

Cannabis use and cognitive dysfunction

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This review considers the effects of cannabis on cognitive functioning, in both short and long term. Although the general impression supported by many studies is that cannabis causes cognitive decline, particularly with long-term usage, some research suggests that this may not be the case. Nevertheless, certain specific neuropsychological parameters have been found to be affected. Most commonly and consistently reported are response time, prolongation of word viewing time, basic oculomotor deficit, residual verbal memory and executive functioning. The pathways to cognitive dysfunction are given particular focus, including the role of the central nervous system (CNS) cannabinoid system. Finally, the psychiatric effects of cannabis are considered in light of the idea that cognitive function may be the common denominator in the association between cannabis and psychotic disorders.

EFFECT OF CANNABIS ON COGNITION

Cannabis is one of the most commonly abused illicit drugs. The World Health Organization^[1] reports that almost 3% of the world's adult population abuses cannabis, with many more individuals reporting less frequent use. Adolescents in particular consume high levels of cannabis, starting generally between 12 and 16 years of age. This is an important factor from a psychiatric and developmental point of view.^[2] Cannabis use is of important consideration in light of its recognized acute and long-term health effects.^[1,3] Active compounds of cannabis, called cannabidiols, have 64 active isomers, each having different effects on human health and behavior. Only one metabolite, tetrahydrocannabinol (THC), is reported to be an active metabolite responsive for its effects.^[4] Studies show that it induces both psychical and physical dependencies,^[5] but the perception of withdrawal

is weak on account of its slow elimination.^[6] There is a widely held belief that cannabis is inert to the brain,^[7] and although the psychological consequences are quite evident, the population at large seems unconvinced. There is much debate about the nature of cannabis dependence, as it is considered non-addicting due to the absence of a withdrawal state. This presumption has also been proved wrong.^[6]

The general impression supported by many studies is that cannabis causes cognitive decline, particularly with long-term usage. Majority of studies have suggested a significant cognitive decline in cannabis abusers compared to non-abusers and healthy controls.^[8-10] A report by Bartholomew *et al.*^[11] suggested that cannabis use has a detrimental effect on prospective memory ability in young adults but users may not be aware of these deficits. Cannabis is known to produce substantial acute effects on human cognition and visuomotor skills. Many recent studies additionally revealed rather long-lasting effects on basic oculomotor control, especially after chronic use.^[12] Even so, it is still unknown to what extent these deficits play a role in everyday tasks that strongly rely on an efficient saccade system, such as reading.

Cannabis has a negative impact on cognition; however, the current body of research literature does not provide evidence of significant, long-term effects due to cannabis use. Several acute effects are noted and some are suggestive of negative mental health consequences.^[13] Evidence from both animal and human studies suggests that the severity of the effects of cannabis use on cognitive development is dependent on the age when cannabis use begins.^[14] One possible explanation is that those who begin cannabis use early in

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adolescence are more likely to become heavily dependent. It is plausible that chronic cannabis abuse will then interfere with educational and vocational training. From a more biological perspective, however, use of cannabis during critical developmental periods in the still maturing brain may induce persistent alterations in brain structure and brain function.^[15] Therefore, the effects of frequent cannabis use during adolescence could be different from and more serious than those during adulthood, an issue increasingly recognized in the field of cannabis research.

A study by Bartholomew showed prospective memory impairments associated with cannabis use in young adults. Analysis revealed no significant differences in the number of self-reported prospective memory failures. Cannabis users recalled significantly fewer location–action combinations than non-users in the video-based prospective memory task. The study concluded that cannabis use has a detrimental effect on prospective memory ability in young adults but users may not be aware of these deficits.^[11]

Certain specific neuropsychological parameters have been found to be affected. Most commonly and consistently reported are response time, prolongation of word viewing time, basic oculomotor deficit, residual verbal memory and executive functioning.^[16] These dysfunctions increase cognitive demands. Based upon such findings occurring in a specific subgroup of patients of schizophrenia and in a normal population, a cognitive endophenotype has been proposed which increases vulnerability for schizophrenia-like disorders.^[17,18]

EVIDENCE FOR DOSE DEPENDENCY

There is some evidence that the cognitive decline is related to dose. The cognitive dysfunction is also reported to be associated with the amount of consumption. Very heavy use of marijuana is associated with persistent decrements in neurocognitive performance.^[19] More specifically, one study demonstrated that the THC dose contained in cannabis cigarettes was linearly related to cognitive and psychomotor performance. Response times slowed down and motor control became worse with increasing THC doses.^[20] There may be relatively subtle performance deficits on the level of basic oculomotor control that scale up as task complexity and cognitive demands increase.^[12] 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.^[21,22] Some studies have reported complete recovery of impairments after 4 weeks of abstinence, whereas other studies describe persisting cognitive deficits, especially in the domains of attention, memory and executive functions^[19,23] or only partial recovery of cognitive impairments in abstinent users.^[24] Finally, a meta-analysis by Grant *et al.*^[25] identified residual

verbal memory impairments as the most consistent deficit associated with chronic cannabis use in otherwise healthy users.

PATHWAYS TO COGNITIVE DYSFUNCTION

There is little information on the neurocognitive and neurophysiological effects of cannabis. Preliminary neuroimaging studies in mainly non-psychotic populations show that cannabis does not affect gross brain anatomy. Cannabis does, however, acutely increase cerebral blood flow and long-term exposure causes an overall reduction of cerebral blood flow. Animal studies using an active cannabidiol (delta-9-THC) demonstrate enhanced dopaminergic neurotransmission in brain regions known to be implicated in psychosis.^[26] In humans, delta-9-THC induces psychotic-like states and memory impairments in healthy volunteers.^[27] Some neurochemical processes are significant to the understanding of links between cannabis and cognitive performance. In particular, the role of the CNS cannabinoid system, the effect of cannabis on brain as seen by imaging and its influences on brain development during adolescence are the key.^[28]

The endogenous cannabinoid system is sensitive to the introduction of exogenous cannabinoids such as delta-9-THC, which are known to impact upon memory functioning.^[29] One study by Battisti *et al.*^[30] sought to examine the impact of chronic cannabis use upon memory-related brain function by examination of the subsequent memory effect (SME) of the event-related potential (ERP). The results of this study indicate that relative to non-using controls, chronic users of cannabis have altered memory-related brain activation in the form of dysfunctional SME production and/or poorer neural efficiency, which is associated with deficits in memory recall.

The role of the cannabinoid system is very important in disorders such as multiple sclerosis spasticity and pain. Basic research is discovering interesting members of this family of compounds that have previously been unknown, the most notable of which is the capacity for neuroprotection.^[31] Cannabinoid receptors in the brain (CB1) take part in modulation of learning and are particularly important for both working memory and short-term memory. It appears that spatial working/short-term memory is not sensitive to cannabidiol (CBD) rich extracts. Potentiating and antagonism of delta-9-THC-induced spatial memory deficits is dependent on the ratio between CBD and delta-9-THC.^[32] It has been found that CB1 cannabinoid receptor (CB1R) activation transiently modulates pathway and the protein synthesis machinery. Moreover, using pharmacological and genetic tools, it was found that THC long-term memory deficits were mediated by CB1Rs expressed on GABAergic interneurons through a glutamatergic mechanism.^[33]

The evidence regarding the effect of cannabis on fetuses in cannabis-consuming pregnant women is also not very clear. Despite the prevalence of marijuana use among pregnant women and adolescents, the impact of cannabis on the developing brain is still not well understood. However, growing evidence supports that the endocannabinoid system plays a major role in CNS patterning in structures relevant for mood, cognition, and reward, such as the mesocorticolimbic system. It is thus clear that exposure to cannabis during early ontogeny is not benign and potential compensatory mechanisms that might be expected to occur during neurodevelopment appear insufficient to eliminate vulnerability to neuropsychiatric disorders in certain individuals. Both human longitudinal cohort studies and animal models strongly emphasize the long-term influence of prenatal cannabinoid exposure on behavior and mental health.^[34] A study by Campolongo *et al.*^[35] shows that the endocannabinoid system plays a crucial role in the ontogeny of the CNS and its activation, during brain development, can induce subtle and long-lasting neurofunctional alterations.

CANNABIS AND PSYCHOSIS

Cannabis is important because of its relation to psychosis. While other psychiatric morbidities have been recently recognized,^[2] it has been known historically that cannabis is related to psychosis.^[36] Recently, several epidemiological studies have proved beyond doubt that cannabis use increases subsequent risk of schizophrenia.^[37,38] It is also clear that cannabis-induced psychosis is different from cannabis as a risk factor for schizophrenia and related psychoses.^[39,40] What are still not clear are the pathways among cognitive dysfunction, schizophrenia, and cannabis consumption.^[41,42] Several aspects of neurobiology have been postulated, but the dilemma of determining a clear trajectory continues.^[42] There are several theories and arguments in favor of and against a vulnerability factor, the possibility of an endophenotype, and the gene–environment interaction. The evidence for each of these comes primarily from experimental human and animal studies of neurobiology.

It seems that there is a small subgroup of cannabis users developing psychiatric sequelae and cognitive decline.^[43,44] Abusers do not seem to be a homogeneous group and their level of risk for cognitive decline also differs.^[45] Majority of the studies done in this area have been hospital based where these subjects also have a concurrent psychiatric or medical condition. In otherwise healthy users, consumption of cannabis results in cognitive impairments that are similar to the cognitive deficits in patients with schizophrenia.^[21] The impairments may persist well beyond the period of intoxication, and the evidence for recovery of functions following periods of abstinence is mixed.^[21,45]

Cognitive function is the common denominator in the

association of cannabis with psychosis and schizophrenia.^[46] Several explanations for this association exist. First, it is possible that the effects on cannabis on intellectual ability are induced by cannabis use in adolescence. Second, it could be that cognitive decline enhances the vulnerability for schizophrenia. Alternatively, cannabis itself may give rise to substance-induced psychosis, which may also have a cognitive basis. It is of note that only a small number of subjects consuming cannabis develop psychological syndromes. The question arises of whether cognitive decline is present amongst those who do not develop psychiatric problems.

One would expect that regular cannabis use will further worsen the impaired cognitive performance in patients with schizophrenia, especially in the domains of attention, memory and executive functions, and that the worsening of performance may exceed the acute and sub-acute intoxication. Surprisingly, a number of recent studies reported similar or even better cognitive functioning in cannabis using patients with schizophrenia compared to patients without co-morbid drug use.^[47-49] However, some studies suffer from small sample sizes, an imprecise history of drug use, or short abstinence time of individuals. Others are limited because of lack of control for potential confounds, such as psychopathology, level of education and extent of nicotine use.^[47,50]

In one study, first-episode schizophrenia (FES) patients with prior cannabis use performed better than normal controls. The study suggests that possibly there is lower individual vulnerability for psychosis in cannabis-use patients in whom cannabis use can be a precipitating factor of psychotic episodes.^[27] Such findings bring out the complexity of the cognition and cannabis connection.^[27] To make it more explicit, an interesting analysis of 23 studies by Loberg and Hugdahl^[42] found 14 studies reporting that cannabis users had better cognitive performance than schizophrenia non-users. Eight studies reported no or minimal differences in cognitive performance in the two groups, but only one study reported better cognitive performance in the schizophrenia non-user group. The findings also suggest that cannabis use may be related to improved neurocognition in bipolar disorder and compromised neurocognition in schizophrenia. The results need to be replicated in independent samples and may suggest different underlying disease mechanisms in the two disorders.^[51]

Studies in humans show that genetic vulnerability may lead to an increased risk of developing psychosis and cognitive impairments following cannabis consumption. For instance, continued cannabis use by persons with schizophrenia causes a small increase in psychotic symptom severity but not vice versa.^[52] The results indicate that relatively subtle performance deficits on the level of basic oculomotor control increase as task complexity and cognitive

demands increase.^[12] Delta-9-THC might differentially affect schizophrenia patients relative to control subjects. The enhanced sensitivity to the cognitive effects of delta-9-THC warrants further study into whether brain cannabinoid receptor dysfunction contributes to the pathophysiology of the cognitive deficits associated with schizophrenia.^[53]

A bigger question is why a great number of subjects develop no pathology or health-related consequences and whether these subjects also develop cognitive decline. It is also not clear what determines this dysfunction: age of onset of cannabis use, or the frequency, amount or duration of abuse. There is some evidence that early onset in age and duration of consumption is possibly more specifically related to cognitive impairment. A patient study by Dekker *et al.*^[54] compared white matter integrity between early-onset cannabis users (before the age of 15 years), late-onset cannabis users (age of 17 years or later), and those who were cannabis naive. Compared with early-onset users, cannabis-naive patients showed reduced white matter density and reduced fractional anisotropy in the splenium of the corpus callosum. This suggests that the age of onset of cannabis use is not an identifying characteristic for white matter abnormalities in schizophrenia patients. Even so, other results indicate that there might be a more vulnerable brain structure in cannabis-naive schizophrenia patients.^[55]

Cannabis abuse is a risk factor for psychosis in predisposed people; it can affect neurodevelopment during adolescence leading to schizophrenia, and a dysregulation of the endocannabinoid system can contribute to schizophrenia.^[56,57] It is also worth noting that some specific cannabinoid alterations can act as neuroprotectants for schizophrenia or can be a psychopharmacogenetic rather than a vulnerability factor.^[58] In one study, cannabis users showed a diminished capacity for monitoring their behavior that was associated with hypoactivity in the anterior cingulate cortex (ACC) and right insula. In addition, increased levels of hypoactivity in both the ACC and right insula regions were significantly correlated with error-awareness rates in the cannabis group (but not controls).^[59]

CLINICAL IMPLICATIONS

Cognitive deficits associated with specific parameters of cannabis use and interactions with neurodevelopment stages and neural substrates will better inform our understanding of the nature of the association between cannabis use and psychosis. Further research in this field will enhance our understanding of underlying pathophysiology and improving treatments for substance abuse and mental illness.^[21,60] Cognitive functions may provide a guide to treating marijuana addiction,^[61] and further, more insight in the cognitive-motivational processes related to cannabis use in schizophrenia may inform treatment strategies.^[62]

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