Cannabis Use and the Adolescent Brain

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Animal and human research suggests that adolescent exposure to cannabis carries a particularly high risk for a range of negative outcomes, including psychosis-related symptoms, cognitive impairment, and substance use problems. Findings of heightened risk associated with adolescent cannabis use, coupled with research pointing to a role of the endocannabinoid system in regulating neurodevelopmental processes, have led to speculation that adolescent cannabis use may disrupt the normal course of neurodevelopmental processes and result in long-term changes in brain functioning. Further, it appears there are a number of factors (e.g., female sex, early trauma experience, genetics) that may moderate the effects of adolescent cannabis use on brain development.

This bulletin reviews the current research in this area, including endocannabinoid influences on adolescent brain maturation and the types of impairments that have most been associated with adolescent cannabis use. Further, this bulletin outlines various factors that have been found to confer vulnerability to either early onset cannabis use and/or its adverse effects. Finally, the current gaps in the literature and the need to better understand how various risk factors interact with adolescent cannabis use to further increase the risk of developing a range of adverse outcomes, including psychosis and substance use disorders, in adulthood are highlighted.

Adolescent brain development

The brain undergoes important structural and functional changes during adolescence and into young adulthood. For instance, there are significant reductions in grey matter across adolescence, which are primarily the result of synaptic pruning (to cull weak and/or unused synapses). Through synaptic pruning, the speed and efficiency within regional brain circuits is enhanced. Areas that undergo considerable synaptic pruning in adolescence are temporal and frontal regions and striatal areas, with prefrontal cortical areas being especially late to mature. Importantly, circuits involving the prefrontal cortex and the striatum are critical to higher order cognitive skills such as decision making, risk and reward processing, and cognitive control.

The endocannabinoid system plays an important role in guiding neurodevelopmental processes, including that of synaptic pruning. Thus, adolescent cannabis use might be associated with long-term changes in brain functioning in part through the disruption of synaptic pruning processes in those areas that are concurrently maturing. Indeed, in line with adolescence being a particularly important period for the maturation of prefrontal brain areas, recent animal studies have shown that altering endocannabinoid neurotransmission in adolescent female rats causes long-lasting changes in prefrontal brain areas reflective of disrupted synaptic pruning. Such research supports the idea that, at least in part, some of the cognitive and behavioural impairments associated with early adolescent cannabis use in human studies might be related to the disruption of endocannabinoid-mediated neurodevelopmental events by cannabis.
Cognitive Impairment

Adolescents who use cannabis regularly typically display a number of non-acute cognitive deficits compared to adolescents who do not use cannabis or use it occasionally. For instance, a recent study found long-lasting deficits in selective attention in a group of adolescent heavy cannabis users compared to a control group who had used cannabis less than 5 times in their lifetime. Changes in verbal learning and memory among this group, however, improved following a period of abstinence. Furthermore, a number of studies have shown that adults who started using cannabis early in adolescence show greater cognitive impairment than adults who started using cannabis later.

Findings of non-acute cognitive deficits in adolescent cannabis users (and in adults who started using cannabis early in adolescence) have been used to support the idea that adolescence may be a particularly sensitive period for the adverse effects of cannabis. There is also research, however, to suggest that pre-existing factors related to cognition (and/or related personality traits) may account for some of the differences found between adolescent cannabis users and non-users. In other words, some group differences in cognition may not be the result of cannabis use per se but rather, may be due to pre-existing group differences leading to earlier onset of cannabis use. For instance, measures of selective attention (which depend on successfully ignoring distracting and/or irrelevant information) taken in early adolescence have been found to predict greater cannabis use by late adolescence. Similarly, impulsivity-related personality traits have also been shown to predict regular adolescent cannabis use.

Studies have also found differences in brain structure between those who commence cannabis use in adolescence and non-users. These include differences in orbitofrontal cortex volume — a prefrontal brain area related to impulsivity, reward processing, and cognitive control — at age 13, which predicted subsequent onset of cannabis use by age 16. Thus, some of the cognitive deficits seen in adolescent cannabis users may in fact have preceded cannabis use.

Animal research also supports the notion that adolescent cannabinoid exposure can result in long-term cognitive impairments, although findings are mixed. For instance, in one study, female rats exposed to a cannabinoid in adolescence showed memory deficits when tested as adults compared with female rats that were exposed to the cannabinoid as adults. In another study, both adolescent and adult male rats exposed to cannabinoids showed long-lasting memory deficits. In yet another study, neither male adolescent or adult rats showed long-lasting cognitive impairments following chronic cannabinoid exposure. Though male rats have not consistently been shown to display cognitive performance deficits related to adolescent cannabinoid exposure, studies have found that adolescent cannabinoid exposure may, nonetheless, induce lasting brain changes in prefrontal areas. This suggests that in some cases, the use of more sensitive measures may have detected differences in performance. Overall, long-term effects of adolescent cannabinoid exposure have been found on various measures of learning and memory, but these effects have not been replicated consistently and appear to vary according to gender and the strain of laboratory rats included in the study. In summary, animal studies do appear to indicate that adolescent rats may be more susceptible than adult rats to the adverse long-term effects of chronic cannabinoid exposure on cognition. More consistently, adolescent rats have been shown to be more sensitive than adult rats to the acute adverse effects of cannabis on cognition.
Psychosis-related symptoms

Longitudinal studies indicate that adolescent cannabis use is associated with an increased risk of psychosis-related symptoms in adulthood\(^1\). For instance, in a longitudinal cohort study\(^3\), adolescents who had used cannabis by age 15 were found to be 6 times more likely to experience psychotic symptoms at age 26 than adolescents who had not (after controlling for psychotic symptoms at age 11). This risk is even higher for adolescents who are already experiencing some sub-clinical symptoms\(^26\) or who carry a genetic predisposition\(^27\).

Consistent with these findings, animal research also appears to support the view that adolescence may be a critical period for exposure to cannabis that results in an increased risk of psychosis-related brain changes. A study of adult rats exposed to THC in adolescence showed significant deficits on a measure of sensorimotor gating, known as prepulse inhibition (PPI), compared to rats exposed equivalent amounts of THC in adulthood\(^4\). Importantly, because PPI deficits are typically used in animal research to model the sensory processing deficits seen in people with schizophrenia, this finding supports the idea that exposure to cannabis during critical neurodevelopmental periods can increase the risk of developing psychosis or, at least, psychosis-related sensory processing impairments.

Drug-related problems

Longitudinal studies suggest that early onset cannabis use may be associated with an increased risk of other drug use\(^2,28\) and an increased likelihood of developing more problematic use of cannabis, alcohol, and other drugs\(^2,28,29\). The complexity of social, psychological, and environmental interactions involved in the initiation and maintenance of cannabis and other drug use in human epidemiology, however, makes it very difficult to address the question of causality in this reported association. One method, such as twin studies has found that early onset cannabis use was strongly associated with later illicit drug use as well as an increased likelihood of alcohol dependence and other substance use disorders\(^2\).

Animal research suggests that exposure to cannabinoids in adolescence may result in long-term brain changes in various reward-related brain areas, which in turn may increase addiction vulnerability\(^30\). For instance, in a recent study, adult rats exposed to THC in adolescence self-administered cannabinoids more quickly and in higher amounts than rats not given THC in adolescence and showed lasting striatal dopamine receptor changes\(^30\). In another study, adult rats exposed to THC in adolescence showed heightened sensitivity to opioids, as evidenced by greater self-administration of heroin, and corresponding brain changes in striatal areas\(^31\). Further, rats exposed to THC in adolescence have been found to be more vulnerable to stress-induced reinstatement of heroin seeking\(^32\).

Individual differences in adolescent vulnerability

Research suggests there are individual differences in adolescent vulnerability to the long-term negative effects of cannabis use\(^7\). The factors mediating this vulnerability remain largely unknown, however, studies have pointed to early life trauma\(^33\) and genes\(^27\) as playing an important role. For instance, Caspi et al (2005) found that participants who carried the COMT val/val genotype and who used cannabis before the age of 17 were over ten times more likely to develop schizophreniform disorder (when symptoms of psychosis are present for at least one month but less than 6 months) than those who carried the met/met genotype. Animal research also supports the role of individual differences in mediating the vulnerability to the long-term effects of
adolescent exposure to cannabinoids. For instance, novelty-seeking in rats moderates the long-term effects of adolescent cannabinoid exposure on cocaine addiction vulnerability and brain changes in areas related to reward processing.

Conclusion

Adolescent exposure to cannabis is associated with a range of long-term adverse effects, such as increased addiction vulnerability, cognitive impairment, and psychosis-related illness, which may be related to cannabis-induced disruptions in neurodevelopmental processes. There are various factors that appear to moderate these effects, with adolescents exposed to early life stress and/or who possess certain genetic and personality predispositions being more likely to experience adverse long term effects. Research is also pointing to the role of gender in moderating vulnerability to different long-term consequences of adolescent cannabis use, including interactions with genetic risk. Further research is needed to uncover exactly how various risk factors interact with cannabis use and how such interactions may affect neurodevelopmental processes in vulnerable individuals.

References

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