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PII: S0149-7634(19)30732-8

DOI: https://doi.org/10.1016/j.neubiorev.2019.10.014

Reference: NBR 3579

To appear in: *Neuroscience and Biobehavioral Reviews*

Received Date: 14 August 2019

Revised Date: 17 October 2019

Accepted Date: 22 October 2019

Please cite this article as: Figueiredo PR, Tolomeo S, Steele JD, Baldacchino A, NEUROCOGNITIVE CONSEQUENCES OF CHRONIC CANNABIS USE: A SYSTEMATIC REVIEW AND META-ANALYSIS, *Neuroscience and Biobehavioral Reviews* (2019), doi: https://doi.org/10.1016/j.neubiorev.2019.10.014

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NEUROCOGNITIVE CONSEQUENCES OF CHRONIC CANNABIS USE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Pedro Rafael Figueiredo[1*], Serenella Tolomeo[2,3*], J. Douglas Steele[3], Alexander Baldacchino[2]

1. Hospital Garcia de Orta, Child and Adolescent Psychiatry, Almada, Portugal
2. University of St. Andrews, School of Medicine, Division of Population and Behavioural Science, Fife, Scotland, UK
3. University of Dundee, School of Medicine, Division of Imaging Science and Technology, Dundee, Scotland, UK

***BOTH AUTHORS CONTRIBUTED EQUALLY TO THIS MANUSCRIPT**

Corresponding Author: A. Baldacchino, University of St. Andrews, School of Medicine, Division of Population and Behavioural Science, North Haugh, KY169FT, St. Andrews, Fife, Scotland, UK

Email Address: amb30@st-andrews.ac.uk

Contact Address: University of St. Andrews, School of Medicine, Division of Population and Behavioural Science, North Haugh, KY169FT, St. Andrews, Fife, Scotland, UK

Highlights

- A meta-analysis was conducted to assess the neuropsychological impact of cannabis.
- A limited association was found between chronic cannabis use and neurocognitive deficits.
- Memory and chronic cannabis smoking were linked.

ABSTRACT

Cannabis is currently the most used illicit substance in the world with a global widespread distribution. Although its acute neurocognitive effects on human

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behaviour have been reported, there is a lack of robust analysis investigating the link, if any, between chronic cannabis use and neurocognitive function. A systematic review of the literature was conducted in order to identify relevant studies published from 2010 to 2019. A meta-analysis was performed on 13 selected studies testing performance of chronic cannabis users compared with non-users in six different neurocognitive domains. There was a low cross-sectional association between neurocognitive impairments and chronic cannabis use in *cognitive impulsivity, cognitive flexibility, attention, short-term memory and long-term memory*. No association was found between chronic cannabis use and *motor impulsivity*. By analysing a specific target population with strict inclusion criteria, these findings provide inconclusive evidence that there are cognitive impairments associated with chronic cannabis use. Future research is needed to determine if the findings of this meta-analysis are biased by the methodological limitations encountered.

KEYWORDS: CANNABIS; CHRONIC CANNABIS USE; NEUROPSYCHOLOGY; IMPULSIVITY; MEMORY; INTELLIGENCE; ATTENTION; COGNITIVE FLEXIBILITY; META-ANALYSIS.

1. Introduction

Cannabis is the most widely cultivated, trafficked and used illicit drug, with an estimated 147 million people (2.5% of the world population) consuming it (WHO, 2019). It contains several chemical compounds, including cannabinoids, terpenoids, flavonoids and alkaloids. The cannabinoids are the most psychoactive constituent with more than 100 different ingredients described in the literature (Andre et al., 2016, Bonini et al., 2018, Curran et al., 2016). So far, most of the research has focused on the two most prominent cannabinoids: Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), describing a range of opposing effects of these substances on human brain receptors during the acute phase of consumption (Atakan, 2012, Curran et al., 2016, Englund et al., 2013). It is argued that Δ^9-THC is linked with impaired learning, psychosis-like events and

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anxiety, whereas CBD enhances learning and has anti-psychotic and anxiolytic properties (Curran et al., 2016, D'Souza et al., 2004, Das et al., 2013, Leweke et al., 2012, McGuire et al., 2018).

Currently, there is also increasing evidence that acute cannabis use is associated with other neurocognitive impairments in decision-making, such as speed of processing, sustained attention, verbal fluency and executive functioning (Bartholomew et al., 2010, Becker et al., 2014, Gonzalez et al., 2012, Grant et al., 2012, Griffith-Lendering et al., 2012, Huestegge et al., 2010, Lorenzetti et al., 2019, Nusbaum et al., 2017). However, studies investigating persistent neurocognitive impairments, if any, due to chronic cannabis exposure are comparatively scarce inhibiting definitive conclusions (Broyd et al., 2016, Crean et al., 2011, Schreiner and Dunn, 2012). Previous reviews have reported that chronic use of cannabis impacts on cognitive functioning in several domains in adolescents and young adults (i.e. episodic memory, sustained attention, decision making, psychomotor speed, executive functioning, new learning) (Broyd et al., 2016, Curran et al., 2016, Ganzer et al., 2016, Lisdahl et al., 2014, Lubman et al., 2015). A meta-analysis performed by Grant and colleagues (2003) reported no substantial effect (*d*, -0.16) of long-term cannabis consumption on neurocognitive functioning (Grant et al., 2003). Similarly, another meta-analysis published by Schreiner and Dunn (2012) indicated a small neurocognitive impairment effect (*d*, -0.29) due to chronic cannabis use that persists after acute intoxication particularly on learning and memory, attention and motor functioning (Schreiner and Dunn, 2012). The same authors argued for no significant effect on neurocognitive performance after a period of abstinence of at least 25 days (Schreiner and Dunn, 2012). A recent meta-analysis by Scott and colleagues (2018) also concluded a small effect size (*d*, -0.25) for neurocognitive impairments in frequent and/or heavy cannabis users, with the largest effects in learning and memory, executive functioning, speed of processing, and attention (Scott et al., 2018).

Although prior meta-analysis provided a quantitative association between chronic cannabis use and neurocognitive impairments, caution is required in interpreting these results. This is mainly due to methodological limitations in the heterogenicity of the studied population and the neurocognitive tasks used, the

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operational definition of “chronic use” and the lack of clear specification of the abstinence period, if any, prior to testing.

We aimed to further analyse the potential association between chronic cannabis use and neurocognitive impairments by addressing some of the previous methodological limitations in previous reviews focusing on individuals with an age of 18 years or older. Stricter inclusion criteria and a clearly delineated specific period of non-use for each group before the day of testing was used. Furthermore, following similar studies in the field of nicotine (Conti et al., 2019) and opioids (Baldacchino et al., 2012, Baldacchino et al., 2017), standardised differential tasks were used to quantify cognitive impairments.

2. Literature search

This review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) and the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009).

To meet the required inclusion criteria, all studies had to describe human participants with an age of 18 years or older, experiencing chronic cannabis use and/or a cannabis dependency diagnosed operationally by Diagnostic and Statistical Manual of Mental Disorders (APA, 2013) criteria. A period of non-use was defined as individuals who have not smoked cannabis for at least 12 hours to explicitly avoid the acute effects of cannabis consumption. There is evidence that the psychotropic effects of the drug starts within seconds to minutes and lasts from 2 to 6 hours, reaching a maximum at 12 hours depending on dose and frequency of use (Colizzi and Bhattacharyya, 2018, Grotenhermen, 2003, Moody, 2012). The comparison group was defined as healthy participants who (a) never used cannabis, (b) did not use cannabis for more than a year and/or (c) used cannabis less than 50 times in their lifetime. Studies where included if they reported at least one standardized neurocognitive test, with name and/or description of the task. Case control, longitudinal, and/or cross-sectional studies

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were included. Baseline data were used for longitudinal studies. Finally, studies were included if cannabis was the primary drug of interest and the manuscripts were published in English, Spanish, Portuguese and Chinese.

The exclusion criteria were the following:

(a) Cohorts including participants under 18 years of age.
(b) Cohorts including participants with a current illicit polydrug use and dependence.
(c) Cohorts including participants with a diagnosis of psychiatric or neurological illnesses.
(d) Cohorts including participants with alcohol dependence.
(e) Cohorts including participants with any history of serious head injury.
(f) Studies focusing on structural or functional neuroimaging parameters as a primary outcome.
(g) Studies in which cannabis users were not asked to abstain prior to testing.
(h) Studies with no healthy non-smoking controls as comparator groups.
(i) Studies that did not provide neurocognitive scores that could be used to derive an effect size (d), (such as means and standard deviation) (Wolf, 1986)

Study selection was performed between January 2010 and January 2019 to identify relevant papers published during the last 8 years in peer-reviewed journals. A computer-based literature search was conducted using the following databases: PubMed (NLM), Embase (Elsevier), Ovid MEDLINE, SciELO (FAPESP-BIREME), Baidu Scholar (Baidu-Inc.) and CNKI (Tsinghua-University). The search terms used were: *marijuana* OR *marihuana* OR *THC** OR *cannabi** AND *neurocog** OR *neuropsy** OR *cognit** OR *assess** OR *abilit** OR *process** OR *intelligen** OR *attent** OR *memory* OR *learn** OR *executive function** OR *impair** AND *residual* OR *long-term* OR *chronic* OR *lasting* OR *persisting* OR *non-acute*. The term neurocognitive/neuropsychological was then replaced with different terms describing cognitive domains and names of a list of specific cognitive tests

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(Baldacchino et al., 2017). These included *"Digit Span"*, *"Rapid Visual Information Processing"*, *"Letter Cancellation Test"*, *"Reaction Time"*, *"Digit Symbol Substitution Test"*, *"Symbol Digit Modalities Test"*, *"Cannabis Stroop Task"*, *"Hopkins Verbal Learning Test"*, *"Spatial Working Memory"*, *"California Verbal Learning Test"*, *"Controlled Oral Word Association Test"*, *"Two Back Test"*, *"Video Prospective Memory Task"*, *"Finger Tapping Test"*, *"Grooved Pegboard"*, *"Rey Auditory Verbal Learning Test"*, *"Iowa Gambling Task"*, *"Go-Stop Task"*, *"Stroop Color Word Task"*, *"Wisconsin Card Sorting Test"*, *"Trail Making Test"*

All of the identified abstracts from the electronic search were independently reviewed by the authors allowing selecting eligible studies for the systematic review and meta-analysis. Finally, the references of the selected papers were examined and a "snowballing" technique employed in order to identify further relevant studies. Several studies did not provide neurocognitive scores on the published papers. In order to have access to the relevant data, six authors were contacted and four replied back, four studies were excluded (two studies due to lack of information and the other two studies due to unmet selection criteria).

3. Analysis

Standard meta-analytic techniques were employed to estimate the consequences of chronic cannabis use on eight neurocognitive domains, such as Cognitive Flexibility, Cognitive Impulsivity, Motor Impulsivity, Non-Planning Impulsivity, Attention, Short-Term Memory, Long-Term Memory and Emotional Cognition. The identification of such domains was performed similarly to previous meta-analytic reviews of cross-sectional studies by Baldacchino, Conti and colleagues (Baldacchino et al., 2012, Baldacchino et al., 2017, Conti et al., 2019) (Tables 1-3).

Since different neurocognitive scales for each domain were employed in the studies, the standardized mean difference statistic was used to measure effect size (Sutton et al., 2000). In case of substantial heterogeneity, a random effect model was preferred (Quintana and Minami, 2006, Hedges and Verea, 1998).

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Study heterogeneity was assessed by Cochran's *Q* and I^2 index (Cochran, 1950, Higgins et al., 2003).

Eligible research studies reporting means and standard deviations from each group were assembled into a database and computed through the Comprehensive Meta-Analysis Version III software (2017). The statistical significance level was p=0.05 and in *Q* statistics p=0.10. A large effect size was defined by a value of 0.80, a medium effect size by a value of 0.50, and a small effect size by a value of 0.20 (Cohen, 1988).

In order to identify possible associations between each of the continuous moderator variables (age, duration of use, period of non-use and dose) and the effect size, we considered using a meta-regression (Thompson and Higgins, 2002). However, due to lack of information in the selected studies, the meta-regression was not feasible.

3.1 *Publication Bias*

Studies with statistically significant results are more often published in comparison to studies with non-significant and/or negative results (Dickersin, 2005, Hedges, 1989). Thus, we considered the possibility that the selected studies were biased affecting the results of the analysis. To assess publication bias a visual inspection of funnel plots was performed in addition to determination of the Fail Safe N (Orwin, 1983). Fail Safe N corresponds to the number of missing studies that would permit to determine how many of these studies need to be added to a meta-analysis in order to bring the overall result from significant to non-significant.

3.2 *Assessment of study quality*

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The quality of the papers included in this review was evaluated and graded using the Scottish Intercollegiate Guidelines Network (NHS, 1993). Studies were classified as “unmatched”, “matched on demographic variables”, “matched on behavioural and demographic variables”, “longitudinal measurements”, “matched with longitudinal study”. The quality of the studies was assessed by two authors (PRF, ST and AB) as we aimed to avoid bias.

4. Results

Computer-based searching yielded 4839 references. After removal of duplicates, the search terms yielded 2827 unique studies and after screening for relevance, 2630 studies were excluded. The remaining 197 studies were assessed for eligibility by title and abstract inspection, eliminating 131 papers. The remaining 66 studies were retrieved for further assessment utilizing the inclusion and exclusion criteria. There were 12 cross-sectional studies and 1 longitudinal study included in this meta-analysis (Figure 1). None of the identified studies recruited non-smoking chronic cannabis users.

From the 13 studies, 6 studies were classified as “matched on demographic variables”, 5 studies as “unmatched” and 2 as “matched on behavioural and demographic variables”. The five studies that were graded as “unmatched” were included in the quantitative synthesis in order to avoid sample size reduction and consequent low statistical power of the meta-analysis (Hedges and Pigott, 2004) as their methodologies didn’t present major flaws.

Furthermore, most of the studies contained reported data from different comparator groups (e.g. “experimenters”, “light cannabis users”, “former heavy users”, “synthetic cannabis users”, “recreational cannabis users”) so only suitable comparator groups were included, in accordance with established criteria. The excluded comparator groups are presented in Table 4.

There were 13 selected studies, with 1382 participants, including 499 chronic cannabis users and 883 comparison participants who had minimal or no cannabis

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use in their lifetime. The reported Mean (Standard Deviation) age of cannabis users varied from 19 (5.0) years (Bartholomew et al., 2010) to 27.5 (5.4) years old (Cohen et al., 2017). Comparison participants had a mean age range of 19 (3.0) years (Bartholomew et al., 2010) to 26.2 (10.7) years old (Morgan et al., 2010). The lowest reported duration of cannabis use was 3 years (Bartholomew et al., 2010) and the highest was 15.2 years (Becker et al., 2014).

Studies were mainly conducted in the United States, Europe and Australia. It was not possible to extract duration of cannabis use (in years) in 6 of the studies due to lack of information. The demographic characteristics and the clinical information of the selected studies are shown in Tables 5 and 6.

4.1 Neurocognitive domains

Twenty-eight effect sizes measurements were conducted from the selected studies. Analysis on the Non-Planning Impulsivity and Emotional Cognition was not possible since there was only one study identified for each neurocognitive domain (Bayrakçı et al., 2015, Becker et al., 2014). Presence of publication bias for testing all cognitive domains was present. These results and related effect sizes are shown in Table 7.

For *Cognitive Impulsivity* a significant and small effect size of 0.30 was found in favour of the control group ($z = 2.11$, $p < 0.05$) showing a slight tendency for chronic cannabis users to opt for small immediate rewards over larger delayed rewards comparing to non-users. Results of *Q* and I^2 tests indicated low heterogeneity between the 4 pooled studies ($Q = 4.76$, $p = 0.19$; $I^2 = 36.97$) (Figure 2).

For *Motor Impulsivity* a non-significant effect size of 0.05 was detected in favour of the control group ($z = 0.37$, $p = 0.72$) revealing no association between chronic cannabis use and the ability to suppress emotional, cognitive and behavioural responses. Results of Q and I^2 tests indicated homogeneity between the 2 pooled studies ($Q = 0.001$, $p = 0.98$; $I^2 = 0.00$) (Figure 3).

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For *Cognitive Flexibility* a significant and small effect size of 0.33 was found in favour of the control group ($z = 3.04$, $p < 0.005$) showing an impaired capacity for chronic cannabis users to make appropriate behavioural decisions while switching between cognitive processes. Results of *Q* and I^2 tests indicated very low heterogeneity between the 6 pooled studies ($Q = 5.22$, $p = 0.39$; $I^2 = 4.29$) (Figure 4).

For *Attention* a significant and small effect size of 0.16 was identified in favour of the control group ($z = 2.27$, $p < 0.05$) revealing a slightly better ability for non-users to reject irrelevant information while attending to relevant input and to detect unpredictable signals during prolonged periods of time, in contrast to chronic cannabis users. Results of *Q* and I^2 tests indicated low heterogeneity between the 6 pooled studies ($Q = 5.52$, $p = 0.36$; $I^2 = 9.48$) (Figure 5).

For *Short-term Memory* a significant medium effect size of 0.48 was found in favour of the control group ($z = 5.63$, $p < 0.001$) showing an impairment for chronic cannabis users to recognize and recall information presented directly or shortly in comparison to non-users. Results of *Q* and I^2 tests indicated homogeneity between the 6 pooled studies ($Q = 4.17$, $p = 0.53$; $I^2 = 0.00$) (Figure 6).

For *Long-term Memory* a significant effect size of 0.43 was detected in favour of the control group ($z = 3.12$, $p < 0.005$) representing a better ability for non-users to retain implicit and explicit information over longer periods of time compared to chronic cannabis users. Results of *Q* and I^2 tests indicated moderate heterogeneity between the 4 pooled studies ($Q = 5.65$, $p = 0.13$; $I^2 = 46.92$) (Figure 7).

5. Discussions

5.1 Key findings

We conducted a quantitative and systematic review of the literature on the impact of chronic cannabis use on neurocognitive functioning. Although the effect sizes and functional consequences may vary, the meta-analysis revealed an association

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between chronic cannabis use and cognitive impairment in a broad range of functional domains such as cognitive impulsivity, cognitive flexibility, attention, short-term memory and long-term memory. The magnitude of the effect size was higher in long-term memory domain and lower in attentional domain but still low in size. Fail Safe N results are not sufficiently high to exclude possible publication bias (Table 7).

Small effect sizes were observed in all neurocognitive domains. A limited association was found between cannabis use and neurocognitive deficits, and memory were linked to chronic cannabis use. These findings contrasts with several neuroimaging studies that reported the impact of cannabis-related memory deficits associated with putative neural substrates, such as hippocampus (Orr et al., 2019, Ashtari et al., 2011, Jager et al., 2007, Smith et al., 2014, Smith et al., 2015). These results are consistent with a previous meta-analysis conducted by Scott and colleagues (2018), that revealed a similar effect size magnitude across all cognitive domains (mean *d*, -0.33 to -0.21) in a young heavy/frequent cannabis users' population. Our findings are also in line with previous meta-analysis that suggested small effect sizes across learning and memory domains with long-term, regular cannabis consumption (Grant et al., 2003, Schreiner and Dunn, 2012).

Collectively, our analysis indicates a limited association between chronic cannabis use and cognitive impairments in adults, with moderate heterogeneity between the 28 pooled studies.

5.2 Strengths and Limitations

The inclusion and exclusion criteria were stringent, thus aiding the elimination of confounding factors such as concomitant alcohol and polydrug abuse, and no current psychiatric or neurological disorder. In this review, cannabis users were well matched with healthy controls. Notably, gender, age, educational level and socioeconomic status were not included as covariates, which could impact on cognitive functioning (Mani et al., 2013, Murman, 2015, Piumatti et al., 2018, Salthouse, 2009). Comparing with a recent meta-analysis reported by Scott and

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colleagues (2018), who evaluated cognitive impairments due to chronic cannabis use on adolescent and young adults, our study only included adult participants. Studies targeting adolescents were excluded as young people are particularly vulnerable to the effects of addictive drugs and their brain is not fully developed (Bernheim et al., 2013, Crews et al., 2007, Winters and Arria, 2011). A recent systematic review of human and animal studies elucidates the age-related impact of cannabis use and cognition. Importantly, Gorey and colleagues found that age-dependent effect of cannabis is associated with cannabis use history and intoxication state (Gorey et al., 2019). Another strength of our work was to use rigorous selection criteria for included participants. We only included studies recruiting comparison groups of individuals who had never used cannabis or who had minimal use in their lifetime (less than 50 times) to attenuate a potential cumulative effect of cannabis use in the comparator group. This is in contrast to previous meta-analysis' (Scott et al., 2018, Schreiner and Dunn, 2012) methodology, where the definition for the comparison group was not explicit. In addition, contrary to these both studies, a strict period of at least 12 hours without using cannabis was defined in the users' group to focus our analysis on long-term effects of cannabis use, excluding possible confounding factors related to acute effects of the drug on the day of testing. There is evidence that some cognitive functioning may recover after abstinence, but reported results are not consistent due to different methodologies (Bosker et al., 2013, Hanson et al., 2010, Hooper et al., 2014, Meier et al., 2012, Tait et al., 2011).

Confounding factors such as educational status, concomitant tobacco smoking or alcohol use were considered by most of the included studies. The mean dose and frequency of use varied throughout the selected studies, including imprecise quantitative measurements (i.e. joints, smoking episodes, grams, hits per day, days per month, days per year). This could be an important confounding factor as several studies reported a positive relationship between the amount of drug exposure and cognitive outcomes (Auer et al., 2016, Gruber et al., 2012, Lisdahl and Price, 2012, Meier et al., 2012). To reduce this discrepancy, we used DSM-5 diagnostic criteria for all included participants, defining chronic cannabis use as continuous and recurrent cannabis consumption as occurring within a 12-month

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period. A recent report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2018a) mentions a large increase in the potency of cannabis, contributing to a great variability regarding cannabis ingredients and concentrations consumed by each individual. Dose, frequency of use, duration and age of onset of use all interact to mediate the neurocognitive impairments of the substance (EMCDDA, 2018a). Our analysis found mixed effects regarding the association between parameters of cannabis use and neurocognitive impairments. Future studies should attempt to measure the diverse cannabis compounds in each consumed drug.

Other possible limiting factors include the lack of information on participants' neurodevelopmental history and the manifestation of previous neuropsychiatric conditions that may predispose to the development of substance misuse and dependency (Dalley et al., 2007, Gouzoulis-Mayfrank et al., 2000). Thus, an important question is whether cognitive impairments identified were simply a consequence of prolonged drug use and/or a premorbid vulnerability to drug dependency (Gonzalez et al., 2012, de Wit, 2009, Goldstein et al., 2006). The lack of information regarding the impact of cannabis exposure on important factors such as gender and age of the participants could also be considered as another limitation of this meta-analysis. In fact, it wasn't possible to draw any significant conclusion on gender differences but some of the included studies have reported that men scored higher on impulsivity measures and poorer on psychomotor speed in comparison with females (Griffith-Lendering et al., 2012, Lisdahl and Price, 2012). These factors should be taken in consideration by future studies.

5.3 Clinical Relevance

During the past decade, the prevalence of cannabis use in Europe has remained continuously high by historical standards, and recent increases have been noted in some EU countries (EMCDDA, 2018a). However, public perception tends to view cannabis as a harmless drug, frequently disregarding its potential long-term health problems (Carliner et al., 2017, Lorenzetti et al., 2019, Volkow et al., 2014). Additionally, several studies have indicated a potential therapeutic

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effect of cannabinoids for some selected illnesses (Andreae et al., 2015, Devinsky et al., 2016, Kafil et al., 2018, Romero-Sandoval et al., 2017) with countries recently legalising the medicinal and recreational use of this substance (EMCDDA, 2018b, Knöss et al., 2019, Millar et al., 2019).

The present meta-analysis identified a cross-sectional association between chronic cannabis use and neurocognitive impairments within specific memory domains when compared to non-cannabis users. Cognitive impairments are negatively associated with quality of life measures (Kurz et al., 2003, Lindeboom and Weinstein, 2004, Logsdon et al., 2002, Tarawneh and Holtzman, 2012) making individuals more susceptible to adverse life events and/or to the development of new psychiatric conditions (Schulte and Hser, 2014, GBD, 2018). Pre-treatment neurocognitive assessments and personalized Cognitive Rehabilitation Treatments (CRTs) could be useful in cannabis users wishing to stop consumption as these initiatives could support an improvement in cognitive function and prevent relapse (Rezapour et al., 2015).

6. Conclusion

A systematic review and meta-analysis were conducted to study the impact of chronic cannabis use on neurocognitive functioning. We found a cross-sectional association between chronic cannabis use and impairments in six neurocognitive domains, including memory function, cognitive impulsivity, cognitive flexibility and attention. The current quantitative analysis does not quantify persistence impairments, but these results should not discourage the provision of specific therapeutic procedures, which may ultimately improve cognitive functioning in vulnerable chronic cannabis users. In that context, researchers and practitioners should also consider the importance of biopsychosocial effects associated with chronic cannabis use and help to create preventative measures against it if needed.

Future studies should further investigate specific aspects of cannabis use in carefully defined individuals (e.g. dose, frequency and cannabinoid content) and try to evaluate whether cognitive impairments due to cannabis exposure would

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remit after an extended period of non-use. Such work would promote better understanding of the impact of cannabis use on each individual.

Conflicts of Interests

AB has no conflicts of interest with regard to the current work. However unrelated to this project he has received educational grants from Schering Plough, Merck Serono, Reckitt Benckiser and Indivior. DS has no conflicts of interest with regard to the current work. However unrelated to this project he has received research funding via an honorarium associated with a lecture from Wyeth and funding from Indivior. ST has no conflicts of interest with regard to the current work. However unelated to this project she has received funding from Indivior, Merck Serono and Lundbeck. PRF has no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

We thank Dr Ajay Shah for his contribution on literature search.

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Figure Captions

FIGURE 1: NEUROCOGNITIVE ASSOCIATIONS WITH CHRONIC CANNABIS USE: QUALITY OF REPORTING OF META-ANALYSIS (QUOROM): 2010-2018

FIGURE 2: COGNITIVE IMPULSIVITY FOREST PLOT

Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; IGT = Iowa Gambling Task; CWIT = Color Word Interference Task; SOA = Stimulus Onset Asynchrony

FIGURE 3: MOTOR IMPULSIVITY

Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; GST = Go-Stop Task; ST = Classical Stroop Task

FIGURE 4: COGNITIVE FLEXIBILITY

Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; SCWT = Stroop Color Word Task; VF = Verbal Fluency; COWAT = Controlled Oral Word Association Test

FIGURE 5: ATTENTION

Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; DS = Digit Span; CaST = Cannabis Stroop Task; RUFF = Ruff 2&7; FACT = Flexible Attentional Control Task.

FIGURE 6: SHORT-TERM MEMORY

Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; HVLT = Hopkins Verbal Learning Test; CVLT = California Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test; 2-BT = 2-Back Test

FIGURE 7: LONG-TERM MEMORY

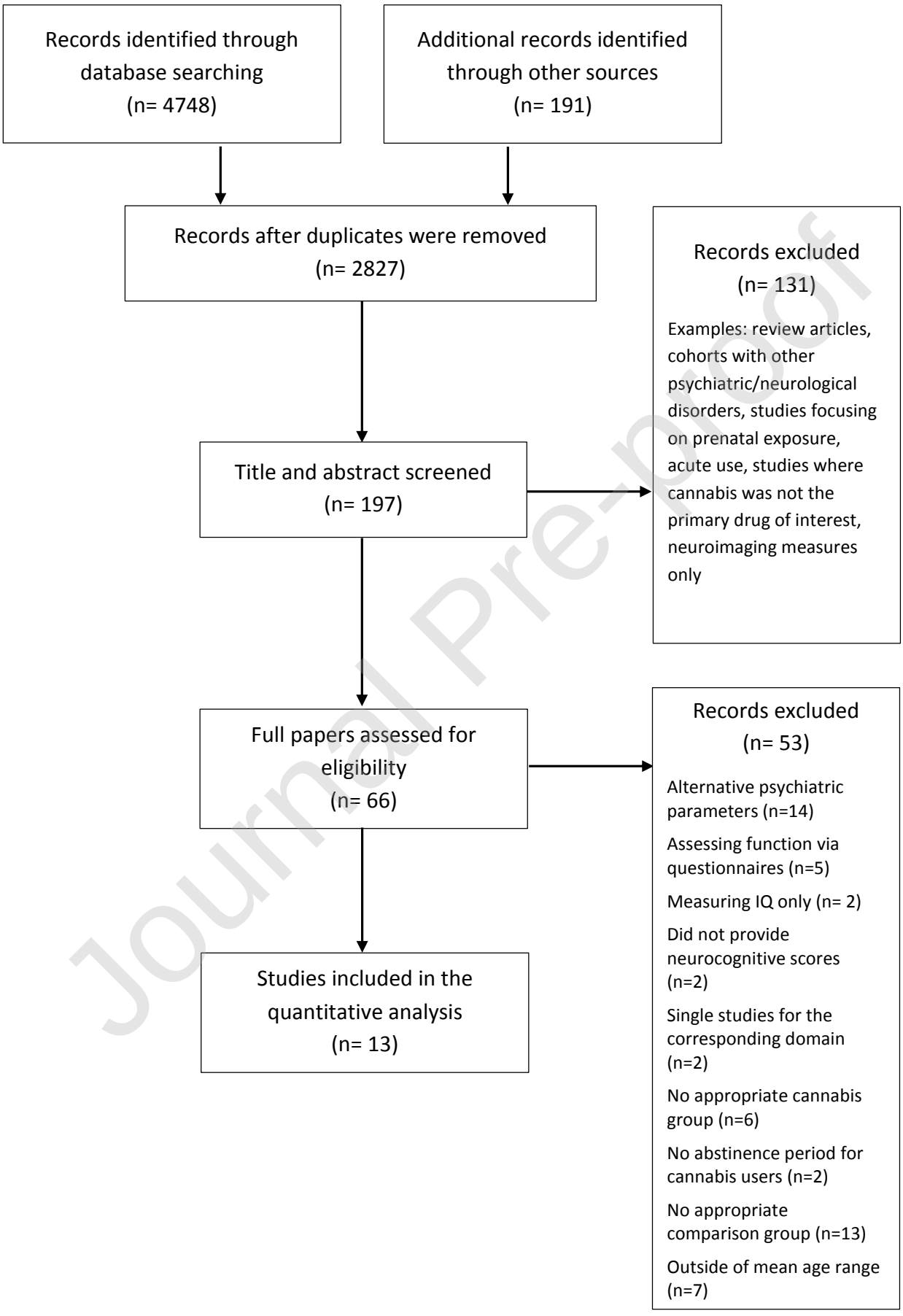
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FIGURE 1

NEUROCOGNITIVE ASSOCIATIONS WITH CHRONIC CANNABIS USE: QUALITY OF REPORTING OF META-ANALYSIS (QUOROM): 2010-2018



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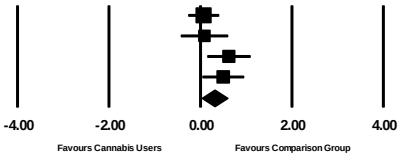
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FIGURE 2

COGNITIVE IMPULSIVITY FOREST PLOT

Cognitive Impulsivity: Chronic Cannabis Users vs Comparision Group

Studyname	Outcome	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Gonzalez et al 2012	IGT	0.071	0.175	0.031	-0.273	0.415	0.404	0.686
Lisdahl et al 2012	CWIT	0.087	0.267	0.071	-0.436	0.611	0.327	0.743
Becker et al 2014	IGT Good choice	0.622	0.245	0.060	0.142	1.102	2.542	0.011
Morgan et al 2010	SOA % errors	0.500	0.236	0.056	0.037	0.963	2.116	0.034
		0.301	0.143	0.020	0.021	0.581	2.107	0.035



Note *Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; IGT = Iowa Gambling Task; CWIT = Color Word Interference Task; SOA = Stimulus Onset Asynchrony*

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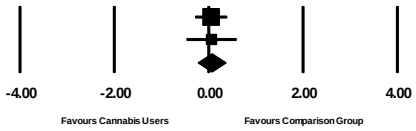
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FIGURE 3

MOTOR IMPULSIVITY FOREST PLOT

Motor Impulsivity: Chronic Cannabis Users vs Comparison Group

Studyname	Outcome	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Gonzalez et al 2012	GST	0.051	0.175	0.031	-0.293	0.395	0.292	0.770
Cousijn et al 2013	ST	0.061	0.275	0.076	-0.478	0.599	0.220	0.826
		0.054	0.148	0.022	-0.236	0.344	0.365	0.715



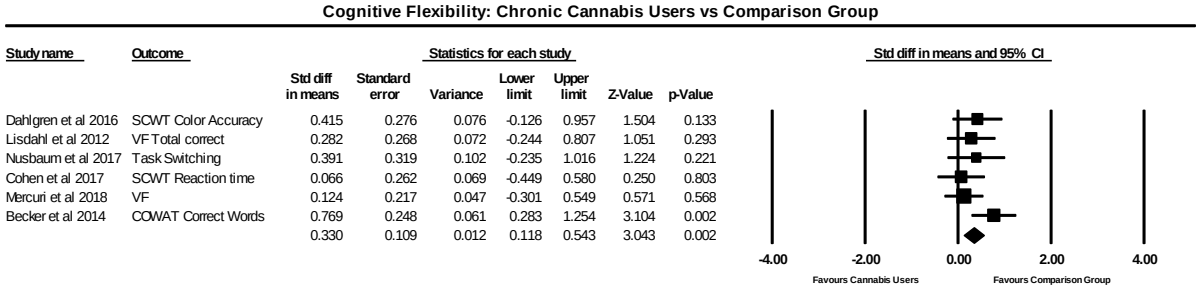
Note *Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; GST = Go-Stop Task; ST = Classical Stroop Task*

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FIGURE 4

COGNITIVE FLEXIBILITY FOREST PLOT



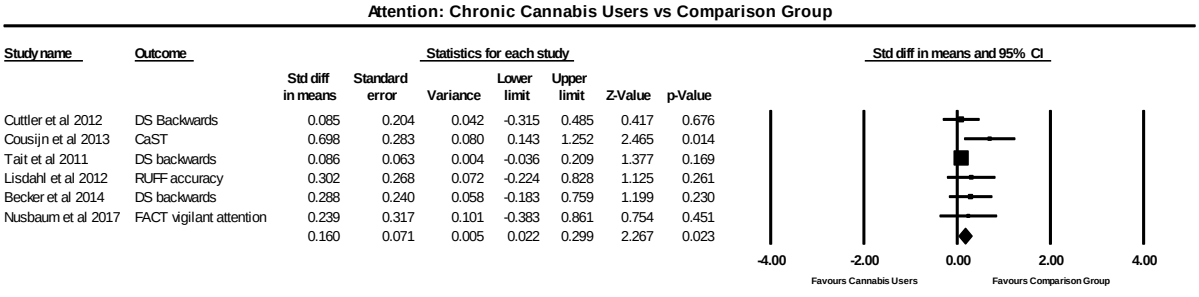
Note *Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; SCWT = Stroop Color Word Task; VF = Verbal Fluency; COWAT = Controlled Oral Word Association Test*

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FIGURE 5

ATTENTION FOREST PLOT



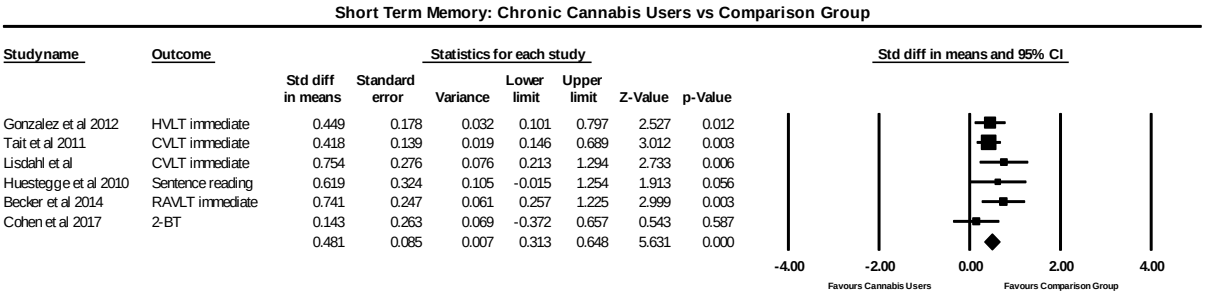
Note *Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; DS = Digit Span; CaST = Cannabis Stroop Task; RUFF = Ruff 2&7; FACT = Flexible Attentional Control Task.*

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FIGURE 6

SHORT-TERM MEMORY FOREST PLOT



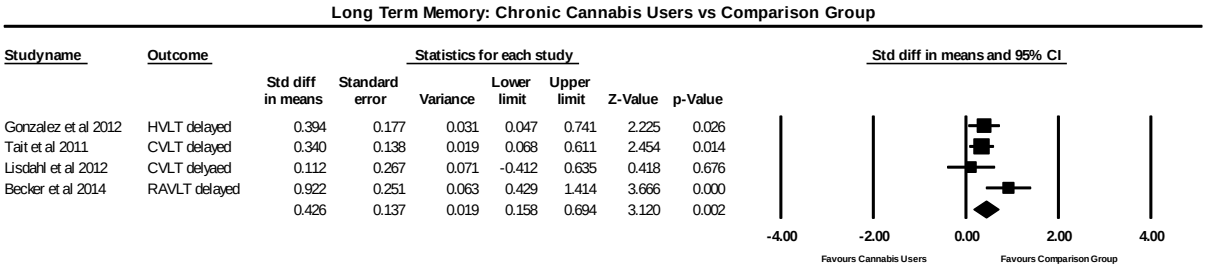
Note *Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; HVLT = Hopkins Verbal Learning Test; CVLT = California Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test; 2-BT = 2-Back Test*

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FIGURE 7

LONG-TERM MEMORY FOREST PLOT



Note *Std diff = standard difference; Z value = one sample Z statistic; p value = probability that Z statistics is significantly different than 0; lower limit = lower limit of the 95% confidence interval for the effect size; upper limit = upper limit of the 95% confidence interval for the effect size; HVLT = Hopkins Verbal Learning Test; CVLT = California Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test*

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TABLE 1 EXECUTIVE FUNCTIONS

Main Domain	Subdomain	Definition	Tests
IMPULSIVITY	**Cognitive Impulsivity**	Ability to opt for larger delayed rewards over smaller more immediate rewards	
		Decision-making under ambiguity	IGT, MFFT, BIS, DDT, CWIT, SOA
		Decision-making under risk	CGT, IGT, RDMT, GDT, BART
	Non-Planning Impulsivity	Ability to think ahead and actively search for an appropriate solution	TOL, SOC, ROCFT, PMT, TOH WAIS-III (Block Design, Matrix Reasoning), SS, SWM
	Motor Impulsivity	Ability to suppress emotional, cognitive and behavioural responses	
		Process required to stop a planned movement	AGN, SST, Go/NoGo, GST
		Process required to suppress a salient but conflicting stimulus while identifying less salient ones	ST

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FLEXIBILITY	**Cognitive Flexibility**	Ability to shift avenues of thought and action in order to perceive process and respond to situations in different ways	
		Ability to realign a behavioural predisposition to altered contingencies	WCST, ST, IED, TMT, HSCT, MCST, SCWT, TS
		Requires the intrinsic generation of responses or alternatives	COWAT, FAS, VF, RFFT, WAIS-III (Similarities), RWT, DF
COMPULSIVITY		The feeling that one has to perform an action, or the inability to stop performing an action	IED
COGNITION	**Emotional Cognition**	Ability to recognize, process and respond to emotions rapidly	EPT, FEIT, FEDT, DEERT, MET

AGN = Affective Go-NoGo; AM = Austine Maze; BADS = Behavioural Assessment of Dysexecutive Syndrome; BART = Balloon Analogue Risk Task; BIS = Barratt Impulsiveness Scale; BLC = Big Little Circle; CBT = Corsi Block Test; CGT = Cambridge Gambling Task; CLFT = Category and Letter Fluency Test; CWIT = Color Word Interference Task; COWAT = Controlled Oral Word Association Test; CTT = Colour Trail Test; CVLT = California Verbal Learning Test; DEERT = Dynamic Emotional Expression Recognition Task; DDT = Delay Discounting Test; DF = Design Fluency; DS = Digit Span; EPT = Emotional Processing Task; FAS = Phonological Fluency Test; FEDT = Facial Emotion Discrimination Test; FEIT = Facial Emotion Identification Test; GDT = Game and Dice Test; GST = Go-Stop Task; HSCT = Hayling Sentence Completion Test; IED = Intra/Extra-Dimensional Set Shifting Task; IST = Information Sampling Test; IGT = Iowa Gambling Task; MFFT = Matching Familiar Figures; MCST = Maudsley Card Sorting Test; PASAT = Paced Auditory Serial Addition Task; PMT = Proteus Maze Test; RAVLT = Rey Auditory Verbal Learning Test; RDMT = Rogers Decision Making Task; ROCFT = Rey-Osterreith Complex Figure Test; RWFT = Regensburger Word Fluency Test; SCT = Logan Stop Change Task; SCWT = Stroop Color Word Task; SOA = Stimulus Onset Asynchrony; SOC = Stockings of Cambridge; SS = Spatial Span, SST = Stop Signal Test; SWM = Spatial Working Memory; ST = Stroop Test; TOH = Tower of Hanoi; TOL = Tower of London; TS = Stroop-like task switching; VF = Benton Verbal Fluency Test; WCST = Wisconsin Card Sorting Test; WAIS-R/III = Wechsler Adult Intelligence Scale -Revised/Third Edition; FAT = Test of Attentional Flexibility; MAT = Matrices for Intelligence Test; MET = Mind in the Eyes Test; RST3 = Multiple Choice under Stress; LL5 = Labyrinth of Lines to Measure Visual Structuring Performance.

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TABLE 2 ATTENTION

Main Domain	Definition	Tests
ATTENTION	Arousal / Alertness	DSST
	Ability to reject irrelevant information while attending to relevant input	TMT, TEA, ST, RT, SSRT, DR2, Q1, CaST, FACT, LCT
	Readiness to detect rarely and unpredictable occurring signals over prolonged periods of time	PASAT, TOVA, TEA, CPT, FTT, ACT, SRT, RUFF
	Ability for individuals to hold information in mind and process; need to process tasks simultaneously	
	Attention span	CVLT, RAVLT
	Reaction time or information processing speed	DSST, WAIS-III, DS, SDMT, DSY

ACT = Attentional Capture Task; CaST = Cannabis Stroop Task; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; DS = Digit Span; DSST = Digit Symbol Substitution Test; DSY = Digit Symbol Substitution Test; DR2 = Simple Choice Reaction; FACT = Flexible Attentional Control Task; LCT = Letter Cancellation Test; FTT = Finger Tapping Test; PASAT = Paced Auditory Serial Addition Task; Q1= Attention under Monotonous Circumstances; RT = Reaction Time; RAVLT = Rey Auditory Verbal Learning Test; RUFF = Ruff 2&7; SDMT = Symbol Digit Modality Test; SSRT = Stop Signal Reaction Time; SRT = Serial Reaction Time; TEA = Test of Everyday Attention; TMT = Trail Making Test; TOVA = Test of Variables of Attention; WAIS-III = Wechsler Adult Intelligence Scale.

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TABLE 3 LEARNING AND MEMORY

Main Domain	Subdomain	Definition	Tests
LEARNING AND MEMORY	**Short-term Memory**	Reproduction, recognition or recall of information directly or some time after presentation	LMT, RAVLT, CVLT, WAIS-III, DS, VRM, WMSR, WRM, GNT, DFDBT, 2-BT, HVLT, WCST, VLT, WPAT, ERT
		Allow information to be evaluated and perhaps stored longer through rehearsal and coding	SWM, DMS, PRM, PAL, BVRT, PAL, SRM, WMSR, RCFT, PASAT, WAIS-III, BVMT, CCDT, 3D-BCM, CBT, WMS, SS, SR, SOS, Free-Recall
	Long-term Memory	Records details salient to individuals Life. Needs conscious thinking "knowing that"	PRM, SRM, CVLT, RAVLT, PAL, RCFT, WMSR, WAIS-III, HVLT, VPMT, FPMT, RPMT, CPMT
		Meaning of words and concepts or propositional knowledge (facts)	RCFT, COWAT, GNT, WMSR, RBMT
		Does not need conscious thinking "knowing how"	

BVMT-R = Brief Visuospatial Memory Test-Revised; BVRT = Benton Visual Retention Test; CBT = Corsi Block Test; CCDT = Colour Change Detection Task; COWAT = Controlled Oral Word Association Test; CPMT = Call-In Prospective Memory Test; CVLT = California Verbal Learning Test; DFDBT = Digit Forward and Digit Backwards Test; DMS = Delayed Matching to Sample; DS = Digit Span; ERT = Eye Reading Test; FPMT = Fruit Prospective Memory Test; GNT = Graded Name Test; HVLT = Hopkins Verbal Learning Test; LMT = Logical Memory Test; SRM = Spatial Recognition Memory; PAL = Paired Associate Learning; PASAT = Paced Auditory Serial Addition Task; PRM = Pattern Recognition Memory; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioural Memory Test; ROCFT = Rey Osterreith Complex Figure Test; RPMT = Reminder Prospective Memory Test; RRLET = Remote and Recent Life Event Test; SAVF = Semantic Association of Verbal Fluency; SOMT = Six Object Memory Test; SOS = Self-Ordered Search; SR = Sentence Reading; SWM =Spatial Working Memory; SS = Spatial Span; 2-BT = Two Back Test; 3D-BCM = Three Dimensional Block Constitution Model; VLT = Verbal Learning Task; VPMT = Video-based Prospective Memory Task; VRM = Verbal Recognition Memory; WAIS-III = Wechsler Adult Intelligence Scale; WMS-III= Wechsler Memory Scale; WPAT = Wechsler Paired Associate Test; WRM = Word Recognition Memory; WSLT = Word Sequence Learning Test.

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TABLE 4 COMPARATOR GROUPS INCLUDED AND EXCLUDED IN THE META-ANALYSIS

	N
Included comparator groups	
Chronic/heavy cannabis smokers	13
Never or Minimal/Non-smokers	13
Excluded comparator groups	
Cannabis-experimenters	1
Early-onset cannabis users	1
Remain light smokers	1
Former light smokers	1
Former heavy smokers	1
Always former	1
Cannabis users on stress tasks	1
Synthetic cannabis users	1
Recreational cannabis users	1

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TABLE 5 CHARACTERISTICS OF THE INCLUDED STUDIES

Study	Year of Publication	Manuscript Title of Selected Study	N	Group = n (% Male, Mean age [SD] in years)	Study Design	Level of Evidence - SIGN (variables)
Huestegge et al.	2010	*Long-term effects of cannabis on eye movement control in reading*	40	CCU = 20 (70.00%, 25.00[NR]) CG = 20 (70.00%, 24.00[NR])	Cross Sectional	2++
Bartholomew et al.	2010	*Does cannabis use affect prospective memory in young adults?*	90	CCU = 45 (44.40%, 19.00[5.00]) CG = 45 (37.70%, 19.00[3.00])	Cross Sectional	2+ (Alcohol)
Morgan et al.	2010	*Hyper-priming in cannabis users: a naturalistic study of the effects of cannabis on semantic memory function*	74	CCU = 36 (60.00%, 26.37[9.63]) CG = 38 (59.50%, 26.24[10.73])	Cross Sectional	2++
Tait et al.	2011	*Cannabis use and cognitive function: 8-year trajectory in a young adult cohort*	480	CCU = 60 (70.00%, 22.50[1.50]) CG = 420 (43.10%, 22.70[1.50])	Longitudinal	2+ (Education, English language status, gender)
Cuttler et al.	2012	*Mechanisms underlying the link between cannabis use and prospective memory*	96	CCU = 48 (52.08%, 20.42[2.52]) CG = 48 (20.87%, 19.71[2.59])	Cross Sectional	2 (Alcohol, education, English language status, gender, IQ, other SU)
Lisdahl and Price	2012	*Increased marijuana use and gender predict poorer cognitive functioning in adolescents and emerging adults*	59	CCU = 23 (44.00%, 21.20[2.80]) CG = 36 (50.00%, 20.70[2.80])	Cross Sectional	2+ (Alcohol, other SU)
Gonzalez et al.	2012	*Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders*	130	CCU = 65 (65.00%, 20.80[1.80]) CG = 65 (51.00%, 20.30[2.00])	Cross Sectional	2+ (Alcohol, tobacco)
Cousijn et al.	2013	*Cannabis dependence, cognitive control and attentional bias for cannabis words*	53	CCU = 27 (70.00%, 24.00[2.80]) CG = 26 (62.00%, 25.30[2.60])	Cross Sectional	2+ (Alcohol)

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Becker et al.	2014	*Neurocognition in college-aged daily marijuana users*	70	CCU = 35 (63.90%, 19.52[0.62]) CG = 35 (37.10%, 19.40[0.93])	Cross Sectional	2 (Age, gender)
Dahlgren et al.	2016	*Marijuana use predicts cognitive performance on tasks of executive function*	76	CCU = 44 (84.09%, 24.14[6.75]) CG = 32 (62.50%, 24.22[6.46])	Cross Sectional	2+ (Alcohol)
Cohen et al.	2017	*The effects of synthetic cannabinoids on executive function*	83	CCU = 42 (52.00%, 27.45[5.35]) CG = 41 (54.00%, 25.56[3.03])	Cross Sectional	2 (Education, tobacco)
Nusbaum et al.	2017	*Altered attentional control strategies but spared executive functioning in chronic cannabis users*	40	CCU = 20 (75.00%, 25.35[8.71]) CG = 20 (40.00%, 25.25[5.57])	Cross Sectional	2 (gender)
Mercuri et al.	2018	*Episodic foresight deficits in regular, but not recreational, cannabis users*	91	CCU = 34 (45.00%, 24.70[3.9]) CG = 57 (45.00%, 21.30[3.5])	Cross Sectional	2 (Age, alcohol)

CCU = Chronic Cannabis Users; CG = Comparator group; N = Total number of participants; % = Percentage; SD = Standard Deviation; SU = Substance users; SIGN= Scottish Intercollegiate Guidelines Network

***Level of evidence** 2: unmatched; 2+: matched on demographic variables; 2++: matched on behavioural and demographic variables; 2*: longitudinal measurements; 2+* matched with longitudinal study (using Scottish Intercollegiate Guidelines Network – SIGN)*

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TABLE 6 CANNABIS USE CHARACTERISTICS AND TESTS ADMINISTERED

Study	Mean Dose and/or Mean Frequency of CCU	Duration of CCU / Age of Onset in years	Period of non-use (CCU) in days	Period of non-use (CG) in days	Neurocognitive Tests	Neurocognitive Domains
Huestegge et al., 2010	10.5 joints per week, 3500 joints in lifetime	9.0 years / 14-16 years old	More than 1 day	Never used CN	ERT	LM
Bartholomew et al., 2010	2 joints per week	3.0 years / NR	10.5 days	Never used CN	VPMT	LM
Morgan et al., 2010	2.3 joints per SM, 12.8 days per month	7.6 years / NR	2.2 days	414.1 days	SOA	EF
Tait et al., 2011	More than 1 SM per week	NR / older than 16 years old	More than 0.5 day	Never used CN	CVLT, DS, SDMT	A, LM
Cuttler et al., 2012	More than 3 SM per week for at least a year	NR	More than 0.5 day	Never used CN	DS, RAVLT, FPMT, RPMT, CPTM	A, LM
Lisdahl and Price, 2012	1014 joints in lifetime, 208 SM per year	NR / 15.0 years old	50.0 days	Less than 10 CN uses in past year, less than 50 CN uses in a lifetime	RUFF, CVLT, TMT, VF, DF, CWIT	A, EF, LM
Gonzalez et al., 2012	60 SM past year, 6 SM past month	5.0 years / 15.6 years old	3.0 days	720.0 days	IGT, BART, GST, HVLT	EF, LM
Cousijn et al., 2013	3.8 grams and 5.1 SM per week	NR / 14.9 years old	2.8 days	837.4 days	ST, CaST	A, EF

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Becker et al., 2014	10.2 hits per day, 334.4 days per year, 25.9 days per month	15.2 years / 13-17 years old	More than 0.5 day	Less than 10 CN uses in a lifetime	TOL, IGT, DSY, LCT, DS, SS, SR, SOS, SDRT, FTT, COWAT, RAVLT, DS	A, EF, LM
Dahlgren et al., 2016	6.30 grams and 14.3 SM per week	6.3 years / 18.1 years old	More than 0.5 day	Less than 15 CN use in a lifetime	ST, WCST	EF
Cohen et al., 2017	NR	NR	(78.6%) <7 days, (19%) >7 days, (2.4%) >30 days	365.0 days	CaST, 2-BT, Free-Recall	A, LM
Nusbaum et al., 2017	26.70 days per month	7.0 years / 15.97 years old	More than 0.5 day	365.0 days	FACT, TS	A, EF
Mercuri et al., 2018	NR	17.2 years old	More than 1 day	Never used CN	TMT, HSCT, VF	EF

CCU = Chronic Cannabis Users; CG = Comparator Groups; SM = Smoking Episodes; CN = Cannabis; NR = Not Reported; ERT = Eye Reading Test; VPMT = Video-based Prospective Memory Test; SOA = Stimulus Onset Asynchrony; CVLT = California Verbal Learning Test; DS = Digit Span; SDMT = Symbol Digit Modality Test; RAVLT = Rey Auditory Verbal Learning Test; FPMT = Fruit Prospective Memory Test; RPMT = Reminder Prospective Memory Test; CPMT = Call-In Prospective Memory Test; RUFF = Ruff 2&7 Test; TMT = Trail Making Test; VF = Verbal Fluency; DF = Design Fluency; CWIT = Color Word Inhibition Test; IGT = Iowa Gambling Task; BART = Balloon Analog Risk Task; GST = Go-Stop Task; HVLT = Hopkins Verbal Learning Test; ST = Stroop Test; CaST = Cannabis Stroop Task; TOL = Tower of London; DSY = Digit Symbol Substitution Test; LCT = Letter Cancellation Test; SS = Spatial Span; SR = Spatial Recognition; SOS = Self-Ordered Search; SDRT = Spatial Delayed Response Task; FTT = Finger Tapping Test; COWAT = Controlled Oral Word Association Test; WCST = Wisconsin Card Sorting Test; 2-BT = Two-Back Test; FACT = Flexible Attentional Control Task; HSCT = Hayling Sentence Completion Test; A = Attention; EF = Executive Function; LM = Learning & Memory; TS = Stroop-like task switching.

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TABLE 7 POOLED EFFECT SIZE OF EACH NEUROCOGNITVE DOMAIN

			Effect size and 95% Confidence Interval				Test for Null (2 fail)		Heterogeneity			Bias
Neurocognitive Domains	**N**	**Studies**	**Effect size**	**SE**	**Lower limit**	**Upper limit**	**Z**	**P for Z**	**Q**	**P for Q**	**I^2**	**Fail Safe N**
Cognitive Impulsivity	159	4	0.30	0.14	0.02	0.58	2.11	0.04*	4.76	0.19	36.97	4
Motor Impulsivity	92	2	0.05	0.15	-0.24	0.34	0.37	0.72	0.001	0.98	0.00	N/P
Non-Planning Impulsivity	35	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cognitive Flexibility	168	6	0.33	0.11	0.12	0.54	3.04	0.002**	5.22	0.39	4.29	10
Attention	810	6	0.16	0.07	0.02	0.30	2.27	0.023*	5.52	0.36	9.48	9
Short Term Memory	236	6	0.48	0.08	0.31	0.65	5.63	0.000*	4.17	0.53	0.00	44
Long Term Memory	199	4	0.43	0.14	0.16	0.69	3.12	0.002**	5.65	0.13	46.92	16
Emotional Cognition	30	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*P = Significance; * significant at the p < 0.05 level; ** significant at the p < 0.01 level; N = Total number of studies; N/A = Data is not available to perform a meta-analysis as one needs more than 1 study to determine effect size; N/P = Not possible as one needs more than 2 studies to determine publication bias.*

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