Journal of Psychiatric Research 45 (2011) 1055–1066

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Medial temporal structures and memory functions in adolescents with heavy cannabis use

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ARTICLE INFO

Article history:
Received 27 October 2010
Received in revised form
4 January 2011
Accepted 6 January 2011

Keywords:
Hippocampus
Cannabis
Adolescence
Magnetic resonance imaging
CVLT
Learning and memory

ABSTRACT

Converging lines of evidence suggest an adverse effect of heavy cannabis use on adolescent brain development, particularly on the hippocampus. In this preliminary study, we compared hippocampal morphology in 14 "treatment-seeking" adolescents (aged 18–20) with a history of prior heavy cannabis use (5.8 joints/day) after an average of 6.7 months of drug abstinence, and 14 demographically matched normal controls. Participants underwent a high-resolution 3D MRI as well as cognitive testing including the California Verbal Learning Test (CVLT). Heavy-cannabis users showed significantly smaller volumes of the right ($p < 0.04$) and left ($p < 0.02$) hippocampus, but no significant differences in the amygdala region compared to controls. In controls, larger hippocampus volumes were observed to be significantly correlated with higher CVLT verbal learning and memory scores, but these relationships were not observed in cannabis users. In cannabis users, a smaller right hippocampus volume was correlated with a higher amount of cannabis use ($r = -0.57$, $p < 0.03$). These data support a hypothesis that heavy cannabis use may have an adverse effect on hippocampus development. These findings, after an average 6.7 month of supervised abstinence, lend support to a theory that cannabis use may impart long-term structural and functional damage. Alternatively, the observed hippocampal volumetric abnormalities may represent a risk factor for cannabis dependence. These data have potential significance for understanding the observed relationship between early cannabis exposure during adolescence and subsequent development of adult psychopathology reported in the literature for schizophrenia and related psychotic disorders.

1. Introduction

Adolescence is a period of increased risk-taking and thrill-seeking, often including drug abuse (Ernst et al., 2006; Casey et al., 2008; Steinberg, 2008; Somerville et al., 2010). According to the 2007 National Survey on Drug Use and Health (NSDUH, United States Department of Health and Human Services) young people show higher rates of drug use as compared with older age groups. U.S. school survey data (Johnston et al., 2008) shows that 15% of 8th graders have tried marijuana at least once and 43% have tried marijuana by 12th grade. Another national survey also reported a history of cannabis use in approximately 45% of 12th graders in the U.S., with 5% reporting current daily use (Terry-McElrath et al., 2005). Further, other studies support the hypothesis that adolescent cannabis use is a gateway to illicit drug use in early adulthood (Fergusson et al., 2006; Luengo et al., 2008).

Adolescence is a period during which the brain undergoes dramatic developmental changes. Maturation of the human brain is a complex and comprehensive process, with critical changes occurring at key points throughout development. Contrary to the once-held belief that the brain completes its development by the end of the childhood years (Kretschmann et al., 1986; Durston et al., 2001), the brain continues to undergo a substantial amount of development throughout adolescence and into early adulthood. Gray matter in the cerebral cortex shows a characteristic "rise and fall" pattern (Giedd et al., 1999; Sowell et al., 2001; Gogtay et al., 2004; Thompson et al., 2005; Hua et al., 2009), while white

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doi:10.1016/j.jpsychires.2011.01.004

matter connecting gray matter areas increases steadily from birth to adulthood (Paus et al., 1999; De Bellis et al., 2001; Schmithorst et al., 2002, 2008; Suzuki et al., 2003; Nagy et al., 2004; Barnea-Goraly et al., 2005; Olson et al., 2009). In a previous study conducted by our group, we compared normal brain development in a group of early adolescents (average age 12 years) as compared with a group of late adolescents (average age 18 years old) and demonstrated accelerated brain development during late adolescence (Ashtari et al., 2007). Results from these studies suggest that in addition to birth and early childhood, adolescence is a key period for neuronal maturation and a critical time for brain development.

In addition to the overall normal brain development, other important processes occur during adolescence such as neurogenesis (the birth of new neurons) in the hippocampus (Benes et al., 1994). Similar processes have been studied in animals and studies report neurogenesis in the dentate gyrus of the hippocampus throughout the lifetime of the animal (Eriksson et al., 1998; Ciaroni et al., 1999; Eisch et al., 2000). In a recent study, Eisch et al. (2008) present evidence that adult hippocampal neurogenesis is strongly implicated in psychiatric disorders, particularly addiction. This data suggests that neurogenesis is regulated by drugs of abuse (Eisch et al., 2000; Abrous et al., 2002; Nixon and Crews, 2002; Noonan et al., 2008) and that the hippocampus influences both drug taking and drug-seeking behaviors (Taepavarapruk et al., 2000; Floresco et al., 2001; Lodge and Grace, 2006). While much is still being learned about the precise role of the hippocampus in cognitive function, it is generally accepted that this region includes "a system of anatomically related structures that are essential for memory functions" (Squire, 2004). Thus, chronic administration of drugs of abuse such as cannabis may decrease hippocampal function and in particular may affect memory performance.

The neurocognitive effects of cannabis use in adults include poor performance on tests of learning, memory, and executive functions (Varma et al., 1988; Pope and Yurgelun-Todd, 1996, 1997; Croft et al., 2001; Bolla et al., 2002; Solowij and Grenyer, 2002; Lyons et al., 2004; Bava and Tapert, 2010) when compared to matched controls. Despite the prevalence of marijuana use in adolescence, few reports have focused on the neurocognitive impact of heavy cannabis use during this time. An earlier study by Schwartz and colleagues studied adolescents ages 14–16 with cannabis dependence and found verbal and non-verbal short-term memory impairments as compared to controls (Schwartz et al., 1989).

Tapert et al. (2002), in an eight year follow up longitudinal study, examined adolescents with a history of substance use disorders and showed accumulative, diminished performance over time on tests of cognitive performance among cannabis users. Harvey et al. (2007) found that adolescents who are regular cannabis users performed worse on tests of attention, learning, and memory and that a greater amount of cannabis use predicted poorer executive functioning and performance on tests of working memory. Schweinsburg et al. (2005) showed abnormalities in brain response using fMRI during a spatial working memory task after 1 month of abstinence for a group of adolescent cannabis users as compared with controls. They observed different patterns of activation in cannabis users when performing the task and attributed these differences to a compensatory brain mechanism or persisting brain abnormalities associated with heavy cannabis use during adolescence (Schweinsburg et al., 2008a). These and other studies (Freedland et al., 2002; Iversen, 2003; Pontieri et al., 1999; Quickfall and Crockford, 2006) show that the brain regions such as the frontal lobe, hippocampus, amygdala, basal ganglia and striatum, which are rich in cannabinoid receptors, are more susceptible to the effects of cannabis.

The neurological effects of cannabis are largely mediated by the binding of its active ingredient, delta9-tetrahydrocannabinol (9-THC), to cannabinoid receptors (Matsuda et al., 1990; Munro et al., 1993; Martin et al., 1995; Puighermanal et al., 2009) localized in the various brain regions. Cannabinoids appear particularly neurotoxic to hippocampal neurons (Chan et al., 1998; Hoffman and Lupica, 2000; Kim and Thayer, 2001; Carlson et al., 2002). Short-term memory dysfunction from cannabis could occur because THC may alter the way in which information is processed by the hippocampus. Laboratory rats treated with THC display the same reduced ability to perform tasks requiring short-term memory as other rats whose hippocampal neurons were destroyed (Heyser et al., 1993). A recent study by Rubino et al. (2009) employed an animal model of adolescent rats with chronic exposure to THC to examine the long-term effects of THC on learning and memory. Adolescent rats were treated with THC or its vehicle from 35 to 45 postnatal days (PND) and left undisturbed until adulthood (75 PND), at which point spatial memory was assessed using the radial maze task. THC pre-exposed animals exhibited worse performance than vehicles, suggesting a specific deficit in spatial working memory (Rubino et al., 2009). Post-mortem analysis of pre-exposed rats revealed a significantly lower overall total dendritic length and spine density than vehicles. The authors suggested that THC pre-exposed rats may establish fewer synaptic contacts and/or less efficient synaptic connections throughout the hippocampus and concluded that this may represent the molecular underpinnings of the cognitive deficit induced by adolescent THC exposure (Rubino et al., 2009). The main conclusion of this work was that chronic and heavy exposure to THC during adolescence produced impairments in spatial working memory in adult animals along with reduced levels of markers of neuroplasticity in the hippocampus and morphological alterations in the dentate gyrus (Rubino et al., 2009).

The present cross-sectional study was designed to examine the human hippocampus, an area of the brain rich in cannabis receptors which also undergoes neurogenesis during adolescence, in a group of adolescents with a history of heavy cannabis use and demographically matched healthy controls. 3D high-resolution MR imaging was performed to evaluate volume differences in the hippocampus and amygdala structures. Although studies reporting the effect of cannabis on amygdala structure are scarce, based on the findings reported by Yücel et al. (2008) and the fact that the amygdala is also rich in cannabinoid receptors, we also evaluated amygdala volume. Since cognitive impairment is one of the most prominent negative consequences associated with cannabis consumption (Fried et al., 2002; Grant et al., 2003; Pope et al., 2003; Jacobsen et al., 2004; Solowij and Battisti, 2008; Battisti et al., 2010), we evaluated all subjects utilizing the California Verbal Learning Test (CVLT) to further study the chronic effect of heavy cannabis use on brain structure and cognition.

2. Materials and method

2.1. Study subjects

Fourteen treatment-seeking male adolescents (mean age = 19.3; SD = 0.8) who claimed cannabis as their drug of choice and met DSM-IV diagnostic criteria for cannabis dependence, in early full remission (American Psychiatric Association, 1994) were recruited from a therapeutic community (Aurora Concept Inc., Queens, NY). Each reported smoking three or more "joints" per day for at least one year prior to commencement of treatment (mean = 5.8 joints per day; SD = 2.1) and were drug-free for at least 30 days and an average of 6.7 months (see Table 1) prior to the time of the MRI. The exact amount of THC in each joint consumed by each subject is hard to accurately quantify (Gray et al., 2009). However, 0.5 g/joint and 4 joints/blunt are the estimates reported by our study participants. Published reports estimate an average of