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# Reflection impulsivity in adolescent cannabis users: a comparison with alcohol-using and non- substance-using adolescents

Nadia Solowij

*University of Wollongong, nadia@uow.edu.au*

Katy A. Jones

*University of Wollongong, katy@uow.edu.au*

Megan E. Rozman

*University of Wollongong*

Sasha M. Davis

*University of Wollongong*

Joseph Ciarrochi

*University of Wollongong, joec@uow.edu.au*

*See next page for additional authors*

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# Reflection impulsivity in adolescent cannabis users: a comparison with alcohol-using and non-substance-using adolescents

## **Abstract**

**Rationale** Reflection impulsivity—a failure to gather and evaluate information before making a decision—is a critical component of risk-taking and substance use behaviours, which are highly prevalent during adolescence. **Objectives and methods** The Information Sampling Test was used to assess reflection impulsivity in 175 adolescents (mean age 18.3, range 16.5–20; 55% female)—48 cannabis users (2.3 years use, 10.8 days/month), 65 alcohol users, and 62 non-substance-using controls—recruited from a longitudinal cohort and from the general community and matched for education and IQ. Cannabis and alcohol users were matched on levels of alcohol consumption. **Results** Cannabis users sampled to the lowest degree of certainty before making a decision on the task. Group differences remained significant after controlling for relevant substance use and clinical confounds (e.g., anxiety, depressive symptoms, alcohol, and ecstasy use). Poor performance on multiple IST indices was associated with an earlier age of onset of regular cannabis use and greater duration of exposure to cannabis, after controlling for recent use. Alcohol users did not differ from controls on any IST measure. **Conclusions** Exposure to cannabis during adolescence is associated with increased risky and impulsive decision making, with users adopting strategies with higher levels of uncertainty and inefficient utilisation of information. The young cannabis users did show sensitivity to losses, suggesting that greater impulsivity early in their drug using career is more evident when there is a lack of negative consequences. This provides a window of opportunity for intervention before the onset of cannabis dependence.

## **Keywords**

users, comparison, alcohol, non, substance, adolescents, reflection, impulsivity, adolescent, cannabis

## **Disciplines**

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## **Authors**

Nadia Solowij, Katy A. Jones, Megan E. Rozman, Sasha M. Davis, Joseph Ciarrochi, Patrick C. L Heaven, Nicole Pesa, Dan I. Lubman, and Murat Yucel

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**Reflection impulsivity in adolescent cannabis users: A comparison with alcohol-using and non-substance-using adolescents**

Running title: Reflection impulsivity in adolescent cannabis users

Nadia Solowij<sup>1,2</sup>, Katy A. Jones<sup>1,3</sup>, Megan E. Rozman<sup>1</sup>, Sasha M. Davis<sup>1</sup>, Joseph Ciarrochi<sup>1</sup>, Patrick C.L. Heaven<sup>1</sup>, Nicole Pesa<sup>1</sup>, Dan I. Lubman<sup>3</sup>, Murat Yücel<sup>4</sup>

<sup>1</sup> School of Psychology, University of Wollongong, Wollongong, NSW, 2522, Australia

<sup>2</sup> Schizophrenia Research Institute, Sydney, NSW, 2010, Australia

<sup>3</sup> Turning Point Alcohol and Drug Centre, Eastern Health and Monash University, Melbourne, Australia

<sup>4</sup> Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, VIC, 3053, Australia

Corresponding Author:

Dr Nadia Solowij

School of Psychology, University of Wollongong, NSW, 2522 Australia

Phone: +61 2 4221 3732; Fax: +61 2 4221 4163; E-mail: [nadia@uow.edu.au](mailto:nadia@uow.edu.au)

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**Abstract**

*Rationale* Reflection impulsivity – a failure to gather and evaluate information before making a decision – is a critical component of risk-taking and substance use behaviours, which are highly prevalent during adolescence.

*Objectives and Methods* The Information Sampling Test was used to assess reflection impulsivity in 175 adolescents (mean age 18.3, range 16.5-20; 55% female) – 48 cannabis users (2.3 years use, 10.8 days/month), 65 alcohol users and 62 non-substance-using controls – recruited from a longitudinal cohort and from the general community and matched for education and IQ. Cannabis and alcohol users were matched on levels of alcohol consumption.

*Results* Cannabis users sampled to the lowest degree of certainty before making a decision on the task. Group differences remained significant after controlling for relevant substance use and clinical confounds (e.g., anxiety, depressive symptoms, alcohol and ecstasy use). Poor performance on multiple IST indices was associated with an earlier age of onset of regular cannabis use and greater duration of exposure to cannabis, after controlling for recent use. Alcohol users did not differ from controls on any IST measure.

*Conclusions* Exposure to cannabis during adolescence is associated with increased risky and impulsive decision making, with users adopting strategies with higher levels of uncertainty and inefficient utilisation of information. The young cannabis users did show sensitivity to losses, suggesting that greater impulsivity early in their drug using career is more evident when there is a lack of negative consequences. This provides a window of opportunity for intervention before the onset of cannabis dependence.

**Keywords:** Cannabis; Alcohol; Adolescence; Reflection impulsivity; Decision making

## Introduction

Impulsivity, risky decision making and deficits in inhibitory control are thought to underlie addictive behaviours (Goldstein and Volkow 2002; Jentsch and Taylor 1999; Yücel et al. 2007) and play a critical role in the maintenance and relapse to substance use (Garavan and Stout 2005). Adult long-term cannabis users have been shown to exhibit deficits in various inhibitory processing measures (e.g., Stroop, Go/NoGo) (Battisti et al. 2010; Bolla et al. 2002; Bolla et al. 2005; Eldreth et al. 2004; Gruber and Yurgelun-Todd 2005; Hester et al. 2009; Novaes et al. 2008; Solowij et al. 2002; Tapert et al. 2007). Poorer performance has been associated with parameters of cannabis use such as duration, dosage and age of onset of use (Battisti et al. 2010; Bolla et al. 2002; Novaes et al. 2008; Solowij et al. 2002). Typically, users show impairment in the ability to self-monitor behaviour, having low error awareness (Hester et al. 2009) and increased error rates (Battisti et al. 2010). In some studies where users have shown comparable performance to controls, this has been accompanied by altered electrophysiology or increased activation of brain regions indicating that users may require increased neural effort in order to maintain adequate performance levels (Battisti et al. 2010; Hester et al. 2009; Tapert et al. 2007).

Cannabis-related deficits have been identified in a small number of studies that used tasks specifically designed to measure risky or impulsive decision making, such as the Matching Familiar Figures Task (MFFT) (Kagan 1966) or the Iowa Gambling Task (IGT; Bechara et al. 1994) (e.g., Fridberg et al. 2010; Hermann et al. 2009; Lamers et al. 2006; Wesley et al. 2011; Whitlow et al. 2004). Whitlow et al. (2004) found that long-term heavy cannabis users made decisions that led to greater immediate gains but with more costly losses than non-user controls. They suggested

that the imbalance between perceived rewards and punishments may contribute to ongoing drug use. Fridberg et al. (2010) enlarged the small sample of Whitlow et al. (2004) and applied mathematical modeling to the data to show that cannabis users' choices were characterized by greater sensitivity to gains, insensitivity to losses, greater dependence upon recent outcomes, and less consistency with expected payoffs. Differences between cannabis users and controls in motivational, learning and memory, and behavioural control processes were thought to underlie their characteristic performance on the IGT. In a recent imaging study, Wesley et al. (2011) showed less activation in cannabis users relative to controls in regions subserving complex decision making and a lack of correlation between performance over time and functional response to losses, indicative of insensitivity to feedback during strategy development in the users.

Impulsivity is a multi-factored concept comprising attentional, predecisional reflection and disinhibition dimensions (Dickman 1993), and includes both motor and cognitive factors (Evenden 1999a). The high demands on visual search, working memory and strategy use of tasks such as the MFFT and the IGT may not be capturing information specific to impulsive or risky decision making in cannabis users, since the former processes are also known to be impaired in cannabis users (Ilan et al. 2004; Jager et al. 2006; Kanayama et al. 2004; Solowij and Battisti 2008). The cognitive construct of reflection impulsivity specifically refers to the tendency to gather and evaluate information prior to decision making (Kagan 1966), which contrasts with 'the tendency to make an impulsive selection of a solution' (Kagan 1965, p.609). The Information Sampling Task (IST) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) was designed to specifically measure reflection impulsivity and decision making (Clark et al. 2009), being deemed

to be a purer measure than previous such tasks (e.g., the MFFT or the IGT). Rather than relying on speed-accuracy indices, the IST measures reflection impulsivity by calculating the probability of the subject selecting the correct answer at the point of decision on the basis of their sampling of information prior to making that decision, and the IST has a low working memory load.

Clark et al. (2009) were the first to examine reflection impulsivity by means of the IST in current and former ecstasy users compared to young adult cannabis users with no lifetime use of ecstasy and to non-drug-using controls. Despite the fact that the primary aim of their study was to examine impulsivity in regular ecstasy users (n=46), they found that the considerably smaller group of current cannabis users (n=15) but not ecstasy users were impaired. The cannabis users sampled significantly less information on the task and tolerated a lower level of certainty in their decision making than did controls, while current and former ecstasy users did not differ from controls. In an earlier study, Clark et al. (2006) reported that current amphetamine and opiate users also sampled less information than controls and had a lower probability of making a correct response on the task. Around half of the drug users in the study were also using cannabis. As such, the IST may be particularly sensitive to the effects of cannabis on information sampling and impulsive decision making.

No studies to date have examined reflection impulsivity in adolescent cannabis users. Risky decision making and impulsivity are also characteristic of adolescence; adolescents show the capability to reflect on risky decisions but often choose not to, and this may underlie substance use and other risky behaviours (Steinberg 2007). Adolescence is the primary period for experimentation and subsequent initiation of regular cannabis use in particular (Copeland and Swift 2009; Jacobus et al. 2009). There are concerns from both human and preclinical research that the adolescent brain

may be especially vulnerable to the adverse effects of exposure to cannabis (Cha et al. 2006; Lubman et al. 2007; Schepis et al. 2008; Schneider 2008; Yücel et al. 2007). A growing literature has reported a range of cognitive deficits in adolescent cannabis users and greater adverse effects the earlier that cannabis use commences, particularly before the age of 17 years (Ehrenreich et al. 1999; Harvey et al. 2007; Huestegge et al. 2002; Jacobsen et al. 2004; Jacobsen et al. 2007; Jacobus et al. 2009; Kempel et al. 2003; Medina et al. 2007; Pope et al. 2003; Schwartz et al. 1989; Solowij and Battisti 2008; Solowij et al. 2011).

In this study, we examined the IST performance of adolescent cannabis users in relation to parameters of cannabis use such as quantity, frequency, duration and age of onset of use. Since adolescent cannabis users often also drink alcohol (Copeland and Swift 2009), and tend to consume more alcohol than non-users (Chun et al. 2010), we also sought to determine the specificity of effects by comparing the cannabis group with an adolescent alcohol user group matched on monthly alcohol use, as well as with a non-user control group. Finally, we had the opportunity to control for premorbid intellectual ability (obtained at entry to high school) and to examine its potential influence on reflection impulsivity and risky decision making.

## **Methods**

### *Subjects*

A total of 175 adolescent participants (mean age 18.3, SD=0.63) were recruited for this study, comprising 48 cannabis users, 65 alcohol users and 62 controls. The majority of participants were recruited from the Wollongong Youth Study (WYS) – a longitudinal study of adolescents followed since entry to six metropolitan and



regional high schools in the wider southern Sydney region of Australia (Heaven and Ciarrochi 2008). Due to the small sample size of cannabis users recruited from this source ( $n=12$ ), a newspaper advertisement was used to recruit an additional 36 adolescent cannabis users to the study from the same demographic catchment as the WYS participants. Externally recruited participants were matched on age, IQ and premorbid intellectual ability to the WYS sample. They did not differ from the WYS cannabis or alcohol users on monthly alcohol consumption and a range of psychological factors as described below, but they were more entrenched in their cannabis use (greater frequency ( $p<0.001$ ) and quantity ( $p<0.001$ ) of cannabis use per month). Full details of the sample are provided in Solowij et al. (2011).

The study was fully approved by the University of Wollongong and South East Sydney and Illawarra Area Health Service Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent and were reimbursed AU\$50 for their time and travel expenses.

#### *Measures of psychological functioning and intellectual ability*

Subjects were screened for potential psychological disorders using the Kessler Psychological Distress Scale K10 (Kessler et al. 2002) and structured interview assessed psychiatric, medical and neurological history. Participants were excluded for any current psychiatric disorders, if they were currently in treatment for substance dependence, and if they had any history of head injury or serious medical conditions.

Participants completed the State-Trait Anxiety Inventory (STAI; Spielberger 1989), the Beck Depression Inventory (BDI; Beck et al. 1996) and the Apathy Evaluation Scale (AES; Marin et al. 1991) as measures of psychological well-being or

symptoms. All participants completed the short form of the Wechsler Abbreviated Scale of Intelligence (WASI) to obtain a measure of current IQ. Measures of premorbid intellectual ability were available for the majority of the sample (66.3%: 24 cannabis users, 47 alcohol users, 45 controls) from standardised verbal and numerical ability tests administered by the Department of Education to all students during their first year of high school (at approximately age 12).

#### *Substance use characteristics of the sample*

Current and past substance use was assessed by structured interview that incorporated the Alcohol Use Disorders Identification Test (AUDIT; Allen et al. 1997) and a TimeLine Follow Back procedure (TLFB; Sobell and Sobell 1992). Average frequency and quantity of cannabis and alcohol consumed per month were calculated from across these measures. TLFB data informed of any other drug use in the past 30 days. Cannabis users were also administered the Marijuana Withdrawal Checklist (MWC; adapted from Budney et al. 1999 and Vandrey et al. 2005) and the Severity of Dependence Scale (SDS; Swift et al. 1998) for cannabis.

Cannabis and alcohol users were required to have used cannabis or alcohol at least twice/month for 6-12 months. The majority were regular users (Table 2) but several participants were included in their respective samples despite a briefer period of exposure to either substance if use in recent months had been particularly frequent or heavy, or if they had less frequent use that had nevertheless been ongoing for >18 months. This policy was applied to be inclusive as possible for participants with available data and since such users would not qualify as non-user controls. Similarly, participants were included in the control group if they reported 'regular' alcohol use that was less than twice/month and may have engaged in such low level drinking for

more than 12 months (or if they drank at least twice/month but had only commenced doing so in the past 2 months, in which case they would not qualify for the alcohol user group). Some participants in the alcohol and control groups had tried cannabis in their lifetime (29.2% of alcohol users and 8.1% of controls; maximum five occasions).

All participants were asked not to consume cannabis, alcohol or any other illicit substances for at least 12 hours before testing and self-reported abstinence was supported by breath analysis (zero alcohol readings for the entire sample), urinalysis (for all illicit drugs) and saliva testing for delta-9-tetrahydrocannabinol (THC) using gas chromatography-mass spectrometry (Cozart Bioscience Ltd 2001-2009). Cannabis users reported a median 22.5 hours abstinence from cannabis. The median carboxy-THC metabolite in urine for the cannabis using sample was 84ug/L [0-4335]. No cannabinoid metabolites were detected in controls or alcohol users. The median THC level in saliva in cannabis users was 0ng/ml [0-7.2]. THC may remain in the oral cavity for 24 hours or more after smoking with levels generally falling below 1ng/ml 12-24 hours after smoking (Huestis and Cone 2004; Niedbala et al. 2001) but with much individual variability. Salivary THC levels were below 1ng/ml in the vast majority of the current sample (82.6%; 54.3% had zero levels) and strong correlations between salivary THC or urinary cannabinoid levels and self-reported hours since last use (Spearman's  $\rho=-0.55$ ,  $p<0.001$  and  $\rho=-0.70$ ,  $p<0.001$ , respectively) provide good corroboration with self-reported abstinence from cannabis prior to testing.

### *The Information Sampling Task (IST)*

Participants first completed a single practice trial, followed by 10 trials in each of the two conditions of the IST. On each trial they were presented with a 5 x 5

matrix of grey boxes with two larger coloured panels at the foot of the screen. Touching a grey box would immediately open that box to reveal one of the two colours displayed at the bottom of the screen. Subjects were able to open boxes at their own rate with no time limit before deciding which of the two colours was in the majority of the 25 boxes. According to manualised instructions and procedures described in Clark et al. (2006), they were told ‘it is entirely up to you how many boxes you open before making your decision’ and they indicated their decision by touching one of the two panels at the bottom of the screen. At this point the remaining boxes were uncovered and one of two messages was presented: “Correct! You have won [x] points” or “Wrong! You have lost 100 points”. In the ‘fixed win’ condition subjects could open any number of boxes to potentially gain 100 points and not lose any points. In the ‘decreasing win’ condition, subjects lost 10 points for every box that they opened. There was a variable delay of at least 1 second before the onset of the next trial.

The primary performance outcome measures were the mean number of boxes opened per trial, the mean probability of being correct at the point of decision:  $P(\text{Correct})$ , and discrimination and sampling errors.  $P(\text{Correct})$  was the probability that the colour chosen by the subject at the point of decision would be correct, based only on the evidence available to the subject at the time (i.e., dependent on the amount of information they had sampled). Discrimination errors occurred when the participant chose a colour that was not at that point in time in the majority, thus making a decision not logically based on the evidence available to them. Sampling errors were the number of trials where the subject chose a colour that was not in the overall majority but was in the majority at the point of decision. Mean box opening latency was also measured (the time elapsed between the subject opening a box and

then opening the subsequent box), as was mean colour decision latency (the time elapsed between the start of a trial and the point at which the subject selects a colour that they believe to be in the overall majority).

### *Statistical Analysis*

Data were analysed using SPSS version 16 using repeated measures (condition: Fixed vs Decreasing win x group) analysis of variance (rmANOVA) with follow up Tukey tests for group comparison on normally distributed variables. Analysis of covariance (ANCOVA) was then conducted for normally distributed variables. For variables that violated the Shapiro-Wilk test of normality, non-parametric Mann-Whitney and Kruskal-Wallis follow up tests were employed examining fixed and decreasing win conditions separately. Pearson correlations were performed for normally distributed variables and Spearman correlations for skewed variables to examine relationships between performance and substance use and clinical variables.

## **Results**

### *Demographics and Patterns of Substance Use*

Demographic and clinical characteristics of the sample are shown in Table 1. The three groups did not differ in current full scale IQ ( $F(2,174)=0.07, p=0.93$ ) or premorbid verbal ( $F(2,116)=1.46, p=0.24$ ) or numerical ability ( $F(2,115)=2.58, p=0.08$ ). While the groups differed significantly in age ( $F(2,174)=11.47, p<0.001$ ), this was due to the precision with which we measured age (in portions of months). The mean age at assessment in each group was 18 years (Table 1) and, while minor variation in portions of months would not be expected to influence performance

outcome measures, we nevertheless included age as a covariate in our between-group analyses. The gender ratio differed between groups ( $\chi^2(2)=10.24$ ,  $p=0.006$ ) with females overrepresented in the control group. Group differences were observed on apathy scores ( $\chi^2(2)=14.80$ ,  $p=0.001$ ; cannabis users > alcohol users and controls), depressive symptoms ( $\chi^2(2)=10.43$ ,  $p=0.005$ ; cannabis users > controls) and state anxiety ( $\chi^2(2)=10.24$ ,  $p=0.006$ ; controls < cannabis users and alcohol users), but not trait anxiety ( $p=0.08$ ). Variables on which groups differed were included as covariates in the analyses.

Table 2 shows the substance use characteristics of the sample. The cannabis users first tried cannabis around age 15, with regular use commencing around age 16.5. They had used cannabis regularly for a mean 2.3 years and were currently using approximately 10 days per month. After self-reported abstinence from cannabis for a median 22.5 h, the cannabis users reported a median score of 5 on the withdrawal scale from a possible 45-point maximum, indicating that withdrawal symptoms were of minor concern to participants during testing. The median score on the SDS suggests that this young sample were not yet dependent on cannabis. Cannabis users did not differ from alcohol users in frequency or quantity of alcohol consumed per month, but cannabis users had started drinking at an earlier age and had higher AUDIT scores. Cannabis users smoked more tobacco cigarettes per day than either other group and alcohol users also smoked more than controls. Cannabis users had used other illicit substances on more occasions than any other group but had never used these on a regular basis. Thirteen cannabis users (27%) had used ecstasy in the past 30 days (0-3 pills consumed). One alcohol user had consumed two ecstasy tablets in the past 30 days. Other recent drug use in the cannabis group was modest with 2 having used amphetamines, 1 having used cocaine and 2 having consumed

hallucinogenic mushrooms in the past 30 days. Cannabis users with and without recent other drug use were compared on their IST performance.

Tables 1 and 2 about here

*IST Performance: P(Correct) and Number of Boxes Opened*

Analyses revealed a significant main effect of group for the probability of being correct at the point of decision ( $F(2,172)=6.02, p=0.003$ ) and for the number of boxes opened per trial ( $F(2,172)=4.32, p=0.015$ ), with cannabis users having a significantly lower  $P(\text{Correct})$  score than both alcohol users ( $p=0.008$ ) and controls ( $p=0.006$ ), while the latter groups did not differ ( $p=0.99$ ). Cannabis users opened fewer boxes than alcohol users ( $p=0.012$ ) but not controls ( $p=0.11$ ), and the latter groups did not differ ( $p=0.63$ ). Table 3 shows  $P(\text{Correct})$  and number of boxes opened for both fixed and decreasing win conditions. In the fixed win condition, cannabis users sampled information to a point of 79% certainty while alcohol users and controls sampled to a point of 85% certainty. This reduced for all groups in the decreasing win condition, with cannabis users sampling to a point of 68% certainty and alcohol users and controls 71% and 72%, respectively. While there was a significant main effect of condition ( $F(1,172)=302.77, p<0.001$ ), there was no significant condition by group interaction ( $p=0.24$ ), with similar results for the number of boxes opened (main effect of condition: ( $F(1,172)= 354.08, p<0.001$ ); condition by group interaction:  $p=0.57$ ).

Figure 1 and Table 3 about here

We next used covariate analyses to control for variables that differed between groups. The main effect of group remained significant for  $P(\text{Correct})$  after controlling for gender ( $F(2,171)=5.72, p=0.004$ ), age ( $F(2,171)=7.07, p=0.001$ ), AUDIT score

( $F(2,170)=6.06, p=0.003$ ), hours since last consumption of alcohol ( $F(2,159)=4.90, p=0.009$ ), age of first alcohol use ( $F(2,163)=5.02, p=0.008$ ), cigarettes smoked per day ( $F(2,165)=3.31, p=0.03$ ), apathy ( $F(2,171)=4.48, p=0.013$ ), depressive symptoms ( $F(2,171)=5.23, p=0.006$ ) and state anxiety ( $F(2,169)=7.28, p=0.001$ ). With all covariates in the model the main effect of group was  $F(2,146)=4.97, p=0.008$ , and apathy was the only significant covariate in the model ( $p=0.012$ ). Including age of onset of regular alcohol use as a covariate however, reduced the significance of the overall group difference for  $P(\text{Correct})$  ( $F(2,143)=2.98, p=0.054$ ). The ages of onset of regular use of cannabis and of alcohol were highly correlated (Spearman's  $\rho=0.49, p<0.001$ ) and we show below that the effects observed on performance were associated with cannabis use and not with alcohol use. The same pattern of results was evident for the number of boxes opened when the above covariates were included in the model.

#### *IST Performance: Errors*

Table 3 shows that cannabis users' task accuracy was impaired specifically in the fixed win condition, with more discrimination errors ( $\chi^2(2)=9.39, p=0.009$ ) than alcohol users ( $Z=2.04, p<0.05$ ) and controls ( $Z=3.04, p<0.01$ ). There were trends toward cannabis users making more discrimination errors in the decreasing win condition also ( $p=0.09$ ), and toward more sampling errors in the fixed win condition ( $p=0.09$ ).

#### *IST Performance: Latency measures*

As shown in Table 3, there were no significant differences between the three groups for mean box opening latency in either condition. Colour decision latency was



significantly different between the groups in the fixed condition only ( $\chi^2(2)=6.06$ ,  $p=0.048$ ), with cannabis users making faster colour decisions than both controls ( $Z=2.31$ ,  $p<0.05$ ) and alcohol users ( $Z=2.02$ ,  $p<0.05$ ).

#### *IST Performance Associations with Cannabis Use and Psychological Measures*

Correlations between primary substance use measures and IST performance measures are shown in Table 4. The majority of associations between IST performance and cannabis use measures were found for age of onset and duration of cannabis use in the fixed win condition. Earlier onset of first or regular use of cannabis was associated with lower  $P(\text{Correct})$ , fewer boxes opened, and more sampling errors in the fixed win condition. An earlier age of onset of regular use was also associated with more discrimination errors and longer box opening latency in the fixed win condition. A longer duration of regular use of cannabis was associated with lower  $P(\text{Correct})$  scores, fewer boxes opened, more sampling errors, more discrimination errors and longer box opening latency in the fixed condition alone.

Table 4 about here

Greater frequency cannabis use was also associated with a lower probability of being correct at point of decision  $P(\text{Correct})$  in the fixed condition alone, and greater frequency and quantity of cannabis use per month were positively correlated with discrimination errors in both fixed and decreasing win conditions. Therefore, the more frequent and heavy the cannabis use, the more likely the subject was to choose a colour that was not in the majority at point of decision. Greater quantity cannabis use was also significantly correlated with a longer box opening latency in the fixed condition. Salivary THC levels correlated with only one IST measure: discrimination errors in the fixed win condition, which also correlated with self-reported hours since

last use, and the only other measure to correlate with self-reported hours since last use was the mean colour decision latency in the decreasing win condition ( $\rho=-0.49$ ,  $p=0.005$ ). Urinary cannabinoid metabolite levels correlated inversely with  $P(\text{correct})$ , and positively with discrimination errors and box opening latency, all in the fixed win condition, and additionally with discrimination errors in the decreasing win condition. These results suggest that recent cannabis use and residues may also exert an influence on reflection impulsivity and decision making.

No IST measures were associated with cannabis dependence or withdrawal scores, depressive symptom scores, state or trait anxiety, apathy or AUDIT scores (all  $p>.05$ ). Current frequency or quantity of alcohol consumption were also not associated with any of the IST measures. However, a later age of onset of first (but not regular) alcohol use in the cannabis group was associated with a greater number of boxes opened in the fixed win condition and fewer sampling errors in the decreasing win condition. Age of onset of regular alcohol use in the cannabis group was not associated with any IST performance measures.

#### *Partial Correlations between various Cannabis Measures*

Partial correlations were performed between various cannabis use measures to determine their relative effects on IST performance, concentrating on the primary outcome measure of  $P(\text{Correct})$ . As shown in Table 5, the association between  $P(\text{Correct})$  and age of onset of cannabis use and duration of cannabis use remained significant after controlling for measures of recent cannabis use (self-reported hours since last use, salivary and urinary cannabinoids). This suggests a greater influence on performance of longer duration cannabis use commencing at an early age, rather than residual effects of recent cannabis use. There were no significant associations

between hours since last use, salivary or urinary cannabinoids and  $P(\text{Correct})$  after controlling for age of onset and duration of cannabis use. Further, a specific effect of early onset and long duration cannabis use over and above recent use was determined by showing that their association with  $P(\text{Correct})$  remained after controlling for current levels of exposure to cannabis (quantity and frequency per month), but not the reverse (i.e., no associations between current quantity and frequency of cannabis use remained with  $P(\text{Correct})$  after controlling for age of onset and duration of use).

Table 5 about here

#### *Recent Other Drug Use*

Within the cannabis group, 27% of participants had used ecstasy in the past 30 days, as had one of the alcohol users. The number of pills consumed in the past 30 days was used as a covariate in the analysis. The main effect of group for  $P(\text{Correct})$  ( $F(2,171)=6.94, p=0.001$ ) and for number of boxes opened ( $F(2,171)=5.49, p=0.005$ ) remained significant with the poorest performance in cannabis users compared to both alcohol users ( $p<0.01$ ) and controls ( $p<0.05$ ), after controlling for ecstasy use.

Cannabis users who had consumed other drugs (including ecstasy, amphetamine, cocaine and hallucinogenic mushrooms) in the past 30 days ( $n=13$ ) were then compared to those cannabis users who had not used any other drugs aside from cannabis and alcohol in the past 30 days ( $n=35$ ). There were no differences between the two groups for  $P(\text{Correct})$  ( $F(1,46)=0.48, p=0.49$ ) or number of boxes opened ( $F(1,46)=0.002, p=0.96$ ), and no differences between groups on any other IST measure (all  $p>0.28$ ). Therefore, other recent drug use did not affect IST performance within the cannabis group, suggesting impaired performance specific to cannabis use.

## **Discussion**

The results of this study demonstrate impairment in the ability to gather and evaluate information prior to decision making in a sample of adolescent cannabis users. These young cannabis users were impaired on most IST performance outcome measures and our findings suggest greater impairment following early initiation and prolonged exposure to cannabis use *over and above* recent exposure. We demonstrated a specific association with cannabis rather than alcohol or other concomitant drug use.

The adolescent cannabis users sampled to a lower probability of certainty, made faster (more impulsive) decisions, and made more discrimination errors. The majority of these deficits remained significant after controlling for recent ecstasy use, alcohol-related problems, tobacco use, apathy and psychological symptoms (depression and state anxiety), and age and gender differences between groups. These findings suggest poor reflection and decision making at a lower level of certainty in adolescent cannabis users relative to adolescent alcohol users and non-substance-using controls.

The majority of IST performance outcome measures worsened with an earlier age of onset of cannabis use and longer duration of use. The earlier that these young users initiated regular cannabis use and the longer the term of their exposure, the more likely they were to open fewer boxes, have faster box opening latencies, and have a lower probability of being correct at the point of decision. Greater sampling and discrimination errors were also associated with an earlier age of onset of use and longer exposure to cannabis. This was particularly evident in the fixed win condition.

Greater frequency and quantity of cannabis use per month were associated with more discrimination errors, and frequency was also associated with lower  $P(\text{correct})$ . Thus, current frequent and heavy use of cannabis led to decision making that was not

logically based on the evidence available. This might suggest that impaired decision making is related to current use of cannabis, but partial correlational analyses revealed a specific effect of earlier age of onset and duration of use on IST performance after controlling for current use, and not the reverse. No significant associations between IST performance and current cannabis use remained after controlling for age of onset and duration of cannabis use. Further, impaired performance could not be attributed to acute intoxication or withdrawal symptoms – 54.3% of the cannabis sample had zero THC levels detected in saliva and a further 28.3% had levels less than 1ng/ml, and no performance measures correlated with withdrawal scores.

As the IST puts minimal demands on working memory (Clark et al. 2006), these findings do not reflect a simple deficit in working memory in the young cannabis users of this study. Despite a lack of condition by group interactions, the majority of significant associations with cannabis use measures were in the fixed win condition, where there were no losses contingent upon performance. The introduction of negative reinforcement (i.e., losing points in the decreasing win condition) may override some of the effects of cannabis on impulsive tendencies and adolescent cannabis users may need more motivation to self-regulate these. Our findings of impaired reflection impulsivity in adolescent cannabis users, with perhaps greater effects in the fixed win condition, are similar to those reported by Clark et al. (2009) in a sample of young adult cannabis users, as well as in opiate and amphetamine users (Clark et al. 2006). However, this study did find that the implementation of a loss condition modified adolescent cannabis users' risky behaviour. This is in contrast to Fridberg et al. (2010) who found that adult cannabis users were less sensitive to loss on the IGT than controls and were also more motivated by immediate reward. Fridberg et al's sample were chronic adult cannabis users who had been using for an

average of 13 years, while our relatively novice sample had been using regularly for just over 2 years. Therefore, it may be that at a relatively young stage of cannabis use without the development of dependence, adolescents may respond to loss with reductions in impulsive behaviour. However, if cannabis use is continued over time and with the development of dependence, they may be less likely to respond to these cues and will show more consistently risky and impulsive behaviour, regardless of consequence. If the tendency toward risky decision making could be modified at an early stage, then this may have benefits for future outcomes not only in a cognitive domain but also for future risky and impulsive behaviour such as unsafe sex, experimentation with other drugs and heavy drinking.

The current sample of adolescent users commenced cannabis use between the ages of 15 and 16 years. This is a period characterised by neurodevelopmental changes where the brain is undergoing significant resculpting, synaptic pruning and ongoing myelination (Paus 2005; Schepis et al. 2008; Schneider 2008). The prefrontal cortex together with its connections with the amygdala and striatum have been implicated in the neurocircuitry of cognitive and affective decision making (Clark et al. 2004; Ernst and Paulus 2005; Krain et al. 2006). Recent neuroimaging studies have demonstrated structural alterations (Lorenzetti et al. 2010; Yücel et al. 2008; Yücel et al. 2010) and altered activation patterns (Nestor et al. 2010; Wesley et al. 2011) in these brain regions in long-term cannabis users. Further investigation into the mechanisms that may potentially underlie the current findings is warranted to determine the impact of cannabis on the developing adolescent brain. That the adolescent brain may be more vulnerable to cannabis insult was highlighted in our introduction. We have reported greater adverse effects on verbal learning and memory in this same sample (Solowij et al. 2011). The current study provides

evidence for greater adverse effects of cannabis on reflection impulsivity in adolescence, in that our results from a young sample with relatively few years and less monthly exposure to cannabis (approximately 17 joints per month) are comparable to those of Clark et al's (2009) study of young adults using 31.3 joints per month.

Poorer reflection impulsivity in cannabis-using adolescents might also be subserved by an altered serotonergic system. The serotonergic system has been implicated in the regulation of impulse control, behavioural inhibition and effective decision-making (Evenden 1999b; Clark et al. 2004; Soubrié 1986), with reductions in serotonin (5-hydroxytryptamine, 5-HT) levels being associated with reduced inhibitory control and increases in impulsive behaviour (Clark et al. 2009; Evenden 1999b). Cannabinoids have been shown to interact with 5-HT receptors (Kelaï et al. 2006; Kimura et al. 1998) and evidence from preclinical studies suggests the involvement of cannabinoid receptors (CB1) in the regulation of serotonergic responses (Lau and Schloss 2008; Mato et al. 2007), whereby stimulation of CB1 receptors reduces (Balazsa et al. 2008) and inhibits (Best and Regehr 2008; Nakazi et al. 2000) 5-HT release. Administration of THC has been shown to decrease serotonergic activity in various brain regions in animal studies (Molina-Holgado et al. 1993; Moranta et al. 2004; Sagredo et al. 2006). Chronic exposure to cannabinoids during adolescence has similarly been shown to attenuate serotonergic activity (Bambico et al. 2010) and differentially affect 5-HT<sub>1A</sub> receptor binding and mRNA expression in adult versus adolescent brains (Zavitsanou et al. 2009).

The limitations of our study include the lack of available promorbid ability scores for a portion of the sample, the recruitment of the larger portion of the sample of adolescent cannabis users from outside of the longitudinal cohort from which alcohol users and controls were recruited and the overrepresentation of females within

the control group. We accounted for the majority of these limitations, as well as differences between groups in other substance use, in the analyses conducted and do not believe that they impact upon our results in any substantial way. While the small sample size for those consuming other drugs in the past 30 days may render those analyses underpowered to detect a difference between groups, the level of recent (and indeed) other drug use was in any case low in the sample (Table 2). Our interpretations of the findings would, however, have been aided by *pre-cannabis* exposure measures of impulsivity and decision-making. For example, it is possible, that the cannabis users were more impulsive than the non-cannabis using groups prior to cannabis exposure. Such pre-existing intrinsic impulsivity may have resulted in both the ultimate use of cannabis, as well as an earlier initiation of cannabis use. Therefore, caution should be taken when interpreting these findings in direct association with cannabis exposure per se. A further limitation may be that the IST was the final test in a battery of cognitive tasks administered in the same order to all groups and lasting approximately one hour. It is possible that sustained vigilance may be worse in cannabis users than in alcohol users and controls, which could lead to greater fatigue effects in this group when performing the IST. Effects of fatigue, effort and motivation in cannabis users could be further explored in relation to reflection impulsivity, and particularly within tasks that include actual rewards and punishment (e.g., monetary gains and losses). Further research could examine the trajectory and nature of impulsive behaviours in the context of losses as cannabis dependence develops, and determine the impact of ongoing cannabis use or cessation of use in the context of the maturing adolescent brain.

In conclusion, regular adolescent cannabis users show deficits in reflecting on responses prior to making a decision. Impulsive decision making in this group



appears to be associated more with cannabis use when there are no negative consequences, but is impaired in conditions both with and without negative consequences. Poor reflection impulsivity was associated with greater exposure to cannabis and a younger age of onset, after controlling for both current and recent cannabis use, and was not associated with alcohol use during adolescence nor exposure to other drugs. Our findings have implications for the development of interventions aimed at reducing impulsive and risky behaviour among young cannabis users before the development of cannabis dependence.

## References

Allen JP, Litten RZ, Fertig JB, Babor T (1997) A review of research on the Alcohol Use Disorders Identification Test (AUDIT). *Alcohol Clin Exp Res* 21:613-619

Balazsa T, Birio J, Gullai N, Ledent C, Sperlagh B (2008) CB1-cannabinoid receptors are involved in the modulation of non-synaptic [H-3]serotonin release from the rat hippocampus. *Neurochem Internat* 52:95-102

Bambico FR, Nguyen N-T, Katz N, Gobbi G (2010) Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission. *Neurobiol Dis* 37:641–655

Battisti RA, Roodenrys S, Johnstone S, Pesa N, Hermens D, Solowij N (2010) Chronic cannabis users show altered neurophysiological functioning on Stroop task conflict resolution. *Psychopharmacology* doi: 10.1007/s00213-010-1988-3

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50:7-15

Beck AT, Steer RA, Brown GK (1996) *Manual for the Beck Depression Inventory-II*. San Antonio, TX, Psychological Corporation.

Best AR, Regehr WG (2008) Serotonin evokes endocannabinoid release and retrogradely suppresses excitatory synapses. *J Neurosci* 28:6508-6515

Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL (2002) Dose-related neurocognitive effects of marijuana use. *Neurology* 59:1337-1343

Bolla KI, Eldreth DA, Matochik JA, Cadet JL (2005) Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage* 26: 480-492.

Budney AJ, Novy P, Hughes JR (1999) Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction* 94:1311–1322

Cha YM, White AM, Kuhn CM, Wilson WA, Swartzwelder HS (2006) Differential effects of delta<sup>9</sup>-THC on learning in adolescent and adult rats. *Pharmacol Biochem Behav* 83:448-455

Chun TH, Spirito A, Hernandez L, Fairlie AM, Sindelar-Manning H, Eaton CA *et al* (2010) The significance of marijuana use among alcohol-using adolescent emergency department patients. *Acad Emerg Med* 17:63-71

Clark L, Cools R, Robbins TW (2004) The neuropsychology of ventral prefrontal cortex: Decision-making and reversal learning. *Brain Cogn* 55:41–53

Clark L, Robbins RW, Ersche KD, Sahakian BJ (2006) Reflection-impulsivity in current and former substance users. *Biol Psychiatry* 60:515-522

Clark L, Rosier JP, Robbins TW, Sahakian B J (2009) Disrupted ‘reflection’ impulsivity in cannabis users but not current or former ecstasy users. *J Psychopharm* 23:14-22

Copeland J, Swift W (2009) Cannabis use disorder: Epidemiology and management. *Int Rev Psychiatry* 21:96-103

Dickman SJ (1993) Impulsivity and information processing. In: McCown W, Shure M, Johnson J (eds), *The Impulsive Client, Theory, Research and Treatment*. American Psychological Association, Washington, DC.

Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, Gigerenzer G, Hoehe MR (1999) Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology* 142:295-301

Eldreth DA, Matochik JA, Cadet JL, Bolla KI (2004) Abnormal brain activity in prefrontal regions in abstinent marijuana users. *Neuroimage* 23:914-920

Ernst M, Paulus MP (2005) Neurobiology of decision making: A selective review from a neurocognitive and clinical perspective. *Biol Psychiatry* 58:597-604

Evenden J (1999a) Impulsivity: a discussion of clinical and experimental findings. *J Psychopharm* 13:180-192

Evenden JL (1999b) Varieties of impulsivity. *Psychopharmacology* 146:348-361

Fridberg DJ, Queller S, Ahn WY, Kim W, Bishara AJ, Busemeyer JR *et al* (2010) Cognitive mechanisms underlying risky decision making in chronic cannabis users. *J Math Psychol* 54:28-38

Garavan H, Stout JC (2005) Neurocognitive insights into substance abuse. *Tr Cogn Sci* 9:195-201

Goldstein RZ, Volkow ND (2002) Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 159:1642-1652

Gruber S, Yurgelun-Todd D (2005) Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Brain Res Cogn Brain Res* 23:107-118

Harvey MA, Sellman JD, Porter RJ, Frampton CM (2007) The relationship between non-acute adolescent cannabis use and cognition. *Drug Alcohol Rev* 26:309-319

Heaven P, Ciarrochi J (2008) Parental styles, gender and the development of hope and self-esteem. *Eur J Pers* 22:707-724

Hermann D, Lemenager T, Gelbke J, Welzel H, Skopp G, Mann K (2009) Decision making of heavy cannabis users on the Iowa Gambling Task: Stronger association with THC of hair analysis than with personality traits of the Tridimensional Personality Questionnaire. *Eur Addict Res* 15:94-98

Hester R, Nestor L, Garavan H (2009) Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology*. 34:2450-2458

Huestegge L, Radach R, Kunert HJ, Heller D (2002) Visual search in long-term cannabis users with early age of onset. *Prog Brain Res* 140:377-394

Huestis MA, Cone EJ (2004) Relationship of  $\Delta^9$ -tetrahydrocannabinol concentrations in oral fluid and plasma after controlled administration of smoked cannabis. *J Anal Toxicol* 28:394-399

Ilan AB, Smith ME, Gevin A (2004) Effects of marijuana on neurophysiological signals of working and episodic memory. *Psychopharmacology* 176:214-222

Jacobsen LK, Mencl WE, Westerveld M, Pugh KR (2004) Impact of cannabis use on brain function in adolescents. *Ann N Y Acad Sci* 1021:384-390

Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE (2007) Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. *Biol Psychiatry* 61:31-40

Jacobus J, Bava S, Cohen-Zion M, Mahmood O, Tapert SF (2009) Functional consequences of marijuana use in adolescents. *Pharmacol Biochem Behav* 92:559-565

Jager G, Kahn RS, Brink W, Ree JM, Ramsey NF (2006) Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. *Psychopharmacology* 185:358-368

Jentsch JD, Taylor JR (1999) Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* 146:373-390

Kagan J (1965) Reflection impulsivity and reading ability in primary grade children. *Child Develop* 36:609-628

Kagan J (1966) Reflection impulsivity: The generality and dynamics of conceptual tempo. *J Abnorm Psychol* 71:17-24

Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA (2004) Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. *Psychopharmacology* 176:239-247

Kelaï S, Hanoun N, Aufrère G, Beaugé F, Hamon M, Lanfumey L (2006) Cannabinoid-serotonin interactions in alcohol-preferring vs. alcohol-avoiding mice. *J Neurochem* 99:308-320

Kempel P, Lampe K, Parnefjord R, Hennig J, Kunert HJ (2003) Auditory-evoked potentials and selective attention: different ways to information processing in cannabis users and controls. *Neuropsychobiology* 48:95-101

Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SLT et al (2002) Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med* 32:959-956

Kimura T, Ohta T, Watanabe K, Yoshimura H, Yamamoto I (1998) Anandamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5-HT) receptor. *Biol Pharm Bull* 21:224-226.

Krain AL, Wilson AM, Arbuckle R, Castellanos FX, Milham MP (2006) Distinct neural mechanisms of risk and ambiguity: a meta-analysis of decision-making. *Neuroimage* 32:477-484

Lamers CTJ, Bechara A, Rizzo M, Ramaekers JG (2006) Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. *J Psychopharm* 20:302-311

Lau T, Schloss P (2008) The cannabinoid CB1 receptor is expressed on serotonergic and dopaminergic neurons. *Eur J Pharmacol* 578:137-141

Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yücel M (2010) Structural MRI findings in long-term cannabis users: What do we know? *Subst Use Misuse* 45:1787-1808

Lubman DI, Yücel M, Hall W (2007) Substance use and the adolescent brain: A toxic combination? *J Psychopharmacol* 21:792-794

Marin RS, Biedrzycki RC, Firinciogullari S (1991) Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 38:143-162

Mato S, Aso E, Castro E, Martin M, Valverde O, Maldonado R, Pazos A (2007) CB1 knockout mice display impaired functionality of 5-HT<sub>1A</sub> and 5-HT<sub>2A/C</sub> receptors. *J Neurochem* 103:2111-2120

Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF (2007) Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol* 29:141–152

Molina-Holgado F, Molina-Holgado E, Leret ML, González MI, Reader TA (1993) Distribution of indoleamines and [<sup>3</sup>H]paroxetine binding in rat brain regions following acute or perinatal delta 9-tetrahydrocannabinol treatments. *Neurochem Res* 18:1183-1191

Moranta D, Esteban S, García-Sevilla JA (2004) Differential effects of acute cannabinoid drug treatment, mediated by CB1 receptors, on the in vivo activity of tyrosine and tryptophan hydroxylase in the rat brain. *Naunyn-Schmiedeberg's Arch Pharmacol* 369:516-524

Nakazi M, Bauer U, Nickel T, Kathmann M, Schlicker E (2000) Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB1 receptors. *Naunyn-Schmiedeberg's Arch Pharmacol* 361:19-24

Nestor L, Hester R, Garavan H (2010) Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *Neuroimage* 49:1133-1143

Niedbala RS, Kardos KW, Fritch DF, Kardos S, Fries T, Waga J, Robb J, Cone EJ (2001) Detection of marijuana use by oral fluid and urine analysis following single-dose administration of smoked and oral marijuana. *J Anal Toxicol* 25:289-303

Novaes MAFP, Guindalini C, Almeida P, Jungerman F, Bolla K, Laranjeira R, Lacerda A, Bressan RA (2008) Cannabis use before Age 15 years is associated with poorer attention and executive function. *Biol Psychiatry* 63:18S-19S.

Paus T (2005) Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci* 9:60-68

Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend* 69:303-310

Sagredo O, Ramos JA, Fernández-Ruiz J, Rodríguez MLL, de Miguel R (2006) Chronic  $\Delta^9$ -tetrahydrocannabinol administration affects serotonin levels in the rat frontal cortex. *Naunyn-Schmiedeberg's Arch Pharmacol* 372:313-317

Schepis TS, Adinoff B, Rao U (2008) Neurobiological processes in adolescent addictive disorders. *Am J Addict* 17:6-23

Schneider M (2008) Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addict Biol* 13:253-263

Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P (1989) Short-term memory impairment in cannabis-dependent adolescents. *Am J Dis Child* 143:1214-1219

Sobell LC, Sobell MB (1992) Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP (eds) *Measuring alcohol consumption: psychosocial and biochemical methods*. Humana, Totowa NJ, pp 41–72



Solowij N, Battisti R (2008) The chronic effects of cannabis on memory in humans: A review. *Curr Drug Abuse Rev* 1:81-98

Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PCL, Lubman DI, Yücel M (2011) Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology*. DOI 10.1007/s00213-011-2203-x.

Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J, for the Marijuana Treatment Project Research Group (2002) Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 287:1123-1131

Soubrié P (1986) Reconciling the role of central serotonin neurons in human and animal behaviour. *Behav Brain Res* 9:319-364

Spielberger CD (1989) *State-Trait Anxiety Inventory: A Comprehensive Bibliography*. Palo Alto, CA: Consulting Psychologists Press.

Steinberg L (2007) Risk taking in adolescence: new perspectives from brain and behavioural science. *Curr Dir Psychol Sci* 16: 55-59

Swift W, Copeland J, Hall W (1998) Choosing a diagnostic cut-off for cannabis dependence. *Addiction* 93:1681-1692

Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, Frank LR (2007) Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology* 194:173-183

Vandrey R, Budney AJ, Kamon JL, Stanger C (2005) Cannabis withdrawal in adolescent treatment seekers. *Drug Alcohol Depend* 78:205-210

Wesley MJ, Hanlon CA, Porrino LJ (2011) Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. *Psychiatry Res Neuroimag* 191:51-59

Whitlow CT, Liguori A, Livengood LB, Hart SL, Mussat-Whitlow BJ, Lamborn CM (2004) Long-term heavy marijuana users make costly decisions on a gambling task. *Drug Alcohol Depend* 76:107-111

Yücel M, Lubman DI, Solowij N, Brewer W (2007) Understanding drug addiction: A neuropsychological perspective. *Aust NZ J Psychiatry* 41:957-969

Yücel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, Lubman DI (2008) Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 65:694-701

Yücel M, Zalesky A, Takagi MJ, Bora E, Fornito A, Ditchfield M, Egan GF, Pantelis C, Lubman DI (2010) White-matter abnormalities in adolescents with long-term inhalant and cannabis use: a diffusion magnetic resonance imaging study. *J Psychiatry Neurosci* 35:409-412

Zavitsanou K, Wang H, Dalton VS, Nguyen V (2010) Cannabinoid administration increases 5HT1A receptor binding and mRNA expression in the hippocampus of adult but not adolescent rats. *Neuroscience* 169:315-324

**Table 1.** Demographic and clinical characteristics of the sample: mean (*SD*) or median [range]

	Cannabis Users n=48	Alcohol Users n=65	Controls n=62	p (three-group comparison)	p (Cann vs. Alc)
Gender (M/F)	27/21	34/31	18/44	<0.01	0.68
Age	18.6 (0.8)	18.3 (0.5)	18.1 (0.5)	<0.001	<0.01
IQ <sup>a</sup>	103.9 (14.2)	104.7 (12.2)	104.6 (10.3)	0.93	0.93
Premorbid verbal ability	90.1 (6.5)	92.4 (5.7)	91.3 (5.2)	0.24	0.22
Premorbid numerical ability	86.5 (7.3)	89.8 (6.5)	87.0 (7.3)	0.08	0.14
State anxiety	32.5 [23-54]	30 [20-56]	27.5 [20-45]	<0.01	0.98
Trait anxiety	39.2 (9.5)	36.5 (9.0)	34.9 (9.0)	0.06	0.28
Apathy Evaluation Scale	11 [2-29]	8 [0-31]	7 [0-31]	<0.001	<0.01
Beck Depression Inventory	6 [0-34]	4 [0-32]	3 [0-23]	<0.01	0.08
Kessler Psychological Distress	17.9 (4.7)	17.2 (4.3)	16.3 (4.2)	0.15	0.63

<sup>a</sup> From WASI short version; Premorbid verbal ability scores available for 24 cannabis users, 48 alcohol users, 45 controls; Premorbid numerical ability scores available for 24 cannabis users, 47 alcohol users, 45 controls.

**Table 2.** Substance use characteristics of the sample: mean (*SD*) or median [range]

	Cannabis Users	Alcohol Users	Controls	p (Cann vs. Alc)
Age of First Cannabis Use	15 [9-18]	17 [15-18.8] <sup>a</sup>	16 [14-17] <sup>a</sup>	<0.001
Age of Regular Cannabis Use	16.5 [12.5-18.8]	-	-	-
Duration of Regular Cannabis Use (years)	2.3 (1.2)	-	-	-
Frequency of Cannabis Use (days/month)	10.8 [0.5-30]	0	0	-
Quantity of Cannabis Use (cones/month) <sup>b</sup>	50 [3.5-1517.5]	0	0	-
Last Use of Cannabis (hours ago)	22.5 [12-2760]	-	-	-
Urinary THC-COOH (ng/mg)	84 [0-4335]	0	0	-
Salivary THC (ng/ml)	0 [0-7.2]	0	0	-
Severity of Dependence (cannabis)	2 [0-14]	-	-	-
Age of First Alcohol Use	15 [10-17]	15.5 [7-18]	16 [10-18]	<0.01
Age of Regular Alcohol Use	16 [12-18]	17 [14-18.5]	-	<0.001
Duration of Regular Alcohol Use (years)	2.5 [0.4-6.6]	1.3 [0.1-4.2]	-	<0.001

Frequency of Alcohol Use (days/month)	4 [0-12.5]	5 [2-12.33]	1.5 [0-4]	0.13
Quantity of Alcohol (std drinks/month)	35.6 [0-155]	27.6 [9.23-241.7]	3.2 [0-17.7]	0.63
Last Use of Alcohol (hours ago)	125 [17-3240]	84 [10-768]	134 [0-2880]	<0.05
AUDIT Total Score	12 [0-26]	9 [3-27]	2 [0-11]	<0.05
Cigarettes per day	1 [0-12.5]	0 [0-8.6]	0 [0]	<0.001
Lifetime Occasions of Illicit Substance use <sup>c</sup>	4 [0-123]	0 [0-8]	0 [0-1]	<0.001

<sup>a</sup> 19 of the alcohol users had tried cannabis, 5 controls had tried cannabis

<sup>b</sup> Approximately 16.7 joints per month

<sup>c</sup> Total number of occasions of use of illicit drugs over the lifetime excluding cannabis: drugs used included ecstasy, amphetamines, cocaine and hallucinogenic mushrooms

**Table 3.** Group differences on IST measures of reflection impulsivity: mean (*SD*) or median [range]; 3 group comparison and subgroup comparisons

	Cannabis Users	Alcohol Users	Controls	p (three- group compari son)	p (Cann vs. Con)	p (Cann vs, Alc)	p (Alc vs. Con)
<i>P</i> (Correct) FW	0.79 (0.11)	0.85 (0.11)	0.85 (0.10)	<0.01	<0.01	<0.01	1.00
<i>P</i> (Correct) DW	0.68 (0.07)	0.71 (0.09)	0.72 (0.07)	<0.05	<0.05	0.07	0.97
Boxes opened per trial FW	14.32 (5.79)	17.02 (5.54)	16.06 (5.34)	<0.05	0.23	<0.05	0.60
Boxes opened per trial DW	7.65 (3.16)	9.36 (4.07)	9.02 (3.64)	<0.05	0.13	<0.05	0.86
Discrimination errors FW	1 [0-5]	0 [0-3]	0 [0-2]	<0.01	<0.01	<0.05	0.31
Discrimination errors DW	1 [0-6]	1 [0-5]	0 [0-3]	0.20	0.09	0.52	0.22
Box opening latency FW ms	583 [237-1194]	568 [229-2650]	655 [265-2001]	0.37	0.46	0.63	0.16
Box opening latency DW ms	1139 [360-2594]	878 [226-2428]	1021 [527-2604]	0.07	0.31	<0.05	0.12
Colour decision latency FW s	10700 [3761-19564]	11946 [5030-35341]	11291 [4980-35343]	<0.05	<0.05	<0.05	0.78
Colour decision latency DW s	9293 [4045-15893]	9131 [3361-35873]	9499 [3879-34535]	0.53	0.29	0.57	0.47

*FW* Fixed win condition; *DW* Decreasing win condition

**Table 4.** Correlations between IST performance measures and substance use in the cannabis user group: Pearson *r* or Spearman *rho*

	<i>P</i> (Correct) FW	<i>P</i> (Correct) DW	No. boxes opened FW	No. boxes opened DW	Sampling errors FW	Sampling errors DW	Discrimination errors FW	Discrimination errors DW	Box opening latency FW
Age first can use	.39**	.22	.33*	.16	-.35*	-.12	-.26	-.21	-.25
Age regular can use	.42**	.13	.37*	.09	-.32*	-.23	-.42**	-.12	-.38**
Duration regular use	-.46**	-.17	-.38*	-.14	.31*	.04	.48**	.27	.39**
Cannabis frequency	-.30*	-.14	-.20	.01	.02	-.09	.36*	.42**	.26
Cannabis quantity	-.23	-.15	-.08	.11	.11	-.09	.43**	.44**	.30*
Hours since last use	.02	-.09	-.08	-.14	.16	.10	-.35*	-.20	-.21
Salivary THC	-.10	.21	.22	.23	-.40	-.26	.56**	-.06	.02
Urinary cannabinoids	-.37**	-.23	-.25	-.07	.19	-.02	.36*	.45**	.41**
Cannabis dependence	-.03	.01	.02	.05	.04	.06	.18	.19	.11
Cannabis withdrawal	-.17	-.02	-.15	.10	.17	-.06	.22	.13	.15
Age first alc use	.25	.13	.32*	.20	-.29	-.31*	-.16	.15	-.18
Age regular alc use	.13	-.04	.15	.02	-.20	.03	-.19	-.01	-.04
Alcohol	.03	-.06	.10	-.05	.06	.01	-.15	-.21	-.07

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frequency									
Alcohol	-0.04	-0.21	.04	-0.15	.10	.03	-0.14	-0.07	-0.01
quantity									

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*FW* Fixed win condition; *DW* Decreasing win condition; \*  $p < 0.05$ ; \*\*  $p < 0.01$



**Table 5.** Partial correlations between cannabis use measures and IST performance ( $P(\text{Correct})$  collapsed across FW and DW conditions): partial  $r$ .

	$P(\text{Correct})$
Controlling for recent cannabis use and cannabinoid levels <sup>a</sup>	
Age of first cannabis use	0.44**
Age of regular cannabis use	0.30*
Duration of regular cannabis use	-0.35*
Cannabis frequency	-0.23
Cannabis quantity	-0.11
Controlling for age of onset and duration of regular use	
Hours since last use	-0.07
Urinary cannabinoid level	-0.17
Salivary THC level	-0.02
Cannabis frequency	-0.09
Cannabis quantity	-0.09
Controlling for frequency and quantity of cannabis use	
Age of first cannabis use	0.37**
Age of regular cannabis use	0.25*
Duration of regular cannabis use	-0.27*

FW Fixed win condition; DW Decreasing win condition

<sup>a</sup> Recent cannabis use as self-reported hours since last use, cannabinoid metabolite levels in urine and salivary THC

\*  $p < 0.05$ ; \*\*  $p < 0.005$

## Figure Captions

**Fig. 1** Mean probability of being correct at the point of decision ( $P(\text{correct})$ ) in fixed win and decreasing win conditions for adolescent cannabis users, alcohol users and controls.

