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Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence

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ABSTRACT

Background: Cognitive deficits that persist up to a month have been detected among adult marijuana users, but decrements and their pattern of recovery are less known in adolescent users. Previously, we reported cognitive deficits among adolescent marijuana users after one month of abstinence (Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007). In this longitudinal study, we characterized neurocognitive changes among marijuana-using adolescents across the first three weeks of abstinence.
Method: Participants were adolescent marijuana users with limited alcohol and other drug use ($n=19$) and demographically similar non-using controls ($n=21$) ages 15–19. Participants completed a brief neuropsychological battery on three occasions, after 3 days, 2 weeks, and 3 weeks of stopping substance use. Abstinence was ascertained by decreasing tetrahydrocannabinol metabolite values on serial urine drug screens. Verbal learning, verbal working memory, attention and vigilance, and time estimation were evaluated.
Results: Marijuana users demonstrated poorer verbal learning ($p<.01$), verbal working memory ($p<.05$), and attention accuracy ($p<.01$) compared to controls. Improvements in users were seen on word list learning after 2 weeks of abstinence and on verbal working memory after 3 weeks. While attention processing speed was similar between groups, attention accuracy remained deficient in users throughout the 3-week abstinence period.
Conclusions: This preliminary study detected poorer verbal learning and verbal working memory among adolescent marijuana users that improved during three weeks of abstinence, while attention deficits persisted. These results implicate possible hippocampal, subcortical, and prefrontal cortex abnormalities.

1. Introduction

Marijuana is the most frequently used illicit drug among adolescents in the United States (Johnston, O'Malley, Bachman, & Schulenberg, 2009). In 2008, 43% of high school seniors reported having tried marijuana, 19% used in the past month, and 5% endorsed daily use (Johnston et al., 2009). Of individuals who initiated marijuana use before age 15, 14% went on to meet criteria for drug abuse or dependence during adulthood (Substance Abuse and Mental Health Services Administration, 2009). Because adolescence is a period of significant neurodevelopment (Giedd et al., 1996; Sowell et al., 2002), the neurocognitive effects of marijuana use are a concern (Ehrenreich et al., 1999; Pope et al., 2003; Wilson et al., 2000).

Marijuana use during adulthood has known effects on cognition. For example, acute marijuana intoxication may interfere with time estimation, suggesting a "speeding up of an internal clock" (Chait & Pierri, 1992; Jones & Stone, 1970; Lieving et al., 2006; Perez-Reyes et al., 1991). Within several hours to days since last use, heavy marijuana users have shown decrements in attention, memory, executive function, time estimation, and psychomotor speed (Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Varma et al., 1988). A meta-analysis found selective deficits in learning and memory among chronic users with a range of abstinence while other cognitive domains appeared unaffected (Grant et al., 2003). Others suggested that executive function, motor speed, and manual dexterity deficits may persist after a month of abstinence among heavy users (Bolla et al., 2002). In general, most deficits related to marijuana use seem to be temporary, and cognition may improve with sustained abstinence of at least a week (Pope et al.,

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2002; Pope et al., 2001). When deficits are found, they tend to be dose-related (Bolla et al., 2002) and may relate to the age of onset of cannabis use (Ehrenreich et al., 1999).

However, adult research may not generalize to adolescents, as significant neuromaturation occurs until early adulthood (Giedd et al., 1996; Sowell et al., 2002). Specifically, gray matter volume peaks in early childhood and decreases thereafter (Pfefferbaum et al., 1994), largely due to synaptic pruning (Huttenlocher, 1990). Gray matter in more basic sensorimotor areas matures earlier than in areas requiring more complex cognitive functions, such as the prefrontal cortex and lateral temporal lobes, which appear to reach maturity during late adolescence or young adulthood (Gogtay et al., 2004). White matter development continues through the late 20s and possibly into middle adulthood as myelination increases (Benes et al., 1994; Jernigan & Gamst, 2005; Pfefferbaum et al., 1994). Importantly, brain maturation during adolescence appears to mirror developments in cognition (Fryer et al., 2008; Nagel et al., 2005; Sowell et al., 2001). Given the confluence of neuromaturational activity and drug use initiation, the potential impact of cannabis use on neuroanatomical and neurocognitive maturation is important to understand.

Thus far, the current literature suggests that adolescents have a heightened vulnerability to the effects of drug and alcohol use (Monti et al., 2005; Spear, 2000). For example, chronic cannabis exposure in adolescent rats has long-lasting effects on learning and memory compared to similar exposure during adulthood (Cha et al., 2006; Schneider & Koch, 2003; Schneider et al., 2008; Stiglick & Kalant, 1982), possibly due to fewer or less efficient synaptic connections in the hippocampus (Rubino et al., 2009). Both cognitive and brain imaging studies in humans suggest critical periods of development that may be impacted by marijuana use (Ehrenreich et al., 1999; Pope et al., 2003; Wilson et al., 2000). Within several hours of intake, regular marijuana use in human adolescents or young adults (≤21 years old) appears to negatively affect learning, memory, attention, and spatial working memory (Fried et al., 2005; Harvey et al., 2007). After at least three weeks of abstinence, memory, complex attention, psychomotor speed, and planning and sequencing decrements are evident among adolescent marijuana users (Medina, Hanson et al., 2007; Millsaps et al., 1994; Schwartz et al., 1989). The effects of abstinence among youth are mixed, but poorer cognition is generally associated with heavier and more recent use (Fried et al., 2005).

Marijuana use during adolescence may have neuroanatomical and functional consequences. Youth recently abstinent from marijuana and alcohol use have demonstrated abnormal associations between verbal learning and hippocampal asymmetry (Medina, Schweinsburg et al., 2007). Irregular activation patterns have been observed in multiple brain regions, including the frontal and temporal lobes, during spatial working memory despite similar task performance (Padula et al., 2007; Schweinsburg et al., 2008; Schweinsburg et al., 2005). Marijuana users have also demonstrated aberrant brain activation patterns in posterior and frontoparietal regions while completing a verbal working memory task (Jacobsen et al., 2007). Finally, increased parietal and dorsolateral prefrontal cortex activity has been observed during a response inhibition task (Tapert et al., 2007). Collectively, these findings suggest that adolescent marijuana use may have detrimental anatomical and functional consequences in the brain, which may result in altered neural networks or compensatory mechanisms during cognitive tasks (Padula et al., 2007; Schweinsburg et al., 2008).

Given that previous studies of adolescent marijuana users have not yet examined the neurocognitive recovery process following regular use, the current study monitored cognition throughout the first three weeks of abstinence from marijuana use. A brief neuropsychological battery, including measures of verbal learning, verbal working memory, visual attention, and time estimation, was administered an average of 3 days, 2 weeks, and 3 weeks after cessation of marijuana use. Based on previous findings, we hypothesized that marijuana users would perform worse than control teens on all measures (Medina, Hanson et al., 2007), but that improvement would be seen over the follow-up period (Pope et al., 2001). While the adult literature suggests that marijuana users may improve to the same level as controls with sustained abstinence (Pope et al., 2002; Pope et al., 2001), the adolescent research to date suggests continued impairment after a month of non-use (Medina, Hanson et al., 2007; Millsaps et al., 1994; Schwartz et al., 1989).

2. Methods

2.1. Participants

Adolescents were recruited from local high schools and colleges via distribution of flyers. Teens responded to the ad as an opportunity to earn money and participate in developmental research, without knowledge that the study examined marijuana use. No information regarding eligibility criteria was described in the flyer or discussed before screening. To assess eligibility, comprehensive screening measures were administered to adolescents and their parents/guardians. Written informed assent (adolescent participant) and consent (adult participant and parent/legal guardian) were obtained prior to participation, in accordance with University of California, San Diego Human Research Protections Program procedures. Teens and their guardians were administered separate, detailed, structured clinical interviews assessing demographic and psychosocial functioning, Axis I psychiatric disorders, and substance use history. To facilitate open disclosure, parents and youths were interviewed by different research associates, and confidentiality was guaranteed within ethical and legal limits.

Inclusion criteria required that youth were fluent in English, and had a parent or legal guardian available to consent and provide medical and psychiatric history. Exclusionary criteria included history of DSM-IV (*Diagnostic and Statistical Manual for Mental Disorders, 4th Ed.*) (APA, 2000) Axis I disorder (other than substance use disorder) or use of psychoactive medications; history of chronic medical illness, neurological condition (e.g., meningitis, human immunodeficiency virus [HIV]), or head trauma with loss of consciousness >2 min; significant prenatal alcohol (≥4 drinks in a day or ≥7 drinks in a week) or drug exposure; complicated delivery or premature birth (<33 weeks gestation); learning disability or mental retardation; first-degree relative with history of bipolar I or psychotic disorders; left-handedness; non-correctable vision, colorblindness or hearing impairments; and substance use during the abstinence protocol.

The current study examined 40 adolescents (ages 15–19) who were classified into two groups: marijuana users ($n=19$) and non-using controls ($n=21$). Similar sample sizes in other studies of adolescent substance users yielded small effect sizes or p-values ranging from $p<.05$ to $p=.001$ in group comparisons (Hanson et al., in press; Jacobsen et al., 2007; Medina, Schweinsburg et al., 2007). Therefore, we regard the current sample size as sufficient to detect group differences on behavioral tasks. Groups were similar in gender and racial composition, general intellectual ability (average to high average range), grades completed in school, grade point averages, and self-reported mood and anxiety scores (see Table 1). Classification criteria for the marijuana-using (MJ user) group included >200 lifetime marijuana use episodes, >4 past month marijuana episodes, <30 lifetime experiences with other drugs, and not meeting DSM-IV criteria for alcohol abuse or dependence. Controls had <5 lifetime experiences with marijuana, no previous use of any other drug except nicotine or alcohol, and did not meet DSM-IV criteria for abuse or dependence on alcohol or any drug (see Table 1). As expected, MJ users reported higher levels of marijuana, alcohol, and other drug use than controls. Several MJ users used marijuana the same day as the first testing session, and all had used within the two weeks prior to study initiation. All but one MJ user met DSM-IV criteria for marijuana abuse or dependence. Controls had very limited or no previous use of