; Piomelli, D.; Davison, J.S.; Marnett, L.J.; Di Marzo, V.; Pittman, Q.J.; Patel, K.D.; Sharkey, K.A. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* **2005**, *310*, 329-332.

29. Gong, J.P.; Onaivi, E.S.; Ishiguro, H.; Liu, Q.R.; Tagliaferro, P.A.; Brusco, A.; Uhl, G.R. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res.* **2006**, *1071*, 10-23.

30. Domenici, M.R.; Azad, S.C.; Marsicano, G.; Schierloh, A.; Wotjak, C.T.; Dodt, H.U.; Zieglgänsberger, W.; Lutz, B.; Rammes, G. Cannabinoid receptor type 1 located on presynaptic terminals of principal neurons in the forebrain controls glutamatergic synaptic transmission. *J. Neurosci.* **2006**, *26*, 5794-5799.

31. Kawamura, Y.; Fukaya, M.; Maejima, T.; Yoshida, T.; Miura, E.; Watanabe, M.; Ohno-Shosaku, T.; Kano, M. The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum. *J. Neurosci.* **2006**, *26*, 2991-3001.
32. Onaivi, E.S. Neuropsychobiological evidence for the functional presence and expression of cannabinoid CB2 receptors in the brain. *Neuropsychobiology* **2006**, *54*, 231-246.

33. Brusco, A.; Tagliaferro, P.; Saez, T.; Onaivi, E.S. Postsynaptic localization of CB2 cannabinoid receptors in the rat hippocampus. *Synapse* **2008**, *62*, 944-949.

34. Morishita, W.; Alger, B.E. Evidence for endogenous excitatory amino acids as mediators in DSI of GABA(A)ergic transmission in hippocampal CA1. *J. Neurophysiol.* **1999**, *82*, 2556-2564.

35. Wilson, R.I.; Nicoll, R.A. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature* **2001**, *410*, 588-592.

36. Ohno-Shosaku, T.; Maejima, T.; Kano, M. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron* **2001**, *29*, 729-738.

37. Varma, N.; Carlson, G.C.; Ledent, C.; Alger, B.E. Metabotropic glutamate receptors drive the endocannabinoid system in hippocampus. *J. Neurosci.* **2001**, *21*, RC188.

38. Hashimotodani, Y.; Ohno-Shosaku, T.; Kano, M. Endocannabinoids and synaptic function in the CNS. *Neuroscientist* **2007**, *13*, 127-137.

39. Hájos, N.; Katona, I.; Naiem, S.S.; MacKie, K.; Ledent, C.; Mody, I.; Freund, T.F. Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. *Eur. J. Neurosci.* **2000**, *12*, 3239-3249.

40. Wager-Miller, J.; Westenbroek, R.; Mackie, K. Dimerization of G protein-coupled receptors: CB1 cannabinoid receptors as an example. *Chem. Phys. Lipids* **2002**, *121*, 83–89.

41. Mackie, K. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handb. Exp. Pharmacol.* **2005**, *168*, 299-325.

42. Hojo, M.; Sudo, Y.; Ando, Y.; Minami, K.; Takada, M.; Matsubara,T.; Kanaide, M.; Taniyama, K.; Sumikawa, K.; Uezono, Y. mu-Opioid receptor forms a functional heterodimer with cannabinoid CB1 receptor: electrophysiological and FRET assay analysis. *J. Pharmacol. Sci.* **2008**, *108*, 308-319.

43. Devane, W.A.; Hanus, L.; Breuer, A.; Pertwee, R.G.; Stevenson, L.A.; Griffi n, G.; Gibson, D.; Mandelbaum, A.; Ettinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **1992**, *258*, 1946-1949.

44. Mechoulam, R.; Ben-Shabat, S.; Hanus, L.; Ligumsky, M.; Kaminski, N.E.; Schatz, A.R.; Gopher, A.; Almog, S.; Martin, B.R.; Compton, D.R. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem. Pharmacol.* **1995**, *50*, 83-90.

45. Sugiura, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* **1995**, *215*, 89-97.

46. Di Marzo, V.; Fontana, A.; Cadas, H.; Schinelli, S.; Cimino, G.; Schwartz, J.C.; Piomelli, D. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature* **1994**, *372*, 686-691.

47. Cadas, H.; di Tomaso, E.; Piomelli, D. Occurrence and biosynthesis of endogenous cannabinoid precursor, N-arachidonoyl phosphatidylethanolamine, in rat brain. *J. Neurosci.* **1997**, *17*, 1226-1242.

48. Gerdesman, G.L.; Ronson, J.; Lovinger, D.M. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. *Nat. Neurosci.* **2002**, *5*, 446-451.
49. Robbe, D.; Alonso, G.; Chaumont, S.; Bockaert, J.; Manzoni, O.J. Role of p/q-Ca\(^{2+}\) channels in metabotropic glutamate receptor 2/3-dependent presynaptic long-term depression at nucleus accumbens synapses. *J. Neurosci.* 2002, 22, 4346-4356.

50. Sjostrom, P.J.; Turrigiano, G.G.; Nelson, S.B. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. *Neuron* 2003, 39, 641-654.

51. Jung, K.M.; Mangieri, R.; Stapleton, C.; Kim, J.; Fegley, D.; Wallace, M.; Mackie, K.; Piomelli, D. Stimulation of endocannabinoid formation in brain slice cultures through activation of group I metabotropic glutamate receptors. *Mol. Pharmacol.* 2005, 68, 1196-1202.

52. Kim, J.; Alger, B.E. Inhibition of cyclooxygenase-2 potentiates retrograde endocannabinoid effects in hippocampus. *Nat. Neurosci.* 2004, 7, 697-698.

53. Makara, J.K.; Mor, M.; Fegley, D.; Szabo, S.I.; Kathuria, S.; Astarita, G.; Duranti, A.; Tontini, A.; Tarzia, G.; Rivara, S.; Freund, T.F.; Piomelli, D. Selective inhibition of 2-AG hydrolysis enhances endocannabinoid signaling in hippocampus. *Nat. Neurosci.* 2005, 8, 1139-1141.

54. Giuffrida, A.; Parsons, L.H.; Kerr, T.M.; Rodriguez de Fonseca, F.; Navarro, M.; Piomelli, D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. *Nat. Neurosci.* 1999, 2, 358-363.

55. Gobbi, G.; Bambico, F.R.; Mangieri, R.; Bortolato, M.; Campolongo, P.; Solinas, M.; Cassano, T.; Morgese, M.G.; Debonnel, G.; Duranti, A.; Tontini, A.; Tarzia, G.; Mor, M.; Trezza, V.; Goldberg, S.R.; Cuomo, V.; Piomelli, D. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc. Natl. Acad. Sci. USA* 2005, 102, 18620-18625.

56. Muntoni, A.L.; Pillolla, G.; Melis, M.; Perra, S.; Gessa, G.L.; Pistis, M. Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. *Eur. J. Neurosci.* 2006, 23, 2385-2394.

57. Weidenfeld, J.; Feldman, S.; Mechoulam, R. Effect of the brain constituent anandamide, a cannabinoid receptor agonist, on the hypothalamo-pituitary-adrenal axis in the rat. *Neuroendocrinology* 1994, 59, 110-122.

58. Manzanares, J.; Corchero, J.; Romero J.; Fernandez-Ruiz, J.J.; Ramos, J.A.; Fuentes, J.A. Pharmacological and biochemical interactions between opioids and cannabinoids. *Trends Pharmacol. Sci.* 1999, 20, 287-294.

59. Beinfeld, M.C.; Connolly, K. Activation of CB1 cannabinoid receptors in rat hippocampal slices inhibits potassium-evoked cholecystokinin release, a possible mechanism contributing to the spatial memory defects produced by cannabinoids. *Neurosci. Lett.* 2001, 301; 69–71.

60. Valverde, O.; Ledent, C.; Beslot, F.; Parmentier, M.; Roques, B.P. Reduction of stress-induced analgesia but not of exogenous opioid effects in mice lacking CB1 receptors. *Eur. J. Neurosci.* 2000, 12, 533-539.

61. Ghoshland, S.; Matthes, H.W.; Simonin, F.; Filliol, D.; Kieffer, B.L.; Maldonado, R. Motivational effects of cannabinoids are mediated by mu-opioid and kappa-opioid receptors. *J. Neurosci.* 2002, 22, 1146-1154.

62. Romero, E.M.; Fernandez, B.; Sagredo, O.; Gomez, N.; Urguen, L.; Guaza, C.; De Miguel, R.; Ramos, J.A.; Viveros, M.P. Antinociceptive, behavioural and neuroendocrine effects of CP 55,940 in young rats. *Brain Res. Dev. Brain Res.* 2002, 136, 85-92.
63. Hill, M.N.; Titterness, A.K.; Morrish, A.C.; Carrier, E.J.; Lee, T.T.; Gil-Mohapel, J.; Gorzalka, B.B.; Hillard, C.J.; Christie, B.R. Endogenous cannabinoid signaling is required for voluntary exercise-induced enhancement of progenitor cell proliferation in the hippocampus. Hippocampus 2010, 20, 513-523.

64. López-Moreno, J.A.; González-Cuevas, G.; Moreno, G.; Navarro, M. The pharmacology of the endocannabinoid system: functional and structural interactions with other neurotransmitter systems and their repercussions in behavioral addiction. Addict. Biol. 2008, 13, 160-187.

65. Atha, M.J.; Blanchard, S. Regular users. Self-reported drug consumption patterns and attitudes towards drugs among 1333 regular cannabis users. IDMU publications: Vigan, UK, 1999.

66. Perez-Reyes, M. The psychologic and physiologic effects of active cannabinoids. In Marihuana and Medicine; Nahas, G.; Sutin, K.M., Harvey, D.J., Agurell, S., Eds.; Humana Press: Totowa, NJ, USA, 1999; pp. 245-252.

67. Reilly, D.; Didcott, P.; Swift, W.; Hall, W. Long-term cannabis use: characteristics of users in an Australian rural area. Addiction 1998, 93, 837-846.

68. Boys, A.; Marsden, J.; Griffiths, P.; Fountain, J.; Stillwell, G.; Strang, J. Substance use among young people: the relationship between perceived functions and intentions. Addiction 1999, 94, 1043-1050.

69. Hollister, L.E. Health aspects of cannabis. Pharmacol. Rev. 1986, 38, 1-20.

70. Thomas, H. A community survey of adverse effects of cannabis use. Drug Alcohol Depend. 1996, 42, 201-207.

71. Hall, W.; Solowij, N. Adverse effects of cannabis. Lancet 1998, 352, 1611-1616.

72. Patton, G.C.; Coffey, C.; Carlin, J.B.; Degenhardt, L.; Lynskey, M.; Hall, W. Cannabis use and mental health in young people: cohort study. BMJ. 2002, 325, 1195-1198.

73. Green, B.; Kavanagh, D.; Young, R. Being stoned: a review of self-reported cannabis effects. Drug Alcohol Rev. 2003, 22, 453-460.

74. Tournier, M.; Sorbara, F.; Gindre, C.; Swendsen, J.D.; Verdoux, H. Cannabis use and anxiety in daily life: a naturalistic investigation in a non-clinical population. Psychiatry Res. 2003, 118, 1-8.

75. Dannon, P.N.; Lowengrub, K.; Amiaz, R.; Grunhaus, L.; Kotler, M. Comorbid cannabis use and panic disorder: short term and long term follow-up study. Hum. Psychopharmacol. 2004, 19, 97-101.

76. D'Souza, D.C.; Perry, E.; MacDougall, L.; Ammerman, Y.; Cooper, T.; Wu, Y.T.; Braley, G.; Gueorguieva, R.; Krystal, J.H. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 2004, 29, 1558-1572.

77. Favrat, B.; Ménétrey, A.; Augsburger, M.; Rothuizen, L.E.; Appenzeller, M.; Buclin, T.; Pin, M.; Mangin, P.; Giroud, C. Two cases of "cannabis acute psychosis" following the administration of oral cannabis. BMC Psychiatry 2005, 1, 5-17.

78. Johns, A. Psychiatric effects of cannabis. Br. J. Psychiatry 2001, 178,116-122.

79. Chopra, G.S.; Smith, J.W. Psychotic reactions following cannabis use in East Indians. Arch Gen Psychiatry 1974, 30, 24-27.

80. Solowij, N.; Michie, P.T.; Fox, A.M. Effects of long-term cannabis use on selective attention: an event-related potential study. Pharmacol. Biochem. Behav. 1991, 40, 683-688.
81. Solowij, N. Do cognitive impairments recover following cessation of cannabis use? *Life Sci.* **1995**, *56*, 2119-2126.

82. Carlini, E.A. The good and the bad effects of (-) trans-delta-9-tetrahydrocannabinol (Delta 9-THC) on humans. *Toxicon* **2004**, *44*, 461-467.

83. Solowij, N.; Pesa, N. Cognitive abnormalities and cannabis use. *Rev. Bras. Psiquiatr.* **2010**, *32*, S31-S40.

84. Kelly, T.H.; Foltin, R.W.; Rose, A.J.; Fischman, M.W.; Brady, J.V. Smoked marijuana effects on tobacco cigarette smoking behavior. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 934-944.

85. Roy-Byrne, P.P.; Uhde, T.W. Exogenous factors in panic disorder: clinical and research implications. *J. Clin. Psychiatry* **1998**, *49*, 56-61.

86. Crippa, J.A.; Zuardi, A.W.; Martin-Santos, R.; Bhattacharyya, S.; Atakan, Z.; McGuire, P.; Fusar-Poli, P. Cannabis and anxiety: a critical review of the evidence. *Hum. Psychopharmacol.* **2009**, *24*, 515-523.

87. Onaivi, E.S.; Green, M.R.; Martin, B.R. Pharmacological characterization of cannabinoids in the elevated plus maze. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 1002-1009.

88. McGregor, I.S.; Dastur, F.N.; McLellan, R.A.; Brown, R.E. Cannabinoid modulation of rat pup ultrasonic vocalizations. *Eur. J. Pharmacol.* **1996**, *313*, 43-49.

89. Rodriguez de Fonseca, F.; Rubio, P.; Menzaghi, F.; Merlo-Pich, E.; Rivier, J.; Koob, G.F.; Navarro, M. Corticotropin-releasing factor (CRF) antagonist [D-Phe12,Nle21,38,C alpha MeLeu37]CRF attenuates the acute actions of the highly potent cannabinoid receptor agonist HU-210 on defensive-withdrawal behavior in rats. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 56-64.

90. Rodriguez de Fonseca, F.; Carrera, M.R.; Navarro, M.; Koob, G.F.; Weiss, F. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science* **1997**, *276*, 2050-2054.

91. Chaperon, F.; Thiebot, M.H. Behavioral effects of cannabinoid agents in animals. *Crit. Rev. Neurobiol.* **1999**, *13*, 243-281.

92. Arevalo, C.; De Miguel, R.; Hernandez-Tristan, R. Cannabinoid effects on anxiety-related behaviours and hypothalamic neurotransmitters. *Pharmacol. Biochem. Behav.* **2001**, *70*, 123-131.

93. Berrendero F.; Maldonado R. Involvement of the opioid system in the anxiolytic-like effects induced by Delta(9)-tetrahydrocannabinol. *Psychopharmacology* **2002**, *163*, 111-117.

94. Marin, S.; Marco, E.; Bisciaia, M.; Fernandez, B.; Rubio, M.; Guaza, C.; Schmidhammer, H.; Viveros, M.P. Involvement of the kappa-opioid receptor in the anxiogenic-like effect of CP 55,940 in male rats. *Pharmacol. Biochem. Behav.* **2003**, *74*, 649-656.

95. Genn, R.F.; Tucci, S.; Marco, E.M.; Viveros, M.P.; File, S.E. Unconditioned and conditioned anxiogenic effects of the cannabinoid receptor agonist CP 55,940 in the social interaction test. *Pharmacol. Biochem. Behav.* **2004**, *77*, 567-573.

96. Bambico, F.R.; Katz, N.; Debonnel, G.; Gobbi, G. Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. *J. Neurosci.* **2007**, *27*, 11700-11711.

97. Jentsch, J.D.; Andrusiak, E.; Tran, A.; Bowers, M.B.Jr.; Roth, R.H. Delta 9-tetrahydrocannabinol increases prefrontal cortical catecholaminergic utilization and impairs spatial working memory in the rat: blockade of dopaminergic effects with HA966. *Neuropsychopharmacology* **1997**, *16*, 426-432.
98. Schneider, M.; Koch, M. The cannabinoid agonist WIN 55,212-2 reduces sensorimotor gating and recognition memory in rats. *Behav. Pharmacol.* **2002**, *13*, 29-37.

99. Castellano, C.; Rossi-Arnaud, C.; Cestari, V.; Costanzi, M. Cannabinoids and memory: animal studies. *Curr. Drug Targets CNS Neurol. Disord.* **2003**, *2*, 389-402.

100. Kosiorek, P.; Hryniewicz, A.; Bialuk, I.; Zawadzka, A.; Winnicka, M.M. Cannabinoids alter recognition memory in rats. *Pol. J. Pharmacol.* **2003**, *55*, 903-910.

101. Arguello P.A.; Jentsch J.D. Cannabinoid CB1 receptor-mediated impairment of visuospatial attention in the rat. *Psychopharmacology* **2004**, *177*, 141-150.

102. Kathuria, S.; Gaetani, S.; Fegley, D.; Valino, F.; Duranti, A.; Tontini, A.; Mor, M.; Tarzia, G.; La Rana, G.; Calignano, A.; Giustino, A.; Tattoli, M.; Palmery, M.; Cuomo, V.; Piomelli, D. Modulation of anxiety through blockade of anandamide hydrolysis. *Nat. Med.* **2003**, *9*, 76-81.

103. Bortolato, M.; Campolongo, P.; Mangieri, R.A.; Scattoni, M.L.; Frau, R.; Trezza, V.; La Rana, G.; Russo, R.; Calignano, A.; Gessa, G.L.; Cuomo, V.; Piomelli, D. Anxiolytic-like properties of the anandamide transport inhibitor AM404. *Neuropsychopharmacology* **2006**, *31*, 2652-2659.

104. Bortolato, M.; Mangieri, R.A.; Fu, J.; Kim, J.H.; Arguello, O.; Duranti, A.; Tontini, A.; Mor, M.; Tarzia, G.; Piomelli, D. Antidepressant-like activity of the fatty acid amide hydrolase inhibitor URB597 in a rat model of chronic mild stress. *Biol. Psychiatry* **2007**, *62*, 1103-1110.

105. Marchalant, Y.; Cerbai, F.; Brothers, H.M.; Wenk, G.L. Cannabinoid receptor stimulation is anti-inflammatory and improves memory in old rats. *Neurobiol. Aging* **2008**, *29*, 1894-1901.

106. Marchalant, Y.; Brothers, H.M.; Wenk, G.L. New neuron production can be increased in the hippocampus of aged rats following cannabinoid treatment. *Mol. Psychiatry* **2009**, *14*, 1068-1069.

107. Rubino, T.; Parolaro, D. Long lasting consequences of cannabis exposure in adolescence. *Mol. Cell. Endocrinol.* **2008**, *286*, S108-S113.

108. Tennant, F.S., Jr.; Groesbeck, C.J. Psychiatric effects of hashish. *Arch. Gen. Psychiatry* **1972**, *27*, 133-136.

109. Millman, R.B.; Sbriglio, R. Patterns of use and psychopathology in chronic marijuana users. *Psychiatr. Clin. North Am.* **1986**, *9*, 533-545.

110. Dorard, G.; Berthoz, S.; Haviland, M.G.; Phan, O.; Corcos, M.; Bungener, C. Multimethod alexithymia assessment in adolescents and young adults with a cannabis use disorder. *Compr. Psychiatry* **2008**, *49*, 585-592.

111. Chait, L.D.; Perry, J.L. Factors influencing self-administration of, and subjective response to, placebo marijuana. *Behav. Pharmacol.* **1992**, *3*, 545-552.

112. Miller, I.L.; Branconnier, R.J. Cannabis: effects on memory and the cholinergic limbic system. *Psychol. Bull.* **1983**, *93*, 441-456.

113. Whitlow, C.T.; Liguori, A.; Livengood, L.B.; Hart, S.L.; Mussat-Whitlow, B.J.; Lamborn, C.M.; Laurienti, P.J.; Porrino, L.J. Long-term heavy marijuana users make costly decisions on a gambling task. *Drug Alcohol Depend.* **2004**, *76*, 107-111.

114. McHale, S.; Hunt, N. Executive function deficits in short-term abstinent cannabis users. *Hum. Psychopharmacol.* **2008**, *23*, 409-415.

115. Voytek, B.; Berman, S.M.; Hassid, B.D.; Simon, S.L.; Mandelkern, M.A.; Brody, A.L.; Monterosso, J.; Ling, W.; London, E.D. Differences in regional brain metabolism associated with marijuana abuse in methamphetamine abusers. *Synapse* **2005**, *57*, 113-115.
116. Degenhardt, L.; Hall, W.; Lynskey, M. The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. *Soc. Psychiatry Psychiatr Epidemiol.* **2001**, *36*, 219-227.

117. Koenen, K.C.; Lyons, M.J.; Goldberg, J.; Simpson, J.; Williams, W.M.; Toomey, R.; Eisen, S.A.; True, W.; Tsuang, M.T. Co-twin control study of relationship among combat exposure, combat-related PTSD, and other mental disorders. *J. Trauma Stress* **2003**, *16*, 433-438.

118. Swadi, H.; Bobier, C. Substance use disorder comorbidity among inpatient youths with psychiatric disorder. *Aust. Nzl. Psychiatry* **2003**, *37*, 294-298.

119. Okulate, G.T.; Jones, O.B. Post-traumatic stress disorder, survivor guilt and substance use a study of hospitalised Nigerian army veterans. *S. Afr. Med. J.* **2006**, *96*, 144-146.

120. Zvolensky, M.J.; Bernstein, A.; Sachs-ericsson, N.; Schmidt, N.B.; Bucker, J.D.; Bonn-Miller, M.O. Lifetime associations between cannabis, use, abuse, and dependence and panic attacks in a representative sample. *J. Psychiatr. Res.* **2006**, *40*, 477-486.

121. Hayatbakhsh, M.R.; Najman, J.M.; Jamroziek, K.; Mamun, A.A.; Alati, R.; Bor, W. Cannabis and anxiety and depression in young adults: a large prospective study. *J. Am. Acad. Child Adolesc. Psychiatry* **2007**, *46*, 408-417.

122. Arseneault, L.; Cannon, M.; Poulton, R.; Murray, R.; Caspi, A.; Moffitt, T.E. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ.* **2002**, *325*, 1212-1213.

123. Fergusson, D.M.; Horwood, L.J.; Swain-Campbell, N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* **2002**, *97*, 1123-1135.

124. Rey, J.M.; Sawyer, M.G.; Raphael, B.; Patton, G.C.; Lynskey, M. Mental health of teenagers who use cannabis. Results of an Australian survey. *Br. J. Psychiatry* **2002**, *180*, 216-221.

125. Szuster, R.R.; Pontieri, F.E.; Campos, P.E. Marijuana sensitivity and panic anxiety, *J. Clin. Psychiatr.* **1988**, *49*, 427-429.

126. Strakowski, S.M.; DelBello, M.P.; Fleck, D.E.; Arndt, S. The impact of substance abuse on the course of bipolar disorder. *Biol. Psychiatry* **2000**, *48*, 477-485.

127. Baethge, C.; Baldessarini, R.J.; Khalsa, H.M.; Hennen, J.; Salvatore, P.; Tohen, M. Substance abuse in first-episode bipolar I disorder: indications for early intervention. *Am. J. Psychiatry* **2005**, *162*, 1008-1010.

128. Strakowski, S.M.; Del Bello, M.P.; Fleck, D.E.; Adler, C.M.; Anthenelli, R.M.; Keck, P.E. Jr, Arnold, L.M.; Amicone, J. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch. Gen. Psychiatry,* **2007**, *64*, 57-64.

129. Gruber, A.J.; Pope, H.G. Jr, Brown, M.E. Do patients use marijuana as an antidepressant? *Depression* **1996**, *4*, 77-80.

130. Stewart, S.H.; Karp, J.; Pihl, R.O.; Peterson, R.A. Anxiety sensitivity and self-reported reasons for drug use. *J. Subst. Abuse* **1997**, *9*, 223-240.

131. Grinspoon, L.; Bakalar, J.B. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J. Psychoactive Drugs* **1998**, *30*,171-177.

132. Ogborne, A.C.; Smart, R.G.; Adlaf, E.M. Self-reported medical use of marijuana: a survey of the general population. *CMAJ* **2000**, *162*, 1685-1686.

133. Agosti, V.; Nunes E, Levin F. Rates of psychiatric comorbidity among U.S. residents with lifetime cannabis dependence. *Am. J. Drug Alcohol Abuse* **2002**, *28*, 643-652.
134. Wittchen, H.U.; Fröhlich, C.; Behrendt, S.; Günther, A.; Rehm, J.; Zimmermann, P.; Lieb, R.; Perkonigg, A. Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. *Drug Alcohol Depend.* **2007**, *88*, S60-S70.

135. Buckner, J.; Schmidt, N.; Lang, A.; Small, J.; Schlauch, R.; Lewinsohn, P. Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. *J. Psychiatr. Res.* **2008**, *42*, 230-239.

136. Glass, R.M.; Uhlenhuth, E.H.; Hartel, F.W.; Schuster, C.R.; Fischman, M.W. A single dose study of nabilone, a synthetic cannabinoid. *Psychopharmacology* **1980**, *71*, 137-142.

137. Fabre, L.F.; McLendon, D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *J. Clin. Pharmacol.* **1981**, *21*, S377-S382.

138. Ilaria, R.L.; Thornby, J.I.; Fann, W.E. Nabilone, a cannabinoi derivative, in the treatment of anxiety neurosis. *Curr. Ther. Res.* **1981**, *29*, 943-949.

139. Vinod, K.Y.; Hungund B.L. Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol. Sci.* **2006**, *27*, 539-545.

140. Bortolato, M.; Piomelli, D. The endocannabinoid system and anxiety responses *Handbook of Behavioral Neuroscience* 17: *Handbook of anxiety and fear*, Elsevier: Amsterdam, Netherlands, **2008**; Chapter 4.5, pp. 303-324.

141. Parolaro, D.; Realini, N.; Vigano, D.; Guidali, C.; Rubino, T. The endocannabinoid system and psychiatric disorders. *Exp. Neurol.* **2010**, *224*, 3-14.

142. Hill, M.N.; Gorzalka, B.B. Pharmacological enhancement of cannabinoid CB1 receptor activity elicits an antidepressant-like response in the rat forced swim test. *Eur. Neuropsychopharmacol.* **2005**, *15*, 593-599.

143. Bersani, G.; Orlandi, V.; Kotzalidis, G.D.; Pancheri, P. Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. *Eur. Arch. Psychiatry Clin. Neurosci.* **2002**, *252*, 86-92.

144. Degenhardt, L.; Hall, W.; Lynskey, M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend.* **2003**, *71*, 37-48.

145. Fergusson, D.M.; Poulton, R.; Smith, P.F.; Boden, J.M. Cannabis and psychosis. *B.M.J.* **2006**, *332*, 172-175.

146. Andréasson, S.; Allebeck, P.; Engström, A.; Rydberg, U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* **1987**, *2*, 1483-1486.

147. van Os, J.; Bak, M.; Hanssen, M.; Bijl, R.V.; de Graaf, R.; Verdouw, H. Cannabis use and psychosis: a longitudinal population-based study. *Am. J. Epidemiol.* **2002**, *156*, 319-327.

148. Barnett, J.H.; Werners, U.; Secher, S.M.; Hill, K.E.; Brazil, R.; Masson, K.; Pernet, D.E.; Kirkbride, J.B.; Murray, G.K.; Bullmore, E.T.; Jones, P.B. Substance use in a population-based clinic sample of people with first-episode psychosis. *Br. J. Psychiatry* **2007**, *190*, 515-520.

149. Lindenmann, E.; Malamud, W. Experimental analysis of the psychopathological effects of intoxication drugs. *Am. J. Psychiatry* **1934**, *90*, 853-881.
150. D’Souza, D.C.; Abi-Saab, W.M.; Madonick, S.; Forselius-Bielen, K.; Doersch, A.; Braley, G.; Gueorguieva, R.; Cooper, T.B.; Krystal, J.H. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol. Psychiatry* **2005**, *57*, 594-608.

151. Bramon, E.; McDonald, C.; Croft, R.J.; Landau, S.; Filbey, F.; Gruzelier, J.H.; Sham, P.C.; Frangou, S.; Murray, R.M. Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study. *Neuroimage* **2005**, *27*, 960-968.

152. Roser, P.; Juckel, G.; Rentzsch, J.; Nadulski, T.; Gallinat, J.; Stadelmann, A.M. Effects of acute oral Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. *Eur. Neuropsychopharmacol.* **2008**, *18*, 569-577.

153. Braff, D.L.; Geyer, M.A.; Swerdlow, N.R. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology* **2001**, *156*, 234-258.

154. Kedzior, K.K.; Martin-Iverson, M.T. Attention-dependent reduction in prepulse inhibition of the startle reflex in cannabis users and schizophrenia patients--a pilot study. *Eur. J. Pharmacol.* **2007**, *560*, 176-182.

155. Peraltar, V.; Cuesta, M.J. Influence of cannabis abuse on schizophrenic psychopathology. *Acta Psychiatr. Scand.* **1992**, *85*, 127-130.

156. Schofield, D.; Tennant, C.; Nash, L.; Degenhardt, L.; Cornish, A.; Hobbs, C.; Brennan, G. Reasons for cannabis use in psychosis. *Aust. N. Z. J. Psychiatry* **2006**, *40*, 570-574.

157. Test, M.A.; Wallisch, L.S.; Allness, D.J.; Ripp, K. Substance use in young adults with schizophrenic disorders. *Schizophr. Bull.* **1999**, *15*, 465-476.

158. Fernandez-Espejo, E.; Viveros, M.P.; Núñez, L.; Ellenbroek, B.A.; Rodriguez de Fonseca, F. Role of cannabis and endocannabinoids in the genesis of schizophrenia. *Psychopharmacology* **2009**, *206*, 531-549.

159. Dean, B.; Sundram, S.; Bradbury, R.; Scarr, E.; Copolov, D. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience* **2001**, *103*, 9-15.

160. Zavitsanou, K.; Garrick, T.; Huang, X.F. Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2004**, *28*, 355-360.

161. Koethe, D.; Llenos, I.C.; Dulay, J.R.; Hoyer, C.; Torrey, E.F.; Leweke, F.M.; Weis, S. Expression of CB1 cannabinoid receptor in the anterior cingulate cortex in schizophrenia, bipolar disorder, and major depression. *J. Neural. Transm.* **2007**, *114*, 1055-63.

162. Eggan, S.M.; Hashimoto, T.; Lewis, D.A. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. *Arch. Gen. Psychiatry* **2008**, *65*, 772-784.

163. Leweke, F.M.; Giuffrida, A.; Koethe, D.; Schreiber, D.; Nolden, B.M.; Kranaster, L.; Neatby, M.A.; Schneider, M.; Gerth, C.W.; Hellmich, M.; Klosterkötter, J.; Piomelli, D. Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. *Schizophr. Res.* **2007**, *94*, 29-36.

164. Giuffrida, A.; Leweke, F.M.; Gerth, C.W.; Schreiber, D.; Koethe, D.; Faulhaber, J.; Klosterkötter, J.; Piomelli, D. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacology* **2004**, *29*, 2108-2114.
165. Bossong, M.G.; Niesink, R.J. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. Prog. Neurobiol. 2010, doi:10.1016/j.pneurobio.2010.06.010.

166. Schneider, M.; Koch, M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. Neupropsychopharmacology 2003, 28, 1760-1769.

167. Bortolato, M.; Aru, G.N.; Frau, R.; Orrù, M.; Luckey, G.C.; Boi, G.; Gessa, G.L. The CB receptor agonist WIN 55,212-2 fails to elicit disruption of prepulse inhibition of the startle in Sprague-Dawley rats. Psychopharmacology 2005, 177, 264-271.

168. McGuire, P.K.; Jones, P.; Harvey, I.; Williams, M.; McGuffin, P.; Murray, R.M. Morbid risk of schizophrenia for relatives of patients with cannabis-associated psychosis. Schizophr. Res. 1995, 15, 277-281.

169. Zhang, P.W.; Ishiguro, H.; Ohtsuki, T.; Hess, J.; Carillo, F.; Walther, D.; Onaivi, E.S.; Arinami, T.; Uhl, G.R. Human cannabinoid receptor 1',5'-exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. Mol. Psychiatry 2004, 9, 916-931.

170. Comings, D.E.; Muhleman, D.; Gade, R.; Johnson, P.; Verde, R.; Saucier, G.; MacMurray, J. Cannabinoid receptor gene (CNR1), association with i.v. drug use. Mol. Psychiatry 1997, 2, 161-168.

171. Ponce, G.; Hoenicka, J.; Rubio, G.; Ampuero, I.; Jiménez-Arriero, M.A.; Rodríguez-Jiménez, R.; Palomo, T.; Ramos, J.A. Association between cannabinoid receptor gene (CNR1) and childhood attention deficit/hyperactivity disorder in Spanish male alcoholic patients. Mol. Psychiatry 2003, 8, 466-467.

172. Schmidt, L.G.; Samochowiec, J.; Finckh, U.; Fiszer-Piosik, E.; Horodnicki, J.; Wendel, B.; Rommelspacher, H.; Hoehe, M.R. Association of a CB1 cannabinoid receptor gene (CNR1) polymorphism with severe alcohol dependence. Drug Alcohol Depend. 2002, 65, 221-224.

173. Ehlers, C.L.; Slutske, W.S.; Lind, P.A.; Wilhelmsen, K.C. Association between single nucleotide polymorphisms in the cannabinoid receptor gene (CNR1) and impulsivity in southwest California Indians. Twin. Res. Hum. Genet. 2007, 10, 805-811.

174. Juhasz, G.; Chase, D.; Pegg, E.; Downey, D.; Toth, Z.G.; Stones, K.; Platt, H.; Mekli, K.; Payton, A.; Elliott, R.; Anderson, I.M.; Deakin, J.F. CNR1 gene is associated with high neuroticism and low agreeableness and interacts with recent negative life events to predict current depressive symptoms. Neupropsychopharmacology 2009, 34, 2019-2027.

175. Chakrabarti, B.; Kent, L.; Suckling, J.; Bullmore, E.; Baron-Cohen, S. Variations in the human cannabinoid receptor (CNR1) gene modulate striatal responses to happy faces. Eur. J. Neurosci. 2006, 23, 1944-1948.

176. Domschke, K.; Dannlowski, U.; Ohrmann, P.; Lawford, B.; Bauer, J.; Kugel, H.; Heindel, W.; Young, R.; Morris, P.; Arolt, V.; Deckert, J.; Suslow, T.; Baune, B.T. Cannabinoid receptor 1 (CNR1) gene: impact on antidepressant treatment response and emotion processing in major depression. Eur. Neuropsychopharmacol. 2008, 18, 751-759.
177. Barrero, F.J.; Ampuero, I.; Morales, B.; Vives, F.; de Dios Luna Del Castillo, J.; Hoenicka, J.; García Yébenes, J. Depression in Parkinson's disease is related to a genetic polymorphism of the cannabinoid receptor gene (CNR1). *Pharmacogenomics J.* 2005, 5, 135-141.

178. Ujike, H.; Takaki, M.; Nakata, K.; Tanaka, Y.; Takeda, T.; Kodama, M.; Fujiwara, Y.; Sakai, A.; Kuroda, S. CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Mol. Psychiatry* 2002, 7, 515-518.

179. Chavarria-Siles, I.; Contreras-Rojas, J.; Hare, E.; Walss-Bass, C.; Quezada, P.; Dassori, A.; Contreras, S.; Medina, R.; Ramírez, M.; Salazar, R.; Raventos, H.; Escamilla, M.A. Cannabinoid receptor 1 gene (CNR1) and susceptibility to a quantitative phenotype for hebephrenic schizophrenia. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* 2008, 147, 279-284.

180. Seifert, J.; Ossege, S.; Emrich, H.M.; Schneider, U.; Stuhrmann, M. No association of CNR1 gene variations with susceptibility to schizophrenia. *Neurosci. Lett.* 2007, 426, 29-33.

181. Hamdani, N.; Tabeze, J.P.; Ramoz, N.; Ades, J.; Hamon, M.; Sarfati, Y.; Boni, C.; Gorwood, P. The CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene for schizophrenia. *Eur. Neuropsychopharmacol.* 2008, 18, 34-40.

182. Henquet, C.; Di Forti, M.; Morrison, P.; Kuepper, R.; Murray, R.M. Gene-environment interplay between cannabis and psychosis. *Schizophr. Bull.* 2008, 34, 1111-1121.

183. Caspi, A.; Moffitt, T.E.; Cannon, M.; McClay, J.; Murray, R.; Harrington, H.; Taylor, A.; Arseneault, L.; Williams, B.; Braithwaite, A.; Poulton, R.; Craig, I.W. 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* 2005, 57, 1117-1127.

184. Henquet, C.; Rosa, A.; Krabbendam, L.; Papiol, S.; Fananás, L.; Drukker, M.; Ramaekers, J.G.; van Os, J. An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* 2006, 31, 2748-2757.

185. Boucher, A.A.; Arnold, J.C.; Duffy, L.; Schofield, P.R.; Micheau, J.; Karl, T. Heterozygous neuregulin 1 mice are more sensitive to the behavioural effects of Delta9-tetrahydrocannabinol. *Psychopharmacology* 2007, 192, 325-336.

186. Benyamina, A.; Bonhomme-Faivre, L.; Picard, V.; Sabbagh, A.; Richard, D.; Blecha, L.; Rahioui, H.; Karila, L.; Lukasiewicz, M.; Farinotti, R.; Picard, V.; Marill, C.; Reynaud, M. Association between ABCB1 C3435T polymorphism and increased risk of cannabis dependence. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2009, 33, 1270-1274.

187. Alenius, M.; Wadelius, M.; Dahl, M.L.; Hartvig, P.; Lindström, L. Hammarlund-Udenaes M. Gene polymorphism influencing treatment response in psychotic patients in a naturalistic setting. *J. Psychiatr. Res.* 2008, 42, 884-893.

188. Kato, M.; Fukuda, T.; Serretti, A.; Wakeno, M.; Okugawa, G.; Ikenaga, Y.; Hosoi, Y.; Takekita, Y.; Mandelli, L.; Azuma, J.; Kinoshita, T. ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2008, 32, 398-404.

189. Pope, H.G., Jr; Gruber, A.J.; Hudson, J.I.; Huestis, M.A.; Yurgelun-Todd, D. Neuropsychological performance in long-term cannabis users. *Arch. Gen. Psychiatry* 2001, 58, 909-915.
190. Jacobsen, L.K.; Mencl, W.E.; Westerveld, M.; Pugh, K.R. Impact of cannabis use on brain function in adolescents. *Ann. N. Y. Acad. Sci.* **2004**, *1021*, 384-390.

191. Novaes, M.A.; Guindalini, C.; Almeida, P.; Jungerman, F.; Bolla, K.; Laranjeira, R.; Lacerda, A.; Bressan, R.A. Cannabis use before age 15 years is associated with poorer attention and executive function. *Biol. Psychiatry* **2008**, *63*, S18-S19.

192. Galve-Roperh, I.; Aguado, T.; Palazuelos, J.; Guzmán, M. The endocannabinoid system and neurogenesis in health and disease. *Neuroscientist* **2007**, *13*, 109-114.

193. Giedd, J.N.; Jeffries, N.O.; Blumenthal, J.; Castellanos, F.X.; Vaituzis, A.C.; Fernandez, T.; Hamburger, S.D.; Liu, H.; Nelson, J.; Bedwell, J.; Tran, L.; Lenane, M.; Nicolson, R.; Rapoport, J.L. Childhood-onset schizophrenia: progressive brain changes during adolescence. *Biol. Psychiatry* **1999**, *46*, 892-898.

194. Crews, F.; He, J.; Hodge, C. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol. Biochem. Behav.* **2007**, *86*, 189-199.

195. Rapoport, J.L.; Addington, A.M.; Frangou, S.; Psych, M.R. The neurodevelopmental model of schizophrenia: update 2005. *Mol. Psychiatry* **2005**, *10*, 434-449.

196. Feeney, G.F.; Connor, J.P.; Young, R.M.; Tucker, J.; McPherson, A. Cannabis dependence and mental health perception amongst people diverted by police after arrest for cannabis-related offending behaviour in Australia. *Crim. Behav. Ment. Health* **2005**, *15*, 249-260.

197. Fattore, L.; Fratta, W. How important are sex differences in cannabinoid action? *Br. J. Pharmacol.* **2010**, *160*, 544-548.

198. O'Shea, M.; Singh, M.E.; McGregor, I.S.; Mallet, P.E. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. *J. Psychopharmacol.* **2004**, *18*, 502-508.

199. O'Shea, M.; McGregor, I.S.; Mallet, P.E. Repeated cannabinoid exposure during perinatal; adolescent or early adult ages produces similar long-lasting deficits in object recognition and reduced social interaction in rats. *Psychopharmacol* **2006**, *20*, 611-621.

200. Rubino, T.; Realini, N.; Braida, D.; Alberio, T.; Capurro, V.; Viganò, D.; Guidali, C.; Sala, M.; Fasano, M.; Parolaro, D. 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.* **2009**, *15*, 291-302.

201. Naliboff, B.D.; Rickles, W.H.; Cohen, M.J.; Naimark, R.S. Interactions of marijuana and induced stress: forearm blood flow, heart rate, and skin conductance. *Psychophysiology* **1976**, *13*, 517-522.

202. Stark-Adamec, C.; Adamec, R.E.; Pihl, R.O. The subjective marijuana experience: great expectations. *Int. J. Addict.* **1981**, *16*, 1169-1181.

203. Davidson, E.S.; Schenk, S. Variability in subjective responses to marijuana: initial experiences of college students. *Addict. Behav.* **1994**, *19*, 531-538.

204. Manzanares, J.; Urigüen, L.; Rubio, G.; Palomo, T. Role of endocannabinoid system in mental diseases. *Neurotox. Res.* **2004**, *6*, 213-224.

205. Henquet, C.; Murray, R.; Linszen, D.; van Os, J. The environment and schizophrenia: the role of cannabis use. *Schizophr. Bull.* **2005**, *31*, 608-612.
206. Cougnard, A.; Marcelis, M.; Myin-Germeys, I.; De Graaf, R.; Vollebergh, W.; Krabbendam, L.; Lieb, R.; Wittchen, H.U.; Henquet, C.; Spauwen, J.; Van Os, J. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychol. Med.* 2007, 37, 513-527.

207. Harley, M.; Kelleher, I.; Clarke, M.; Lynch, F.; Arseneault, L.; Connor, D.; Fitzpatrick, C.; Cannon, M. Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychol. Med.* 2009, 9, 1-8.

208. Kendler, K.S.; Schmitt, E.; Aggen, S.H.; Prescott, C.A. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Arch. Gen. Psychiatry.* 2008, 65, 674-682.

209. Ramsay, M.; Percy, A. Drug misuse declared: results of the 1994 British Crime Survey. Home Office Research and Statistics Department: Croydon, UK, 1996

210. Pertwee, R. The evidence for the existence of cannabinoid receptors. *Gen. Pharmacol.* 1993, 24, 811-824.

211. Zuardi, A.W.; Guimaraes, F.S.; Moreira, A.C. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. *Braz. J. Med. Biol. Res.* 1993, 26, 213-217.

212. Malone, D.T.; Kearn, C.S.; Chongue, L.; Mackie, K.; Taylor, D.A. Effect of social isolation on CB1 and D2 receptor and fatty acid amide hydrolase expression in rats. *Neuroscience* 2008, 152, 265-272.

213. Sciolino, N.R.; Bortolato, M.; Eisenstein, S.A.; Fu, J.; Oveisi, F.; Hohmann, A.G.; Piomelli, D. Social isolation and chronic handling alter endocannabinoid signaling and behavioral reactivity to context in adult rats. *Neuroscience* 2010, 168, 371-386.

214. Burns, H.D.; Van Laere, K.; Sanabria-Bohórquez, S.; Hamill, T.G.; Bormans, G.; Eng, W.S.; Gibson, R.; Ryan, C.; Connolly, B.; Patel, S.; Krause, S.; Vanko, A.; Van Hecken, A.; Dupont, P.; De Lepelere, I.; Rothenberg, P.; Stoch, S.A.; Cote, J.; Hagmann, W.K.; Jewell, J.P.; Lin, L.S.; Liu, P.; Goulet, M.T.; Gottesdiener, K.; Wagner, J.A.; de Hoon, J.; Mortelmans, L.; Fong, T.M.; Hargreaves, R.J. [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. *Proc. Natl. Acad. Sci. USA* 2007, 104, 9800-9805.

215. Hamill, T.G.; Lin, L.S.; Hamann, W.; Liu, P.; Jewell, J.; Sanabria, S.; Eng, W.; Ryan, C.; Fong, T.M.; Connolly, B.; Vanko, A.; Hargreaves, R.; Goulet, M.T.; Burns, H.D. PET imaging studies in rhesus monkey with the cannabinoid-1 (CB1) receptor ligand [11C]CB-119. *Mol. Imaging. Biol.* 2009, 11, 246-252.

216. Van Laere, K.; Goffin, K.; Casteels, C.; Dupont, P.; Mortelmans, L.; de Hoon, J.; Bormans, G. Gender-dependent increases with healthy aging of the human cerebral cannabinoid-type 1 receptor binding using [(18)F]MK-9470 PET. *Neuroimage* 2008, 39, 1533-1541.

217. Van Laere, K.; Goffin, K.; Bormans, G.; Casteels, C.; Mortelmans, L.; de Hoon, J.; Grachev, I.; Vandenbulcke, M.; Pieters, G. Relationship of type 1 cannabinoid receptor availability in the human brain to novelty-seeking temperament. *Arch. Gen. Psychiatry* 2009, 66, 196-204.

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