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ORIGINAL INVESTIGATION

Verbal learning and memory in adolescent cannabis users, alcohol users and non-users

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Abstract
Rationale Long-term heavy cannabis use can result in memory impairment. Adolescent users may be especially vulnerable to the adverse neurocognitive effects of cannabis.
Objectives and methods In a cross-sectional and prospective neuropsychological study of 181 adolescents aged 16–20 (mean 18.3 years), we compared performance indices from one of the most widely used measures of learning and memory—the Rey Auditory Verbal Learning Test—between cannabis users (n=52; mean 2.4 years of use, 14 days/month, median abstinence 20.3 h), alcohol users (n=67) and non-user controls (n=62) matched for age, education and premorbid intellectual ability (assessed prospectively), and alcohol consumption for cannabis and alcohol users.
Results Cannabis users performed significantly worse than alcohol users and non-users on all performance indices. They recalled significantly fewer words overall (p<0.001), demonstrating impaired learning (p<0.001), retention (p<0.001) and retrieval (p<0.05) (Cohen's d 0.43–0.84). The degree of impairment was associated with the duration, quantity, frequency and age of onset of cannabis use, but was unrelated to alcohol exposure or other drug use. No gender effects were detected and the findings remained after controlling for premorbid intellectual ability. An earlier age of onset of regular cannabis use was associated with worse memory performance after controlling for extent of exposure to cannabis.
Conclusions Despite relatively brief exposure, adolescent cannabis users relative to their age-matched counterparts demonstrated similar memory deficits to those reported in adult long-term heavy users. The results indicate that cannabis adversely affects the developing brain and reinforce concerns regarding the impact of early exposure.

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Introduction

Verbal episodic memory and verbal learning impairments are consistently found in adult long-term and heavy cannabis users and thought to represent the enduring adverse effects of the drug (Solowij and Battisti 2008; Solowij and Pesa 2010). Characteristic performance by cannabis users on verbal learning tasks includes learning fewer words on each trial, recalling fewer words overall and forgetting more words due to interference or decay over time. Poor performance has been shown in some studies to be related to the duration of exposure to cannabis (Fletcher et al. 1996; Solowij et al. 2002; Messinis et al. 2006), while in other studies frequency (Pope and Yurgelun-Todd 1996; Pope et al. 2001) or dose of exposure (Bolla et al. 2002) were critical correlates. We previously reported verbal memory performance deficits in adults with a prolonged history of heavy cannabis use that developed gradually with ongoing use, but were only detectable as a significant impairment by standard neuropsychological tests after more than a decade of use (Solowij et al. 2002). However, less extensive use among adolescents is of concern, as evidence from both human and animal studies suggests that the adolescent brain may be particularly vulnerable to the adverse effects of cannabis exposure (Cha et al. 2006; Lubman et al. 2007; Yücel et al. 2007; Schepis et al. 2008; Schneider 2008).

Adolescence is the primary period for experimentation and subsequent initiation of regular cannabis use (Copeland and Swift 2009; Jacobus et al. 2009) and a growing literature reports either cognitive deficits in adolescent cannabis users or greater adverse effects among those commencing cannabis use during early adolescence, particularly prior to the age of 17 (Schwartz et al. 1989; Ehrenreich et al. 1999; Huestegge et al. 2002; Kempel et al. 2003; Pope et al. 2003; Jacobsen et al. 2004; Harvey et al. 2007; Jacobsen et al. 2007; Medina et al. 2007; Jacobus et al. 2009). Only two studies have reported impaired word list learning in adolescent or early onset young adult cannabis users (Pope et al. 2003; Jacobsen et al. 2004; Harvey et al. 2007), while in a third study, poor performance was associated with lifetime cannabis use despite a lack of significant difference between users and non-users (Medina et al. 2007).

An important consideration for research in this area is that adolescent cannabis users rarely use cannabis in isolation, with concomitant alcohol use being most common (Martin et al. 2002; Copeland and Swift 2009; Kuntsche et al. 2009). Heavy alcohol use has been found to have neurotoxic effects in adolescents (Barron et al. 2005; Monti et al. 2005) and is also associated with poor verbal memory (Brown et al. 2000). Further, cannabinoids have been shown to enhance the susceptibility of the immature brain to ethanol-induced neurotoxicity in rats (Hansen et al. 2008). Thus, use of both substances together is hypothesised to further adversely affect adolescent brain development. Although two cross-sectional studies have found functional and structural brain differences between adolescents who use both cannabis and alcohol, in comparison to alcohol only users and non-user controls (Schweinsburg et al. 2005; Medina et al. 2007), there is a paucity of research aimed at isolating long-term cognitive effects associated with each substance separately and in combination.

A further issue pertinent to all studies investigating cognitive deficits in cannabis users is consideration of the premorbid functionality of the cannabis-exposed sample. While demonstrated dose-related worsening of cognitive outcomes may suggest causality, it remains possible that cognitive deficits precede any such exposure. In addition, pre-existing low intellectual capacity may predispose individuals to using cannabis or moderate the extent of cognitive deficits resulting from exposure to cannabis (Solowij and Battisti 2008; Yücel et al. 2009). While most studies have incorporated measures of current intellectual ability (IQ) or estimates of premorbid IQ (e.g. the National Adult Reading Test), few have incorporated truly premorbid measures, obtained prior to the initiation of any substance use.

In order to address such limitations, we recruited a sample of adolescent cannabis users, alcohol users and non-users with premorbid intellectual ability ascertained during their first year of high school and compared these groups in verbal learning and memory performance, controlling for premorbid ability as well as other potential confounds. We examined the influence of various parameters of cannabis and alcohol use (quantity, frequency, duration, and importantly, age of onset of substance use) separately and in combination to determine the specificity of the findings, and also examined potential gender effects. We hypothesised that there would be specific effects of cannabis compared to alcohol and that the poorest performance would be observed in adolescents with the greatest exposure to cannabis and who had commenced using regularly at a young age.

Methods

Subjects

Participants were recruited in the first instance from the Wollongong Youth Study (WYS; Ciarrochi and Heaven

2008)—a longitudinal sample of adolescents followed from entry to six regional and metropolitan high schools near Sydney, Australia, and were assessed for the current study at age 16–20 years (mean age 18.3, SD 0.64). Three groups were targeted from the WYS: (1) regular cannabis users; (2) alcohol users with no history of regular cannabis use; (3) controls with no regular substance use histories. Due to difficulty obtaining a sufficient sample of cannabis users from the WYS (n=12), 40 age-matched cannabis users were also recruited from the general community by advertising in newspapers that would reach the same demographic population. Externally recruited cannabis users were well matched with the WYS cannabis users: they did not differ in age, education, IQ or on most of the other clinical or demographic characteristics, but they were more entrenched in their cannabis use and had more years of regular alcohol use without differing on current quantity or frequency of alcohol use (see Electronic supplementary material and Table S1). The final sample of n=181 participants comprised 52 cannabis users, 67 alcohol users and 62 controls. Demographic characteristics of the sample are shown in Table 1.

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 travel expenses and time involved.

Clinical screening and assessment of substance use

Participants were screened to ensure they met inclusion and exclusion criteria pertaining to substance use, head injury, neurological or psychiatric disorders. The Kessler Psychological Distress Scale K10 (Kessler et al. 2002) was used to screen for potential disorders and structured interview assessed psychiatric, medical and neurological history (none identified). All participants completed the State-Trait Anxiety Inventory (STAI; Spielberger 1989) and the Beck Depression Inventory (BDI; Beck et al. 1996).

Table 1 Demographic, clinical and substance use characteristics of cannabis users, alcohol users and controls: mean (*SD*) or median [range]

	Cannabis users n=52	Alcohol users n=67	Controls n=62	p (three-group comparison)	p (Cann vs. alc)
Age	18.67 (*0.82*)	18.27 (*0.46*)	18.07 (*0.48*)	<0.001	0.001
Gender M:F	31:21	35:32	18:44	<0.01	0.32
IQ[a]	103.53 (14.55)	104.68 (12.19)	104.61 (10.26)	0.86	0.87
Education (years)	12.75 [10–14.5]	13.00 [10.5–13.5]	13.00 [10–13.27]	<0.05	<0.01
Premorbid verbal ability scores[a]	89.13 (*7.14*)	92.18 (*5.88*)	91.31 (*5.22*)	0.11	0.09
Premorbid numerical ability scores[a]	85.73 (*7.53*)	89.29 (*7.01*)	87.03 (*7.27*)	0.10	0.11
BDI scores[b]	5.50 [0–34]	4.0 [0–32]	3.0 [0–23]	<0.005	0.05
STAI state scores[b]	33 [23–54]	30 [20–56]	27.5 [20–45]	<0.005	0.86
STAI trait scores[b]	38 [23–62]	35 [22–62]	34 [14–59]	0.09	0.17
AUDIT scores[b]	12.0 [0–26]	9.0 [3–27]	2.0 [0–11]	<0.001	<0.05
Alcohol use					
Age of first use	15.00 [10–17]	15.50 [7–18]	16.00 [10–18]	<0.001	<0.01
Age of regular use	16.00 [12–18]	17.00 [14–18.6]	–	<0.001	<0.001
Duration of regular use (years)	2.53 [0.38–6.57]	1.33 [0.13–4.19]	–	<0.001	<0.001
Frequency of alcohol use (days/month)	4.00 [0–12.5]	5.00 [2–12.3]	1.46 [0–4]	<0.001	0.13
Quantity of alcohol use (standard drinks/month)	38.23 [0–155]	27.36 [9–242]	3.21 [0–18]	<0.001	0.51
Cannabis use					
Age of first use	15.00 [9–18]	–	–	–	
Age of regular use	16.30 (*1.29*)	–	–	–	
Duration of regular use (years)	2.36 (*1.17*)	–	–	–	
Frequency of cannabis use (days/month)	13.87 [0.5–30]	–	–	–	
Quantity of cannabis use (cones/month)	52.12[c] [3.5–1518]	–	–	–	

[a] Premorbid verbal ability scores available for 26 cannabis users, 50 alcohol users, 45 controls; premorbid numerical ability scores available for 26 cannabis users, 49 alcohol users, 45 controls

[b] *BDI* Beck Depression Inventory; *STAI* Spielberger State-Trait Anxiety Inventory

[c] Approximately 17.5 joints per month

Cannabis or alcohol users were required to have used cannabis or alcohol regularly (defined as at least twice/month) for at least the past 6 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. The majority of the alcohol group and the control group had never tried cannabis (70% and 92%, respectively), while of the remainder (20 alcohol users, 5 controls), most had tried cannabis just once or twice, with maximum use five times. Five controls had never drunk alcohol, while for the remainder alcohol use was less frequent than twice/month on average over the past 6 months or more. A few control subjects had only started drinking higher quantities of alcohol and/or more frequently than twice/month since turning 18 in the past few months, explaining the top range for these measures of *current* use depicted in Table 1. A structured assessment interview obtained information about current and past substance use, incorporating a Time Line Follow-Back procedure (TLFB; Sobell and Sobell 1992) and the Alcohol Use Disorders Identification Test (AUDIT; Allen et al. 1997). Composite measures of frequency and quantity of cannabis and alcohol use per month were derived from the structured interview, the TLFB and the AUDIT (Table 1). TLFB data for the past 30 days were further examined to identify days on which alcohol and cannabis (or any other substances) were co-used.

No participants used other drugs on a regular basis. There was occasional use of other illicit substances among the cannabis users, including ecstasy, amphetamines, cocaine, hallucinogenic mushrooms or amyl-nitrate. Median use of any substance was 0 days of the past 30 (range 0–4). Ecstasy was the most commonly used substance in the cannabis group, with 17 participants (33%) consuming the drug in the past 30 days. Ecstasy users and non-users within the cannabis group were compared on memory indices. Cannabis users smoked more tobacco cigarettes per day (median 1.25 cigarettes, range 0–15) than either other group (controls, median 0, range 0–0, $p<0.001$; alcohol users: median 0, range 0–15, $p<0.001$). Although tobacco use was minimal, its impact on memory performance was also examined in correlational analyses and with cigarettes smoked per day included as a covariate in the analyses.

All participants were requested to abstain from any substance use for at least 12 h prior to the test session (median self-reported abstinence from cannabis was 20.3 h), were breathalysed (all had zero blood alcohol readings) and provided urine and saliva samples for drug assay. Urinalysis quantified cannabinoid metabolites and detected the presence of all other major classes of drugs—the only drugs detected in any subjects (presumptive levels of opiates, sympathomimetic amines or benzodiazepine in two controls, two alcohol users and five cannabis users) were explained by self-reported prescription medications. No cannabinoid metabolites were detected in controls or alcohol users. The mean creatinine-normalised carboxy-THC level in the cannabis group was 454.37 ng/mg (SD=846.37, range 0–4335). Salivary assays, conducted for cannabis users only, measured the presence of THC by gas chromatography–mass spectrometry (Cozart Bioscience Ltd 2001-2009). Fifty percent of the sample returned zero THC readings. For the remainder, 21 participants had values of between 0.4 and <10 ng/ml, while four participants had values of ≥10 ng/ml, suggestive of possible recent use within hours of testing. Median salivary THC levels for the entire sample of cannabis users were 0.2 ng/ml. THC may remain in the oral cavity for 24 h or more after smoking and levels generally fall below 1 ng/ml 12–24 h after smoking (Niedbala et al. 2001; Huestis and Cone 2004) but there is much individual variability. Salivary THC levels in our sample correlated with urinary cannabinoid metabolite levels (rho=0.84, $p<0.001$) and negatively with self-reported hours since last use of cannabis (Spearman's rho=−0.61, $p<0.001$) providing good corroboration. We repeated our analyses of verbal learning and memory performance excluding the four participants with high salivary THC and we examined the relationship between salivary THC levels and performance.

Cannabis users were also administered the Marijuana Withdrawal Checklist (Budney et al. 1999; Vandrey et al. 2005) and the Severity of Dependence Scale for cannabis (Swift et al. 1998; Martin et al. 2006) to respectively determine the severity of any potential withdrawal symptoms as a result of abstinence, and to assess cannabis dependence.

Premorbid intellectual ability and neuropsychological testing

Premorbid intellectual ability was assessed at entry to high school (approximately age 12) by standardised Department of Education verbal and numerical ability tests. Premorbid verbal and numerical ability scores were available for 75% of the alcohol users, 73% of the controls, and 50% of the cannabis users, having been obtained from the Department of Education for the externally recruited cannabis users where available.

The Wechsler Abbreviated Scale of Intelligence was administered to provide an index of current IQ, which correlated well with the premorbid measures of intellectual ability ($r=0.64$, $p<0.001$). Participants were administered the Rey Auditory Verbal Learning Test (RAVLT) according to standardised instructions (Lezak et al. 2004). This widely used test of verbal learning and memory involves the assessor reading aloud a list of 15 words over five learning

trials (I–V) and participants are asked to freely recall as many words as they can remember at the end of each trial. This is followed by the administration of an interference list (another list of 15 words; list B, which participants freely recall), with subsequent free recall of the original list without further presentation of that list (trial VI). Finally, after a 20-min delay (in this study filled with a computerised task) participants are asked to recall the original list again (delayed recall; trial VII) after which they complete a recognition test that involves visual presentation of 50 words (the 15 words of lists A and B among semantic and phonemic distracter words). The primary outcome measures from the RAVLT were: total words recalled across five learning trials (I–V), recall following interference (VI), recall following a delay (VII), and the number of words correctly recognised. Several other memory indices were also examined as described below.

Statistical analysis

Data were analysed using SPSS version 15.0 with univariate analysis of variance (ANOVA) and covariance (controlling for variation in premorbid intellectual functioning, alcohol use and tobacco use, and psychological symptoms of anxiety and depression) or Kruskal–Wallis non-parametric tests for skewed data, after excluding outliers on the dependent variable (each memory outcome measure). Post-hoc Tukey tests were conducted for normally distributed variables and Mann Whitney U planned comparisons for skewed data. Cohen's *d* effect sizes were calculated for significant pairwise group comparisons. Pearson's or Spearman correlations were used to examine relationships between RAVLT performance and substance use measures. Multiple regression was performed to determine the relative contribution of cannabis and alcohol use parameters to RAVLT performance in the cannabis users and alcohol use measures in the alcohol users. Covariate analyses, correlations and multiple regression concentrated on the most frequently used outcome measure from the RAVLT: total words recalled over Trials I–V.

Results

Demographic, clinical and substance use characteristics

As shown in Table 1, cannabis users were a few months older and had a few months less education than either alcohol users or controls. The comparison was significant because of the precision with which we measured each of these variables (in portions of months). However, the mean age at assessment in each group was 18 years (Table 1) and the median and range of years of education were similar in each group, and since minor variation in portions of months would not be expected to impact upon verbal learning and memory performance indices, we did not use age or education as a covariates in our between group analyses. Importantly, groups did not differ in current IQ or premorbid intellectual ability (Table 1).

Controls scored significantly lower in state anxiety compared to either other group, while cannabis and alcohol users did not differ, and there were no differences between groups in trait anxiety (Table 1). Cannabis users had elevated depressive symptoms compared to both alcohol users and controls, whereas the latter groups did not differ ($p=0.13$). Several participants in each group scored within the clinically significant range for depression, but the median BDI scores were well outside this range (Table 1). STAI-state and BDI scores were used as covariates in the analyses.

The cannabis users first tried cannabis around age 15, with regular use commencing around age 16. They had used cannabis regularly for a mean 2.36 years and were currently using approximately 14 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 was 2 (range 0–14), suggesting that overall this young sample were not yet dependent on cannabis.

AUDIT scores for both cannabis users and alcohol users placed both groups in the range of moderate risk of harm associated with their drinking patterns (Table 1). On average, nine standard drinks per drinking occasion were consumed by cannabis users and seven by alcohol users according to the TLFB, suggesting that binge drinking was occurring in both groups. While cannabis users' AUDIT scores were higher than alcohol users' scores, composite quantity and frequency measures of alcohol consumption per month did not differ between these groups (Table 1). The impact of alcohol use on memory performance was examined in a series of analyses as reported below.

Verbal learning and memory performance

Cannabis users learned significantly fewer words than alcohol users ($p<0.001$) and controls ($p<0.001$) across all learning trials, with no difference between alcohol users and controls ($p>0.83$; repeated measures ANOVA main effect of group: $F(2,163)=10.38$, $p<0.001$; Table 2, Fig. 1). There was no group by trial interaction for learning across the five trials ($p=0.44$). Cannabis users recalled fewer words in total over Trials I–V than both alcohol users ($p<0.001$; 95% Confidence Interval (CI) 2.95–10.29, effect size Cohen's $d=0.74$) and controls ($p<0.001$; 95% CI 2.20–

Table 2 RAVLT Performance measures: mean (*SD*) or median [range]

	Cannabis	Alcohol	Controls	p^a	CAN vs. CON	CAN vs. ALC	ALC vs. CON
Trial I	7.48 (*1.97*)	8.47 (*1.63*)	8.42 (*1.81*)	<0.05	<0.01	<0.05	0.56
Trial II	10.04 (*2.82*)	11.72 (*1.79*)	11.17 (*2.16*)	0.05	0.13	<0.05	0.33
Trial III	11.00 [6–15]	13.00 [7–15]	13.00 [7–15]	0.10	–	–	–
Trial IV	13.00 [7.15]	14.00 [8–15]	14.00 [9–15]	0.12	–	–	–
Trial V	13.00 [8–15]	14.00 [9–15]	14.00 [7–15]	<0.05	<0.01	<0.05	0.45
Trial B	7.00 [3–11]	7.00 [4–14]	7.00 [3–11]	0.53	–	–	–
Trial VI (after interference)	12.00 [5–15]	12.00 [6–15]	13.00 [7–15]	<0.05	<0.01	0.07	0.22
Trial VII (after delay)	10.50 [4–15]	13.00 [7–15]	13.00 [8–15]	<0.001	<0.001	<0.01	0.20
Sum I–V total words recalled	53.33(*11.68*)	59.95 (*5.79*)	59.23 (*6.80*)	<0.001	<0.001	<0.001	0.89
Correct recognition list A	14.00 [10–15]	15.00 [13–15]	15.00 [13–15]	0.07	<0.05	0.10	0.46
Correct recognition list B	8.23 (*3.15*)	9.55 (*2.93*)	9.82 (*2.75*)	<0.05	<0.05	<0.05	0.86

Total words recalled or correctly recognised

[a] Pairwise comparisons performed using Tukey tests for normally distributed data (indicated by mean (*SD*)); Mann–Whitney *U* tests for skewed data (indicated by median [range])

9.59; Cohen's d=0.63; main effect of group: $F(2,172)$=10.57, p<0.001).

Inclusion of BDI and state anxiety scores, tobacco cigarettes smoked per day and alcohol quantity consumed per month as covariates, and with gender as a factor, made no difference to the results, with cannabis users remaining significantly impaired compared to alcohol users and controls in total words recalled (with all covariates and gender in the model: $F(2, 158)$=4.82, p=0.009; and neither gender nor any covariate were significant in the model. For results of analysis with each covariate separately, see Electronic supplementary material). Exclusion of the four users with high salivary THC levels did not alter the significant group difference in total words recalled ($F(2,168)$=9.07, p<0.001; with all covariates in the model $F(2,157)$=5.52, p=0.005). Inclusion of premorbid ability scores as covariates is described separately below.

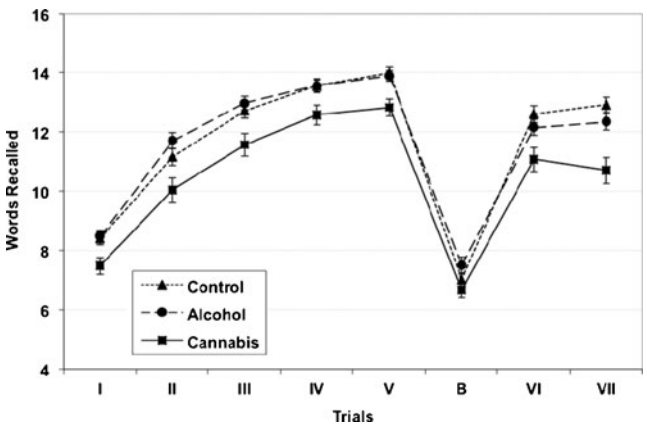

Fig. 1 Mean words recalled on each trial of the RAVLT by cannabis users, alcohol users and controls

Cannabis users' retention of verbal information following interference (Trial VI) and after a 20-min delay (Trial VII) was also significantly impaired (main effect of group Trial VI: $\chi^2(2)$=8.07, p<0.05; cannabis users vs. controls Z=2.77, p<0.01, Cohen's d=0.60; cannabis users vs. alcohol users p=0.074; main effect of group Trial VII: $\chi^2(2)$=15.44, p<0.001; cannabis users vs. controls Z=3.74, p<0.001, Cohen's d=0.84; cannabis users vs. alcohol users Z=2.86, p<0.01, Cohen's d=0.60). Cannabis users lost more words between Trials V (maximum learning) and VII (median two words) overall (main effect of group: $\chi^2(2)$=10.24, p=0.006), significantly more than controls (0.5 word; Z=3.14, p=0.002, Cohen's d=0.55) and marginally more than alcohol users (one word; Z=1.82, p=0.068).

Alcohol users did not differ from controls on any measure (total words recalled p=0.88; interference, p=0.22; delay, p=0.20; words lost, p=0.24).

Recognition performance and other memory indices

Cannabis users recognised significantly fewer words from list A (the well-learned list) than controls (Z=2.20, p=0.043, Cohen's d=0.56) and fewer words from list B (single trial) than both alcohol users (p=0.042; 95% CI 0.04–2.60, Cohen's d=0.44) and controls (p=0.012; 95% CI 0.28–2.90, Cohen's d=0.54; main effect of group: $F(2,178)$=4.66, p<0.01). There was no effect of gender (p=0.74) or gender by group interaction (p=0.12), and the group difference for recognition of list B remained significant after controlling for all covariates except premorbid ability scores which are described below ($F(2,164)$=3.14, p<0.046; results for individual covariates in Electronic supplementary material). Cannabis users'

recognition of list B remained impaired after exclusion of the four cannabis users with high salivary THC levels ($F(2,169)=6.98$, $p=0.001$). There were no significant group differences in the number of false positives on the recognition task ($p>0.18$).

Cannabis users did not differ in the number of repetitions made across any learning or recall trials ($p>0.06$), but they made significantly more intrusions (recalled non-list words) across Trials VI and VII than both controls ($p=0.015$, Cohen's $d=0.61$) and alcohol users ($p=0.012$, Cohen's $d=0.43$; $\chi^2(2)=9.54$, $p=0.008$ overall three group comparison).

Correlations with cannabis use measures

As shown in Table 3 and Fig. 2, total recall over the five learning trials and recall following interference and a delay were significantly associated inversely with frequency, quantity and duration of regular cannabis use, and positively with age of onset of first and regular cannabis use. Essentially, the younger the age of commencement of cannabis use, the longer that cannabis had been used, and the greater the extent of current cannabis use (quantity and frequency)—the fewer the total words learned and recalled and the fewer the words recalled after interference and a delay. Recognition measures were only associated with a few of the cannabis use measures (age of first cannabis use for recognition of List A; frequency of cannabis use for List B). Recency of cannabis use (self-reported hours since last use) was only associated with two outcome measures (recall following delay and recognition of List B) but measures of cannabinoid levels in the body (urine and saliva) were negatively correlated with total and delayed recall. Further, withdrawal scores correlated with total recall, recall following interference and a delay and intrusions during post-interference and delayed recall, but withdrawal symptoms were minimal in the sample. Dependence scores were not associated with any RAVLT outcome measures. Thus, almost all of the verbal learning and memory outcome measures worsened as a function of quantity, frequency, duration and age of onset of cannabis use in the sample, suggesting an enduring impairment associated with cumulative exposure to cannabis, while some appeared to also worsen in association with indicators of 'recent' cannabis use.

To explore the relative contributions of potential recent cannabis use versus a more enduring impairment associated with age of onset, duration and quantity/frequency measures, we conducted a series of partial correlations using the most robust measures of verbal learning and memory: total words recalled across the five learning trials and delayed recall. As shown in Table 4, relationships with age of onset, duration, quantity and frequency of cannabis use held after controlling for urinary and salivary cannabinoid levels and self-reported recency of use. In contrast, no relationships between memory performance and cannabinoid levels or recent use remained after controlling for the former cannabis use variables. This supports our interpretation of more enduring deficits in adolescent cannabis users. No relationships held with withdrawal scores after controlling for quantity, frequency, duration and age of onset of cannabis use (total words: partial $r=0.17$; delayed recall:

Table 3 Bivariate relationships between cannabis use measures and RAVLT performance

	Total words recalled I–V	Interference VI	Delay VII	Intrusions VI–VII	Recognition A	Recognition B
Cannabis frequency	−0.48***	−0.48***	−0.52***	0.10	−0.24	−0.32*
Cannabis quantity	−0.48***	−0.44***	−0.51***	0.11	−0.22	−0.24
Age of first cannabis use	0.31[a]*	0.31*	0.34*	0.01	0.36*	−0.11[a]
Age of regular cannabis use	0.43[a]**	0.42**	0.39**	−0.20	0.24	0.01[a]
Duration since first cannabis use	−0.25[a]	−0.19	−0.24	−0.07	−0.26	0.02[a]
Duration of regular cannabis use	−0.41[a]**	−0.41**	−0.41**	0.19	−0.24	−0.12[a]
Hours since last use	0.27	0.26	0.33*	−0.21	0.18	0.30*
Marijuana withdrawal score	−0.34*	−0.42**	−0.43*	0.35*	−0.19	−0.05
Severity of dependence score	−0.22	−0.26	−0.21	0.22	−0.09	−0.07
Urinary cannabinoid metabolite level (ng/mg)	−0.37**	−0.25	−0.40**	0.15	−0.07	−0.17
Salivary THC level (ng/ml)[b]	−0.32*	−0.19	−0.33*	0.21	−0.16	−0.23

Words recalled across Trials I through V, on Trials VI and VII, number of intrusions made over Trials VI and VII, and number of words correctly recognised from the well learned list (A) or the list presented once only (B)

*$p<0.05$, **$p<0.01$, ***$p<0.001$

[a] Pearson's correlations; all others are Spearman

[b] Salivary THC after exclusion of four users with ≥10 ng/ml

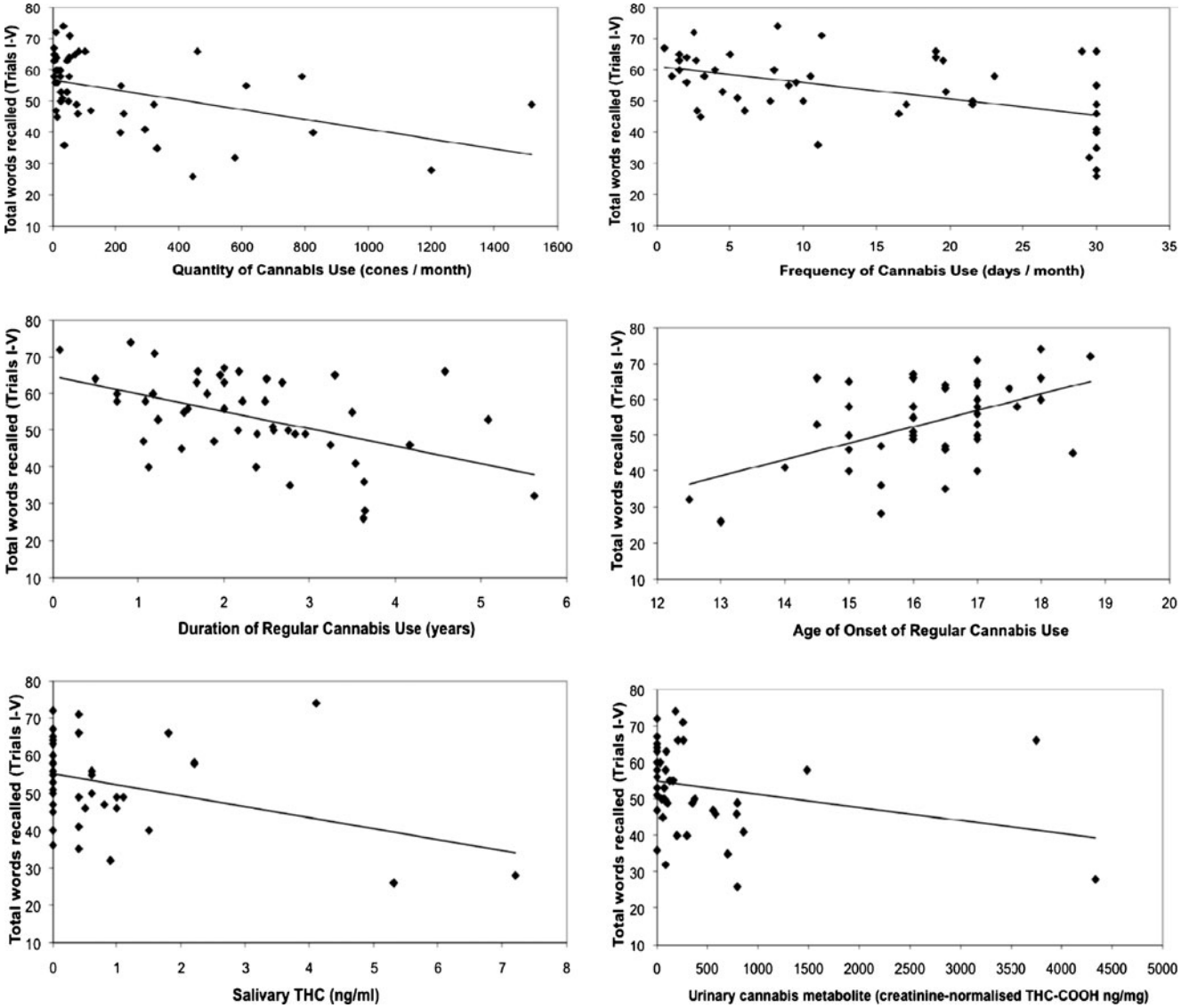

Fig. 2 Scatterplots depicting bivariate relationships between total words recalled over RAVLT Trials I–V and quantity, frequency, duration and age of onset of regular cannabis use, and urinary and salivary cannabinoid levels (after exclusion of four users with high salivary THC)

partial r=−0.14). Further, significant correlations between memory performance and age of onset of regular cannabis use also remained after controlling for quantity and frequency of use (Table 4), confirming an adverse effect of younger initiation to cannabis use regardless of extent of exposure to cannabis.

Correlations with alcohol use measures

Relationships between alcohol use and RAVLT performance were examined separately in each group and the results for cannabis and alcohol users are shown in Table S2. No performance measures were adversely associated with alcohol use in any group. In the alcohol group, delayed recall was positively associated with frequency of alcohol consumption, recall after interference was positively associated with frequency and quantity of alcohol use, and recognition of List A was positively associated with quantity of alcohol use. Age of onset of first or regular alcohol use, duration of alcohol use, recency of alcohol use and AUDIT scores were not significantly associated with any RAVLT outcome measure. Thus, there was some indication of better performance with greater current use of alcohol and a similar pattern was evident when alcohol use measures were examined in the cannabis user group. Total words recalled, recall after interference and delayed recall were positively associated with frequency of alcohol use, but not quantity, with no other associations between alcohol use and RAVLT performance among the cannabis users.

Table 4 Partial correlations between various cannabis use measures and RAVLT total words recalled and delayed recall

	Total words recalled I–V	Delay VII
Controlling for recent cannabis use and cannabinoid levels[a]		
Cannabis frequency	−0.38*	−0.47**
Cannabis quantity	−0.33*	−0.37*
Age of first cannabis use	0.33*	0.38*
Age of regular cannabis use	0.53***	0.58***
Duration of regular cannabis use	−0.47**	0.49***
Controlling for age of onset, duration, quantity and frequency of cannabis use		
Hours since last use	0.27	0.26
Marijuana withdrawal score	0.17	−0.14
Urinary cannabinoid metabolite level (ng/mg)	0.05	0.20
Salivary THC level (ng/ml)[a]	−0.13	0.22
Controlling for frequency and quantity of cannabis use		
Age of first cannabis use	0.22	0.23
Age of regular cannabis use	0.40**	0.43**

[a] Recent cannabis use as self-reported hours since last use, cannabinoid metabolite levels in urine and salivary THC after exclusion of four users with ≥10 ng/ml

*$p<0.05$, **$p<0.01$, ***$p<0.001$

Multiple regression: average monthly cannabis and alcohol consumption as predictors of recall

Multiple regression analyses were conducted with total words recalled over the five learning trials as the dependent variable in the cannabis group alone. With cannabis quantity and alcohol quantity as predictors, a significant model emerged ($F(2,48)=7.40$, $p<0.01$). These two predictors accounted for 23.6% of the variation in total words recalled. However, cannabis quantity alone accounted for 21.2% of the variance; therefore, adding alcohol quantity accounted for only an additional 2.4% of the variance. Further, a more powerful model was achieved by removal of alcohol, thus with cannabis quantity alone ($F(1,49)=13.22$, $p<0.001$). Frequency of cannabis use alone produced a highly significant model to explain 24.2% of the variance in total word recall ($F(1,49)=15.66$, $p<0.001$). Frequency of cannabis use and frequency of alcohol use were negatively correlated (Spearman's *rho*=-0.46, $p<0.001$), preventing their inclusion in a regression analysis.

Cannabis quantity and age of onset of regular cannabis use were also highly significant predictors of total words recalled ($F(2,48)=11.03$, $p<0.001$). The number of cones smoked per month and age of onset of regular cannabis use accounted for 31.5% of the variance in words recalled. Importantly, the combined model accounted for 10.3% more of the variance than cannabis quantity alone.

Frequency of alcohol use in the alcohol user group explained 6.6% of the variance in total words recalled ($F(1,61)=4.34$, $p=0.042$), with better recall with more frequent use, and adding age of onset of alcohol use did not improve the model, while quantity of alcohol use alone explained only 1% of the variance.

Inclusion of premorbid intellectual ability scores in regression models is described below.

Ecstasy use among the cannabis users

There were no significant differences between cannabis users who also used ecstasy and those who did not use ecstasy on total words recalled (53.1 vs. 53.5 words, respectively; $p=0.93$), recall after interference ($p=0.63$) or delayed recall ($p=0.88$).

Interrelationships between cannabis use and alcohol use

Co-use of substances, in particular cannabis and alcohol on the same occasion of use was also examined in the TLFB. TLFB summaries in Table S3 show that cannabis users consumed cannabis alone, with no other substances on a median 14 days (range 0–30). They used it in combination with alcohol on a median of 1.5 days (range 0–7) and together with ecstasy or other drugs on a median of 0 days (range 0–4). Differing values in Table 1 reflect composite measures averaged across several assessments of frequency and quantity of use and factoring in whether the past month assessed in the TLFB was reported as being atypical.

Frequency of cannabis use and frequency of alcohol use were correlated within the cannabis group, but in a negative direction (Spearman's rho=−0.46, $p<0.001$). That is, the more frequently that cannabis was used, the less frequently alcohol was used by the cannabis users. A similar relationship was observed between frequency of cannabis use and quantity of alcohol consumed per month by cannabis users (Spearman's rho=−0.31, $p<0.05$; as well as between frequency of alcohol use and quantity of cannabis use: rho=−0.43, $p<0.01$; the relationship between quantity of cannabis and quantity of alcohol consumed per month was also in a negative direction, but non-significant: rho=−0.21, $p=0.13$). These results indicate that despite some occasions of high alcohol consumption among the cannabis users, cannabis appears to be their drug of choice and the more that cannabis was used the less alcohol use was engaged in. The patterns observed in the TLFB (Table S3) support this in terms of separate occasions of cannabis use versus alcohol use, and very few days of co-use. Thus, the results of this study in terms of poorer verbal learning and memory in young cannabis users can not be attributed to a combined effect of cannabis and

alcohol together, and specific adverse effects associated with alcohol use were not found.

Influence of premorbid intellectual ability on RAVLT performance

The three groups did not differ in premorbid intellectual ability. Nevertheless, further analyses explored the influence of this on RAVLT performance. With premorbid standardised verbal and numerical ability scores included as covariates, the difference between groups in total words recalled remained highly significant ($F(2,110)=12.72$, $p<0.001$), with cannabis users impaired compared to either other group (control: $p<0.001$; alcohol: $p<0.001$), while alcohol users and controls did not differ ($p=0.64$). Verbal ability scores alone as covariates produced essentially the same results ($F(2,114)=16.74$, $p<0.001$). However, the significant group difference for recognition of list B (less rehearsed list) was lost after controlling for premorbid intellectual ability using both verbal and numerical ability scores ($F(2,113)=0.80$, $p=0.45$), and verbal ability alone ($F(2,117)=0.67$, $p=0.52$).

The remainder of the RAVLT outcome variables were not normally distributed, precluding analysis of covariance and transformation failed to normalise these variables. Therefore, a median split was performed on the combined verbal and numerical ability scores for the cannabis group only, to compare low (median score 80.67) and high (median score 93.25) premorbid ability cannabis users ($n=12$ in each group after exclusion of outliers). These two groups did not differ in repetitions ($p>0.55$), intrusions ($p>0.71$), recognition of List A ($p=0.82$) or false positives during recognition ($p=0.52$). Neither did low and high premorbid ability groups differ in recognition of list B ($p=0.72$), but there was a significant difference in total words recalled (low group, 46.7; high group, 55.5; $F(1,22)=4.68$, $p<0.05$). Despite this difference, we showed above that cannabis users' total recall was significantly poorer than both alcohol users and controls after controlling for premorbid intellectual ability scores.

Inclusion of premorbid verbal ability scores in regression analysis together with quantity of cannabis use per month and age of onset, produced a model that explained 61.7% of the variance in total words recalled ($F(3,22)=11.79$, $p<0.001$), but premorbid verbal ability contributed little as the latter two variables explained 61.5% of the variance ($F(2,23)=18.38$, $p<0.001$). In fact quantity of cannabis use alone provided the most significant model ($F(1,24)=23.19$, $p<0.001$), explaining 49% of the variance in this reduced sample for whom premorbid verbal scores were available. Premorbid verbal ability together with frequency of alcohol use explained 18.5% of the variance in total words recalled in the alcohol group ($F(2,45)=5.09$, $p<0.01$), with both variables predicting better recall. Finally, we explored potential interactions between low/high premorbid ability, gender and heavy/light or frequent/infrequent cannabis or alcohol use but no significant interactions were found (three-way interactions $p>0.30$ in both the cannabis group and the alcohol group).

Clinical significance and level of cannabis use for impairment to manifest

The clinical significance of the differences between groups is indicated by the proportion of cannabis users falling 1 or 2 SD below the control group mean on each measure. Thus, 42.3% of the cannabis users fell 1 SD below the mean of controls on total words recalled and 21.2% were 2 SD below the mean. For recall after interference, 38.5% were 1 SD and 21.2% 2 SD below the control mean. For delayed recall, 50% were 1 SD and 21.2% 2 SD below the control mean. For recognition, 30.6% fell both 1 and 2 SD below the control mean for list A, 44.2% fell 1 SD and 11.5% 2 SD below the control mean for list B.

While cannabis users differed overall from alcohol users and non-users, the extent of use required before significant impairment may manifest was examined by comparing the performance of lighter and less frequent cannabis users (by median split on quantity and frequency measures) with each of the non-cannabis-using groups. No significant differences were found for total words recalled ($p>0.31$), recall following interference ($p=0.29$), after delay ($p=0.17$) or recognition of list A ($p>0.51$) or list B ($p>0.20$). Thus, in adolescents who consumed on average 1.5 joints four times/month (the lighter, less frequent users in the sample), performance was not impaired relative to alcohol users and non-users of any substance.

Discussion

The results of this study demonstrate impaired verbal learning and memory in a sample of adolescent cannabis users with strong evidence for greater impairment the younger that regular cannabis use commenced. Despite their relatively short duration of exposure to cannabis (less than 2.5 years on average), these young cannabis users were impaired on most outcome measures from the RAVLT when compared with matched groups of adolescent alcohol users and non-substance-using controls.

The adolescent cannabis users learned fewer words across the five learning trials, recalled significantly fewer words in total over the five trials and after interference and a delay, forgot more words after interference and delay, and recognised fewer words from a less well-learned list than both alcohol users and controls. They recognised fewer

words from a well-learned list than non-user controls but did not differ from alcohol users on this measure. There was no evidence of differential effects of cannabis by gender or level of premorbid intellectual ability, and the majority of these deficits remained after controlling for premorbid intellectual ability, alcohol and tobacco consumption, ecstasy use, and psychological symptoms (anxiety and depressive symptoms). Overall, our findings suggest impaired acquisition, storage, retention and retrieval in adolescent cannabis users.

The vast majority of memory performance outcome measures worsened as a function of quantity, frequency, duration and early age of onset of cannabis use. A few measures were also associated with recency of cannabis use and urinary or salivary cannabinoid levels in zero-order correlations but not after controlling for quantity, frequency, duration or age of onset of cannabis use in partial correlational analyses. These results indicate that the greater the extent of exposure to cannabis and the younger the age at which cannabis use is initiated, the poorer the memory function, despite the potential for recent exposure to cannabis to also adversely affect performance. Some associations with withdrawal scores were observed in zero-order correlations, but such symptoms were minimal in the sample, are generally observed only in dependent heavy cannabis users 2 days or more following cessation of use (Vandrey et al. 2005), and these associations also disappeared after controlling for the more enduring cannabis use variables. As such, the poor performance observed in this study can not be attributed to withdrawal effects after this relatively light cannabis-using sample abstained from cannabis for 12–24 h prior to testing.

The cannabis users were not seeking treatment, were not dependent on cannabis, nor were they using on a daily basis or particularly heavily; average use was approximately 3 days per week, 17.5 joints per month, equating to approximately 1.25 joints on each occasion of use. Our results show that this level of use (but not use at once/week) was sufficient to produce memory deficits in adolescents, with medium-large effect sizes for most comparisons (ranging from 0.43 to 0.84). Further, the real-world or clinical significance of the differences between groups is indicated by the proportion of cannabis users falling one (30.6–50%) or two standard deviations (11.5–30.6%) below the control group mean on each of the memory indices. These results are similar to those we reported for adult long-term heavy cannabis users (Solowij et al. 2002) and could translate to impaired functioning in daily life, such as poorer educational outcomes. Indeed, educational underachievement has been consistently associated with adolescent cannabis use in a number of epidemiological studies (Lynskey and Hall 2000).

There has been some conjecturing regarding the possibility that cannabis use may exert greater adverse cognitive effects in individuals of lower IQ, or that high-IQ individuals may compensate for the impairing effects of cannabis (Bolla et al. 2002; Yücel et al. 2007; Solowij and Battisti 2008). We found no support for this in the current study, where the range of IQ could have enabled an interaction effect to be detected. Groups were matched on premorbid intellectual ability, and inclusion of these premorbid measures in our analyses made no difference to our results. While there has been scant evidence for gender-specific cognitive effects of cannabis (Pope and Yurgelun-Todd 1996; Pope et al. 2003), we found no evidence for differential gender effects and no interactions between gender, premorbid intellectual function and quantity/frequency measures of cannabis use. Females are generally greatly under-represented in studies of cannabis users, but in this study we had a reasonable proportion of females in the cannabis group, and equal gender distribution in the alcohol group.

Adolescent alcohol users did not differ from non-user controls on any of the RAVLT outcome measures. There was evidence in both the cannabis group and the alcohol group that greater frequency or quantity of alcohol consumption was associated with *better* memory performance (total words recalled, recall after interference and during recognition), but no associations between memory performance and age of onset or recency of alcohol use. Alcohol-related neurocognitive impairments have certainly been reported among adolescent drinkers (Monti et al. 2005) and there is some evidence of hippocampal volume reduction in adolescents with alcohol use disorders (De Bellis et al. 2000; Nagel et al. 2005). However, the adolescent alcohol users of this study were not seeking treatment and were not particularly heavy or frequent drinkers (despite some risky to hazardous drinking patterns), which may explain the lack of memory deficits observed.

In this study, we were also able to show that memory impairment was specific to cannabis use and was not attributable to co-use of cannabis and alcohol or other drugs. The adolescent cannabis users of this study tended to drink less alcohol the more entrenched they were in cannabis use, and cannabis was used separately to when alcohol was used. Simons et al. (2000) reported that experienced cannabis users had different motives for using cannabis versus alcohol and similarly found that participants in their sample did not consistently use the two substances concurrently. We had intended to examine potential effects of co-use of both substances but found that they were rarely ever used together on the same day. There has been a scant literature suggesting neuroprotective effects of cannabis when co-used with alcohol or ecstasy

(Consroe et al. 1979; Parrott et al. 2004). However, any such effects could not explain our unexpected findings of better memory function being associated with more frequent alcohol use—cannabis users did not use cannabis together with alcohol, and the alcohol users did not use cannabis at all, yet showed the counterintuitive relationship. With regard to ecstasy use, we showed that the memory impairments observed were specific to cannabis since ecstasy users did not differ from non-users within the sample. This accords with other research that has emphasised the relative importance of cannabis rather than ecstasy use in memory performance in adult samples (Croft et al. 2001; Simon and Mattick 2002).

The results of this study support the findings of two other studies that found verbal memory deficits in adolescent cannabis users (Harvey et al. 2007) and in young adults with early onset cannabis use during adolescence (Pope et al. 2003), although in the latter study deficits were no longer significant after controlling for verbal IQ. Here, we showed that deficits remained after controlling for premorbid verbal ability. Our findings suggest a specific impairment of verbal memory rather than generalised cognitive deficit as attentional and visuospatial impairments were minimal in a range of other neuropsychological tests administered to the same sample (to be reported elsewhere). While we have not previously found evidence for greater adverse effects associated with age of onset in our prior studies (Solowij et al. 2002), those studies were not designed to capture adolescent onset cannabis use and were conducted with much older adult cannabis users (mean age 35 years, range 19–55) with an average onset of regular use at 17.5 years.

Of note, we previously reported no significant impairment in RAVLT performance of adult cannabis users with a mean 10 years of use on a near daily basis, while adult users with 24 years use were impaired (Solowij et al. 2002). Performance worsened overall, however, as a function of increasing duration of use. The fact that the young cannabis users within the current study, with their far lesser exposure to cannabis over an average 2.4 years, showed similar significantly impaired performance relative to their age-matched counterparts as adult users with 24 years use, suggests indeed greater adverse effects of cannabis use on the developing brain. Cannabis quantity or frequency were highly significant predictors of total words recalled in regression models, which were enhanced by the inclusion of age of onset of cannabis use as a predictor in the model, but where neither alcohol consumption nor premorbid intellectual ability were found to contribute significantly. A greater adverse effect of early onset use was retained after controlling for frequency of cannabis use and quantity of exposure to cannabis.

The commencement of cannabis use between ages 15 and 16 coincides with the neurodevelopmental phase in which the brain is undergoing significant resculpting, synaptic pruning and ongoing myelination (Paus 2005; Schepis et al. 2008; Schneider 2008), and insults to these processes may manifest in the types of memory impairment observed in this study. Early-onset cannabis users (before age 17) have been found to have smaller whole brain volumes, lower percent cortical grey matter, higher percent white matter and increased cerebral blood flow compared to later onset users (Wilson et al. 2000). Altered cortical gyrification in the frontal lobe and abnormal age-related changes to gyrification and cortical thickness have recently been reported in adolescent and young adult users (Mata et al. 2010), and further studies of young adult (Arnone et al. 2008; Allin et al. 2009) and adolescent (Ashtari et al. 2009; Bava et al. 2009; Yücel et al. 2010) cannabis users have provided evidence for pathology in the corpus callosum and various fronto-temporal, occipito-frontal and posterior connections that develop during adolescence. It is suggested that cannabis use during adolescence may affect the trajectory of normal brain maturation resulting in white matter aberrations, which may underlie compromised cognitive processing. We have evidence for cerebellar white matter reduction in adult long-term heavy users (Solowij et al. 2011) and previously we reported hippocampal structural alterations in adult long-term heavy cannabis users (Yücel et al. 2008), although these were not related to performance on the RAVLT. Further specific investigations of brain structure and function are clearly warranted in adolescent cannabis using-samples.

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, the over-representation of females within the control group, and the reliance on self-reported therapeutic prescription medication to explain urinalysis results of nine participants (spread across each group). We accounted for the majority of these limitations as best we could in the analyses conducted and do not believe that they impact upon our results in any substantial way.

In conclusion, our findings demonstrate that adolescent cannabis users have impaired verbal learning and memory, which appears to be specific to cannabis and not alcohol exposure. After controlling for a number of potential confounds, including other substance use, psychological symptoms of anxiety and depression, and importantly, premorbid intellectual functioning, we were also able to show that impairment increased as a function of quantity, frequency, duration and age of onset of cannabis use. An earlier age of onset of regular use was associated with worse performance even after controlling for extent of exposure to cannabis. This is particularly concerning given

not only the high prevalence of cannabis use among adolescents per se, but with epidemiological evidence for decreasing age of first use (Degenhardt et al. 2000; 2008; Copeland and Swift 2009; European Monitoring Centre for Drugs and Drug Addiction 2009; Johnston et al. 2010). Since we were able to show that light and less frequent cannabis users did not differ from alcohol users or controls, further research might determine whether there may be a threshold of use beyond which adolescent cannabis users place themselves at risk of experiencing cognitive impairment. Nevertheless, adolescents should be warned about the potential risk of cognitive impairment from early initiation to, and continued regular use of cannabis. The extent to which such memory impairment may recover with abstinence remains to be determined.

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