Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders

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Recent studies suggest that abstinent cannabis users show deficits on neurocognitive laboratory tasks of impulsive behavior. But results are mixed, and less is known on the performance of non-treatment-seeking, young adult cannabis users. Importantly, relationships between performance on measures of impulsive behavior and symptoms of cannabis addiction remain relatively unexplored. We compared young adult current cannabis users (CU, n = 65) and nonusing controls (NU, n = 65) on several laboratory measures of impulsive behavior, as well as on a measure of episodic memory commonly impacted by cannabis use. The CU group performed more poorly than the NU group on the Hopkins Verbal Learning Test–Revised Total Immediate Recall and Delayed Recall. No significant differences were observed on the measures of impulsive behavior (i.e., Iowa Gambling Task, IGT; Go–Stop Task; Monetary Choice Questionnaire; Balloon Analogue Risk Task). We examined relationships between neurocognitive performance and symptoms of cannabis use disorder symptoms (Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition, DSM–IV CUD) among the CU group, which revealed that poorer IGT performance was associated with more symptoms of DSM–IV CUD. Our results show poorer memory performance among young adult cannabis users than among healthy controls, but no differences on measures of impulsive behavior. However, performance on a specific type of impulsive behavior (i.e., poorer decision making) was associated with more cannabis use disorder symptoms. These results provide preliminary evidence to suggest that decision-making deficits may be more strongly associated with problems experienced from cannabis use, rather than solely being a consequence of cannabis use, per se.

Keywords: Cannabis; Addiction; Decision making; Neuropsychology; Memory; Cognitive effects.

About 8% of individuals that try cannabis develop a cannabis use disorder (Anthony, Warner, & Kessler, 1994; Lopez-Quintero et al., 2011). Because of its high prevalence of use, more people meet Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM–IV; American Psychiatric Association, 1994) criteria for substance use disorders from cannabis than for any other illicit drug (Substance Abuse and Mental Health Services Administration, SAMHSA, 2009), and more individuals sought substance use treatment for cannabis than any other illicit drug in

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Cannabis use continues to increase among adolescents and young adults alongside a decreasing perception of harm and less disapproval of its use (Johnston, O’Malley, Bachman, & Schulenberg, 2010). Importantly, as we describe below, neurocognitive deficits have been documented among heavy cannabis users, primarily in the areas of memory and more recently on laboratory measures of impulsive behavior. However, most studies have relied on treatment-seeking samples or on those with diagnoses of cannabis use disorders. Less is known about the performance of community-dwelling, young adults who are not seeking treatment for their cannabis use (who constitute a large proportion of all cannabis users). More importantly, to date, studies have compared neurocognitive performance between cannabis-using and nonusing samples, but have not explored how neurocognitive performance relates to symptoms of cannabis use disorder. As we describe below, there are theoretical reasons to suspect that neurocognitive problems with impulsive behavior may be related to more symptoms of cannabis use disorder, as they may contribute to compulsive use of cannabis in the face of negative consequences. The primary aims of this study were twofold: (a) to compare the performance of non-treatment-seeking cannabis users and nonusers on neurocognitive laboratory measures of impulsive behavior; (b) to examine the relationship of such measures with severity of cannabis use disorder symptoms in this sample.

Cannabis use is known to alter brain functioning through the binding of its primary psychoactive constituent, Δ9-tetrahydrocannabinol (THC), to cannabinoid (CB1) receptors. CB1 receptors are localized throughout cortex, with high concentrations in prefrontal cortex, anterior cingulate, and striatum: brain structures critical to many neurocognitive functions and implicated in addiction neuropathogenesis. Results from functional imaging studies often show differences in brain activity between abstinent cannabis users and nonusers in the prefrontal cortex of adolescents (Jager, Block, Luijten, & Ramsey, 2010; Schweinsburg et al., 2005; Tapert et al., 2007) and adults (Block et al., 2002; Eldreth, Matochik, Cadet, & Bolla, 2004; Gruber & Yurgelun-Todd, 2005; Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004; Pillay et al., 2004). Although neurocognitive deficits are evident both during acute intoxication and during abstinence (Fried & Smith, 2001; Gonzalez, 2007; Gonzalez, Carey, & Grant, 2002; Pope, Gruber, & Yurgelun-Todd, 1995; Ranganathan & D’Souza, 2006; Schweinsburg, Brown, & Tapert, 2008; Solowij & Battisti, 2008), substantial controversy exists regarding the nature of the deficits, their magnitude, and their duration. Nonetheless, the most consistent deficits among cannabis users are arguably in episodic memory (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001; Ranganathan & D’Souza, 2006; Solowij & Battisti, 2008), although such deficits are thought to dissipate after approximately a month of abstinence (Hanson et al., 2010; Medina et al., 2007; Pope et al., 2001).

Recently, several studies also report that cannabis users demonstrate problems in neurocognitive functions associated with impulsivity: defined as a predisposition toward rapid, unplanned reactions without regard to the negative consequences (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Deficits among cannabis users have been reported on measures of motor inhibition, risk taking, and decision making both in laboratory studies of acute use (Lane, Cherek, Tcheremissine, Lieving, & Pietras, 2005; McDonald, Schleifer, Richards, & de Wit, 2003; Ramaekers, Kauert, et al., 2006; Ramaekers, Moeller, et al., 2006) and cross-sectional studies of cannabis users after varying lengths of recent abstinence (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Clark, Roiser, Robbins, & Sahakian, 2009; Fernandez-Serrano, Perez-Garcia, Schmidt Rio-Valle, & Verdejo-Garcia, 2009; Hermann et al., 2009; Lamers, Bechara, Rizzo, & Ramaekers, 2006; Verdejo-Garcia et al., 2007; Whitlow et al., 2004). However, results are mixed (Crean, Crane, & Mason, 2011). For example, others have found no differences between cannabis users and controls on measures of delay discounting (Johnson et al., 2010) or among other measures of impulsive behavior after acute cannabis administration (McDonald et al., 2003; Vadhan et al., 2007). Most studies to date have focused on samples comprised primarily of individuals in treatment or with cannabis use disorders, have employed only a single neurocognitive measure of impulsive behavior, or only attempt to examine the neurocognitive sequelae of cannabis use. It is important to consider that problems of impulse control have been hypothesized to influence the development of drug addiction (de Wit, 2009; Goldstein & Volkow, 2002; Schepis, Adinoff, & Rao, 2008). Most cannabis users do not meet criteria for cannabis use disorders and vary substantially in their amount of use, as well as to the degree they experience problems from their cannabis use. It is possible that deficits in neurocognitive functions associated with impulsivity may influence the extent to which a cannabis user experiences symptoms of a cannabis use disorder (and therefore problems from cannabis), yet this has been largely unexplored.
In this study, we compared the neurocognitive performance of a carefully selected community sample of young adult current cannabis users that identified cannabis as their drug of choice and nonusing controls. Participants were assessed on several commonly used laboratory measures of impulsive behavior, including measures of decision making, intertemporal choice (delay discounting), risk taking, and motor inhibition. They also completed a measure of episodic memory. Episodic memory was assessed to determine whether cannabis use among our community, non-treatment-seeking sample of cannabis users was sufficient to manifest with memory deficits—a common finding in other studies of cannabis use and neurocognitive functioning. Finally, we examined relationships between the measures of neurocognitive performance and severity of cannabis use disorder symptoms. We hypothesized that cannabis users would demonstrate poorer performance on measures of impulsive behavior and episodic memory than would nonusers. More importantly, we anticipated that poorer performance on neurocognitive measures of impulsive behavior would be associated with more severe symptoms of cannabis use disorders.

METHOD

Participants

Participants were 65 current cannabis users (CU group) and 65 nonusers (NU group) ages 17 to 24 years, recruited from the Chicago metropolitan area through flyers placed throughout the community and through word of mouth. Participants were part of a study on neurocognitive functioning among young adult cannabis users (PI: R.G.), and a small subset (5%) of the final enrolled sample were recruited from a program project on tobacco use trajectories (PI: RM). Participant demographic information is presented in Table 1.

Inclusion and exclusion criteria were selected to minimize confounds to neurocognitive performance. Inclusion criteria for the entire sample were having more than 8 years of education, being fluent in English, and having an estimated full scale IQ greater than 75. Participants were excluded if they were on current psychotropic medications, had a history of any neurological disorder (including open head injury, closed head injury with loss of consciousness for greater than 10 minutes, epilepsy, brain tumor, cerebrovascular accident, or other systemic medical disorder known to adversely affect brain functioning), or self-reported a history of a diagnosed mental illness (including major depression; bipolar disorder; schizophrenia or other psychotic disorders; attention-deficit/hyperactivity disorder; ADHD; developmental disorder; or learning disability). Four participants in the CU group and three in the NU group obtained scores exceeding the clinical cutpoint suggestive of ADHD on the Wender–Utah Rating Scale (WURS), but reported no history of ADHD or a clinical history suggestive of ADHD and were therefore retained for analyses. In order to minimize substance use confounds and to obtain a relatively homogenous group of current users.

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>NU (n = 65)</th>
<th>CU (n = 65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.3 (2.0)</td>
<td>20.8 (1.8)</td>
<td>.15</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>51</td>
<td>65</td>
<td>.11</td>
</tr>
<tr>
<td>Estimated FSIQ</td>
<td>104 (10.8)</td>
<td>102.6 (9.9)</td>
<td>.42</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.6 (1.8)</td>
<td>13.5 (1.6)</td>
<td>.76</td>
</tr>
<tr>
<td>Ethnicity/race</td>
<td></td>
<td></td>
<td>.55</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>43</td>
<td>43</td>
<td>.55</td>
</tr>
<tr>
<td>African-American (%)</td>
<td>31</td>
<td>37</td>
<td>.56</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>11</td>
<td>12</td>
<td>.56</td>
</tr>
<tr>
<td>Other (%)</td>
<td>15</td>
<td>8</td>
<td>.56</td>
</tr>
<tr>
<td>Annual household income</td>
<td>75 [45, 150]</td>
<td>70 [40, 145]</td>
<td>.71</td>
</tr>
<tr>
<td>Mother’s education (years)</td>
<td>13.9 (3.7)</td>
<td>14.3 (2.8)</td>
<td>.55</td>
</tr>
<tr>
<td>WURS (% over ADHD cutpoint)</td>
<td>5</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td>BIS-11</td>
<td>57.9 (9.5)</td>
<td>59.1 (9.8)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Note. All values are means and standard deviations, unless otherwise noted; participants were between 17 and 24 years of age; CU = current cannabis users; NU = nonusing controls; Mdn = median; IQR = interquartile range; FSIQ = Full Scale IQ; BDI-2 = Beck Depression Inventory–2nd Edition; BAI = Beck Anxiety Inventory; WURS = Wender–Utah Rating Scale; BIS-11 = Barratt Impulsiveness Scale–11th version; ADHD = attention-deficit/hyperactivity disorder.
CU and NU, participants were also excluded if they reported use of any substance more than 10 times in their lifetime or any use at all during the 30 days prior to their evaluation (other than cannabis use among the CU group and alcohol, nicotine, and hallucinogens across both groups), history of DSM-IV lifetime alcohol dependence or drinking more than 3 drinks per day on average during the 30 days prior to their evaluation, or DSM-IV diagnoses of lifetime abuse or dependence for any other substance (other than alcohol or nicotine). One participant in the CU group and one in the NU group that did not meet criteria suggestive of an alcohol use disorder at screening were later found to meet criteria for lifetime history for alcohol dependence during their study visit; however, the days since they last met alcohol dependence criteria were very remote (730 days ago and 1,460 days ago), thus their data were retained for analyses. Inclusion criteria specific for participants in the CU group were identifying cannabis as their drug of choice, use of cannabis more than 200 times, use of cannabis at least 4 times per week during their peak use, and use in the 45 days prior to their evaluation. Cannabis users were asked to abstain for at least 24 hours prior to their evaluation to minimize acute effects or withdrawal symptoms. Inclusion criteria specific to the NU group were use of cannabis fewer than 10 times, use of cannabis never more than 4 times per week, and no cannabis use during the 90 days prior to their evaluation. Seventy-seven percent of participants in the CU group and no participant in the NU group tested positive for cannabis on a Drug Check Cup; Express Diagnostics, Blue Earth, MN). Detailed information on participant substance use history is presented in Table 2.

Procedures and measures

The study was approved by the University of Illinois Chicago Institutional Review Board. All participants provided informed consent (or assent and parental consent where appropriate). Participants were administered a counterbalanced battery of tests that included structured interviews, self-report questionnaires, and neurocognitive tests. All participants received a cash payment for participating in the study.

Demographics, medical history, and mental health

Premorbid full scale IQ was estimated with the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). Current symptoms of depression and anxiety were assessed with the Beck Depression Inventory–2nd Edition (BDI–II; Beck, Steer, Ball, & Ranieri, 1996) and the Beck Anxiety Inventory (BAI; Beck & Steer, 1990), respectively. The Wender–Utah Rating Scale (WURS; Ward, Wender, & Reimherr, 1993) was used to evaluate symptoms associated with ADHD. The Barratt Impulsiveness Scale–11 (BIS) assessed impulsive personality traits (Patton, Stanford, & Barratt, 1995). The Mood Disorders portion of the Structured Clinical Interview for DSM-IV disorders (SCID) assessed for lifetime and current (past 30 days) diagnoses of major depression and bipolar disorder (First, Spitzer, Gibbon, & Williams, 2002).

Substance use history

All participants completed a detailed semistructured interview that incorporated methods of the time-line followback procedure and assessed patterns of substance use for 13 different substance classes, similar to methods employed in other studies (e.g., Gonzalez, 2004; Rippeth et al., 2004). For each substance queried, participants were asked about frequency and quantity of use across various epochs in their lifetime to arrive at estimates of cumulative lifetime use, as well as amount and frequency of use in the 12 months and in the 30 days prior to their evaluation. The substance use module of the Structured Clinical Interview for DSM-IV (SCID) was administered to diagnose the presence of alcohol and substance use disorders during participants’ lifetime and in the 30 days prior to their evaluation (First et al., 2002). We assessed for the presence and severity of symptoms associated with cannabis addiction with the Marijuana Severity Index (MSI; Alexander, 2003): a 31-item yes/no forced-choice questionnaire on problematic patterns of cannabis use that a participant has “ever” experienced from cannabis use. We also quantified severity of cannabis addiction by tabulating the total number of current DSM–IV symptoms of cannabis abuse and dependence endorsed by a participant in the 30 days prior to their evaluation (DSM–IV CUD symptoms).

Laboratory measures of neurocognitive functioning

The Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) was
TABLE 2
Substance use parameters by group

<table>
<thead>
<tr>
<th>Substance Use Measures</th>
<th>NU (n = 65)</th>
<th>CU (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (30-day) DSM–IV SUD (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Cannabis abuse**</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Cannabis dependence**</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Lifetime DSM–IV SUD (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse*</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cannabis abuse*</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Cannabis dependence**</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Cannabis use parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM–IV CUD symptoms: Mdn [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana Severity Index</td>
<td>—</td>
<td>10.0 (4.3)</td>
</tr>
<tr>
<td>Age at cannabis use onset (years)</td>
<td>—</td>
<td>15.6 (3.1)</td>
</tr>
<tr>
<td>Years of cannabis use</td>
<td>—</td>
<td>5.0 (2.4)</td>
</tr>
<tr>
<td>% THC+**</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>Days since last use: Mdn [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol**</td>
<td>14 [4, 30], n = 60</td>
<td>6 [3.5, 14], n = 65</td>
</tr>
<tr>
<td>Nicotine**</td>
<td>14 [4, 450], n = 23</td>
<td>2 [1, 8.75], n = 54</td>
</tr>
<tr>
<td>Cannabis**</td>
<td>720 [365, 1,278], n = 17</td>
<td>3 [2, 4.5], n = 65</td>
</tr>
<tr>
<td>Lifetime: Mdn [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks**</td>
<td>108 [13, 498]</td>
<td>492 [163, 1,254]</td>
</tr>
<tr>
<td>Cigarette packs**</td>
<td>0 [0, 0.1]</td>
<td>68.4 [1.1, 291]</td>
</tr>
<tr>
<td>Cannabis joints**</td>
<td>0 [0, 0]</td>
<td>270 [102, 815]</td>
</tr>
<tr>
<td>12 months: Mdn [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks**</td>
<td>24 [4, 120]</td>
<td>108 [34, 258]</td>
</tr>
<tr>
<td>Cigarettes**</td>
<td>0 [0, 0]</td>
<td>3 [0, 36]</td>
</tr>
<tr>
<td>Cannabis joints**</td>
<td>0 [0, 0]</td>
<td>60 [26, 216]</td>
</tr>
<tr>
<td>30 days: Mdn [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol drinks*</td>
<td>4 [0, 14]</td>
<td>10 [2, 20]</td>
</tr>
<tr>
<td>Cigarettes**</td>
<td>0 [0, 0]</td>
<td>0.35 [0, 3]</td>
</tr>
<tr>
<td>Cannabis joints**</td>
<td>0 [0, 0]</td>
<td>6 [3, 18]</td>
</tr>
</tbody>
</table>

Note. All values are means and standard deviations unless otherwise noted; CU = current cannabis users; NU = nonusing controls; DSM–IV SUD = Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition substance use disorder diagnosis; CUD = cannabis use disorder; THC+ = positive rapid urine toxicology testing for cannabis; Mdn = median; IQR = interquartile range; — denotes not applicable.

*p < .05, **p < .01.

developed to quantify the poor judgment and impulsive decision making typically observed among patients with lesions of the orbitofrontal cortex. It is deemed a measure of “decision making” and is thought to assess a bias toward immediate over longer term rewards. Participants make 100 choices from a computerized display of four card decks, with each choice followed by a win of some money and sometimes also a loss. Participants are not informed that two of the decks most frequently result in small rewards and few losses (“good” decks). Choices from the other decks more frequently result in larger rewards but also larger losses (“bad” decks). Choices primarily from the “good decks” yield overall positive net scores by the end of the task, whereas choices primarily from “bad decks” will yield a net loss. Substance users typically show poorer performances than healthy controls (Bechara et al., 2001; Grant, Contoreggi, & London, 2000). We used the total net score (choices from good decks minus choices from bad decks) as our outcome measure, with higher scores indicating better decision making.

The Balloon Analogue Risk Task (BART) is a laboratory measure of risk taking (Lejuez et al., 2002). Participants are shown a graphic of a deflated balloon on a computer screen and are instructed to press a key to “inflate” the balloon. Participants earn $0.05 with each key press. They can collect the total money accumulated at any time and move on to the next trial, which starts with another deflated balloon. A balloon may “pop” after a key press, with a probability unknown to the participant, and all money earned during that trial would be lost. The BART is often performed more poorly by substance users (Crowley, Raymond,
Mikulich-Gilbertson, Thompson, & Lejuez, 2006; Fernie, Cole, Goudie, & Field, 2010). The outcome measure is the “adjusted” average number of pumps, which excludes the number of pumps on balloons that explode. Higher scores are suggestive of greater risk taking.

The Monetary Choice Questionnaire (MCQ; Kirby, Petry, & Bickel, 1999) is a self-report measure of intertemporal choice that consists of 27 fixed hypothetical choices between smaller immediate rewards and larger delayed rewards. The MCQ assesses delay discounting by allowing estimation of the degree to which an individual reduces their perceived value of a reward as the time delay to obtaining that reward increases. Delay discounting is characterized by Mazur’s hyperbolic function (Mazur, Commons, Mazur, Nevin, & Rachlin, 1987): \( V_D = A/(1 + kD) \), where \( V_D \) is the value of a present value of a delayed reward \( (A) \) at a given delay \( (D) \). The parameter \( k \) quantifies individual differences in delay discounting, with a higher value indicating steeper discounting, and log-transformed \( k \) values were used as our outcome measure using established methods (Kirby et al., 1999). Higher \( k \) values have been shown among substance users than among healthy controls (Kirby et al., 1999; Madden, Petry, Badger, & Bickel, 1997; Petry, Bickel, & Arnett, 1998).

The Go–Stop Task (Dougherty, Mathias, Marsh, & Jagar, 2005) is a computerized stop signal task (Logan, Cowan, & Davis, 1984) that assesses the participant’s ability to stop an already initiated motor response. Participants were asked to quickly press a key on the computer keyboard on go (or no-stop) trials: whenever a 5-digit number presented in black font was identical to the previously presented number. On some trials, the font color of the second matching number changes to red, and participants are to withhold a response. A total of 80 stop, 80 no-stop, and 160 novel trials (non-matching number in black) are administered in pseudorandom order. The latency from stimulus onset to the appearance of the stop trial was 150, 250, 350, or 450 ms (20 trials of each), with longer latencies expected to be associated with more inhibition failures. Individuals with substance use disorders are known to exhibit more inhibition failures than healthy controls (Acheson, Richard, Mathias, & Dougherty, 2011; Dougherty, Marsh-Richard, Hatzis, Nouvion, & Mathias, 2008; Fillmore & Rush, 2002; Reynolds et al., 2007). We used the total number of correct inhibitions minus number of “misses” on the go trials. This was done to adjust for individuals who responded to fewer trials (either on purpose or through inattention) and would otherwise have obtained a misleadingly high number of correct inhibitions. Higher scores were indicative of better inhibitory control.

The Hopkins Verbal Learning Test–Revised (HVLT; Benedict, Schretlen, Groninger, & Brandt, 1998) is a test of episodic verbal memory that consists of three groups of four (nonconsecutive) semantically associated words. Participants are asked to immediately repeat words after each of three trials, and then again after a 25-min delay. Finally, participants are administered a forced-choice recognition trial. Total immediate recall was calculated as the total number of words correctly recalled across learning trials, whereas delayed recall was the number of correct words spontaneously recalled after the 25-min delay. Recognition discriminability was the number of words correctly identified on the forced-choice recognition trial minus any false-alarm errors. All scores were generated using published normative data (Benedict et al., 1998).

General statistical approach

All analyses were carried out using JMP 9.0 (SAS, Carey, NC). Data were inspected for non-normal distribution and outliers. When appropriate, square-root transformations or nonparametric procedures were used with data that violated assumptions of parametric procedures (these included all measures on amount of substance use). MCQ \( k \) values underwent log transformation. In order to control for the influence of 12-month alcohol and nicotine use for between-group comparisons on neurocognitive performance, both variables were first regressed on each of the neurocognitive measures in order to obtain residuals. Comparisons between the CU and NU on neurocognitive performance were conducted on the residualized variables.

RESULTS

Demographics, mental health, substance use and other potential confounds

The CU and NU groups showed no statistically significant differences in age, sex, race/ethnicity, years of education, mother’s years of education, household income, estimated full scale IQ (WTAR), current symptoms of depression (BDI–II) or anxiety (BAI), lifetime DSM–IV diagnosis of major depression (SCID), impulsive personality traits (BIS), and prevalence of possible ADHD (WURS), all \( p > .10 \) (Table 1). No participant met DSM–IV criteria for
bipolar disorder, and none met criteria for major depression in the 30 days prior to their evaluation.

No participant met DSM–IV criteria for current or lifetime abuse or dependence for cocaine, sedatives, stimulants, opiates, or hallucinogens, and none reported injection drug use. Furthermore, none met current diagnosis for alcohol dependence. Detailed substance use parameters are reported in Table 2. Compared to the NU group, the CU group reported a higher prevalence of past alcohol abuse ($\chi^2 = 5.91, p = .02$). When comparing the CU and NU groups on amount of use for various substances, square-root transformations were employed to improve the distribution of the variables. The CU group reported more use of alcohol, nicotine, and cannabis during their lifetime, last 12 months, and last 30 days (all $p \leq .01$). Similarly, among those reporting use of alcohol, nicotine, or cannabis, those in the CU group reported more recent use than those in the NU group for all three substances (all $p < .01$, See Table 2). Among the CU group, neurocognitive performance was not significantly correlated with days since last use of alcohol ($p > .10$), nicotine ($p > .32$), or cannabis ($p > .41$). The lack of associations may be due to our inclusion/exclusion criteria resulting in a fairly homogenous sample. No participant in the NU group reported other substance use, with the exception of one participant reporting a one-time use of a nonprescription opiate. Participants in the CU group were more likely to have experimented with other substances, but reported use of other substances was less than 10 lifetime occasions (median occasions of use were <7 times across all substances), and no CU participant reported use of any other illicit substance within the 30 days prior to the evaluation ($Mdn$ days since last use of each substance = 365 days). These results suggested that only use of nicotine and alcohol use were of sufficient recency and magnitude to warrant controlling for them in our analyses. When considering which of the estimates of amounts of nicotine and alcohol use to employ as covariates, we decided that amount of use in the last 12 months would be optimal, as it would capture the severity of use while being less susceptible to recent and perhaps uncharacteristic changes in use when compared to last 30 days use. Similarly, use in the last 12 months would be less confounded by a participant’s age than cumulative lifetime use, as an older participant could obtain higher cumulative amounts of use despite less frequent and more distal use than a younger participant. Thus the influence of 12-month alcohol and nicotine use were controlled for in our between-group analyses by regressing both variables on each neurocognitive measure and using the residuals as the outcome measure. Multiple linear regressions with 12-month alcohol and nicotine use as independent variables were conducted separately using each neurocognitive measure as the dependent variable. Twelve-month nicotine use was significantly associated with MCQ $k$ ($t = 2.12, \beta = .18, p = .04$) and HVLT total immediate recall ($t = 2.26, \beta = -0.20, p = .03$), whereas alcohol use was significantly associated with IGT performance ($t = 2.04, \beta = .18, p = .04$).

**Differences in neurocognitive performance between cannabis users and nonusers**

One-way analyses of variance (ANOVAs) were conducted employing group (CU or NU) as the independent variable and one index of neurocognitive performance as the dependent variable (using the residuals obtained after regressing 12-month alcohol and nicotine use). Statistically significant differences in mean performance between the CU and NU groups were observed for HVLT total immediate recall, $F(1, 128) = 5.61$, Cohen’s $d = -0.42, p = .019$, and HVLT delayed recall, $F(1, 128) = 4.38$, Cohen’s $d = -0.37, p = .038$, with the CU group performing more poorly on both tasks. No statistically significant differences were observed for HVLT recognition discriminability, $F(1, 128) = 3.89, p = .051$; IGT net score, $F(1, 128) = 0.92, p = .34$; MCQ $k$, $F(1, 128) = 0.41, p = .52$; Go–Stop, $F(1, 128) = 0.019, p = .89$; or BART performance, $F(1, 128) = 0.045, p = .83$; see Table 3. Figure 1 presents the results of these analyses using $z$ scores calculated from the means and standard deviations of the entire sample on each of the neurocognitive tasks. Significant differences in HVLT delayed recall did not emerge when controlling for performance on HVLT total immediate recall ($p = .94$), suggesting that differences in HVLT performance was due to problems with the acquisition of new information, rather than recall. HVLT total immediate and delayed recall were strongly correlated within the NU ($r = .73, p < .001$) and the CU group ($r = .72, p < .001$).

**Relationships between neurocognitive performance and symptoms of cannabis use disorders**

We conducted two linear regressions among the CU group with performance on each of the neurocognitive measures as independent variables, amount of alcohol and nicotine use in the last 12 months as covariates, and one of the two
TABLE 3
Neurocognitive differences by group

<table>
<thead>
<tr>
<th>Neurocognitive Measure</th>
<th>NU (n = 65)</th>
<th>CU (n = 65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVLT–R total immediate recall</td>
<td>−.26 (.16)</td>
<td>−.82 (1.33)</td>
<td>.019</td>
</tr>
<tr>
<td>HVLT–R delayed recall</td>
<td>−.41 (1.13)</td>
<td>−.89 (1.30)</td>
<td>.038</td>
</tr>
<tr>
<td>HVLT–R recognition discriminability</td>
<td>−.10 (2.63)</td>
<td>−.13 (1.08)</td>
<td>.069</td>
</tr>
<tr>
<td>Inhibitory control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT net score</td>
<td>8.13 (29.49)</td>
<td>6.06 (28.87)</td>
<td>.34</td>
</tr>
<tr>
<td>Go–Stop (correct inhibitions – misses)</td>
<td>23.09 (17.47)</td>
<td>22.14 (19.57)</td>
<td>.89</td>
</tr>
<tr>
<td>MCQ k</td>
<td>.05 (.05)</td>
<td>.05 (.05)</td>
<td>.52</td>
</tr>
<tr>
<td>BART (adjusted pumps)</td>
<td>32.0 (12.2)</td>
<td>32.7 (11.8)</td>
<td>.83</td>
</tr>
</tbody>
</table>

Note. All values are means and standard deviations; NU = nonusers; CU = cannabis users; HVLT = Hopkins Verbal Learning Test–Revised; IGT = Iowa Gambling Task; MCQ = Monetary Choice Questionnaire; BART = Balloon Analogue Risk Task.

Figure 1. Neurocognitive performance by group. The values presented in the graph are mean z scores (and standard errors) calculated for each group on each task using the average performance of the entire sample. This allows us to present performance across all tasks on the same graph. The NU (nonusers) and CU (cannabis users) groups differed significantly only on HVLT–R (Hopkins Verbal Learning Test–Revised) and total immediate recall (HVLT total). IGT = Iowa Gambling Task; BART = Balloon Analogue Risk Task. *p < .05.

measures of cannabis addiction symptoms (MSI and DSM–IV CUD symptoms) as dependent variables. To prevent multicollinearity, only one of the three possible HVLT indices, HVLT total immediate recall, was included in the model, as it evidenced the largest effect in prior between-group analyses. No statistically significant associations were observed between any of the neurocognitive measures and MSI (all p-values > .05). However, poorer IGT performance was associated with more
DSM–IV CUD symptoms ($\beta = -0.30$, $p = .03$). No other neurocognitive task was found to be associated with DSM–IV CUD symptoms (all $p > .42$). Because DSM–IV CUD symptoms are count data and were not normally distributed, we conducted these analyses again using Poisson regression with control for overdispersion (Gardner, Mulvey, & Shaw, 1995; Karazsia & van Dulmen, 2008) and obtained the same results—only IGT net score was significantly associated with DSM–IV CUD symptoms ($p = .02$).

**Additional exploratory analyses**

Pairwise Pearson correlations among the neurocognitive measures of impulsive behavior revealed no significant correlations ($r$-values ranged from .07 to .16; $p$-values ranged from .07 to .69).

In order to further explore the relationship between cannabis use and DSM–IV symptoms of cannabis use disorders, we examined bivariate correlations between three parameters of cannabis use (total lifetime use, use in last 12 months, and use in the last 30 days) and the total number of DSM–IV cannabis use disorder symptoms (DSM–IV CUD) in the CU group. All three parameters exhibited statistically significant, moderate correlations with DSM–IV CUD (lifetime: $\rho = .41$, $p = .0007$; 12 months: $\rho = .53$, $p < .0001$; 30 days: $\rho = .52$, $p < .0001$).

**DISCUSSION**

In this study, we examined whether a community sample of non-treatment-seeking young adult, current cannabis users (CU) demonstrated deficits on neurocognitive laboratory tasks of impulsive behavior compared to nonusing controls (NU). We also assessed their episodic memory to replicate common findings of poorer memory among cannabis users. More importantly, we examined whether neurocognitive performance was associated with the severity of cannabis use disorder symptoms endorsed by the cannabis users. Consistent with the current literature, we found significantly poorer episodic memory performance among the CU group, which appeared to be due to problems with the acquisition of new information. Contrary to our hypotheses, we found no evidence of deficits on laboratory measures of impulsive behavior among the CU. Nonetheless, significant associations between IGT performance and DSM–IV symptoms of cannabis use disorders (DSM–IV CUD) were observed. Our results suggest that deficits in neurocognitive measures of impulsive behavior may not be as prominent as memory deficits among non-treatment-seeking cannabis users. However, problems specifically with decision making appear to be associated with more symptoms of cannabis use disorders, indicating that individual differences in decision making may place cannabis users at greater risk for cannabis use disorders and to potentially experience more problems from their cannabis use.

Although we found no between-group differences on neurocognitive measures of impulsive behavior in our sample, other studies have reported such deficits. However, a recent synthesis of studies on cannabis use and executive functions (which include laboratory measures of impulsive behavior) suggest that findings vary substantially depending on the specific measures employed and whether cannabis users are tested while acutely intoxicated or when abstinent (Crean et al., 2011). A factor that may have contributed to the lack of differences between CU and NU on laboratory measures of impulsive behavior in our study may have been our stringent inclusion criteria, which required that all cannabis users identify cannabis as their drug of choice, used cannabis recently, and had very minimal history of other drug use, with the exception of alcohol and nicotine use (both of which were controlled for in our analyses). Moreover, our study did not require for our CU participants to be treatment seeking or to meet criteria for a cannabis use disorder. We were also careful to exclude individuals with numerous other mental health, substance use, and neurological confounds. It is important to note that despite this careful control of confounds, the CU group continued to show significantly poorer memory performance than the NU group, of a magnitude consistent with (or larger than) those observed among samples of older, long-term, heavy cannabis users (e.g., Grant et al., 2003). Thus, even though cannabis users in our sample may not have used as heavily as those in other studies, cannabis use in our non-treatment-seeking sample was clearly sufficient to still manifest with neurocognitive deficits in episodic memory relative to controls.

Although the CU and NU groups did not differ in decision-making performance, poorer IGT performance was significantly associated with more DSM–IV CUD symptoms. This is an interesting finding, especially when considering the lack of differences between the NU and CU groups on IGT performance. Although speculative in the absence of a prospective longitudinal design, it is possible that poorer decision making may be more relevant to whether an individual experiences symptoms of a cannabis use disorder rather than being a direct
consequence of cannabis use, per se. In this study, we find that cannabis consumption is associated with poorer episodic memory performance, but not with decision making. In contrast, decision making is related to symptoms of cannabis use disorder, but memory performance is not. It is conceivable that an individual with intact decision making may be more likely than an individual with impaired decision making to inhibit using cannabis in situations more likely to lead to significant adverse consequences (e.g., driving, working, or in school), thus making the latter more likely to experience symptoms of a cannabis use disorder. Theoretically, two individuals with similar amounts of cannabis use may experience differing degrees of problems from their use. Our findings suggest that problems with decision making may have an influence on the amount of significant problems experienced by cannabis users (as reflected by DSM-IV symptoms of cannabis use disorders). We acknowledge that both cannabis consumption and symptoms of cannabis use disorder are related; however, their correlation is not invariably strong. This is likely due to the fact that abuse/dependence is defined by several symptoms, which do not require escalating use. In our own sample, symptoms of cannabis addiction and amount of cannabis use were only moderately correlated ($\rho = .41$ to $.53$). It is important to note that relationships between laboratory measures of impulsive behavior were not invariably related to symptoms of cannabis use disorder. Our results suggest that of the constructs examined, problems with decision making may be most pertinent in influencing the magnitude of current cannabis use disorder symptoms. A future study will focus on decision making and the problems that individuals specifically report from their cannabis use.

Several characteristics of our study need to be considered when interpreting our findings. First, it is important to underscore that the cross-sectional design of the study prevents us from establishing causation or determining any clear temporal relationships among our variables. Secondly, the CU group showed higher amounts of alcohol and nicotine use and was more likely to have a history of other experimental drug use than the NU group. In addition to adequately matching groups and excluding individuals with a history of drug abuse/dependence and current alcohol dependence, recent heavy alcohol use, and frequent or recent use of other substances, we also controlled statistically for amount of alcohol and nicotine use to address these common group differences and to better isolate the effects of cannabis. We also note that we found no relationships between neurocognitive measures and the MSI. This may be due to the MSI querying about behaviors that have happened “ever” in a participant’s life, in contrast to the DSM-IV CUD variable that specifically asked about symptoms in the last 30 days. Furthermore, it is worth noting that not all participants in the cannabis-using group tested positive for THC or its metabolites on urine toxicology testing. This is not surprising given the levels of detection of the urinalysis and the fact that THC metabolites accumulate in adipose tissue and have erratic elimination that may be affected by many factors (e.g., chronicity and amount of use; recent exercise; water intake; body mass index, BMI; resting metabolic rate; and diet). Thus, it is possible for a positive test to be obtained after several weeks of use or a recent user may yield a negative test result under some circumstances. Because we included both cannabis users and nonusers in our study, we do not think that non-cannabis-using participants were motivated to falsely endorse recent cannabis use.

It is also important to consider that our sample consisted of 17- to 24-year olds. We focused on recruiting emerging adults because this is the population where our findings may have the most impact, given the high prevalence of cannabis use in this age range. Furthermore, in this age range it is likely to find participants with minimal use of other illicit drugs. However, our results may not generalize to other age groups. We must also consider that in the age range sampled in the current study, the brain is continuing to undergo important neuromaturational changes. For example, cortical development peaks around 12 to 14 years of age and continues to decrease in volume and thickness into emerging adulthood with synaptic pruning of gray-matter density occurring first in more primary sensorimotor areas and last in higher order association areas like the prefrontal cortex (Giedd et al., 1999; Gogtay et al., 2004). Although the CU and NU group were well matched on age, participants in the CU group showed some variability in their age at first cannabis use, which may be of more relevance to neurocognitive functioning than the participants’ age at testing (see reviews by Crane, Schuster, Fusar-Poli, & Gonzalez, 2012; Schweinsburg et al., 2008). This important issue will require more careful consideration and investigation in future studies along with the emerging evidence of important sex differences in the neurocognitive performance, brain activity, and morphometry of male and female cannabis users (McQueen et al., 2011; Medina et al., 2009).

Our study benefited from including multiple neurocognitive measures of impulsive behavior; however, only the IGT revealed significant
relationships with cannabis use disorder symptoms. Although the laboratory measures of impulsive behavior we employed are conceptually related, they assess multiple underlying processes that oftentimes are weakly correlated (Castellanos & Tannock, 2002; Dougherty et al., 2009; Monterosso, Ehrman, Napier, O’Brien, & Childress, 2001; Nigg, 2000). Indeed, we found that these measures were not significantly correlated in our sample. In future studies, it will be important to include specifically multiple measures of decision making to determine whether our findings are specific to the IGT, affect only some aspects of decision making, or are associated with decision making in general. Furthermore, like many other studies that employ similar measures, we provided participants with hypothetical earnings on the tasks that involved rewards, rather than real money. Although we cannot rule out the possibility that our results may have been different if we provided tangible incentives based on performance, studies comparing real to hypothetical money reinforcement on IGT generally suggest no significant overall differences (Bowman & Turnbull, 2003; Fernie & Tunney, 2006), but may have some consequences depending on the sample and task parameters (Fernie & Tunney, 2006; Vadhan, Hart, Haney, van Gorp, & Foltin, 2009). However, the standardized and normed version of the IGT (Bechara, 2007), as well as the methods used in seminal studies (Bechara et al., 1994; Grant et al., 2000), also employ hypothetical money. In contrast, many studies with the BART or with measures of delay discounting employ some type of incentive, although several studies suggest that these tasks remain valid with hypothetical rewards (Benjamin & Robbins, 2007; Lagorio & Madden, 2005; Madden, Begotka, Raiff, & Kastern, 2003; Madden et al., 2004).

In summary, this study extends findings of neurocognitive performance among cannabis users and, to our knowledge, is the first to specifically examine how laboratory measures of impulsive behavior relate to symptoms of cannabis use disorder. Our results support the notion that problems with decision making may influence the degree to which a cannabis user experiences symptoms of a cannabis use disorder. Future studies will examine whether measures of decision making are valuable for identifying cannabis users who are likely to experience significant negative consequences from its use. Investigations of cognitive strategies for remediation of decision-making deficits may also prove fruitful in ameliorating cannabis use disorders. However, the important question of whether problems of decision making are an antecedent or consequence of drug use, which has also been raised by others (e.g., de Wit, 2009; Goldstein, Alia-Klein, Cottone, & Volkow, 2006), remains unanswered. It is possible that problems with inhibition, risk taking, and decision making may serve as a risk factor for the development of substance use disorders (de Wit, 2009; Goldstein & Volkow, 2002; Schepis et al., 2008), as they may make it more difficult to resist the urge to continue using a drug even when its use is harmful (Bechara, 2005). This question will need to be addressed more directly through longitudinal studies, similar to those that have been employed by others to demonstrate relationships between externalizing behaviors and future development of substance use disorders (Giancola, Moss, Martin, Kirisci, & Tarter, 1996; Kirisci, Tarter, Reynolds, & Vanyukov, 2006; Tarter, Kirisci, Habeyeh, Reynolds, & Vanyukov, 2004; Tarter et al., 2003) and alcohol use (Deckel & Hesselbrock, 1996; Norman et al., 2011).

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BRIEF COMMUNICATION

Preliminary Evidence for a Sex-Specific Relationship between Amount of Cannabis Use and Neurocognitive Performance in Young Adult Cannabis Users

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Abstract
Accumulating evidence suggests neuropsychological deficits from cannabis use, with a burgeoning area of preclinical research indicating possible sex-differences. However, few studies have examined how cannabis use may differentially impact neurocognition in male and female cannabis users. As such, we examined potential sex-differences in associations between amount of cannabis use (across several time frames) and neurocognitive performance among young adult regular cannabis users. Consistent with previous studies, more cannabis use was generally associated with poorer episodic memory and decision-making, but not other measures of inhibitory control. However, patterns of results suggested sex-specific dissociations. In particular, more cannabis use was more consistently associated with poorer episodic memory performance in females than males. Conversely, more cannabis use was associated with poorer decision-making performance for males, but not females. These results provide further evidence for residual cannabis-associated neurocognitive deficits and suggest the importance of examining the impact of cannabis on neurocognition separately for males and females. (JINS, 2013, 19, 1–7)

Keywords: Cannabis, Cognition, Marijuana, Neuropsychology, Sex differences, THC

INTRODUCTION
Cannabis use is prevalent among young adults, with rates of use rising in recent years (Johnston, O’Malley, Bachman, & Schulenberg, 2012). Accumulating evidence suggests neuropsychological deficits from cannabis use (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001; Solowij et al., 2002), and a burgeoning area of research points to possible sex-differences. Neurodevelopmental, pharmacological, metabolic, behavioral, and hormonal differences may all be contributing factors (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013). As more states decriminalize use, it is critical that we develop a thorough understanding of the neurocognitive effects of cannabis use. In this study, we examined sex-differences in the impact of cannabis use on episodic memory and inhibitory control: neurocognitive domains thought to be affected by cannabis use and on which healthy males and females often show differences in performance.

Adverse effects of cannabis on neurocognitive functioning are well documented, but the magnitude, duration, and the specific conditions under which impairment manifests remain unclear. Deficits in episodic memory are some of the most commonly reported, especially with recent use (Crane et al., 2013; Pope et al., 2001). Studies also find problems in inhibitory control among cannabis users (Grant, Chamberlain, Schreiber, & Odlaug, 2012; Verdejo-Garcia et al., 2007; Wesley, Hanlon, & Porrino, 2011; Whitlow et al., 2004) (a predisposition toward unplanned, rapid reactions without regard to negative consequences; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001), a domain including impulsivity, decision-making, risk-taking, delay-discounting, and motor inhibition. Further evidence of cannabis-associated deficits come from studies reporting relationships between amount of self-reported cannabis use and episodic memory (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Cunha, Nicastri, de Andrade, & Bolla, 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010), decision-making (even after 25-days abstinence) (Bolla, Eldreth, Matochik, & Cadet, 2005; Verdejo-Garcia et al., 2007), and motor inhibition (Cunha et al., 2010).
Several lines of evidence suggest females may be more vulnerable than males to cannabis-associated neurocognitive deficits. For example, females show greater cannabinoid receptor-1 (CB1) desensitization in several brain regions, including the prefrontal cortex and hippocampus (Burston, Wiley, Craig, Selley, & Sim-Selley, 2010)—regions especially involved in inhibitory control and episodic memory—suggesting they may be more sensitive than males to neural changes from consumption of cannabis. In addition, preclinical evidence indicates that females preferentially metabolize cannabis only to its most highly active metabolite, while males metabolize cannabis to multiple compounds, which may make females more vulnerable to the negative neural effects of cannabinoids than males (Narimatsu, Watanabe, Yamamoto, & Yoshimura, 1991). However, evidence of pharmacokinetic sex-differences in human studies is not currently well understood (Pigott, Walker, Teitelbaum, & Lu, 2009).

Despite some neuroimaging data suggesting cannabis-related sex-differences, with some evidence that female cannabis users may have larger right amygdala volumes (McQueeney et al., 2011) and prefrontal cortex volumes (Medina et al., 2009) compared to females controls, while male cannabis users had similar amygdalar volumes (McQueeney et al., 2011) and smaller prefrontal cortex volumes (Medina et al., 2009) compared to male controls; many studies to date report no interactions between cannabis use and non-using group status and sex (Pope, Jacobs, Miale, Yurgelun-Todd, & Gruber, 1997; Solowij et al., 2011; Tait, Mackinnon, & Christensen, 2011). Recently, Lisdlah and Price (2012) examined how amount of cannabis use may differentially affect neurocognition in male and female cannabis users. Although they found cannabis users had poorer immediate recall and interference inhibition than controls, sex did not moderate these relationships. However, they used only one temporal parameter of cannabis use (past year), one measure of inhibitory control, and had a fairly small sample size (n = 10 males, 13 females) that may have made it challenging to detect more subtle effects.

In this study, we examined how amount of cannabis use during different periods of time (i.e., lifetime, past year, and past month) may be differentially associated with measures of episodic memory and several aspects of inhibitory control in young adult cannabis users. We hypothesized that recent cannabis use (i.e., past month) will be associated with poorer immediate and delayed recall (but not recognition), while lifetime cannabis use will be associated with poorer decision-making and motor inhibition, and these relationships will be stronger in females. Given the multi-dimensional nature of inhibitory control, we also examined other measures including risk-taking and delay-discounting.

METHODS

Participants

Participants were cannabis users from the Chicago-metropolitan area recruited through word-of-mouth and informational fliers. All participants: (1) were 18–24 years old; (2) had education >8 years; (3) had estimated full-scale IQ >75; (4) had no diagnosis of a learning disability, developmental delay, mental illness (including Attention Deficit Hyperactivity Disorder; ADHD), or neurological condition; (5) had no significant birth complications; (6) had no loss of consciousness >10 min; (7) had no current use of psychotropic medication; (8) demonstrated English fluency; (9) had no significant recent alcohol use (AlcoMate Prestige Model AL6000; Palisades Park, NJ); (10) had no illicit drug use other than cannabis in the past 30 days or >10× in life for each drug class; (11) had no recent illicit drug use other than cannabis (10-panel Drug Check Cup; Express Diagnostics, Blue Earth, Minnesota); (12) used cannabis; >200 in life, >4× per week during peak use, and in the last 45 days; (13) had no cannabis use on testing day; and (14) identified cannabis as their drug of choice. The Institutional Review Board at the University of Illinois at Chicago approved the study and written informed consent was obtained. Additional details regarding the larger study, methods, and participants have been previously reported (Gonzalez et al., 2012).

Demographics, Potential Confounds, and Substance Use

Demographic information, including race/ethnicity, and family of origin information was obtained through an examiner-led questionnaire. The Wechsler Test of Adult Reading assessed premorbid full-scale IQ, current and lifetime substance use were diagnosed with the Structured Clinical Interview for DSM-IV, the Beck Depression Inventory-II and Beck Anxiety Inventory assessed depression and anxiety symptoms, the Barratt Impulsiveness Scale-11 evaluated trait impulsivity, and the Wender-Utah Rating Scale assessed ADHD (scores >46 indicates possible ADHD diagnosis). An examiner-led semi-structured interview collected participants’ amount and frequency of alcohol, nicotine, and illicit substance use during their lifetime, the past year, and the past month (Gonzalez et al., 2012).

Laboratory Measures of Neurocognitive Functioning

Verbal episodic memory

The Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998) norm-based, age corrected Z-scores for immediate recall (cumulative words recalled over three learning trials), delayed recall (total words recalled after a 20— to 25-min delay), and recognition discrimination (hits minus false positives) indexed verbal episodic memory.

Inhibitory Control

The Iowa Gambling Task (IGT) total net norm-based T-score (choices from advantageous decks minus disadvantageous
RESULTS

Demographics, Mental Health, Substance Use and Other Potential Confounds

As evident in Table 1, males and females reported minimal mental health complaints and did not differ on any potential confounds, with the exception that males drank more alcohol in the past 30 days than females.

Relationships between Amount of Cannabis Use, Sex, and Neurocognitive Performance

Neurocognitive performance did not statistically differ by gender, with the exception that females showed better motor inhibition than males (Table 1). It is important to note that in general, males and females demonstrated poorer performance on immediate and delayed recall compared to the normative sample (Table 1) and compared to a non-using control group in a prior analyses from the same parent study (Gonzalez et al., 2012), suggesting mild memory impairments in both groups. On the other hand, mean decision-making performance was not significantly poorer than the normative sample for male or female cannabis users. Measures for risk-taking, delayed discounting, and motor inhibition do not have published normative samples. Of note, cannabis users in this study did not significantly differ from non-using controls on their performance on any of the aforementioned inhibitory control tasks in our parent study (Gonzalez et al., 2012).

We found a significant negative relationship between amount of lifetime, past year, and past month cannabis use and immediate and delayed recall (but not recognition) on the HVLT-R, and decision-making performance on the IGT (Table 2). Cannabis use was not significantly associated with any other neurocognitive measure regardless of time frame (Table 2).

The interaction between lifetime cannabis use and sex trended toward significance on delayed recall and also on decision-making (Table 2). In addition, the interaction between past month cannabis use and sex trended toward significance on decision-making (Table 2).

Given our a priori hypotheses of potential sex-differences and multiple trends suggesting such, we performed follow-up exploratory analyses of the simple slopes for interaction terms that trended significance and for interactions where there was a main effect of amount of cannabis use in the model to better understand if neurocognitive measures related to cannabis use may have sex-specific patterns. All analyses used the same covariates as the reduced omnibus models (Table 2).

Immediate recall of both males or females was not associated with cannabis use in the past year (β = −.19, t(65) = −1.58, p = .12 and β = −.18, t(65) = −1.54, p = .13, respectively) or past month (β = −.21, t(65) = −1.76, p = .08 and β = −.15, t(65) = −1.22, p = .23, respectively). However, more lifetime cannabis use was associated with poorer immediate and delayed recall for both females (immediate: β = −.30, t(65) = −2.59, p = .01; delayed: β = −.41, t(65) = −3.81, p < .001) and males (immediate: β = −.23, t(65) = −2.01, p = .049; delayed: β = −.28, t(65) = −2.59, p = .01). On the other hand, more past year and past month cannabis use was associated with worse delayed recall for females (β = −.32, t(65) = −2.72, p = .008 and β = −.30, t(65) = −2.56, p = .01, respectively), but not for males (β = −.17, t(65)β = −1.50, p = .15 and β = −.20, t(65) = −1.73, p = .09, respectively). In contrast, poorer decision-making was associated with more lifetime (β = −.38, t(64) = −3.32, p = .001), past year (β = −.37, t(64) = −3.36, p = .001), and
Table 1. Participant characteristics

<table>
<thead>
<tr>
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<th>Male CU (n = 44)</th>
<th>Female CU (n = 25)</th>
<th>p-value</th>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age</td>
<td>20.75 ± 1.89 (18–24)</td>
<td>20.72 ± 1.62 (18–24)</td>
<td>.95</td>
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<tr>
<td>Estimated FSIQ</td>
<td>102.11 ± 10.24 (76–118)</td>
<td>102.80 ± 10.02 (82–120)</td>
<td>.79</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.34 ± 1.67 (10–16)</td>
<td>13.64 ± 1.68 (11–18)</td>
<td>.48</td>
</tr>
<tr>
<td><strong>Ethnicity/race</strong></td>
<td></td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>Caucasian</td>
<td>43%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>34%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td><strong>Annual household income in thousands of dollars [Md, IQR]</strong></td>
<td>26 [9, 61]</td>
<td>33 [7, 94]</td>
<td>.84</td>
</tr>
<tr>
<td><strong>Mental health</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-II Total Score [Md, IQR]</td>
<td>5 [2.25, 7.75]</td>
<td>5 [1.50, 10]</td>
<td>.81</td>
</tr>
<tr>
<td>BAI Total Score [Md, IQR]</td>
<td>4 [2, 9]</td>
<td>5 [3, 8]</td>
<td>.21</td>
</tr>
<tr>
<td>WURS, % of scores &gt;46 [IQR]</td>
<td>2% [15.25, 30]</td>
<td>8% [9.50, 18.50]</td>
<td>.27</td>
</tr>
<tr>
<td><strong>Substance Use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current (30 day) DSM-IV SUD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>11%</td>
<td>0%</td>
<td>.08</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>0%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Cannabis abuse</td>
<td>34%</td>
<td>28%</td>
<td>.60</td>
</tr>
<tr>
<td>Cannabis dependence</td>
<td>27%</td>
<td>28%</td>
<td>.95</td>
</tr>
<tr>
<td><strong>Lifetime DSM-IV SUD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>25%</td>
<td>16%</td>
<td>.38</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>2%</td>
<td>4%</td>
<td>.68</td>
</tr>
<tr>
<td>Cannabis abuse</td>
<td>41%</td>
<td>44%</td>
<td>.80</td>
</tr>
<tr>
<td>Cannabis dependence</td>
<td>34%</td>
<td>28%</td>
<td>.60</td>
</tr>
<tr>
<td><strong>Neuropsychological performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal Episodic Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVLT Immediate Recall (z score)</td>
<td>−0.81 ± 1.23 (−3.62–1.51)</td>
<td>−0.77 ± 1.45 (−3.89–1.24)</td>
<td>.90</td>
</tr>
<tr>
<td>HVLT Delayed Recall (z score)</td>
<td>−0.83 ± 1.32 (−4.13–0.88)</td>
<td>−0.90 ± 1.26 (−2.88–0.88)</td>
<td>.83</td>
</tr>
<tr>
<td>HVLT Recognition Discrimination (z score)</td>
<td>0.01 ± 0.82 (−2.83–0.5)</td>
<td>0.03 ± 0.95 (−2.86–0.5)</td>
<td>.95</td>
</tr>
<tr>
<td><strong>Inhibitory Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT Net Total (T score)</td>
<td>45.59 ± 9.50 (26–63)</td>
<td>45.60 ± 10.26 (22–65)</td>
<td>1.00</td>
</tr>
<tr>
<td>BART (Mean Adjusted Pumps)</td>
<td>30.51 ± 12.28 (2.86–58.19)</td>
<td>31.16 ± 13.61 (6.54–56.17)</td>
<td>.84</td>
</tr>
<tr>
<td>MCQ (log-transformed k)</td>
<td>−1.50 ± 0.47 (−2.64–0.67)</td>
<td>−1.41 ± 0.53 (−2.87–0.80)</td>
<td>.49</td>
</tr>
<tr>
<td>Go/Stop (Inhibitions-Misses)</td>
<td>−37.39 ± 21.34 (−78–31)</td>
<td>−26.52 ± 15.08 (−61–5)</td>
<td>.03*</td>
</tr>
</tbody>
</table>

Note: All values are means, standard deviations, or ranges, unless otherwise noted. CU = cannabis users; Md = Median; IQR = interquartile range; FSIQ = Full Scale IQ; BDI-2 = Beck Depression Inventory-2nd Edition; BAI = Beck Anxiety Inventory; WURS = Wender-Utah Rating Scale; BIS = Barratt Impulsiveness Scale-11th version; DSM-IV SUD = Diagnostic and Statistical Manual IV substance use disorders; THC+ = positive rapid urine toxicology testing. *p < .05.
past month ($\beta = -0.10$, $t(65) = -0.85$, $p = .40$).

**DISCUSSION**

In this study, we examined relationships between amount of cannabis use and neurocognitive functioning on indices of episodic memory and inhibitory control among a non-treatment-seeking, community-dwelling sample of young adult regular cannabis users who had minimal mental health problems or other drug use. We replicated prior findings of poorer episodic memory and decision-making with more cannabis use (Bolla et al., 2002; Cunha et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Wagner et al., 2010), indicating decision-making is more strongly associated with cannabis use than other inhibitory control measures. Indeed, we previously found decision-making performance, but not performance on other inhibitory control measures, was associated with more symptoms of cannabis addiction (Gonzalez et al., 2012). Although significant sex by cannabis use interactions were not observed, several trends toward significant interactions point to potential sex-differences in relationships between cannabis use and neurocognitive functioning. Indeed, a more complex pattern of results emerged when examining exploratory relationships among cannabis use parameters and neurocognition for males and females.

When taken together, follow-up exploratory analyses found amount of cannabis use was more consistently associated with poorer episodic memory performance in females than males. Conversely, more cannabis use was associated with poorer decision-making performance for males, but not females. Cannabis use may disrupt estrogen-related dendritic spine maturation in the hippocampus, especially in females (Gillies & McArthur, 2010), while males’ protracted neurodevelopment and earlier initiation of use compared to females
may make them more vulnerable to cannabis-related disruptions in neuromaturation in the orbitofrontal cortex (Crane et al., 2013).

The time frame of cannabis use also had some bearing on the pattern of findings. Immediate recall was only associated with cumulative lifetime use, suggesting it is more influenced by cumulative burden than recent use. On the other hand, poorer delayed recall of females and decision-making performance for males were associated with more cannabis use across all time frames, indicating that more recent use, in addition to cumulative lifetime burden, is relevant to performance.

It is important to keep in mind that, in general, male and female cannabis users in this study demonstrated deficits in episodic memory, especially immediate and delayed recall, but not in decision-making, compared to their non-using counterparts recruited for the parent project (Gonzalez et al., 2012). Of note, there were no group differences, sex-differences, or interaction effects of group and sex between cannabis users in this sample and their non-using counterparts on decision-making, risk-taking, and delayed discounting in the parent project (Gonzalez et al., 2012). When compared to normative data, male and female cannabis users in this study scored in the low average range of abilities, yet a sizable proportion evidenced at least mild impairments in episodic memory (Table 1; Z-scores \( \leq 1.0 \) were observed on immediate recall for 45% of male cannabis users and 32% of female cannabis users and on delayed recall for 45% of males and 56% of females). Overall, participants’ decision-making was not impaired when compared to the normative sample (Table 1; but 30% of males and 20% of females scored in the mildly impaired range or worse (T-score \( \leq 40 \)). This is important because, despite mild overall episodic memory impairment and no overall decision-making impairment in our sample, we still found evidence for important relationships in how cannabis use may differentially impact these domains in a sex-specific manner. It is possible that our findings of poorer episodic memory among cannabis users is due in part to the residual (or semi-acute) effects of cannabis, as many of the participants in this study still tested positive for THC (Table 1), and similar to what other studies have found, participants performance may improve over time with abstinence (Hanson et al., 2010). Due to the fact that these young cannabis users are in their early stages of cannabis use, it is also possible that continued cannabis use may result in the emergence of clinically significant impairments in these domains.

In summary, our study expands on previously reported associations between more cannabis use and poorer episodic memory and decision-making, using a non–treatment-seeking community sample of young adult current cannabis users with minimal mental health problems and use of other substances. Patterns of results across various time frames suggested dissociations between males and females. Although we speculate on potential mechanisms for the observed relationships, our study is limited by its cross-sectional design and requires replication in a larger sample. A limitation of the study is that our sample consists only of young adult cannabis users who began their cannabis use between the ages of 11 and 21, with a mean age of 16. Given evidence of more negative neurocognitive consequences with an earlier onset of use (see Crane et al., 2013), our findings may not be generalizable to individuals who begin cannabis use at a later age or to older cannabis users. In addition, participants earned hypothetical rewards and losses, as opposed to real rewards and losses, on measures of decision-making, risk-taking, and delayed discounting, which may have influenced participant motivation; however, this remains a controversial issue (e.g., Bornova et al., 2009; Johnson & Bickel, 2002). Furthermore, family history of substance use was not measured, a factor that may have influenced the results. Ongoing and future studies will use longitudinal designs to better explore mechanisms for the observed patterns of results, including the possible role of sex hormones. The current study provides further evidence for residual cannabis-associated neurocognitive deficits and underscores the importance of examining the impact of cannabis on neurocognition separately for males and females. Sex-differences in the neurocognitive effects of cannabis may mean different functional consequences from use and have implications for intervention efforts.

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REFERENCES


Cognition, sex-differences, and cannabis


