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DUAL DIAGNOSIS (TP GEORGE AND MS BARR, SECTION EDITORS)

Neurobiology of Comorbid Substance Use Disorders in Mental Illness: A Closer Look at the Underlying Commonalities between Cannabis and Schizophrenia

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Abstract The high rate of cannabis use disorders (CUDs) among patients with schizophrenia is well established. The implications of this comorbidity are extensive and include symptom exacerbation, frequent relapses leading to hospitalization and an overall worsening of prognosis. Therefore, a greater understanding of why cannabis use and schizophrenia frequently present in the same individual is critical. In this article, we propose that common neurobiological pathways and substrates independently contribute to the predisposition of developing these disorders. Dysregulation of the endocannabinoid system, as well as abnormalities in neurophysiology, neurocognition, genetics, and brain morphology may contribute to this comorbidity. Future studies are needed to confirm these commonalities between CUDs and schizophrenia, given that better understanding of their etiology may guide integrated treatment interventions and the development of prevention strategies for these prevalent comorbid disorders.

Keywords Mental illness · Schizophrenia · Drug addiction · Dual diagnosis · Neurocognition

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Introduction

Patients with mental illness suffer from high rates of addiction. For example, an estimated 50 % of patients with schizophrenia meet the criteria for a substance use disorder at some point in their lifetime [1]. Schizophrenia is arguably the most serious of mental illnesses, with approximately 25 % of patients meeting the criteria for a cannabis use disorder (CUD) [2]. CUDs are associated with a wide range of devastating consequences in mentally ill patients. These patients have an earlier mortality rate of approximately 25 years, with an increased vulnerability to medical illness, accidental death, and suicide [3, 4]. Additionally, the severity and prognosis of the primary mental illness, in this case schizophrenia, is often worsened in the context of CUDs. For example, cannabis use has been associated with symptom exacerbation, higher relapse rates, and poor treatment outcome, including medication non-compliance [5, 6].

Many theories have been proposed to help explain the high prevalence of substance use among mentally ill patients. The self-medication hypothesis posits that patients use substances in order to alleviate undesirable symptoms associated with the primary illness (i.e. depression, anxiety, negative symptoms) or attenuate side effects from medication used to treat the disorder [7]. However, there is a lack of empirical evidence supporting this hypothesis. By contrast, the addiction vulnerability hypothesis (AVH) theorizes that rather than being a compensatory reaction to the symptoms of psychiatric illness, substance use may be a clinical manifestation of the disorder [8]. Specifically, the neural circuitry mediating reward and positive reinforcement may be disrupted in individuals with mental illness, which could contribute to enhanced vulnerability to addiction. Thus, the same pathophysiology that increases the risk of mental illness also increases vulnerability to drug addiction, thereby rendering high rates of comorbidity. Among schizophrenia patients, dysregulation of hippocampal-prefrontal dopamine release in the nucleus accumbens (NAcc)

compromises executive-inhibitory regulation of motivational processes resulting in a robust response to drugs and associated stimuli, thus predisposing one to both psychotic symptoms and addiction [8]. This theory thus supports a neurobiological link between schizophrenia and CUDs.

There are striking similarities between schizophrenia and CUDs. For example: (1) disease onset during adolescence; (2) cognitive impairment; (3) impulsivity and poor decision making; and (4) low motivation [9–12]. Given these similar phenotypes, overlapping neurobiological substrates and neurocircuitry may *independently* underlie the development of comorbid CUDs in schizophrenia. In this review, we outline the neurobiology of the endocannabinoid (eCB) system and provide evidence for its dysregulation in schizophrenia and CUDs. In the following sections we discuss abnormalities in neurophysiology and neurocognition, genetic variants, and brain morphology that may also contribute to this comorbidity.

The Endocannabinoid (eCB) System: Relationship to Comorbidity

Neurobiology of the eCB System

Cannabis acts on the eCB system and is one of the most abundant neuromodulatory systems in the brain. While delta-9-tetrahydrocannabinol (THC) is the primary psychoactive component in cannabis, over 400 additional chemical components including cannabidiol (CBD), and cannabinol are also present in its preparation [13]. In the brain, THC causes pleasurable and psychotropic effects, including feelings of euphoria, relaxation, anxiety, paranoia and, notably, cognitive dysfunction [14]. THC also causes activation of the mesolimbic dopamine system, which mediates the reinforcing and rewarding properties of the drug [15]. Adverse health effects of chronic cannabis use include cancer, bronchitis, and emphysema [16].

The eCB system is comprised of two G protein-coupled receptor subtypes—cannabinoid 1 receptors (CB1R) and cannabinoid 2 receptors (CB2R). Cannabis, cannabis-related drugs, and eCBs act primarily at these receptors. CB1R are the most abundant G protein-coupled receptors in the human brain. Stimulation of these receptors induce a series of intracellular events, namely modulation of calcium and potassium currents, inhibition of adenylyl cyclase and activation of kinase proteins, which in turn regulate transcription factors.

CB1R are populated in high densities in the hippocampus, NAcc, the dorsal striatum, and cerebellum, and moderate to low densities are present in the amygdala and cerebral cortex [17]. Within these brain regions, CB1R are predominantly located presynaptically on gamma-amniobutyric acid (GABA)ergic (inhibitory) interneurons and glutamatergic (excitatory) neurons. Arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol are considered the two primary endogenous mediators of cannabinoid signaling, with the latter playing a more vital and integral role in neuroplasticity. eCBs are rapidly inactivated by the enzyme fatty acid amide hydrolase (FAAH) [18]. CB1R efficiently modulate both excitatory and inhibitory transmission at central synapses. These receptors are implicated in multiple forms of neuroplasticity, another mechanism underlying the pathophysiology of both schizophrenia and CUDs [19].

Could Dysfunction of the eCB System Explain CUD Comorbidity in Schizophrenia?

Deleterious effects of cannabis use in schizophrenia have been linked to underlying disturbances in eCB signaling in the brain and this may, in part, be due to genetic variation of cannabinoid-related genes. The cannabinoid receptor gene (*CNR1*), which encodes CB1R, modulates striatal response to rewarding stimuli [20], and polymorphisms of this gene may influence the development of this comorbidity [21, 22]. A polymorphic triplet repeat (AAT) nearby the CNR1 gene has been linked to schizophrenia (hebephrenic subtype) in Japanese [23] and Spanish [24] populations and in individuals with addictive disorders [25]. Few studies have examined single-nucleotide polymorphisms (SNPs) in CNR1. While some studies do not support an association between CNR1 polymorphisms in schizophrenia and cannabis use [26, 27], other data suggest that heavy cannabis use in conjunction with specific *CNR1* gene variants (rs12720071-G-allele carriers) contributes to greater white matter brain volume and cognitive deficits in patients [28••]. Thus, these variants may predispose patients to engage in heavy cannabis use, which may then exacerbate already-present cognitive impairments.

CB1R density may mediate the magnitude of eCB-mediated neuroplasticity as well as the ability of a CB1R agonist to suppress inhibitory activity [29]; thus, the introduction of cannabis in individuals with altered receptor levels may have critical neurobiological consequences. Post-mortem brain and imaging studies have reported increased CB1R densities in the dorsolateral prefrontal cortex (DLPFC) [30], NAcc, and anterior and posterior cingulate cortex [31] in schizophrenia patients. Augmented CB1R levels have also been reported in the caudate putamen in those with detectable levels of THC in their blood at autopsy irrespective of a diagnosis of schizophrenia [30].

However, there are contradictory reports suggesting that CB1Rs are unchanged in schizophrenia patients and that cannabis exposure has no effect on CB1R density in schizophrenia [32, 33]. A very recent study reveals methodological confounds that may explain inconsistent findings. Using the novel CB1R selective ligand [^{3}H]-OMAR, Volk et al. reported that schizophrenia patients with lower CB1R messenger RNA (mRNA) and protein immunoreactivity levels also have higher levels of [^{3}H]-OMAR binding to CB1R. Therefore, greater CB1R receptor availability may contribute to the

increased susceptibility of schizophrenia subjects to the deleterious effects of cannabis use [34••].

Elevated anandamide has been documented in the cerebrospinal fluid (CSF) of both prodromal and untreated schizophrenia patients, as well as in the blood of patients in the acute phase of schizophrenia [35, 36]. In contrast, heavy cannabis use in controls is associated with lower CSF anandamide levels [37]. In comorbid patients, both increased anandamide levels (substance-using patients, including cannabis) [38] and decreased anandamide levels (cannabis-using patients) [39] compared with controls and non-using patients, have been reported. Interestingly, CBD, which has antipsychotic, anti-addictive and pro-cognitive properties, was recently demonstrated to increase anandamide levels in schizophrenia patients [40]. Anandamide may 'protect' against hyperdopaminergia [36] and FAAH, the enzyme responsible for anandamide degradation, may serve to compensate for increased anandamide levels [35]. Given that increased anandamide levels are not observed in controls, a hyperactive eCB system specific to patients may be a predisposing factor triggering cannabis use among this population.

In summary, while inconsistencies exist with respect to the association between the eCB system and CUDs in schizophrenia patients, it is apparent that there are alterations in the eCB system and its signaling that may contribute to comorbid cannabis use in schizophrenia. Variants of eCB-related genes, altered levels of circulating anandamide levels and CB1R density, as well as their affinities, should be investigated further to better determine their role in schizophrenia and CUDs.

Clinical and Neurobiological Factors That May Contribute to Cannabis Comorbidity in Schizophrenia

In the following sections we will review evidence suggesting that neurophysiological, neurocognitive, genetic, and brain morphological abnormalities may contribute to the comorbidity of CUDs in schizophrenia.

Neurophysiology

Studies have documented neurophysiological impairments in both schizophrenia patients and otherwise healthy cannabis users. Transcranial magnetic stimulation (TMS) is a non-invasive technique that is used to index cortical inhibition and excitability. Moreover, $GABA_A$ and $GABA_B$ receptor-mediated inhibitory neurotransmission can be differentially indexed through single and paired TMS protocols. Among patients with schizophrenia, several studies have demonstrated pervasive cortical inhibition deficits. For example, Daskalakis et al. [41] reported pervasive $GABA_B$ deficits in the motor and DLPFC using TMS-EEG. In healthy cannabis users, Fitzgerald et al. examined light versus heavy cannabis use in healthy controls, and reported reduced cortical inhibition regardless of cannabis use status [42]. Wobrock et al. [43•] conducted a study in first-episode patients with schizophrenia who used cannabis, and reported deficits in cortical inhibition selective to $GABA_A$ receptor activity compared with non-using patients. Given that these studies are cross-sectional, it is not clear if cannabis produces such deficits. We posit that these deficits in GABA activity increase the likelihood of engaging in cannabis use. Moreover, indices of cortical inhibition have been strongly correlated with working memory performance in healthy subjects and may be important in modulating high-frequency oscillations in the DLPFC that influences working memory [44]. Given that schizophrenia is related to abnormal neural oscillations [45] and that cannabis has been associated with similar impairments, this supports our hypothesis that common underlying substrates may lead to the development of comorbid CUDs in schizophrenia.

Prepulse inhibition (PPI) of the startle response involves an attenuation of responsiveness to a sudden-onset high-intensity stimulus when the stimulus is immediately preceded by a lower-intensity stimulus. PPI is an operational measure of sensorimotor gating that may underlie cognitive symptoms of the schizophrenia [46, 47], but the additional effects of cannabis are less clear. Kedzior and Martin-Iverson [47] impaired attentional modulation and reduced PPI among chronic users relative to controls. Other studies are consistent with these results [48, 49], but not all [50]. In examining the interaction between schizophrenia and cannabis use on PPI, impaired modulation of PPI was demonstrated in schizophrenia patients (users and non-users) and in control users compared with non-cannabis-using controls [51]. PPI deficits are clinically important, given that they may be predictive of or lead to further disruption of cognition [52]. A study conducted by Kedzior et al. [53] suggests that neural oscillations may mediate these deficits, which is expected given that abnormal neural oscillations have been reported in both schizophrenia and CUDs [45, 54].

Amplitude changes in P50 event-related potentials during a dual-click *conditioning–testing* procedure has been proposed as a neurophysiological marker of deficient sensory gating in schizophrenia [55]. Sensory gating is the brain's ability to modulate its sensitivity to irrelevant sensory stimuli and thus filter out repetitive and redundant sensory stimulation [46]. Cross-sectional studies report both disrupted and intact P50 in cannabis-using schizophrenia patients [56, 57]. Despite the lack of gating differences in these patient studies, it is interesting to note that P50 gating deficits in heavy chronic cannabis users have been linked to abnormal oscillatory activity [58, 59], which is similarly disrupted in schizophrenia patients [45].

Taken together, neurophysiology studies suggest that alterations in cortical inhibition, attention and sensory gating may be related to alterations in oscillations mediated by GABAergic inhibitory neurotransmission in both schizophrenia and CUDs. Thus, while further evidence is needed, preliminary data suggest similar underlying pathophysiology exists between schizophrenia and CUDs.

Neurocognition

Cognitive deficits are core features of schizophrenia, and most prominent impairments are observed in the domains of working and verbal memory and attention. While consistent impairments are seen in non-psychiatric individuals who engage in cannabis use [60], equivocal findings of associations exist between cannabis and schizophrenia. In 2005, D'Souza and colleagues elegantly demonstrated the detrimental effects cannabis has on cognitive performance [5]. Their group showed that cannabis dose-dependently impairs verbal memory and attention in both schizophrenia patients and controls, with the former group having enhanced sensitivity to these effects. While evidence suggests better cognition in cannabis-dependent patients compared with non-using patients [61], this does not imply improved cognition as a result of cannabis use. This observation likely reflects that patients who engage in cannabis use have a better premorbid IQ and better social cognition that those who do not [61, 62]. A recently published study by our group speaks to this effect. We showed that while there is a strong relationship between cannabis consumption and cognitive impairment in current cannabis users, such an association is absent in former users. This suggests that abstinence may reverse cannabis-induced impairments [63•], especially in domains of memory, mediated by the hippocampus, a structure rich in CB1R.

Taken together, similar cognitive deficits are observed in both patients with schizophrenia and with cannabis use in controls, particularly in the attention, working memory, and verbal memory domains.

Genetics

Genetic variants that influence dopamine represent interesting candidates that may contribute to this comorbidity given its role in schizophrenia [64] and addiction [65]. Catechol-O-methyltransferase (COMT) gene encodes the enzyme responsible for the degradation of dopamine and is essential for dopamine signalling in the prefrontal cortex (PFC) [66]. COMT activity is genetically polymorphic, with high enzymatic activity in the Val/Val genotype, intermediate activity in the Val/Met genotype, and low activity in the Met/Met genotype; with increased enzymatic activity there is a greater overall reduction in synaptic dopamine availability. Caspi et al. [67] demonstrated that individuals homozygous for the Val^{158} allele were more likely to display psychotic symptoms and exhibit an earlier age of onset if they used cannabis in adolescence. Henquet et al. [68] showed that patients and their first-degree relatives homozygous for the Val allele showed an increased sensitivity to THC-induced psychotic symptoms and diminished attention and memory. However, this association has not been found in other studies [26] and thus the contribution of COMT to the cannabis–psychosis relationship remains under investigation.

The *AKT1* gene codes for a protein kinase that forms an integral part of the dopamine receptor signaling cascade in the striatum [69]. This gene has been linked to schizophrenia [70], and in vitro studies have shown that cannabinoids are capable of stimulating the AKT1 pathway via CB1R [71]. Polymorphisms in this gene may increase the risk of schizophrenia in the presence of cannabis use [72, 73]. These investigators also reported an *AKT1*–cannabis interaction on cognitive performance in that patients with the C/C genotype performed significantly worse on a test of sustained attention compared with T/T carriers [74]. Preliminary experimental evidence has also implicated a different polymorphism of the *AKT1* gene (the GG genotype of the SNP rs1130233) as a moderator of sensitivity to the acute psychosis-inducing effect of THC [75]. Further characterization of these variants in this comorbidity is warranted.

While single genetic variants represent attractive candidates for increasing vulnerability to comorbidity, current evidence is weak. Analysis of whole genome sequence data may uncover alternative genetic contributors; however, it is likely a number of genes, rather than a single polymorphism or variant of one gene, contribute to comorbidity in schizophrenia. Future genetic research warrants large samples that use prospective designs in order to reach more definitive conclusions regarding the genetic influence on this comorbidity.

Structural Brain Morphology Changes

Regional and global morphological abnormalities such as ventricular enlargements and decreased brain volume have been documented in the frontal and temporal lobes of patients with schizophrenia [76]. Moreover, morphological changes have been shown to pre-date the first episode of psychosis, suggesting that structural irregularities set the stage for the development of schizophrenia [77].

With respect to associations between cannabis and brain abnormalities, significant volume reductions of the (para-) hippocampus, amygdala, and cerebellum have been reported in adult heavy cannabis users compared with controls [78, 79]. However, a review of other

studies reports contrary results, suggesting that cannabis use has no effect on gray- or white-matter volume [80].

Among schizophrenia patients, cannabis use reportedly has a detrimental effect on grey-matter density in various brain regions [81, 82]. In adolescent-onset schizophrenia, cannabis use was associated with grey-matter density loss in widespread cortical areas and the cerebellum [83]. A study that focused specifically on the cerebellum demonstrated an addictive effect of having a diagnosis of schizophrenia and cannabis use and schizophrenia on white-matter cerebellar volume loss [84]. However, another study found no differences in brain morphology between cannabis-using and non-using patients [85].

Among comorbid patients, Smith et al. [86•] examined the relationship of CUDs in at least 6 months of remission on subcortical brain structures in individuals with and without schizophrenia. Shape differences in the dorsal striatum, anterior thalamus, and anteriodorsal and ventral globus pallidus in patients with lifetime CUD were congruent with those observed among the cannabis-using controls; alterations were significantly more pronounced in cannabis-using patients compared with controls. Longitudinally, Rais and colleagues [87] examined the relationship between brain volume-loss over a 5-year interval in first-episode schizophrenia patients ($n = 19$) compared with non-using patients ($n = 32$). Cannabis-using patients demonstrated greater lateral and third ventricle enlargement and grey-matter loss compared with non-using patients and healthy controls.

Brain atrophy may be the consequence of abnormal brain developmental processes that occur during adolescence; thus, deficits are present even before the onset of schizophrenia and cannabis use. Brain volume loss may represent impairment in cortical inhibition and neuroplasticity, thereby adversely affecting maturation of neural circuitries within cortical areas. Reduced synapses, altered dendrites, and lack of generation of new neurons may result due to diminished glutamatergic neurotransmission [88]. Moreover, individuals who develop schizophrenia may be particularly sensitive to brain tissue loss on exposure to cannabis. Future studies should employ prospective designs to determine whether brain volume and white matter loss result in greater risk for using cannabis or whether continuous use of cannabis (versus non-use or abstinence) leads to excessive brain volume loss in schizophrenia.

Discussion

Data presented here suggest that discrete risk factors converge onto common neural pathways and circuits fostering the initiation and maintenance of comorbid CUDs among patients with schizophrenia. Disturbances in the eCB system, aberrant neurophysiological and neurocognitive processing, genetic variants, and brain atrophy likely predate the onset and are consequences of schizophrenia and CUDs. Moreover, these dysfunctional factors are likely inextricably intertwined; thus, when one is disturbed it likely affects the others, creating a domino effect, and having widespread consequences. See Table 1 for relevant clinical studies addressing the association between cannabis and schizophrenia.

Within the eCB system, CB1Rs are located primarily on GABAergic interneurons, and activation of these presynaptic receptors, either by endogenous or exogenous cannabinoids, leads to a reduction in GABA release by interneurons. This reduction can in turn increase glutamatergic neurotransmission and disrupt the synchronization of pyramidal cell activity leading to abnormal neuroplasticity which underlies neurophysiological processes and, ultimately, cognitive performance [89]. Excess or deficient levels of eCBs, either the result of already present alterations or those due to the introduction of cannabinoids such as THC, can abolish retrograde signaling that underlies eCB-mediated activity, thereby blocking neuroplasticity [90]. Furthermore, developmental studies suggest that anandamide may play a role in determining the direction of neuroplasticity [91]. Both of these mechanisms may result in compromised cognition [92].

Brain atrophy may also be the result of neuroplastic processes gone awry. Brain volume loss in individuals with schizophrenia and/or cannabis use may reflect diminished neuroplasticity, such as reduced number of synapses or altered synapses, thereby preventing full maturation of brain development [88]. Interestingly, measures of cognitive functioning have been shown to correlate with measures of brain structure in both patients with schizophrenia and healthy controls [93].

Cognitive dysfunction has been considered an endophenotype of schizophrenia and given that analogous deficits are well documented in chronic cannabis users [10], and that underlying neurobiological processes contribute to this comorbidity, provides support for the exploration of cognitive function as a biomarker for comorbid cannabis use and schizophrenia. This is important to establish that candidate endophenotypes are crucial tools to help understand and treat such disorders. Such knowledge may also guide individualized treatment approaches. For example, conceivably, CB1R agonists or partial agonists may counteract increased anandamide levels as a result of eCB dysregulation in an attempt to restore homeostatic conditions. Non-pharmacological treatments should also be considered. Brain stimulation

Table 1 Relevant clinical studies addressing the association between cannabis use and schizophrenia

Author (year)	Study design	Sample	Neurobiological target	Findings	Supports common neurobiological link of comorbidity
Endocannabinoids					
Potvin et al. (2008) [38]	Longitudinal	Patients (n=29): Schizophrenia (n=16) Schizoaffective disorder (n=11) Schizophreniform disorder (n=2) Controls (n=17)	Anandamide	Increased anandamide levels in patients with comorbid substance abuse compared with controls	Yes
Leweke et al. (2007) [39]	Cross-sectional	Patients (n=44): LFC (n=55), HFC (n=26) Controls (n=81)	Anandamide	Greater than tenfold increase in CSF anandamide levels in LFC patients compared with HFC patients LFC and HFC patients both had higher CSF anandamide levels compared with controls	Inconclusive
Genetics					
Caspi et al. (2005) [67]	Longitudinal	N= 803 representative birth cohort	Functional polymorphism of COMT	Individuals homozygous for the Val^{158} allele more likely to display psychotic symptoms, and at an earlier age, if they used cannabis in adolescence	Yes
Di Forti et al. (2012) [73]	Case-control	First-episode psychosis (n=489) Controls (n=278)	AKT1 (rs2494732) genotype	In cannabis users, genetic variation at this AKT1 locus influences risk of developing a psychotic disorder	Yes
Henquet et al. (2006) [68]	Cross-sectional	Patients (n=30) Relatives of patients (n=12) Controls (n=32)	Functional polymorphism of COMT	Patients and first-degree relatives homozygous for Val^{158}Met allele displayed increased sensitivity to THC-induced psychotic symptoms and diminished attention and memory	Yes
Van Winkel et al. (2011) [74]	Cross-sectional	Patients (n=611): Cannabis users (n=339) Non-cannabis users (n=272)	Polymorphisms of AKT1	Patients with C/C genotype performed significantly worse on a sustained-attention task compared with T/T carriers	Yes
Zammit et al. (2007) [26]	Case–control	Patients genotyped for CNR1 (n=797)	Variants within the CNR1 gene	Lacking effects of a CNR1 polymorphism in patients between non-cannabis users and self-reported cannabis users 1 year prior to illness onset	No
Brain morphology					
Bangalore et al. (2008) [82]	Cross-sectional	First-episode schizophrenia patients (n=29): Cannabis users (n=15) Non-cannabis users (n=24) Controls (n=42): Non-cannabis users only	Dorsolateral prefrontal cortex, hippocampus, posterior cingulate cortex, and cerebellum	Decrease in gray-matter density in the right posterior cingulate cortex as a function of cannabis use	Yes
*Rais et al. (2008) [87]	Longitudinal	Patients (n=51): Cannabis users (n=19)	Total gray and white cerebrum matter,	Larger third ventricle volumes found in non-cannabis-	Inconclusive

Table 1 (continued)

		Non-cannabis users (n=32) Controls (n=31): Non-substance use only	lateral and third ventricle volumes	using patients compared with cannabis-using patients and healthy controls Cannabis-using patients demonstrated greater lateral and third ventricle enlargement and gray-matter loss compared with non-cannabis-using patients and healthy controls	
*Smith et al. (2014) [86•]	Cross-sectional	Patients (n=43): CUD (n=15) No CUD (n=28) Controls (n=54): CUD (n=10) No CUD (n=44)	Striatum, globus pallidus, thalamus	Structural brain differences were present in patients with lifetime CUD compared with the CUD control group Mediodorsal thalamus and dorsal striatum appeared more sensitive to the effects of cannabis in patients compared with controls	Yes
Solowij et al. (2011) [84]	Cross-sectional	Patients (n=17): Cannabis users (n=8) Non-cannabis users (n=9) Controls (n=31): Cannabis users (n=15) Non-cannabis users (n=16)	Cerebellar gray and white matter	Cannabis use and schizophrenia are independently associated with smaller cerebellar white-matter volume No group differences in cerebellar gray matter or total volumes	Yes
Szeszko et al. (2007) [81]	Cross-sectional	Patients (n=51): Cannabis users (n=20) Non-cannabis users (n=31) Controls (n=56): Non-substance use only	Anterior cingulate cortex	Decrease in gray-matter density in the anterior cingulate cortex as a function of cannabis use	Yes
Author (year)	Study design	Sample	Measure	Findings	Supports common neurobiological link of comorbidity
Neurophysiology					
Rentzsch et al. (2007) [57]	Longitudinal	Patients (n=27): Chronic cannabis abusers (n=15) Non-cannabis abusers (n=12) Controls (n=29): Chronic cannabis abusers (n=11) Non-cannabis abusers (n=18)	P50	No differences in P50 sensory gating between schizophrenia cannabis abuser and non-abuser groups or healthy controls	No
Scholes-Balog and Martin-Iverson (2011) [51]	Cross-sectional	Patients (n=64): Cannabis users (n=20) Non-cannabis users (n=44) Controls (n=66): Cannabis users (n=34) Non-cannabis users (n=32)	PPI	Cannabis-using controls, patients with and without cannabis use all demonstrated impaired modulation of PPI compared with healthy controls	No
*Wobrock et al. (2010) [43•]	Cross-sectional	Patients (n=29): History of comorbid cannabis abuse (n=12) No cannabis abuse history (n=17)	Cortical inhibition	Reduction in $GABA_A$ activity in patients with a history of cannabis abuse compared with non-using patients No difference in CSP between groups	Yes

Table 1 (continued)

Author (year)	Study design	SCZ spectrum	Sample	Findings	Supports common neurobiological link of comorbidity
Neuropsychology					
D'Souza et al. (2005) [5]	Crossover	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	All participants used cannabis at least once Patients (n=13) Controls (n=22)	THC impaired verbal memory and attention in both patients and controls. Patients with schizophrenia also performed worse than the control group in these domains	Yes
Rabin et al. (2013) [63•]	Cross-sectional	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	Patients: Cannabis dependence (n=18) No cannabis dependence (n=29) Non cannabis users: Lifetime dependence (n=21) No lifetime cannabis dependence (n=8)	Patients, both current and former cannabis users, have superior performance on the continuous performance test and on the Trails Making A test compared with patients with no history of use	Yes

*signifies the citations of importance as listed in the manuscript

LFC low-frequency cannabis use, *HFC* high-frequency cannabis use, *COMT* Catechol-O-methyltransferase, *CNR1* cannabinoid receptor, *CUD* cannabis use disorder, *PPI* prepulse inhibition, *CSF* cerebrospinal fluid, *THC* delta-9-tetrahydrocannabinol, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition

techniques such as repetitive TMS (rTMS) that targets the DLPFC may also be effective in restoring normal eCB signaling and neurotransmitter levels that are disturbances as a result of specific genetic variants.

While technology has advanced immensely in the neurosciences, more research further developing the neurobiological underpinnings between SUDs and other psychiatric illnesses are clearly needed. Studies employing state-of-the art technology with a multidisciplinary approach, both prospectively and longitudinally, should be a focus for future research. While we have examined these potential contributing factors in isolation, it is imperative that these multiple influences be examined simultaneously. Ultimately, it is hoped that appropriate and effective interventions and prevention strategies for these prevalent comorbid disorders can be developed, and the prevalence of individuals suffering from comorbid disorders can be reduced.

Conclusion

In this review we have highlighted overlapping neurobiological substrates and neurocircuitry that *independently* underlie the development of comorbid CUDs in schizophrenia. The continued exploration of these and other factors as the molecular mechanisms facilitating this comorbidity will hopefully lead towards a better understanding of the illness and the development of novel therapeutic interventions for addictions, cognitive deficits, and treatment approaches for schizophrenia.

Compliance with Ethics Guidelines

Conflict of Interest Rachel A. Rabin, Michelle S. Goodman, and Mera S. Barr declare no conflicts of interest. Tony P. George declares a consultancy fee from Novartis and a grant from Pfizer, not related to this article.
Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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