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ORIGINAL ARTICLE

Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia

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Background. The effects of cannabis use on neuropsychological indices that show characteristic disturbances in schizophrenia are unclear. The effect of cannabis use on these cognitive functions is of particular interest given the hypothesized association between cannabis use and schizophrenia. Therefore, this study aimed to examine the effects of cannabis use on attentional control, working memory and executive functioning, in both healthy individuals and patients with schizophrenia.

Method. Neuropsychological performance was assessed in 36 cannabis users who were otherwise healthy, 35 healthy non-users, 22 cannabis-using patients with schizophrenia, and 49 non-using patients with schizophrenia. Participants were administered the Stroop task, the letter–number sequencing and spatial span subtests of the Wechsler Memory Scale, and the Wisconsin Card Sorting Test (WCST).

Results. Patients with schizophrenia (both cannabis users and non-users) showed significantly poorer performance across all neuropsychological tasks, relative to controls; however, there were no significant differences between schizophrenic cannabis users and schizophrenic non-users on any measures, with the exception of increased non-perseverative errors on the WCST in cannabis-using patients. Similarly, healthy cannabis users showed no significant differences from healthy non-users in any of the cognitive domains, with the exception of a schizophrenic-like increase in perseveration on the WCST.

Conclusions. Amongst both healthy individuals and patients with schizophrenia there appears to be little difference in cognitive performance between cannabis users and non-users, suggesting that cannabis use has only subtle effects on the neurocognitive performance indices assessed here, which have been well established to be disturbed in schizophrenia.

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Introduction

Cognitive deficits have been described as a core feature of schizophrenia (Elvevåg & Goldberg, 2000; Wobrock *et al*. 2008). These deficits are observed across a wide range of neuropsychological tests that assess a range of cognitive functions, including attention, working memory and executive functioning (Heinrichs & Zakzanis, 1998). It has been suggested that cannabis use in healthy individuals can produce cognitive impairment which resembles that which is evident in schizophrenia (Solowij & Michie, 2007). This is particularly interesting given the hypothesized association between cannabis use and schizophrenia (Degenhardt *et al*. 2003*b*; Degenhardt & Hall, 2006).

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Despite similarities in cognitive dysfunction being observed between patients with schizophrenia and healthy cannabis users, particularly with respect to episodic memory, the effects of cannabis use on a number of key tasks and processes that are found to be deficient in schizophrenia are still inconclusive. For instance, poor performance on the Stroop task has been demonstrated numerous times in patients with schizophrenia (for a review, see Henik & Salo, 2004) and deficits in attentional control have long been regarded as a fundamental aspect of the cognitive disturbances in schizophrenia (McGhie & Chapman, 1961; Andreasen, 1994). However, the effects of cannabis use on Stroop performance in healthy individuals are inconsistent. While some studies have found poor performance on the interference condition of the Stroop with acute cannabis intoxication (Hooker & Jones, 1987; Henquet *et al*. 2006), or with heavy chronic use (Pope & Yurgelun-Todd, 1996), others have not (Miller *et al*. 1972; Pope *et al*. 2001;

Solowij *et al*. 2002; Eldreth *et al*. 2004; Gruber & Yurgelun-Todd, 2005). Similarly, a deficit in working memory, in both the visual and spatial domains, as measured across various tasks, has been well documented and is also thought to be a key feature of schizophrenia (Gold *et al*. 1997; Perry *et al*. 2001; Chey *et al*. 2002; Silver *et al*. 2003; Lee & Park, 2005; Pirkola *et al*. 2005; Tan *et al*. 2006; Twamley *et al*. 2006). However, the effects of cannabis use on working memory in healthy individuals are variable. Acute cannabis administration has been shown to impair spatial working memory in one study (D'Souza *et al*. 2004), improve spatial working memory, but only in females, in another study (Makela *et al*. 2006), and have no effect in another still (Curran *et al*. 2002) while chronic cannabis use has been found to have no effect on working memory in some studies (Solowij *et al*. 2002; Kanayama *et al*. 2004; Jager *et al*. 2006), and to impair it in others (Wadsworth *et al*. 2006; Harvey *et al*. 2007). Lastly, a deficit in executive function, as assessed with the Wisconsin Card Sort Test (WCST), has been demonstrated numerous times in patients with schizophrenia, particularly in terms of reduced categories achieved and increased perseverative errors (e.g. Park, 1997; Heinrichs & Zakzanis, 1998; Laws, 1999; Everett *et al*. 2001; Hartman *et al*. 2003; Li, 2004; El Hamaoui *et al*. 2006). However, the effects of cannabis use on WCST performance in healthy individuals have been inconsistent; some studies have found heavy cannabis use to be associated with fewer categories achieved (Bolla *et al*. 2002) and more perseverative errors (Pope & Yurgelun-Todd, 1996), others have not (Pope *et al*. 2001; Solowij *et al*. 2002).

Given that there may be similarities in cognitive performance between patients with schizophrenia and healthy individuals who use cannabis, it may be hypothesized that patients with schizophrenia who use cannabis would show even further decrements in performance of these cognitive processes. However, the literature examining neuropsychological performance in patients with schizophrenia who use cannabis is mixed. For instance, decision-making performance has been shown to be impaired in cannabis-using patients in one study (Mata *et al*. 2008), while another found no such difference (Sevy *et al*. 2007). A number of studies have found largely no significant differences in performance of a range of cognitive tasks between cannabis-using patients and non-users (Jockers-Scherubl *et al*. 2007; Sevy *et al*. 2007; Mata *et al*. 2008) or between substance-using patients (primarily cannabis) and non-users (Addington & Addington, 1997; Pencer & Addington, 2003; Thoma *et al*. 2007; Wobrock *et al*. 2008), while other studies have found improved cognitive performance in cannabis-using patients relative to non-users (Joyal *et al*. 2003; Stirling *et al*. 2005; Coulston *et al*. 2007; Potvin *et al*. 2008; Schnell *et al*. 2009). However, the improvements in cognition that have been reported are not consistent across cognitive domains, or between studies.

There are a number of possible reasons for this variability, including methodological differences in terms of type of cannabis effect examined (acute *versus* residual) and definition of cannabis use (lifetime cannabis misuse diagnosis, or definitions based on recency or frequency of use). Further, many of these studies fail to screen, or control, for confounds associated with age, education, antipsychotic medications, age of onset of illness and of cannabis use, and, importantly, use of other substances including alcohol, caffeine, nicotine and illicit substances. Additionally, many of these studies have a very small samples size on which comparisons are based, some do not include a healthy control group for comparison, and many fail to statistically correct for multiple comparisons. Finally, inclusion of both healthy individuals and patients with schizophrenia (cannabis users and non-users) in the one study is also of interest in order to examine any similarities or differences in performance between healthy people who use cannabis and patients with schizophrenia who do not, given the hypothesized association between cannabis use and schizophrenia, and also to examine any additive or interactive effects between the factors of cannabis use and schizophrenia.

Therefore, the present study aimed to address many of these issues by examining the effects of cannabis use on neuropsychological performance indices that have been well established to be deficient in schizophrenia (attentional control, as assessed by the Stroop task; working memory, as assessed by the letter–number sequencing (LNS) and spatial span (SS) subtests of the Wechsler Memory Scale (WMS); and executive functioning, as assessed by the WCST), in both healthy individuals, and patients with schizophrenia.

Method

Participants

The study included four groups: (1) 50 patients with a diagnosis of schizophrenia ($n=48$) or schizo-affective disorder ($n=2$) who were not current users of illicit substances (non-using patients with schizophrenia; SZN); (2) 22 patients with a diagnosis of schizophrenia ($n=21$) or schizo-affective disorder ($n=1$) who were current users of cannabis (cannabis-using patients with schizophrenia; SZC); (3) 38 healthy controls who were not current users of illicit substances (non-using

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controls; CN); and (4) 36 healthy controls who were current users of cannabis (cannabis-using controls; CC). Healthy controls (both CN and CC) were recruited from the general community through the use of advertisements in local media, and from a database of potential willing volunteers at the research centre. Patients (both SZN and SZC) were in-patients and out-patients of the major psychiatric hospital in Perth (Australia), and were recruited via direct contact from a researcher (K.E.S.). Prior to inclusion in the study, each patient's treating psychiatrist was contacted, with the patient's permission, to ascertain the patient's ability to provide informed consent. All participants were screened prior to inclusion in the study and exclusionary criteria included: self-reported presence of any hearing disorders; any neurological disorders or head injury; or loss of consciousness for over 15 min. In addition, both CN and CC participants were excluded if they had any past or present diagnosis of psychiatric illness or current use of psychiatric medications (such as antidepressants), or if they reported having a first-degree relative with a diagnosis of schizophrenia or schizo-affective disorder, as healthy relatives of patients with schizophrenia may show poorer cognitive performance than healthy non-relatives (Egan *et al*. 2001; Sitskoorn *et al*. 2004). Further, SZN and CN participants were excluded if they had current or past treatment for a substance-use disorder, if they currently used any illicit substances, or if they had used any illicit substance more than once in the previous 12 months.

All healthy control participants (CN and CC) were administered the Mini International Neuropsychiatric Interview (MINI; Sheehan *et al*. 1998), after recruitment, to assess for the presence of Axis I disorders. The MINI has established reliability and validity (Sheehan *et al*. 1997; Amorim *et al*. 1998). Subsequently, two CN participants were excluded from analysis. Fifteen CC participants (42%) screened positively for a range of psychiatric disturbances (mood disorder, 13; panic disorder, three; anxiety disorder, six; antisocial personality disorder, four). However, given that exclusion of these participants would have almost halved the sample size, and these participants had no official medical psychiatric diagnoses, the decision was made to retain them in the analyses. It should be noted that many studies have found increased rates of a range of psychiatric symptoms in chronic cannabis users (e.g. Troisi *et al*. 1998; Degenhardt *et al*. 2003*a*). In addition, we repeated the analyses with the exclusion of these 15 healthy cannabis users who screened positively for these psychiatric symptoms, and the findings were consistent with those observed in the sample as a whole. We excluded one CN and one SZN participant, as they were unable to provide urine samples, and as a result, absence of illicit drug use could not be confirmed. Thus, the final sample consisted of 142 participants: 49 SZN, 22 SZC, 35 CN and 36 CC.

All of the patients with schizophrenia were on antipsychotic medications. Of the SZN group, 43 were on atypical antipsychotics, one was on typical antipsychotics, and five were on both atypicals and typicals. Of the SZC group, 15 were on atypical antipsychotics, three were on typical antipsychotics, and four were on both atypical and typical. The average daily chlorpromazine equivalent dose (Atkins *et al*. 1997; Wood, 2003) for the SZN group was 592.53 (S.D. = 349.42) mg, and for the SZC group it was 648.24 (S.D. = 263.10) mg. There was no significant group difference in the daily chlorpromazine equivalent dose [$t(67) = -0.66$, $p = 0.509$]. For the SZN group, in addition to antipsychotics, four patients were taking anticholinergics, 16 were taking antidepressants, nine were taking benzodiazepines and 10 were taking mood stabilizers. For the SZC group, one patient was taking anticholinergics, two were taking antidepressants, seven were taking benzodiazepines and six were taking mood stabilizers. The average age of onset of illness for the SZN group was 22.65 (S.D. = 6.69) years, and for the SZC group it was 20.45 (S.D. = 2.76) years. There was no significant difference in age of onset of illness [$t(68.70) = 1.96$, $p = 0.054$]. International Classification of Diseases (ICD-10) psychiatric diagnoses in patients were confirmed with the Diagnostic Interview for Psychoses (Castle *et al*. 2006). The demographic and substance-use characteristics of the sample can be found in Table 1. The illicit substance-use characteristics of the CC and SZC groups can be found in Table 2. This study was approved by the Western Australia North Metropolitan Area Mental Health Service Ethics Committee.

Substance-use assessment

Recent use of nicotine, alcohol, caffeine, cannabis and other illicit substances was assessed with a self-report questionnaire and with the alcohol and substance-misuse modules of the MINI, as previously described (Scholes & Martin-Iverson, 2009*a*, *b*). Urine samples were also obtained and cloned-enzyme-donor-immunoassay was performed to screen for the presence of opiates, amphetamines, benzodiazepines, cannabis metabolites and cocaine metabolites according to the Australian/New Zealand standard AS/NZ 4308:2001 cut-off levels. Further, cotinine (nicotine metabolite) and 11-nor-Δ^9-carboxy-tetrahydrocannabinol (THC-COOH) (cannabis metabolite) levels were quantified with gas chromatography–mass spectrometry.

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Table 1. *Demographic and substance-use characteristics of the sample*

	CN	CC	SZN	SZC
n	35	36	49	22
Sex, *n*				
Male	27	32	43	21
Female	8	4	6	1
Cigarette smoking, *n*				
Smokers	3	23 ***	26 ***§§§	21 ***††
Non-smokers	32	13	23	1
Cigarettes today, *n*				
Yes	3	18	25	2
No	0	5	1	19
Alcohol drinking, *n*				
Alcohol drinkers	30	34	24 **†††§§§	19
Non-drinkers	5	2	25	3
Alcohol today, *n*				
Yes	0	3	3	1
No	30	31	21	18
Caffeine drinking, *n*				
Caffeine drinkers	32	34	45	22
Non-drinkers	3	2	4	0
Caffeine today, *n*				
Yes	20	20	32	19
No	12	14	13	3
THC use, *n*				
THC users	0	36	0	22
Non-users	35	0	49	0
THC today, *n*				
Yes	0	20	0	7
No	35	16	49	15
Mean age, years (S.D.)	34.2 (12.7)	28.9 (8.8)‡‡‡	37.8 (9.2)	31.4 (7.5)
Education, years	14.0 (9–20)§§	12.0 (10–17)‡‡	11.0 (7–16)***	11 (10–15)††
Cotinine, μg/l	0 (0–1622)	320 (0–2365)***§§§	703.0 (0–7690)***	1169 (29–3786)***‡
No. of cigarettes today	4 (2–6)	2 (0–23)	5 (0–25)	4 (0–12)
Time since last cigarette, h	0.5 (0.01–1)	0.6 (0.08–96)	0.25 (0.08–14.5)	0.6 (0.16–48)
Cigarettes on average, per day	20 (4–20)	10 (0–50)§	25 (10–50)†††	20 (1–50)
No. of alcoholic drinks today	0 (0)	0 (0–4)	0 (0–2)	0 (0–0.1)
Time since last alcohol, h	24.0 (6.5–336)	42.0 (2–336)	72.0 (0.75–672)	48.0 (2–672)
Average alcoholic drinks, per week	6 (0.5–25)	10 (0–55)‡‡	3.5 (0.1–75)	4 (0–20)
Alcohol30	10 (0–30)‡‡‡	9.5 (0–30)‡‡‡	0 (0–30)	4 (0–30)†‡‡
No. of caffeinated drinks today	1 (0–5)§§	1 (0–5)§§	1 (0–10)§	2 (0–6)
Time since last caffeine, h	3.3 (0.5–168)	4.4 (0.12–48)	2 (0.1–168)	2 (0.3–48)
Average caffeinated drinks, per day	2 (0–8)‡‡§§§	1.5 (0–15)§§§	4 (0–15)	4 (1–13)
Caffeine30	28.5 (2–30)	30 (2–30)	30 (4–30)*	30 (10–30)

Values are given as median (range) unless otherwise indicated.

CN, healthy non-using controls; CC, healthy cannabis-using controls; SZN, non-using patients with schizophrenia; SZC, cannabis-using patients with schizophrenia; THC, tetrahydrocannabinol; S.D., standard deviation; alcohol30, number of days of alcohol use in the previous 30 days; caffeine30, number of days of caffeine use in the previous 30 days.

Significant difference from CN: * $p<0.05$, ** $p<0.01$, *** $p<0.0001$.

Significant difference from CC: † $p<0.05$, †† $p<0.01$, ††† $p<0.001$.

Significant difference from SZN: ‡ $p<0.05$, ‡‡ $p<0.01$, ‡‡‡ $p<0.001$.

Significant difference from SZC: § $p<0.05$, §§ $p<0.01$, §§§ $p<0.001$.

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Table 2. *Recent illicit substance-use characteristics of cannabis-using controls and patients*

	CC	SZC	*U*	*p*
THC-COOH level, μg/l	117.5 (0–4137)	50.0 (0–949)	255.0	0.023
No. of times of cannabis use in previous 24 h	0.8 (0–4)	0.0 (0–3)	300.5	0.095
Time since last use of cannabis, h	9.5 (0.5–1344)	24.0 (1.25–1344)	257.5	0.026
No. of times of cannabis use on average, per day	2.0 (0–25)	1.0 (0.1–10)	381.5	0.816
Age of first cannabis use, years	16.0 (10–24)	14.0 (12–18)	284.0	0.074
Total duration of cannabis use, years	10.0 (1–34)	16.5 (3–27)	210.5	0.003
Days of use of cannabis in the previous 30 days	25.0 (0–30)	10.5 (0–30)	263.0	0.031
Time since last use of other drug, h	84.0 (4–840)	336.0 (10–840)	50.5	0.033
Days of use of other drug in the previous 30 days	2.0 (0–20)	1.5 (0–15)	85.5	0.631

Values are given as median (range).

CC, healthy cannabis-using controls; SZC, cannabis-using patients with schizophrenia; THC-COOH, 11-nor-Δ^9-carboxy-tetrahydrocannabinol.

Neuropsychological assessment

Stroop colour and word test

Attentional control was assessed with the standardized version of the Stroop task (Golden & Freshwater, 2002), and raw scores were converted to T-scores in accordance with standard procedures (Golden & Freshwater, 2002).

WMS-III: LNS and SS

The LNS (as a measure of auditory working memory) and the SS (both SS forward and SS backward subtasks, as a measure of spatial working memory) subtests of the WMS-III (Wechsler, 1997) were administered. Raw scores for each subtask were converted to scaled scores (Wechsler, 1997), and the scaled scores for LNS and SS were summed to give an overall measure of working memory.

WCST

The standard computerized version of the WCST was administered (Heaton & PAR Staff, 2005*b*). Scoring was completed by the WCST computer scoring program (Heaton & PAR Staff, 2005*a*) according to the standardized scoring procedures (Heaton *et al*. 1993).

Procedure

All participants provided written informed consent upon arrival at the research centre (Centre for Clinical Research in Neuropsychiatry, Graylands Hospital, Perth, Australia). Demographic information was collected, and then participants completed the substance-use questionnaire, and were administered the alcohol and substance-use modules of the MINI. They then provided a urine sample. In order to reduce the likelihood of participants experiencing an abstinence syndrome during the testing session (e.g. Haney *et al*. 1999*a*, *b*, 2004; Hart *et al*. 2002), cannabis users were instructed not to alter their cannabis use on the day of testing. Smoking of cigarettes was permitted *ad libitum* prior to the testing session, in order to reduce the likelihood of nicotine withdrawal affecting cognitive performance (e.g. George *et al*. 2002; Evins *et al*. 2005). Potential acute effects of nicotine (e.g. Waters & Sutton, 2000; Smith *et al*. 2006) were minimized, as participants spent approximately 20 min with the researcher performing consent procedures and collecting demographic and substance-use information before the testing began. As this study was part of a larger study, participants were then prepared for psychophysiological recording, and recording of the startle reflex then took place (reported elsewhere; see Scholes & Martin-Iverson, 2009*a*, *b*). Participants were then administered the Stroop task, the WMS-III subtasks and then the WCST.

Statistical analysis

Group differences in demographic and substance-use variables were investigated with one-way analysis of variance (ANOVA) (for normally distributed metric variables), non-parametric χ^2 or Fisher's exact tests (for categorical variables) or non-parametric Kruskal–Wallis tests (for non-normally distributed metric variables).

Neuropsychological performance was analysed with repeated-measures multivariate analysis of covariance (RM MANCOVA) with two between-subjects factors [group: SZ (schizophrenia) and C (control); drug: C (cannabis user) and N (non-cannabis user)], the neuropsychological performance measures as the within-subjects factor (i.e. Stroop: word, colour, colour-word, interference) and six covariates [age, education, cotinine level, number of days of alcohol

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use in the previous 30 days (alcohol30), number of caffeinated drinks in the previous 24 h (caffeine number today) and average number of caffeinated drinks per day (average caffeine)]. Equality of error variances for each analysis was assessed with Levene's test, and no violations were observed. All covariates for all analyses met the assumptions of homogeneity of regression and multicollinearity. Planned pairwise comparisons with Sidak correction ($p<0.05$) were used to examine differences between groups for each neuropsychological performance measure.

Results

Demographics and substance use

As can be seen in Table 1, there were significant between-group differences in a number of the measures. Of these variables that differed significantly amongst the groups, there were significant correlations between the dependent measures (cognitive performance indices) and the variables age, education, cotinine level, alcohol30, caffeine number today and average caffeine; these variables were included as covariates in the subsequent analysis of the cognitive performance indices.

Table 2 shows the illicit substance-use characteristics of the cannabis-using participants. Of the CC participants, 21 were daily/nearly daily users, 12 were weekly users, one was a monthly user, and two used cannabis less than monthly. Additionally, 16 (47%) CC participants reported using other drugs in the last month (amphetamines, 12; hallucinogens, four). Toxicology analysis of the CC sample revealed that two screened positive for opiates (from reported pain medication taken the day before testing), eight screened positive for amphetamines, and one screened positive for benzodiazepines. The alcohol and substance-use modules of the MINI (for use of substances in the last 12 months) indicated that, of the CC group, eight screened positive for cannabis abuse, while 22 screened positive for cannabis dependence. Further, 12 (33%) screened positive for abuse/dependence of other substances.

Of the SZC participants, nine were daily/nearly daily users, seven were weekly users, four were monthly users and two used cannabis less than monthly. All SZC participants reported initiating cannabis use prior to their diagnosis of schizophrenia. Further, 12 (55%) SZC participants reported using other drugs in the last month (amphetamines, eight; narcotics, one; benzodiazepines, one; hallucinogens, two). Toxicology analyses of the SZC sample indicated that six patients screened positive for benzodiazepines, one screened positive for opiates, and two screened positive for amphetamines. The alcohol and substance-use modules of the MINI indicated that, of the SZC group, four screened positive for cannabis abuse and 15 screened positive for cannabis dependence. Further, 12 (55%) screened positive for abuse/dependence of other substances.

Neuropsychological performance

RM MANCOVA revealed a significant measure × group interaction for Stroop performance [$F(3,130)=13.30$, $p<0.0005$, partial $\eta^2=0.24$], but no significant drug × measure [$F(3,130)=0.07$, $p=0.976$, observed power = 0.06] or drug × group × measure [$F(3,130)=0.28$, $p=0.844$, observed power = 0.10] interactions. Similarly, there was a significant measure × group interaction for the WMS-III [$F(4,129)=4.49$, $p=0.002$, partial $\eta^2=0.12$], but no measure × drug interaction [$F(4,129)=1.29$, $p=0.276$, observed power = 0.40], and the group × measure × drug interaction was just off significance [$F(4,129)=2.43$, $p=0.051$, observed power = 0.68]. Finally, there was a significant measure × group interaction [$F(9,124)=2.71$, $p=0.007$, partial $\eta^2=0.16$] and measure × drug interaction for WCST performance [$F(9,124)=2.53$, $p=0.011$, partial $\eta^2=0.16$], but no significant group × measure × drug interaction [$F(9,124)=1.86$, $p=0.064$, observed power = 0.80]. Findings from the planned pairwise comparisons can be found in Table 3.

These analyses were repeated controlling for the cannabis-use variables that differed significantly between the two cannabis-using groups (Table 2). The pairwise comparisons between the CC and SZC groups from these analyses were consistent with those obtained without controlling for the cannabis-use variables, with the majority of significant comparisons exhibiting even greater differences.

Frequency and recency of cannabis use

Given that one study found recent and frequent use of cannabis in patients to be associated with better cognitive performance on some tasks (Coulston *et al*. 2007), the analyses were re-performed including only those from the cannabis-using groups who were daily or nearly daily users of cannabis. Despite the reduced sample sizes in the cannabis-using groups (CC = 21, SZC = 9), the significance of pairwise comparisons was entirely consistent with that observed in the sample as a whole. To examine recency of use, only those cannabis users who had used cannabis within the previous 24 h were included (CC = 20, SZC = 7). Again, the findings were consistent with those observed in the sample as a whole. Lastly, analyses were repeated including only those who had not used

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Table 3. *Neuropsychological performance across the four groups: CN, CC, SZN and SZC*

	CN	CC	SZN	SZC
Stroop				
Word	51.53 (2.09)§§	51.94 (1.94)‡‡‡	41.00 (1.74)***	41.22 (2.56)†††
Colour	50.06 (1.83)§§§	50.28 (1.70)‡‡‡	37.27 (1.52)***	36.69 (2.24)††
Colour–word	56.02 (1.70)§§§	54.82 (1.59)‡‡‡	44.85 (1.42)***	45.11 (2.09)†††
Interference	53.66 (1.27)	52.89 (1.18)	49.81 (1.06)*	50.01 (1.56)
Wechsler Memory Scale				
Letter–number sequencing	10.06 (0.51)§	11.46 (0.47)‡‡	9.67 (0.42)	8.35 (0.62)†††
Spatial span	11.12 (0.47)§	10.87 (0.44)	9.80 (0.39)*	9.51 (0.58)
Working memory	21.18 (0.82)§	22.34 (0.76)‡‡	19.47 (0.68)	17.86 (1.00)††
Spatial span forward	10.20 (0.54)	10.23 (0.50)	9.50 (0.45)	8.89 (0.66)
Spatial span backward	12.20 (0.47)§§	11.26 (0.44)	10.21 (0.39)**	9.71 (0.58)†
Wisconsin Card Sorting Test				
Trials administered	96.09 (3.85)§§	100.93 (3.54)‡	111.27 (3.17)**	114.89 (4.67)†
Total correct	70.05 (2.30)	72.17 (2.11)	68.55 (1.89)	70.01 (2.78)
Total errors, %	51.31 (2.14)§§	48.31 (1.97)‡	41.09 (1.76)***	40.10 (2.59)†
Perseverative responses, %	56.21 (2.69)§§	49.54 (2.47)	44.39 (2.21)**	40.87 (3.26)†
Perseverative errors, %	54.60 (2.67)†§§	47.87 (2.45)	43.40 (2.19)**	41.78 (3.23)†
Non-perseverative errors, %	49.76 (1.98)§§§	48.97 (1.81)‡‡	41.79 (1.62)**§	36.02 (2.39)†††
Conceptual level responses, %	50.95 (2.28)§§	47.95 (2.10)‡	41.83 (1.88)**	38.53 (2.76)††
Categories completed	5.07 (0.38)§	4.89 (0.35)‡‡	3.54 (0.31)**	3.70 (0.46)†
Trials to first category	18.12 (3.06)	25.91 (5.57)	26.62 (4.98)	36.63 (7.34)
Failure to maintain set	0.79 (0.23)	1.10 (0.21)	1.14 (0.19)	0.93 (0.28)

CN, healthy non-using controls; CC, healthy cannabis-using controls; SZN, non-using patients with schizophrenia; SZC, cannabis-using patients with schizophrenia.

Values are given as mean (standard error).

Significant difference from CN: * $p<0.05$, ** $p<0.01$, *** $p<0.0001$.

Significant difference from CC: † $p<0.05$, †† $p<0.01$, ††† $p<0.001$.

Significant difference from SZN: ‡ $p<0.05$, ‡‡ $p<0.01$, ‡‡‡ $p<0.001$.

Significant difference from SZC: § $p<0.05$, §§ $p<0.01$, §§§ $p<0.001$.

cannabis within the previous 24 h (CC = 16, SZC = 15). These analyses were consistent with those observed when utilising the whole sample.

In addition, partial correlations (with the same covariates as included in the ANOVAs) between the cannabis-use variables and cognitive performance were performed for both the CC and SZC groups. There were no significant correlations between cannabis use and neuropsychological performance, for either the CC or SZC group, after Bonferroni–Holm correction for multiple comparisons.

Use of other substances

In order to investigate whether the use of other substances (both alcohol and illicit substances) could have contributed to the observed findings, the analyses were again completed using various subgroups of the cannabis-using groups. The results of these analyses were all consistent with the analyses completed utilising the whole sample. These subgroup analyses included: only those who did not screen positive to any other substance with the urine toxicology screen (CC = 27, SZC = 16); only those who reported no use of any other illicit substance in the previous 30 days (CC = 20, SZC = 10); only those with no other substance abuse/dependence in the previous year, according to the MINI (CC = 22, SZC = 8).

Discussion

The current study examined the effects of chronic cannabis use on neuropsychological performance, in both healthy people and patients with schizophrenia. The neuropsychological domains assessed represented those that have been well established to be disturbed in patients with schizophrenia: attentional control, as assessed with the Stroop task; working memory, as assessed here with the WMS III; and executive functioning, as assessed by the WCST. Consistent with the literature (for a review, see

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Heinrichs & Zakzanis, 1998), patients with schizophrenia showed poorer performance on all tasks, as compared with healthy controls. Interestingly, there were few differences in cognitive performance between cannabis users and non-users, for both patients with schizophrenia and healthy controls. These findings suggest that cannabis use has very little effect on the cognitive functions examined.

Consistent with a multitude of studies, patients with schizophrenia showed poorer performance than controls on all measures of the Stroop task (for a review, see Henik & Salo, 2004). However, there were no significant differences between the CC and CN participants on any Stroop measures, nor were there any significant differences between the SZC and SZN groups. This suggests that chronic cannabis use had no effect on Stroop performance. These findings are in line with a number of other studies that have found no effects of chronic cannabis use on performance of the Stroop task in healthy people (Miller *et al*. 1972; Pope *et al*. 2001; Solowij *et al*. 2002; Eldreth *et al*. 2004; Gruber & Yurgelun-Todd, 2005). While acute cannabis intoxication may disturb Stroop performance in healthy people (Hooker & Jones, 1987; Henquet *et al*. 2006), the subjects in the current study were not acutely intoxicated at the time of testing. Further, those previous studies that have shown impaired Stroop performance in healthy chronic cannabis users have only shown this to be the case in select groups, such as very heavy users who are males (Pope & Yurgelun-Todd, 1996). Our findings are also consistent with those reported in patients with schizophrenia, with no difference found between cannabis users and non-users (Coulston *et al*. 2007; Thoma *et al*. 2007). Although one early study did find that lifetime cannabis-use disorder in patients was associated with poor interference performance on the Stroop task (Liraud & Verdoux, 2002), the sample of this study consisted of patients diagnosed with a range of both psychotic and mood disorders, and thus the specificity of this relationship in schizophrenia could be questioned.

Patients with schizophrenia also showed poorer spatial working memory, relative to controls. Spatial working memory deficits have been suggested to be the most robust working memory disturbance observed in schizophrenia (Lee & Park, 2005). Consistent with the Stroop findings, there were no significant differences in any of the working memory measures, between CC and CN participants, nor were there significant differences between SZC and SZN patients. However, SZC patients did show more widespread deficits in the working memory measures, when compared with CN participants, than did SZN patients. While one previous study found contrasting findings, whereby superior working memory performance was displayed by cannabis-using patients, as compared with non-users (Schnell *et al*. 2009), other studies have found no such differences between users and non-users (Cleghorn *et al*. 1991; Jockers-Scherubl *et al*. 2007; Sevy *et al*. 2007; Mata *et al*. 2008), as in the current study. However, these latter studies did not include a healthy non-using control group (Cleghorn *et al*. 1991; Mata *et al*. 2008) or did not conduct the relevant pairwise comparisons between the healthy non-using control group and the cannabis-using patients (Jockers-Scherubl *et al*. 2007). Hence, it cannot be ascertained whether, as in the current study, cannabis-using patients showed more widespread deficits in memory function than did non-using patients. Although the published literature on the effects of chronic cannabis use on working memory in healthy individuals is somewhat mixed, the lack of difference between cannabis users and non-users, as observed here, is supported by a number of studies (Solowij *et al*. 2002; Kanayama *et al*. 2004; Jager *et al*. 2006).

Similarly, both SZC and SZN patients showed poorer WCST performance across most WCST measures, as compared with the CN group. Poor WCST performance in patients has been well documented (e.g. Park, 1997; Heinrichs & Zakzanis, 1998; Bustini *et al*. 1999; Everett *et al*. 2001; Hartman *et al*. 2003; El Hamaoui *et al*. 2006), and the current study demonstrates that patients with schizophrenia who use cannabis exhibit similar deficits. This finding is consistent with Jockers-Scherubl *et al*. (2007) and Coulston *et al*. (2007) who both found no additive effect of cannabis use on WCST disturbances in schizophrenia.

In addition, both patient groups showed deficits in WCST measures relative to cannabis-using controls, with one exception. That is, there were no significant differences in perseverative responses and perseverative errors between the CC and SZN groups. In line with this, CC participants had significantly lower scores for perseverative errors, relative to CN participants. Thus, it appears that CC participants show more perseverative errors during the WCST, which is consistent with the deficit observed in schizophrenia. This finding is in accordance with a previous study which found a specific increase in perseveration in healthy cannabis users (Pope & Yurgelun-Todd, 1996). While a latter study by this research group found no such difference (Pope *et al*. 2001), this may be attributed to methodological differences, as a 28 day abstinence period was employed in the 2001 study. This suggests that the schizophrenic-like increase in perseveration observed here may be associated with the residues of cannabis in the body, and, thus, may resolve after these residues are cleared following sufficient abstinence. However, the current study did not

detect any significant correlations between recency of cannabis use and WCST perseveration.

The findings from the ANOVAs and pairwise comparisons suggest that there is very little effect of chronic cannabis use on the cognitive performance measures administered. This is supported by the lack of correlations observed between the cannabis-use measures and the neuropsychological indices examined. The neuropsychological measures employed in the current study are measures which have been consistently demonstrated to be disturbed in schizophrenia, and hence the findings of the current study suggest that cannabis use in healthy individuals does not produce deficits, in these measures, that resemble those in schizophrenia (with the exception of increased perseveration in the WCST), and cannabis use in patients with schizophrenia does not produce further decrements in these fundamental processes. It should be noted that the lack of significant differences between SZN and SZC patients cannot be explained by a floor effect in cognitive performance, as the T-scores for many of the measures were above 40. Further, given that our cannabis-using groups consisted of participants who also used other illicit drugs, we completed a second round of analyses excluding individuals based on use of other substances (both alcohol and illicit drugs). These analyses were all consistent with the findings utilizing the whole cannabis-using sample, suggesting that our findings are not confounded by our participants' infrequent use of other substances.

A number of recent studies have suggested that cognitive performance is actually superior in patients who use cannabis relative to non-users (Stirling *et al*. 2005; Coulston *et al*. 2007; Potvin *et al*. 2008; Henderson *et al*. 2009; Schnell *et al*. 2009; Yucel *et al*. 2009). There are a number of possible reasons for this. First, many of these studies suffer from small sample sizes. For example, the study by Coulston *et al*. (2007) examined a number of indices of cannabis use and their relationship to cognitive performance. Although the overall sample of cannabis-using patients was sufficient, the samples on which the conclusions were based, when separating the sample according to frequency and recency of cannabis use, were only very small. Further, cannabis-using patients have been suggested to reflect a relatively distinct group who differ from non-using patients in terms of pre-morbid social adjustment and/or intelligence quotient (IQ), abilities that are needed in order to initiate and maintain drug-seeking behaviour (e.g. Joyal *et al*. 2003; Wobrock *et al*. 2007; Potvin *et al*. 2008; Schnell *et al*. 2009). Although a recent study suggested that drug-using patients do not differ from non-using patients in terms of pre-morbid social functioning or competency (Stirling *et al*. 2005), there is some evidence that cannabis-using patients may show a higher IQ (Kumra *et al*. 2005), which may account for the improved performance observed in some studies. Such a contention is supported by the study by Schnell *et al*. (2009) who found improved performance in cannabis-using patients, relative to non-using patients, after an abstinence period of 78 days on average. Given that a number of studies in healthy cannabis users have suggested the deficits in cognitive performance associated with cannabis use can resolve after sufficient periods of abstinence (over 30 days) (e.g. Pope *et al*. 2001), it might be suggested that the improved cognition in studies such as the one by Schnell *et al*. (2009) may be indicative of superior pre-morbid IQ/cognition which becomes evident after resolution of the deficits associated with cannabis use, upon sufficient periods of abstinence. Such an interpretation would be supported by our study, and others who examine cannabis-using patients (Jockers-Scherubl *et al*. 2007; Sevy *et al*. 2007; Mata *et al*. 2008) and also substance-using patients (primarily cannabis users) (Addington & Addington, 1997; Pencer & Addington, 2003; Thoma *et al*. 2007; Wobrock *et al*. 2008), without any imposed abstinence period, and find largely no differences in cognitive performance between users and non-users. Whether this interpretation is correct remains to be investigated in a longitudinal design where chronic cannabis-using patients are tested during normal use of cannabis, and then again after a prolonged period of abstinence.

In conclusion, it appears that cannabis use in both healthy individuals and patients with schizophrenia has only very subtle effects on performance of the neuropsychological tasks administered here, which have long been established to index characteristic disturbances in schizophrenia. As such, current chronic cannabis use in healthy individuals produces little similarity in cognitive dysfunction to that evident in schizophrenia, with the exception of a schizophrenic-like increase in perseveration. Similarly, patients with schizophrenia who are current chronic users of cannabis appear to show little difference in cognitive performance to those who do not use cannabis, and, as such, it may be that chronic cannabis use has no additive effect on cognitive dysfunction in schizophrenia.

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Declaration of Interest

None.

References

Addington J, Addington D (1997). Substance abuse and cognitive functioning in schizophrenia. *Journal of Psychiatry and Neuroscience* **22**, 99–104.

Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan BD (1998). DSM-III-R psychotic disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. *European Psychiatry* **13**, 26–34.

Andreasen NC (1994). The mechanisms of schizophrenia. *Current Opinion in Neurobiology* **3**, 245–251.

Atkins M, Burgess A, Bottomley C, Riccio M (1997). Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. *Psychiatric Bulletin* **21**, 224–226.

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

Bustini M, Stratta P, Daneluzzo E, Pollice R, Prosperini P, Rossi A (1999). Tower of Hanoi and WCST performance in schizophrenia: problem-solving capacity and clinical correlates. *Journal of Psychiatric Research* **33**, 285–290.

Castle DJ, Jablensky A, McGrath JJ, Carr V, Morgan V, Waterreus A, Valuri G, Stain H, McGuffin P, Farmer A (2006). The diagnostic interview for psychoses (DIP): development, reliability and applications. *Psychological Medicine* **36**, 69–80.

Chey J, Lee J, Kim Y, Kwon S, Shin Y (2002). Spatial working memory span, delayed response and executive function in schizophrenia. *Psychiatry Research* **110**, 259–271.

Cleghorn JM, Kaplan RD, Szechtman B, Szechtman H, Brown GM, Franco S (1991). Substance abuse and schizophrenia: effect on symptoms but not on neurocognitive function. *Journal of Clinical Psychiatry* **52**, 26–30.

Coulston CM, Perdices M, Tennant CC (2007). The neuropsychological correlates of cannabis use in schizophrenia: lifetime abuse/dependence, frequency of use, and recency of use. *Schizophrenia Research* **96**, 169–184.

Curran HV, Brignell C, Fletcher S, Middleton P, Henry J (2002). Cognitive and subjective dose–response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology* **164**, 61–70.

Degenhardt L, Hall W (2006). Is cannabis use a contributory cause of psychosis? *Canadian Journal of Psychiatry* **51**, 556–565.

Degenhardt L, Hall W, Lynskey M (2003*a*). Exploring the association between cannabis use and depression. *Addiction* **98**, 1493–1504.

Degenhardt L, Hall W, Lynskey M (2003*b*). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence* **71**, 37–48.

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu Y, Braley G, Gueorguieva R, Krystal JH (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* **29**, 1558–1572.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences USA* **98**, 6917–6922.

Eldreth D, Matochik JA, Cadet JL, Bolla KI (2004). Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *NeuroImage* **23**, 914–920.

El Hamaoui Y, Elyazaji M, Yaalaoui S, Rachidi L, Saoud M, d'Amato, T, Moussaoui D, Dalery J, Battas O (2006). Wisconsin card sorting task in patients with schizophrenia and their siblings. *Canadian Journal of Psychiatry* **51**, 48–54.

Elvevåg B, Goldberg TE (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Critical Reviews in Neurobiology* **14**, 1–21.

Everett J, Lavoie K, Gagnon JF, Gosselin N (2001). Performance of patients with schizophrenia on the Wisconsin Card Sorting Test (WCST). *Journal of Psychiatry and Neuroscience* **26**, 123–130.

Evins AE, Deckersbach T, Cather C, Freudenreich O, Culhane MA, Henderson DC, Green MF, Schoenfeld DA, Rigotti NA, Goff DC (2005). Independent effects of tobacco abstinence and bupropion on cognitive function in schizophrenia. *Journal of Clinical Psychiatry* **66**, 1184–1190.

George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler B (2002). Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* **26**, 75–85.

Gold JM, Carpenter C, Randolph C, Goldberg TE, Weingerger DR (1997). Auditory working memory and Wisconsin card sorting test performance in schizophrenia. *Archives of General Psychiatry* **54**, 159–165.

Golden CJ, Freshwater SM (2002). *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Stoelting Co: Chicago.

Gruber SA, Yurgelun-Todd D (2005). Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Cognitive Brain Research* **23**, 107–118.

Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW (2004). Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology* **29**, 158–170.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999*a*). Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* **141**, 385–394.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999*b*). Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* **141**, 395–404.

Hart CL, Ward AS, Haney M, Comer SD, Foltin RW, Fischman MW (2002). Comparison of smoked marijuana and oral Δ^9-tetrahydrocannabinol in humans. *Psychopharmacology* **164**, 407–415.

Hartman M, Steketee MC, Silva S, Lanning K, Andersson C (2003). Wisconsin Card Sorting Test performance in schizophrenia: the role of working memory. *Schizophrenia Research* **63**, 201–217.

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

Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G (1993). *Wisconsin Card Sorting Test Manual. Revised and Expanded*. Psychological Assessment Resources Inc.: Lutz, FL.

Heaton RK, PAR Staff (2005*a*). *WCST: Computer Version 4 Scoring Program: Research Edition*. Psychological Assessment Resources Inc.: Lutz, FL.

Heaton RK, PAR Staff (2005*b*). *WCST: Computer Version 4: Research Edition*. Psychological Assessment Resources Inc.: Lutz, FL.

Heinrichs RW, Zakzanis KK (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* **12**, 426–445.

Henderson A, Coulston CM, Lagopoulos J, Degabriele R, Das P, Malhi G (2009). Cannabis use and cognitive functioning in schizophrenia. In *Abstracts of the 9th World Congress of Biological Psychiatry*, p. 126. World Federation of Societies of Biological Psychiatry: Paris.

Henik A, Salo R (2004). Schizophrenia and the Stroop effect. *Behavioral and Cognitive Neuroscience Reviews* **3**, 42–59.

Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, Van Os J (2006). An experimental study of *catechol-O-methyltransferase* Val^{158}Met moderation of Δ-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* **31**, 2748–2757.

Hooker WD, Jones RT (1987). Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psychopharmacology* **91**, 20–24.

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

Jockers-Scherubl MC, Wolf T, Radzei N, Schlattmann P, Rentzsch J, Gomez-Carrillo de Castro AG, Kuhl K (2007). Cannabis induces different cognitive changes in schizophrenic patients and healthy controls. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **31**, 1054–1063.

Joyal C, Halle P, Lapierre D, Hodgins S (2003). Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophrenia Research* **63**, 297–299.

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

Kumra S, Thaden E, DeThomas C (2005). Correlates of substance abuse in adolescents with treatment-refractory schizophrenia and schizoaffective disorder. *Schizophrenia Research* **73**, 369–371.

Laws KR (1999). A meta-analytic review of Wisconsin Card Sort studies in schizophrenia: general intellectual deficit in disguise? *Cognitive Neuropsychiatry* **4**, 1–30.

Lee J, Park S (2005). Working memory impairments in schizophrenia: a meta-analysis. *Journal of Abnormal Psychology* **114**, 599–611.

Li CR (2004). Do schizophrenia patients make more perseverative than non-perseverative errors on the Wisconsin Card Sorting Test? A meta-analytic study. *Psychiatry Research* **129**, 179–190.

Liraud F, Verdoux H (2002). Effect of comorbid substance use on neuropsychological performance in subjects with psychotic or mood disorders. *Encephalography* **28**, 160–168.

Makela P, Wakeley J, Gijsman H, Robson PJ, Bhagwagar Z, Rogers RD (2006). Low doses of Δ-9 tetrahydrocannabinol (THC) have divergent effects on short-term spatial memory in young, healthy adults. *Neuropsychopharmacology* **31**, 462–470.

Mata I, Rodriguez-Sanchez JM, Pelayo-Teran JM, Perez-Iglesias R, Gonzalez-Blanch C, Ramirez-Bonilla M, Martinez-Garcia O, Vazquez-Barquero JL, Crespo-Facorro B (2008). Cannabis abuse is associated with decision-making impairment among first-episode patients with schizophrenia-spectrum psychosis. *Psychological Medicine* **38**, 1257–1266.

McGhie A, Chapman J (1961). Disorders of attention and perception in early schizophrenia. *British Journal of Medical Psychology* **34**, 103–116.

Miller LL, Drew WG, Kiplinger GF (1972). Effects of marijuana on recall of narrative material and Stroop colour–word performance. *Nature* **237**, 172–173.

Park S (1997). Association of an oculomotor delayed response task and the Wisconsin Card Sort Test in schizophrenic patients. *International Journal of Psychophysiology* **27**, 147–151.

Pencer A, Addington J (2003). Substance use and cognition in early psychosis. *Journal of Psychiatry and Neuroscience* **28**, 48–54.

Perry W, Heaton RK, Potterat E, Roebuck T, Minassian A, Braff DL (2001). Working memory in schizophrenia: transient 'online' storage *versus* executive functioning. *Schizophrenia Bulletin* **27**, 157–176.

Pirkola T, Tuulio-Henriksson A, Glahn D, Kieseppa T, Haukka J, Kaprio J, Lonnqvist J, Cannon TD (2005). Spatial working memory function in twins with schizophrenia and bipolar disorder. *Biological Psychiatry* **58**, 930–936.

Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D (2001). Neuropsychological performance in longterm cannabis users. *Archives of General Psychiatry* **58**, 909–915.

Pope HG, Yurgelun-Todd D (1996). The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association* **275**, 521–527.

Potvin S, Joyal CC, Pelletier J, Stip E (2008). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. *Schizophrenia Research* **100**, 242–251.

Schnell T, Dagmar K, Daumann J, Gouzoulis-Mayfrank E (2009). The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology* **205**, 45–52.

Scholes KE, Martin-Iverson M (2009*a*). Altered prepulse inhibition in chronic cannabis users is secondary to sustained attention deficits. *Psychopharmacology*. Published online: 9 October 2009. doi: 10.1007/s00213-009-1679-0.

Scholes KE, Martin-Iverson MT (2009*b*). Disturbed prepulse inhibition in patients with schizophrenia is consequential to dysfunction of selective attention. *Psychophysiology*. Published online: 12 October 2009. doi: 10.1111/j.1469-8986.2009.00927.

Sevy S, Burdick KE, Visweswaraiah H, Abdelmessih S, Lukin M, Yechiam E, Bechara A (2007). Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophrenia Research* **92**, 74–84.

Sheehan DV, Lecrubier Y, Sheehan H, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59** (Suppl. 20), 22–57.

Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Weiller E, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry* **12**, 232–241.

Silver H, Feldman P, Bilker W, Gur RC (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry* **160**, 1809–1816.

Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, Kahn RS (2004). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia Research* **71**, 285–295.

Smith RC, Warner-Cohen J, Matute M, Butler E, Kelly E, Vaidhyanathaswamy S, Khan A (2006). Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology* **31**, 637–643.

Solowij N, Michie PT (2007). Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia. *Journal of Psychiatry and Neuroscience* **32**, 30–52.

Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA: Journal of the American Medical Association* **287**, 1123–1131.

Stirling J, Lewis S, Hopkins R, White C (2005). Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow-up. *Schizophrenia Research* **75**, 135–137.

Tan H, Sust S, Buckholtz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, Weinberger DR, Callicott JH (2006). Dysfunctional prefrontal regional specialization and compensation in schizophrenia. *American Journal of Psychiatry* **163**, 1969–1977.

Thoma P, Wiebel B, Daum I (2007). Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. *Schizophrenia Research* **92**, 168–180.

Troisi A, Pasini A, Saracco M, Spalletta G (1998). Psychiatric symptoms in male cannabis users not using other illicit drugs. *Addiction* **93**, 487–492.

Twamley EW, Palmer BW, Jeste DV, Taylor MJ, Heaton RK (2006). Transient and executive function working memory in schizophrenia. *Schizophrenia Research* **87**, 185–190.

Wadsworth EJK, Moss SC, Simpson SA, Smith AP (2006). Cannabis use, cognitive performance and mood in a sample of workers. *Journal of Psychopharmacology* **20**, 14–23.

Waters AJ, Sutton SR (2000). Direct and indirect effects of nicotine/smoking on cognition in humans. *Addictive Behaviors* **25**, 29–43.

Wechsler D (1997). *WMS-III Administration and Scoring*. The Psychological Corporation: San Antonio, TX.

Wobrock T, Ecker UK, Scherk H, Schneider-Axmann T, Falkai P, Gruber O (2008). Cognitive impairment of executive function as a core symptom of schizophrenia. *World Journal of Biological Psychiatry* **29**, 1–12.

Wobrock T, Sittinger H, Behrendt B, D'Amelio R, Falkai P, Caspari D (2007). Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* **257**, 203–210.

Wood SW (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *Journal of Clinical Psychiatry* **64**, 663–667.

Yucel M, Bora E, Lubman D, Brewer WJ, Cotton S, Conus P, Condello A, Wood S, McGorry P, Pantelis C (2009). Effects of cannabis use on cognitive deficits in first-episode psychosis. In *Abstracts of the 9th World Congress of Biological Psychiatry*, p. 126. World Federation of Societies of Biological Psychiatry: Paris.