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The neuropsychological correlates of cannabis use in schizophrenia: Lifetime abuse/dependence, frequency of use, and recency of use

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Abstract

This study examined the relationship between neuropsychological performance and three different indices of cannabis use in schizophrenia. These indices were DSM-IV lifetime abuse/dependence, frequency of use, and recency of use.

Sixty males with schizophrenia/schizoaffective disorder and 17 healthy males were recruited. The two groups were matched for age, years of education, and premorbid IQ. Medical history, substance use, and psychiatric symptoms were assessed. A neuropsychological battery was also administered to assess attention/processing speed, executive functions, memory, and perceptual organisation. Substance use within 24 hours of cognitive assessment was screened by urine analysis, and a range of confounds were controlled.

In the schizophrenia group, 44 participants met DSM-IV criteria for lifetime cannabis abuse/dependence. In addition, there were three mutually exclusive frequency-of-cannabis-use subgroups comprising "high" frequency users ($n=11$), "medium" frequency users ($n=7$), and "low" frequency users ($n=34$) over the preceding year. There were also four mutually exclusive recency-of-cannabis-use categories comprising "cannabis abuse/dependence in the past week" ($n=11$ users), "non-dependent cannabis use in the past week" ($n=7$ users), "non-dependent cannabis use in the past month, but prior to the past week" ($n=7$ users), and "non-dependent cannabis use prior to the past month" ($n=9$ users).

The control group performed better than the schizophrenia group in all cognitive domains. Within the schizophrenia group, a larger proportion of participants with lifetime cannabis abuse/dependence demonstrated better performance than those without lifetime abuse/dependence on a component of psychomotor speed. Frequency and recency of cannabis use were also associated with better neuropsychological performance, predominantly in the domains of attention/processing speed and executive functions.

In conclusion, cannabis use is associated with enhanced cognitive functioning in schizophrenia. Implications of the results, limitations of the study, and directions for future research are discussed.

Keywords: Schizophrenia; Neuropsychological; Cognition; Cannabis

1. Introduction

The neuropsychological correlates of cannabis use in schizophrenia are not well understood. This is due to two main factors. First, only seven studies to date have

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- Not used cannabis or other illicit substances more than once in the past six months, or more than twice in the past 12 months.
- No alcohol or illicit drug use within 24 hours of cognitive assessment as screened by urine analysis.
- No caffeine consumption or nicotine intake within one hour of cognitive assessment.
- No history of a developmental disorder or intellectual disability.
- No history of ABI or neurological illness (as stipulated for the schizophrenia group).

2.2. Measures

2.2.1. Psychiatric and substance use measures

The diagnosis of schizophrenia or schizoaffective disorder was confirmed with the Psychotic Disorders module of the Structured Clinical Interview for DSM-IV (SCID-I: First et al., 2001). Severity of psychiatric symptoms was assessed with the Scale for the Assessment of Positive Symptoms (SAPS: Andreasen, 1984), and the Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1983). Severity and extent of symptoms of depression and anxiety were assessed with the Calgary Depression Scale (CDS: Addington et al., 1992, 1993, 1996), and the Depression Anxiety Stress Scales (DASS: Lovibond and Lovibond, 1995).

The Substance Use Disorders module of the Structured Clinical Interview for DSM-IV (SCID-I: First et al., 2001) was used to record lifetime substance use and diagnose current and past substance abuse/dependence. The range of substances assessed were cannabis, caffeine, nicotine, alcohol, amphetamine types (including ecstasy and other "designer" amphetamines), LSD, opiates, cocaine, sedatives, and "other" substances (e.g., glue, paint, inhalants).

There was good agreement between one of the investigator's (Coulston) diagnostic rating on the SCID-I and the diagnosis made by the participants' treating psychiatrist (kappa = 0.83). Internal consistency was high on the SAPS (Cronbach's alpha = 0.83), the SANS (Cronbach's alpha = 0.90), and the CDS (Cronbach's alpha = 0.81). Good inter-rater reliability was established for the Hallucinations, Delusions, Bizarre Behaviour, and Formal Thought Disorder subscales of the SAPS (ICC = 0.87, 0.68, 0.82, and 0.66 respectively), and the Affective Flattening, Alogia, Avolition–Apathy, Anhedonia–Asociality, and Inattention subscales of the SANS (ICC = 0.72, 0.77, 0.88, 0.81, and 0.80 respectively). In addition, there was good inter-rater reliability on the CDS (ICC = 0.87), and moderate convergent validity between symptom scores on the CDS and the Depression subscale of the DASS ($r = 0.66$, $p < 0.001$).

Further to these, a semi-structured interview adapted from Barry et al. (1995) was used to record a more detailed history of drug and alcohol use with respect to recency, quantity, frequency, and duration of use. This instrument was originally developed by Barry et al. (1995) to assess alcohol and other drug disorders in psychiatric populations. Participants are firstly asked to indicate "yes" or "no" as to whether they had used each substance in the preceding week and month. If "yes", they are asked to specify how many days in the past week and month they used the substance, and the quantity used on each occasion.

2.2.2. Neuropsychological measures

The Shipley Institute of Living Scale – Vocabulary Component (SILS-V: Shipley, 1940; Revised Manual: Zachary, 1994) was used to assess premorbid IQ. In addition, four cognitive domains were assessed: attention and processing speed, executive functions, memory, and perceptual organisation.

Attention and processing speed was assessed with a computerised battery of tasks known as the "CogState" (Collie et al., 2001). This battery measures simple reaction time, complex/choice reaction time, sustained attention, working memory, and divided attention.

The Wisconsin Card Sorting Test (WCST-64 Card Version: Kongs et al., 2000) and the Trail Making Test (TMT), Verbal Fluency Test, Color–Word Interference Test, and Tower Test of the Delis–Kaplan Executive Function System (D-KEFS: Delis et al., 2001) were used to assess planning and organisation, problem solving, inhibition, cognitive flexibility, abstract reasoning and conceptualisation, set-shifting, self-monitoring, utilising error feedback, and rule abstraction.

Memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT: Taylor, 1959; Rey, 1964) to evaluate span of immediate retention and recall, learning and acquisition, retroactive and proactive interference, and storage of information in long-term memory.

Tests of perceptual organisation were administered to measure the ability to make sense of distorted, incomplete, or fragmented stimuli. These included the Hooper Visual Organisation Test (HVOT: Hooper, 1958, 1983), an adapted version of the Gollin Incomplete Pictures Test (GIPT: Gollin, 1960), and the four visual subtests of the Visual Object and Space Perception Battery (i.e., VOSP Incomplete Letters, Silhouettes, Object Decision, and Progressive Silhouettes; Warrington and James, 1991).

2.3. Procedures

Assessment took place over two occasions for the schizophrenia group. On the first occasion, demographic

information was recorded followed by administration of the SCID-I: Psychotic Disorders and Substance Use Disorders modules, SANS, SAPS, CDS, DASS, and the instrument adapted from Barry et al. (1995). Participants were requested not to consume alcohol or use illicit drugs (including cannabis) over the following 24 hour period, or smoke any cigarettes/consume caffeine within one hour prior to the scheduled session for cognitive assessment the next day. A urine sample was also taken at the end of the first occasion.

Approximately 24 hours later, testing equipment was set up, the second urine sample was obtained to screen recreational drug use at the time of cognitive assessment, and the participants were engaged in general conversation. These procedures ensured abstinence from caffeine and nicotine for at least another 30 min. The neuropsychological battery was subsequently administered, consisting of the SILS-V, RAVLT, CogState, HVOT, GIPT, VOSP, WCST, and D-FEFS subtests.

Assessment for each participant in the control group was undertaken on a single occasion. The SCID-I was used to assist in the screening for psychiatric history. The neuropsychological battery was subsequently administered. A urine sample was also taken to screen recreational drug use at the time of cognitive assessment.

2.3.1. Drug screening

Drug testing was independently performed by the Toxicology Unit, Pacific Laboratory Medicine Services, the NSW State (Australia) reference laboratory for testing of drugs of abuse in urine. Urine samples were screened for the presence of cannabis, opiates, benzodiazepines, amphetamine types, and cocaine using AS/NZS 4308 cut-off levels. Alcohol was tested using an alcohol dehydrogenase assay, and samples were tested for excessive hydration by measuring the Creatinine level using the Jaffe method. In addition, samples were tested for the presence of caffeine, nicotine and its metabolite cotinine using Gas Chromatography/Mass spectrometry (GC/MS). Samples showing positive result on Immunoassay for cannabis were confirmed by a GC/MS method which quantitated the major urinary metabolite, 11-carboxy-THC, after hydrolysis of glucuronide conjugates.

For the purposes of screening acute cannabis use prior to cognitive assessment in the schizophrenia group, two urine samples were obtained. These were taken 24 hours apart, based on research which has demonstrated that a minimum of 24 hours must lapse between the times the two samples are taken to confirm abstinence with an adequate degree of reliability (Huestis and Cone, 1998). If a cannabis user refrains from use for at least 24 hours, the carboxy-THC creatinine ratio in the second urine sample should be approximately 50% less than the first (Huestis and Cone, 1998). Urine analysis indicated that six of the schizophrenia participants had used cannabis within 24 hours of cognitive assessment. Cannabis use within this timeframe was subsequently explored as a potential confounding variable on cognitive performance.

Given that no cannabis use at the time of cognitive assessment was permitted for the control group, only one urine sample needed to be taken, as the required carboxy-THC creatinine ratio was 0 ng/mg. Analysis confirmed absence of alcohol and other illicit drug use for all participants in both groups.

2.3.2. Preliminary data cleaning

A total of 69 variables were derived from the neuropsychological battery, and a total of 13 variables were derived from the psychiatric measures. The data was screened for multivariate and univariate outliers, normality of distributions, multicollinearity, and singularity. One participant in the schizophrenia group was excluded because his cognitive performance was deemed to reflect an intellectual disability diagnosed in childhood. The neuropsychological and psychiatric variables for the schizophrenia group were then submitted respectively to two sets of Principal Components Analysis (PCA) with varimax rotation, in order to reduce the number of variables. Variables with loadings ≥ 0.71 were treated as primary variables, and loadings ≥ 0.32 were treated as secondary variables to aid interpretation (Comrey and Lee, 1992). Subsequent analyses were performed on the components yielded by PCA.

2.3.3. Identification of confounds

In a recent review, Coulston et al. (in press) emphasised the impact of potential confounding variables which need to be considered in the area of substance use and cognition. Hence, potential confounds within the schizophrenia and control groups were explored using One-Way Analysis of Variance (ANOVA), and are shown in Table 1. None of these potential confounds were significant ($p > 0.05$), and thus did not need to be controlled for in subsequent analyses.

Differences between the schizophrenia and control groups with respect to age, years of education, premorbid IQ, and depression/anxiety component scores were explored using One-Way ANOVA. Also, differences between cannabis users and non-users in the schizophrenia group with respect to age, years of education, duration of mental illness (defined by the number of years the participants had been in contact with a mental health service, and had been prescribed antipsychotic medications), premorbid IQ, and psychiatric component scores were

Table 1
Potential confounds explored on cognitive performance

Confound	Group	
	Schizophrenia (N=59)	Control (N=17)
Medications		
Atypical antipsychotics	45 (76.3%)	na
Conventional antipsychotics	14 (23.6%)	na
Antidepressants	23 (38.9%)	na
Mood stabilisers	18 (30.5%)	na
Sedatives	8 (13.6%)	na
Anticholinergics	3 (5.1%)	na
Early-age onset of psychosis (<17 yrs)	8 (13.6%)	na
Later-age onset of psychosis (≥17 yrs)	51 (86.4%)	na
Early-age onset of cannabis use (<17 yrs)	39 (66.1%	5 (29.4%)
Later-age onset of cannabis use (≥17 yrs)	16 (27.1%)	5 (29.4%)
Early-age onset of other illicit substance use (<17 yrs)	14 (23.7%)	na
Later-age onset of other illicit substance use (≥17 yrs)	36 (61.0%)	na
Cannabis use within 24 h of cognitive assessment	6 (10.2%)	na
Lifetime duration of regular substance use (at least monthly use, based on median split-years)		
Cannabis (<5 years)	30 (50.8%)	na
Cannabis (≥5 years)	21 (35.6%)	na
Other illicit substance use (<5 years)	7 (11.8%)	na
Other illicit substance use (≥5 years)	17 (28.8%)	na
Cannabis and other illicit substance use		3 (17.6%)
Current (daily) nicotine use	43 (72.9%)	1 (5.9%)
Current (daily) caffeine consumption	50 (84.7%)	15 (88.2%)
Non-dependent alcohol consumption (past week/month)	26 (44.1%)	11 (64.7%)
Alcohol and other substance abuse 3 months prior to cognitive assessment	9 (15.3%)	na
Lifetime history of other substance abuse/dependence		
Alcohol	6 (10.2%)	na
Amphetamines	3 (5.1%)	na
Hallucinogens (LSD/ecstasy)	3 (5.1%)	na
Amphetamines and hallucinogens	3 (5.1%)	na
Alcohol plus one other illicit substance	8 (13.6%)	na
Alcohol plus two or more other illicit substances	3 (5.1%)	na
Alcohol and sedatives	1 (1.7%)	na

na: not applicable.

explored using One-Way ANOVA. Furthermore, the relationship of each cannabis use index to other potential conflating indices of cannabis use were explored using chi-square tests.

Any between-group confounds that were identified were used as stratification variables, or were included as covariates in relevant subsequent analyses.

2.3.4. Criteria for impairment

Scores derived from the control group were used to classify cognitive performance as "impaired", "normal", and "above average". Impairment was defined as performance which fell 1.5 – 2.0 SDs or more below the mean of the control group, and performance was classified as above average if scores were 0.5 SDs or more above the mean of the control group (Spreen and Strauss, 1998; Ruff and Allen, 1996).

2.3.5. Between- and within-group analyses

One-Way Analysis of Covariance (ANCOVA) was used to examine differences in neuropsychological performance between the schizophrenia and control groups. Within the schizophrenia group, logistic regression analyses were performed to determine if scores on the cognitive components yielded by the PCA predicted lifetime cannabis abuse/dependence, recency of cannabis use, and frequency of cannabis use. Any confounding variables identified were entered in Block 1 of each regression analysis, and cognitive components were entered in Block 2. Finally, chi-square tests were undertaken to examine differences in the proportion of cannabis users and non-users whose performance was classified as impaired/normal and above average on each of the cognitive components. Critical α levels for each analysis were Bonferroni-adjusted to account for multiple comparisons and reduce the risk of Type I errors.

3. Results

A summary of the PCA solution for the neuropsychological variables is presented in Table 2. The analysis yielded 21 cognitive components reflecting performance in the domains of attention/processing speed, executive functions, memory, and perceptual organisation. In addition, the PCA solution yielded three components reflecting the psychiatric variables. These were "depression and anxiety", "positive symptoms", and "negative symptoms".

3.1. Comparing the schizophrenia and control groups

There were no significant differences between the schizophrenia and control groups with respect to age, years of education, or premorbid IQ (see Table 3). The schizophrenia group had a significantly higher level of depression and anxiety than the control group ($F_{1,75}$=11.59, p=0.001).

Mean group scores for the schizophrenia and control groups on the cognitive components yielded by PCA are

Table 2
Summary of the PCA solution for the neuropsychological variables

Domain /component	Test/subtest	Primary loadings	Secondary loadings
Attention/processing speed	*Cogstate*		
Speed of information processing	Complex reaction time (ms)	0.82	
	Matching task (ms)	0.82	
	Working memory (ms)	0.75	
	Divided attention (ms)	0.71	
	Choice reaction time (ms)		0.67
	Simple reaction time (ms)		0.61
	Continuous monitoring (ms)		0.54
Simple information processing	Choice reaction time (accuracy %)	0.81	
	Matching task (accuracy %)		0.68
	Choice reaction time (ms)		0.35
	Simple reaction time (ms)		0.34
	Continuous monitoring (ms)		0.33
	Divided attention (ms)		0.33
Complex information processing	Complex reaction time (accuracy %)	0.83	
	Working memory (accuracy %)		0.67
	Matching task (accuracy %)		0.41
	Divided attention (counted sequences)		0.36
Divided attention	Divided attention (errors in counting)	0.92	
	Divided attention (counted sequences)		0.66
Executive functions	*Trail Making Test*		
Psychomotor speed	Visual scanning (seconds)	0.83	
	Number sequencing (seconds)	0.83	
	Letter sequencing (seconds)	0.83	
	Number–letter switching (seconds)	0.79	
	Motor speed (seconds)	0.76	
Visual conceptual switching	Number–letter switching (errors)	0.96	
	Number–letter switching (seconds)		0.39
Visual scanning accuracy	Visual scanning (errors)	0.96	
	Verbal Fluency Test		
Verbal fluency	Category fluency (total score)	0.90	
	Letter fluency (total score)	0.81	
	Category switching (total score)	0.76	
Verbal rule adherence	Letter fluency (errors)	0.83	
	Category fluency (errors)	0.76	
Verbal conceptual switching	Category switching (errors)	0.94	
	Category switching (total score)		0.40
	Color–Word Interference Test		
Inhibition speed	Inhibition/switching (seconds)	0.88	
	Inhibition (seconds)	0.82	
	Color naming (seconds)	0.78	
	Word reading (seconds)		0.70
	Inhibition/switching (errors)		0.58
Inhibition accuracy	Word reading (errors)	0.82	
	Inhibition (errors)	0.75	
	Color naming (errors)		0.45

Table 2 (*continued*)

Domain /component	Test/subtest	Primary loadings	Secondary loadings
Inhibition accuracy	Word reading (seconds)		0.34
	Tower Test		
Planning and organisation	Achievement score	0.92	
	Towers completed within time limit	0.84	
Planning speed	First move time (seconds)	0.94	
Planning efficiency	Total number of moves	0.96	
Visual spatial rule adherence	Rule violations	0.95	
	Wisconsin Card Sorting Test		
Cognitive flexibility	Number of categories completed	0.83	
	Perseverative responses		0.52
	Conceptual level responses		0.52
Memory	*Rey Auditory Verbal Learning Test*		
Encoding and retrieval	Recognition discriminability	0.87	
	Short delay recall (total words)	0.76	
	Long delay recall (total words)	0.75	
	Intrusions		0.66
	Trials 1–5 (total words)		0.65
Immediate memory	List B (total words)	0.80	
	Trial 1 (total words)	0.75	
	Trials 1–5 (total words)		0.70
	Long delay recall (total words)		0.51
	Short delay recall (total words)		0.48
Perceptual organisation			
Complex perceptual organisation	VOSP Silhouettes	0.84	
	Gollin Incomplete Pictures Test	0.77	
	Hooper Visual Organisation Test		0.68
	VOSP Progressive Silhouettes		0.56
	VOSP Object Decision		0.44
Simple perceptual organisation	VOSP Incomplete Letters	0.93	
	VOSP Progressive Silhouettes		0.45

shown in Table 4.[1] The "depression and anxiety" psychiatric component was entered as a covariate in the between-group analyses. The critical α level was set at 0.002 (i.e., Bonferroni adjustment of 0.05/21 components) to control for Type I errors.

The control group performed significantly better than the schizophrenia group on the components of "psychomotor speed" ($F_{1,75}=16.30$, $p=0.0001$), "inhibition speed" ($F_{1,75}=12.33$, $p=0.001$), "visual spatial rule adherence" ($F_{1,75}=14.58$, $p=0.0003$), "cognitive flexibility" ($F_{1,75}=11.12$, $p=0.001$), and "immediate memory" ($F_{1,75}=14.56$, $p=0.0003$). Differences between the groups approached significance (i.e., $p<0.05$) on the components of "speed of information processing" ($F_{1,75}=7.60$, $p=0.007$), "visual scanning accuracy" ($F_{1,75}=6.53$, $p=0.013$), "verbal fluency" ($F_{1,75}=8.82$, $p=0.004$), "encoding and retrieval" ($F_{1,75}=5.36$, $p=0.023$), and "complex perceptual organisation" ($F_{1,75}=7.08$, $p=0.009$), on all of which the control group performed better than the schizophrenia group.

3.2. Lifetime cannabis abuse/dependence

In the schizophrenia group, 44 participants met DSM-IV criteria for lifetime cannabis abuse/dependence ("users"), and the remaining 15 participants did not ("non-users").

[1] Only the cognitive components which yielded significant results are reported in this paper. For further details of analyses and non-significant results, please contact the corresponding author.

Table 3
Demographic variables, premorbid IQ, and "depression and anxiety" component scores for the schizophrenia and control groups

	Group						
	Schizophrenia (N=59)		Control (N=17)				
	M	SD	M	SD	F	df	p
Age (years)	26.39	5.35	27.94	6.96	0.96	1,75	0.33
Years of education	12.32	1.77	13.07	2.16	2.12	1,75	0.15
Shipley (SILS-V) T-score	48.27	9.04	51.06	7.74	1.79	1,75	0.19
Depression and anxiety	2.28E− 16	1.00	−0.86	0.51	11.59	1,75	0.001**

E Denotes number of decimal places to the left of the numerical value specified (e.g., 5E− 3=0.005).
** Statistically significant (p<0.05).

3.2.1. Demographic variables, premorbid IQ, and psychiatric component scores

The users were significantly younger than the non-users ($F_{1,58}$=9.36, p=0.003), and the users had a shorter duration of mental illness than the non-users ($F_{1,58}$=6.32, p=0.015). Both age and duration of mental illness were therefore treated as confounds. There were no differences between the users and non-users in terms of years of education, premorbid IQ, and positive/negative and depression/anxiety psychiatric component scores (p>0.05).

3.2.2. Other conflating indices of cannabis use

Lifetime cannabis abuse/dependence was significantly related to cannabis abuse/dependence in the past month (χ^2=5.14, df=1, p=0.026), and frequency of cannabis use in the past year (χ^2=11.16, df=2, p=0.002). The latter two indices were therefore treated as confounds to avoid conflation with lifetime abuse/dependence.

3.2.3. Logistic regressions

The results of binary logistic regressions showed that the confounds entered in Block 1 of each analysis were significant predictors of lifetime cannabis abuse/dependence (χ^2=24.47, df=4, p=0.0006, Nagelkerke R^2=0.50, classification rate=79.7%). However, no single cognitive component entered in Block 2 significantly predicted lifetime cannabis abuse/dependence (p>0.05).

3.2.4. Classification of cognitive performance

A larger proportion of the users compared to the non-users were classified in the normal range on the "psychomotor speed" component, a result which approached,

Table 4
Cognitive component scores for the schizophrenia and control groups

Domain/component	Group						
	Schizophrenia (N=59)		Control (N=17)				
	M [a]	SD	M	SD	F	df	p
Attention/processing speed							
Speed of information processing	−2.96E− 15	1.00	0.66	0.87	7.60	1,75	0.007 *
Executive functions							
Psychomotor speed	4.55E− 16	1.00	1.25	1.05	16.30	1,75	0.0001 **
Visual scanning accuracy	−2.5E− 16	1.00	0.70	0.61	6.53	1,75	0.013 *
Verbal fluency	−6.4E− 17	1.00	0.92	1.03	8.82	1,75	0.004 *
Inhibition speed	−1.54E− 15	1.00	0.84	0.54	12.33	1,75	0.001 **
Visual spatial rule adherence	−1.92E− 16	1.00	1.03	0.51	14.58	1,75	0.0003 **
Cognitive flexibility	−2.0E− 04	1.00	1.05	1.00	11.12	1,75	0.001 **
Memory							
Encoding and retrieval	−5.7E− 16	1.00	0.42	0.65	5.36	1,75	0.023 *
Immediate memory	9.32E− 16	1.00	1.18	1.07	14.56	1,75	0.0003 **
Perceptual organisation							
Complex perceptual organisation	−7.4E− 16	1.00	0.96	1.18	7.08	1,75	0.009 *

** Statistically significant (p<0.002 determined by Bonferroni adjustment of α=0.05/21 components).
* Approaching statistical significance (p<0.05).
[a] All mean component scores for the schizophrenia group were extremely close to zero (e.g., Inhibition Speed: 1.54E16) with a SD of 1.00. This is because PCA scores are essentially standard (z) scores with a mean of 0 and SD of 1. Given that the PCAs were undertaken on the data derived from the schizophrenia group, the scores reported in Table 3 reflect what was computed by SPSS for the overall schizophrenia group.

but did not reach significance according to criterion ($\chi^2=5.63$, $df=1$, $p=0.031$).

3.3. Frequency of cannabis use

Frequency of cannabis use in the schizophrenia group was characterised by three distinct patterns over the year preceding assessment. There were 11 participants who reported regular use of cannabis on at least a weekly or more frequent basis, and hence, were deemed "high" frequency users. Another seven participants reported regular use of cannabis between two and four times per month, and were deemed "medium" frequency users. Lastly, 34 participants reported either no cannabis use or virtually no cannabis use throughout the past year (which was only once every few months at most), and were deemed "low" frequency users. The remaining seven participants in the schizophrenia group were irregular and intermittent cannabis users over the year preceding assessment, and were excluded from analysis.

All participants in the "low" frequency subgroup had a carboxy-THC creatinine ratio of 0 ng/mg at the time of cognitive assessment.

3.3.1. Demographic variables, premorbid IQ, and psychiatric component scores

There were no significant differences between the "high", "medium", and "low" frequency users with respect to age, years of education, duration of mental illness, premorbid IQ, and positive/negative and depression/anxiety psychiatric component scores ($p>0.05$).

3.3.2. Other conflating indices of cannabis use

Frequency of cannabis use was significantly related to lifetime cannabis abuse/dependence ($\chi^2=11.16$, $df=2$, $p=0.002$), cannabis abuse/dependence in the past month ($\chi^2=41.41$, $df=2$, $p=0.0001$), and non-dependent cannabis use in the past month ($\chi^2=23.02$, $df=2$, $p=0.0001$). The latter three indices were therefore treated as confounds to avoid conflation with frequency of use.

3.3.3. Logistic regressions

Results of multinomial logistic regressions are shown in Table 5. The confounds were significant predictors of frequency of cannabis use ($\chi^2=69.16$, $df=6$, $p=0.0006$, Nagelkerke $R^2=0.89$, classification rate=92.3%).

Performance on two cognitive components significantly predicted frequency of cannabis use. These were "divided attention" ($\chi^2=13.17$, $df=2$, $p=0.001$, Nagelkerke $R^2=0.96$, classification rate=96.2%), and "planning efficiency" ($\chi^2=13.15$, $df=2$, $p=0.001$, Nagelkerke $R^2=0.96$, classification rate=96.2%). On both components, "high" frequency use was associated with the best level of performance. Scores on another two cognitive components predicted frequency of cannabis use at a level approaching significance (i.e., $p<0.05$). These were "speed of information processing" ($\chi^2=9.54$, $df=2$, $p=0.008$, Nagelkerke $R^2=0.94$, classification rate=96.2%), and "visual conceptual switching" ($\chi^2=10.21$, $df=2$, $p=0.006$, Nagelkerke $R^2=0.95$, classification rate=96.2%). On both components, "high" frequency use was again associated with the best level of performance.

3.3.4. Classification of cognitive performance

A significantly larger proportion of the "high" frequency users were classified in the above average range on the "planning efficiency" component ($\chi^2=12.11$, $df=1$, $p=0.002$). Also, a larger proportion of the "medium" frequency users were classified as impaired on the "complex information processing" component ($\chi^2=7.25$, $df=1$, $p=0.016$) and on the "planning efficiency" component ($\chi^2=10.88$, $df=1$, $p=0.002$). The former

Table 5
Multinomial logistic regressions: The relationship between cognitive performance and frequency of cannabis use

Domain/component	Frequency of cannabis use									
	High ($N=11$)		Medium ($N=7$)		Low ($N=34$)					
	M	SD	*M*	SD	*M*	SD	χ^2 ($df=2$)	*p*	Nagelk. R^2	Class. rate (%)
Attention/processing speed										
Speed of information processing	0.20	1.03	0.10	0.91	−0.11	0.92	9.54	0.008 *	0.94	96.2
Divided attention	0.24	0.58	−0.45	0.78	0.20	0.98	13.17	0.001 **	0.96	96.2
Executive functions										
Visual conceptual switching	0.34	0.81	−0.40	0.66	−0.07	1.06	10.21	0.006 *	0.95	96.2
Planning efficiency	0.93	0.65	−0.85	0.57	−0.03	0.92	13.15	0.001 **	0.96	96.2

** Statistically significant ($p<0.002$ determined by Bonferroni adjustment of $\alpha=0.05/21$ components).
* Approaching statistical significance ($p<0.05$).

result approached significance, and the latter result reached the criterion for significance.

3.4. Recency of cannabis use

There were four mutually exclusive recency-of-cannabis-use categories in the schizophrenia group. These incorporated 11 participants who met criteria for "cannabis abuse/dependence in the past week", another seven who had used cannabis at a "non-dependent level in the past week", another seven who had used cannabis at a "non-dependent level in the past month, but prior to the past week", and another nine who had used cannabis at a "non-dependent level prior to the past month".

For those who reported "non-dependent cannabis use in the past month, but prior to the past week", as well as those who reported most recent "non-dependent cannabis use prior to the past month", the carboxy-THC creatinine ratio in all urine samples was 0 ng/mg at the time of cognitive assessment.

In analysis of each recency-of-use category, other concurrent or more recent levels of cannabis use were excluded. Specifically, in analysis of "cannabis abuse/dependence in the past week", those who had used cannabis at a non-dependent level in the past week were excluded. In analysis of "non-dependent cannabis use in the past week", those who had met criteria for cannabis abuse/dependence in the past week were excluded. In analysis of "non-dependent use in the past month, but prior to the past week", those who had used cannabis at a non-dependent level in the past week were excluded, as were those who had met criteria for cannabis abuse/dependence in the past week. Lastly, in analysis of "non-dependent cannabis use prior to the past month", all participants who had met criteria for cannabis abuse/dependence at any time in the past month or prior to the past month were excluded, as were those who had used cannabis at a non-dependent level in the past month.

3.4.1. Demographic variables, premorbid IQ, and psychiatric component scores

According to "non-dependent cannabis use in the past week", the users had a significantly lower estimate of premorbid IQ than the non-users ($F_{1,47}=4.39$, $p=0.042$), and according to "non-dependent cannabis use in the past month, but prior to the past week", the users had a significantly shorter duration of mental illness than the non-users ($F_{1,39}=4.98$, $p=0.032$). These variables were therefore treated as confounds in the respective recency-of-use analyses. There were no other significant differences between the cannabis users and non-users within any of the four recency-of-use categories in terms of age, years of education, or positive/negative and depression/anxiety psychiatric component scores ($p>0.05$).

3.4.2. Other conflating indices of cannabis use

"Cannabis abuse/dependence in the past week" was significantly related to lifetime cannabis abuse/dependence ($\chi^2=5.66$, $df=1$, $p=0.022$), and to frequency of cannabis use in the past year ($\chi^2=48.00$, $df=3$, $p=0.0005$). "Non-dependent cannabis use in the past week" was significantly related to frequency of cannabis use in the past year ($\chi^2=22.62$, $df=3$, $p=0.0002$). "Non-dependent cannabis use in the past month, but prior to the past week" was significantly related to frequency of cannabis use in the past year ($\chi^2=18.68$, $df=3$, $p=0.001$). Lifetime abuse/dependence and frequency of use were therefore treated as confounds in the respective recency-of-use analyses to avoid conflation.

3.4.3. Logistic regressions

Results of binary logistic regression analyses are shown in Table 6. The confounds were significant predictors of "cannabis abuse/dependence in the past week" ($\chi^2=27.80$, $df=2$, $p=0.0009$, Nagelkerke $R^2=0.64$, classification rate=84.6%), "non-dependent cannabis use in the past week" ($\chi^2=18.31$, $df=3$, $p=0.0001$, Nagelkerke $R^2=0.56$, classification rate=89.6%), and "non-dependent cannabis use in the past month, but prior to the past week" ($\chi^2=18.33$, $df=2$, $p=0.0001$, Nagelkerke $R^2=0.61$, classification rate=87.5%).

"Cannabis abuse/dependence in the past week" was associated with worse performance on the "immediate memory" component ($\chi^2=6.28$, $df=1$, $p=0.012$, Nagelkerke $R^2=1.00$, classification rate=100.0%), and better performance on the "complex perceptual organisation" component ($\chi^2=6.28$, $df=1$, $p=0.012$, Nagelkerke $R^2=1.00$, classification rate=100.0%). These results approached, but did not reach significance according to criterion.

"Non-dependent cannabis use in the past week" was associated with worse performance on the "planning and organisation" component ($\chi^2=7.22$, $df=1$, $p=0.007$, Nagelkerke $R^2=0.74$, classification rate=93.8%). This result approached, but did not reach significance.

"Non-dependent cannabis use in the past month, but prior to the past week" was associated with better performance on the "planning and organisation" component ($\chi^2=4.81$, $df=1$, $p=0.028$, Nagelkerke $R^2=0.84$, classification rate=95.0%), and the "planning efficiency" component ($\chi^2=5.60$, $df=1$, $p=0.018$, Nagelkerke $R^2=0.86$, classification rate=97.5%). These results approached, but did not reach significance. Better

Table 6
Binary logistic regressions: The relationship between cognitive performance and recency of cannabis use

Domain/component	Cannabis abuse/dependence in the past week							
	Users (*N*=11)		Non-users (*N*=41)					
	M	SD	*M*	SD	χ^2 (*df*=1)	*p*	Nagelk. R^2	Class. rate (%)
Memory								
Immediate memory	−0.70	0.55	0.28	1.02	6.28	0.012 *	1.00	100.0
Perceptual organisation								
Complex perceptual organisation	0.17	0.64	0.02	1.08	6.28	0.012 *	1.00	100.0
	Non-dependent cannabis use in the past week							
	Users (*N*=7)		Non-users (*N*=41)					
	M	SD	M	SD	χ^2 (*df*=1)	*p*	Nagelk. R^2	Class. rate (%)
Executive functions								
Planning and organisation	− 0.67	0.79	0.19	0.86	7.22	0.007 *	0.74	93.8
	Non-dependent cannabis use in the past month, but prior to the past week							
	Users (*N*=7)		Non-users (*N*=33)					
	M	SD	*M*	SD	χ^2 (*df*=1)	*p*	Nagelk. R^2	Class. rate (%)
Attention/processing speed								
Complex information processing	0.43	0.88	0.13	0.89	13.49	0.0002 **	1.00	100.0
Executive functions								
Planning and organisation	0.90	0.77	0.003	0.78	4.81	0.028 *	0.84	95.0
Planning efficiency	0.23	1.10	−0.11	0.86	5.60	0.018 *	0.86	97.5
	Non-dependent cannabis use prior to the past month							
	Users (*N*=9)		Non-users (*N*=22)					
	M	SD	M	SD	χ^2(*df*=1)	*p*	Nagelk. R^2	Class. rate (%)
Attention/processing speed								
Speed of information processing	0.37	0.89	−0.32	0.90	3.93	0.047 *	0.17	74.2
Executive functions								
Inhibition accuracy	0.48	0.94	−0.33	1.08	4.06	0.044 *	0.18	71.0

** Statistically significant ($p<0.002$ determined by Bonferroni adjustment of $\alpha=0.05/21$ components).
* Approaching statistical significance ($p<0.05$).

performance on the "complex information processing" component, was however, significantly associated with "non-dependent cannabis use in the past month, but prior to the past week" ($\chi^2=13.49$, $df=1$, $p=0.0002$, Nagelkerke $R^2=1.00$, classification rate=100.0).

"Non-dependent cannabis use prior to the past month" was associated with better performance on the "speed of information processing" component ($\chi^2=3.93$, $df=1$, $p=0.047$, Nagelkerke $R^2=0.17$, classification rate=74.2%), and the "inhibition accuracy" component ($\chi^2=4.06$, $df=1$, $p=0.044$, Nagelkerke $R^2=0.18$, classification rate=71.0%). These results approached, but did not reach significance.

3.4.4. Classification of cognitive performance

A larger proportion of the users who met criteria for "cannabis abuse/dependence in the past week" were classified as impaired on the "immediate memory" component ($\chi^2=9.69$, $df=1$, $p=0.007$), and in the above average range on the "planning

efficiency" component ($\chi^2 = 12.93$, $df = 1$, $p = 0.001$). The former result approached significance, and the latter reached significance. A larger proportion of the "non-dependent cannabis users in the past week" were classified as impaired on the "complex information processing" component ($\chi^2 = 6.16$, $df = 1$, $p = 0.024$), a result which approached significance. A larger proportion of the "non-dependent cannabis users in the past month" were classified in the normal range on the "psychomotor speed" component ($\chi^2 = 6.27$, $df = 1$, $p = 0.014$), and above average on the "planning and organisation" component ($\chi^2 = 5.84$, $df = 1$, $p = 0.034$), results which approached significance.

4. Discussion

This study examined the relationship between neuropsychological performance and three indices of cannabis use in persons with schizophrenia. These indices were DSM-IV lifetime cannabis abuse/dependence, frequency of use, and recency of use. Neuropsychological performance was represented by cognitive components in the domains of attention/processing speed, executive functions, memory, and perceptual organisation. A control group was also recruited to ascertain criteria for "impaired", "normal", and "above average" classification of cognitive performance.

The control group performed better than the schizophrenia group on several components in all cognitive domains, consistent with the vast literature that has demonstrated neuropsychological deficits in schizophrenia relative to the normal population (Hemsley, 1976, 1993a,b; Mueser and McGurk, 2004; Peters et al., 2002; Seaton et al., 2001).

4.1.1. Lifetime cannabis abuse/dependence

A larger proportion of the lifetime cannabis abuse/dependence subgroup was classified in the normal range on the psychomotor speed component. No other results were yielded, consistent with previous research where few associations were found between cannabis use and cognition in schizophrenia, using lifetime abuse/dependence as the index (e.g., Liraud and Verdoux, 2002). However, albeit a single finding, this result was the first to demonstrate that aspects of cognitive performance associated with cannabis use in schizophrenia fall within the "normal" range of functioning with reference to a control group. Moreover, the results of this study are reported in context of having considered a wide range of potential confounding variables which prior studies did not acknowledge or control. Subsequently, the results of this study are reported with greater confidence in the validity of the findings.

The overall lack of any relationship between cognitive performance and lifetime cannabis abuse/dependence suggests that using this very gross index to categorise participants as "users" does not yield levels of neuropsychological performance which substantially differ from those of "non-users". Individuals with a DSM-IV diagnosis of lifetime cannabis abuse/dependence may vary markedly with respect to frequency, recency, and duration of drug use, given that the diagnosis is not guided by amounts or frequency of use, and can pertain to any point in a person's life. Hence, current/past users and frequent/seldom users are likely to be conflated, which warrant the investigation of other more precise indices, such as frequency and recency of cannabis use.

4.1.2. Frequency of cannabis use

High frequency cannabis use was associated with better performance on four cognitive components which reflected speed of information processing, divided attention, visual conceptual switching, and planning efficiency.

By contrast, a larger proportion of the medium frequency users were classified as impaired on the components which reflected planning efficiency and complex information processing. Although there were no significant differences between the three frequency-of-use subgroups in terms of premorbid IQ, the mean estimated premorbid IQ of the "medium" frequency users was notably lower (almost half a standard deviation) than that of the other subgroups, and most likely accounted for the generally poorer cognitive performance of this subgroup.

4.1.3. Recency of cannabis use

All recency of cannabis use categories (except non-dependent use in the past week) were associated with better performance in the domains of attention/processing speed, executive functions, and perceptual organisation. These components reflected speed of information processing, complex information processing, psychomotor speed, planning and organisation, planning efficiency, inhibition accuracy, and complex perceptual organisation.

By contrast, cannabis abuse/dependence in the past week was associated with worse performance on the immediate memory component, and non-dependent cannabis use in the past week was associated with worse performance on the components of planning and organisation and complex information processing. However, for this

latter recency-of-cannabis-use category, it is likely that the poorer performance of the users was attributable to their lower premorbid IQ compared to the non-users.

4.2. Primary implication of the results

All cognitive components which predicted frequency and recency of cannabis use, and on which cannabis use was associated with better performance, were predominantly in the domains of attention/processing speed and executive functions.

Attention/processing speed and executive functions rely most heavily on prefrontal cortical processes which are deficient in schizophrenia (Pantelis and Maruff, 2002). Specifically, cognitive impairment has been associated with decreased prefrontal dopamine, acetylcholine, serotonin, noradrenaline, glutamate, and GABA (Benes et al., 1996; Clarke et al., 2004; Coyle, 2004; Dalley et al., 2002; Friedman et al., 1999; Ichikawa et al., 2002; Ohnuma et al., 1998, 1999; Sarter and Bruno, 1999; Weinberger, 1987; Zavitsanou et al., 2002). It has also been demonstrated that cannabinoids mediate increases in prefrontal noradrenaline (Jentsch et al., 1996), acetylcholine (Acquas et al., 2001; Verrico et al., 2003), and glutamate (Ferraro et al., 2001; Pistis et al., 2002). In this context, our findings suggest that cannabis use may enhance executive functions and attention/processing speed in schizophrenia by stimulating prefrontal neurotransmission. These findings have important implications for the treatment of cognitive impairment in schizophrenia, for example, by way of an agonist or partial agonist on cannabinoid receptors (e.g., a cannabinoid).

4.3. Limitations of the study and other considerations

In context of a proposed treatment of cognitive impairment, there are a number of limitations of this study and other considerations which need to be discussed.

4.3.1. Psychiatric symptoms and possible therapeutic properties of cannabis

There were no significant differences between the subgroups with respect to psychiatric symptoms (i.e., positive, negative, and depression/anxiety symptoms). Subsequently there exists a subgroup of the schizophrenia population who do not experience exacerbation of positive symptoms when using cannabis, and/or who experience antipsychotic efficacy and amelioration of the negative symptoms when using cannabis. For further discussion on the potential role of cannabinoids in antipsychotic and other therapeutic efficacy for schizophrenia, see Coulston et al. (in press).

4.3.2. Compromised memory functions

Cannabis abuse/dependence in the past week was associated with worse performance on the immediate memory component. Impairment of memory has also been reported in studies of schizophrenia and comorbid cocaine use (e.g., Serper et al., 2000a,b), and among cannabis users in the normal population (e.g., Pope et al., 2001; Solowij et al., 2002). This raises the question of whether the potential benefits of cannabis use on attention/processing speed and executive functions in schizophrenia exist as a trade-off for impairments in memory. Therefore, the ethical consideration for a proposed treatment of cognitive impairment by way of a cannabinoid concerns the possibility that such a treatment could lead to some impairment of immediate memory functions. Such a treatment may be worth this trade-off given that those higher-order prefrontal brain processes which can be improved by such medical treatment may assist an individual to compensate for other cognitive deficits such as memory.

4.3.3. Sample size and power

The numbers of participants within each frequency and recency of cannabis use index were very small, accounting for the few significant results. Power analyses for each cannabis use index demonstrated very small effect sizes where results did not reach or approach significance, and indicated that much larger numbers of participants were needed to establish 80% power. The capacity to recruit larger numbers of participants was beyond the resources of this study.

The small sample size of the present study also meant that more concise ranges of frequency of cannabis use could not be explored. For example, frequency of cannabis use in the "high" subgroup was quite variable, ranging between weekly and daily over the preceding year. Therefore, future research would benefit from exploring the relationship between daily cannabis use and cognition, alternate daily cannabis use and cognition, weekly cannabis use and cognition, and so forth in order to ascertain what precise frequency of use would be associated with better cognition.

Furthermore, recency of non-dependent cannabis use could not be explored in more specific time intervals beyond the past month. It would be important for future research to investigate more precisely how long cannabis may exert a beneficial impact on cognition

after a period of use, because the results of our study demonstrated that non-dependent cannabis users in the past month and prior to the past month demonstrated better cognitive performance than non-users *and* had a carboxy-THC creatinine ratio of 0 ng/mg at the time of cognitive assessment, suggesting that cannabis can exert a beneficial effect on performance in schizophrenia after it has been virtually fully metabolised, indicating an enduring, positive effect at very low blood concentrations. Jockers-Scherübl et al. (2007) similarly found that schizophrenia participants with comorbid cannabis use performed significantly better than non-users on a test of psychomotor speed, after the users had been abstinent for at least 28 days.

4.3.4. Chronic cannabis use

Participants in this study were young, and therefore, whilst the results indicate an enhancement of cognition associated with cannabis use in the schizophrenia population, it is known that chronic exposure to cannabis in otherwise healthy populations can lead to down-regulation of cannabinoid receptors (Rhee et al., 2000; Sim-Selley, 2003) which in turn, can result in reduced neurotransmission in the prefrontal cortex and other brain regions (Jentsch et al., 1998; Verrico et al., 2003). Future research would therefore need to determine if a longer lifetime duration of cannabis use impacts on cognitive performance differently to that observed in younger populations, and if cannabis use is at all associated with better cognitive performance in older individuals.

4.4. Summary and concluding comments

In essence, the findings of this study suggest that cannabinoids, via their agonistic effects on cannabinoid receptors in the forebrain, may have a potentially useful role in the treatment of higher-order cognitive processes known to be impaired in schizophrenia. However, several important issues need to be considered and investigated when contemplating such a role.

First, the potentially beneficial effect of medically administered cannabinoids needs to be carefully evaluated against its potentially adverse effects, given that non-medical cannabis use may trigger or exacerbate psychotic symptoms (Degenhardt et al., 2003; Hall, 1998, 2001). Future research therefore needs to establish which subgroups of the schizophrenia population would a) gain amelioration of cognitive impairment from such a treatment, b) demonstrate nil or minimal exacerbation of the positive symptoms in relation to cannabis use, and/or c) may indeed experience antipsychotic and other therapeutic effects of cannabis. Second, the dosage regimen necessary to achieve a therapeutically effective, subacute level of THC in the blood needs to be determined with well designed randomised placebo-controlled clinical trials. Third, it needs to be established how other cognitive functions (e.g., immediate memory) might be adversely affected by cannabinoids, and if so, whether the trade-off for improvements in higher-order executive functions and attention/processing speed lends support to the ethical consideration of such a treatment. Fourth, there needs to be careful investigation of how such a treatment may complement or interact with standard antipsychotic and other psychiatric treatments. Finally, given that participants in our study were young males with a relatively short duration of mental illness, it needs to be established whether medical treatment with cannabinoids is equally effective for both males and females, as well as for older individuals who are likely to have had schizophrenia for much longer than participants in our study.

Cognitive impairment is a core characteristic of schizophrenia. A viable and effective intervention can therefore potentially benefit very large numbers of people worldwide. If cognition in individuals with schizophrenia can be improved, especially those functions pertaining to higher order brain processes (e.g., strategic planning and organisation, maintenance of goal-directed behaviour, problem solving, cognitive flexibility, processing speed, divided attention, and inhibition), it is likely that quality of life can also be improved. In particular, independence in instrumental activities of daily living, vocational, and community participation are likely to be enhanced, thus diminishing social isolation and dependence on institutionalised care that are characteristically experienced by individuals with schizophrenia.

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Contributors

The first author (Coulston) designed the study, recruited the participants, undertook data collection, data analysis, and wrote the first draft of the manuscript. The second and third authors (Perdices and Tennant) supervised these processes. All authors have contributed to and approved the final manuscript.

Conflict of interest

None.

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