Review Paper
Examen critique

Cannabis and cognitive dysfunction: Parallels with endophenotypes of schizophrenia?

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Currently, there is a lot of interest in cannabis use as a risk factor for the development of schizophrenia. Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia. In this overview, we examine the similarities between these in the context of the neurobiology underlying cognitive dysfunction, particularly implicating the endogenous cannabinoid system, which plays a significant role in attention, learning and memory, and in general, inhibitory regulatory mechanisms in the brain. Closer examination of the cognitive deficits associated with specific parameters of cannabis use and interactions with neurodevelopmental stages and neural substrates will better inform our understanding of the nature of the association between cannabis use and psychosis. The theoretical and clinical significance of further research in this field is in enhancing our understanding of underlying pathophysiology and improving the provision of treatments for substance use and mental illness.

La consommation de cannabis comme facteur de risque d'apparition de la schizophrénie suscite actuellement beaucoup d'intérêt. Le dysfonctionnement de la cognition associé à la consommation de longue durée ou importante de cannabis ressemble à de nombreux égards aux endophénotypes cognitifs que l'on a proposés comme marqueurs de la vulnérabilité à la schizophrénie. Dans cet aperçu, nous analysons les similitudes entre ces facteurs dans le contexte de la neurobiologie qui soustend le dysfonctionnement de la cognition, en mettant en cause particulièrement le système cannabinoïde endogène qui joue un rôle important dans l'attention, l'apprentissage et la mémoire et, en général, dans les mécanismes régulateurs de l'inhibition dans le cerveau. Une étude plus attentive des déficits de la cognition associés à des paramètres particuliers de la consommation de cannabis et aux interactions avec les stades neurodéveloppementaux et les substrats nerveux nous aidera à mieux comprendre la nature du lien entre la consommation de cannabis et la psychose. L'importance théorique et clinique de recherches plus poussées dans ce domaine vise à nous aider à mieux comprendre la pathophysiologie sous-jacente et à améliorer la prestation des traitements contre les toxicomanies et les maladies mentales.

Introduction

There have been sporadic hypotheses regarding an association between cannabis use and schizophrenia for over 3 decades.[1–4] Interest in this putative link has seen a recent resurgence as a result of further evidence from large-scale epidemiological studies,[5–8] developments in understanding the neurobiological effects of cannabis[9–11] and the neural substrates and predictors of schizophrenia.[12–14] A meta-analysis of prospective studies determined a pooled estimated odds ratio of 2.1 (95% confidence interval [CI] 1.7–2.5) for prior cannabis use leading to the subsequent development of psychosis, an association that could not be explained by confounds or reverse causality, suggesting that cannabis is a component cause in the development and prognosis of schizophrenia.[15] The purpose of this overview is not to provide another critique of the evidence for cannabis use as a risk factor in the development of schizophrenia — this has been

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admirably covered by several recent reviews[16–18] and discussed at length in the epidemiological studies cited above. Rather, this paper focuses on a specific aspect pertinent to this association, that of cognitive dysfunction.

Cannabis intoxication impairs cognitive processes. There is an increasing body of evidence demonstrating that cannabis users show persistent deficits in specific cognitive functions beyond the period of acute intoxication. The extent of persistence of these deficits is still a matter of contention. Further, recent neurobiological studies have uncovered mechanisms involving the endogenous cannabinoid (eCB) system that inform the neural substrates underlying persistent deficits in cognition after repeated exposure to cannabis. In this paper, we integrate this evidence within the framework of endophenotypes of schizophrenia and propose that the similarity between the cognitive dysfunctions associated with cannabis use and schizophrenia is more than purely coincidental.

The endogenous cannabinoid system

The discovery of the eCB system over a decade ago spurred substantial animal research on the effects of exogenous and endogenous cannabinoids on receptor and overall brain function. Cannabinoid receptors (CB1) are the most abundant metabotropic receptors in the brain and are involved in many important physiological and behavioural events.[9,11] They occur in high density at presynaptic terminals in regions involved in cognition, particularly learning and memory, in the hippocampus, prefrontal cortex (PFC), anterior cingulate, basal ganglia and cerebellum. The eCB system, via its endogenous ligands anandamide and 2-arachidonoylglycerol (2-AG), mediates the flow of information in the brain through retrograde signalling, modulating inhibitory and excitatory neurotransmitter release crucial for synaptic plasticity, depolarization-induced suppression of inhibition or excitation, long-term potentiation (and hence learning), memory and other higher cognitive functions.[10,11,19,20] eCBs are synthesized on demand through cleavage of membrane precursors and are involved in various short-range signalling processes.[19] Research has demonstrated alterations in the functioning of the brain in CB1-rich regions and in cognitively relevant neuromodulator systems (e.g., dopaminergic, cholinergic, serotonergic, gamma-aminobutyric acid [GABA]-ergic, glutamatergic) as a result of exposure to cannabinoids.[19–21] Alterations in the functionality of the eCB system, such as receptor downregulation, desensitization and downstream effector changes accompanying the development of tolerance, dependence and resultant regional neuroadaptations, occur after the chronic administration of cannabinoids.[22,23] There is also good evidence for alterations in the eCB system in schizophrenia, with an increased density of CB1 receptors in the dorsolateral prefrontal cortex (DLPFC)[24] and anterior cingulate[25] of postmortem brains of patients with schizophrenia and elevated levels of anandamide in the cerebrospinal fluid (CSF) in acute schizophrenia.[26] Further, patients with schizophrenia show an enhanced sensitivity to the cognitive effects of delta-9-tetrahydrocannabinol (THC).[27]

Endophenotypes of schizophrenia

Impaired cognition is a fundamental feature of schizophrenia. The impact on patients' daily lives is considerable, restricting functional capacity and contributing to social disability. Cognitive impairments are more strongly predictive of functional outcome than any other symptomatic measure, including overt psychotic symptoms,[28] and residual impairments remain even with atypical antipsychotic medication.[29,30]

In a comprehensive meta-analyis of multiple aspects of schizophrenia, Heinrichs[31] identified cognitive and psychophysiological aspects of brain function as the most powerful and robust case-control differences, rather than neuroanatomical or neurochemical alterations. Thirteen measures were found to produce effect sizes (ESs) large enough to describe abnormalities that occur in 50% of the schizophrenia population. Eight of these were cognitive psychometric findings, and another 3 used psychophysiological measures of cognition. The 2 measures with the largest ESs were the P50 evoked potential deficit (1.55; CI 1.21–1.89) and impaired general verbal memory (1.41; CI 1.20–1.62). Other cognitive measures pertained to tasks requiring learning, reasoning, selective attention, visual or auditory perception and expressive language. Only 2 neuroanatomical measures yielded ESs large and stable enough for inclusion, both pertaining to the hippocampus postmortem: reduced volume (0.92; CI 0.63–1.21) and reduced cell count (0.86; CI 0.38–1.34). Remarkably, no neurotransmitter receptor density differences (dopaminergic, glutamatergic or serotonergic) or neurodevelopmental findings yielded large or stable enough ESs for inclusion, despite the prominence of these in current hypotheses of schizophrenia. Only 1 neuroimaging measure, of reduced frontal brain metabolism (hypofrontality) during mental activity, met the minimum requirements for validity and stability. Accordingly, recent attention has focused on the characterization of putative cognitive endophenotypes of schizophrenia.

Endophenotypes are internal markers, that is, biochemical, physiological, neuroanatomical, neuropsychological, perceptual or cognitive measures of functional capacity. In complex disorders such as schizophrenia, endophenotypes are conceptualized as quantitative traits intermediate between the predisposing genes (genotype) and overt signs and expressed symptoms (phenotype), reflecting more proximal effects of gene action and being closer to the underlying neuropathology of the disorder.[32,33] Research on endophenotypes can, in principle, assist in identifying aberrant genes conferring vulnerabilities to schizophrenia, because the number of genes producing variations in endophenotypes may be smaller, as endophenotypes are more elementary than the complex spectrum of symptoms and signs of psychiatric disorders.

For a marker to be defined as a genetically mediated endophenotype, certain criteria need to be met.[32] The endophenotype must be associated with illness in the population, be heritable, be primarily state-independent, cosegregate with illness within families and be found in nonaffected family members at a higher rate than in the general population (see Snitz and others[34]). Several putative cognitive endopheno-

types have been identified for schizophrenia. None of these have been shown to meet all criteria for a true endophenotype. Several measures show promise, and further research may validate their candidacy. Here we propose a taxonomy of endophenotypes based on conceptual distinctions about the domain of cognition that is most affected. The primary purpose of this taxonomy is to provide a means of organizing substantial literature on the nature of the cognitive deficits in schizophrenia into a smaller subset by capturing the most salient of the presumed mechanisms. However, while the proposed endophenotype clusters are conceptually distinguishable, they may not reflect the same cognitive mechanisms within clusters. Further, there may be a good deal of overlap between clusters. Future research will need to empirically evaluate this and other proposed taxonomies of cognitive deficits in schizophrenia.

Pre-attentive or automatic endophenotype

Three primary psychophysiological measures comprise evidence toward a pre-attentive endophenotype characterized by abnormalities in automatic processing of auditory stimuli: P50 suppression, prepulse inhibition (PPI) and the mismatch negativity (MMN) of the event-related potential (ERP). Each of these measures can be elicited in the absence of active attention and are therefore characterized as pre-attentive or automatic. Each has been shown to meet the most stringent of the criteria for an endophenotype — that is, they have been observed in nonaffected first-degree family members.

The P50, a positive component of the auditory evoked potential peaking around 50 ms poststimulus, provides a measure of sensory motor gating, because P50 amplitude is reduced to a test click when preceded by an identical conditioning click. The degree of suppression, indexed by the test:conditioning P50 ratio, reflects the brain's ability to automatically inhibit irrelevant repetitive sensory input. P50 test:conditioning ratios are larger in patients with schizophrenia[35,36] and their first-degree relatives,[36,37] consistent with impaired sensory gating mechanisms. A recent meta-analysis of 25 schizophrenia studies of P50 suppression determined an effect size of 1.56.[38] P50 suppression shows linkage to the chromosome 15q14 locus of the α-7-nicotinic receptor gene.[39] The neural substrates of the P50 effect have been identified as temporo-parietal (peri-Sylvian area near the auditory cortex), prefrontal cortical in an early pre-attentive phase and hippocampal in later attentive steps of the sensory gating process.[40]

Prepulse inhibition (PPI) of the startle reflex refers to the diminished response to a startling sound when it is preceded by a weaker sound and is also regarded as an index of sensory motor gating. PPI reduction in schizophrenia patients is the basis of most rodent models of schizophrenia.[41] The neural substrates of PPI include the hippocampus, amygdala, thalamus and basal ganglia. PPI is modulated by an increase of mesolimbic dopamine and can be used as a marker of central serotonergic functioning in rodents and in humans.[42]

MMN is an ERP elicited by any discriminable change by a deviant stimulus within a regular background of repetitive auditory stimuli while attention is directed elsewhere. It is automatic or pre-attentive in that it is not reliant on active attention but on an intact auditory sensory memory. The neural generator of MMN is well established as the superior temporal gyrus, with a probable additional frontal generator. MMN amplitude is reduced in patients,[43,44] and a meta-analysis of MMN studies in schizophrenia established an effect size of 0.99 (95% CI 0.79–1.29).[45]

Inhibition endophenotype

This endophenotype is characterized primarily by effortful response inhibition processes measured by well-validated behavioural inhibition tasks, such as the Go/No-Go Task and Stop-Signal Task, and others that require interference control of a prepotent response, such as the Stroop Task and the antisaccade task. Impairments on these tasks are not unique to schizophrenia, but the nature of the deficit in schizophrenia may be unique and involves the anterior cingulate cortex and inhibitory control networks in the PFC.[46–50]

Attention/working memory/dysexecutive endophenotype

Evidence for this endophenotype comes from deficits in tasks of sustained attention, working memory and other executive functions. Sustained attention is the capacity to maintain attention over a relatively prolonged period to detect infrequent targets, ensuring that goals of behaviour are maintained over time. This is most often measured with variants of continuous performance tasks (CPTs); versions differ in complexity and demands on other processes, such as working memory and sensory processing. People with schizophrenia are impaired on simple and complex versions, whereas nonaffected relatives are impaired only on more demanding versions of the task.[51,52] Effect sizes of over 1.0 have been reported.[53] The event-related P300 component elicited in auditory oddball attention tasks (essentially variants of CPT tasks), is also a strong candidate for endophenotypic status, with meta-analyses of patient[54] and relative[38,55] studies showing moderate effect sizes for reduced amplitudes and delayed latencies. We have recently confirmed reduced P300 amplitude in patient and family member groups but could find no evidence of latency changes in either group.[36]

Working memory is a multicomponent system involving active maintenance and manipulation of stored information critical for planning and guiding behaviour. It is, therefore, a core component of executive functions of cognition and is subserved by a network of prefrontal, parietal and subcortical regions of the brain. Several tasks are widely used to assess working memory, including the visual span subtest of the Wechsler Memory Scale; the spatial span and spatial working memory tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB); other spatial working memory tasks, such as oculomotor delayed response tasks; digits backward and letter-number sequencing subtests of the Wechsler Adult Intelligence Scale III; and *n-back* tasks. People with schizophrenia are consistently impaired on spatial working memory tasks, less reliably on verbal working memory tasks.[56,57] Visuo-spatial working memory and

attentional deficits in schizophrenia may also be regulated by α-7-nicotinic receptor stimulation, because cigarette smoking enhances performance on such tasks in patients, possibly explaining the high rate of nicotine use among patients.[58] Functional magnetic resonance imaging (fMRI) studies of working memory have shown altered activation of the DLPFC in people with schizophrenia and their unaffected siblings with similar performance levels to control subjects.[32] This suggests there is a functional inefficiency of the DLPFC. It has therefore been suggested that DLPFC activation during working memory may be a more sensitive endophenotype than performance on working memory tasks.[32]

People with schizophrenia are also impaired on executive tasks associated with frontal lobe function, such as the Wisconsin Card Sorting Test (WCST), verbal fluency tasks and the Tower of London.[53,59]

Verbal memory endophenotype

Evidence underlying this endophenotype comes from verbal declarative memory tasks where people with schizophrenia typically show learning deficits in acquisition or encoding.[31,60] Increased rates of forgetting are present but mild. Verbal declarative memory is among the most impaired cognitive domains in schizophrenia.[31,53] Impaired attention, symptom fluctuations and medication status do not account for the deficit.[60] Verbal learning and recall of word lists and stories produce large effect sizes of around 1.4, distinguishing more than 70% of patients from control subjects.[53] Verbal learning deficits are present in first-episode psychosis,[61] remain stable over the course of illness[62] and are evident in nonaffected relatives.[63] They are underpinned by the medial temporal lobe and hippocampus and connections with PFC as part of a dysfunctional network in schizophrenia.

Eye movement control endophenotype

People with schizophrenia show abnormal eye movement control. Smooth pursuit eye movement deficits when tracking an object moving at a fixed speed have been reported.[64] Typically, patients show low gain, that is, a slower speed of eye movement relative to the speed of the object, and exhibit increased catch up saccades.[32] Other oculomotor disturbances in schizophrenia also contribute to this endophenotype, including antisaccade performance.

Evidence linking cannabinoid function to schizophrenia endophenotypes

In the sections below, we present evidence from studies of cannabis users and studies in which cannabinoids were administered to animals. We address the specific measures outlined above for each endophenotype of schizophrenia, with additional evidence from the cannabis literature pertinent to the conceptualization of each endophenotype. A recent review focused on the overlap between the acute effects of cannabis (and ketamine) on verbal and episodic memory and similar deficits in schizophrenia,[65] emphasizing that these drug models can offer insights into the core pathophysiology of the disorder. Here we examine a more comprehensive range of cognitive functions within the schema of endophenotypes of schizophrenia and report on acute and chronic cannabinoid effects in human and preclinical research, considering neurobiological underpinnings with a focus on the eCB system. Table 1 summarizes the findings, with the evidence detailed below.

Preattentive/automatic endophenotype

A series of replication studies have shown P50 suppression to be reduced in chronic cannabis users who were rigorously screened and medically and psychiatrically normal and who did not use any substances other than cannabis.[66–68] Those with the greatest extent of exposure to cannabis showed the greatest degree of reduction in P50 suppression. Anandamide modulates the α-7-nicotinic receptor,[69] which is linked to P50 suppression, suggesting longer-term effects of smoked cannabis on this system.

Evidence for PPI reduction in human cannabis users has been mixed. PPI was reduced in longer-term cannabis users in one study and correlated with duration but not recency of cannabis use,[70] whereas 2 studies found some evidence of altered startle reflex[71] or no evidence of alteration in PPI in abstinent cannabis users.[42] Effects on PPI from administration of cannabinoid agonists to animals have been mixed as well but do indicate some modulation of sensorimotor gating by the eCB system with apparent differences after short- versus longer-term administration. For example, cannabinoid agonists such as CP55,940 or WIN55,212-2 (WIN) have been shown to increase PPI,[72] decrease PPI[73,74] and reduce the startle response itself in the absence of a prepulse,[74,75] confounding the ability to determine an effect on PPI. Several studies have shown that antagonism of the CB1 receptor by SR141716A alone has no effect on PPI, although this cannabinoid antagonist has been shown to reverse the disruption of PPI induced by dopamine or N-methyl-D-aspartate (NMDA) agonists or antagonists in some studies[76,77] but not others.[74] One study showed that acute and chronic administration of the anandamide reuptake and degradation inhibitor AM404 disrupted PPI in mice and that this effect was blocked by SR141716A.[78] The authors interpreted these findings as indicative of a psychosis-like state after enhancement of anandamide bioavailability. Most recently, Bortolato and colleagues[79] demonstrated no acute or chronic effects of WIN on PPI at any dose in Sprague-Dawley rats, although previous studies had demonstrated a disruption of PPI by this compound acutely in Wistar rats,[73] suggesting that genetic differences may be critical for the development of cannabis-induced cognitive dysfunction.

Critical periods of neurodevelopment may also underlie cannabis-induced effects on PPI and, indeed, other cognitive functions. A long-lasting PPI deficit was found in adult rats after long-term (25 d) administration of WIN during puberty but not when WIN was administered during adulthood, suggesting that cannabinoids interfere with the development of the eCB system during puberty.[80] The pubertal-treated rats

also showed deficits in object recognition memory and performance on a progressive ratio operant behaviour task, whereas those treated in adulthood did not. The authors proposed cannabinoid administration during puberty as a model for the etiology of schizophrenia.

Interestingly, Malone and colleagues[81] used an animal model to show how cannabis might precipitate psychosis in vulnerable individuals with compromised dopaminergic function. They found that THC alone did not affect PPI in mice, but when apomorphine was administered before THC, there was a significantly greater disruption than that caused by this dopamine agonist alone. Thus when sufficient dopaminergic stimulation is present, THC will exacerbate altered sensorimotor gating and could result in a compromised system being more vulnerable to the development of psychosis. While PPI continues to be widely used in animal models of psychosis, Braff and others[41] caution that much work is required to clarify the degree of correspondence between pharmacological manipulation of PPI in animals and humans given the evidence of species differences.

There are no published studies of MMN in human cannabis users or in animal models of cannabinoid administration. MMN reduction is thought to be an index of deficient NMDA receptor functioning.[82] NMDA antagonists, such as ketamine, reduce MMN in monkey models,[83] and similarities between cognitive effects of ketamine and cannabis have been highlighted elsewhere.[65] Research has shown that anandamide modulates NMDA receptor activity directly through proexcitatory potentiating effects as well as indirectly inhibiting activity through cannabinoid receptor–mediated inhibition of voltage-sensitive calcium channels.[84] A dysfunction in the eCB system, for example, owing to cannabis use or to pathological processes in schizophrenia, might therefore be expected to impact upon MMN and other preattentive processes. Since cannabinoids modulate NMDA receptor activity, an investigation of MMN and other preattentive processes in cannabis users may prove interesting.

Inhibition endophenotype

Substance abuse disorders are generally thought to be characterized by behavioural disinhibition and low impulse control resulting from reduced neural inhibition.[85] Inhibitory control is discussed below in the context of aberrant incentive salience. Few studies have investigated the effects of cannabis on the specific measures contributing to the inhibition endophenotype of schizophrenia, although many studies have determined effects of cannabinoids on various inhibitory processes and neural systems. These are mentioned throughout this paper. Antisaccade performance is discussed under the eye-movement endophenotype, below. Several recent neuroimaging studies of long-term, heavy cannabis users (or young adults prenatally exposed to cannabis) have found evidence of altered inhibitory processing (in the Stroop, No/No-Go and decision-making tasks involving response selection and inhibition) and are reviewed separately below.

The Stroop Task has frequently been assessed in human studies of cannabis users; impairments are found inconsistently.[86–90] Where impaired performance on the Stroop was not clinically significant or did not differ from nonusers,

Table 1: Summary of the evidence linking cannabinoid function and effects to schizophrenia endophenotypes

Cognitive endophenotypes of schizophrenia	Measures	Evidence for impaired functioning in cannabis users?	Evidence for direct involvement of the eCB system from animal studies?	Neural substrates interacting with eCB system?
Pre-attentive or automatic	P50, PPI, MMN	P50, yes PPI, mixed MMN, NA	P50, NA PPI, yes MMN, NA	Yes (α-7-nicotinic receptor, NMDA, PFC, hippocampus)
Inhibition	Response inhibition	Yes	NA	Yes (PFC, anterior cingulate, cerebellum)
Attention/working memory/ dysexecutive	Sustained attention, working memory, executive function	Yes	Yes (includes interaction with dopamine and GABA)	Yes (PFC, anterior cingulate, orbitofrontal cortex, hippocampus, cerebellum)
Verbal memory	Verbal learning, declarative memory	Yes	NA	Yes (PFC, medial temporal cortex, hippocampus, cerebellum)
Eye movement control	Smooth pursuit, antisaccade, oculomotor disturbances	Mixed	NA	Yes (substantia nigra, PFC)

eCB = endogenous cannabinoid; GABA = gamma-aminobutyric acid; MMN = mismatch negativity; NA = not applicable or not available; NMDA = N-methyl-D-aspartate; PFC = prefrontal cortex; PPI = pre-pulse inhibition.

performance decrements were nevertheless found to be related to cannabis use parameters, such as duration of cannabis use[90] or dosage (joints/wk) interacting with lower IQ.[89] Imaging studies show altered frontal cortical activation (DLPFC and anterior cingulate) during the interference condition of the Stroop Task, despite the reasonable task performance in cannabis users[91] and 1-month abstinent cannabis users.[92]

One human study found that acute administration of THC increased impulsive responding on a Stop Signal Task but did not affect Go/No-Go Task performance,[93] whereas another found evidence of a greater incidence of premature responding during intoxication, which was discussed in terms of failures of inhibitory control over inappropriate responses.[94]

Attention/working memory/dysexecutive endophenotype

Cannabis has been shown to affect sustained attention, as measured by the CPT after acute administration, as well as in some studies of long-term cannabis users (for review, see Solowij[87]). Pope and colleagues[88] found CPT performance to be insensitive to long-term cannabis use, whereas Jacobsen and others[95] found that adolescent cannabis users made significantly fewer correct hits than did nonusers. There was also a trend toward more false alarms with greater exposure to cannabis. A recent study of relative regional cerebral glucose metabolism in abstinent methamphetamine users performing a CPT task found that those who also regularly used cannabis showed lower glucose metabolism in orbitofrontal, temporal, hippocampal and parahippocampal regions during task performance, in the absence of overt performance deficits.[96] Carefully controlled longitudinal studies of children prenatally exposed to cannabis have found impaired performance on CPT tasks between ages 6 and 12 years, with greater errors of commission and impulsivity errors.[97–101] These deficits continue through adolescence (13–16 yr), with factor analysis of a range of attentional mechanisms demonstrating a specific impairment of stability of attention over time.[102,103] Deficits in learning and memory are also apparent.[101,104]

Several studies have assessed sustained attention by means other than the CPT or have made inferences regarding sustained attentional processes from combined test data. For example, a recent study reported a disruption of sustained and transient attention after smoked cannabis in human volunteers[105] that resulted in impaired memory task performance. Pope and Yurgelun-Todd[86] interpreted the pattern of results from a large neuropsychological test battery administered to college students who used cannabis as reflecting a primary effect on the attentional/executive system, in particular, abilities to shift or sustain attention.

Other kinds of attentional processes, such as selective and divided attention, have also been investigated in cannabis users and were found to be impaired. Ehrenreich and colleagues[106] found that cannabis users differed from control subjects on phasic alertness and divided attention and that early-onset cannabis use (before age 16 yr) was the strongest predictor of attentional dysfunction in adulthood on a visual scanning test. They attributed this to vulnerable periods during brain development that are subject to persistent alterations by exogenous cannabinoids. Fletcher and colleagues[107] reported a 17-year follow-up of long-term cannabis users, in which older (i.e., 45 years of age) long-term users were found to perform more poorly than were older nonusers on complex tasks of selective and divided attention associated with working memory; no differences were found between younger (i.e., 28 years of age) users and nonusers. Conversely, Skosnik and others[108] found that even light cannabis use (once/wk) in college students can result in increased disinhibition on a negative priming task, a measure of automatic inhibition of irrelevant information in an attention task. Negative priming performance is also impaired in patients with schizophrenia.[109]

We have identified specific deficits in selective attention processes in cannabis users, whereby the ability to focus attention and filter irrelevant information was progressively impaired with the number of years that cannabis was used.[87,110,111] This was indexed by frontal brain ERP measures, whereas speed of information processing indexed by the latency of the P300 component was increasingly slower with increasing frequency of cannabis use, suggesting differential impairments associated with shorter- versus longer-lasting effects of cannabis. People with schizophrenia also inappropriately allocate attention to task-irrelevant stimuli.[112] A recent study found evidence of impaired attentional processes in a similar ERP task in cannabis users,[113] and a reduced P300 amplitude was more pronounced in early-onset cannabis users. P300 amplitude is thought to reflect the allocation of attentional resources as well as inhibitory brain processes. An association between a polymorphism of the cannabinoid receptor gene and the P300 component has been reported, with the gene contributing to 20% of the variance in frontal P300 amplitude.[114] Several brain imaging studies of cannabis users have employed attentional tasks and are described below.

Impaired attentional processing has also been demonstrated in animal studies after the administration of cannabinoids.[115–117] Some elegant studies pertinent to attentional deficits were conducted by Verrico and colleagues.[118,119] They found that acute administration of THC potently increased dopamine metabolism and release in PFC but that repeat administration led to a persistent anatomically selective reduction of dopamine metabolism in PFC. This was found to underlie impairments on a visuospatial attention task that persisted for at least 14 days after the last drug administration (longer time periods were not tested). Interestingly, these deficits were transiently reversed by acute amphetamine, suggesting monoaminergic dysfunction related to the attentional deficits.

Cannabis alters the perception of time,[87,90,93] and temporal processing is significantly disrupted in schizophrenia.[120–123] Neural substrates implicated in these processes include the cerebellum, basal ganglia, PFC and parietal cortex. Animal studies have confirmed the involvement of the cannabinoid system in temporal processing, with specific mediation by cannabinoid receptors.[114,124,125] Computational modelling suggested that the reduction in sensitivity to time induced by

cannabinoids could be attributed to dysfunction in attentional mechanisms.[125] Alternatively, it has been suggested that distortions in time judgement may be caused by deficits in strategic processing in cortical systems involved in encoding or rehearsal,[126] once again suggesting the involvement of executive processes.

Working memory is also disrupted by cannabis. D'Souza and colleagues[127] conducted a rigorous investigation of the effects of intravenous THC administered to healthy volunteers who had experience with cannabis use but who were not heavy users. THC impaired working memory, distractibility and verbal fluency and induced transient positive and negative schizophrenia-like symptoms. In other studies, performance, electroencephalography (EEG) and ERP measures were impaired on a spatial *n-back* task after smoked cannabis,[105] and short-term THC administration impaired delay-dependent discrimination within working memory in a delayed-matching-to-sample (DMTS) task.[128] Conversely, acute THC was found to spare perceptual priming and working memory but produced a riskier speed-accuracy trade off and impaired episodic memory, with no residual effects 24 or 48 hours later in infrequent cannabis users.[129] Similarly, simple measures of working memory were relatively unimpaired by a low dose of THC administered to heavy, presumably tolerant cannabis users,[94] but evidence of greater impulsivity in responding during intoxication may have reflected failures of inhibitory control.

Neuropsychological studies of long-term users in the unintoxicated state[86,88–90,130] have generally reported various memory, attention and executive functions to be impaired (e.g., verbal fluency, WCST, Ravens Progressive Matrices, Stroop Task), but few have specifically assessed working memory. We have preliminary evidence of impaired working memory processes on several CANTAB measures.[131] Several neuroimaging studies of cannabis users have used *n-back* and other working memory and executive function tasks, as reported below.

Despite a relative paucity of human studies, there is a substantial body of evidence from animal studies that establishes an unequivocal role of the eCB system in working memory and associated functions. A large number of studies conducted in the 1990s reported generally dose-dependent impairments from cannabinoid administration on radial arm and Morris water maze tests and DMTS tasks in rats and mice and showed that these were cannabinoid receptor-mediated, because they were reversed by SR141716A. These studies have been reviewed elsewhere[132]; we cite the more recent studies here. In several studies, Hampson and Deadwyler[133,134] established dose-dependent cannabinoid reduction in hippocampal cell ensemble firing and impairment of DMTS performance that resembles hippocampal removal. Studies continue to confirm that the deficits are delay-dependent.[135]

Chronic exposure to cannabinoids has been found to result in lasting impairment of working memory in an object recognition task and social interaction (increased anxiety) in adolescent but not adult rats 21 drug-free days after 21 days of drug administration.[136] Several studies have demonstrated impairments after short- and longer-term cannabinoid administration to rats and mice in the hippocampal-dependent Morris water maze task,[137–139] and Varvel and colleagues[140] have shown that these cannabinoid-induced impairments are dependent on interactions with GABA(A) receptors. THC administration pretest specifically impairs the acquisition of spatial learning and working memory performance on this task, while consolidation and retrieval of previously learned material is delay-dependent.[139] Interestingly, impaired reversal learning and increased perseveratory behaviour in this task (as induced by stress) were accompanied by the downregulation of CB1 receptors and reduced 2AG levels in the hippocampus and were reversed by the administration of an exogenous cannabinoid (HU-210).[141] Task acquisition was unimpaired by stress. Varvel and Lichtman[138] also showed that CB1 knockout mice did not differ from wild type mice on acquisition but showed significant deficits in reversal learning, most likely because of perseveration. The evidence from this study strongly suggested that the eCB system may have a role in facilitating extinction or forgetting processes, as confirmed by subsequent studies, described below.

Learning on a virtual Morris water maze task in humans has been shown to be impaired by ketamine, and this impairment was related to the induction of schizophrenia-like symptoms.[142] However, the authors distinguished the learning and memory mechanisms involved in this task from simple working memory processes that were unimpaired. This virtual task has been demonstrated to be impaired in humans with hippocampal damage[143] and in people with schizophrenia.[144] NMDA antagonism impairs learning by disrupting long-term potentiation (LTP) in the hippocampus, a hallmark of exogenous cannabinoid activity;[133] eCB-mediated modulation of NMDA receptor activity was discussed above. Studies have also determined the importance of cannabinoid receptor-mediated inhibition of hippocampal extracellular acetylcholine and D_2 receptor activation in cannabinoid effects on working memory in rats.[145,146] Fadda and others[147] showed that potentiation and antagonism of THC-induced spatial working memory deficits in rats are dependent on the ratio between cannabidiol and THC.

Although interactions between cannabinoid receptors and their endogenous ligands have been shown to play an essential role in the extinction of aversive memories,[148] involvement of the cannabinoid receptor has now been shown to be inessential for the extinction of positively reinforced memories.[149] This may have implications for eCB involvement in reward mechanisms, and the CB1 knockout mice showed alterations in motivation.[142] Further work by Alvares and colleagues[150] supported a selective action, suggesting that the eCB system requires some degree of aversiveness to be recruited; effects were demonstrated in an aversive inhibitory avoidance task but not in an open-field habituation task. However, in this study, CB1 antagonism by AM251 was shown to disrupt memory consolidation, whereas antagonists such as SR141716A have generally shown facilitation of working memory (see Lichtman[151]) and agonists result in impaired memory function. The various compounds tested in animal studies have complex actions that are not yet fully understood, and may be acting as partial or inverse agonists

or acting on a putative CB3 receptor.[11] Differences are also observed between systemic administration and direct intrahippocampal injection. Alvares and colleagues[150] proposed that increased levels of eCBs in the hippocampus that occur immediately after training contribute to facilitate memory consolidation, perhaps by decreasing the activity of GABAergic inhibitory networks. It appears that the eCB system is involved in modulating memory processes in a fine-tuned regulation; dysfunction either by excess or deficit may have adverse consequences in a task-dependent manner. For example, although pharmacological administration of cannabinoid agonists inhibits hippocampal LTP and impairs memory, eCBs can facilitate LTP at the single-cell level,[152] possibly by eCB-mediated depolarization induced suppression of inhibition.[10,19] Chronic exposure to THC blocks synaptic plasticity,[22] but even a single exposure transiently modifies functional properties of cannabinoid receptors and abolishes the retrograde signalling that underlies eCB-mediated synaptic plasticity in the hippocampus and nucleus accumbens.[153]

The fine tuning role of the eCB system in regulating cortical information processing is increasingly apparent. Melis and others[154] report a novel eCB-mediated self-regulatory role of dopamine neurons by which they release 2-AG selectively to suppress PFC-stimulation-evoked activity. They infer that a dysfunction in the eCB system may be involved in altered stress responses and contributes to inappropriate incentive salience to irrelevant stimuli. More specifically, they suggest that a functional eCB system might be a candidate for the modulation of the cortical afferents that provide a filter for nonsalient information and that are disrupted by long-term cannabis use manifested as a difficulty in filtering irrelevant information evident in our ERP studies of selective attention in cannabis users.[87,110,111,155,156]

Verbal memory endophenotype

Cannabinoids exert a profound influence on synaptic plasticity underlying learning and memory. Verbal learning and memory have been, perhaps, the most consistently impaired cognitive functions in studies of acute cannabis administration, as well as in long-term cannabis users. Recent research is highlighted here, while Solowij[87] provides an extensive review of the literature on short- and longer-term effects on verbal memory. Performance on word list learning tasks, such as the Rey Auditory Verbal Learning Test (RAVLT), California Verbal Learning Test, Buschke's Selective Reminding task and variants has been demonstrated to be impaired in multiple neuropsychological studies of heavy or long-term cannabis users in the unintoxicated state,[86,88–90,107,157,158] and impaired learning and retrieval of information were the only cognitive domains to demonstrate a significant effect size in a meta-analysis of a small number of select studies of cannabis users.[159] Fletcher and others[107] found that only older (≥ 45 yr) cannabis users differed from control subjects in list learning, whereas (≤ 28 yr) users were unaffected. Deficits in verbal learning and memory tasks in long-term heavy cannabis users have variously been attributed to duration of cannabis use,[90] frequency of cannabis use[88] or cumulative dosage effects.[89] The most pronounced effects are found on recall after interference or delay, but impaired learning is apparent also in flatter learning curves, fewer words learned (recalled) on each trial and poorer total recognition performance. Intrusion errors are frequent. Block and colleagues'[160] brain imaging study of verbal memory is described below. We are currently investigating verbal learning and memory processes in cannabis users and people with schizophrenia with and without comorbid cannabis use in a series of ongoing fMRI studies.[161,162]

Immediate and delayed recall of words has also been shown to be impaired by acute intravenous administration of THC to human volunteers.[127] Recognition performance was spared in D'Souza et al's study[127], whereas Ilan and colleagues[105] found that acute intoxication resulted in greater intrusion errors during recognition. Those subjects who were most affected by cannabis showed a reduced ERP difference between previously studied words and new distracter words, suggesting a disruption of neural mechanisms underlying memory for recent study episodes.[105] Curran and colleagues[129] found that a high dose of THC (15 mg) resulted in no learning occurring over a 3-trial selective reminding task.

Eye movement control endophenotype

Evidence for involvement of the eCB system in high-level control of eye movements and associated cognitive functions comes from Ploner and others'[163] extensive investigation of oculomotor effects after acute oral administration of THC to human volunteers. They found that THC affected specific aspects of saccade control, namely, spatial attentional shifts, fine tuning of volitional saccades, spatial working memory and inhibition of inappropriate saccades. They suggested that the pattern of effects implied modulation of neuronal activity in substantia nigra pars reticulata and/or DLPFC, reflecting distribution of cannabinoid receptors and their involvement in inhibitory control of inappropriate saccades, rather than the eye fields and final motor pathway for saccades. Smooth pursuit eye movements, however, are not impaired by short-term THC administration to humans.[164,165]

Visual search has been investigated in several studies of cannabis users and of acute cannabinoid administration. Huestegge and colleagues[166] found that longer-term cannabis users with an early age of onset of use showed less effective search behaviour, including longer response times and more fixations, conservative search patterns and frequent reinspections of previously fixated areas. They interpreted these findings, however, as reflecting an impairment in visual short-term memory and less effective visual processing at a more strategic, top–down controlled level, rather than specific eye-movement control deficits. Visual search processes have also been investigated in association with effects on driving ability.[167,168]

Recent neuroimaging studies of cannabis users

There has been a growing interest in the application of structural and functional brain imaging methods to gain insight into the neurobiology of cannabis effects on cognition, and

neuroimaging techniques are providing a sensitive means of investigating the genetics of schizophrenia and its behavioural manifestation.[169] Further, regional brain activation may more sensitively inform endophenotypes than performance measures on cognitive tasks.[32] Positron emission tomography (PET) and regional cerebral blood flow (rCBF) studies of cannabis users have been used to assess neural activation during attention and memory tasks. O'Leary and colleagues[170,171] examined acute and chronic effects of cannabis on rCBF using PET during dichotic listening (auditory attention) tasks. They found that cannabis intoxication resulted in increased blood flow in paralimbic regions and in the anterior cingulate and cerebellum, which they suggested was associated with the intoxicating and mood enhancing effects of the drug.[170,171] Decreased blood flow was observed in temporal lobe regions sensitive to auditory attention, visual cortex and an attentional network consisting of frontal and parietal lobe regions and thalamus. Despite an intact performance on the relatively simple dichotic task, they interpreted the decreased flow as being related to perceptual and cognitive changes that occur with intoxication. Mathew and others[172] found that acute intravenous administration of THC increased activity primarily in the right hemisphere in the orbitofrontal cortex, insula, cingulate gyrus and subcortical structures in a dose-dependent manner related to the degree of subjective intoxication.

Memory-related rCBF in frequent users was examined after at least 26 hours of supervised abstinence.[160] Subjects learned a list of words (from the RAVLT) over multiple trials to a criterion of 2 perfect recalls, with Buschke's selective reminding technique, 1 day before the PET session. Cannabis users required significantly more trials than did control subjects to achieve the learning criterion, and they showed decreased memory-related blood flow in PFC, increased flow in memory-relevant regions of the cerebellum and altered lateralization in the hippocampus, with the greatest differences apparent in episodic encoding during new list learning. Users relied more on short-term memory, recalling more words than control subjects from the end of the word list and fewer from the middle. This pattern of altered distribution of memory processes contributes to poor list learning over trials. We have preliminary data from an fMRI study of verbal learning and memory in long-term cannabis users that suggests altered activation of frontal, medial temporal, parietal and cerebellar regions during encoding and retrieval of words learned from the RAVLT.[161,162]

Other paradigms employed in recent fMRI research with cannabis users have included visual attention, working memory, response inhibition and decision-making tasks. Chang and colleagues[173] found similar task performance between current and former cannabis users and control subjects on a visual-attention task, but both user groups showed altered activation of frontal, parietal, occipital and cerebellar regions, some of which normalized with duration of abstinence. Earlier age of first use and greater cumulative dose of cannabis exposure were related to lower frontal and cerebellar activation and suggested neuroadaptive processes and greater use of reserve networks. Kanayama and colleagues[174] assessed spatial working memory in heavy cannabis users with fMRI. Users made nonsignificantly more errors on the task and showed increased activation of brain regions typically used in spatial working memory tasks, such as the PFC and anterior cingulate, with the additional recruitment of areas not typically used in such tasks, such as the basal ganglia regions. The authors interpreted their findings in terms of cannabis users experiencing subtle neurophysiological deficits for which they compensate by working harder and calling on additional brain regions to meet the demands of the task. Increased activation of the anterior cingulate in particular was thought to reflect an increased effort to overcome cannabis-induced attentional impairments and to coordinate activity from the wide range of regions recruited to perform the task.

Two studies have assessed cannabis users on a decision-making task requiring intact executive functions, the Iowa Gambling Task. In contrast to Kanayama and colleagues' findings, Porrino and others[175] found underactivation specifically of the anterior cingulate in heavy cannabis users in an fMRI study. The users showed poorer performance on the task, reflecting an inability to learn from previous experience. This was correlated with age of first cannabis use. The authors interpreted these findings in terms of cannabis use being associated with impaired decision making and learning, reflected by a failure to activate the anterior cingulate. Bolla and colleagues[176] used PET to assess heavy and moderate cannabis users after 25 days of supervised abstinence. They found dose-related impairments in performance and regional brain activation. All users showed greater activation in the left cerebellum and reduced activation in the right lateral orbitofrontal cortex and right DLPFC than control subjects. The heavy group showed less activation in the left medial orbitofrontal cortex but greater activation of a large left hemisphere region, including the cerebellum, para-hippocampus/lingual gyrus and posterior cingulate, than the moderate users. A threshold effect was suggested, such that dysfunction may only become apparent after a certain amount of drug exposure is reached. Right cerebellar activation decreased as the number of years of cannabis use increased. In accordance with Porrino and colleagues' study[175] learning was observed in moderate users and control subjects but was absent in heavy users. The pattern of behaviour on the task led Bolla and colleagues[176] to interpret the faulty decision making in terms of heavy cannabis users focusing on immediate reinforcing aspects of a situation while ignoring the negative consequences. Differences in activation observed between these 2 studies may be a result of the different imaging technologies or the fact that Bolla and colleagues' cohort was abstinent for 25 days before testing.

Activation elicited by a modified Stroop Task has been examined in 2 studies. Eldreth and others[92] used PET to assess 25-day abstinent cannabis users and found hypoactivity in the left anterior cingulate cortex and left PFC and hyperactivity in the bilateral hippocampus, compared with control subjects, despite intact task performance. The authors discussed possible recruitment of an alternative neural network as a compensatory strategy to overcome persistent cannabis-induced functional deficits. In an fMRI study, Gruber and

Yurgelun-Todd[91] found that cannabis users showed significantly lower anterior cingulate activity, higher midcingulate activity and altered activation of the DLPFC than did control subjects. The users made more errors of commission in the interference condition of the Stroop Task, but their task performance was good overall, suggesting again that they used different cortical processes to achieve similar task performance to control subjects. The altered frontal neural functioning during the performance of this task requiring inhibition and performance monitoring has implications for decision making ability.[91]

An fMRI study of adolescent cannabis users performing an *n-back* working memory task with additional selective attention load focused analyses on the hippocampus.[95] Cannabis users were less accurate and failed to deactivate the right hippocampus across task conditions, compared with control subjects. The authors interpreted this as a dysfunction of inhibitory hippocampal interneurons that "may be mediated by cannabis-induced inhibition of neurotransmitter release disrupting hippocampal synaptic plasticity or by cannabis-induced apoptosis of hippocampal neurons."[95] Smith and colleagues[177] used fMRI to investigate the effects of prenatal exposure to cannabis in adolescents aged 18 to 22 years on a Go/No-Go response inhibition task. They found increased activity of bilateral PFC and right premotor cortex and attenuation of left cerebellar activity with increasing prenatal exposure to cannabis. Exposed offspring also made more errors of commission. It was suggested that prenatal exposure to cannabis may induce long-lasting alterations (into young adulthood) in neural substrates underlying response inhibition.

Thus, the neuroimaging studies have shown altered blood flow or activation in the PFC, orbitofrontal cortex, anterior cingulate, basal ganglia, cerebellum and hippocampus. Alterations in the PFC, orbitofrontal and anterior cingulate (among other regions) support altered inhibitory processing in cannabis users and are interesting in light of the increased density of cannabinoid receptors that have been determined in these regions in schizophrenia patients postmortem.[24,25] Activation of these regions is also altered in neuroimaging studies of schizophrenia using similar paradigms (see Niznikiewicz and colleagues[178] for a review). Differential findings of overactivation or underactivation of brain regions are evident in these studies of human cannabis exposure and may reflect differences in tasks, performances and populations tested, and differing effects associated with various parameters of cannabis use, just as in the schizophrenia literature, hypoactivity and hyperactivity of brain regions may be task-, performance- or medication-dependent.[178] For example, the DLPFC shows either increased (e.g.,[179]) or decreased activation (e.g.,[180]) in working memory tasks in people with schizophrenia, compared with control subjects. Reduced activation of specific brain regions in patients versus control subjects is observed more frequently than increased activation of the same regions when performance decrements are also present, but the latter more often accompanies similar performance between groups. This implies a functional inefficiency of that region, which is compensated for by recruiting additional regions to perform the task or the application of different strategies. Differential regional activation may also be explained by faulty functional connectivity (e.g., between temporal and frontal regions) contributing to functional abnormalities in schizophrenia.[178] The complexity of effects from the vast neuroimaging literature in schizophrenia remains to be integrated, clarified and fully understood; neuroimaging studies of cannabis users are in their infancy and hold much promise for elucidating cognitive dysfunction associated with cannabis use and for exploring interactions with the neuropathology of schizophrenia.

Recovery of cognitive function / persistence of cognitive deficits

Investigations of recovery of cognitive function with abstinence from cannabis have produced conflicting evidence, with some studies suggesting full recovery after 28 days of abstinence,[88] others showing partial early recovery after a mean 2 years abstinence[87,155,156] and still others finding no recovery after 25 to 28 days of abstinence.[89,92,176] The reasons for these differences are unclear but may be partly owing to varying tasks assessed and differing characteristic populations. Few studies have assessed very long-term users (histories of 20–30 years or more of use) as in our ERP and neuropsychological studies. In a reanalysis of their 2001 study, Pope and others[157] found that deficits were more likely to persist beyond 28 days in participants who had commenced cannabis use before age 17. Recent studies of 1-month abstinent heavy cannabis users have reported elevated blood flow velocities[181] and tissue composition changes, as measured by voxel-based morphometry.[182] The latter study found grey and white matter density changes in the same regions (e.g., parahippocampal gyrus) that showed altered activation in a decision-making task[176,182] with some density changes correlating with duration of cannabis use.

Changes associated with the number of years of cannabis use could reflect long-term neuroadaptations requiring significant time to revert to normal functioning. Changes associated with frequency or dosage of cannabis use may reflect adaptations associated with accumulation of drug residues that should resolve once these cannabinoids have been fully eliminated from the body/brain. In most cases, elimination occurs within 4 to 6 weeks of cessation of use. Where deficits have been shown to persist beyond this period of abstinence, neuroadaptations may differ in nature to those associated with cannabis use duration and may or may not be shorter lasting. Further research is required to elucidate the mechanisms involved in persistence or recovery of cognitive deficits in human cannabis users. Human patterns of use can extend to 20–30 or more years of heavy use. This has not been well-modelled by animal research on the long-term effects of cannabinoid administration. While the neurophysiology of the eCB system that might explain persistent cognitive deficits is exceedingly complex, G-protein coupled receptor dependent signalling involving metabotropic glutamate receptors (which initiate eCB release) can produce permanent changes in hippocampal synaptic transmission if cannabinoid stimulation is sufficiently prolonged.[11]

Genetic linkage to cognitive dysfunction and schizophrenia

Despite the multiplicity of evidence for multiple genes involved in schizophrenia, Coolen and colleagues[183] have recently demonstrated in an animal model how a subtle imbalance in the expression of a single gene protein that is involved in a wide variety of developmentally important signalling pathways may be sufficient to form the molecular basis of a complex phenotype such as schizophrenia. The diversity of functional roles of the eCB system imply that a subtle imbalance in this system could manifest as a complex phenotype. The CB1 receptor gene is located on chromosome 6q14-q15.[184] Suggestive evidence links global cognitive impairment in schizophrenia to susceptibility genes on chromosome 6,[185] albeit in the 6p24 region, with CPT and RAVLT performance showing linkages to this region. Genetic variants of the CB1 receptor have been shown to differ between substance using and nonusing patients with schizophrenia.[186] A triple repeat polymorphism of the CB1 receptor gene has been reported to be significantly associated with the hebephrenic subtype of schizophrenia.[187] In that study, a 9-repeat allele of an AAT-repeat polymorphism of the cannabinoid receptor gene was associated with a 2.3-fold higher susceptibility to schizophrenia. Other studies have, however, failed to support an association between CB1 receptor polymorphisms and schizophrenia, psychotic symptoms or psychosis proneness.[188–190]

There is growing interest in epigenetic influences within the genotype-endophenotype-phenotype pathways in schizophrenia, whereby multiple genetic and environmental factors become integrated over time through dynamic processes.[33] Levenson and Sweatt[191] have described epigenetic mechanisms in memory formation and define epigenetics as "a set of self-perpetuating, post-translational modifications of DNA and nuclear proteins that produce lasting alterations in chromatin structure as a direct consequence, and lasting alterations in patterns of gene expression as an indirect consequence."[191] Alterations of DNA protein (chromatin) structure, which, in turn, regulates gene expression through histone acetylation, may mediate long-lasting behavioural changes in the context of learning and memory that require a highly coordinated pattern of gene expression. Exposure to learning paradigms that result in the formation of long-term memories leads to changes in histone acetylation. Levenson and Sweatt[191] describe how exposure to various environmental conditions leads to changes in the epigenetic profile of the genome in relevant brain regions and propose that drugs that target the epigenome may be viable therapies for treating neurocognitive disorders. Mechanisms inherent in these processes include synaptic plasticity, LTP, depolarization-induced suppression of inhibition and NMDA receptor activation, all of which the eCB system is known to be directly involved in. This suggests a rich area for research on cannabinoid-mediated epigenetic mechanisms in schizophrenia from both a therapeutic perspective (synthetic cannabinoid agonist/antagonist medications) but also from a deleterious perspective in terms of the potentially negative effects of exogenous cannabinoids on the epigenome. Susceptible genes may influence vulnerability to environmental pathogens.[192,193]

Short- and long-term administration of antipsychotic drugs have been shown to alter the expression of genes involved in synaptic plasticity and intracellular calcium regulation.[194,195] Calcineurin is a calcium- and calmodulin-dependent protein phosphatase that plays a significant role in brain development and synaptic plasticity and affects working memory. Calcineurin-knockout mice display behaviours that have been likened to schizophrenia, and alterations affecting calcineurin signalling have been proposed as a contributing factor in the pathogenesis of schizophrenia.[195,196] Decreased expression of calcineurin subunits in the hippocampus has been reported in schizophrenia.[197] Cannabinoid effects on calcium channels are modulated by cyclic AMP-dependent protein kinase and calmodulin.[198] Adaptations in the signalling pathways involved in the development of tolerance to cannabinoids have been shown to involve the activity of protein kinases,[199] and increased adenylyl cyclase activity is stimulated by calcium/calmodulin during cannabinoid withdrawal.[200] The involvement of the eCB system in the extinction of aversive memories appears to involve the activity of kinases and phosphatases such as calcineurin.[201] Intriguingly, the extract of hemp seed has been shown to activate calcineurin and improve memory function in mice.[202]

The following sections examine evidence of 2 common gene variants that have been associated with specific cognitive processes, cannabinoid effects and schizophrenia. These are the catechol O-methyltransferase (COMT) polymorphism associated with PFC-based executive functions and neurophysiology and a brain-derived neurotrophic factor (BDNF) polymorphism associated with medial-temporal-cortex based declarative memory processes.[203] BDNF is a cyclic-AMP response-element binding protein (CREB)-regulated gene. Interference with the function of CREB impairs long-term memory formation. Significant numbers of genes and proteins are altered after short- and long-term exposure to cannabinoids, including CREB, BDNF, calmodulin and GABA receptor subunit proteins.[204] Large doses of THC applied directly to cultured hippocampal neuronal slices have been shown to cause significant toxicity, shrinkage of cell bodies and DNA strand breaks characteristic of neuronal apoptosis.[205] Currently, there is also significant interest in the DISC1 gene in relation to schizophrenia, memory and hippocampal function,[169,206,207] and DISC1 regulates cyclic–AMP signalling.[208] However, allelic variation of DISC1 has not yet been investigated in relation to cannabis use or the eCB system.

COMT and tonic/phasic dopamine

The COMT gene, located on chromosome 22q11, is essential for the metabolic degradation of dopamine in PFC and has been implicated in schizophrenia.[209,210] Evidence for an association between COMT genotype and schizophrenia has, however, been mixed[211–213] (with some studies failing to find support for a link[214,215]). COMT involvement in dopamine metabolism and specific cognitive functions affected in schizo-

phrenia have prompted ongoing interest in a potential association. Dopamine dysregulation and a functional Val158Met polymorphism in the COMT gene have each been associated with deficits in attention, working memory and other executive functions and in PFC pathophysiology.[216,217] Goldberg and colleagues[218] found *n-back* working memory tasks to be associated with the COMT polymorphism in the same manner across schizophrenia, healthy siblings and control subjects. They suggested "an additive genetic model in which the effect of allele load is similar in its effects on prefrontally based working memory irrespective of the genetic or environmental background in which it is expressed."[218] Variations in the COMT gene have also been linked to episodic and semantic memory with better recall (but not recognition) performance by Met homozygotes.[219] Bearden and colleagues[220] investigated the COMT genotype as a predictor of executive functioning in Velocardiofacial (22q11.2 deletion) syndrome, one of the highest known risk factors for schizophrenia. They found that Met-hemizygous patients performed significantly better on a composite measure comprising set-shifting, verbal fluency, attention and working memory than Val-hemizygous patients. Nolan and others[221] found that the Met allele may promote cognitive stability in schizophrenia by increasing tonic dopamine but may limit cognitive flexibility: Met homozygotes showed better rule acquisition but poorer ability to switch to reversal learning. Gallinat and colleagues[222] found smaller frontal P300 amplitudes in Met homozygous individuals, particularly those with schizophrenia. Conversely, another study demonstrated an association between COMT and executive functioning in healthy siblings but not their counterparts with schizophrenia.[223]

Meyer-Lindenberg and colleagues[224] have recently shown that the COMT Val/Met polymorphism predicted reduced dopamine synthesis in the midbrain and affected the interaction with PFC, implicating a dopamine tuning mechanism in PFC and suggesting "a systems-level mechanism for cognitive and neuropsychiatric associations with COMT." [224] The activity of dopamine neurons in the midbrain is under both excitatory and inhibitory control of the PFC, and a marked increase in prefrontal dopamine is seen in COMT-knockout mice.[224] An eCB-mediated self-regulatory role of dopamine neurons in the ventral tegmental area to suppress PFC-stimulation-evoked activity was described above.[154] Melis and colleagues[154] highlight how finely the eCB system might regulate dopamine modulation of cortical information processing, explaining a relation between unbalanced eCB signalling and altered dopamine-dependent processes associated with stress, substance abuse and psychiatric disorders such as schizophrenia. Bilder and colleagues[192] discuss the COMT polymorphism findings in the context of tonic/phasic dopamine activity and resultant effects on cognitive stability versus flexibility in working memory, sustained attention and mismatch tasks. These tonic and phasic actions of dopamine may explain why people with schizophrenia (and perhaps cannabis users) fluctuate between impaired and unimpaired performance over time, suggesting influences that are perhaps transitory in nature.[31]

From a longitudinal birth cohort study, Caspi and colleagues[193] reported a significant interaction between the COMT genotype and early onset cannabis use in the risk of developing psychosis. They showed that Val carriers were most likely to exhibit psychotic symptoms and develop a schizophreniform disorder if they used cannabis in adolescence. Those with the Val/Val genotype and early onset cannabis use (before age 15 or monthly use by age 18) had the highest risk of developing adult schizophreniform disorder (OR 10.9, 95% CI 2.2–54.1), followed by Val/Met individuals with early onset cannabis use (OR 2.9, CI 0.78–8.2), but not Met/Met individuals (OR 1.1, CI 0.21–5.4). Adult onset cannabis use (> 18 yr) did not interact with genotype in predicting psychosis outcomes. This exceptionally well-controlled study ruled out alternative explanations for the demonstration of a susceptibility gene by environment interaction in which adolescent, but not adult-onset, cannabis use interacts with the COMT gene polymorphism to predict the emergence of adult psychosis. The genetic polymorphism alone, and adolescent cannabis use alone, did not predict the development of psychosis. This may explain the inconsistent findings with regard to the COMT gene polymorphism association with schizophrenia and underscores the conditional exposure to an environmental pathogen,[193] in this instance, adolescent cannabis use. Caspi and colleagues discuss possible neurobiological interactions between cannabinoids and dopamine underpinning this association. Most recently, the COMT genotype has been shown to moderate the effects of cannabis on inducing positive psychotic symptoms, with Val homozygotes being most susceptible.[225] Psychosis liable (patients or relatives) Val carriers were more sensitive to acute THC-induced psychotic experiences and impairment of memory and attention.[226,227]

BDNF

The BDNF gene, located on chromosome 11p13, plays a critical role in activity-dependent neuroplasticity underlying learning and memory (e.g., LTP) in the hippocampus, where its expression and protein levels are highest in the brain, followed by the PFC. BDNF has also been implicated in the neurobiology of schizophrenia.[228] Hariri and colleagues[229] used fMRI to examine the relation between BDNF Val^{66}Met polymorphism and hippocampal activity during episodic memory processing. Val homozygotes showed greater memory-related hippocampal activity during both encoding and retrieval and better recognition memory performance than Met carriers. The interaction between genotype and left hippocampal activity during encoding accounted for 25% of the variance in recognition memory performance, indicating a key role for BDNF modulation of hippocampal engagement in the acquisition of information. Val/val homozygotes have also been shown to have larger hippocampal volumes than val/met heterozygotes, and the val/met polymorphism of the BDNF gene accounted for a greater proportion of the variance in hippocampal volumes in first-episode schizophrenia patients than in control subjects.[228] Neurotrophins such as BDNF also play a critical role in neurodevelopment, neuronal survival and plasticity of dopaminergic, cholinergic

and serotonergic neurons and, as such, have been implicated in the pathophysiology of schizophrenia.[230,231] However, the evidence is mixed. Some studies report no association of the BDNF gene polymorphism with schizophrenia,[232] whereas others have shown reduced BDNF levels and receptor mRNA in DLPFC of schizophrenia patients, which may compromise the function and plasticity of the PFC.[233] Hashimoto and colleagues[234] found reduced PFC BDNF levels in schizophrenia and reported that signalling mediated by BDNF contributes to altered inhibitory GABA-related gene expression that may underlie cognitive deficits.

Bayatti and others[235] report inhibition of BDNF expression by short-term in vitro application of WIN. CB1 receptors are negatively coupled with the cAMP signalling cascade and that their activation inhibits CREB phosphorylation which might explain reduced BDNF expression. However, Butovsky and colleagues[236] report that long-term administration of THC to rats resulted in increased expression of both mRNA and protein levels of BDNF in specific brain regions associated with reward, notably a tenfold increase in nucleus accumbens. Smaller increases were found in the ventral tegmental area, medial PFC and paraventricular nucleus. There was no change in the hippocampus. The authors suggest that THC-induced upregulation of BDNF expression has an important role in the neuroadaptive processes resulting from exposure to cannabinoids.

Jockers-Scherübl and colleagues[237,238] report raised levels of the neurotrophins nerve growth factor (NGF) and BDNF in serum of unmedicated schizophrenia patients with past chronic cannabis use, compared with nonusing patients, and the patient using cannabis had an earlier onset of the disorder. They interpret the raised NGF and BDNF as neuroprotective mechanisms to counter putative neurotoxic damage to vulnerable brains by cannabis and other drug use (polydrug users also showed raised NGF and BDNF serum concentrations, and BDNF levels are high after traumatic brain injury). Otherwise healthy control subjects who were using cannabis in this study did not differ from nonusing control subjects or patients. Other studies have shown reduced serum neurotrophin levels in schizophrenia patients.[239]

Aberrant incentive salience and inhibitory control

Schizophrenia may be conceptualized as a "state of aberrant salience" induced by dysregulated neurochemistry, particularly of the dopaminergic system.[240] Phasic dopamine transmission has been linked to the updating, resetting or gating of relevant novel information and, specifically, to incentive-reward signals and uncertainty in these.[192] This role extends to conditioned learning to update links between stimulus and response when an unexpected reward does not occur.[192] Similar mechanisms involving attribution of aberrant incentive salience and reward processes have long been posited to underlie substance use and addiction.[241–243] Tsapakis and colleagues[244] discuss how the development of dopamine sensitization underlies both a craving for drugs and the positive symptoms of schizophrenia. Attribution of aberrant incentive salience to stimuli entails the kinds of dysfunction in cognitive processes in schizophrenia that have been discussed above also in relation to cannabis effects. Hypersensitization of drug incentives and of the dopaminergic reward system is accompanied by cognitive impairments associated with PFC function, difficulties in decision making, impulse control and judgement of consequences associated with further drug seeking and is linked to the efficiency of learning and memory.[245,246] Accordingly, there has been a shift in the conceptualization of addiction mechanisms, from a subcortical pleasure and reward system focus to an acknowledged dysfunction in cortically mediated response selection and inhibition processes.[247] Deficient inhibitory control may be a central feature of addiction, with dysfunction of anterior cingulate and orbitofrontal cortices affecting the regulation of the reward system.[247] Jentsch and Taylor[248] comprehensively reviewed the evidence that suggests that altered dopaminergic activity, impaired frontal cortical inhibitory response control and cognitive dysfunction resulting from long-term drug use, together with impulsivity and altered incentive motivational processes owing to limbic/amygdala dysfunction, underlie continued drug-seeking behaviour. Further, the neuroadaptations associated with sensitization are independent of those associated with physiological dependence and persist long after drug-use cessation.[249]

Impaired functioning in various cognitive tasks by people with schizophrenia could collectively be considered within a framework of failure to inhibit dominant responses in the face of pervasive generalized noise. The complex role of the eCB system in inhibitory processes and identified mechanisms by which eCBs may mediate key processes involved in incentive salience implicate this system in schizophrenia and serve to highlight the potential for deregulation of the eCB system as a consequence of long-term or heavy cannabis use. eCBs are involved in the PFC-mediated development of inappropriate incentive salience and resultant effects on attention.[154] Cannabinoids potently increase dopamine metabolism and release in PFC, but repeat administration leads to a persistent anatomically selective reduction of dopamine metabolism in PFC that underlies attentional deficits.[118,119] Cannabinoids have a profound influence on learning and memory via effects on eCB-mediated hippocampal metaplasticity.[153] A dysfunction in hippocampal eCB signalling, and resultant effects on related circuitry (e.g., PFC), may underlie impairments of learning and memory in long-term cannabis users.[90] There is a good degree of overlap between a dysfunction of these cognitive mechanisms in schizophrenia and in long-term cannabis use.

Nonspecificity of cognitive dysfunction and neural substrates

The deficits in cognitive functions highlighted in this paper, as well as their purported underlying neural substrates, are not unique to schizophrenia or to cannabis. Many other clinical disorders and substance using populations show similar kinds of neuroadaptations and cognitive deficits. Multiple substances have been shown to affect PPI, saccadic and

smooth pursuit eye movements and attention, learning and memory and are associated with COMT polymorphism and altered expression of BDNF. Cannabinoid receptors have also been implicated in Alzheimer's disease[250] and Parkinson's disease,[251] largely in terms of neuroprotection; in addition, the eCB system has been demonstrated to promote neural progenitor cell proliferation in the hippocampus.[252] Long-term but not short-term administration of the potent but nonselective cannabinoid agonist HU-210 increased adult rat hippocampal neurogenesis and produced anxiolytic and antidepressant-like effects.[253] Other endogenous compounds, such as neurosteroids, have been shown to display neuroprotective properties in rodents but exacerbate psychotic symptoms in humans.[254] The complexity of sometimes opposite effects of short- and long-term endogenous and exogenous cannabinoids of different types and possible inverted U dose–response actions on cognition, neurobiology and related systems provide a wealth of apparent discrepancy for future research to disentangle and interpret.

The concept of endophenotypes in schizophrenia has itself been contested.[255] However, as Heinrichs[31] acknowledged,

> Several endophenotypes could underpin any single clinical syndrome or diagnostic classification. Moreover, there is no reason to assume that illnesses defined by consensus or convention represent unique or mutually exclusive combinations of endophenotypes. Psychiatric disorders often overlap in terms of symptoms and they may overlap in their biological underpinnings as well. Although the endophenotype concept is rooted in genetic theory it is possible to broaden the idea to include environmental and complex interacting etiologies.

A broader focus of research on endophenotypes that underlie multiple psychiatric disorders and psychopathology in general will facilitate identification of biological substrates and conferred risks and provide clinical relevance to factors that increase risk by 2- to 3-fold, such as cannabis.[256,257] The particular association between cannabis and schizophrenia identified in epidemiological studies and the degree of overlap of their cognitive effects and associated brain neurochemistry support the focus of the current paper in highlighting their similarities. In some studies, an apparent relation between cannabis use and depression, for example, did not hold after controlling for symptoms of psychosis, but not the reverse (e.g.,[258]). Combining cognitive tasks and neuroimaging techniques, exploring gene-by-environment interactions and neurochemical and neurobiological underpinnings in the context of specific endophenotypes has the potential to further elucidate our understanding of the complexity of the schizophrenic disorder and its relation with cannabis use and the eCB system.

Cannabis use by schizophrenia patients

An ongoing puzzle is the high rate of cannabis use by people with schizophrenia, with 30% to 70% of the population with schizophrenia using cannabis[259–262]. The primary reasons given by patients for their use are similar to those reported by the general population, including enhancement of affect, coping with unpleasant affect and social reasons, with limited support for relief of symptoms and side effects.[263] The expectation that cannabis use will improve affect maintains use and potentially leads to the development of dependence and worsening of symptoms and course of the illness.[264,265] There is little direct evidence for a self-medication hypothesis,[8,258,266] although Hambrecht and Häfner's[267,268] hypotheses regarding self-medication have found some support from Ferdinand and colleagues'[269] 14-year follow-up of a youth cohort from the general population. They found that not only did cannabis use predict future psychotic symptoms (CI 1.79–4.43) but that the onset of psychotic symptoms predicted future cannabis use in people who had never used cannabis before (CI 1.13–2.57). This suggests self-medication (and also provides support for reverse causality theories, although cannabis use has most often been found to precede the development of schizophrenia rather than the reverse). Neurobiologically, it is possible that the initial enhancement of prefrontal dopamine by cannabis might ameliorate certain negative symptoms. The persistent reduction of PFC dopamine with long-term cannabis use would, however, most likely further impair cognition and other negative symptoms; the increased mesolimbic dopamine transmission associated with cannabis ingestion explains a general worsening of positive symptoms. There is a convincing body of evidence that cannabis use triggers more psychotic episodes in patients and worsens the course of the disorder (eg.,[264]). Given the complexity of cannabinoid effects and the multiplicity of cannabinoid compounds in cannabis plant matter and products (e.g., the antioxidant cannabidiol that possesses some anxiolytic and antipsychotic properties), it is possible that aspects of smoked cannabis do serve to temporarily relieve certain symptoms or serve potential neuroprotective functions. However, more research is required to understand these complex actions in the context of this complex disorder.

Limited evidence that patients who use cannabis may be more functional before the onset of illness and that higher levels of functionality are required to maintain substance use (e.g., [270–272]), may explain the preliminary results of 3 studies that found either no or minor additional adverse cognitive effects on cognitive functions in patients with psychoses and comorbid cannabis use compared with those without cannabis use.[273–275] Another small study of schizophrenia patients with dual diagnosis of abuse or dependence on any drug found better performance on frontal tasks such as the WCST and verbal fluency tasks.[276] The authors conjectured that better planning and organizational abilities are required to initiate, procure and maintain drug use. Stirling and colleagues,[277] however, showed in a 10- to 12-year follow-up of first-episode psychosis admissions that ongoing cannabis use preserved neurocognitive function in several domains, with users outperforming nonusers and groups being indistinguishable with respect to premorbid adjustment or social functioning. These studies counter the intuitive hypothesis that cognitive impairments known to be associated with cannabis use in a healthy population could well exacerbate deficits in the already cognitively compromised schizophrenia patients who also use cannabis, but there has been a surprising dearth of specific research in this area. There is

preliminary evidence that a history of cannabis use significantly predicted poorer semantic clustering scores in a verbal learning task in adolescents with early onset schizophrenia.[278] We are currently exploring these interactions in ongoing neuropsychological and neuroimaging studies of patients with and without comorbid cannabis use. It has also been hypothesized that there are socialization benefits to maintaining a peer network of cannabis users and that this is a factor in recreational cannabis use by patients before they develop aberrant inhibitory and incentive-sensitization mechanisms that accompany drug dependence and associated problems. D'Souza and colleagues[27] discuss the problems inherent in retrospective studies based on self-report. They also speculate that patients may derive some immediate benefits of using cannabis at the expense of negative consequences.

D'Souza and colleagues[27] have definitively demonstrated exacerbation of cognitive and psychotic symptoms in a well-controlled study of acute intravenous THC administration to schizophrenia patients. They found transient adverse effects on verbal learning and recall; perceptual alteration; vigilance; positive, negative, general and extrapyramidal symptoms; and plasma prolactin and cortisol that were often dose-dependent. Patients were more vulnerable to THC effects on learning and memory than were healthy control subjects, and no beneficial effects were observed. The authors discuss multiple neurobiological mechanisms that might explain the enhanced sensitivity to the cognitive effects of THC. Among these are intriguing links between the growing focus on deficits in synchronous neural activity in schizophrenia (e.g.,[279–281]) and the involvement of eCBs in hippocampal oscillations, synchronous activity, integration and binding in the gamma range (e.g.,[9,282]) and high-frequency ripple and theta range.[283] Disruption of this synchronous activity could result from either activation of CB1 receptors by exogenous cannabinoids or a dysfunctional eCB system. Thus, exacerbation of cognitive deficits by cannabis use in patients may be explained in neurobiological terms, whereas the onus is on researchers to replicate and explain potential preservation of neurocognition in cannabis using patient cohorts. In this vein, a recent study demonstrated that hyperdopaminergia in an animal model of schizophrenia is accompanied by decreased eCB signalling and that administration of indirect agonists (anandamide reuptake inhibitors) alleviated the accompanying hyperlocomotion.[284] Clearly, additional research is required to fully understand the fine tuning role of the eCB system and complex interactions with exogenous cannabinoids in this disorder.

Cannabinoid consequences for neurodevelopment and adolescence

The nature of adverse consequences of cannabis use may differ across the life span,[285] with educational and psychosocial effects apparent in adolescents and young adults and long-term cognitive or physiological effects becoming manifest only after many years of exposure to the drug. However, an increasing number of studies are detecting cognitive impairments in adolescent users (e.g.,[95]) as well as a greater incidence of psychotic symptoms (e.g.,[286]).

Evidence is growing for greater adverse cognitive consequences of cannabis when use begins during early adolescence (e.g., before age 16 or 17) as opposed to young adulthood. Early onset cannabis use was shown to impair attentional processes measured by reaction time during visual scanning,[106] visual search and short-term memory[166,287] and result in the most reduced P300 amplitudes in an attention task.[113] Early onset cannabis users were found to have smaller whole brain volume, lower percentage of cortical grey matter, higher percentage of white matter and increased resting CBF, compared with late onset users.[288] Cannabis users who commenced use before age 17 were least likely to show recovery of cognitive functions after 28 days abstinence.[130]

Rey and colleagues[286] review the evidence that early regular cannabis use has substantial negative effects on psychosocial functioning and psychopathology in the context of developing juvenile psychiatric disorders. Early-onset cannabis use confers the greatest risk of developing psychosis, either in its own right (e.g.,[258]) or as a gene-by-environment interaction with the COMT Val/Met polymorphism most associated with cognitive deficits.[193] Fergusson and Horwood[289,290] have shown adverse outcomes associated with adolescent cannabis use, including the development of psychotic symptoms, and recently showed that the direction of causality is from cannabis use to symptoms and not the reverse[291] (although Ferdinand and others[269] do provide evidence for the latter). There is evidence that adolescent-onset cannabis use is associated with more rapid development of dependence and a greater incidence of dependence and associated problems than when onset occurs during adulthood.[292,293] Thus individuals who begin to use cannabis when the brain is still developing may be most vulnerable to its deleterious effects.[193]

This is of concern when these adverse neurodevelopmental effects are posited to occur at the same time that neurodevelopmental changes and cognitive decline may be occurring in the development of schizophrenia or its prodrome. Davalos and colleagues[294] studied children genetically at risk for schizophrenia and found deficits in verbal skills, working memory and inhibition that they suggest may progress into more generalized or global deficits with the development of the disorder. The neuropsychological performance of adolescents referred for prodromal symptoms was shown to be intermediate between population norms and the performance of established schizophrenia patients.[295] This suggests that the cognitive decline that accompanies first psychotic episodes may not only be prevented or lessened by prodromal interventions but may also be exacerbated by concomitant cannabis use. Adolescence is increasingly being viewed as a unique period of brain development, during which the functional organization of the brain responsible for higher-order cognitive processes, mature level control and decision making and social information processing is not yet fully mature, with ongoing myelination and synaptic pruning toward achieving greater synchronous and collaborative activity.[296–298] Dysregulation of these developing networks, by substance use, for example, may contribute to the onset of mood, anxiety, depressive and psychotic disorders. There is a growing recognition that

substances affect the brain in different ways during adolescence versus adulthood (e.g.,[299]). Insufficient research has investigated the unique effects of cannabis during this neurodevelopmentally vulnerable period.

Animal studies have demonstrated greater adverse consequences when cannabinoids are administered to adolescent rats (see for example[80,136,300,301]). Early life experiences have been shown to increase the likelihood of developing schizophrenia later in life. It has been conjectured that an early insult (e.g., a lesion or maternal deprivation), when compounded by cannabinoid exposure during puberty, may confer the greatest risk of psychopathological consequences in adulthood. Evidence for this, however, is scant, and there are mixed potentially harmful versus beneficial effects of exposure to cannabinoids during development (e.g.,[302–304]).

Prenatal (or neonatal) exposure to cannabinoids has, however, unequivocally been shown to be harmful in multiple animal (e.g.,[305–308]) and human studies, as reviewed above (e.g.,[101,104]). Mereu and colleagues[305] found that in utero exposure to WIN disrupted retention in a passive-avoidance task in 40- and 80-day-old rats, and this was accompanied by decreased hippocampal LTP and glutamate release, suggesting long-lasting, if not permanent, impairment of memory processes and their neural substrates by exposure to cannabinoids during a critical developmental period. The authors surmised that these mechanisms may explain the observations of cognitive impairments in humans exposed to cannabis in utero. The eCB system is intimately involved in neurodevelopment. Cannabinoid receptors are present in the brain from early stages of gestation and play a vital role in the developing organism.[306,307]

Despite the convincing evidence for periods of neurodevelopmental vulnerability, we have not found any evidence of age of onset effects in our neuropsychological or ERP studies of adult long-term heavy cannabis users, finding the number of years of cannabis use to be the most robust predictor of impairment (e.g., [87,111,132]). It is clear that early onset cannabis users have a longer duration of exposure to cannabis than their age-matched counterparts with later onset of use, and these interactions can be difficult to disentangle. However, some studies report that age of onset effects held after controlling for duration of exposure to cannabis (e.g.,[288]). Studies of adult cannabis users, most of whom commenced use during adolescence, continue to show fairly consistent cognitive deficits, but these are variously related either to duration, frequency or dose/quantity of cannabis use. Further research on the parameters of cannabis use that result in dysfunction, monitoring of age of commencement of cannabis use and their interactions is of utmost importance. This is of particular concern given the growing evidence for an association between cannabis use and the development of psychosis in young people.

Conclusion

In this paper, we highlight the similarities between cognitive dysfunction associated with cannabis use and the cognitive endophenotypes of schizophrenia, drawing on recent developments in the understanding of the neurobiology of cannabinoid effects. We propose that the use of cannabis leads to cognitive deficits of a similar nature to those seen in schizophrenia but of a lower magnitude. We further propose that the neurobiology underpinning the development of cognitive deficits in cannabis users may overlap with the neurobiological underpinnings of schizophrenia. We have reviewed a multitude of evidence that taken together could inform our understanding of the potential for cannabis use to trigger the onset of psychosis in vulnerable individuals and explain the exacerbation of symptoms in schizophrenia patients.

Our central tenet in this paper is that the eCB system is involved, either directly or through its interactions with other neuromodulators (and, critically, dopamine), in both the development of similar cognitive deficits associated with cannabis use and schizophrenia, respectively, and in the pathophysiology and symptoms of psychiatric disorders in general. We concur with evidence that suggests that cannabis is but one of many causal factors that may precipitate psychosis, and its propensity to do so needs to be better understood within the context of predisposing genetic and environmental vulnerabilities. It has been proposed that the psychosis phenotype may exist as a continuous distribution throughout the general population.[309] There are critical periods of neurodevelopment in which cannabis use may exert greater adverse effect (e.g., during adolescence) to combine with other vulnerabilities and precipitate the onset of psychosis. As suggested by Weiser and colleagues,[256] cannabis use itself may not necessarily lie along a causal pathway to psychosis, but an association with schizophrenia may be due to dysfunction of the eCB system. This may lead to an increased propensity to use cannabis and an increased risk for the development of psychosis in cannabis users. Van Os and colleagues[310] point out how genetic factors that influence the sensitivity to the psychosis-increasing effects of cannabis may also influence the probability of initiation of cannabis use. Leweke and colleagues[311] report preliminary evidence that anandamide levels in CSF differ between patients who use and do not use cannabis, and we have preliminary evidence for altered functionality of the eCB system in patients who were former cannabis users versus those who have never used cannabis,[312] with further research in progress. It is possible that contradictory evidence in the field may be explained by genetic differences in subpopulations or by cannabinoids having differential effects in people with dysfunctional versus intact eCB systems. In line with the trend toward classification of clusters of cognitive measures as endophenotypes of psychiatric disorders and investigations of their underlying neurobiology, we propose that a closer consideration of the cognitive deficits associated with specific parameters of cannabis use, and interactions with neural substrates and age may better inform the nature of the association between cannabis use, the eCB system, and schizophrenia or psychosis or psychiatric disorders of multiple kinds.

Not all of the cognitive endophenotypes of schizophrenia classified in this paper have been found to be impaired by cannabis, but not all have been studied directly or investigated in large-scale, well-controlled studies. Even if the

cognitive measures in our taxonomy fail to meet all criteria for endophenotype status,[32] the consistency of their association with schizophrenia and the increasing evidence of similar deficits associated with cannabis use warrant an exploration of the potential involvement of the eCB system. As the eCB system is largely inhibitory in its modulation of neurotransmitter release (decreasing the release of either excitatory or inhibitory transmitters[10]), and since drug dependence entails a loss of inhibitory control,[247,248] acute and chronic effects of cannabinoids on inhibitory processes might be expected to underlie many of the cognitive deficits outlined above. The putative endophenotypes of schizophrenia are also not mutually exclusive. A particular cognitive mechanism may contribute to more than one endophenotype and multivariate endophenotypes, for example, as demonstrated based on a combination of electrophysiological measures,[36] may provide improved diagnostic classification than any single endophenotype. Further elucidation of cognitive deficits associated with short[65] and long-term drug use has important theoretical and clinical significance in terms of understanding fundamental pathophysiology and improving treatment and rehabilitation programs for substance use and mental illness.[313]

In addition to combining multidisciplinary research approaches (e.g., cognitive, neuroimaging, neurochemical and genetic), future directions for this field include empirical evaluation of the putative endophenotypes of schizophrenia; more refined investigations in animal models and human studies of short- and long-term effects of different endogenous and exogenous cannabinoids on specific and multiple measures contributing to endophenotypes, particularly where these have not been investigated (for example, MMN and inhibitory processes); determination of cognitive effects of varying parameters of cannabis use by humans, and their recovery, as may be impacted also by genotype and neurodevelopmental stage, with complimentary preclinical studies; assessment of the effects of exogenous cannabinoids on the functionality of the eCB system and of cannabinoid effects in general in hyperdopaminergic states and other animal models of psychosis; and greater exploration of the fine tuning role of the eCB system and implications of excess versus deficits in the system and on other neuromodulators.

The prevalence of cannabis use among people with mental illnesses, the potential for cannabis to trigger psychotic symptoms and episodes, and the neurobiological interactions between the eCB system and the neuropathology associated with psychotic disorders suggest a need to focus greater attention on investigating the nature of and mechanisms underlying cognitive impairments associated with cannabis use.

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