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The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample

Abstract

Cannabis use is highly prevalent among people with schizophrenia, and coupled with impaired cognition, is thought to heighten the risk of illness onset. However, while heavy cannabis use has been associated with cognitive deficits in long-term users, studies among patients with schizophrenia have been contradictory. This article consists of 2 studies. In Study I, a meta-analysis of 10 studies comprising 572 patients with established schizophrenia (with and without comorbid cannabis use) was conducted. Patients with a history of cannabis use were found to have superior neuropsychological functioning. This finding was largely driven by studies that included patients with a lifetime history of cannabis use rather than current or recent use. In Study II, we examined the neuropsychological performance of 85 patients with first-episode psychosis (FEP) and 43 healthy nonusing controls. Relative to controls, FEP patients with a history of cannabis use (FEP 1 CANN; n 5 59) displayed only selective neuropsychological impairments while those without a history (FEP 2 CANN; n 5 26) displayed generalized deficits. When directly compared, FEP 1 CANN patients performed better on tests of visual memory, working memory, and executive functioning. Patients with early onset cannabis use had less neuropsychological impairment than patients with later onset use. Together, these findings suggest that patients with schizophrenia or FEP with a history of cannabis use have superior neuropsychological functioning compared with nonusing patients. This association between better cognitive performance and cannabis use in schizophrenia may be driven by a subgroup of “neurocognitively less impaired” patients, who only developed psychosis

Keywords

analysis, existing, findings, data, first, meta, episode, schizophrenia, sample, cannabis, cognitive, impact, functioning, patients

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The Impact of Cannabis Use on Cognitive Functioning in Patients With Schizophrenia: A Meta-analysis of Existing Findings and New Data in a First-Episode Sample

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Cannabis use is highly prevalent among people with schizophrenia, and coupled with impaired cognition, is thought to heighten the risk of illness onset. However, while heavy cannabis use has been associated with cognitive deficits in long-term users, studies among patients with schizophrenia have been contradictory. This article consists of 2 studies. In Study I, a meta-analysis of 10 studies comprising 572 patients with established schizophrenia (with and without comorbid cannabis use) was conducted. Patients with a history of cannabis use were found to have superior neuropsychological functioning. This finding was largely driven by studies that included patients with a lifetime history of cannabis use rather than current or recent use. In Study II, we examined the neuropsychological performance of 85 patients with first-episode psychosis (FEP) and 43 healthy nonusing controls. Relative to controls, FEP patients with a history of cannabis use (FEP + CANN; $n = 59$) displayed only selective neuropsychological impairments while those without a history (FEP – CANN; $n = 26$) displayed generalized deficits. When directly compared, FEP + CANN patients performed better on tests of visual memory, working memory, and executive functioning. Patients with early onset cannabis use had less neuropsychological impairment than patients with later onset use. Together, these findings suggest that patients with schizophrenia or FEP with a history of cannabis use have superior neuropsychological functioning compared with nonusing patients. This association between better cognitive performance and cannabis use in schizophrenia may be driven by a subgroup of “neurocognitively less impaired” patients, who only developed psychosis after a relatively early initiation into cannabis use.

Key words: schizophrenia/psychosis/marijuana/drug/neuropsychology/comorbidity

Introduction

Rates of substance use disorders among individuals with schizophrenia are higher than the general population,^{1–3} with cannabis being the most commonly abused illicit drug.⁴ While cannabis use has been associated with poorer treatment outcomes, including symptom exacerbation,^{5–7} whether it is also associated with cognitive deficits remains contentious. Cannabis use among healthy users has been associated with cognitive impairments,^{8–12} including residual deficits in memory and attention, even several days following abstinence.^{13–16} Our studies in individuals with no medical or psychiatric history have shown that long-term cannabis use is associated with structural brain abnormalities and subthreshold psychotic symptoms in a dose-dependent manner.⁸ However, among patients with schizophrenia, the association is less clear. While acute administration of tetrahydrocannabinol (THC) to patients with schizophrenia exacerbates symptoms and cognitive impairments and may have enduring effects,¹⁷ cannabis has also been found to have some beneficial effects on cognition, at least in certain subgroups of patients.^{18–20} Thus, while cannabis use is traditionally associated with cognitive impairment, the relationship is more complex in the case of schizophrenia.

Although a recent meta-analysis conducted by Potvin and colleagues²¹ supports this notion, their analysis does not include studies conducted after 2006 and is not

focused on cannabis specifically but includes patients with polysubstance abuse. Here, we present 2 studies that aim to clarify the nature of the association between cannabis use and cognitive impairments observed in schizophrenia. The first study comprises a meta-analysis of empirical investigations of cannabis effects on cognition in patients with established schizophrenia. In the second study, we compared the neuropsychological functioning of patients with first-episode psychosis (FEP) with and without a history of cannabis use as well as healthy controls with no substance use history.

Study I: Meta-analysis of Findings To Date

Methods

We performed a literature search using PUBMED, PsycINFO, and Scopus covering the period between 1987 and March 2010. Combinations of the following keywords were used: schizophrenia, psychosis, cannabis, substance, cognit*, and neuropsycholog*. The reference lists of the published articles were also reviewed. Inclusion criteria included: (1) diagnosis of schizophrenia, (2) cognitive abilities of patients with and without cannabis use were directly compared, (3) cannabis was the predominant substance used by patients, and (4) studies reported sufficient data to calculate effect sizes in *d* metrics.

The initial search yielded 145 studies but only 15 studies considered the effect of cannabis on cognition in schizophrenia (table 1). Five of these studies were excluded because: (1) they lacked data for calculating effect size,^{22,23} (2) the study sample included a mixture of patients with schizophrenia and affective disorders,²⁴ and (3) they were primarily FEP studies (too few studies in this group to conduct appropriate meta-analyses).^{25,26} In 6 of the 10 studies included in the meta-analysis, cannabis use was defined as lifetime use and in the other 4 studies it was defined as recent use (current use or use in last 6 months). In 2 of the included studies,^{27,28} not all patients in the substance-using groups were abusing cannabis, but they were still included in the meta-analysis since cannabis was the most commonly used substance within the samples. In one study,²⁹ we used data from the 3-month follow-up assessment only since some patients had very recently used substances at baseline or were acutely intoxicated at the time of testing. Overall, our meta-analysis included 10 studies involving 572 patients with schizophrenia (with and without comorbid cannabis use).

Neuropsychological Variables. Neuropsychological variables were grouped according to the 6 cognitive domains of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery³⁰ (table 2). A “Global cognition index” was calculated by averaging effect sizes from each domain for

each study. We used global scores of cognition from the Study I of Løberg *et al*²⁹ because their classification of cognitive domains differed from the MATRICS.

Meta-analytical Procedure. For each cognitive test, effect size (Cohen’s *d*) and SE were calculated. Effect sizes were defined as the mean difference between the schizophrenia patients’ and healthy controls’ performance divided by the pooled SD. Effect sizes were weighted using the inverse variance method. A random effects model was used. Homogeneity of the mean-weighted effect sizes was tested using the Q-test, while publication bias was assessed using Egger’s test. Only instances where there were heterogeneity or publication biases are described in the Results. Meta-analyses were performed using MIX software.³¹ Meta-regression analyses examined the effect of moderator variables on between-group differences. This was performed with random effects modeling using the restricted-information maximum likelihood method with a significance level set at $P < .05$. These analyses were conducted in SPSS version 16.0 using the macros written by DB Wilson (<http://mason.gmu.edu/~dwilsonb/ma.html>). Separate meta-analyses were also performed for studies defining cannabis use as “lifetime” or “recent” (current/last 6 months) use.

Results

There were significant differences between the SCZ + CANN and SCZ – CANN groups for gender, age, education, age of onset of illness, and positive symptoms. The SCZ + CANN group comprised more males (RR = 1.10, CI = 0.99–1.22, $Z = 1.75$, $P = .08$), had less education ($d = 0.40$, CI = 0.21–0.60, $Z = 4.01$, $P < .001$), a younger age ($d = 0.57$, CI = 0.36–0.79, $Z = 5.29$, $P < .001$), more severe positive symptoms ($d = 0.65$, CI = 0.41–0.90, $Z = 5.15$, $P < .001$), and earlier illness onset ($d = 0.42$, CI = 0.19–0.65, $Z = 3.59$, $P = .003$). There were no significant between-group differences for duration of illness, negative symptoms, and premorbid IQ.

Global Cognition Index. Eight studies reported superior performance for SCZ + CANN patients on global cognition (see table 3; figure 1). The studies that reported better performance in SCZ + CANN tended to define cannabis use as lifetime use. Overall, SCZ + CANN patients performed significantly better than SCZ – CANN patients ($d = 0.35$). The distribution of effect sizes observed in these studies was not homogeneous. In separate analyses for studies using lifetime or recent cannabis use criteria, no more heterogeneity was observed. SCZ + CANN patients performed significantly better only in the studies defining use by lifetime exposure ($d = 0.55$) but not in the studies using recent use criteria ($d = 0.03$). Meta-regression analyses did not reveal any

Table 1. Studies that Investigated Cannabis Use and Cognition Association in Schizophrenia

Studies	Sample	Cannabis Criteria	Cannabis Use	Other Drugs	Cognitive Tests	Results
Lifetime history Joyal et al ²⁷	16 SCZ + SUD 14 SCZ – SUD	Cannabis abuse or dependency Not all the patients use cannabis but cannabis was the preferred substance for the sample	No information regarding abstinence and duration/onset of cannabis use		TMT-A, TMT-B, WCST, COWAT, RCFT, WAIS PA, Porteus Maze, Go/No Go	Impaired WCST, COWAT in nonusers Fewer neurological soft signs
Stirling et al ³³	24 SCZ + CANN 39 SCZ – CANN	Cannabis use prior to onset of psychosis	No information regarding abstinence and duration/onset of cannabis use		Design memory, verbal fluency, WAIS OA, BD, PC, PA, face recognition memory	SCZ + CANN better in 7/9 measures SCZ – CANN more deficit schizophrenia and more neurological soft signs
Jockers-Scherubl et al ¹⁹	19 SCZ + CANN 20 SCZ – CANN 39 HC	At least 0.5 g daily For 2 y prior to onset	Abstinence, at least 4 wk (weekly urine screenings)	Alcohol excluded, SCZ – no other substance abuse	CPT-IP, TMT-A, TMT-B, WCST, WMS-R verbal and visual memory, WAIS-R (BD, PA, DSST, Comprehension)	SCZ + CANN performs better than SCZ – CANN in some cognitive domains. Regular use before 17 associated with even better performance
Sevy et al ³²	14 SCZ + CANN 13 SCZ – CANN	Cannabis abuse or dependency 0.5 g/day, >4 d of the week. Only 1 subject used in last 2 mo	No information regarding abstinence and duration/onset of cannabis use 78% started prior to onset of psychosis	Cannabis main substance, 7 alcohol abuse, 3 cocaine abuse Nicotine use is more in SCZ + CANN	WRAT, CPT-IP, CVLT, DS (backward and forward), TMT-A, TMT-B, COWAT (semantic and phonemic), IGT	No difference No impact of alcohol
Løberg et al ²⁹ (Study I)	13 SCZ + CANN 18 SCZ – CANN	History of cannabis abuse or dependency	No information regarding abstinence and duration/onset of cannabis use	All abuse cannabis 8 additional substance abuse mainly amphetamine	Memory, attention, psychomotor speed, general abilities, and executive function domains based on various test	SCZ + CANN performs better except memory
Schnell et al ²⁰	35 SCZ + CANN 34 SCZ – CANN	Cannabis abuse or dependency All started prior to onset of illness (average 6 y)	Minimum 3 wk abstinence (self and medical reports and urine screening) Age of onset = 17 Duration = 8.5 y Frequency/month = 53 joints	No other substances except nicotine	AVLT, LNS, DSST, TMT-B, MWT-B, CPT, Verbal fluency, Dual processing task	SCZ + CANN better in WM, executive functions, and verbal memory. High frequency use was associated with even better performance

4 **Table 1.** Continued

Studies	Sample	Cannabis Criteria	Cannabis Use	Other Drugs	Cognitive Tests	Results
Current/recent use Potvin et al ²⁸	44 SCZ + CANN 32 SCZ – CANN	Abuse or dependence Not all the patients use cannabis but cannabis was the preferred substance for the sample Last 6 mo	No information regarding abstinence and duration/ onset of cannabis use	12 cocaine, 17 polysubstance	PAL, MOT	SCZ + CANN better in MOT No difference for PAL. However, SCZ + CANN patients who use cocaine are more impaired in PAL. Non cocaine user but SCZ + CANN patients are better than SCZ – CANN in PAL
Løberg et al ²⁹ (Study II)	13 SCZ + CANN 13 SCZ – CANN	Current cannabis abuse or dependency Acute admission with schizophrenia or schizophrenia like psychoses	No information regarding abstinence and duration/ onset of cannabis use	All abuse cannabis 10 also abuse other substances (4 amphetamine, 3 cocaine, 4 alcohol)	Global cognition score based on various cognitive tests longitudinal study, 3 mo follow-up	In acute admission, SCZ + CANN performs worse, in follow-up they significantly improved SCZ – CANN no change in follow-up
Ringen et al ⁷⁸	117 SCZ + CANN 23 SCZ – CANN	Cannabis use in last 6 mo			DSST, Digit span, 2-Back, Verbal fluency, Logical memory, word interference, CVLT	SCZ + CANN performs worse in verbal memory and attention
Scholes et al ⁷⁹	22 SCZ + CANN 49 SCZ – CANN	Current cannabis use			Stroop, WCST, Spatial span, LNS	No difference

Note: TMT-A, Trial Making Test—Part A; TMT-B, Trial Making Test—Part B; TMT B/A, Trial Making Test—Part B minus Part A; WCST, Wisconsin Card Sorting Task; COWAT, Controlled Oral Word Association Task; RCFT, Rey Complex Figure Test; PAL, Paired Associate Learning; MOT, Motor Screening; OA, Object Assembly; BD, Block Design; PC, Picture Completion; PA, Picture Arrangement; DS, Digit Span; WAIS, Wechsler Adult Intelligence Scale; WRAT, Wide Range Achievement Test; CPT-IP, Continuous Performance Task—Identical Pairs; CVLT, California Verbal Learning Task; IGT, Iowa Gambling Task; RAVLT, Rey Auditory Verbal Learning Task; LNS, Letter Number Sequencing; DMST, Delayed Matching to Sample Test; MWT-B, Mehrfachwahl-Wortschatztest—Form B; HC, Healthy Control; SUD, Substance Use Disorder; FEP, First-Episode Psychosis; SCZ, Schizophrenia; DSST, digit symbol substitution task. Superscript numbers refer to the relevant reference number in the citations list.

Table 2. NIMH-MATRICES Cognitive Domains

Cognitive Domain	Cognitive Test
Processing Speed	Phonetic fluency, semantic fluency, Trail-Making Test, Symbol Coding, Motor Screening Task, Stroop
Attention	Continuous Performance Test, Dual Processing Task
Working Memory	Digit span, Letter Number Sequencing, Wechsler Memory Scale—Revised Verbal Memory
Reasoning and Problem Solving	WAIS Block Design, Object Assembly, Picture Arrangement, Porteus Maze, Wisconsin Card Sorting Test
Verbal Learning and Memory	California Verbal Learning Test, Rey Auditory Verbal Learning Test

Note: Abbreviations are explained in the footnote to table 1.

effect of demographic (effect size of age difference and gender ratio) or clinical variables (effect size of differences for onset of illness, duration of illness, positive, and negative symptoms) on the magnitude of the between-group differences.

Attention. Three studies examined attention. There were minimal between-group differences on a sustained attention task ($d = 0.26$).

Processing Speed. Eight studies examined processing speed. The SCZ + CANN patients had significantly faster processing speeds than SCZ – CANN patients ($d = 0.40$). Effect sizes were not homogeneously distributed,

however, when recent use vs lifetime defining studies was examined separately, there was no evidence for heterogeneous distribution of effect sizes. SCZ + CANN patients performed significantly better than SCZ – CANN only within the lifetime defining studies ($d = 0.65$) but not in those studies with recent use criteria ($d = 0.09$).

Visual Memory. Three studies assessed visual memory. Again, SCZ + CANN patients performed better than SCZ – CANN patients ($d = 0.45$).

Verbal Memory. Four studies reported verbal memory measures. There was no significant between-group difference for verbal memory ($d = 0.0$). The Q-test showed evidence for heterogeneity for distribution of effect sizes. When the 3 lifetime defining studies were examined separately, between-group comparisons remained nonsignificant ($d = 0.18$).

Working Memory. Four studies examined working memory. There was no significant between-group difference ($d = 0.13$). While distribution of effect sizes was heterogeneous, the between-group difference for 2 lifetime defining studies was $d = 0.64$, with the SCZ + CANN group demonstrating significantly superior performance. The between-group difference for recent use criteria studies was not significant ($d = -0.28$). There was no evidence of heterogeneity for these separate analyses.

Executive Functioning. In the 4 studies included in this domain, cannabis use was associated with better planning and reasoning abilities ($d = 0.47$). When the lifetime

Table 3. Mean-Weighted Effect Sizes for Cognitive Domains for Cannabis Using and Nonusing Schizophrenia Patients Defined by Lifetime Use Vs Current or Recent Use Criteria

Test	Number of Studies	SCZ + CANN	SCZ – CANN	Cohen's d	95 % CI	z	P	Q-test, P	Bias Test
Global cognition	10	223	349	0.35	0.09 to 0.61	2.63	.009	17.13*	0.34
Lifetime	6	121	138	0.55	0.30 to 0.80	4.29	.001	3.95	
Current/recent	4	102	211	0.03	-0.30 to 0.37	0.20	.84	4.59	
Attention	3	68	67	0.26	-0.08 to 0.61	1.51	.13	0.50	0.26
Processing speed	8	192	322	0.40	0.11 to 0.69	2.75	.006	14.62*	0.39
Lifetime	5	103	124	0.65	0.38 to 0.92	4.70	.001	1.72	
Current/recent	3	89	198	0.09	-0.34 to 0.52	0.42	.67	4.87	
Visual memory	3	87	91	0.45	0.13 to 0.77	2.76	.006	2.24	0.98
Verbal memory	4	101	184	0.0	-0.51 to 0.51	0	.99	10.1*	0.75
Lifetime	3	78	67	0.18	-0.32 to 0.77	0.63	.53	4.78	
Planning	4	81	122	0.47	0.05 to 0.90	2.20	.03	5.92	0.39
Lifetime	3	59	73	0.67	0.31 to 1.03	3.65	.001	1.20	
Working memory	4	94	213	0.13	-0.40 to 0.55	0.48	.63	11.58*	0.61
Lifetime	2	49	47	0.64	0.22 to 1.05	3.00	.003	0.16	
Current/recent	2	45	166	-0.28	-0.61 to 0.06	1.62	.10	0.12	

Note: Bold values indicate comparisons that were significantly different between the SCZ + CANN and the SCZ – CANN groups. * $P < .05$.

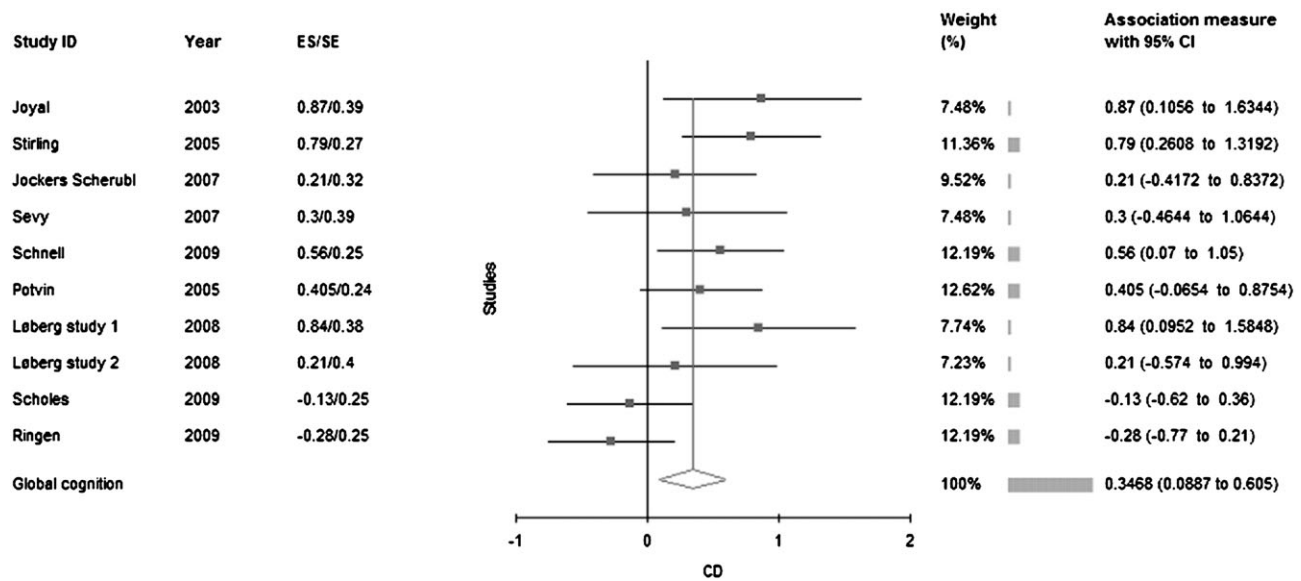


Fig. 1. Effect Size Analysis of All Studies Conducted To Date. A summary score global cognition index was calculated by averaging effect sizes from each domain for each study.

defining studies were examined separately, the between-group difference was larger ($d = 0.67$).

Recency of Cannabis Use. For this analysis, we excluded the study by Jockers *et al.*¹⁹ as they did not exclude patients using cannabis in the week prior to testing. Patients with SCZ + CANN without recent use demonstrated better verbal memory performance than the SCZ – CANN group ($d = 0.46$, CI = 0.05–0.88, $Z = 2.20$, $P = .03$). Distribution of effect sizes was more homogenous with this analysis ($P = .52$).

Frequency of Cannabis Use. One study reported an association between higher frequency of cannabis use and better cognitive performance (working memory and attentional tasks; Schnell *et al.*)²⁰

Age of Onset of Cannabis Use. Only one study examined the relationship between age of onset of cannabis use and cognitive deficits.¹⁹ In this study, earlier starting age of cannabis use (ie, before 17 years of age) was associated with superior cognitive performance.

Effect of Other Substances. A separate meta-analysis for the 2 studies^{19,20} consisting of patients without comorbid substance use (other than nicotine) was conducted. We found a similar mean effect size for global cognition ($d = 0.43$) to that observed in the overall meta-analysis. One study also examined the effect of comorbid alcohol use in cannabis-using patients and failed to find any significant difference between alcohol-using and nonusing groups.³² One study found that cocaine-using SCZ + CANN patients were cognitively more impaired.²⁸

Summary of Study I

These meta-analyses demonstrate that patients with established schizophrenia with a cannabis use history display superior cognitive abilities compared with non-cannabis-using patients. These results may appear counterintuitive because healthy individuals who are heavy cannabis users have cognitive deficits and brain abnormalities.^{8,9} However, our findings are consistent with previous studies conducted in schizophrenia patients with comorbid polysubstance use,²¹ while showing specificity to a cannabis-using sample. Furthermore, we showed that better cognitive performance is seen only in lifetime users but not in recent users.

Importantly, the majority of studies to date have been conducted in patients with chronic illness without assessing whether cannabis use preceded the onset of psychosis. It is possible that the cognitive profile of patients whose cannabis use may have contributed to the onset of their psychosis might be different from those who started using cannabis after the onset of their psychosis. Studies examining cannabis use prior to the onset of FEP are especially useful in this regard because cannabis use may contribute to the onset of psychosis only in these patients. Five studies have examined cognitive functioning in a sample who used cannabis before the onset of psychosis.^{25,26,33} However, the studies of Stirling *et al.*,³³ Jockers-Scherubl *et al.*,¹⁹ and Schnell *et al.*²⁰ included a chronic sample, and it was not possible to exclude the effects of cannabis use after the onset of psychosis or illness-related factors. While the studies of de la Serna *et al.*²⁵ and Mata *et al.*²⁶ were also FEP samples, they only assessed cannabis use in the previous one month or in the previous 12 months, meaning that their cannabis nonuser samples were likely

to have also included patients who had a past history of cannabis use.

Thus, there are no FEP studies that have examined cognitive functioning in FEP patients with a lifetime history of cannabis use. In our second study, we report on such a sample. Additionally, given that the age of cannabis use onset has been found to be an important moderator of the association between cannabis use and psychotic illness,^{34–37} we investigated the impact of age of cannabis use onset on cognitive functioning.

Study II: New Data in FEP Patients

Methods

Sample and Setting. Participants included 85 FEP patients and 43 healthy nonusing controls. Participants were selected from a larger neuropsychological research database (described previously^{38–40}) only if they were assessed for substance use. While all participants agreed to a cognitive test battery, some participants had an incomplete cognitive assessment. A detailed substance use history, including information concerning the amount, frequency, duration, and type of substance use, diagnosis, time since last use, and age of onset of regular use, was obtained using a combination of medical history notes and structured clinical and research interviews (ie, substance use module of the Structured Clinical Interview for DSM-IV [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*], Patient version [SCID-I/P],⁴¹ Clinical Global Impressions-Severity of Illness Scale⁴²). In addition, substance use data were gathered from the Early Psychosis File Questionnaire,⁴³ which was used to systematically extract data on premorbid, entry, treatment, and discharge characteristics from consecutive medical files. Cannabis was the predominant substance used in FEP patients. FEP patients with a history of regular use (defined as >2 years of use and >2 g per week) were classified as cannabis users ($n = 59$; FEP + CANN), and a large majority of these patients met criteria for *Diagnostic and Statistical Manual of Mental Disorders, Third Revision* (DSM-III-R) cannabis abuse or dependence (see below). FEP patients without a history of regular cannabis use were classified as nonusers ($n = 26$; FEP – CANN). Cannabis use was assessed over each subject's lifetime, and none of the FEP – CANN group had ever used cannabis regularly (ie, had not used on a weekly basis for >12 months), while all FEP + CANN patients used cannabis before the onset of the illness. Of the 26 FEP – CANN patients, 3 had a past history of alcohol abuse and 4 others had experimented with stimulants and lysergic acid diethylamide (LSD).

All patients with FEP were recruited from the Early Psychosis Prevention and Intervention Centre at Orygen Youth Health and were diagnosed with schizophrenia-spectrum disorders according to DSM-III-R criteria

based on a medical record review and structured clinical interview using the Positive and Negative Syndrome Scale,⁴⁴ SCID-I/NP⁴¹ and the Royal Park Multi-diagnostic Instrument for Psychosis (McGorry et al⁴⁵). For controls, we used the SCID-I (nonpatient edition). Of the 59 patients classified as cannabis users (FEP + CANN), 55 met criteria for past or current cannabis abuse or dependence. Thirty-two of the FEP + CANN had started to use cannabis at 16 years of age or earlier (FEP + CANN[early]) and 27 had started at age 17 or thereafter (FEP + CANN[later]). We chose to compare those who had commenced using cannabis before or after ages 16–17 years on the basis of previous literature suggesting that exposure to cannabis prior to this period of adolescence has relatively greater adverse consequences compared with later initiation,^{12,46} and this cutoff enabled a roughly equal division of the sample. All were abstinent at the time of assessment (according to self-report, medical records/case notes, and researcher observations), 34 for >1 month, while 10 had consumed cannabis within the previous week, and a further 10 for between 8 and 30 days prior to the assessment (data were missing for 5 cases). Fifteen of the FEP + CANN patients also had a history of stimulant and hallucinogen use (mainly amphetamine), and 16 others had a history of alcohol abuse. Most patients ($n = 51$) were prescribed antipsychotic medication (35 risperidone, 14 olanzapine, and 2 typical antipsychotics), while 10 were prescribed mood stabilizers (5 lithium and 5 sodium valproate) and 7 were prescribed antidepressants (5 SSRI, 1 imipramine, and 1 moclobemide). Chlorpromazine equivalents (cpz) of antipsychotics were calculated.⁴⁷

Healthy controls comprised 43 individuals with no current or past history of illicit substance abuse or dependence. Healthy volunteers were recruited by approaching ancillary hospital staff (eg, nonprofessional staff and students) and through advertisements in local newspapers in the same catchment area as the patients (ie, north-western regions of Melbourne) as well as through “word of mouth” (ie, friends of patients).

All participants were screened for comorbid medical conditions. Exclusion criteria were a history of head injury causing loss of consciousness for greater than 1 minute and/or hospitalization, neurological disorders, thyroid disorders, documented poor eyesight or hearing, and history of corticosteroid use. Control participants with family or personal histories of psychiatric illness were also excluded. Local research and ethics committees approved the study, and written informed consent was obtained from all individuals prior to study participation.

Cognition. All participants were administered a cognitive test battery by experienced psychologists. Neuropsychological tasks targeted general intelligence, processing speed, verbal memory, visual memory, working memory, and executive functioning (planning and reasoning).

These domains reflect 5 of 6 dimensions in the MATRICS battery.³⁰ In order to facilitate comparison with the meta-analysis in Study I, tasks that were, and those that were not reflected in the MATRICS battery were allocated to a relevant domain following a consensus agreement between 2 authors (E.B. and M.Y.).

General Intellectual Ability. Performance on the National Adult Reading Test was used to estimate premorbid IQ.⁴⁸ The Wechsler Adult Intelligence Scale—Revised (WAIS-R) was used to estimate current IQ.⁴⁹

Processing Speed. The Trail-Making Test (Part A) and Digit Symbol Coding were used as measures of processing speed.^{49,50}

Visual Memory. Visual Paired Associates (part I) and Visual Reproduction (part I) from the Wechsler Memory Scale—Revised (WMS-R) provided measures of visual learning and memory.⁵¹ Spatial and Pattern Recognition tests from the Cambridge Automated Neuropsychological Test Automated Battery (CANTAB) were used to index recognition memory.^{52,53}

Verbal Memory. A modified version (3 trials instead of 5) of the Rey Auditory Verbal Learning Test was used as a measure of verbal learning and delayed recall.⁵⁴ The Logical Memory (parts I and II) component of the WMS-R was also used.⁵¹

Working Memory. Spatial Span and Spatial Working Memory (SWM) from the CANTAB were used to index working memory.^{53,55} Regarding SWM, 2 scores were included in the analysis: (1) total between-search errors (SWM-errors), which is the number of times that a subject returns to a box in which a token had already been found during a previous search sequence and (2) strategy score (SWM-strategy), a measure of the ability to adopt a systematic search approach (ie, initiating a search from the same token across trials shows better strategy use). While SWM-errors is a more pure measure of short-term working memory, strategy score also measures central executive functioning.

Executive Functioning. Block Design from the WAIS-R and the Tower of London (ToL) tests were used as measures of planning and reasoning ability.^{49,56}

Statistical Analyses. Statistical analyses were conducted using the Statistical Package for Social Sciences Version 16.0 (SPSS 16.0). Between-group differences on categorical variables were tested using chi-square analysis. Patients' scores on cognitive tests were converted to *z* scores based on the controls' performance. ANCOVA was used to test group differences between FEP – CANN and FEP + CANN on continuous measures with gender and age as covariates. ANCOVA analyses

Table 4. Demographic and Clinical Characteristics of Patient and Control Groups

	Control	FEP + CANN	FEP – CANN	<i>P</i>
Number (male/female)	43 (33/10)	59 (43/16)	26 (15/11)	.44
Age	21.6 (5.8)	20.7 (2.8)	20.6 (3.5)	.49
Education	12.3 (1.4)	10.9 (1.8)	11.6 (2.0)	.001^a
PANSS positive		24.7 (6.3)	21.8 (6.5)	.06
PANSS negative		20.7 (7.4)	20.9 (8.2)	.93
GAF-premorbid		70.1 (13.5)	76.2 (12.0)	.20
GAF-entry		29.9 (8.5)	31.7 (7.5)	.32

Note: Bold values indicate comparisons that were significantly different between the FEP + CANN and the FEP – CANN groups. GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale. Additional abbreviations are explained in the footnote to table 1.

^aFEP + CANN < Controls.

were also used to compare FEP – CANN, FEP + CANN[early], and FEP + CANN[late]. Significant *F*-statistics were followed up with post hoc analyses using the Tukey test. Cohen's *d* also characterized between-group differences.⁵⁷ Pearson product moment correlation was used to examine relationships between cognition, parameters of cannabis use, and clinical measures.

Results

Demographic. There was no significant between-group difference for age and gender (see table 4). FEP patients who use cannabis were less educated than controls but did not differ from FEP – CANN, while the latter did not differ from controls.

FEP – CANN and FEP + CANN vs Controls. FEP patients (with and without comorbid cannabis) were significantly impaired on all 16 tasks compared with controls. Effect sizes of these impairments in all 6 cognitive domains were moderate to large, ranging from 0.52 to 2.11. The most pronounced impairments were observed for Current IQ ($d = 2.11$), Logical Memory ($d = 1.70$), SWM-errors ($d = 1.60$), and Digit Symbol Coding ($d = 1.48$).

When we compared each of the FEP + CANN and FEP – CANN groups separately to controls, the FEP – CANN patients were significantly impaired on 15 of the 16 tasks administered across the 6 cognitive domains, while the FEP + CANN group showed only selective impairments (9 of the 16 tasks) (table 5; figure 2). Both FEP + CANN and FEP – CANN patients were significantly impaired for all tasks of general intelligence, verbal memory, and processing speed. Unlike the FEP – CANN group, the FEP + CANN group was not significantly different from controls on most tasks of visual memory and planning/reasoning. In the working memory domain, FEP + CANN patients were impaired

Table 5. Mean Z Scores and Between-Group Differences for Cannabis Using and Nonusing FEP Groups

	<i>N</i>	FEP + CANN	<i>N</i>	FEP – CANN	<i>p</i>	ES
General Intelligence						
Current IQ	54	–1.65 (1.40)*	20	–2.39 (0.96)*	.07	0.40
Premorbid IQ	41	–0.50 (1.14)	16	–0.57 (1.24)	.83	0.06
Verbal Memory						
RAVLT—total	40	–0.73 (0.88)*	19	–1.05 (1.17)*	.21	0.33
RAVLT—recall	40	–0.65 (0.96)*	19	–1.09 (1.24)*	.15	0.44
Logical Memory	41	–1.33 (0.85)*	16	–1.59 (0.80)*	.21	0.30
Visual Memory						
Visual PA—total errors	47	–0.17 (0.99)	23	–0.59 (1.08)*	.10	0.50
Visual Reproduction	35	–0.19 (0.70)	19	–0.71 (1.17)*	.05	0.60
Spatial Recognition	49	–0.39 (1.01)	23	–0.83 (1.39)*	.18	0.39
Pattern Recognition	49	–1.04 (1.20)*	23	–1.65 (1.50)*	.09	0.47
Processing Speed						
Trails A	39	–1.54 (1.58)*	19	–1.98 (3.24)*	.48	0.19
Digit Symbol Coding	44	–1.83 (1.61)*	17	–1.90 (1.60)*	.67	0.04
Working Memory						
SWM-errors	49	–0.94 (1.13)*	22	–1.80 (1.30)*	.01	0.74
SWM-strategy	49	–0.48 (0.91)	22	–0.88 (0.86)*	0.12	0.44
Spatial Span	49	–0.58 (0.91)	22	–1.01 (1.02)*	0.09	0.44
Executive Functioning						
Block Design	36	–0.92 (1.23)*	18	–1.19 (1.65)*	0.62	0.22
ToL minimum solution	24	–0.19 (0.93)	12	–1.15 (1.37)*	0.03	0.90

Note: Corrected for age and gender differences; ES, effect size (Cohen's *d*; unadjusted values); Asterisks reflect that these measures are significantly different to healthy controls. “*p*” represents the *P* values for comparisons between the FEP + CANN and FEP – CANN groups. Values in parentheses represent the SD of *z* scores. SWM, Spatial Working Memory; ToL, Tower of London. Additional abbreviations are explained in the footnote to table 1. Bold values indicate comparisons that were significantly different between the FEP + CANN and the FEP – CANN groups.

in SWM-errors but not in SWM-strategy or Spatial Span. FEP + CANN patients did not differ from controls on the ToL task involving planning and reasoning.

FEP – CANN vs FEP + CANN. FEP + CANN patients tended to perform better than FEP – CANN patients but this difference was significant only for 3 variables (table 5; figure 2). On verbal and nonverbal memory, between-group differences were small to moderate (*d* ranged from 0.3 to 0.6) and FEP + CANN performed significantly better on visual reproduction. For the working memory domain, small to medium effect sizes were observed and a between-group difference for SWM-errors reached significance (ie, with FEP + CANN performing better). For executive functioning, a significant between-group difference with a large effect size (*d* = 0.90) was observed for the ToL test (again with FEP + CANN performing better).

Comorbid Substance Use. ANCOVA analyses were conducted to examine the effect of additional illicit substance use (over lifetime) on cognition in the FEP + CANN patients. FEP + CANN patients who also used amphetamines (*n* = 12) did not perform significantly differently to the remaining (nonamphetamine using) FEP + CANN patients on any cognitive measure (*d* ranged from –0.50

to –0.39). Similarly, no significant differences were found between the alcohol-using and nonusing FEP + CANN patients (*d* ranged from –0.10 to +0.54).

Age of Onset of Cannabis Use. When comparing the non-cannabis-using patients (FEP – CANN) with early onset (≤ 16 years; FEP + CANN[early]) and later onset (≥ 17 years; FEP + CANN[later]) cannabis-using patients, we found group differences for 4 cognitive tests (SWM-errors, ToL, Pattern Recognition, and Spatial Recognition). The FEP – CANN patients did not differ from FEP + CANN [later] on any cognitive tests (figure 3). FEP + CANN[early] patients performed significantly better than FEP – CANN on all 4 of the above cognitive tests and better than FEP + CANN[later] on 2 tests (Pattern Recognition and Spatial Recognition). The FEP + CANN[early] group were younger than the FEP + CANN[later] group (table 6) but did not differ in duration or monthly quantity of cannabis use, diagnosis, treatment, or antipsychotic levels (based on chlorpromazine equivalents; see table 6).

Recency of Cannabis Use. FEP patients who had used cannabis in the previous week were more impaired on Logical Memory compared with patients who were abstinent for greater than 1 month prior to testing (*P* = .04). There were no significant correlations between cognition

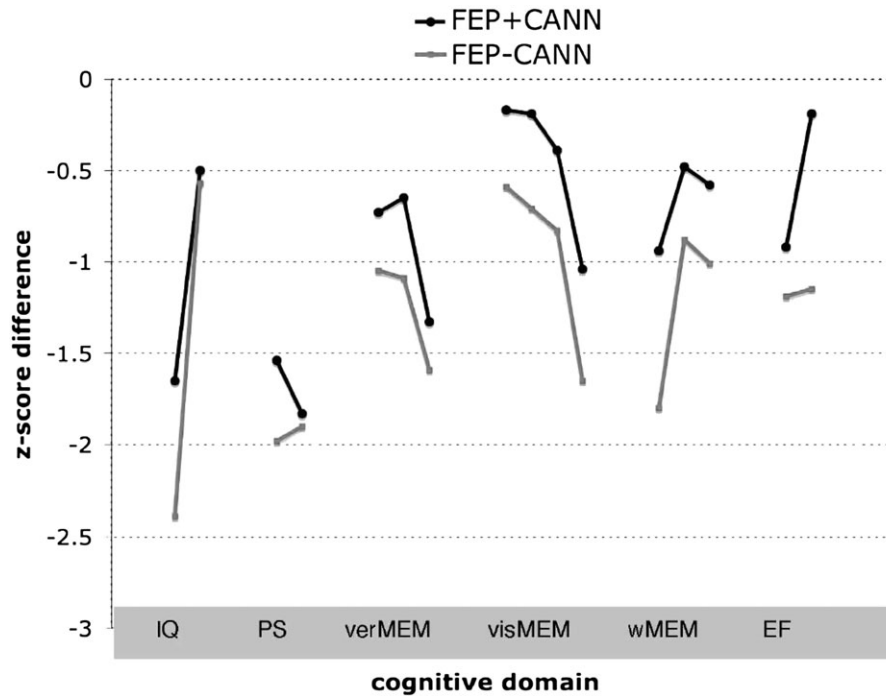


Fig. 2. Mean Z Score Differences for Cannabis Using and Nonusing FEP Groups. Note: IQ, intelligence; PS, processing speed; verMEM, verbal memory; visMEM, visual memory; wMEM, working memory; EF, executive functioning. Note that each point reflects a specific task within the 6 domains of interest (refer to the Methods section and table 5 for the specific tasks).

and other cannabis use parameters (frequency, quantity, and duration of use).

Associations between Clinical Variables and Cognition. In both FEP groups, the Positive and Negative Syndrome Scale negative symptoms score was negatively correlated with Digit Symbol Coding (FEP + CANN: $r = -.41$, $P = .006$, FEP - CANN: $r = -.58$, $P = .02$) and Current IQ (FEP + CANN: $r = -.43$, $P = .002$, FEP - CANN: $r = -.55$, $P = .01$). The positive symptoms score was not significantly correlated with any cognitive measure.

Discussion

In Study I, we demonstrated that regular cannabis use was associated with better cognitive performance in schizophrenia. Cannabis-using patients performed moderately better than nonusing patients on measures of global cognition, visual memory, processing speed, working memory, planning, and reasoning. This difference was largely driven by studies that included patients with a lifetime history of cannabis use rather than just those with current or recent use. Consistent with previous studies, cannabis use was associated with a younger age of psychosis onset, male sex, and more positive symptoms.^{7,36,58–60} Study II examined the effect of regular cannabis use on cognition in FEP patients. Cognitive performance of FEP patients with a history of cannabis use was compared with FEP patients without a history of substance use and healthy controls on 6 cognitive

domains. Unlike most previous studies, we also examined the effect of variables such as recency and frequency of use and age of onset of cannabis use. The findings were consistent with Study I and demonstrated that FEP patients who used cannabis (especially those who used prior to age 17) also performed better than nonusing patients in some domains and were less impaired relative to healthy controls on cognitive domains, including visual memory, working memory, planning, and reasoning. When age of onset of cannabis use was considered, superior cognitive performance in cannabis-using patients relative to nonusing patients was only observed among those who started using cannabis at an early age (≤ 16 years). Together, the findings of our meta-analysis and empirical study suggest that comorbid cannabis use is associated with a superior cognitive profile in schizophrenia-spectrum disorders.

Several explanations regarding the nature of the association between pre-illness onset cannabis use and subsequent development of schizophrenia have been suggested. One explanation is that cannabis is a risk factor that precipitates (but does not cause) the onset of psychosis in genetically predisposed individuals.⁶¹ However, there is also evidence that cannabis use prior to illness onset is “causally” related to the development of subsequent psychosis in vulnerable individuals.^{62–64} Similarly, several recent systematic reviews have indicated that cannabis may double the risk of later developing a psychotic illness and that this association is dose dependent.^{34,63,65}

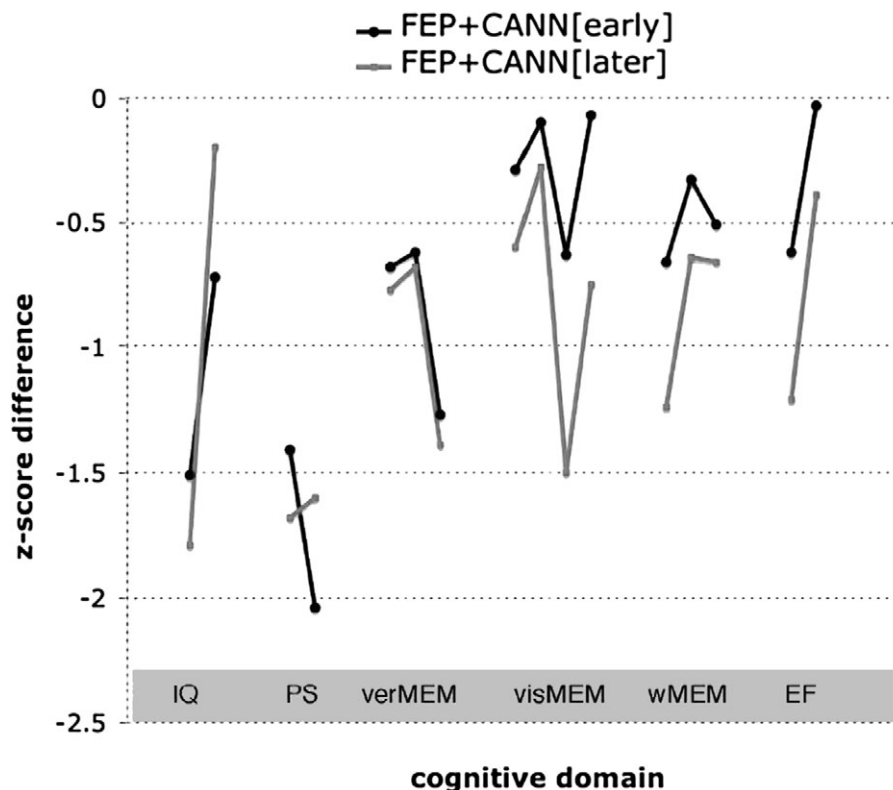


Fig. 3. Mean Z Score Differences for Early and Late Cannabis Using FEP Groups. Note: IQ, intelligence; PS, processing speed; verMEM, verbal memory; visMEM, visual memory; wMEM, working memory; EF, executive functioning. Note that each point reflects a specific task within the 6 domains of interest (refer to the Methods section and table 5 for the specific tasks).

However, few previous studies have considered the role of cognition. Our findings raise a number of further questions concerning the relationship between cannabis, cognition, and schizophrenia.

Some authors have suggested a neuroprotective role of cannabis⁶⁶ to explain the association between cannabis use and enhanced cognition in schizophrenia patients.^{19,67} Other authors suggest that, in the short-term, cannabinoids could stimulate prefrontal neurotransmission to enhance cognitive functions,^{22,34,67,68} but in the long-term, repeated administration is detrimental.¹² However, these postulates remain speculative and further work is necessary. It is well recognized that acute administration of THC impairs rather than enhances cognitive performance in both healthy controls^{12,17} and patients with psychosis^{17,69}, suggesting that acute neuroprotective effects of THC are unlikely. Findings of our meta-analysis and FEP study also provide evidence regarding adverse effects of recent cannabis use, which may partly mask the positive association between lifetime cannabis use and better cognition. Another possibility is that cannabis-using patients had superior social skills in order to be able to acquire and sustain a drug habit,^{12,21} which is also reflected in their cognition. Few studies have directly examined this possibility, and this notion is not always supported by the extant data⁷⁰; however,

we did not find any current or premorbid Global Assessment of Functioning (GAF) differences between FEP users and nonusers in our study.

While the FEP patients with a cannabis use history were generally superior in their cognitive profile to those without a history of cannabis use, the former group was not homogeneous. Indeed, the cognitive profile was markedly different depending on the age of onset of cannabis use, with the early onset group having superior cognition, which cannot be explained by differences in the duration or dosage of cannabis used. This finding is somewhat against expectation and is counterintuitive given the associations between cannabis use and cognition in healthy controls (ie, worse cognition in those with early onset use¹²). It is possible that in the FEP group with comorbid cannabis use (characterized by only relatively mild cognitive impairments), early onset cannabis use increased the risk for developing psychosis, thereby facilitating the transition to frank psychosis that might otherwise not have occurred. That is, early cannabis use may induce psychosis onset in less cognitively vulnerable individuals. Schnell and colleagues²⁰ as well as Løberg and colleagues²⁹ have proposed a similar hypothesis. Support for this comes from findings that early onset of cannabis use in adolescence, particularly before the age of 15, is associated with greater risk for the subsequent

Table 6. Cannabis Use and Clinical Characteristics of Patient Groups Based on Age of Onset of Cannabis Use

	FEP – CANN (<i>n</i> = 26)	FEP + CANN[later] (<i>n</i> = 27)	FEP + CANN[early] (<i>n</i> = 32)	<i>P</i> Value
Demographic				
Age (y)	20.6 (3.5)	22.2 (2.6)	19.5 (2.5)	.003 ^a
Gender (male/female)	15/11	20/7	23/9	.39
Education	11.1 (1.6)	11.0 (1.5)	11.5 (1.5)	.52
GAF-premorbid	74.8 (11.7)	64.9 (14.3)	75.8 (10.4)	.06
GAF-entry	32.4 (7.5)	31.2 (6.3)	27.9 (8.9)	.34
Cannabis Use				
Age of Onset (y)		17.9 (1.0)	14.4 (1.6)	<.001
Duration (y)		3.9 (2.4)	4.8 (2.3)	.13
Quantity (g/month)		11.5 (15.8)	20.8 (21.5)	.10
Diagnosis				
Schizophreniform	8 (31%)	8 (30%)	11 (34%)	.68
Schizophrenia	7 (27%)	11 (41%)	12 (38%)	
Mood disorder	8 (31%)	5 (18%)	6 (19%)	
Other Psychoses	3 (11%)	3 (11%)	3 (9%)	
Symptom				
Positive	21.9 (6.7)	25.8 (6.3)	24.3 (5.8)	.08
Negative	20.4 (8.1)	20.8 (7.4)	21.4 (7.3)	.89
Antipsychotic use				
Risperidone	12 (46%)	18 (67%)	18 (56%)	.77
Olanzapine	7 (27%)	5 (19%)	7 (22%)	
Typicals	2 (8%)	0 (0%)	1 (3%)	
No antipsychotics	4 (16%)	4 (15%)	4 (13%)	
Missing	1 (4%)		2 (6%)	
Chlorpromazine equivalent	204 (259)	136 (102)	169 (141)	0.40

Note: GAF, Global Assessment of Functioning. Additional abbreviations are explained in the footnote to table 1.

^aPost hoc tests; FEP + CANN[later] vs FEP + CANN[early] *P* = .002; FEP + CANN[later] vs FEP – CANN *P* = .12; FEP + CANN[early] vs FEP – CANN *P* = .36.

development of psychotic disorders, even after controlling for preexisting psychotic symptoms.⁴⁶ It is possible that these individuals would have remained asymptomatic or would have been symptomatic only in subsequent years, if they did not abuse cannabis. This notion is consistent with Jockers-Scherubl *et al*¹⁹ who found an association between earlier onset of cannabis use and better cognition in schizophrenia. Such a notion could also help explain why cessation of substance use after the first onset of psychosis significantly increases the probability of remission and improves long-term outcomes in FEP patients.⁷¹ Interestingly, a recent study also found fewer neurological soft signs in heavy cannabis-using FEP patients, supporting the notion that these patients have less neurological impairment.⁷²

Other factors might also influence the association between cannabis use and cognitive deficits in schizophrenia, including dosage and frequency of use and cumulative exposure. Interestingly, while higher frequency of cannabis use could be expected to be associated with poorer cognition, the only 2 studies that have examined frequency of use in schizophrenia patients found the opposite effect (ie, better performance).^{20,67} While some authors propose that such results relate to the neuroprotective effects of cannabis,^{19,66,67} the findings also sup-

port our hypothesis of less severe cognitive impairment in a subgroup of neurocognitively less vulnerable patients, with more frequent and heavy use of cannabis necessary to induce psychosis.

Our findings should be interpreted in the context of several limitations. First, while the preceding discussion raises several alternative explanations for the association between cannabis use and cognition in schizophrenia, the cross-sectional nature of the studies considered prevents firm conclusions being drawn. Longitudinal studies are necessary to better understand causal interactions between relevant factors.

Second, our findings of poorer cognitive performance in patients without comorbid cannabis use could relate to a sampling bias, whereby the FEP – CANN group may include a greater proportion of “deficit syndrome” patients or patients with poorer premorbid functioning, worse cognition,⁷³ and lower substance use.⁷⁴ However, the fact that the FEP + CANN group in our Study II did not differ from the FEP – CANN group in terms of positive or negative symptoms, suggests that the latter group cannot be readily identified as deficit syndrome type. Furthermore, prepsychotic GAF scores and education did not differ between the 2 FEP groups. Consequently, our findings do not support this contention, but more

detailed measures of premorbid functioning are required to conclusively address this issue.

Third, given the high rates of cannabis use in FEP and the relationship between cannabis use and the development of psychotic symptoms, it is important to consider what proportion of the FEP + CANN group had a cannabis-induced psychosis. The diagnostic criteria for substance-induced psychosis have recently been criticized,⁷⁵ as a diagnosis of cannabis-induced psychosis is unlikely to be made if psychotic symptoms are still apparent 1 month following intoxication. Therefore, better cognitive performance, early onset use, and improvement with abstinence may be partially explained by inclusion of FEP + CANN patients with a cannabis-induced psychosis rather than an actual schizophrenia-spectrum disorder. Better diagnostic instruments and longitudinal assessments are required to examine this issue further.

Fourth, comorbid abuse of other substances could also affect the results because both cocaine and alcohol use have been associated with worse cognitive functioning in schizophrenia. However, the 2 studies (including our own) that examined the effect of comorbid alcohol use on cognition did not find an association.²¹ Examination of larger samples is necessary to properly examine the effect of comorbid alcohol abuse on cognition. The study of Potvin et al²¹ suggested that comorbid cocaine use could have a detrimental effect on cognition in cannabis-abusing patients with schizophrenia,²⁸ but this finding is unlikely to influence the current results because there was minimal cocaine abuse in the studies included in our meta-analysis or among patients in our FEP study.

Fifth, it is possible that some components of cannabis, such as cannabidiol (a nonintoxicating constituent of cannabis sativa), might relieve psychotic symptoms and thereby improve cognition.^{76,77} There is also some evidence to suggest that, in certain subgroups of schizophrenia patients, THC administration shows beneficial effects.¹⁸ However, more research is required to understand these complex actions in the context of schizophrenia.

Sixth, the number of studies included was small and restricted our analysis to investigate broad rather than specific aspects of cognition (or individual cognitive tasks). Finally, studies included in the meta-analysis had small samples and low quality of data on several important parameters, such as duration of illness; age of onset of either cannabis use or psychosis; and frequency, quantity, or duration of cannabis use.

In conclusion, our meta-analysis and experimental data converge to indicate that cannabis use in both FEP and established schizophrenia is associated with better cognitive performance than nonuse, and fewer cognitive impairments relative to healthy controls. The association between better cognitive performance and cannabis use is driven by a subgroup of neurocognitively less impaired patients, who only developed psychosis

after an early initiation of cannabis use (ie, during early adolescence). However, longitudinal studies in high-risk populations are needed to test this notion more decisively. Together, these findings suggest that a subgroup of psychotic patients may show improved outcomes (ie, partial recovery of cognitive functioning and less disability) if their cannabis use can be controlled. Moreover, our findings support the notion that, in some vulnerable individuals, abstinence from cannabis abuse could potentially prevent the development of psychosis.

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