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Exposure to cannabinoids can lead to persistent cognitive and psychiatric disorders

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Abstract

Background: Cannabinoids are proposed in a wide array of medical indications. Yet, the evaluation of adverse effects in controlled clinical studies, following the evidence-based model, has partly been bypassed. On the other hand, studies on the consequences of recreational use of cannabis and experimental studies bring some insights on the potential long-term consequences of cannabinoids use.

Results: Epidemiological studies have consistently demonstrated that cannabis use is associated with a risk of persistent cognitive deficits and increased risk of schizophrenia-like psychoses. These risks are modulated by the dose and duration of use, on top of age of use and genetic factors, including partially shared genetic predisposition with schizophrenia. Experimental studies in healthy humans showed that cannabis and its principal psychoactive component, the delta-9-tetrahydrocannabinol (THC), could produce transient, dose-dependent, psychotic symptoms as well as cognitive effects, which can be attenuated by cannabidiol (CBD). Studies in rodents have confirmed these effects and shown that adolescent exposure results in structural changes and impaired synaptic plasticity, impacting fronto-limbic systems that are critically involved in higher brain functions. The endocannabinoid system plays an important role in brain maturation. Its over-activation by cannabinoid receptor type 1 agonists (e.g., THC) during adolescence and the resulting changes in neuroplasticity could alter brain maturation and cause long-lasting changes that persist in the adult brain.

Conclusions: Exposure to cannabinoids can have long-term impact on the brain, with an inter-individual variability that could be conveyed by personal and family history of psychiatric disorders and genetic background. Adolescence and early adulthood are critical periods of vulnerability.

Significance: The assessment of benefice–risk balance of medical use of cannabis and cannabinoids needs to carefully explore populations that could be more at-risk of psychiatric and cognitive complications.

1 | INTRODUCTION

In the last decade, public and media have advocated the use of cannabis as a therapy in various medical conditions, and especially as a safe and natural pain reliever (Whiting et al., 2015). Currently, several European countries, Canada and many states in the United States have already legalized medical cannabis but only a minority of states in the United

States (9 out of 50) have legalized recreational cannabis. Considering that nowadays cannabinoids can be available through the web, medical cannabis has become a reality in many countries, mostly through self-medication. Public and political pressures have somewhat bypassed the usual evidence-based medicine approach that carefully weighs the benefit–risk balance (D'Souza & Ranganathan, 2015). In absence of well-designed studies leading to recommendations on dose, identification of potential interactions or contra-indications, patients explore by themselves therapeutic strategies in a trial-and-error process that can be harmful. The variation in cannabinoids composition of the various strain of cannabis is also often overlooked, at least in the information available to the community. A recent overview on the use and approval of cannabis-based medicine in Europe has shown inconsistent findings on the efficacy of these medications in neuropathic pain (Häuser, Petzke, & Fitzcharles, 2018). Current studies with cannabis-based medicines for chronic pain syndromes are being conducted, and an update of these studies will be necessary in a few years to make a conclusion (Häuser et al., 2018). While the benefit in each medical condition will require specific clinical studies, the adverse effects after exposure to cannabis can be inferred from numerous studies that explored the consequences of recreational use of cannabis, including prospective epidemiological studies and experimental studies in humans and rodents (e.g., Curran et al., 2016; Gruber & Sagar, 2017; Murray et al., 2017; Renard, Krebs, Le Pen, & Jay, 2014; Rubino & Parolaro, 2016; Sherif, Radhakrishnan, D'Souza, & Ranganathan, 2016). The acute psychotropic effect of cannabinoids is well-known, since its ancestral use in several social rituals and more specifically since the description by the French doctor, Moreau de Tours, reporting on the observations of the "Hashishin club" members, including the famous poet Charles Baudelaire (Moreau, 2012). The main psychoactive effects of cannabis are due to its action on cannabinoid receptor type 1 (CB1R). Their activation induces the synthesis and release of endocannabinoids (eCB), including anandamide, or 2-arachidonoylglycerol (2-AG) that can be released to back modulate the presynaptic terminals. In addition to its high concentration in the cerebellar cortex, CB1R is present at high density in limbic areas of the brain (e.g., the amygdala, prefrontal cortex and hippocampus; reviewed in Curran et al., 2016). These brain areas that play a role in processing emotional information, learning and memory are involved in neuropsychiatric disorders (including anxiety, depression and schizophrenia; Godsil, Kiss, Spedding, & Jay, 2013). In this narrative review, our objective is to outline the main lessons to bear in mind regarding the potential alterations in brain function that can result from cannabis exposure, and especially the cognitive and psychiatric consequences.

2 | CANNABIS USE AND CANNABIS USE DISORDERS

Cannabis is among the most widely used illicit drug in adolescents and young adults. Prevalence of experimentation at the age of 17 is almost one out of two in 43 countries and regions in the WHO European Regions and North America (Currie et al., 2012). As many as 20% of all 16-year-old surveyed persons reported using cannabis. Cannabis contains several cannabinoids. Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive component acting as a partial agonist of the CB1R. Its concentration largely varies in the different strains of cannabis, ranging from 6%–14% to 20% in certain strain (e.g., "skunk"). Cannabis use disorder (CUD) is the continued use of cannabis despite clinically significant distress or impairment. CUD is defined in the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). Typically, it includes a strong desire to take the drug, difficulties in controlling its use, a persistent use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, an increased tolerance, and sometimes a physical withdrawal state. There is now no doubt that long-term cannabis use can lead to addiction. Approximately one in 11 people who experienced cannabis will become dependent in their lifetime, but this risk is almost doubled if use starts in adolescence. 25% to 50% of daily users will become dependent (Englund, Freeman, Murray, & McGuire, 2017). In more recent US national data (2012–2013), among 9.52% of US adults using cannabis in the past year, 2.9% had a diagnosis of DSM-IV CUD, i.e., three out of 10 cannabis users (Hasin, 2018). Moreover, extending analyses of DSM-5 diagnoses of CUD, 19.5% of lifetime users met criteria for DSM-5 CUD, of whom 23% were symptomatically severe (>6 criteria). Since 2001–2002, the prevalence of adult past-year cannabis use and past-year CUD approximately doubled. In the United States, medical marijuana laws appear to have contributed to increased prevalence of illicit cannabis use and CUD (Hasin, 2018).

3 | CANNABIS USE AND PSYCHIATRIC DISORDERS, EPIDEMIOLOGICAL EVIDENCE

The first prospective study that demonstrated an association between cannabis use and schizophrenia in later life was conducted in young conscripts to the Swedish Military and published in 1987 by Andréasson, Allebeck, Engström, and Rydberg (1987). The authors found that "heavy" cannabis use at age 18 (more than 50 times, approximately corresponding to once a week for 1 year) led to a sixfold increased

risk of schizophrenia 15 years later. Extending the sample (more than 50,000 persons), the duration of the follow-up and the analysis to address all possible confounders, they confirm an increased risk of schizophrenia after cannabis exposure, even after eliminating potential unravelled prodromal psychosis, association of other drugs, family vulnerability, etc. This study also revealed that early cannabis consumption (i.e., at age 15) further increased the risk of developing schizophrenic symptoms at age 26 by a factor of four compared to cannabis consumption after age 18, even after controlling for predating psychotic symptoms (Arseneault et al., 2002). There are now 13 studies that consistently demonstrate that the use of cannabis increases the risk of schizophrenia-like psychosis (see for review Murray et al., 2017). A significant association was found in 10 studies and a trend in the three remaining studies. The psychotic syndrome induced by cannabis is diagnosed either cannabis-induced psychosis (when the symptoms rapidly regress after withdrawal) or schizophrenia, when the symptoms persist. This chronic condition requires antipsychotics medication for long periods (minimum 2 years, most of the time for decades if not lifetime). Noteworthy, approximately 40%–50% of patients with cannabis-induced psychosis will finally be diagnosed with schizophrenia within 3 years (Arendt, Rosenberg, Foldager, Perto, & Munk-Jørgensen, 2005), underlining the potential of cannabis to induce chronic, persistent psychotic symptoms.

The questions that are still debated are (a) the effect size and (b) the direction of association (causality). Regarding the effect size, the results vary in the different studies, which were conducted in different settings (birth cohort or general population), levels of use, type of cannabis, age thresholds, etc. A meta-analysis has recently estimated the effect as an increased risk of fourfold in a regular use of cannabis before the age of 18 with a clear dose effect (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016), an estimation which is higher than the previous ones but includes more recent studies. It may reflect the recent global increase in THC concentration in cannabis and/or the increased frequency of high-potency cannabis or synthetic cannabinoids ("spice", K2).

Regarding the direction of the association, the debate is still open. The majority of studies do not support the so-called self-medication hypothesis (i.e., people using cannabis to relieve symptoms). The high prevalence of cannabis use in early phase of psychosis might reflect the psychological distress, and anxiety seek relief by consuming cannabis. However, longitudinal studies have shown that predating psychotic symptoms strongly increase the risk for psychosis symptoms when exposed to cannabis (e.g., 75-fold in van Os et al., 2002). Cannabis use is also consistently associated with more severe psychosis, more hospitalization and poor outcome (reviewed in Murray et al., 2017; Curran et al., 2016). Patients with schizophrenia who continue to use cannabis have higher relapse rates, longer hospital admissions and more severe positive symptoms than former users who discontinued cannabis or neverusers (Schoeler et al., 2016). In addition, patients with first-episode psychosis experience both the positive and negative effects of cannabis more intensely than do healthy controls (Bianconi et al., 2016), further supporting the link between psychosis and cannabis. On the other hand, several studies have shown that cannabis-using patients with schizophrenia have higher cognitive functioning than nonusing patients (Meijer et al., 2012; Murray et al., 2017; Potvin, Joyal, Pelletier, & Stip, 2008). In addition of a possible bias due to a cross-sectional design of these studies, a possible explanation is that cannabis use and continuation require sufficient social skills and premorbid functioning. Moreover, high neurological soft signs, a marker of vulnerability for schizophrenia, were found associated with not having been a heavy cannabis user in patients with first-episode psychosis, suggesting that cannabis-using patients do not carry vulnerability to schizophrenia (Ruiz-Veguilla et al., 2009). Although in partial contradiction with the genetic findings exposed hereafter suggesting shared genetic background, the data suggest a potentially different pathway to psychosis in relation to cannabis use. Some authors estimated 8%–13% of the patients in their study might never have developed schizophrenic symptoms had they not used cannabis (Arseneault, Cannon, Witton, & Murray, 2004). Overall, the general view is that cannabis is neither necessary nor sufficient, to induce schizophrenia, stressing the need to identify factors, clinical characteristics and/or biomarkers that could predict a higher vulnerability to psychosis triggered by cannabis.

There is also some support for increased risk of depression and suicidal attempts in persons with cannabis use (Agrawal et al., 2017). In the NESARC study, regular cannabis use predicted the development of bipolar disorder, panic disorder with agoraphobia and social phobia as well as declines in mental, but not physical health (Cougle, Hakes, Macatee, Chavarria, & Zvolensky, 2015). In a longitudinal cohort study, adolescent cannabis use (before 17) was also identified as a potential risk factor for hypomania at the age of 23 (Marwaha, Winsper, Bebbington, & Smith, 2018). In a 3-year longitudinal population-based study, the association was, however, no longer significant when adjusted for other illicit drugs, (Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016). A recent twin study supports that depression is more frequent in persons with CUDs (Smolkina 2017, in Hasin, 2018). Adolescent cannabis use has also been shown to be independently associated with hypomania in early adulthood (Marwaha et al., 2018). Overall, the association of cannabis use with mood and anxiety disorders is demonstrated, especially in women, and depends on the severity of cannabis use. Nevertheless, the causal link is still debated and shared predisposition has been hypothesized (Hasin, 2018). Noteworthy, the CB1R-inverse agonist rimonabant (a molecule formerly proposed in obesity now withdrawn

worldwide), which blocks the action of eCB, was associated with frequent anxious and depressive side effect.

Altogether several associations there are, however, inherent limitations of observational studies due to potential confounders that cannot always be addressed such as associated consumption (alcohol, tobacco and other drugs) or other environmental factors (childhood trauma, stress, inflammation, etc.), stressing the need for experimental studies.

4 | CANNABIS USE AND PSYCHIATRIC DISORDERS: EXPERIMENTAL STUDIES IN HUMAN

Experimental studies of acute exposure to THC in human offer an experimental setting to study transient psychosis-like phenomena in a precise temporal relationship between cause (drug administration) and effect (psychosis), controlling the dose and modality of administration of the drug. In addition, the respective effects of the different constituents of cannabis (e.g., THC and cannabidiol [CBD]) can be isolated (Murray et al., 2017; Sherif et al., 2016). CBD is a major non-psychoactive constituent of Cannabis. It is devoid of both CB1R and CB2R activities, but CBD alleviates adverse effects (anxiety, panic attacks, psychotic symptoms, cognitive impairments and, possibly, dependence) but not the pleasurable effects of THC (reinforcing effect, subjective feeling of "stoned" or relaxed; Englund et al., 2017).

These studies have clearly confirmed that THC can induce positive symptoms as well as conceptual disorganization, depersonalization and derealization, distorted sensory perceptions and slowing down of time perception in almost 50% of participants. These studies have also confirmed a high inter-individual variability, as it is seen in spontaneous reports of subjective effects during first experience of cannabis use in young adults (Krebs, Morvan, Jay, Gaillard, & Kebir, 2014). THC can also induce effects which are similar to negative symptoms (included blunted affect, lack of spontaneity and being internally preoccupied). Persistent amotivational syndrome has been reported with chronic use. Persistent depersonalization syndromes have also been reported sometimes after limited exposure (Dadi et al., 2016). These studies have also unambiguously demonstrated that cannabinoids produce acute transient dose-related deficits in cognitive functions, especially in memory, and attention, also impacting executive function, abstract ability, decision making, immediate and delayed (30-min) verbal recall (Murray et al., 2017). These effects are attenuated by CBD. Interestingly, CBD in addition to antipsychotic medication has been initially found to reverse psychotic symptoms in patients with schizophrenia (McGuire et al., 2018) but not replicated in another study (Boggs et al., 2018).

5 | CANNABIS USE, COGNITION AND BRAIN STRUCTURE

The majority of studies assessing the chronic effects of cannabis have shown that regular users exhibit poorer cognitive performance across a large range of domains compared to nonusers. Verbal learning and memory, attention and psychomotor function are consistently impaired by acute and chronic exposure to cannabis (Broyd, van Hell, Beale, Yücel, & Solowij, 2016). Acute effects of cannabis use include executive functions (especially inhibition) and memory (including working memory) while chronic effects are less consistent. The deficits are more important in early age at onset, heavy use and high THC/CBD ratio (Broyd et al., 2016). Processing speed is also affected. Findings regarding IQ are less consistent. In the large Dunedin birth cohort, persistent cannabis use was associated with decline in general functioning (IQ). The impairment was more important in adolescent-onset cannabis users (vs. in adult-onset users) and when the exposure persists (Meier et al., 2012). Nevertheless, in a limited sample of co-twins, short-term cannabis uses in adolescence did not appear to cause IQ decline or impair executive functions, even when cannabis use reaches the level of dependence (Meier et al., 2018). Impaired verbal memory, attention and psychomotor functions may persist after prolonged abstinence (Broyd et al., 2016) as well as IQ deficit in adolescent users, although discontinuation attenuates the deficit (Meier et al., 2012). Impaired verbal memory, attention and psychomotor functions may persist after prolonged abstinence (Broyd et al.,2016) as well as IQ deficit in adolescent users, although discontinuation attenuates the deficit (Meier et al., 2012). Noteworthy, persistence or recovery across all cognitive domains and in the long time remains poorly explored (Broyd et al., 2016).

Overall, brain-imaging studies have shown that chronic cannabis exposure induces brain alterations, (reviewed in Gruber & Sagar, 2017; Murray et al., 2017). Lorenzetti, Solowij, & Yücel (2016) reviewed 23 anatomical neuroimaging studies and reported that regular cannabis users consistently exhibit reductions in grey matter volume especially in brain regions with high concentration of CB1R, that is in the hippocampus, prefrontal cortex, amygdala and cerebellum. However, there are some inconsistencies in the literature, possibly due to modulating or confounding factors that are not always described in the studies, calling for a minimum set of criteria to be used in future studies (Lorenzetti et al., 2016). For instance, the alterations are more marked for high THC/CBD ratio and for early age at onset of cannabis use. Comorbid substance use should also be taken into account: no association between cannabis use and standard volumetric or shape measurement of subcortical structures were found when controlling for alcohol use, gender and age

(Weiland et al., 2015). Longitudinal studies could be more appropriate to control for pre-existing inter-individual differences. In a small 3-year longitudinal study with young adults (mean age around 21), Koenders et al. (2017) found that continued daily cannabis use did not affect hippocampal neuroanatomical changes although smaller grey matter volume was seen in cannabis users compared to controls. The authors suggest that small volumes are a risk factor for heavy cannabis use or that the effect of cannabis is limited to early adolescence with no further damage of continued use after early adulthood. Regarding white matter, several studies report reduced integrity in many brain areas (prefrontal, limbic, parietal and cerebellar tracts) in adolescent and emerging adult cannabis users (Gruber & Sagar, 2017).

Finally, several functional magnetic resonance imaging studies have found strong evidence that cannabis use is associated with altered activation patterns in tasks involving executive functioning, attention, working memory, verbal learning, affective processing and reward processing (Gruber & Sagar, 2017; Murray et al., 2017). A recent meta-analysis reported differential activation profiles in adults and adolescents using cannabis. In adult cannabis users, brain activation was increased in the superior and posterior transverse temporal and inferior frontal gyri and decreased in the striate area, insula and middle temporal gyrus, whereas in adolescent cannabis users, activation was increased in the inferior parietal gyrus and putamen compared to healthy controls (Blest-Hopley, Giampietro, & Bhattacharyya, 2018). Again, earlier onset of use and longer duration of use relate to more altered activation during cognitive tasks requiring decision making and inhibition (Gruber & Sagar, 2017). Neurochemical imaging studies indicate that acute cannabis is associated with a small increase in dopamine release in the striatum, whereas chronic cannabis use is associated with decreased dopamine release as well as decreased CB1R receptors (Murray et al., 2017). The persistence of these alterations after withdrawal is unknown except that positron emission tomography imaging studies showed that decreased CB1R densities could be reversed within 4 weeks of abstinence (Hirvonen et al., 2012).

6 | GENETIC VULNERABILITY AND THE RISK OF PSYCHOSIS WHEN EXPOSED TO CANNABIS

Only a small minority of cannabis users develops psychotic symptoms. It is therefore likely that, in addition with dose, THC concentrations, other environmental factors and genetic predisposition may play a role in the strength of a causal association. A shared genetic aetiology between cannabis use and schizophrenia has been suggested, where the genetic risk could promote exposure to the environmental risk (Power et al., 2014). A Genome-Wide Association Study (GWAS) found shared genetic factors between CUD, mood disorders and schizophrenia (Sherva et al., 2016). Among patients with schizophrenia, hypersensitivity to the psychotomimetic effects of cannabis was found associated with early cannabis exposure and a family history of psychosis (Goldberger et al., 2010). Along the same line, polygenic risk score of schizophrenia could predict cannabis use (Aas et al., 2018; Power et al., 2014). Patients suffering from schizophrenia or bipolar disorder were more likely to use daily or weekly cannabis before illness onset if their polygenic risk score for schizophrenia was high (Aas et al., 2018). However, this shared genetic vulnerability does not account for the strength of the association (Murray et al., 2017) and cannabis use in early adolescence actually moderates the association between the polygenic risk for schizophrenia and cortical maturation among male individuals (French et al., 2015). The relationship between adolescent cannabis use and psychosis may also be attributed to a functional polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene, which encodes an enzyme that degrades catecholamines such as dopamine (DA) and/or in AKT1, a serine/threonine kinase that helps regulate dopaminergic signalling cascades. Caspi et al. found that carriers of the COMT valine 158 alleles (coding for faster enzyme) who use cannabis are more likely to exhibit psychotic symptoms and develop a schizophrenic disorder (Caspi et al., 2005). Finally, a study of nearly 1,200 young healthy students revealed that the psychotomimetic effects at first cannabis use were associated with *CNR1* variants but not with *COMT* or *AKT1* variants (Krebs et al., 2014). This finding supports the notion that individual variability in the psychotomimetic effect of cannabis may be attributed to specific genetic backgrounds that influence the individual's first response to cannabis, potentially revealing a susceptibility of developing psychosis when exposed to cannabis. However, these candidate gene studies are limited by their small samples and absence of replication. The largest GWAS for lifetime cannabis use to date ($n = 184{,}765$) identified eight genome-wide significant independent single nucleotide polymorphisms in six regions (Pasman et al., 2018). In this study, all measured genetic variants combined explained 11% of the variance. The strongest finding across the different analyses was CADM2 (encoding for a synaptic cell adhesion molecule), which has been associated with substance use and risk-taking. Interestingly, mendelian randomization analysis showed evidence for a causal positive influence of schizophrenia risk on cannabis use contrasting with another Mendelian randomization analysis using ten genetic variants previously associated with cannabis use, which strongly supports that cannabis plays a causal role in the development of schizophrenia (Vaucher et al., 2018). Altogether, these studies suggest that the link between psychosis and cannabis could be bidirectional.

7 | EXPERIMENTAL STUDIES IN RODENTS

Endocannabinoids provide a retrograde feedback system, via the activation of presynaptic CB1 receptors, located in on inhibitory and excitatory neurons. Endocannabinoids, THC and other plant-derived or synthetic cannabinoids bind CB1 receptors and regulate basal synaptic transmission and synaptic plasticity through changes in CB1 receptor signalling, resulting modification in neurotransmitter release probability and the regulation of synaptic strength. Animal models are useful for investigating the neurobiological basis of cannabis-induced effects on brain and even more the long-term behavioural effects of cannabis exposure during adolescence (reviewed in Renard et al., 2014; Rubino & Parolaro, 2016; Curran et al., 2016).

Cannabinoids act on the reward habit and cognition networks. Among other changes, acute use leads to increased firing of dopamine (DA) neurons and DA release, while chronic use results in decreased DA release in the ventral striatum (Curran et al., 2016). In addition, the eCB system modulates synaptic efficacy and plasticity (Castillo, Younts, Chávez, & Hashimotodani, 2012). The main eCBs, 2-AG and anandamide, are synthesized "on demand" from phospholipid precursors in the postsynaptic membrane by Ca^{2+}-dependent and independent mechanisms and feedback in a retrograde manner onto presynaptic terminals, thus suppressing afferent neurotransmitter release via activation of CB1Rs (Ohno-Shosaku & Kano, 2014). Electrophysiological and biochemical data strongly support a model of postsynaptic synthesis and a presynaptic site of action. Retrograde eCB signalling promotes Long-term depression (LTD), but these eCB forms of synaptic plasticity after stress have also been found to promote long-term potentiation (LTP) for review Morena, Patel, Bains, and Hill(2016).

Adults rats that have been chronically exposed to CB1R agonists or THC during their adolescence display short-term memory impairment in the novel object recognition and novel-place recognition paradigms, as well as deficits in spatial working memory and reduced social interactions (Renard et al., 2014; Rubino & Parolaro, 2016). These deficits were milder or not significant when rodents were exposed during adulthood. Our studies and others reported a reduced expression of synaptic plasticity proteins (PSD95, synaptophysin, protein kinase C-dependent signalling), of cytoskeletal and structural proteins, and activity-regulated cytoskeletal-associated protein (Arc) as well as a reduced expression of CB1R in the hippocampus and/or prefrontal cortex in adult rats that were treated with CB1R agonists or THC during adolescence. (for review Curran et al., 2016; Renard et al., 2014). Those proteins have a close interaction with N-Methyl-D-aspartate (NMDA) receptors and determine the size and strength of excitatory synapses. A significant reduction of NMDA receptors was found in the hippocampus of adolescent treated rats as well as a reduced glutamic acid decarboxylase 67 (GAD 67) and basal gamma-Aminobutyric acid levels in the prefrontal cortex (Rubino & Parolaro, 2016). In addition, rats exposed to cannabinoids during adolescence have, when adults, reduced total dendritic length, arborization, and spine numbers in the dentate gyrus and the prefrontal cortex and an impaired synaptic plasticity in the prefrontal cortex as reflected by a decrease in LTP at hippocampal to prefrontal cortex synapses pathway (Renard et al., 2016). This glutamate dysregulation likely contributes to the altered plasticity and cognitive impairments observed in schizophrenia.

The hippocampal–prefrontal pathway is a hub for the regulation of emotions and behaviours and is implicated in anxiety, depressive and psychotic disorders. There is inconsistent support for anxiety-related behaviours after adolescent cannabinoid exposure (reviewed Rubino & Parolaro, 2016). For instance, increased anxiety behaviours were described in the elevated plus maze and in the open-field test. Similarly, a depressive-like phenotype in adulthood has been described after adolescent exposure to cannabinoids in some studies (e.g., in sucrose preference test, a measure of anhedonia, or in the forced-swim test) and with a more pronounced effect in females. These findings support that exposure to cannabinoid during adolescence may affect the susceptibility to develop mood disorders later in life. This could be due to a decrease in CB1R expression in the amygdala, ventral tegmental area and Nucleus Accumbens (NAcc), accompanied by changes in the levels of CREB protein and to hyperactivity of noradrenergic neurons concomitant with an hypoactivity of serotonergic neurons (Curran et al., 2016).

In terms of psychotic-like behaviours, animal studies have focused on disruptions in sensorimotor gating measured using prepulse inhibition (PPI), an endophenotype of schizophrenia with high translational validity. Several authors, but not all, reported that chronically treating rats with a cannabinoid agonist during adolescence (PND40 to PND65, but not in adults) induced long-lasting impairment of PPI in adulthood, with a correlation with basal neuronal activity (i.e., c-Fos activity) in the NAcc, amygdala, caudate putamen and hippocampus (reviewed in Renard et al., 2014; Rubino & Parolaro, 2016). Discordance discrepancy may be due to differences in the period of exposure, cannabinoid compound used or rat strains.

8 | CANNABINOID SYSTEMS ARE INVOLVED IN BRAIN DEVELOPMENT AND MATURATION

Endocannabinoid eCB systems are active during early brain development and modulate several neurodevelopmental

processes, including neuronal migration, axonal guidance, positioning of cortical interneurons, neurite outgrowth and morphogenesis (Berghuis et al., 2007). During adolescence, the brain undergoes major brain maturation processes including grey matter reduction, myelination, rewiring, decrease in synapses and dendrites, changes in neurotransmitters ratio (Insel, 2010). These changes occur, in human, between the ages of 13–30 (for the latest myelination processes), with a peak of modifications between 15 and 25 years old. The eCB system also undergoes functional development and changes. For instance, CB1R expression increases in the frontal cortex, striatum and hippocampus in humans and CB1R expression increases in the shell of the NAcc, but decreases in the core of the NAcc and in the cingulate, prelimbic and infralimbic cortices. Concomitantly, levels of anandamide (AEA) and 2-AG vary throughout adolescence in a region- and time-specific manner (Rubino & Parolaro, 2016). These changes in eCB system during adolescence indicate that this system is involved in the maturation of the central nervous system and that activation by exogenous THC may dysregulate this maturation, either directly or through indirect regulation processes resulting in inhibition of the CB1R signalling.

9 | CONCLUSIONS

While the precise mechanisms still require more investigations, lessons from epidemiological and experimental studies in human or rodent clearly demonstrated that chronic exposure to THC can lead to brain alterations. The causal link remains controversial as observational findings can always be hampered by confounding (where another risk factor associated with cannabis causes the disease) and/or reverse causality bias (where individuals affected by schizophrenia may be more prone to consume cannabis). When cannabis is used during the critical period of brain maturation during adolescence and early adulthood, these alterations may lead to more persistent cognitive deficits and/or to psychiatric disorders and more specifically to psychosis. When exposed during the adulthood, the cognitive deficits and psychiatric symptoms persist during the exposure (e.g., lack of motivation, concentration deficits, dyscoordination) but there remains a debate about whether cannabis use leads to long-term cognitive impairments following abstinence. Some individuals, especially when a psychotic disorder preexists could me more at-risk of persisting deficits but in any case, it is clear that ongoing regular cannabis use impairs cognition and therefore impact educational achievement. Altogether, the risk of cognitive and psychiatric adverse effects depends (a) on the kind of cannabinoids used: they are related to THC while CBD attenuates these effects; (b) on the level and duration of exposure; (c) on an individual vulnerability, that could partly be genetically defined; and (d) on the age of exposure. Because exogenous cannabinoids interfere with endo-cannabinoids regulation of brain maturation during adolescence, they can induce long-term changes. Hence, adolescence and early adulthood are, per se, periods of vulnerability to long-term cognitive and psychiatric consequence of cannabis use. Further studies are needed to identify populations that could be more at-risk of psychiatric and cognitive complications in order to personalize the evaluation of benefice–risk of potential medical use of cannabinoids. In addition, the risk (or benefit) conveyed by the different cannabinoids should be more thoroughly studied: while THC is clearly associated with long-term brain alterations, CBD is less prone to induce such complications, and may even have protector effects that deserve more investigations.

CONFLICTS OF INTEREST

None declared.

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REFERENCES

Aas, M., Melle, I., Bettella, F., Djurovic, S., Le Hellard, S., Bjella, T., … Tesli, M. (2018). Psychotic patients who used cannabis frequently before illness onset have higher genetic predisposition to schizophrenia than those who did not. *Psychological Medicine*, *48*, 43–49. https://doi.org/10.1017/S0033291717001209

Agrawal, A., Nelson, E. C., Bucholz, K. K., Tillman, R., Grucza, R. A., Statham, D. J., … Lynskey, M. T. (2017). Major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins: A retrospective cohort study. *Lancet Psychiatry*, *4*, 706–714. https://doi.org/10.1016/S2215-0366(17)30280-8

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Andréasson, S., Allebeck, P., Engström, A., & Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*, *2*, 1483–1486. https://doi.org/10.1016/S0140-6736(87)92620-1

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., & Munk-Jørgensen, P. (2005). Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: Follow-up study of 535 incident cases. *British Journal of Psychiatry*, *187*, 510–515.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *BMJ*, *325*, 1212–1213. https://doi.org/10.1136/bmj.325.7374.1212

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: Examination of the evidence. *British Journal of Psychiatry*, *184*, 110–117. https://doi.org/10.1192/bjp.184.2.110

Berghuis, P., Rajnicek, A. M., Morozov, Y. M., Ross, R. A., Mulder, J., Urbán, G. M., … Harkany, T. (2007). Hardwiring the brain: Endocannabinoids shape neuronal connectivity. *Science*, *316*, 1212–1216. https://doi.org/10.1126/science.1137406

Bianconi, F., Bonomo, M., Marconi, A., Kolliakou, A., Stilo, S. A., Iyegbe, C., … Di Forti, M. (2016). Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychological Medicine*, *46*, 995–1003. https://doi.org/10.1017/S0033291715002494

Blest-Hopley, G., Giampietro, V., & Bhattacharyya, S. (2018). Residual effects of cannabis use in adolescent and adult brains – A meta-analysis of fMRI studies. *Neuroscience and Biobehavioral Reviews*, *88*, 26–41. https://doi.org/10.1016/j.neubiorev.2018.03.008

Boggs, D. L., Surti, T., Gupta, A., Gupta, S., Niciu, M., Pittman, B., … Ranganathan, M. (2018). The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology (Berl)*, *235*, 1923–1932. https://doi.org/10.1007/s00213-018-4885-9

Broyd, S. J., van Hell, H. H., Beale, C., Yücel, M., & Solowij, N. (2016). Acute and chronic effects of cannabinoids on human cognition – A systematic review. *Biological Psychiatry*, *79*, 557–567. https://doi.org/10.1016/j.biopsych.2015.12.002

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., … Craig, I. W. (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. *Biological Psychiatry*, *57*, 1117–1127. https://doi.org/10.1016/j.biopsych.2005.01.026

Castillo, P. E., Younts, T. J., Chávez, A. E., & Hashimotodani, Y. (2012). Endocannabinoid signaling and synaptic function. *Neuron*, *76*, 70–81. https://doi.org/10.1016/j.neuron.2012.09.020

Cougle, J. R., Hakes, J. K., Macatee, R. J., Chavarria, J., & Zvolensky, M. J. (2015). Quality of life and risk of psychiatric disorders among regular users of alcohol, nicotine, and cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). *Journal of Psychiatric Research*, *66–67*, 135–141. https://doi.org/10.1016/j.jpsychires.2015.05.004

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J. A., & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews Neuroscience*, *17*, 293–306. https://doi.org/10.1038/nrn.2016.28

Currie, C., Zanotti, C., Morgan, A., Currie, D., de, Looze, M., Roberts, C., & Barnekow, V. (Eds.) (2012). Social determinants of health and well-being among young people. Health Behaviour in School-aged Children (HBSC) study: International report from the 2009/2010 survey. Copenhagen, Denmark: WHO Regional Office for Europe, (Health Policy for Children and Adolescents, No. 6). pp. 252. Retrieved from http://www.euro.who.int/en/publications/abstracts/social-determinants-of-health-and-well-being-among-young-people.-health-behaviour-in-school-aged-children-hbsc-study

Dadi, G., Dervaux, A., Krebs, M.-O., Gaillard, R., Laqueille, X., & Plaze, M. (2016). Persistent depersonalization/derealization disorder induced by synthetic cannabinoids. *American Journal of Psychiatry*, *173*, 839–840. https://doi.org/10.1176/appi.ajp.2016.16010029

Danielsson, A.-K., Lundin, A., Agardh, E., Allebeck, P., & Forsell, Y. (2016). Cannabis use, depression and anxiety: A 3-year prospective population-based study. *Journal of Affective Disorders*, *193*, 103–108. https://doi.org/10.1016/j.jad.2015.12.045

D'Souza, D. C., & Ranganathan, M. (2015). Medical marijuana: Is the cart before the horse? *JAMA*, *313*, 2431–2432. https://doi.org/10.1001/jama.2015.6407

Englund, A., Freeman, T. P., Murray, R. M., & McGuire, P. (2017). Can we make cannabis safer?. *The Lancet Psychiatry*, *4*, 643–648.

French, L., Gray, C., Leonard, G., Perron, M., Pike, G. B., Richer, L., ... Paus, T. (2015). Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. *JAMA Psychiatry*, *72*, 1002–1011. https://doi.org/10.1001/jamapsychiatry.2015.1131

Godsil, B. P., Kiss, J. P., Spedding, M., & Jay, T. M. (2013). The hippocampal-prefrontal pathway: The weak link in psychiatric disorders? *European Neuropsychopharmacology*, *23*, 1165–1181. https://doi.org/10.1016/j.euroneuro.2012.10.018

Goldberger, C., Dervaux, A., Gourion, D., Bourdel, M.-C., Lôo, H., Laqueille, X., & Krebs, M.-O. (2010). Variable individual sensitivity to cannabis in patients with schizophrenia. *International Journal of Neuropsychopharmacology*, *13*, 1145–1154. https://doi.org/10.1017/S1461145710000647

Gruber, S. A., & Sagar, K. A. (2017). Marijuana on the mind? The impact of marijuana on cognition, brain structure, and brain function, and related public policy implications. *Policy Insights from the Behavioral and Brain Sciences*, *4*, 104–111. https://doi.org/10.1177/2372732216684851

Hasin, D. S. (2018). US epidemiology of cannabis use and associated problems. *Neuropsychopharmacology*, *43*, 195–212. https://doi.org/10.1038/npp.2017.198

Häuser, W., Petzke, F., & Fitzcharles, M. A. (2018). Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management – An overview of systematic reviews. *European Journal of Pain*, *22*, 455–470. https://doi.org/10.1002/ejp.1118

Hirvonen, J., Goodwin, R. S., Li, C. T., Terry, G. E., Zoghbi, S. S., Morse, C., … Innis, R. B. (2012). Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular Psychiatry*, *17*, 642–649. https://doi.org/10.1038/mp.2011.82

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*, 187–193. https://doi.org/10.1038/nature09552

Koenders, L., Lorenzetti, V., de Haan, L., Suo, C., Vingerhoets, W., van den Brink, W., … Cousijn, J. (2017). Longitudinal study of hippocampal volumes in heavy cannabis users. *Journal of Psychopharmacology*, *31*, 1027–1034. https://doi.org/10.1177/0269881117718380

Krebs, M. O., Morvan, Y., Jay, T., Gaillard, R., & Kebir, O. (2014). Psychotomimetic effects at initiation of cannabis use are associated with cannabinoid receptor 1 (CNR1) variants in healthy students. *Molecular Psychiatry*, *19*, 402–403. https://doi.org/10.1038/mp.2013.188

Lorenzetti, V., Solowij, N., & Yücel, M. (2016). The role of cannabinoids in neuroanatomic alterations in cannabis users. *Biological Psychiatry*, *79*, e17–e31. https://doi.org/10.1016/j.biopsych.2015.11.013

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, *42*, 1262–1269. https://doi.org/10.1093/schbul/sbw003

Marwaha, S., Winsper, C., Bebbington, P., & Smith, D. (2018). Cannabis use and hypomania in young people: A prospective analysis. *Schizophrenia Bulletin*, *44*, 1267–1274. https://doi.org/10.1093/schbul/sbx158

McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., … Wright, S. (2018). Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *American Journal of Psychiatry*, *175*, 225–231. https://doi.org/10.1176/appi.ajp.2017.17030325

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., & Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the USA*, *109*, E2657–E2664. https://doi.org/10.1073/pnas.1206820109

Meier, M. H., Caspi, A., Danese, A., Fisher, H. L., Houts, R., Arseneault, L., & Moffitt, T. E. (2018). Associations between adolescent cannabis use and neuropsychological decline: A longitudinal co-twin control study. *Addiction*, *113*, 257–265. https://doi.org/10.1111/add.13946

Meijer, J. H., Dekker, N., Koeter, M. W., Quee, P. J., van Beveren, N. J., Meijer, C. J., & Genetic Risk and Outcome of Psychosis (GROUP) Investigators (2012). Cannabis and cognitive performance in psychosis: A cross-sectional study in patients with non-affective psychotic illness and their unaffected siblings. *Psychological Medicine*, *42*, 705–716. https://doi.org/10.1017/S0033291711001656

Moreau, J. (2012). *Hashish and mental illness*. New York, NY: Raven.

Morena, M., Patel, S., Bains, J. S., & Hill, M. N. (2016). Neurobiological interactions between stress and the endocannabinoid system. *Neuropsychopharmacology*, *41*, 80–102. https://doi.org/10.1038/npp.2015.166

Murray, R. M., Englund, A., Abi-Dargham, A., Lewis, D. A., Di Forti, M., Davies, C., & D'Souza, D. C. (2017). Cannabis-associated psychosis: Neural substrate and clinical impact. *Neuropharmacology*, *124*, 89–104. https://doi.org/10.1016/j.neuropharm.2017.06.018

Ohno-Shosaku, T., & Kano, M. (2014). Endocannabinoid-mediated retrograde modulation of synaptic transmission. *Current Opinion in Neurobiology*, *29*, 1–8. https://doi.org/10.1016/j.conb.2014.03.017

Pasman, J. A., Verweij, K. J. H., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J. L., … Vink, J. M. (2018). GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nature Neuroscience*, *21*, 1161–1170. https://doi.org/10.1038/s41593-018-0206-1

Potvin, S., Joyal, C. C., Pelletier, J., & Stip, E. (2008). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis. *Schizophrenia Research*, *100*, 242–251. https://doi.org/10.1016/j.schres.2007.04.022

Power, R. A., Verweij, K. J., Zuhair, M., Montgomery, G. W., Henders, A. K., Heath, A. C., … Martin, N. G. (2014). Genetic predisposition to schizophrenia associated with increased use of cannabis. *Molecular Psychiatry*, *19*, 1201–1204. https://doi.org/10.1038/mp.2014.51

Renard, J., Krebs, M.-O., Le Pen, G., & Jay, T. M. (2014). Long-term consequences of adolescent cannabinoid exposure in adult psychopathology. *Frontiers in Neuroscience*, *8*, 361.

Renard, J., Vitalis, T., Rame, M., Krebs, M.-O., Lenkei, Z., Le Pen, G., & Jay, T. M. (2016). Chronic cannabinoid exposure during adolescence leads to long-term structural and functional changes in the prefrontal cortex. *European Neuropsychopharmacology*, *26*, 55–64. https://doi.org/10.1016/j.euroneuro.2015.11.005

Rubino, T., & Parolaro, D. (2016). The impact of exposure to cannabinoids in adolescence: Insights from animal models. *Biological Psychiatry*, *79*, 578–585. https://doi.org/10.1016/j.biopsych.2015.07.024

Ruiz-Veguilla, M., Gurpegui, M., Barrigon, M. L., Ferrin, M., Marin, E., Rubio, J. L., … Cervilla, J. (2009). Fewer neurological soft signs among first episode psychosis patients with heavy cannabis use. *Schizophrenia Research*, *107*, 158–164. https://doi.org/10.1016/j.schres.2008.08.001

Schoeler, T., Monk, A., Sami, M. B., Klamerus, E., Foglia, E., Brown, R., … Bhattacharyya, S. (2016). Continued versus discontinued cannabis use in patients with psychosis: A systematic review and meta-analysis. *Lancet Psychiatry*, *3*, 215–225. https://doi.org/10.1016/S2215-0366(15)00363-6

Sherif, M., Radhakrishnan, R., D'Souza, D. C., & Ranganathan, M. (2016). Human laboratory studies on cannabinoids and psychosis. *Biological Psychiatry*, *79*, 526–538. https://doi.org/10.1016/j.biopsych.2016.01.011

Sherva, R., Wang, Q., Kranzler, H., Zhao, H., Koesterer, R., Herman, A., … Gelernter, J. (2016). Genome-wide association study of cannabis dependence severity, novel risk variants, and shared genetic risks. *JAMA Psychiatry*, *73*, 472–480. https://doi.org/10.1001/jamapsychiatry.2016.0036

van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: A longitudinal population-based study. *American Journal of Epidemiology*, *156*, 319–327.

Vaucher, J., Keating, B. J., Lasserre, A. M., Gan, W., Lyall, D. M., Ward, J., … Holmes, M. V. (2018). Cannabis use and risk of schizophrenia: A Mendelian randomization study. *Molecular Psychiatry*, *23*(5), 1287–1292. https://doi.org/10.1038/mp.2016.252

Weiland, B. J., Thayer, R. E., Depue, B. E., Sabbineni, A., Bryan, A. D., & Hutchison, K. E. (2015). Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. *Journal of Neuroscience*, *35*, 1505–1512. https://doi.org/10.1523/JNEUROSCI.2946-14.2015

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., … Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*, *313*, 2456–2473. https://doi.org/10.1001/jama.2015.6358

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