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Cognitive performance in a placebo-controlled pharmacotherapy trial for youth with marijuana dependence

Amanda Roten [a,*], Nathaniel L. Baker [b], Kevin M. Gray [a]

[a] Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, 125 Doughty Street, Suite 190, MSC 861, Charleston, SC 29425, United States
[b] Medical University of South Carolina, Department of Public Health Sciences, 135 Cannon Street, MSC 835, Charleston, SC 29425, United States

HIGHLIGHTS

- Cognitive performance was measured using CNS Vital Signs®.
- Abstinence was significantly associated with increased composite memory scores.
- Abstinence was significantly associated with increased verbal memory scores.
- Abstinence was significantly associated with modest increase in psychomotor speed.
- No significant differences in cognitive performance between placebo and control.

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ABSTRACT

Background: Adolescent marijuana use is associated with neurocognitive impairment, but further work is needed to assess the relationship between treatment-associated abstinence and cognitive performance.
Methods: This secondary analysis, conducted in the context of a marijuana cessation pharmacotherapy trial in adolescents, examined cognitive performance at baseline and at two time points during treatment using the CNS Vital Signs assessment battery.
Results: Abstinence from marijuana, relative to continued use, as assessed via urine cannabinoid testing, was associated with significant improvement in composite memory ($p < 0.001$), verbal memory (the most impacted component of composite memory) ($p < 0.001$), and psychomotor performance ($p = 0.045$) scores.
Conclusions: These findings suggest that some domains of cognitive performance improve significantly even in the early stages of treatment-associated abstinence.

1. Introduction

Marijuana is the most widely used illicit substance among adolescents. In 2013, Monitoring the Future data indicated daily marijuana use in 1.1% of 8th graders, 4.0% of 10th graders, and 6.5% of 12th graders (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2014). There is growing evidence that heavy marijuana use during adolescence, a time of dynamic brain development, may impact cognition (Randolph, Turull, Margolis, & Tau, 2013). In adults with persistent marijuana use that started during adolescence, Meier et al. found a decline in intelligence quotient (IQ), with impairments evident in executive functioning and processing speed (Meier, Caspi, Ambler, et al., 2012).

Cognitive performance is multifaceted, and results of studies of marijuana's effects on cognitive performance are mixed. There appear to be certain neuropsychological constructs or domains that are influenced by marijuana use. A recent review of the relevant literature by Randolph et al. (2013) concluded that attention, processing speed, verbal declarative memory, and cognitive control are affected by heavy marijuana use in adolescents. In contrast, language, visual declarative memory, perceptual reasoning, inhibition, and planning did not appear to be consistently affected by marijuana (Randolph et al., 2013).

The literature in this area may often appear contradictory. For example, attention is complex and can be divided into subcategories (complex attention, sustained attention, etc.); some studies have very small sample sizes and methodologies as well as populations studied often differ drastically. Additionally, tests used to examine the same domain or construct can be different across studies. Abdullaev and colleagues found that on tests requiring executive attention (attention required when conflicting information is presented), adolescents who used marijuana performed worse than controls (Abdullaev, Posner, Nunnally, & Dishion, 2010). Hanson et al., concluded that while impairments in verbal memory among cannabis users improve to the level of controls within 3 weeks of abstinence, deficits in attention remain

* Corresponding author. Tel.: +1 843 792 2300.
E-mail address: rotena@musc.edu (A. Roten).

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within this same time frame (specifically accuracy in tasks that require attention) (Hanson et al., 2010). Fried and colleagues did not find a significant difference in tests of attention among groups of marijuana users (heavy and light) and controls whereas they did find significant differences in other domains (overall IQ, processing speed, immediate memory, and delayed memory). Interestingly, the negative impact of marijuana on the cognitive domains that were affected resolved at 3 months of sustained abstinence. The sample in this study consisted of individuals exposed to drugs in utero and so must be interpreted with that in mind (Fried, Watkinson, & Gray, 2005).

The purpose of the current study was to evaluate potential changes in cognitive task performance among adolescents enrolled in a randomized, placebo-controlled trial of *N*-acetylcysteine (NAC) added to brief weekly cessation counseling and contingency management for marijuana cessation (Gray et al., 2012). To our knowledge, there are no previous studies that examine cognitive performance within the framework of a placebo-controlled pharmacotherapy treatment trial for cannabis dependence in adolescents. We hypothesized that cognitive performance would improve with marijuana cessation, and that longer periods of abstinence would predict greater improvements in cognitive performance. Participants were cannabis-dependent upon study enrollment, allowing for assessment of possible improvements in cognition with abstinence among a group of relatively heavy marijuana users seeking treatment.

2. Materials and methods

2.1. Participants

Participants were 78 treatment-seeking adolescents, ages 15–21, who met DSM-IV criteria for cannabis dependence, enrolled in the parent trial, and completed a baseline cognitive task performance battery at the treatment initiation visit and at least one additional time point (4 and/or 8 weeks after treatment initiation). Participants ages 18 and above provided informed consent. For participants under age 18, the legal guardian provided informed consent and participant provided assent. The university institutional review board approved all procedures for the parent study. All study procedures were performed at the Medical University of South Carolina in Charleston, South Carolina.

2.2. Measurements

CNS Vital Signs (CNS Vital Signs, LLC) is a computer-administered battery of performance tests used in the study to assess cognitive performance at baseline, 4 weeks, and 8 weeks. CNS Vital Signs measures certain clinical domains, including composite memory, verbal memory, visual memory, processing speed, executive function, psychomotor speed, reaction time, complex attention and cognitive flexibility. Tests used to calculate domains include the verbal memory test (identifying words previously presented), visual memory test (identifying symbols or shapes previously presented), finger tapping test, the symbol digit coding test, the Stroop test, the shifting attention test, and the continuous performance test (Gualtieri & Johnson, 2006). CNS Vital Signs has been used to examine the effect of substances on cognitive performance (Loring, Marino, Parfitt, Finney, & Meador, 2012).

Abstinence data was obtained from urine cannabinoid tests (UCT) that occurred twice weekly during the study. Marijuana use at each treatment visit was categorized as not abstinent (NA), recently abstinent (RA), or consistently abstinent (CA). Participants were deemed NA if the urine cannabinoid test was positive (i.e., $\geq$50 ng/mL) at that visit. Participants were deemed RA if their urine cannabinoid test was negative (i.e., <50 ng/mL) at the visit that the cognitive assessment took place but had been positive at least once between the cognitive assessments. Participants were deemed CA if all urine cannabinoid tests were negative since the last cognitive assessment. Abstinence was grouped this way in light of the secondary nature of this analysis. The study was not sufficiently powered to detect smaller differences in performance that may or may not be present between participants abstinent for one week versus those abstinent for two or three weeks. We thus grouped those individuals together.

Further details of the parent trial are discussed elsewhere (Gray et al., 2012; Roten, Baker, & Gray, 2013).

2.3. Data processing and statistical analysis

The study hypothesis was that increasing lengths of abstinence from marijuana would correlate with improved cognitive performance as measured by CNS Vital Signs (cnsvs.com). Validity of responses to the various components of the CNS Vital Signs was assessed through criteria defined by the CNS Vital Signs Interpretation guide (https://www.cnsvs.com/WhitePapers/CNSVS-InterpretationGuide.pdf). Invalid CNSVS scores and measures that were dependent on invalid scores were marked as such and not included in the analysis models. Since the primary aim of the study was to determine the association between abstinence (via UCT) duration and cognitive performance scores, sporadic missing data from the urine cannabinoid test was *not* noted as a failed screen (as was assumed in the primary study analysis). Individual self-reported use was examined in conjunction with both the UCT from the visit previous and the visit following the missing visit. If it was determined that abstinence was likely maintained, missing data was noted as such. If abstinence could not be confirmed or multiple consecutive UCT visits were missed, it was assumed that the participant would have had a positive urine cannabinoid test.

Prior to analysis, standard descriptive statistics were used to summarize the demographic and clinical characteristics of the cohort. Demographic, clinical, and marijuana use characteristics were examined for univariate predictive relationships with cognitive response outcome as well as possible confounding effects with marijuana abstinence. Marijuana use characteristics included craving which was assessed at baseline with the 12-item, short form of the Marijuana Craving Questionnaire (MCQ). This measurement has been shown to be reliable and valid (Heishman et al., 2009). In the primary analysis model, the effect of abstinence from marijuana on cognitive outcome measures was assessed simultaneously at the 4- and 8-week treatment visits using mixed effect regression models. Group level means were constructed using model based estimates and standard errors. Restricted maximum likelihood (REML) methods were used to estimate fixed effects and variance components in the presence of imbalanced data (Patterson and Thompson, 1971). Initial models contained abstinence duration (NA, RA, CA), visit, the interaction of abstinence and visit number, and baseline measures of cognitive variables. When the interaction of abstinence and visit number is insignificant, a time naïve cluster analysis of group means was performed. Secondarily, it was also of interest to investigate the effect of abstinence over the entire 8-week treatment period on cognitive outcomes (For this, the NA group meant positive cannabinoid test at week 8, RA meant negative urine cannabinoid test at week 8 but a positive urine cannabinoid test at some point during treatment, and CA meant a negative urine cannabinoid test at week 8 and throughout treatment.). As the primary aim of the parent study was to estimate the effects of NAC on abstinence from marijuana use, all models were additionally adjusted for treatment group assignment. The normality and homoscedasticity of the residuals were checked using graphical techniques and when violations of assumptions were found, outcome measures were appropriately transformed.

Model based statistical results are shown as means and associated standard errors unless otherwise noted. All statistical analyses were conducted using SAS version 9.3 (SAS® 9.3, 2011). Significance for all planned comparisons was set at a 2-sided p-value of 0.05.