The relationship between non-acute adolescent cannabis use and cognition

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Abstract

Research indicates that cannabis continues to be a popular illegal drug internationally. Furthermore, adolescent rates of use appear to be significant. Whilst the non-acute effect of cannabis use on adult cognition has been extensively researched, there has been less examination of adolescents. This study aimed to investigate the non-acute relationship between cannabis and cognitive function in a sample of adolescents with a continuum of cannabis use, taking into account additional predictor variables (psychiatric functioning, general functioning, demographics and other drug use). Seventy adolescents were recruited from clinical and community sources as well as through newspaper advertisements. After 12 hours abstinence from cannabis, adolescents completed a two-hour interview covering: demographics; alcohol and drug use history; drug use in the past 28 days; depression; further psychiatric functioning (including ADHD and Conduct Disorder); and cognitive functioning as measured by computerised tasks (CANTAB) and traditional pen and paper tests. Adolescents who were regular cannabis users (more than once a week) had a significantly poorer performance on four measures of cognitive function reflecting attention, spatial working memory and learning. Cannabis use remained an independent predictor of performance on the working memory and strategy measures after additional predictor variables were included in a multivariate regression analysis. The results suggest that aspects of adolescent cognitive function are independently related to the frequency of cannabis use beyond acute intoxication. [Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev 2007;26:309 – 319]

Key words: adolescents, cannabis, cognition, predictor variables, working memory.

Introduction

Cannabis is the most popular, illegal, recreationally-used drug in New Zealand with estimates that 52% of the general population have tried cannabis and 20% have used it in the past 12 months [1]. The Christchurch Health and Development study (CHDS) found that by the age of 21 years, around 70% of adolescents (that is, youth aged between 13 and 18 years) had tried cannabis [2]. Moreover, the Dunedin Multidisciplinary Health and Development Study (DMHDS) [3] found that in its cohort, approximately 62% had tried cannabis by the age of 21 years. The CHDS and DMHDS presentation of higher rates of use may be due in part to the differences in methodology of these longitudinal studies and other [1] cross-sectional approaches. Additionally, 30% of people presenting to Alcohol and Other Drug (AOD) services are having problems with cannabis [4].

Since the 1970s there have been a large number of studies considering the non-acute effects of cannabis on cognition. Non-acute refers to the effects of the drug after acute intoxication, that is, residual effects from cannabis use. There are few consistent and replicated results in this area. Pope, Yurgelun-Todd and Gruber [5,6,8,9] have reported findings from the comparison of...
65 heavy and 64 light cannabis users after a minimum of 19 hours abstinence [10]. They found some compromise in memory function, but mainly effects on attention or executive functioning. Results remained after controlling for confounding variables including psychiatric illness, use of other drugs, previous head injury, gender, age and education. When they explored this sample further (with 25 heavy users and 30 light) using more sensitive computerised tasks [9], they found no significant results in the sample, but did find a gender-specific effect on visuospatial memory whilst still controlling for demographics, head injury and psychiatric illness with no difference between light and heavy smoking males, but heavy smoking females showing significantly greater impairment on visuospatial memory tests than female light cannabis smokers. Pope et al. [8] have also investigated 77 current heavy users and 87 controls (who had used cannabis fewer than 50 times) and found deficits on working memory of word lists in the heavy users.

In 2003 Pope et al. [46] published the full sample results of their earlier studies with 209 subjects discussing the relationship between age of onset of cannabis use and neuropsychological performance. Subjects, aged between 30 and 55 years, were grouped into 77 heavy users (smoked at least 5000 times in their life and smoking daily at the start of the study), 45 former heavy users (as with current heavy users, but smoked fewer than 12 times in the past 3 months) and 87 controls (smoked fewer than 50 times ever and only once in the last year). Heavy users were also divided into those that had started cannabis use before age 17 (early-onset) and post age 17 (late-onset). They excluded use of other illicit drugs more than a 100 times, alcohol dependence, current use of psychotropic medication, head injury causing concussion, medical or neurological conditions effecting cognitive functioning and current DSM-IV Axis I disorders. After 28 days abstinence, early-onset users differed significantly from late-onset users and controls most notably on verbal intelligence. Once adjusted for verbal intelligence, all other cognitive differences between early-onset users and controls ceased to be significant.

Block et al. [11,12] used premorbid school tests as a way of matching for intellectual functioning in a sample of 144 cannabis users and 72 non-users. Users and non-users were matched on scores on the Iowa Tests of Basic Skills given in the fourth grade of school (approximately age 10 years). The age range at the time of testing, in order to obtain school results, was 18–42 years. After 24 hours abstinence, heavy users (seven times a week or more) showed a small yet significant impairment in mathematics, verbal expression and memory retrieval despite prior matching for age, education and intellectual functioning (including language and mathematic skills). The authors concede that there may be confounding factors occurring, such as gender distribution and use of other drugs. Medical and psychiatric functioning were not assessed in the sample and thus their contribution was not analysed.

Bolla et al. [47] looked at cognitive functioning in cannabis users after 28 days of abstinence. They tested 22 cannabis users (who used at least three times a week for at least two years) with an average age of 22 years, with no other drug dependence except caffeine and nicotine and with no past or present psychiatric disorder and no past or present neurologic illness. Subjects were divided into light \( (n = 7) \), middle \( (n = 8) \) and heavy \( (n = 7) \) users based on joints per week. As joints per week increased, performance decreased on tests measuring verbal and visual memory, executive functioning, visuoperception, psychomotor speed and manual dexterity. Though there were dose-related effects, in contrast to previous studies, duration of use had little effect on neurocognitive performance. The authors concluded that heavy cannabis use is associated with persistent decrements in neurocognitive performance after 28 days abstinence. They noted that this study does not clarify whether decrements would resolve with continued abstinence or worsen with continued heavy use.

More recent work on the non-acute effects of cannabis has been able to utilise modern technology such as EEGs and PET scans. Solowij [13] employed brain event-related potential (ERP) recording technology to investigate further attentional mechanisms implicated in earlier studies of non-acute cannabis and cognition. In a series of experiments (with sample sizes varying from 9–32), she looked at long term cannabis users (minimum of five years use at least twice a week) after 12 hours abstinence and found subtle impairments of selective attention related to the frequency and duration of cannabis use. Further work by Solowij and colleagues [14] considered 51 long and 51 short term users compared to 33 controls. This study, including use of the Rey Auditory-Verbal Learning Test (RAVLT), confirmed findings of cognitive impairment in chronic, heavy long term, but not shorter term, cannabis users regardless of near-daily use by all users. The greatest impairment was on the RAVLT in regard to learning and delayed recall. These results have not been widely replicated in adolescent samples. Furthermore, the literature on adolescent cognition and cannabis use is limited and suffers from methodological flaws such as limited numbers, retrospective estimates of drug use, and the lack of control for confounding variables.

While not researching adolescents themselves, Ehrenreich et al. [48] considered the effects on cognition from early-onset cannabis use compared to late-onset use. Their sample consisted of 99 regular (once a week
or more for at least six months) cannabis users and 49 controls with comparable age, sex and education who were currently aged on average between 21 and 24 years with no other past or present drug abuse or history of neuropsychiatric disease. Subjects were tested on average 29 hours after intoxication. Early-onset (before 16 years) predicted impaired reaction times solely in visual scanning. The authors concluded that beginning cannabis use during early adolescence may lead to enduring effects on specific attentional functions in adulthood. This is in keeping with Kempel et al.’s [49] findings on early-onset use and selective attention.

A number of studies consider the effects of cannabis within the context of other drug use. Giancola et al. [15] investigated executive functioning in 188 female adolescents with substance use disorders and 94 controls aged 14–18 years. Adolescents with psychosis, neurologic or neuromuscular disease or past head injury were excluded. Adolescents were abstinent from drugs for two weeks before testing. They found that female substance users (68% with a cannabis use disorder) had lower executive functioning scores than controls. Executive function was significantly related to drug use involvement even when controlling for age, socio-economic status and vocabulary level. Another study by Teichner et al. [16], considered whether there were differences within a sample of drug using adolescents in terms of neuropsychological impairment where the primary diagnoses were cannabis related. They tested 77 adolescents with drug and conduct problems with a mean age of 15.3 years. Sixty-nine percent had a diagnosis of cannabis dependence. They found no significant relationship between neuropsychological functioning and drug use measures.

Two large scale Australasian papers investigated educational attainment related to cannabis use [18,19] and found cannabis users to have poorer educational achievement, but the author’s state that this was likely to be related to social context such as neighbourhood, early conduct problems, or strong connection with delinquent or drug using peers. A pilot study, with 10 cannabis dependent adolescents and 17 controls [20] found evidence of a residual effect of heavy cannabis use on selected short-term auditory and visual memory processes.

Following up on an earlier adolescent sample of drug users after eight years (to an average age of 24 years), Tapert et al. [17] looked at the effect of cannabis on cognition. Cannabis use was quantified as the average days per month of cannabis use. They tested 47 youths with substance use disorders and a comparison sample \( n = 26 \) with similar age, gender, socio-economic status, education and family history of substance use disorders. Cannabis use in the past 48 hours was excluded. In this sample, attentional abilities were sensitive to cannabis use with frequent cannabis use predicting poorer attention, particularly speeded psychomotor processing even after accounting for baseline attention functioning, age and practice effects. This finding fits well with results in the adult literature [10,13].

A pilot study by Schwartz et al. [50] evaluated auditory/verbal and visuospatial memory of 10 cannabis-dependent adolescents, 8 past users and 9 non-users matched for age, IQ and absence of learning disabilities. Frequent alcohol or phencyclidine use was excluded as were histories of seizures, concussions or psychosis. Tests were administered at baseline and after six weeks of abstinence from cannabis. At baseline, significant differences were found on selected measures of short-term auditory and visual memory processes with cannabis dependent adolescents performing worse than non-users and past users. No differences were found on verbal IQ. Cannabis dependent adolescents improved on memory measures after six weeks abstinence, but not significantly.

Jacobsen et al. [50] used fMRI to look at 7 cannabis and nicotine smokers, 7 nicotine only smokers and 7 non-smoking controls all with similar age and gender. All adolescents were free of medical or psychiatric illness as well as other illicit drug use. On a task of selective, divided and sustained attention cannabis users had a significantly lower percentage of hits than non-smokers. Also performance accuracy of cannabis users on a working memory task was significantly lower than that of non-smokers. Measures of cannabis use and performance accuracy were not significantly correlated with right hippocampal activity. However, across the working memory task conditions adolescent cannabis users failed to deactivate the right hippocampus.

Fried et al. [51] investigated cognitive consequences of cannabis in a sample of 113 young adults who had been followed since birth and cognitively assessed over the years as part of the Ottawa Prenatal Prospective Study. This enabled them to consider cognitive function prior to the onset of cannabis use in the analysis of cognitive performance and cannabis use. They tested 59 non-users, 19 current light users (less than five joints a week), 19 current heavy users (more than five joints a week) and 16 past users (abstinent three months or more). Subjects had no use of psychotropic medication or drugs other than cannabis, alcohol and nicotine. Potential confounders measured were socio-economic status, prenatal exposure to drugs, age, gender, nicotine and alcohol use and DSM-IV Axis I disorders. After factoring in confounders and pre-drug performance, current heavy users did significantly worse than non-users in overall IQ and processing speed as well as immediate and delayed memory.
After controlling for pre-drug performance, there was no relationship between current cannabis use and working memory or verbal IQ. Past users showed no cognitive impairment, despite having high levels of exposure to cannabis (average of 2203 joints).

Therefore, similar to the adult literature on cannabis and cognitive functioning, some associations can be drawn between adolescent cannabis use and cognition. Early-onset cannabis use was also related to impairments in attention. There is further evidence that executive functioning may be impaired in adolescent cannabis users and of possible differential affects of cannabis on adolescent hippocampal memory function. Some significant associations between cannabis use and cognition dissipate when premorbid intelligence is accounted for. Consequently, whilst the non-acute relationship between adult cognitive functioning and cannabis has been explored, further attention needs to be given to this relationship in adolescents. Solowij et al. [13] concluded that long-term cannabis use does not have a severe debilitating impairment on cognitive function, but leads to subtle selective impairment, primarily affecting the ability to focus, sustain and shift attention. This subtle impairment may have more significance for adolescents who are in an accelerated phase of life in terms of developing cognitive abilities and expanding their knowledge base through education. Additionally concerning for adolescents is the finding that cognitive deficits from cannabis in adults may not be entirely reversible or reversible for all individuals [13]. Particular attention needs to be paid to the effects that cannabis may continue to have following consumption of the drug and what other factors may affect the relationship.

It has been hypothesised that additional predictor variables may affect the outcome of the relationship between cannabis use and cognition. Whilst the literature is complex, there is evidence that cognitive function may be affected by mood [21,22], Attention Deficit Hyperactivity Disorder (ADHD) and conduct disorder [23 – 25], gender [26,27], alcohol [28,29], use of other drugs, particularly 3,4-methylenedioxy-methamphetamine (MDMA) or amphetamines [30,31] and menstruation [32,33].

The present study conducted an investigation of the non-acute relationship between cannabis use and cognitive functioning in a broad sample of adolescents recruited from both clinical and community settings and set out to answer two main questions: Is there a significant non-acute relationship between cannabis and cognitive function in adolescents aged 13–18 years; and if there is a significant relationship, are there additional predictor variables (psychiatric functioning, general functioning, demographics and other drug use) that can account for the relationship beyond the use of cannabis?

Methods

Sample

Adolescents were recruited from the Youth Specialty Service at Hillmorton Hospital in Christchurch, two Christchurch Secondary Schools and by newspaper advertisement. Inclusion criteria were: adolescents aged 13–18 years and not currently suffering from a psychotic condition (as reported by referring clinician). Informed written consent was obtained from participants and their parents or caregiver. Adolescents completed the two hour interview (after a minimum of 12 hours self-reported cannabis abstinence: self-report occurred in a safe and confidential setting) at the location of their choosing, most typically (70%) the National Addiction Centre offices. The study was approved by the Canterbury Ethics Committee.

Measures

Adolescents completed a demographics questionnaire including age, ethnicity, school enrolment status, and self-rated ability in Primary School in reading, spelling and arithmetic. In New Zealand children attend Primary School from ages 5 – 10 years and Intermediate School at ages 11 and 12 years.

Alcohol and drug measures. The Alcohol and Drug measures used were a drug and alcohol use history and the Timeline Follow-back (TLFB) questionnaire [34] for drug use in the past 28 days. To assess how representative the past 28 days of drug use was of use in the previous six months, each subject was asked to rate how typical their reported drug use was, as assessed in the TLFB, compared to the prior five months. A 5-point Likert scale was used to represent typicality with the range of: 1 = much less, 2 = less, 3 = typical, 4 = more, and 5 = much more. In addition, adolescents gave a urine sample at the time of the interview, for testing of the presence of cannabis.

Cognitive tests. The cognitive test battery measured intelligence, memory, attention and executive functioning using a combination of computerised tasks and pen and paper tests.

Intelligence was measured using the Wechsler Abbreviated Scale of Intelligence [WASI: 35], which can be applied to individuals aged 6 – 89 years. The WASI was employed in this study as the age range of participants was not adequately covered by either the Wechsler Intelligence Scale for Children [36] or Wechsler Adult Intelligence Scale [37]. The WASI covered the entire range of ages of participants. The WASI is linked to the Wechsler Intelligence Scale for Children and the Wechsler Adult Intelligence Scale.
This standardised test produces verbal, performance (matrix reasoning) and full-scale IQ scores.

The Cambridge Neuropsychological Test Automated Battery [CANTAB: 38] is a computerised test battery that utilises touch screen technology. The tests used were: Motor Screening – a training procedure and screening test for visual and movement problems; Rapid Visual Information Processing (RVIP) – a test of sustained attention with a working memory component; Spatial Working Memory (SWM) – that requires the adolescent both to formulate a strategy and to remember which spatial locations (boxes) have previously contained a counter; Intradimensional Extradimensional shift (ID/ED) – an attentional set shifting task; Paired Associates Learning (PAL) – a form of delayed response procedure, which tests two different aspects of the ability to form visuo-spatial associations; and Spatial Span – a test of spatial memory span.

Pen and paper cognitive tests applied were: the Rey Auditory-Verbal Learning Test (RAVLT) [39] – a test of verbal declarative memory with a working memory component; Digit Span [37] – a task of attention and working memory; and Symbol Digit Modalities Test [40] – a task of sustained attention.

Psychiatric measures. Psychiatric functioning measures included: Visual Analogue Scale for Mood (present mood); Beck Depression Inventory II [41]; Hamilton Depression Rating Scale [42]; Conduct Disorder and Attention Deficit Hyperactivity Disorder (ADHD) (semi structured interviews based on DSM-IV criteria: [43]; Structured Clinical Interview for the DSM-IV (for current or past – major depressive episodes; manic episodes; hypomanic episodes; dysthymic disorder; major depressive disorder; alcohol abuse; alcohol dependence; other substance abuse (including cannabis); other substance dependence (including cannabis); panic disorder; agoraphobia; social phobia; post traumatic stress disorder; generalised anxiety disorder; anorexia nervosa; bulimia nervosa; and binge eating disorder [SCID-I: 44]; and the Global Assessment of Functioning Scale, Axis 5 of the DSM-IV [43].

Results

The mean age of the sample was 16.2 years (range 13.5 – 18.4 years). Sixty percent were female and 27% were Māori. Nearly 60% were currently attending secondary school and the median number of secondary school years completed was two. Table 1 presents the differences between non-regular and regular cannabis users on gender, ethnicity and age.

Psychiatric and general functioning results for the two groups are reported in Table 2. In regard to results of the Structured Clinical Interview for the DSM-IV, regular user and non-regular user groups differed significantly on cannabis abuse current and past (\(\chi^2 = 25.04, df = 1, p < 0.001\) and \(\chi^2 = 11.21, df = 1, p = 0.001\) respectively), and cannabis dependence current and past (\(\chi^2 = 26.16, df = 1, p < 0.001\) and \(\chi^2 = 14.64, df = 1, p < 0.001\) respectively). Non-regular and regular users also differed significantly on alcohol abuse current (\(\chi^2 = 4.05, df = 1, p = 0.044\)) and past (\(\chi^2 = 6.89, df = 1, p = 0.009\)) and alcohol dependence past (\(\chi^2 = 4.94, df = 1, p = 0.026\). Non-regular and regular cannabis users did not differ significantly on any other psychiatric disorders.

Drug use

Timeline Follow-back showed that 68.5% of the sample had used cannabis in the past 28 days (for medians and range of cannabis use in all groups, see Table 4). To define cannabis use groups using total days of use in the past 28 days (Timeline Follow-back), the sample was split on the median days of use (median = 4), which produced groups of adolescents who used either once a week or less (non-regular users, n = 36) and those who used more than once a week (regular users, n = 34).

Days of cannabis use in the past 28 days was strongly correlated with all other cannabis measures (e.g. total days and total quantity of use in the past 28 days, \(r = 0.76, p < 0.01\) and was subsequently used as the standard cannabis measure in all analyses, including regressions.

The presence of cannabis in urine samples is presented in Table 3. The proportion of non-regular users with cannabis in their urine was 2 (5.6%) and for regular users, it was 29 (85.3%: \(\chi^2 = 45.06, df = 1, p < 0.001\)). As expected, the presence of cannabis in urine could not substantiate the 12 hours abstinence.

Of the total sample, 88.6% had tried cannabis while 70% had used it more than five times in a month at some stage. The median age of initiation was 13 years (range 5 – 17 years) for the total sample, 13 years (range 5 – 17 years) for the non-regular users and 12 years (range 7 – 16 years) for the regular users. The median age of heaviest use was 15 years for both groups with the range differing only minimally between non-regular and regular users (11 – 16 years and 11 – 18 years respectively).

In the past 28 days there was no use of any injected drugs or of non-injected benzodiazepines. The most commonly used drugs were cannabis, alcohol and nicotine (see Table 4). As results for cannabis, alcohol and nicotine use were skewed, Mann-Whitney U tests were used for comparison. There were significant differences between regular and non-regular cannabis users on total days of use of cannabis (\(z = -7.31, p < 0.001\)) and nicotine (\(z = -4.28, p < 0.001\)). Other
non-injected drug use was: stimulants 5.7% (8.3% of non-regular users, 2.9% of regular); opioids 1.4% (2.8% non-regular users, 0% regular); 5.7% hallucinogens (0% non-regular users, 11.8% regular); inhalants 11.4% (2.8% non-regular users, 20.6% regular); and ‘herbal’ drugs 10% (largely Benzylpiperazine based) with 2.8% of non-regular users using and 17.6% of regular users.

Non-regular and regular users did not differ in their assessment of the typicality of the last month of drug use compared to the prior five months ($\chi^2 = 2.91$, df = 1, $p = 0.09$) with medians of 2.5 and 3 respectively both representing typical use. The total sample, non-regular users and regular users all had a range of 1 – 5.

Cannabis use and cognitive tests

T-tests or Mann Whitney U tests were used to compare cognitive tests between the two cannabis use groups (non-regular and regular users) depending on whether data were normally distributed or not. Four of the cognitive measures showed a significant ($p < 0.05$) association with cannabis use (see Table 5). These measures were Rapid Visual Information Processing A' ($t = 2.701$, df = 68, $p = 0.009$), Spatial Working Memory total errors ($t = -2.836$, df = 68, $p = 0.006$), Spatial Working Memory strategy ($t = -2.804$, df = 68, $p = 0.007$) and the sum of Trials A1 to A5 on the Rey Auditory-Verbal Learning Test ($t = 3.199$, df = 68, $p = 0.002$).

For the RAVLT, scores on trials A6 (distraction) and A7 (delayed recall) were adjusted to reflect the learning effect through trials A1 – A5: thus A6 adjusted was A6 as a percentage of A1 – A5 and A7 adjusted was A7 as a percentage of A1 – A5. Regular cannabis users performed less well, though not necessarily significantly, on all these tasks.

Additionally, in regard to the main effect by trial on the RAVLT, there was a learning effect for all groups ($f(4, 272) = 143.72$, $p < 0.001$). This learning effect, however, was not significantly different between the non-regular and regular users ($f(4, 272) = 0.50$, $p = 0.735$) and thus no main effect of trial by group.

The mean general intelligence score for the sample was 99.74, which is classed as average. Non-regular cannabis users had a mean general intelligence score of 103.36 and regular of 95.91 ($t = 2.47$, df = 68, $p = 0.02$), both also average. The mean verbal intelligence score for the sample was 49.01 (51.06 for
non-regular users and 46.85 for regular: $t = 1.5$, $df = 68$, $p = 0.13$) and the mean matrix reasoning score was 50.19 for the sample (52.42 for non-regular users and 47.82 for regular: $t = 2.65$, $df = 60.31$, $p = 0.01$).

From the WASI results the verbal intelligence score taken as a covariate of verbal intelligence has traditionally been the more stable intelligence measure [45].

### Table 4. Timeline follow-back: cannabis, alcohol and nicotine use for the previous 28 days

<table>
<thead>
<tr>
<th></th>
<th>Total sample, $N = 70$</th>
<th>Non-regular users, $n = 36$</th>
<th>Regular users, $n = 34$</th>
<th>Difference between non-regular versus regular $p$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis number of days</td>
<td>4 (0–28)</td>
<td>0.0 (0–4)</td>
<td>12 (5–28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cannabis quantity per session$^a$</td>
<td>0.5 (0–3)</td>
<td>0.0 (0–6)</td>
<td>1.1 (0.3–3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cannabis quantity total 28 days$^a$</td>
<td>2.9 (0–84.8)</td>
<td>0.0 (0–6)</td>
<td>11.3 (2.2–84.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol number of days</td>
<td>2 (0–28)</td>
<td>1 (0–14)</td>
<td>2.5 (0–28)</td>
<td>0.180</td>
</tr>
<tr>
<td>Alcohol quantity per session$^b$</td>
<td>4.5 (0–41.3)</td>
<td>3.8 (0–41.3)</td>
<td>5.4 (0–35.4)</td>
<td>0.291</td>
</tr>
<tr>
<td>Alcohol quantity total 28 days$^b$</td>
<td>13.5 (0–320)</td>
<td>8.5 (0–320)</td>
<td>20.5 (0–120)</td>
<td>0.145</td>
</tr>
<tr>
<td>Nicotine number of days</td>
<td>28 (0–28)</td>
<td>28 (0–28)</td>
<td>28 (13–28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nicotine quantity per session$^c$</td>
<td>8.6 (0–28.6)</td>
<td>4.7 (0–18)</td>
<td>12.9 (2.7–28.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nicotine quantity total 28 days$^c$</td>
<td>240 (0–800)</td>
<td>84 (0–400)</td>
<td>360 (35–800)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^a$Cannabis quantity measured in joint equivalents, $^b$alcohol quantity measured in standard drinks and $^c$nicotine quantity in cigarettes.

### Table 5. Adolescent cognitive measures by cannabis use group (mean (SE))

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>Non-regular users, $n = 36$</th>
<th>Regular users, $n = 34$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weschler Abbreviated Scale of Intelligence Verbal scores</td>
<td>51.1 (11.9)</td>
<td>46.9 (11.0)</td>
<td>0.130</td>
</tr>
<tr>
<td>Weschler Abbreviated Scale of Intelligence Matrix reasoning scores</td>
<td>52.4 (6.9)</td>
<td>47.8 (8.4)</td>
<td>0.010</td>
</tr>
<tr>
<td>Weschler Abbreviated Scale of Intelligence General scores</td>
<td>103.4 (13.0)</td>
<td>95.9 (12.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>Motor screening</td>
<td>822.083 (187.78)</td>
<td>794.18 (145.83)</td>
<td>0.492</td>
</tr>
<tr>
<td>Rapid Visual Information Processing A</td>
<td>0.88 (0.01)</td>
<td>0.85 (0.01)</td>
<td>0.009</td>
</tr>
<tr>
<td>Rapid Visual Information Processing B$^a$</td>
<td>0.97 (0.94–1.0)</td>
<td>0.96 (0.90–1.0)</td>
<td>0.218</td>
</tr>
<tr>
<td>Spatial Working Memory (total errors)</td>
<td>21.25 (2.34)</td>
<td>31.12 (2.58)</td>
<td>0.006</td>
</tr>
<tr>
<td>Spatial Working Memory (strategy)</td>
<td>31.42 (0.90)</td>
<td>34.76 (0.77)</td>
<td>0.007</td>
</tr>
<tr>
<td>Intra/Extra-Dimensional shift (extra-dimensional shift)$^b$</td>
<td>24 (67%)</td>
<td>19 (56%)</td>
<td>0.354</td>
</tr>
<tr>
<td>Paired Associates Learning (mean trials to success)$^a$</td>
<td>1.25 (1.25–1.75)</td>
<td>1.50 (1.25–1.75)</td>
<td>0.395</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>6.39 (0.28)</td>
<td>6.47 (0.23)</td>
<td>0.824</td>
</tr>
<tr>
<td>Rey Auditory-Verbal Learning Test A1–A5</td>
<td>56.36 (1.31)</td>
<td>49.44 (1.74)</td>
<td>0.002</td>
</tr>
<tr>
<td>Rey Auditory-Verbal Learning Test A6 adjusted</td>
<td>21.97 (0.63)</td>
<td>22.79 (1.18)</td>
<td>0.535</td>
</tr>
<tr>
<td>Rey Auditory-Verbal Learning Test A7 adjusted</td>
<td>17.92 (0.50)</td>
<td>17.27 (0.61)</td>
<td>0.422</td>
</tr>
<tr>
<td>Digit span</td>
<td>14.39 (0.74)</td>
<td>14.03 (0.55)</td>
<td>0.698</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>51.19 (1.92)</td>
<td>48.79 (1.92)</td>
<td>0.379</td>
</tr>
</tbody>
</table>

$^a$Median (range) compared with Mann-Whitney U test. $^b$Number (percentage) compared with Chi Square (Cognitive measures show as follows: Motor Screening – the time taken for the subject to touch visual stimulus after it appeared; Rapid Visual Information Processing A – represents the measure of sensitivity to errors, regardless of error tendency (i.e. how good the adolescent was at detecting target sequences); Rapid Visual Information Processing B – the tendency to respond regardless of whether the target sequence was present; Spatial Working Memory total errors – the number of times the subject selected an incorrect box; Spatial Working Memory strategy – an estimate of the use of the most efficient strategy for completing this task; Intra/Extra-Dimensional Shift – number of adolescents to reach stage eight, indicating an extradimensional shift; Paired Associates Learning First trial memory score – the number of patterns correctly located after the first presentation summed across the stages completed; Paired Associates Learning Mean trials to success – calculated as the total number of trials for all stages and then divided by the number of stages; Spatial Span – span length, which was the longest sequence successfully recalled by the subject; Rey Auditory-Verbal Learning Test A1–A5 – total words recalled on Trials 1–5; Rey Auditory-Verbal Learning Test A6 adjusted – total words recalled on Trial A6 adjusted; Rey Auditory-Verbal Learning Test A7 adjusted – total words recalled on Trial A7 adjusted; Digit span – number of digits recalled from Digits Forward and Digits Backwards combined; and Symbol Digit Modalities Test – the sum of correct responses completed in the time limit).
Stepwise regressions to determine the independent contribution of cannabis use groups for each of the significant cognitive measure results

Four stepwise linear regressions were undertaken. As cannabis use measures were all skewed, the cannabis groups of non-regular and regular users was entered as a binary variable as appropriate in the regressions. Each cognitive measure regression included all of the additional predictor variables that were significantly related on univariate testing to the specific cognitive test. The significant variables varied from measure to measure (see Table 6). Where a cognitive measure was significantly related to more than one measure of a drug other than cannabis in the past 28 days, only one measure of the drug use was used: the total days of use for the particular drug in the last 28 days, as in all other drug categories. This related significantly to additional measures of other drug use.

The stepwise regression for Rapid Visual Information Processing produced a final model with three significant predictors. These were: years of secondary school completed ($p < 0.001$), self-rated arithmetic ability in Primary School ($p < 0.014$) and ever used ‘herbal’ drugs more than five times in a month ($p < 0.032$). The total variance explained by this model was $R^2 = 0.26$. Cannabis use (user groups based on total days of use on a median split of 4 days) did not independently predict performance on the Rapid Visual Information Processing test ($p = 0.11$).

In the stepwise regression model for Spatial Working Memory (strategy), cannabis use was an independent predictor of performance ($p < 0.04$). The final model, with a variance of $R^2 = 0.51$, also included years of secondary school completed ($p < 0.001$) and WASI vocabulary score ($p < 0.001$).

Cannabis use was also an independent predictor of performance on Spatial Working Memory in terms of total errors ($p < 0.041$). The final five factor model had a variance of $R^2 = 0.48$, and also included the predictors WASI vocabulary score ($p < 0.038$), years of secondary school completed ($p < 0.007$), self-rated arithmetic ability in Primary School ($p < 0.005$) and Beck Depression Inventory score ($p < 0.029$).

Finally, cannabis was also an independent predictor of performance on Rey Auditory-Verbal Learning Test trials A1 – A5 combined ($p < 0.041$). The final model had a variance of $R^2 = 0.32$ and also included WASI vocabulary score ($p < 0.004$) and age of first conduct disorder symptoms ($p < 0.011$).

Thus, cannabis use independently predicted performance on three out of four significant cognitive measure results – Spatial Working Memory strategy and total errors, and Rey Auditory-Verbal Learning

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>Additional predictors</th>
<th>B</th>
<th>T</th>
<th>P</th>
<th>Variance explained by cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Visual Information Processing</td>
<td>Years of secondary school completed</td>
<td>0.02</td>
<td>3.33</td>
<td>0.001</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>Self-rated arithmetic ability in Primary School</td>
<td>0.02</td>
<td>2.53</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ever used ‘herbal’ drugs &gt; five times in a month</td>
<td>-1.79</td>
<td>-5.12</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>Median split total days of cannabis use</td>
<td>0.18</td>
<td>2.05</td>
<td>0.041</td>
<td>6.4%</td>
</tr>
<tr>
<td>Spatial Working Memory strategy</td>
<td>Years of secondary school completed</td>
<td>0.17</td>
<td>3.17</td>
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<tr>
<td></td>
<td>WASI vocabulary score</td>
<td>-0.20</td>
<td>-2.93</td>
<td>&lt; 0.005</td>
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<tr>
<td></td>
<td>Self-rated arithmetic ability in Primary School</td>
<td>0.31</td>
<td>2.05</td>
<td>0.041</td>
<td>10.05%</td>
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<tr>
<td></td>
<td>Median split total days of cannabis use</td>
<td>0.30</td>
<td>2.23</td>
<td>0.029</td>
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</tr>
<tr>
<td>Rey Auditory Verbal Learning Test Trial A1 – A5</td>
<td>Median split total days of cannabis use</td>
<td>-0.30</td>
<td>-2.11</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The present study found there was a significant non-acute relationship between cannabis and cognitive function in adolescents aged 13 – 18 years despite controlling for the additional predictor variables of psychiatric functioning, general functioning, demographics and other drug use. There was a significant relationship between the frequency of cannabis use and four cognitive measures in the adolescent sample. Three of these cognitive measures remained significantly associated with cannabis use even after allowing for additional predictor variables. From these findings, it appears that aspects of cognitive function are independently related to the frequency of cannabis use beyond acute intoxication and despite additional predictor variables. The cognitive measures that had a significant relationship to cannabis use were primarily measures of executive function and working memory. The significant findings in this study were despite what could be seen as relatively low cannabis use in the regular users.

The current results from the Spatial Working Memory task fit with Solowij's [13] conclusions that cannabis effects the organisation and integration of complex information involving mechanisms of attention and working memory. The present results also echo research such as Bolla et al.'s (2002) findings of persistent decrements in neurocognitive performance after 28 days abstinence in cannabis users. In their study, increased cannabis use was associated with decreased performance on tests measuring verbal and visual memory, as well as executive functioning. Similar effects were seen in the current study in deficits on the RAVLT and SWM task. Results from the RAVLT are comparable to the findings of Solowij et al. [14] with the same task. Both the present study and Solowij et al. found a learning effect across trials. Solowij et al. also found a significant relationship between the sum of words recalled and cannabis use, as did this study. Therefore, there is a clear effect of cannabis on word recall in both studies. It is difficult to disentangle the exact contribution of encoding or working memory as opposed to consolidation. This study did not find the specific effect of cannabis on learning found by Solowij et al. (i.e. there was no list by group effect on the ANOVA). Also, taking into account the number of words recalled on the first five trials, there was then no effect of cannabis on delayed recall. We therefore do not interpret the RAVLT results as indicating a specific effect of cannabis on learning (i.e. consolidation). Further, Pope and Yurgelun-Todd [10] also found on the California Verbal Learning Test that heavy users recalled significantly fewer words across the first five trials. Pope et al. [6] also found word recall deficits in heavy cannabis users 1 and 7 days after cessation of drug use compared to controls.

The results of the current study found the same deficits, such as drug use relating to executive functioning, that other studies of adolescent cannabis use and cognition have found [15,18,19,23]. The present findings are very much in keeping with Schwartz et al. [20] in finding deficits in short-term auditory and visual working memory processes, as well as no difference on verbal intelligence with a sample of cannabis dependent adolescents. Whilst effects of cannabis on overt measures of attention did not persist after regression of additional predictor variables, similar to Kempel et al.'s [49] ERP results with selective attention, there was evidence of cannabis having an effect on sustained attention in the form of the Rapid Visual Information Processing test. Whilst the present study found a more significant difference between non-regular and regular users than Teichner et al. [16], this may well be due to the fact that their sample was solely drug users and the current sample had a number of non-users within the non-regular users group.

Factors found to affect the non-acute cannabis use and cognition relationship independent of cannabis use included years of secondary school completed, WASI vocabulary score, self-rated ability in arithmetic in Primary School, Beck Depression Inventory score, age of first conduct disorder symptom and gender. The WASI verbal intelligence score is a particularly complex additional predictor, which did not differ significantly between the two groups. Verbal intelligence is a robust predictor of premorbid cognitive function [45]. Lower pre-morbid intelligence could predict a tendency to smoke cannabis and explain a relationship found between cannabis and cognitive function. However, a relationship between cannabis consumption and aspects of executive function was found despite co-varying for pre-morbid intelligence, suggesting that cannabis is a causal factor.

These results have implications for the memory of adolescent regular cannabis users and their functioning in the school setting, as well as the information they will retain long-term from treatment sessions. Executive functioning and working memory are important in order to process and efficiently store information and utilise strategies, and in turn these functions are important at a time of accelerated learning in adolescents' lives.

There were a number of strengths to the present study. These included comprehensive coverage of psychiatric co-morbidity through an established clinical
interview (SCID) and particular attention to depression with two recognized mood scales (BDI and Hamilton). The Cambridge Neuropsychological Test Automated Battery also provided comprehensive and sensitive cognitive testing with the addition of traditional pen and paper tests (RAVLT, Digit Span and Symbol Digit Modalities Test). Furthermore, an established and thorough measure of recent drug use was utilised in the form of the Timeline Follow-back.

The present study has several limitations. First is the arguable effect of 12 hours abstinence. The debate continues in the literature as to the exact time it takes for the acute effects of cannabis to dissipate [5,6,12]. While 12 hours was chosen as a compromise between the intoxication and withdrawal effects of cannabis, this has not been established as a definite time period, although it is likely to be a pragmatic compromise for research purposes. Furthermore, the present study did not supervise subjects during abstinence and it is possible that some may have consumed cannabis during this period. This would mean that some of the effects found may be attributable to acute rather than non-acute effects. Consideration also needs to be given to the measures of intellectual functioning prior to the onset of drug use. The Primary School measures obtained in this study were retrospective self-report for functioning three to 10 years earlier and their validity may be questionable. Additionally, other drug use, that was minimal in this sample, may affect cognition.

Future research should consider the confounding variables discussed above as well as confirming with monitoring or toxicology the time of abstinence before testing. Following on the work of Solowij, and the cessation of cannabis use, it may also be beneficial to study a group of regular cannabis users over time and investigate their cognitive function before and after cessation or reduction of cannabis use.

Acknowledgements

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References


