Cannabis and the Maturing Brain: Role in Psychosis Development

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A common viewpoint has proliferated that cannabis use is mostly harmless. Some argue that by not supporting its use, we are missing a great therapeutic opportunity. The general public view on cannabis may partially be a result of poor knowledge translation. In fact, the “war on drugs” approach has not allowed for basic education on the varied effects of cannabis on the brain, especially at highly critical phases of brain development such as adolescence.

Schizophrenia and other psychotic disorders affect ~4% of the population and indirectly affect many more. The majority of psychosis cases begin in early adult years at a time when young people are developing life skills and experiences needed for independent living. A risk factor for psychosis onset in this age group is cannabis use, not entirely surprising, as this drug affects the serotonergic, dopaminergic, and glutamatergic systems of the brain that are also affected in schizophrenia. We will discuss the relationship between brain maturation and cannabis in adolescents and young adulthood, as a potential process model for psychosis development. Important to this discussion is the role that cannabinoid receptor-type 1 (CB₁) plays in brain development and maturation.

CB₁R is expressed on nervous system tissues from the early embryonic period onwards, with work in rodents showing that in cortical projection neurons, endogenous cannabinoids are acting through CB₁R on presynaptic terminals; coordinate the guidance of axons from both descending efferents and thalamic afferents; promote neurite outgrowth; and are tightly controlled during fetal development to prevent ectopic neurite outgrowth and inappropriate synapses. Exposure to tetrahydrocannabinol (THC) in the fetal brain could thus result in unwanted inappropriate neurite outgrowth with potential long-term physiological, behavioral, and cognitive sequelae.¹ The distribution of CB₁R changes from the fetal period to adulthood, with early greater white matter expression that slowly changes to a greater gray matter receptor density in adulthood. Cannabis is not without negative effects at any age. Chronic use in adults can cause impairment on a number of cognitive domains that does not consistently resolve on cannabis cessation; however, this discussion will focus on its effects in the adolescent brain.

Adolescence is a key brain developmental time period in which the endogenous cannabinoid system plays a role and, thus, THC can exert negative effects. Synaptic density decreases by 40% between the ages of 7–15, demonstrating that active synaptic remodeling is taking place during this phase of development. Brain regions, such as the hippocampus and frontal cortex, are continuing to develop and mature during this period. The levels of endocannabinoids are increased in these brain regions during adolescence and, correspondingly, CB₁ receptors are also increased. Synaptic remodeling is impaired in a measurable way in adolescent cannabis users compared to nonusers when axonal connectivity is examined by diffusion-weighted magnetic resonance imaging (MRI) and mapping in the right fimbria and the corpus callosum, two structures that contain abundant levels of cannabinoid receptors at this age. Structural MRI studies in humans have reported decreased gray matter volumes and whole brain volumes with regular cannabis use in adolescents.² One study examining both brain volumes and global cerebral blood flow by positron emission tomography (PET) showed that males who began cannabis use prior to age 17 had higher cerebral blood flow in addition to decreased whole brain and gray matter volumes.² One very recent clinical study suggests that even irregular cannabis use may be detrimental to brain development. Functional MRI studies have also demonstrated abnormal activation in the prefrontal cortex, a region critically affected in psychosis, and parietal brain regions with regular adolescence cannabis use.²

Epidemiological evidence has accumulated supporting the notion that adolescent cannabis use is a risk factor in the development of psychosis.³ These studies demonstrated an increased risk of developing psychosis with a higher frequency of cannabis use, with up to a 6-fold increased risk for psychosis in heavy users (over 50 lifetime occasions by 18 years of age).

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compared to nonusers. A limitation of the first such large study, of Swedish conscripts followed for 15 years, was that the conclusions were based on a heavy cannabis users cohort. Interestingly, more than half of the heavy users had a psychiatric diagnosis other than psychosis at conscription; however, when corrected for this, the association between schizophrenia and adolescent cannabis remained. More compelling evidence are prospective studies, including one that controlled for psychotic symptoms at baseline and went on to show an increased risk of psychosis at age 26 associated with cannabis use between the ages of 15 to 18.3 Other studies have reported that the earlier the age of regular use (e.g., prior to age 15), the increased risk of developing psychosis compared to minimally later use (e.g., prior to age 18).2 Furthermore, research has shown that cannabis use in early adolescence is associated with a significantly younger age of onset of psychosis, especially in the context of higher potency cannabis, which in turn predicts a poorer prognosis of the disorder.1 Possibly the most interesting angle of this prospective research can be viewed from the limitations of this group of studies. Each group decided to control for different variables such as previous psychiatric disorder, age, gender, etc. Regardless of what variables were chosen the whole body of research shows some significant association between adolescent cannabis use and early onset, but not late onset, schizophrenia.

How would cannabis use during adolescence act as a potential trigger leading to psychosis? This potential outcome may be mediated by the effect of cannabis use on white matter (WM) development. Significant levels of endocannabinoid receptors have been found in WM tracts of the adolescent brain (comparing to adult brain), for example on the glial cells responsible for the production and maintenance of WM (e.g., astrocytes and oligodendrocytes). It has therefore been postulated that early adolescent cannabis exposure interacts with these processes and adversely affects the trajectory of WM development and its function, ultimately triggering psychosis in individuals who are vulnerable to the illness.2 This resonates with the contemporary theories that disturbances in connectivity between different brain regions, rather than abnormalities within the separate regions themselves, are responsible for the clinical symptoms and cognitive dysfunctions observed in schizophrenia.

Animal research illustrates that another potential psychosis triggering effect of cannabis on the adolescent brain is the influence it has on neurotransmitter systems, especially dopamine. Cannabis use can induce receptor changes that modulate dopaminergic projections in the midbrain, and mu opioid receptor function in the nucleus accumbens, both of which enhance reward systems.1 Of particular note is work showing THC exposure in prepubertal rats led to irreversible deficits that were not seen with the same level of exposure to adult rats.4 CB1 receptors are located on presynaptic terminals and regulate the release of dopamine and other neurotransmitters.1 Dopamine release may be part of the key to why some cannabis users develop psychosis and some do not. PET work in humans with 18F-Fallypride showed a differential release of dopamine in response to THC between control subjects, psychotic patients, and their first-degree relatives.5 While this study had small group sizes, it is another possible angle of investigation. Variants of the cannabinoid receptor 1 and its associated signaling have not been well studied to date.

We must always keep in mind in this line of investigation that not all teenagers who smoke cannabis will develop psychosis; genetics is the additional factor that has to be considered and should be included in any clinical research trial on this topic. Having a first-degree family member with schizophrenia increased the odds ratio of developing psychosis with cannabis use.2 Gene polymorphisms that are also being examined in this context include, but are not limited to, the COMT, AKTI, CNRI, and FAAH genes. Studies report an association with having the COMT valine158 allele and development of psychosis with adolescent cannabis use; however, these findings need to be reproduced across samples. AKTI encodes a serine/threonine kinase that can be activated via CB1R. Cannabis users with the rs2494732 variant had a 2-fold increased risk of developing psychosis; however, daily cannabis use increased this risk to 7-fold.4 Clinical trials that focus on Gene x Environment (cannabis use) interactions on neuroimaging and clinical outcomes (psychosis) are extremely important in moving this field further.

Many states in the USA have approved medical marijuana for use in adolescents and some have approved use for children. In cases such as epilepsy, where medical cannabis may be used in children, we do not yet know all the implications on adult outcomes, although we have discussed a potentially severe problem in this article. Additionally, the reported clinical outcomes of using cannabis to treat a variety of conditions have been varied and there is a lack of controlled clinical trial evidence to support improved medical prognosis over use of other conventional pharmaceutical products. Despite the increasing public pressure for medical access to cannabis, improved safety evidence is required prior to approving the compound for wider use, especially its use in an adolescent population. The current situation is comparable to putting a drug on the market without phase II clinical trials. Cannabis has some positive benefits, for example in appetite improvement in cancer patients; however, safety and dosage information are sorely lacking. The key concern is that currently we are unable to predict which adolescents have the genetic liability for development of psychosis, and thus would be more sensitive to the effects of cannabis (medical or otherwise) on their developing brain. Until we know, education is key for the general public, and specific to youth, caution when considering cannabis use during adolescent years.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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