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Meta-analysis of neurocognition in young psychosis patients with current cannabis use

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ABSTRACT

Objective: Adult psychosis patients (i.e. over the age of 25 years) who are also lifetime cannabis users (CANN ±) appear to exhibit superior cognition compared to never-using patients (CANN-). The objective of this meta-analysis was to evaluate the cognitive differences between CANN- and patients who currently use cannabis (CANN +) (i.e. during the CANN ± patients' cannabis-using stage). Specifically, focusing on young patients under the age of 25 years, the typical stage of both psychosis- and cannabis-onset.

Method: Of the 308 studies identified through database searches and secondary referencing, 14 compared neurocognition of CANN + and CANN- in young people with psychotic disorders (mean age between 15 and 45 years). Effect sizes were extracted using neurocognitive test performance between CANN + and CANN- and random effects modelling was conducted on pooled ES and moderator analyses.

Results: CANN + performed worse on several cognitive domains (i.e. premorbid IQ, current IQ, verbal learning, verbal working memory, motor inhibition) compared to CANN-. The association between age and performance in CANN + cognition was varied, with older age predictive of worse performance in processing speed, sustained attention, verbal memory, and better performance in verbal learning and very fluency. Of note, CANN + outperformed CANN- in tests of conceptual set-shifting.

Conclusion: These results are consistent with previous findings indicating that CANN + demonstrate poorer neurocognition than CANN-; and that this is exacerbated with increasing age. Our findings demonstrate significant cognitive differences between patients with CANN + versus CANN- even at early-onset psychosis, which could suggest a different underlying mechanism towards psychosis for cannabis users.

1. Introduction

Cannabis remains the most prevalent illicit drug used by individuals with schizophrenia-spectrum disorders (Koskinen et al., 2010; Smucny et al., 2014; Amminger et al., 2006), and current chronic use has been shown to significantly worsen positive psychotic symptoms in patients (Talamo et al., 2006; Dubertret et al., 2006). Counterintuitively, meta-analyses and systematic reviews suggest that cognitive functioning in chronic schizophrenia patients with a history of, but not current, cannabis use (CANN ±) is superior to that of their peers who have never used cannabis (CANN-) (Yücel et al., 2012; Løberg and Hugdahl, 2009). This suggests that there may be different phenotypes among older individuals with chronic psychotic disorders. However, relatively little is known about the cognitive profiles in the context of cannabis use in younger individuals with early psychosis. Prevalence of psychoses in pre-pubertal children is relatively rare (Thomsen, 1996), although the incidence of first episode psychosis (FEP) rapidly increases after the age of 15 years (Amminger et al., 2006; Gillberg et al., 1986; Hare et al., 2010), with the highest rate of a first episode between the ages of 15 and 24 years (Amminger et al., 2006; Archie et al., 2007). Young people, aged 12–24 years, represent an important population to study psychotic disorders as such individuals represent a subgroup of patients less likely to be exposed to critical environmental factors such as chronic use of antipsychotic medication (Epstein et al., 2014). There is also evidence that the corpus callosum, the highest order, latest maturing network of the brain, continues to grow until the middle 20's (i.e. 25.45 years) (Pujol et al., 1993). This, as well as synaptic pruning, which continues until the mid-20's, suggests full brain development is incomplete until around 25 years of age (Andersen, 2003). Young people are also at a great risk of substance abuse, particularly those for whom the age of onset of drug use (alcohol and cannabis, in particular) occurs prior to around 15 years of age (Archie et al., 2007; Wells et al.,

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2009; Palmer et al., 2009). Archie et al. (2007) stratified FEP subjects, between 15 and 50 years, into age ranges and found that those between the ages of 18–24 years accounted for the largest faction (i.e. 45%) of patients engaged in concurrent drug use (Archie et al., 2007). It would appear both psychotic episodes and substance use during a time when the brain has not fully developed could have detrimental effects for patients in the long-term, and cognition and symptomatology during this formidable time needs to be further investigated. Thus, in terms of evaluating the potential cognitive dissimilarities associated with and without concurrent cannabis use in psychotic disorders a focus on young individuals is highly warranted.

Crean et al.'s (2011) extensive review demonstrates the various effects of acute (i.e. 0–6 h after use), residual (7 h–20 days after use), and long-term (at least 21 days since use) effects of cannabis on neuropsychological functions in healthy populations (Crean et al., 2011; Broyd et al., 2016; Curran et al., 2016; Ranganathan and D'Souza, 2006). Acute effects of cannabis tend to show the greatest degree of dysfunction, with subjects demonstrating impairment across attention, decision making, impulsivity and working memory. Both residual and long-term effects appear to largely revert to near-normal functioning, specifically in attention, impulsivity and working memory, with a greater period of abstinence showing the most advanced improvement in cognition. Theoretically, cannabis using patients with a psychotic disorder would be expected to perform worse than their non-using counterparts across several cognitive domains, in keeping with studies in healthy individuals; whereby poorer cognitive performance in those who are either CANN+ or CANN ± is most pronounced in tests of executive functioning and processing speed (Meier et al., 2012). In contrast, there is evidence that chronic schizophrenia patients who have a history of cannabis use (CANN ±) outperform their CANN- peers (with schizophrenia) in general intelligence, attention, working memory, executive abilities and visuo-spatial abilities (Yücel et al., 2012; Bugra et al., 2013; Jockers-Scherübl et al., 2007; Rabin et al., 2011). Following this logic, one might assume that younger individuals with psychotic disorders (e.g. FEP) who use cannabis, but abstain later, will demonstrate improved cognitive functioning compared to their peers who never used cannabis. Given this, it is possible that the cannabis using patients' psychoses stem from an inherent gene-environment interaction partially owing to their early onset of cannabis use. Such a subgroup of patients may be diagnosed with psychosis, but may also have an atypical neurocognitive profile. This reflects Pearlson's (2015) review examining significant clinical overlap of psychoses and schizophrenia-spectrum disorders (Pearlson, 2015). Furthermore, there is evidence such as that provided by the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study, showing that there are clusters of individuals with shared biological features (known as 'biotypes') despite there being a commingling of their traditional clinical phenotype (i.e. schizophrenia or affective psychoses disorders) (Hill et al., 2013; Tamminga et al., 2014). Importantly, one of the three biotypes identified appears to be associated with higher cannabis use, better cognition, and lower percentage of affected relatives (Tamminga et al., 2017). This theory is supported by evidence, which shows that chronic schizophrenia patients with CANN ± who first began using cannabis before the age of 17 years exhibit some superior cognitive functioning compared to patients with later (i.e. after 16 years of age) cannabis-use onset (Yücel et al., 2012; Jockers-Scherübl et al., 2007; Hanna et al., 2016).

Yücel et al.s' (2012) meta-analysis investigated the effect of past cannabis use, typically prior to psychosis onset, on neuropsychological performance of older adults (i.e. mean age of patients was above 27 years) with a diagnosis of schizophrenia (Yücel et al., 2012). CANN ± outperformed patients with no history of use (CANN-) in tests of global cognition, processing speed, visual memory, planning, and working memory. However, they also found that patients who currently use cannabis (CANN+) did not demonstrate superior cognitive performance across a range of measures. Although, these groups differed significantly in one cognitive domain: the CANN+ showed worse performance in tests of verbal memory. Similarly, a separate study utilized biological radioimmunoassay testing rather than drug-use questionnaires to measure current drug use in schizophrenia patients, and found no significant cognitive differences between current cannabis-using patients and their non-using counterparts (Bahorik et al., 2014). However, there are several factors that may affect cognitive results, including frequency, dosage, and time since last cannabis intake. D'Souza et al. (2005) found evidence of dose-specific effects of THC on the cognition of schizophrenia patients (D'Souza et al., 2005). They demonstrated temporarily increased learning and recall deficits after 2.5 mg or 5 mg of intravenous THC, compared to 0 mg, with patients in the 5 mg group showing a pattern of worse cognitive performance compared to 2.5 mg.

On the surface, a history of moderate, (potentially regular) lifetime use of cannabis followed (importantly) by a period of abstinence in psychosis patients reveals a 'superior' cognitive profile compared to those with a psychotic disorder who never used or those who have continued to use (i.e. current use in older, more chronic stages of schizophrenia). Intriguingly, it appears that when cannabis use begins during adolescence, before the age of 17, those who later abstain (i.e. CANN ±) demonstrate better neurocognitive performance than their CANN ± peers who began using after 17 years. However only a handful of studies report any evidence of cognitive dysfunction in cannabis-using adolescents diagnosed with psychosis. Furthermore, cannabis use in the neurodevelopmental period of adolescence has been shown to confer a range of cognitive, social, and psychological harms (Meier et al., 2012; Tien and Anthony, 1990; Henquet et al., 2004; Szoke et al., 2014; Di Forti et al., 2014; Scholes-Balog et al., 2016; Meier et al., 2015; Mackie et al., 2013). In fact, Henquet et al. (2004) found that any cannabis use exacerbates psychotic symptoms in young people, particularly in those who have a predisposition for psychosis (Henquet et al., 2004).

Given the above-mentioned findings, the aim of the current study was to systematically review the potential effects of cannabis use on cognition in adolescent and young adult patients with psychosis. From previous evidence, we expected cannabis users to show significant deficits across a range of neurocognitive tests, as compared to non-using patients. However, young cannabis-using patients were expected to demonstrate superior neurocognitive performance compared to older CANN+ and CANN-, or young CANN-.

2. Methods

2.1. Search strategy and selection criteria

Studies were identified through extensive online database searches, including PubMed, Medline, and Psycinfo. Searches included keywords involving psychosis (i.e. schizophrenia, schizophreniform, psychosis, schizoaffective, schizo*, FEP, first, episode), cannabis (i.e. cannabis, marijuana, THC, tetrahydrocannabinol), and cognition (i.e. neuropsycho*, neurocognit*, cogniti*), and were limited to English-language articles with human participants. All articles up to October 2016 (i.e. the month the searches were conducted) were considered for analysis. A secondary search was conducted by reviewing the reference lists of relevant review and meta-analytic papers.

The inclusion criteria were: (1) diagnosis of a psychotic disorder according to DSM (i.e. Schizophrenia Spectrum and Other Psychotic Disorders) or ICD (i.e. Schizophrenia Spectrum and Other Primary Psychotic Disorders) criteria; (2) studies had to compare a psychotic (or schizophrenia spectrum disorder) cannabis-using group to an appropriate clinical control group (i.e. psychotic nonusers); (3) cannabis was the predominate substance used by patients, as stated by the authors in the methodology; (4) the assessment of traditional neuropsychological functions using valid and reliable tests, used routinely in clinical practice (Strauss et al., 2006); and (5) sufficient statistical data were

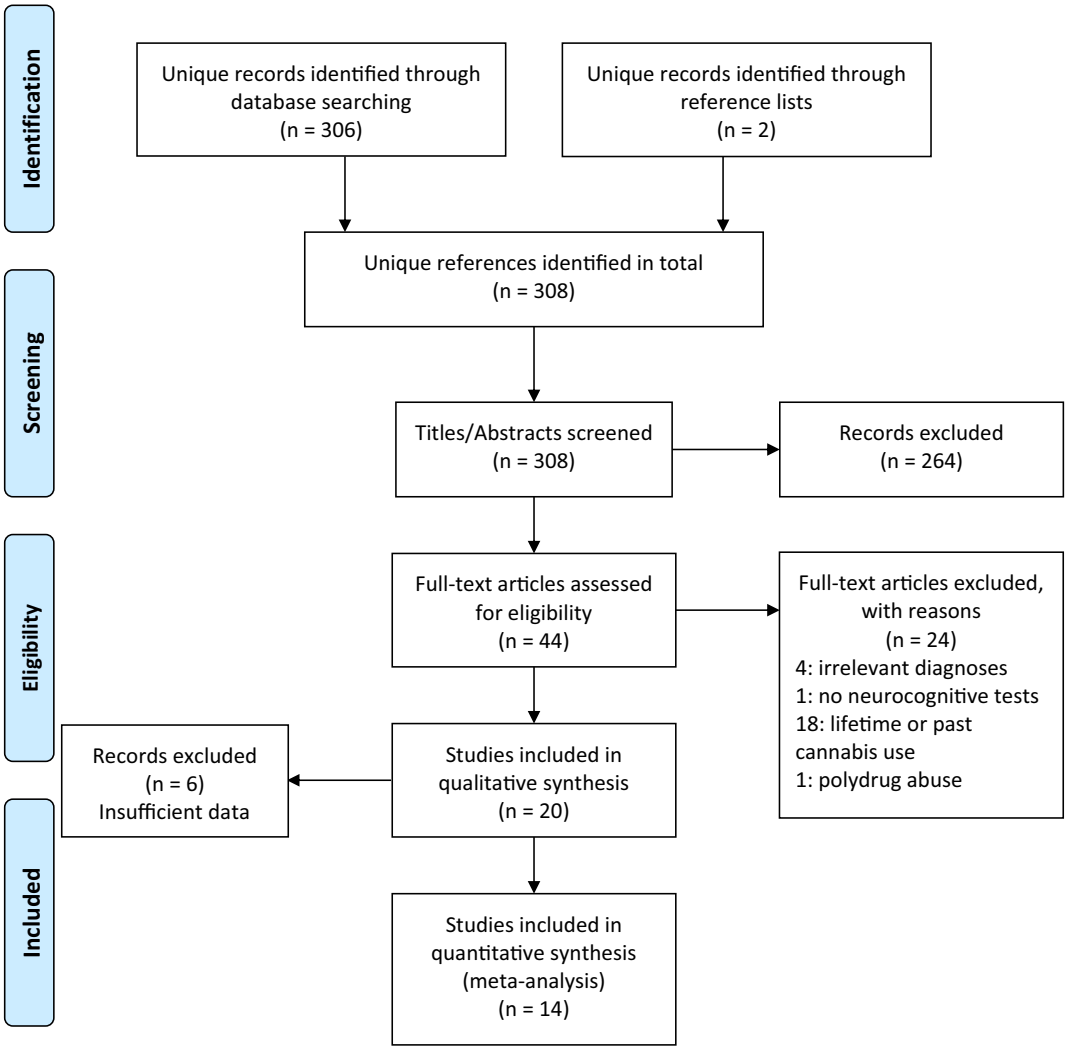

Fig. 1. Flow chart of the studies considered and selected for review.

reported for transformation into effect sizes (ES), or the relevant data were available from the original researchers.

Studies were excluded if they included cases who: (1) were diagnosed with a substance/medication-induced psychotic disorder, or were intoxicated at time of testing; or (2) investigated individual components of cannabis (e.g. tetrahydrocannabinol [THC] or cannabidiol [CBD] on their own); or (3) investigated synthetic cannabis. Only studies with the largest sample were included in the instance of overlapping samples.

As shown in Fig. 1, 308 titles and abstracts were initially identified, but only 44 studies assessed both cannabis use and cognition in psychotic patients. Thirty of these studies were excluded because: (1) the patient sample had irrelevant diagnoses (Hollis et al., 2008; Buchy et al., 2015; Korver et al., 2010; van Tricht et al., 2013), (2) the study included no relevant neuropsychological tests (Bourque et al., 2013), (3) they lacked patients involved in current cannabis use (Yücel et al., 2012; Epstein et al., 2014; Jockers-Scherübl et al., 2007; Hanna et al., 2016; Cunha et al., 2013; DeRosse et al., 2010; Krzysztof et al., 2012; Leeson et al., 2012; Løberg et al., 2012; Mata et al., 2008; Moreno-Granados et al., 2014; Power et al., 2015; Rentzsch et al., 2016; de la Serna et al., 2010; Schnell et al., 2009; Sevy et al., 2007; Stirling et al., 2005; Wobrock et al., 2007), (4) cannabis was not the predominate substance abused (Harrison et al., 2008), and (5) there was insufficient data and we were unable to obtain data from the authors (Løberg and Hugdahl, 2009; Bahorik et al., 2014; Pencer and Addington, 2003; Meijer et al., 2012; Arnold et al., 2015; Potvin et al., 2005).

All studies in the meta-analysis included a psychotic patient sample who were current cannabis users, defined as at least weekly cannabis use in the past 6 months. In 4 of the 14 studies, the patients were considered a young sample (mean age is less than 25 years), while the other 10 studies comprised of adult patients (mean age is older than 24 years). Overall, our meta-analysis included 14 studies involving 1430 patients with psychosis, with (N = 529) and without (N = 901) comorbid cannabis use.

2.2. Meta-analytic procedure

All meta-analytic procedures were conducted using Comprehensive Meta-Analysis Version 2.0 (Comprehensive meta-analysis, 2005). One author (S.B.) extracted patients' demographic data and cognitive test results from the articles. In cases where raw data was not available, the authors were contacted and demographic data and/or test results requested. Effect size (Hedges' *g*) was calculated for each cognitive domain. In cases where a study used two cognitive tests for one domain, the tests were grouped together, and the average ES was calculated. A more positive ES indicated better performance for CANN+ than CANN-, and in keeping with the literature, the size of the ES was interpreted according to Hedge's *g* (0.2 = small; 0.5 = medium; 0.8 = large) (Lee et al., 2012; Hedges and Olkin, 1985). A random effects model was used for meta-regression (i.e. unrestricted-maximum likelihood) and subgroup analyses (i.e. method of moments), with a

Table 1
Cognitive domains and the corresponding neuropsychological tests included in each analysis.

Cognitive Domain	Neuropsychological test
Processing Speed	Trail Making Test-Part A; WAIS Digit Symbol-Coding; WAIS Symbol Search; CogState Matching Task; D-KEFS TMT2
Sustained Attention	Continuous Performance Task; CogState Continuous Monitoring; CANTAB Rapid Visual Information Processing
Cognitive Flexibility	Trail Making Test-Part B; D-KEFS TMT4
Working Memory (Verbal)	WAIS Digits Backward; WAIS Letter-Number Sequencing
Verbal Learning	Rey Auditory Verbal Learning Test Total; WMS Logical Memory; California Verbal Learning Test Total; TAVEC Total
Verbal Memory	Rey Auditory Verbal Learning Test Long Delay Free Recall; TAVEC Long Delay Free Recall; WMS Verbal Delayed Recall; California Verbal Learning Test Long Delay Free Recall
Conceptual Set-Shifting	Wisconsin Card Sorting Test
Verbal Fluency	Letter Fluency (F-A-S, *p*)
Motor Inhibition	Stroop Color-Word Interference; D-KEFS Color-Word Interference
Current IQ	WAIS; WASI; MWT-A; Leistungsprufsystem, scale 3
Premorbid IQ	SILS; WTAR; NART

WAIS = Wechsler Adult Intelligence Scale.
D-KEFS = Delis-Kaplan Executive Function System.
CANTAB = Cambridge Neuropsychological Test Automated Battery.
WMS = Wechsler Memory Scale.
TAVEC = Test de Aprendizaje Verbal Esapaña-Complutense (Spanish version of the California Verbal Learning Test).
TAP = Test for Attentional Performance.
WASI = Wechsler Abbreviated Scale for Intelligence.
MWT-A = Mehrfachwahl-Wortschatz Test.
SILS = Shipley-Institute of Living Scales.
NART = National Adult Reading Test.

significance level set at $p < .10$ (Zeggini and Ioannidis, 2009).

As described in Table 1, cognitive domains included were premorbid IQ, current IQ, processing speed, cognitive flexibility, sustained attention, verbal learning, verbal memory, verbal working memory, conceptual set-shifting, motor inhibition, and verbal fluency. In longitudinal studies, only cross-sectional neuropsychological results were used to circumvent practice effects (Wobrock et al., 2013; McCleery et al., 2006; Sánchez-Torres et al., 2013).

Heterogeneity between studies was tested using the Q-test, and publication bias was assessed using Egger's test (Higgins et al., 2003; Egger et al., 1997). Subsequent tests of Rosenthal's Fail-Safe N, and Duval and Tweedie's Trim and Fill method were carried out to determine the number of studies required to establish no publication bias (Duval and Tweedie, 2000a, 2000b; Rosenthal, 1979).

2.3. Moderator analyses

Predictors of between-study variability in ES were examined using meta-regression (for continuous predictors) and subgroup analyses (Q_{bet}, for categorical predictors). The predictors were included if a sufficient number of studies had reported these variables (i.e. no more than one study missing per cognitive domain). These were grouped as either:

1) *Demographic predictors* included 'age' and 'sex'. A number of studies have indicated the significance of age in confounding the differences between CANN+ and CANN- (Potvin et al., 2008; Ochoa et al., 2012). As we are also interested in neuropsychological differences between young and adult patients, regressions for age were performed for each cognitive domain. Similarly, gender differences are well-recognized among both cannabis-users, and psychosis patients, where cannabis-users more often tend to be men (Ochoa et al., 2012; Spauwen et al., 2003).
2) *Diagnostic predictors* included patient diagnosis ('psychotic disorder' or 'schizophrenia-spectrum disorder'). In the present study, we classified psychosis and schizophrenia as two distinct diagnoses (A.P.A, 2013). Although psychosis is a core symptom of schizophrenia, patients with a diagnosis of psychosis alone do not experience the full spectrum of a psychotic illness. Schizophrenia patients also display greater cognitive deficits than patients with first-episode psychosis alone (Yücel et al., 2012), the latter of which is a more heterogeneous group comprising substance use disorders and affective disorders with psychotic features.

3. Results

A total of 14 studies, published up to October 2016, met inclusion criteria and were incorporated into the meta-analysis (see Table 2). Six of the studies included patients diagnosed with solely psychotic disorders (Bugra et al., 2013; de la Serna et al., 2010; McCleery et al., 2006; González-Pinto et al., 2016; Núñez et al., 2016; Lev-Ran et al., 2012), while the remaining eight focused on patients diagnosed with narrower schizophrenia-spectrum disorders (Wobrock et al., 2013; Sánchez-Torres et al., 2013; Rabin et al., 2013; Ringen et al., 2010; Scholes and Martin-Iverson, 2010; Ferraro et al., 2013; Coulston et al., 2007; Fischer et al., 2015). Four studies originated in Spain, two each from Australia, and Canada, and one each from the United Kingdom, Switzerland, Norway, the United States, Israel, and Germany. Sample sizes varied from 26 to 319. There was a total of 529 CANN+ cases, compared with a total of 901 CANN- controls. The proportion of female participants was a weighted average of 17.4% for CANN+ and 39% for CANN-. The mean age was a weighted average of 25.0 years for CANN + and 27.9 years for CANN-. Five studies explicitly defined cannabis users as having cannabis dependence, whereas the remaining nine studies included users with any sort of cannabis use over at least the previous month.

The effect sizes and related statistics of differences in performance between CANN+ and CANN- are presented in Table 3. Effect sizes were in the small to medium range (Hedges $g = 0.13$–0.55), with the exception of verbal working memory (Hedges $g = 0.76$). Most ES suggest poorer cognitive performance in CANN+ compared to CANN-. Table 4 presents the moderator analyses for predictors of heterogeneity. A more positive ES indicates better performance in CANN+ than CANN- (see Supplementary Figures for forest plots of each cognitive domain).

3.1. Current and premorbid IQ

All seven studies that incorporated tests of premorbid IQ reported poorer performance for CANN+, with the overall ES significantly in favour of CANN- ($g = -0.40$). Similarly, the six studies that measured current IQ also reported significant deficits in CANN + subjects ($g = -0.17$). There was no significant heterogeneity in premorbid and

Table 2
Summary of key characteristics of studies.

	PSY + CANN		PSY-CANN		Other Drugs	Diagnosis	Cognitive Tests Used	Key Neuropsychological Findings
	N (% female)	Mean age (years ± SD)	N (% female)	Mean age (years ± SD)				
de la Serna et al. (2010)	32 (31.3)	16.34 ± 0.16	76 (34.2)	15.16 ± 0.22		Psychosis	CPT, Letter Fluency, SCWT, TAVEC, TMT-A, TMT-B, Digit Span, LNS, WCST.	CANN+ performed better in sustained attention (CPT).
McCleery et al. (2006)	91		35		Cannabis main substance. 49 alcohol abuse, 8 polysubstance abuse.	Psychosis	CPT, Letter Fluency, NART, RAVLT, SPAN-12, TMT-A, TMT-B, Digit Symbol Coding, WCST, WMS.	CANN+ outperformed CANN- in TMT-A, CPT, RAVLT, RCFT, TMT-B, WCST, and Premorbid IQ.
González-Pinto et al. (2016)	107 (18.7)	23.0 ± 4.96	161 (40.4)	24.02 ± 6.33		Psychosis	CPT, Letter Fluency, SCWT, TMT-A, TMT-B, LNS, WAIS-III, WCST.	CANN- performed better in memory tasks.
Nunez et al. (2016)	34 (23.53)	20.65 ± 5.40	40 (55.0)	19.45 ± 7.58	All used cannabis, some occasional use of other substances (cocaine, alcohol, sedatives). Users had a higher tobacco intake than non-users.	Psychosis	CPT, SCWT, TAVEC, TMT-A, TMT-B, Digit Span, LNS, WAIS-III.	No difference between CANN+ and CANN-.
Bugra et al. (2013)	23 (30.4)	28.3 ± 8.48	24 (37.5)	33.2 ± 9.69		Psychosis	CPT, WCST, MWT-A, Leistungsprufsystem-3.	CANN+ outperformed CANN- in executive functioning (Go/No-Go).
Lev-Ran et al. (2012)	12 (8.33)	29.17 ± 4.39	16 (31.25)	27.62 ± 4.84	Substance use other than cannabis was limited to less than five occasions during lifetime. None of these occasions were during the previous year to testing.	Psychosis	RVIP	CANN- performed better in response inhibition.
Rabin et al. (2013)	18 (0.00)	31.6 ± 9.6	8 (0.00)	45.5 ± 6.5	Non-cannabis using patients had a higher tobacco intake than cannabis-users.	Schiz	CPT, CVLT, SCWT, TMT-A, TMT-B, WCST, WTAR.	No differences between CANN+ and CANN-.
Ringen et al. (2010)	23 (26.09)	27.74 ± 8.09	117 (48.72)	34.44 ± 10.21	Sporadic other substance (cocaine, amphetamine) use.	Schiz	CVLT, Color-Word Interference, Letter Fluency, NART, Digit Symbol Coding, Digit Span, WASI, WMS.	CANN+ performed better in verbal memory and cognitive flexibility. CANN- outperformed CANN+ in attention.
Sánchez-Torres et al. (2013)	12 (8.33)	37.00 ± 5.85	30 (36.67)	37.03 ± 5.17		Schiz	CPT, Letter Fluency, SCWT, TAVEC, TMT-A, TMT-B, Digit Symbol Coding, Digit Span, LNS, Symbol Search, WAIS-III, WCST.	CANN+ performed worse in working memory.
Scholes and Martin-Iverson (2010)	22 (4.5)	31.4 ± 7.5	49 (12.2)	37.8 ± 9.2	12 used other substance in the previous month (8 amphetamines, 1 narcotics, 1 benzodiazepines, 2 hallucinogens).	Schiz	SCWT, WCST, LNS.	CANN+ performed better in cognitive flexibility.
Ferraro et al. (2013)	34 (20.6)	26.2 ± 6.5	53 (42.4)	32.0 ± 8.8		Schiz	WAIS-III, Digit Symbol Coding, WTAR.	Lifetime cannabis users had higher scores in both IQ and premorbid IQ compared to patients who never used cannabis.
Wobrock et al. (2013)	85 (16.5)	23.9 ± 4.4	234 (48.5)	26.4 ± 5.6	All used cannabis (main abused substance). 14 also abused other illegal substances (mainly amphetamines, ecstasy, cocaine).	Schiz	RAVLT, TMT-A, TMT-B, Digit Symbol Coding.	No difference between CANN+ and CANN-.
Coulston et al. (2007)	18 (0.00)	25.8 ± 4.0	34 (0.00)	27.6 ± 5.9		Schiz	CogState: Continuous Monitoring, Matching Task; Color-Word Inhibition, TMT, Letter Fluency, RAVLT, SILS-V, WCST.	Dependent CANN+ were impaired in immediate memory, but above average in planning efficiency.
Fischer et al. (2015)	18 (5.6)	30.72 ± 8.17	24 (16.7)	40.75 ± 12.47		Schiz	WTAR	CANN+ reported more sensation-seeking than PSY-CANN-.

Table 3
Number of studies (k), pooled sample size (N), pooled ES (Hedge's g), homogeneity (Q, I, tau (Smucny et al., 2014)), and publication bias.

				Meta-Analysis		Heterogeneity			
	k	PSY + CANN N	PSY-CANN N	Hedges' g	95% CI	Q	*I*	tau (Smucny et al., 2014)	Egger's test (*t*)
Premorbid IQ	7	214	301	−0.40***	−0.59–−0.20	4.73	0%	0.00	1.42
Current IQ	6	268	479	−0.17*	−0.34–−0.00	5.64	11%	0.01	0.37
Processing Speed	10	672	1151	0.20	−0.05–0.44	43.35	79%	0.11	1.24
Cognitive Flexibility	8	397	618	0.19	−0.15–0.54	39.11***	82%	0.19	0.87
Sustained Attention	9	347	424	0.55	−0.11–1.62	126.70***	94%	0.94	0.55
Verbal Learning	8	427	726	−0.39†	−0.8–0.04	61.93***	89%	0.32	0.99
Verbal Memory	8	427	726	−0.13	−0.42–0.16	28.04***	75%	0.12	0.43
Working Memory (Verbal)	6	308	619	−0.76**	−1.30–−0.22	64.10***	92%	0.41	1.65
Conceptual Set-Shifting	8	323	417	0.32†	−0.05–0.68	32.86***	79%	0.20	0.47
Motor Inhibition	8	266	515	−0.19†	−0.40–0.02	11.65	34%	0.04	1.26
Verbal Fluency	6	283	453	−0.47	−1.22–0.28	89.61***	94%	0.82	0.65
Total *k*/N	14	529	901						

PSY = Psychosis. CANN = Cannabis. ES = effect size.
*p ≤ .05. **p ≤ .01. ***p ≤ .001.
†p ≤ .10.

Table 4
Moderator analyses to determine predictors of heterogeneity.

	Demographic factors				Diagnostic factors	
	Sex		Pooled Age		Diagnosis	
Cognitive Domain	%*k*	*Z*	%*k*	*Z*	%k	Q_{bet}
Premorbid IQ	86	0.10	86	0.21	100	0.79
Current IQ	100	2.03*	100	−0.25	100	1.82
Processing Speed	90	1.83†	90	−1.87†	100	7.22*
Cognitive Flexibility	88	1.41	88	−0.68	100	1.67
Sustained Attention	89	1.37	89	−2.61**	100	5.29*
Verbal Learning	88	−1.11	88	1.84†	100	0.08
Verbal Memory	88	0.58	88	−1.90†	100	5.30*
Working Memory (Verbal)	100	−2.28*	100	−0.80	100	0.79
Conceptual Set-Shifting	88	0.77	88	−0.81	100	0.49
Motor Inhibition	100	−1.50	100	0.14	100	0.28
Verbal Fluency	83	−1.80†	83	2.36**	100	0.93

*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.
†$p \leq .10$.

current IQ across studies. A more equal proportion of sexes (i.e. increased female representation) was predictive of greater superiority in current IQ in CANN+ (Z = 2.03).

3.2. Processing speed

Ten studies reported tests of processing speed, demonstrating no effects between cannabis groups. A more equal sex distribution was indicative of better performance in CANN+ (Z = 1.83). Both increasing age and a diagnosis of schizophrenia were predictive of poorer performance in tests of processing speed for CANN+ (Z = −1.87; Q_{bet} = 7.22).

3.3. Cognitive flexibility

Eight studies included tests of cognitive flexibility, with only one test used in all articles (i.e. TMT-B). ES were not significant. There was a high level of heterogeneity among studies, but none of the moderators were predictive for this result.

3.4. Sustained attention

The nine articles that reported tests of sustained attention demonstrated non-significant ES. ES across studies were significantly heterogeneous. Both increasing age and a diagnosis of schizophrenia resulted in poorer performance for CANN+ (Z = −2.61; Q_{bet} = 5.29).

3.5. Verbal learning

CANN+ showed significant deficits in tests of verbal learning ($g = -0.39$). ES across studies were significantly heterogeneous. Increasing age was predictive of superior performance in tests of verbal learning for CANN+ (Z = 1.84).

3.6. Verbal memory

ES for verbal memory tests was non-significant, and heterogeneous across studies. Increasing age and diagnosis of schizophrenia were predictive of poorer performance in CANN+ (Z = −1.90; Q_{bet} = 5.30).

3.7. Verbal working memory

Six studies incorporated tests of (verbal) working memory, and show significant difference between cannabis groups ($g = -0.761$). ES across studies was significantly heterogeneous. A more equal sex distribution was indicative of poorer performance in CANN+ (Z = −2.28).

3.8. Conceptual set-shifting

Eight studies reported results from Wisconsin Card Sorting Test (WCST), which measures conceptual set-shifting. CANN+ performed significantly better than CANN- ($g = 0.318$), with high heterogeneity across studies. None of the moderators were predictive of this result.

3.9. Motor inhibition

Motor inhibition was significantly poorer in CANN+ ($g = -0.189$). Studies were not heterogeneous.

3.10. Verbal fluency

Tests of verbal fluency were non-significant between groups. Studies were significantly heterogeneous. Both a more equal sex distribution and decreasing age result in poorer performance for CANN+ (Z = −1.80; Z = 2.36).

3.11. Publication bias

Of the neuropsychological domains that differentiated CANN+ from CANN-, there was no evidence to suggest that these domains were influenced by publication bias ($p > .10$) (See Supplementary Materials for funnel plots).

4. Discussion

To our knowledge, this was the first meta-analysis to systematically investigate the neurocognitive profile of psychotic disorders in young people who use cannabis. As expected, never-using patients (CANN-) outperformed current cannabis-using cases (CANN+) across tests of premorbid and current IQ, verbal learning, verbal working memory, and motor inhibition. This is consistent with previous studies showing that patients with current or recent cannabis use display cognitive deficits when compared to those with a lifetime history of past cannabis use, as well as those with no history of cannabis use (Løberg and Hugdahl, 2009). Unexpectedly, CANN+ in the present study performed better than CANN- in conceptual set-shifting tasks (i.e. Wisconsin Card-Sorting Task), an outcome that contrasts with previous findings (Scholes and Martin-Iverson, 2010). However, most ES in these analyses have appeared to show a relatively small to medium degree (i.e. 0.2 to 0.5 ES range) of dysfunction in cannabis-users (Hedges and Olkin, 1985; Lee et al., 2014). This is unsurprising, as a number of epidemiological studies have instead reported non-significant to small cognitive differences between CANN+ and their non-cannabis using peers. The largest ES observed in this study was for verbal working memory, whereby CANN+ performed worse than CANN-. Yücel et al. (2012) also found that non-using patient groups performed better in verbal memory than recent users (Yücel et al., 2012). Similarly, Schoeler et al.'s (2016) meta-analysis investigating memory function in older psychosis patients (i.e. mean age of patients was above 27 years) with CANN ± found users who abstained less than 10 days performed poorly in memory tasks compared to prolonged-abstinent psychosis patients. Thus, consistent with these previous meta-analyses of older adult patients (i.e. typically after the age of 25), our findings indicate that there are significant cognitive deficits in the recent cannabis-using patient groups, despite age (Yücel et al., 2012; Schoeler et al., 2016). In other words, it appears that cannabis use at any age is associated with (an overall tendency for) poorer cognitive capacity.

Thus, the findings of this study provide support for current cannabis-users with psychosis having inferior cognitive abilities. Consistent with previous papers, cannabis use was associated with a younger age and male gender (Linszen et al., 1994; Veen et al., 2004; Malone et al., 2010; Green et al., 2005; Myles et al., 2016; Winklbaur et al., 2006; Dixon, 1999; Mueser et al., 1992). Several studies indicate poorer performance of CANN+ groups in immediate verbal learning, and working memory (Yücel et al., 2012; Cunha et al., 2013; de la Serna et al., 2010; Meijer et al., 2012; McCleery et al., 2006; González-Pinto et al., 2016; Ringen et al., 2010; Coulston et al., 2007). Decreased memory capability is however a well-known effect of recent cannabis use, with evidence showing any more than one cannabis joint per week was associated with poorer verbal working memory capacity in healthy individuals (Fant et al., 1998; Chait and Perry, 1994; Heishman et al., 1990). CANN+ also demonstrated motor inhibition deficits in the present study, supporting the notion that individuals, whether diagnosed with a psychotic disorder or otherwise healthy, perform significantly worse than non-users in tests of cognitive inhibition (Wrege et al., 2014; Prashad and Filbey, 2017). Functional magnetic resonance imaging (fMRI) has shown that individuals under the influence of delta-9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis, attenuates activation in the right inferior frontal and anterior cingulate gyrus during the Go/No-Go task. Activation in these regions during the response-inhibition task is thus likely responsible for impairments in the inhibitory control of thoughts and emotions, as well as motor responses, as often viewed symptomatologically in schizophrenia (Bhattacharyya et al., 2015; Borgwardt et al., 2008).

There is evidence that CANN+ present with a higher premorbid IQ (Yücel et al., 2012; Løberg and Hugdahl, 2009; Ferraro et al., 2013), which contrasts with findings in the present study. Ferraro et al. (2013) found a significant increase in premorbid and current IQ in patients who had any lifetime experience with cannabis, but not in CANN+ (Ferraro et al., 2013). Interestingly, they also found CANN+ who engaged in their use socially tended to have higher premorbid IQ than patients who chose to use cannabis alone. Despite evidence demonstrating superior premorbid IQ in patients engaged in cannabis use, several studies have instead found no differences between CANN+ and CANN- (Bugra et al., 2013; Núñez et al., 2016; Scholes and Martin-Iverson, 2010; Waterreus et al., 2017). Scholes and Martin-Iverson (2010) found no significant cognitive differences between CANN+ and CANN- in older (i.e. above 24 years of age) schizophrenia patients, with the exception of CANN+ instead showing deficits in conceptual set-shifting (i.e. Wisconsin Card Sorting Task) when compared to CANN- (Scholes and Martin-Iverson, 2010). On the other hand, Jockers-Scherubl and colleagues claim there are no differences between CANN ± and CANN- in conceptual set-shifting (Jockers-Scherübl et al., 2007), indicating the superior adaptive ability of CANN+ in the current study does not transcend all patient ages and varying recency of cannabis use. A recent cross-sectional study has also concluded that there are no significant differences present between CANN+ and CANN- in domains of premorbid and current IQ, attention, processing speed, and memory (Waterreus et al., 2017). Clearly several confounders influence the subsequent outcomes of neurocognitive testing in these patient groups. Unfortunately, there are very few studies available that examine the neurocognition in current cannabis-using psychosis patients. While the literature in this area is already extremely limited, there are only a handful of reports that look at cannabis' influence on young people with psychosis (i.e. under 25 years). As one of the most paramount factors in this study is the impact of patients' age, we performed meta-regressions to view the influence of age on cognitive performance.

Onset of cannabis use tends to begin during the adolescent years, with initial use on average occurring at 15 years of age (Archie et al., 2007; Wells et al., 2009; Palmer et al., 2009). This is also the age many early-onset psychosis patients, particularly males, experience their first episode. In the present study, young (i.e. below 25 years of age) CANN + performed significantly better in processing speed, sustained attention, and verbal memory than older (i.e. above 24 years) CANN+ patients. Previous studies have suggested that in some cases for older CANN+ patients, cumulative exposure to cannabis over several years may contribute to poorer results in cognitive tests compared to younger patients. Young patients are also more likely to have had less treatment exposure (e.g. antipsychotic medications) over their lifetimes (Kolb and Gibb, 2011; Bossong and Niesink, 2010). On the other hand, young CANN+ showed greater deficiencies in verbal learning and verbal fluency. As previously noted, cannabis effectively influences the user's memory and learning abilities. In younger patients, this would be more influential given the critical brain maturation processes occurring in the 16–25 years age period; further compounded by the early age of cannabis use onset (Bagot et al., 2015). These results generally fall in line with Løberg and Hugdahl's (2009) reanalysis of previous data, in which CANN ± outperformed CANN- in a number of cognitive domains, including learning and memory, attention and working memory, executive functions, and psychomotor speed (Løberg and Hugdahl, 2009). They also showed CANN+, who were admitted to a psychiatric emergency ward, demonstrated a significantly larger improvement in their cognitive performance only three months after admission, compared to their non-using counterparts. In fact, evidence suggests cannabis onset preceding 17 years of age leads better cognitive outcomes for CANN ± later in life (i.e. within 2–10 years after cannabis abstinence) (Yücel et al., 2012; Løberg and Hugdahl, 2009; Jockers-Scherübl et al., 2007; Helle et al., 2014). One explanation regarding this paradoxical

phenomenon is that the patients with such early onset of cannabis use instead triggers their own illness, and represent a subgroup of psychoses patients with high genetic loading, likely due to a specific gene polymorphism in this cohort (Malone et al., 2010; Tost et al., 2010). Caspi and colleagues' conducted a longitudinal study of 800 adolescent cannabis onset users; they found that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderates the influence of adolescent cannabis use on developing adult psychosis (Caspi et al., 2005). However, this study has not been replicated, and the evidence on whether such polymorphisms modulate the risk for psychosis associated with exposure to cannabis is mixed with some (Caspi et al., 2005) but not other (Tunbridge et al., 2015; Henquet et al., 2006; Zammit et al., 2007) studies showing an effect. In some cases, cannabis use, combined with polymorphisms in the COMT gene appeared to not only increase the risk of schizophreniform disorder, but also results in younger age of psychosis onset (Caspi et al., 2005; Pelayo-Terán et al., 2010). On the other hand, there is also evidence of no cognitive or affective differences mediated by the COMT gene with cannabis use (Zammit et al., 2007; Kantrowitz et al., 2009). This indicates the observed gene-environment interaction may be limited to a sensitive period of brain development in adolescence.

The proportion of females in each cannabis group played a significant function in the subsequent performance of the psychoses groups. Males are three times more likely than females to be diagnosed with a psychotic disorder (Iacono and Beiser, 1992). Furthermore, several studies have found substance use by men (typically with cannabis and alcohol) well outnumber women, both in cases with and without psychotic disorders (Ochoa et al., 2012; Schepis et al., 2011). Our results parallel the underrepresentation of females in psychosis populations, as males outnumbered females in all studies, specifically in CANN+. Equal sex distributions were predictive of better performance in current IQ and processing speed for CANN+, whereas more equal distributions implied deficiencies in verbal working memory and verbal fluency. Our findings contrast Rabin et al. (2013), who found no cognitive differences between male schizophrenia CANN+ and CANN- patients (Rabin et al., 2013). In addition to age and sex, it may be important to consider diagnostic subtypes (e.g. affective-versus schizophrenia-spectrum) as a key factor in our understanding of concurrent psychosis and cannabis use. Løberg et al. (2014) support previous hypotheses in their detailed literature review that pre-illness cannabis use confers a greater risk for affective psychosis, which appears to have a better cognitive prognosis than cannabis-using schizophrenia-spectrum patients (Krabbendam et al., 2005; Bora et al., 2009; Løberg et al., 2014; Manrique-Garcia et al., 2012). Although several studies indicate only small effect sizes between affective psychosis and schizophrenia diagnoses, schizophrenia patients consistently perform worse than affective psychosis patients in tests of crystallized knowledge, verbal skills, information processing speed, and verbal memory (Hill et al., 2013; Krabbendam et al., 2005; Depp et al., 2007; Schretlen et al., 2007; Barch, 2009). In fact we found CANN+ (affective-) outperformed CANN+ (schizophrenia-spectrum) in tests of processing speed, sustained attention and verbal memory. Schizophrenia-spectrum CANN+ showed no cognitive lead over affective- CANN+. To our knowledge, there are no present studies directly investigating cognitive differences between affective- and non-affective psychoses, however neuroimaging studies suggest atypical dopamine synthesis in the striatum may account for the induction of psychosis in a different mechanism typically seen in schizophrenia (Tost et al., 2010; Batalla et al., 2014).

Notably, the dopaminergic and cannabinoid systems in the brain develop early on in young adulthood. A number of brain regions that are implicated in psychosis and other schizophrenia-spectrum disorders, are also densely populated with cannabinoid receptors, and are as such, heavily affected by THC in cannabis (D'Souza et al., 2005). Several abnormalities of the endogenous cannabinoid system in patients with schizophrenia, occurring before the use of cannabis, are apparent. These include increased levels of cannabinoids in both the frontal cortex and cerebral spinal fluids (Dean et al., 2001; Leweke et al., 1999). It is therefore possible that changes to this atypical endocannabinoid system, by external cannabinoids, could be involved in the pathology of psychotic disorders. The findings presented here support the notion that there are distinct cognitive profiles according to the patients' age as well as the pattern of their cannabis use. While increased cumulative exposure to cannabis may account for some of these results, it is also possible that the developing brain in young people, especially with psychosis, are more vulnerable to the effects of cannabis than a matured brain. It would be important to understand the initial effects of cannabis on the brain of a psychosis patient, specifically that of a young person, to better understand the prognostic implications of concurrent cannabis use in psychoses, and recognise how to treat young adults and adults who currently engage, and have a lifetime history, in cannabis use.

There are some limitations in our study that should be considered. First, there are a few key factors that were not investigated in this study. Frequency and dosage, which was addressed in only three of the present studies, are notable influences that impact the effect of cannabis on patients. Nunez and colleagues demonstrated that heavy cannabis users (i.e. more than three cannabis joints per day) showed significant cognitive deficiencies in tasks of verbal learning, attention and processing speed when compared to medium users (i.e. less than three cannabis joints per day) and non-using patients (Núñez et al., 2016). Similarly, duration of cannabis use varies among the studies analysed. The findings in the present study should be taken with some caution, given the diverse range of duration of cannabis use among patients (i.e. 6 months to 2+ years). Interestingly, the majority of studies found that a higher frequency of cannabis use predicts better performance in cognition, specifically attention and working memory (Schnell et al., 2009; Coulston et al., 2007).

Second, different methodologies across studies prove to be a limitation for reviews and meta-analyses. As the included studies all measured separate outcomes, we were unable to compare several clinical and demographic characteristics of the patient groups. Several studies have indicated the significance of general psychopathy subscores and symptomology on prognosis, progression and performance on cognition (Power et al., 2015; Meijer et al., 2012; Linszen et al., 1994; Helle et al., 2014; Grech et al., 2005). The magnitude of cognitive dysfunction may also be dependent on the patient's diagnosis, or subgroup of psychotic disorder (i.e. affective psychosis or schizophrenia-spectrum disorder). Schizophrenia-spectrum patients appear to be more cognitively compromised than those with affective psychosis or FEP alone (Reichenberg et al., 2009), however all psychotic disorders consistently underperform in tests of memory, executive functions, attention, and processing speed (Hill et al., 2004, 2013; Tamminga et al., 2014; Reichenberg et al., 2009; Heinrichs et al., 2008; Gooding and Tallent, 2002). Future studies must tease out these discrete disorders in order to best represent schizophrenia-spectrum, FEP, and affective-psychosis patients, as varying heterogeneity between subgroups appears to somewhat effect cognitive outcomes of each clinical group (Van Rheenen et al., 2017; Welham et al., 2003). Discrepancies between potential and actual performance of patients due to these confounding factors may in fact significantly alter results if not matched between patient groups. Similarly, comorbid cannabis use and psychoses patients with a family history of psychosis suggests better performance in areas of verbal memory, executive function and global cognition compared to patients without the family history of illness (González-Pinto et al., 2016), further indicating the influence of confounding factors often undisclosed to us in this study.

Third, some studies used in our analyses included patients engaging in other comorbid substance abuse, particularly alcohol and cocaine. However studies that investigated the effect of alcohol use on cognition of psychosis patients found no association (Yücel et al., 2012; Pencer and Addington, 2003; Potvin et al., 2008), instead suggesting regular alcohol use leads to greater positive symptoms. Bahorik et al. (2014)

analysed the neurocognitive functioning of schizophrenia patients who currently use cocaine and/or methamphetamine and also found no associations between the drugs and cognition (Bahorik et al., 2014).

Fourth, there is evidence that some components of cannabis (e.g. cannabidiol [CBD]) might ameliorate psychotic symptoms and improve acute cognition (Morgan and Curran, 2008). On the other hand, different strains of, as well as synthetic, cannabis, which was not taken into account in a majority of the studies analysed, may also mediate the drug's effect on cognition (Radhakrishnan et al., 2014; Morrison et al., 2009). Future studies should consider the effect of varying proportions of THC and CBD in different strains of cannabis, as well as the more neurotoxic and harming effects involved with synthetic cannabis.

Unfortunately, the literature on the neurocognitive effects of cannabis use in psychosis patients who are under the age of 25 years is exceptionally limited. Although a number of studies show evidence to suggest that older CANN ± patients (i.e. above 25 years) possess a superior capability to adapt to changing environments and circumstances, which may incorporate social settings (Meijer et al., 2012; Arnold et al., 2015; Potvin et al., 2005; Bossong and Niesink, 2010; Ringen et al., 2008; Larsen et al., 2006; Joyal et al., 2003), to our knowledge there are no reports investigating the cognitive effects of lifetime cannabis use in psychosis patients who are under the age of 25 years. Similarly, despite one prevalent theory that addresses the superior social abilities of CANN+ is the social demand required to obtain illicit drugs, (Yücel et al., 2012; Løberg and Hugdahl, 2009; Bossong and Niesink, 2010; Bhattacharyya and McGuire, 2011; Burns, 2013) only a limited number of studies have actually looked into any potential cognitive differences at the time of both psychosis- and cannabis-onset, as often observed in young people. In conclusion, our meta-analysis supports previous findings of cognitive deficiencies in psychosis patients who currently use cannabis. Most noteworthy is the superior performance of young patients who use cannabis, which could suggest a subgroup of psychosis patients. While prior research indicates lifetime users outperform non-using patients in several neuropsychological tests, our findings indicate young people with both an early-onset of cannabis use and FEP may represent a subgroup of patients who develop psychosis through an alternative pathway not otherwise observed in traditional psychosis patients who aren't involved in drug use. This evidence indicates distinct treatment plans for psychosis patients need to be utilized to properly care for, perhaps, differing forms of psychosis that arise through varying mechanisms. However, more research needs to be conducted into the effects of cannabis use on young psychosis patients to further investigate the cognitive changes and differences during the time of both psychosis- and cannabis-onset. This will facilitate greater understanding of the superior capabilities observed in lifetime, but not current, cannabis users, as compared to non-using psychosis patients.

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Contributors

SERB conducted the literature search, data collection, meta-analytic procedures, data analysis, and drafting the manuscript. RSCL was responsible for data analysis and drafting the manuscript. IBH edited the manuscript. DFH was responsible for study design and drafting the manuscript. All authors contributed to, and have approved the final manuscript.

Conflicts of interest

All authors declare that they had no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2018.01.010.

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