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

Running title: Reflection impulsivity in adolescent cannabis users

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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. They found that the cannabis 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. 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. Similarly, participants were also 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). 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 total correct (the number of trials for which the subject correctly chose the colour that was in the overall majority), mean number of boxes opened per trial, and the mean probability of being correct at point of decision: *P*(Correct). This 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). Also measured were discrimination errors and sampling errors. 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 20.3 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 ($F(2,172)=6.02$, $p=0.003$), with cannabis users having a significantly lower *P*(Correct) score than both alcohol users ($p=0.008$) and controls ($p=0.006$), while the latter groups did not differ ($p=0.99$). Table 3 shows *P*(Correct) 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 ($p=0.24$).

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*(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*(Correct) ($F(2,143)=2.98$, $p=0.054$). The ages of onset of regular use of cannabis and of alcohol were highly correlated (Spearmans' *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.

Analysis of the mean number of boxes opened per trial showed that there was a significant main effect of group ($F(2,172)=4.32$, $p=0.015$), with cannabis users opening fewer boxes than alcohol users ($p=0.012$) but not controls ($p=0.11$), and the latter groups did not differ ($p=0.63$). As above for *P*(Correct), there was a significant main effect of condition ($F(1,172)= 354.08$, $p<0.001$) but no condition by group interaction ($p=0.57$). There was no change to the main effect of group after controlling for gender ($F(2,171)=4.31$, $p=0.015$), age ($F(2,171)=5.30$, $p=0.006$), AUDIT score ($F(2,170)=4.20$, $p=0.017$), apathy ($F(2,171)=3.43$, $p=0.035$), depressive symptoms ($F(2,171)=3.81$, $p=0.024$), state anxiety ($F(2,169)=5.54$, $p=0.005$), last use of alcohol ($F(2,159)=3.64$, $p=0.028$) or age of first alcohol use ($F(2,163)=4.15$, $p=0.017$). Inclusion of all of these covariates in the model still produced a significant main effect of group ($F(2,146)=4.19$, $p=0.017$), and apathy was the only significant covariate in the model ($p=0.03$). Again however, including age of onset of regular alcohol use as a covariate resulted in the group difference for mean number of boxes opened becoming only a trend (F(2,143)=2.41, $p=0.094$), and with cigarettes smoked per day as a covariate the significant group difference was lost ($F(2,165)=1.76$, $p=0.17$). The number of boxes opened did not correlate with cigarettes smoked per day ($r=-0.04$), but did with the age of onset of regular alcohol use ($r=0.21$, $p<.01$).

The diminution of group differences when age of alcohol use was included as a covariate can only be explained by the fact that the ages of onset of cannabis and alcohol use were correlated.

*IST Performance: Accuracy*

Table 3 shows that cannabis users' task accuracy was impaired specifically in the fixed win condition, with fewer total correct trials ($\chi 2(2)=9.45$, $p=0.009$) than alcohol users ($Z=2.89$, $p<0.01$) and controls ($Z=2.47$, $p<0.05$). They also made more discrimination errors ($\chi 2(2)=9.39$, $p=0.009$) than alcohol users ($Z=2.04$, $p<0.05$) and controls ($Z=3.04$, $p<0.01$) in the fixed condition alone, but with a median of only 1 versus 0 errors. There were trends toward fewer correct and more discrimination errors in cannabis users in the decreasing win condition, but no significant differences between groups for sampling errors in either condition.

*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*(Correct), fewer boxes opened, fewer total correct trials 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, and additionally, fewer total correct trials in the decreasing win condition. A longer duration of regular use of cannabis was associated with lower *P*(Correct) scores, fewer boxes opened, fewer total correct trials, 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*(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 fewer total correct and 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*(correct) and total 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 two primary outcome measures: *P(*Correct) and number of boxes opened. As shown in Table 5, the associations between these measures 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 IST performance 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 IST performance 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 IST performance 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*(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*(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, opened fewer boxes, had fewer correct trials, 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, have a lower probability of being correct at the point of decision and lower total correct trials. 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 fewer correct trials and more discrimination errors, and frequency was also associated with lower *P*(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-HT1A 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. A further limitation may be that the IST was the final test administered within a battery of cognitive tasks lasting approximately one hour. Performance may have been affected by fatigue, but this would apply equally to alcohol users and controls. Effects of fatigue, effort and motivation in cannabis users could be further explored in relation to reflection impulsivity 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.

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