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REVIEW

ADDICTION SSA

Evidence on the acute and residual neurocognitive effects of cannabis use in adolescents and adults: a systematic meta-review of meta-analyses

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Abstract

Background: Cannabis is among the most consumed psychoactive substances worldwide. Considering changing policy trends regarding the substance, it is crucial to understand more clearly its potential acute and residual adverse effects from a public health viewpoint. Cognitive function is one of the targeted areas with conflicting findings. This meta-review measured the magnitude of acute and residual effects of cannabis on cognition in adolescents and adults provided by meta-analyses and evaluated quality of evidence.

Methods: A systematic search was performed in PubMed, PsycINFO, Web of Science and Google Scholar. Meta-analyses were included if they quantitatively examined the performances of users from the general population on cognitive tasks.

Results: The search retrieved 10 eligible meta-analyses (71 effects sizes, n = 43 761) with evidence ranging from low to moderate quality, which were categorized into domains of cognitive functions: executive functions (k = 7), learning and memory (k = 5), attention (k = 4), processing speed (k = 5), perceptual motor function (k = 2) and language (k = 2). Verbal learning and memory displayed the most robust evidence and were most impaired by acute cannabis intoxication that persisted after intoxication passed. Small-to-moderate acute and residual adverse effects were reported for executive functioning. Cannabis use led to small deficits in inhibitory processes and flexibility, whereas small-to-moderate deficits were reported for working memory and decision-making. Evidence regarding processing speed and attention has shown that cannabis administration induced small-to-moderate adverse effects and residual neurocognitive deficits were observed in heavy cannabis-using youths. Results showed no significant difference between cannabis users and non-users on language, and small-to-moderate effects for simple motor skills.

Conclusion: Meta-analytical data on the acute effects of cannabis use on neurocognitive function have shown that cannabis intoxication leads to small to moderate deficits in several cognitive domains. These acute impairments accord with documented residual effects, suggesting that the detrimental effects of cannabis persist beyond acute intake.

KEYWORDS
Adults, cannabis use, meta-analyses, meta-review, neurocognitive effects, youths

INTRODUCTION

Cannabis is the most consumed psychoactive substance in the world after alcohol and nicotine use, with approximately 3.8% of the worldwide population using the substance [1]. Cannabis use remains an illegal substance in most countries. Nevertheless, an increasing number of countries and US states have supported the legalization of cannabis for medical and/or recreational purposes, reflecting changing public attitudes towards its perceived safety and social acceptability [2, 3]. Although loosening of restrictions on cannabis has been outlined to lessen human, social and economic costs related to the criminal justice system [4], it has similarly provoked apprehensions about possible public health consequences. This has been especially the case for adolescents and young adults as they display the highest rates of cannabis use [5–7] and they are in a particularly critical period of vulnerability to cannabis-induced cerebral function alterations, as the brain undergoes significant developmental changes throughout this period [8]. Moreover, paralleling changes supporting cannabis legalization, literature has shown increases in the prevalence of cannabis use and cannabis use disorder (CUD) during the past decade [2, 9–12]. Most of the psychoactive and mood-related effects in addition to the addictive properties of cannabis are mediated by Δ-9-tetrahydrocannabinol (THC), which is the main pharmacologically active cannabinoid in the cannabis plant [13]. Research has shown that THC exerts a wide range of transient and dose-dependent effects by acting on the central nervous system primarily via cannabinoid receptor type 1 (CB1) [14–17]. CB1 receptors mediate inhibitory action on the release of a variety of neurotransmitters (e.g. serotonin, acetylcholine, dopamine and glutamate) and are situated throughout the cerebral cortex, with dense concentrations in regions (e.g. hippocampus, amygdala, basal ganglia and cerebellum) related to cognitive and psychomotor functioning [13, 18, 19]. THC, thereby, functions as a partial agonist at CB1 receptors, inhibiting the release of neurotransmitters typically regulated by endocannabinoids bringing forth cognitive alterations [19, 20]. Recently, there have been concerns regarding the increased potency in cannabis as measured by the proportion of THC content in relation to cannabidiol (CBD) content (THC:CBD ratio) [21, 22], which has been associated with several adverse health outcomes (e.g. psychosis, CUD, cognitive impairments) [23–25]. Understanding the potential acute and residual adverse effects of cannabis use from a public health viewpoint has emerged as a priority considering changing policy trends regarding the substance. Cognitive function is one of these targeted areas that, nevertheless, has conflictual findings.

Cannabis consumption is often related to impairments in cognitive function [26], although cannabis does not seem to lead to deficits in cognitive domains equally and there are unresolved conundrums that need to be further addressed to grasp the differential acute and residual effects of cannabis use on cognition. Cannabis administration studies have led to substantial contributions to the understanding of the acute effects of cannabis; that is, cannabis-induced intoxication [20]. Most of these administration studies have reported impaired cognitive performances following cannabis/THC administration [27]. Indeed, experimental studies in which healthy volunteers have received varying doses of cannabinoid partial agonists have suggested negative impacts of cannabis use on executive functions, learning and memory, attention and psychomotor function, and some of these impairments may thereby be weakened with CB1 antagonists [26, 28, 29]. Several reviews [20, 26, 27, 30, 31] have consistently shown that the acute cannabis effects were most often reported in the domain of verbal learning and memory, although less constantly for working memory. Other domains that have similarly been impaired include inhibitory processes, attention and psychomotor functioning. However, reported effects on executive functioning domains, such as planning, reasoning, interference control and decision-making, have provided more mixed literature. Authors have also noted that the acute effects of cannabis on cognition may be moderated by different factors such as cannabis composition (e.g. THC:CBD ratio), genetics and cannabis use history [20]. For instance, studies investigating the effects of acute THC administration have provided evidence of larger cognitive deficits in non-users and recreational cannabis users in comparison to more chronic cannabis users [28, 32–34]. Accordingly, a review noted similar findings among cannabis users when evaluating the development of tolerance, which indicated that cognition was most impaired upon acute intoxication and that there was minimal tolerance [35].

Although acute intoxication can last several hours, research has revealed that THC is a fat-soluble compound that may be stored in body fat and, thus, gradually released into the bloodstream for months [36, 37]. Such a characteristic has urged, among others, research to evaluate potential '*residual*' cognitive effects that persist after acute intoxication has passed [38]. Indeed, studies have shown impaired cognition that persists beyond the acute intoxication period in both adult and adolescent cannabis users, particularly in tasks related to learning and memory, attention and executive function [30, 39–42]. Several systematic reviews have examined the long-term effects of cannabis use on cognition. Broyd *et al.* [26], Nader *et al.* [43] and Sorkhou *et al.* [31] identified verbal learning and memory as well as executive functions as the domains most consistently impaired with long-term cannabis use. Evidence pertaining to other domains, including attention and processing speed, led to more divergent findings. These reviews concluded that neurocognitive impairments may be dose-dependent, particularly for domains related to memory [31], and effects may persist for at least 1 week when cannabis use is chronic, although these deficits are often resolved with long abstinence periods [26, 43]. Furthermore, Ganzer *et al.* [40] noted that findings regarding neurocognition specifically after a prolonged period of abstinence (more than 14 days) were heterogeneous. Most studies reported some deficits in attention or concentration in abstinent cannabis users, as well as in different aspects of memory. Findings in the

domains of inhibition, visuospatial functioning and decision-making were less clear-cut. Furthermore, results suggested that heavy use was found to be more consistently associated with effects in diverse domains on cognition than early age of onset [20]. While there is more consensus that acute cannabis intoxication may result in cognitive deficits, residual cognitive effects from cannabis are still debated, particularly after periods of abstinence.

Numerous meta-analyses have therefore been emerging on adolescent and adult samples to attempt to shed light on the effects of acute and non-acute cannabis use on cognitive functioning. In this sense, meta-analyses are important as they provide a tool to investigate the magnitude of an effect, which may aid to establish the extent to which there is an association between variables [44]. Meta-analytical approaches allow the statistical integration of results from multiple individual studies that, on their own, may have been insufficiently powered to detect the effects of cannabis. Meta-analyses also address inconsistencies by standardizing outcomes and diminishing the effects of varying statistical power. Nevertheless, emerging meta-analyses carried on the subject with varying levels of quality of evidence have similarly produced discordant findings on differential cognitive functions. Overall, mixed evidence for several cognitive domains may be due to variability in the control variables employed, cognitive tests utilized, operationalization of cognitive domains, participants' cannabis use histories, varying types of cannabinoids and cannabis exposure heterogeneity [20, 31]. To summarize and untangle the effects provided by meta-analyses, we conducted a critical meta-review to investigate the magnitude of both acute and residual effects of cannabis on cognitive functioning in the general population provided by meta-analyses. We also evaluated the quality of evidence as well as possible confounding factors. Markedly, we have opted to distinguish between higher-order cognitive functions, as cannabis use has been shown to lead to domain-specific deficits. In this sense, we hypothesized that the cognitive domains most affected by cannabis use would be verbal learning and memory in addition to executive functions (i.e. working memory, response inhibition).

METHODOLOGY

Search strategy

A search was independently carried out by two graduate students (L.D. and S.G.) in the electronic databases of PubMed, PsycINFO, Web of Science and Google Scholar from each database's inception to May 2021. Search terms were inclusive for neurocognitive functions (e.g. 'cognition', 'neurocognition', 'working memory'), cannabis use (e.g. 'cannabis', 'THC', 'cannabinoid') and review design literature (e.g. 'review', 'systematic review', 'meta-analysis'). For the purpose of this manuscript, we only selected meta-analytical approaches that were conducted on studies including individuals from the general population (i.e. not on psychiatric samples). No restrictions for setting, date or geographical location were applied. English and French language sources were eligible. Authors of articles to which we had restricted access were contacted. The search syntax was tailored for each database. For the specific search strategy adapted to each database, please see Supporting information. A secondary search was conducted by reviewing the reference lists of reviews on the subject.

Study eligibility

Meta-analyses were included if they quantitatively examined the effects of cannabis use on any neurocognitive domain (or subdomain) in studies involving healthy individuals from the general population. The comparison group was defined within each meta-analysis as either healthy individuals receiving a placebo or who never/minimally used the substance. We did not restrict the search to any specific neurocognitive domain nor any age group to maximize the number of meta-analyses and obtain a better overview of results. Both the acute effects of cannabis as evaluated by experimental administration studies and non-acute residual effects of cannabis as measured by comparative studies (i.e. cross-sectional, longitudinal studies) were included. To avoid overlap between meta-analyses, we generally selected a meta-analysis that was more recent and included more studies unless an older meta-analysis included a particular subanalysis that was of interest and not addressed in a more recent meta-analysis. Study eligibility was conducted both by L.D. and S.G. independently and discussions on the inclusion of meta-analyses were held with a senior researcher (A.D.) to ensure consensus. Meta-analytical analyses were excluded if they (i) combined several substances together (polysubstance use); (ii) did not provide an effect size [standardized mean difference (SMD), Cohens *d* (*d*), Hedges *g* (*g*)] for the effects of cannabis use on particular cognitive domains, (iii) did not use neuropsychological tests/tasks to quantify cognitive impairments or (iv) included fewer than two studies per analysis.

Data extraction

Study information was extracted individually by L.D. and S.G. using a standardized form for the sample, effect sizes, outcome measured, control group, confounding factors (i.e. moderator analyses), heterogeneity (i.e. *Q*-statistics, I^2 index) and publication bias (i.e. funnel plot examination, Egger's test). See Supporting information for an overview of extracted data. Negative effect sizes were indicative of worse performances on cognitive tasks for individuals being administered or having used the substance. The effect sizes were categorized as small, moderate and large effects (0.2, 0.5 and > 0.8, respectively) [44]. Furthermore, L.D. and S.G. independently undertook quality assessment for the effect sizes reported in the meta-analyses using a set of criteria based on the Grading of Recommendations, Assessment, Development, and. Evaluation (GRADE) checklist [45–48]. We assigned lower scores to analyses that comprised small sample sizes (e.g. under 500 participants), conducted no moderator analyses (e.g. distinguished between current and life-time use, abstinence period, duration of use, age of onset) and reported substantial

heterogeneity, as well as the presence of publication bias and measured a higher rank neurocognitive function that was broadly defined, rather than specific subdomains. Although some meta-analyses may have included longitudinal studies, evidence provided was largely based on cross-sectional data (e.g. baseline data), which limited the quality of evidence. Any doubts on the rating of the quality of evidence were resolved by a discussion with A.D. Studies were assigned: very low quality, low, moderate-to-low, moderate, moderate-to-high and high. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to achieve a high standard of reporting data [49] (Supporting information). The review has not been pre-registered and thus results should be considered exploratory. Nevertheless, it is worth mentioning that our team has already used a methodology comparable to this one in a prior published meta-review [50].

RESULTS

Description of studies

The systematic search retrieved 2306 potential articles that were screened for eligibility after removing duplicates. Among the retrieved articles, 10 meta-analyses were selected providing 71 effects sizes [38, 51–59]. Each meta-analysis included two to 40 studies, with samples ranging between 65 and 5683 individuals (n = 43 761). The neurocognitive functions were categorized based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [60] for key domains of cognitive functions: (i) executive functions (k = 7), (ii) learning and memory (k = 5), (iii) complex attention (k = 4), (iv) processing speed (k = 5), (v) perceptual-motor function (k = 2) and (vi) language (k = 2). Within each of these higher rank cognitive functions were placed subdomains as defined by authors of the meta-analyses. The PRISMA flow-chart for the inclusion of studies in the meta-review is shown in Fig. 1. When several analyses were conducted within meta-analyses for a cognitive outcome, we retrieved one specific effect size estimate for the effects of (i) overall cognitive domain (merged subdomains of a higher rank cognition) and subdomains of a higher rank domain; (ii) type of cannabis exposure (e.g. acute CB1 administration, chronic use, abstinence); (iii) particular age groups (e.g. adolescents and young adults, only adults). Main results reported in the meta-analyses were cross-sectional in nature. Most findings were evaluated as being of low-to-moderate to moderate quality evidence. See Supporting information for a summary of the quality of evidence provided by the included meta-analyses.

Executive functions

Overall executive functions

Concerning the acute effects of cannabis, a meta-analysis by Zhornitsky *et al.* [58] comprising 13 studies found significant small-to-moderate diminished performances on executive functioning (e.g. Stroop-interference) for healthy adult volunteers administered partial CB1 receptor agonist compounds relative to the placebo group [g = −0.37; Confidence interval (CI) = −0.485, −0.254]. Evidence was graded as moderate quality due to the consideration of moderation analyses, the presence of no heterogeneity and the lack of publication bias.

Furthermore, the residual effects of frequent/heavy cannabis use were observed in a meta-analysis of 28 studies by Scott *et al.* [53] on a large sample of 5457 adolescents and young adults (SMD = −0.3, CI = −0.40, −0.20). Although the analysis comprised a large sample, the overall meta-analysis showed presence of publication bias and heterogeneity was not assessed, which resulted in evidence being evaluated as being of low quality.

A meta-analysis by Lovell *et al.* [51] comprising 15 studies on adults (n = 993, mean age 30 years, range = 20–56) found a small significant impairment (g = −0.18, CI = −0.31, −0.05) of regular daily cannabis use on overall executive functioning (e.g. Stroop task and Wisconsin card sorting test). Evidence was graded as moderate quality due to the consideration of moderation analyses, the presence of no heterogeneity and the lack of publication bias.

With regard to subanalyses within the same meta-analysis, this effect was found to increase for adults who had chronic cannabis use (g = −0.3, CI = −0.57, −0.03) and for individuals with an earlier age of onset of use defined as use before age 16 years (g = −0.27, CI = −0.53, −0.01). There was a small, albeit non-significant, negative effect for late-onset of use (g = −0.16; CI = −0.35, 0.03). Additionally, regarding the four studies on cannabis abstinence, it was reported that 25 days of abstinence was associated with a small non-significant effect (g = −0.18; CI = −0.44, 0.08).

Decision-making

More particularly related to decision-making (e.g. Iowa Gambling Task), evidence graded as being of low-to-moderate quality provided from the meta-analysis by Lovell *et al.* [51] including five studies on 208 adults, found a statistically significant negative moderate residual effect of regular daily cannabis on decision-making (g = −0.52, CI = −0.93, −0.11). The analysis showed moderate levels of heterogeneity, but no publication bias.

There was, however, no significant effect of age of onset for decision-making based on the analyses graded as low-to-moderate quality evidence (early-onset: g = −0.4, CI = −1.15, 0.35; late-onset: g = −0.46, CI = −1.14, 0.23) [51].

Response inhibition

Regarding response inhibition measured for instance with the Stop-Signal task, a meta-analysis by Zhornitsky *et al.* [58] consisting of 12 studies found significant small impairments for healthy adult volunteers administered partial CB1 receptor agonists in comparison to the placebo group (g = −0.294; CI = −0.414, −0.174). Although meta-

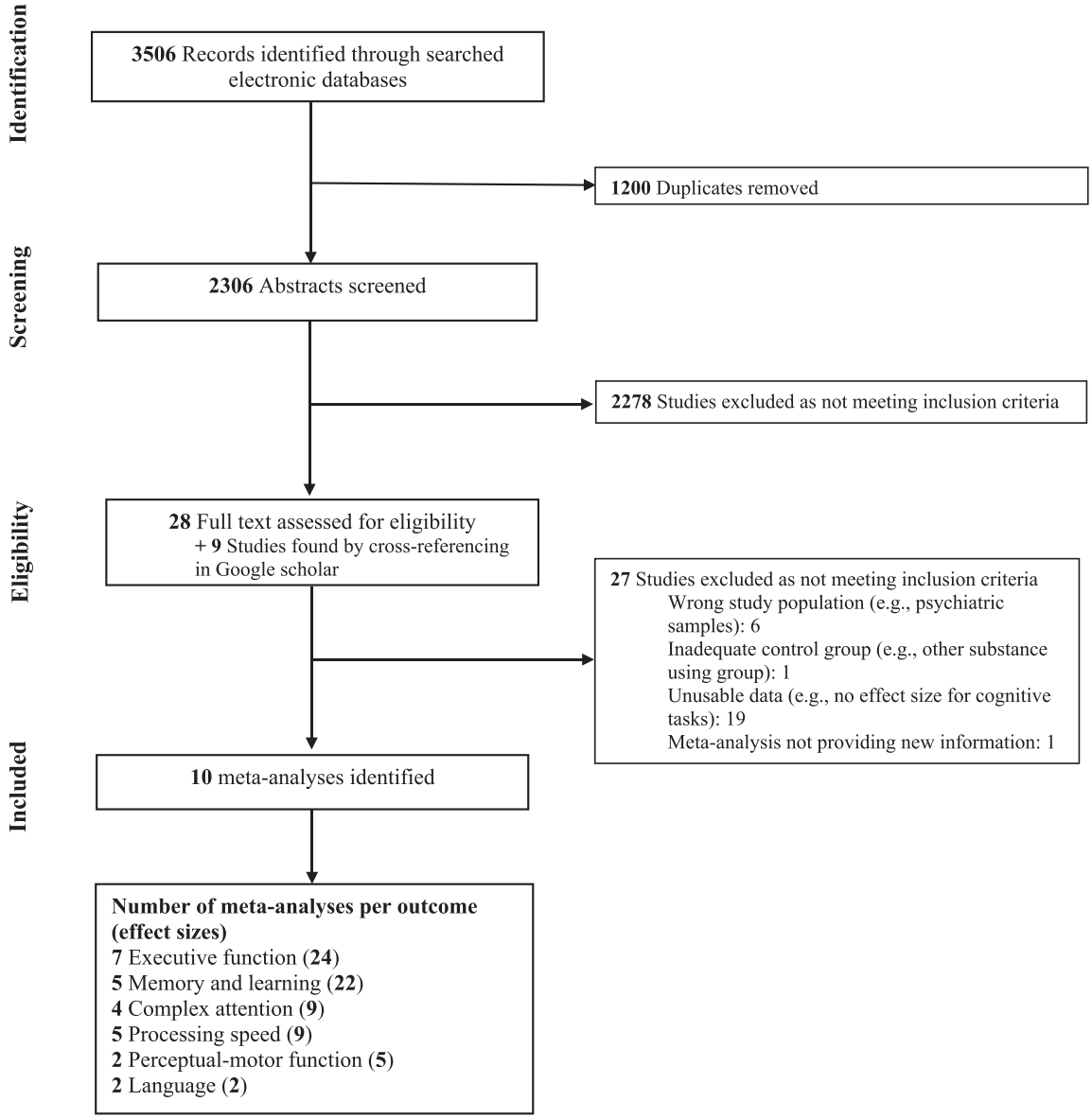

FIGURE 1 Flow-chart depicting the search strategy employed to find the meta-analyses to include in this review

regression analyses revealed that the impairments in response inhibition produced by such compounds were significantly influenced by sex, the result was no longer significant after correction for multiple comparisons. Evidence was graded as moderate quality due to the consideration of moderation analyses, the presence of no heterogeneity and the lack of publication bias.

Concerning the residual effects of cannabis use, the meta-analysis by Scott *et al.* [53] comprising 23 studies on 1353 adolescents and young adults under the age of 26 years showed a small residual negative effect (SMD = −0.25, CI = −0.38, −0.13) of frequent or heavy cannabis use on inhibition (e.g. D-KEFS color word interference–inhibition/switching). This analysis was graded as being of low quality notably due to the presence of publication bias on the overall meta-analysis and heterogeneity was not measured.

Nevertheless, when inhibition was evaluated solely with the Go/NoGo task and the Stop signal task in the meta-analysis by Smith *et al.* [54] on young adults (mean age = 26 years), there were no statistically significant inhibitory deficits that were apparent for chronic use. These analyses, based on two to six studies, were also graded as being of low quality, which generally showed no significant heterogeneity. However, no moderator analyses were conducted, and publication bias was not assessed.

Flexibility

A meta-analysis based on six studies on young adults (n = 168) revealed a significant small effect size of 0.33 (CI = 0.12, 0.54) in favour of the

control group for cognitive flexibility (e.g. Stroop color word task colour accuracy, controlled oral word association test correct words) [55]. This suggested an impaired capacity for chronic cannabis users to make appropriate behavioural decisions while switching between cognitive processes. This analysis was graded as being of low-quality evidence as no presence of heterogeneity and publication bias was assessed, although moderator analyses were not feasible for the authors.

Working memory

Concerning the acute effects of cannabis on working memory, evidence graded as low-to-moderate quality on 36 studies found significant small-to-moderate impairments in working memory (e.g. N-Back task, spatial working memory task) for healthy adult volunteers administered THC compounds relative to placebo (g = −0.36, CI = −0.52, −0.20) [59]. Though, the analysis showed presence of heterogeneity and publication bias was not reported.

Nevertheless, evidence graded as being of moderate quality based on six studies with adults (mean age = 30 years, range = 20–56 years) observed no residual effect of regular cannabis use on overall working memory (g = 0.01, CI = −0.23, 0.25) [51]. There was, moreover, no effect based on age of onset (early-onset: g = −0.12, CI = −0.43, 0.18; late-onset: g = 0.19, CI = −0.18, 0.57) [51]. These analyses were graded as moderate evidence due to the consideration of moderation analyses, the presence of no heterogeneity and the lack of publication bias.

Based on a larger sample size of young adult users (mean age = 26 years) provided from 39 studies (n = 4277), there was a very small significant effect highlighting worse ability for chronic cannabis users to hold/manipulate information and remember it following a short delay (d = −0.11, CI = −0.17, −0.04) [52]. Nevertheless, the effect was not significant for visual working memory based on seven studies (n = 454) [52]. These latter analyses were graded as being of low to low-to-moderate quality, mainly due to the presence of heterogeneity and lack of moderation analysis. However, there was no presence of publication bias.

Summary

In summary, the meta-analyses on overall executive functioning showed small-to-moderate effects for acute cannabis intake and small residual effects for regular cannabis use, with cannabis users displaying worse performance on tasks in comparison to controls. A higher magnitude of effect was found for chronic and earlier age of onset. Evidence was graded as being of low to moderate quality. When looking more profoundly into the subdomains of executive functioning, small deficits were observed for response inhibition (both acute and residual effect), flexibility (residual effect) and working memory (residual effect). There were small-to-moderate and moderate effects for working memory following acute intake and for decision-making in regular daily cannabis users, respectively.

Learning and memory

Visual learning

Concerning residual effects, evidence provided from a meta-analysis by Schoeler *et al*. [52], consisting of 19 studies (n = 3168) graded as being of low-to-moderate quality, found no statistically significant effect retrieved for visual immediate recall (d = −0.06, CI = −0.16, 0.04). Although there was no presence of publication bias, the overall meta-analysis displayed high heterogeneity.

Visual memory

Evidence provided from a meta-analysis by Schoeler *et al*. [52] consisting of 14 studies (n = 3365) graded as being of low-to-moderate quality found no statistically significant effect retrieved for visual delayed recall (d = −0.09, CI = −0.31, 0.13). Although there was no presence of publication bias, the overall meta-analysis displayed high heterogeneity.

Verbal learning

Evidence graded as being of low-to-moderate quality by Zhornitsky *et al*. [58], which comprised 14 studies of healthy adult volunteers, found moderate-to-large negative effects of acute cannabis use in comparison to placebo on verbal learning (g = −0.688, CI = −0.888, −0.488). There was presence of heterogeneity and publication bias.

Concerning residual effects, evidence evaluated to be of moderate quality provided from 11 studies (n = 704) on adult samples showed that regular daily cannabis use was associated with a small-to-moderate negative effect on verbal learning (g = −0.37, CI = −,0.52; −0.22) [51]. There was no presence of heterogeneity nor publication bias.

This was in accordance with evidence provided from a meta-analysis by Schoeler *et al*. [52] consisting of 40 studies (n = 3168) graded as being of low-to-moderate quality. Based on a large sample size, a small-to-moderate effect for verbal immediate recall was observed for young chronic cannabis users (d = −0.4, CI = −0.53, −0.27). Although consisting of a large sample size, the overall meta-analysis displayed high heterogeneity and publication bias.

A meta-analysis by Krzyzanowski *et al*. [56] further distinguished the effects of days of abstinence (i.e. fewer than 3 days, 3–7 days and more than 7 days of abstinence) on verbal learning. Results showed statistically significant small-to-moderate deficits for regular cannabis users on total immediate recall and short-delay free recall, which reached to moderate magnitude for abstinence up to 7 days. However, results were not significant for an abstinence period of more than 7 days. These analyses were evaluated to be of low-to-moderate to moderate quality evidence due to the lack of publication bias, moderator analyses and large sample sizes. Lower

quality of evidence was due to the presence of heterogeneity and smaller sample sizes.

Verbal memory

Evidence graded as being of moderate quality by Zhornitsky *et al*. [58], which comprised 12 studies of healthy adult volunteers found moderate impairments of acute cannabis use in comparison to placebo on verbal memory (g = −0.513, CI = −0.653, −0.374). Although not significant, there was a trend towards significance for publication bias and moderate heterogeneity.

Concerning residual effects, evidence provided from a meta-analysis by Schoeler *et al*. [52], consisting of 38 studies (n = 3365) graded as being of low-to-moderate quality, noted a small-to-moderate impairment on verbal delayed recall for young chronic cannabis users (d = −0.36, CI = −0.49, −0.22).

The meta-analysis by Krzyzanowski *et al*. [56] showed statistically significant small-to-moderate deficits for regular cannabis users on long-delay free recall, which reached to moderate magnitude for abstinence up to 7 days. However, results were no longer significant for an abstinence period of more than 7 days.

Prospective memory

A meta-analysis by Schoeler *et al*. [52], including five studies (n = 294) with evidence graded as being of low quality, showed pronounced impairments for chronic cannabis users on prospective memory in comparison to controls (d = −0.61, CI = −0.85, −0.38). Although there was substantial overall heterogeneity for the analysis, there was no presence of publication bias.

More precisely, a meta-analysis by Platt *et al*. [57], including six studies (n = 356) and four studies (n = 159), further distinguished between event- and time-based prospective memory, respectively. There was a small and moderate-to-large effect size, with the cannabis groups performing worse on both types of tasks (event-based: SMD = −0.31, CI = −0.63, −0.004 and time-based: SMD = −0.70, CI = −0.80, −0.61). Evidence, graded as being of low quality, showed no presence of heterogeneity; however, moderator analyses were not conducted and publication bias was not assessed.

Summary

In summary, evidence for learning and memory was generally graded as being of low-to-moderate quality. There were no significant residual effects of cannabis use on visual learning and memory. Small-to-moderate impairments were generally observed for verbal learning and memory for regular and chronic cannabis use in adolescents and adults. Larger negative effects were reported for acute use relative to placebo. Small-to-high magnitude residual impairments were also observed for prospective memory in cannabis users.

Complex attention

Concerning the acute effects of cannabis, a meta-analysis by Zhornitsky *et al*. [58] consisting of 28 experimental studies found significant small worse performances in attention (e.g. continuous performance test–omission errors) for healthy adult volunteers administered partial CB1 receptor agonist compounds relative to placebo (g = −0.223, CI = −0.348, −0.099). Although meta-regression analyses showed no relationship between dosage and cognitive performance in the oral administration studies, they found a trend towards a significant difference between oral administration and other routes of administration. Evidence was graded as moderate quality due to the consideration of moderation analyses and the lack of publication bias, but there was a high level of heterogeneity.

When distinguishing between the effects of acute cannabis intoxication on sustained and divided attention, both cognitive functions were found to be mildly impaired in healthy adult volunteers in comparison to the placebo group (sustained attention: g = −0.23, CI = −0.37, −0.10; divided attention: g = −0.28, CI = −0.36, −0.20) [59]. These analyses were graded as being of moderate and low-to-moderate quality, respectively. Whereas moderate quality was provided due to a larger sample size, both analyses showed no presence of heterogeneity and publication bias was not measured.

Evidence of low-to-moderate quality comprising five studies (n = 221) on adults found no significant effects on overall attention between regular cannabis users and non-users (g = 0.05, CI = −0.21, 0.31). There were, moreover, no statistically significant effects for more chronic long-term use nor for age of onset and long abstinence [51]. These analyses, graded as low-to-moderate quality, had small samples, but considered moderator analyses, and lacked heterogeneity as well as publication bias.

Conversely, based on evidence graded as being of low quality, a small significant deficit was observed for young frequent or heavy cannabis users (SMD = −0.21, CI = −0.31, −0.12) in the meta-analysis by Scott *et al*. [53] comprising of 30 studies (n = 5683).

Summary

In summary, the meta-analyses on overall attention functioning showed small negative effects in healthy adult volunteers administered partial CB1 receptor agonists (acute effect) and in frequent/heavy adolescent as well as young adult cannabis users (residual effect), although there were no residual effects for regular and chronic adult cannabis users, regardless of abstinence period and age of onset. Evidence was generally graded as being of low-to-moderate quality.

Processing speed

Concerning the acute effects of cannabis, evidence graded as being of moderate quality provided by Zhornitsky *et al*. [58], which comprised 38 studies of healthy adult volunteers, found small-to-moderate

impairments in processing speed following acute cannabis use in comparison to placebo (g = −0.384, CI = −0.492, −0.276). There was no publication bias, but presence of high heterogeneity. Meta-regression analyses showed that a greater ratio of male to female was associated with greater deficits in speed of processing. Although there was no relationship between dosage and processing speed in the oral administration studies and smoked administration studies, there was a trend towards a significant difference between oral administration and other routes of administration, with smaller deficits being observed in the oral administration studies.

When distinguishing between the effects of acute cannabis intoxication on information processing and reaction time, both were significantly impaired in healthy adult volunteers in comparison to the placebo group (information processing: g = −0.38, CI = −0.55, −0.21); reaction time: g = −0.28, CI = −0.43, −0.13) [59]. These analyses were graded as being of moderate and low-to-moderate quality, respectively. Evidence was graded as being of low-to-moderate quality.

Evidence graded as being of moderate quality showed no statistically significant effect of residual cannabis use, both regular and chronic use, nor abstinence and age of onset on information processing speed in adult samples [51]. There was no publication bias, nor heterogeneity.

Based on evidence graded as being of low quality, a small significant processing speed impairment was observed in young frequent or heavy cannabis users (SMD = −0.26, CI = −0.38, −0.15) [53].

However, residual effects were not maintained in time based on any type of abstinence (e.g. > 25 days) in adolescents and adults [38]. Evidence was graded as being of low-to-moderate quality showing no heterogeneity.

Summary

In summary, the meta-analyses on processing speed showed small-to-moderate negative effects in healthy adult volunteers following acute intake and in frequent/heavy adolescent and young adult cannabis users in comparison to control groups, although there were no residual effects for regular and chronic cannabis use in adults, regardless of abstinence period and age of onset. Evidence was generally graded as being of low-to-moderate and moderate quality.

Perceptual motor function

Evidence graded as being of low-to-moderate quality by McCartney *et al*. [59], which comprised 12 studies of 310 healthy adult volunteers, found small-to-moderate impairments of acute cannabis use in comparison to placebo (g = −0.36, CI = −0.60, −0.12) in fine motor function (e.g. finger-tapping test, grooved pegboard). Publication bias was not reported and there was moderate heterogeneity.

A meta-analysis by Schreiner *et al*. [38] (k = 4, n = 351), with evidence being graded as being of low-to-moderate quality, found a significant small effect for simple motor, suggesting worse performance for adolescent and adult cannabis users in comparison to controls (g = −0.34, CI = −0.57, −0.11). There were, however, no significant long-term residual effects after 25 days of abstinence (g = −0.19, CI = −0.53, 0.14) [38]. These analyses showed no presence of heterogeneity.

Evidence evaluated to be of low-to-moderate quality from the meta-analysis by Schreiner *et al*. [38] (k = 10, n = 650) showed that there were no significant effects (g = 0.02, CI = −0.15, 0.18) that were noted between groups on perceptual-motor abilities (e.g. block design, object assembly). There were no significant long-term residual effects after 25 days of abstinence (g = 0.09, CI = −0.09, 0.27) [38]. These analyses showed no presence of heterogeneity.

Summary

In summary, the meta-analyses with evidence graded as being of low-to-moderate quality showed small-to-moderate effects for simple motor skill, with no long-term residual effects, and no effect was observed for perceptual-motor skills.

Language

Evidence graded as being of low quality in a large sample of adolescents and young adults (k = 15, n = 1008) found a small, but non-significant, negative effect (SMD = −0.14, CI = −0.27; 0.001) of frequent/heavy cannabis use on language (e.g. D-KEFS verbal fluency test, letter fluency) [53]. Heterogeneity was not assessed and publication bias for the overall study showed presence of publication bias.

There were no long-lasting residual effects (k = 4, n = 380) for more than 25 days of abstinence in adolescents and adults (g = −0.1, CI = −0.31, 0.11) [38]. Evidence was evaluated to be additionally of low quality due to the small sample size and lack of assessment of publication bias for the specific subanalysis. There was no heterogeneity.

Summary

In summary, the meta-analyses on language functioning generally showed no effects for cannabis use on language. Evidence was graded as being of low quality.

DISCUSSION

The objectives of this critical meta-review were to synthesize the current state of evidence on the acute and residual neurocognitive effects of cannabis use on adolescents in addition to adults from the general population and to assess the quality of evidence provided by meta-analytical studies. Although the effect sizes and cognitive consequences varied, our meta-review enabled us to show both acute and

residual effects of cannabis on many aspects of cognition provided from meta-analyses being generally graded as being of low-to-moderate to moderate quality.

First, limited evidence mainly showed no significant difference between cannabis users and non-users in domains of language and perceptual-motor functioning. At most, mild impairments that did not remain significant after 25 days of abstinence were observed. Secondly, only mild detrimental effects on attentional processing were reported in studies on healthy adults following acute cannabis administration and on heavy cannabis-using youths. Thirdly, better quality of evidence regarding speed of processing showed that cannabis administration seemed to provoke mild-to-moderate adverse effects that were smaller with oral administration in comparison to other routes of administration (e.g. smoked). Residual neurocognitive deficits in this domain were also noted in heavy cannabis-using youths. Hence, cannabis may disrupt both attention and speed of processing by its effects on CB1 receptors in frontoparietal and frontostriatal regions [61–63]. Similarly, small-to-moderate acute and residual adverse effects were reported for executive functioning. This is not unexpected, given that executive functions are subserved by the prefrontal cortex in which there is a higher density of CB1 receptors [19, 64–66]. More specifically, cannabis use led to small deficits in inhibitory processes and flexibility, whereas moderate deficits were reported for working memory and decision-making. Lastly, learning/memory, mainly in relation to verbal subsets, were the cognitive domains with most robust evidence and most impaired by acute cannabis intoxication that persisted after acute intoxication passed. Notably, this diminished ability to learn, retain and retrieve verbal information may have repercussions for users' occupational functioning, independent living and ability to navigate through their daily life adequately [56]. Cannabis may impair these domains via their action at CB1 receptors in the prefrontal and medial temporal regions [66–68]. This is in accordance with neuroanatomical alterations observed among regular cannabis users in these regions in addition to differences in neural activation when completing cognitive tasks, such as verbal memory, under the influence of cannabis, without necessarily observing a corresponding difference in task performance [19, 64, 65, 68–72]. Accordingly, the meta-analysis by McCartney *et al.* [59] showed that regular cannabis users experienced less acute cognitive impairments than other types of cannabis users, consisting mainly of occasional users. Taken together, most of the negatively impaired domains that were reported with acute intoxication, such as verbal learning and memory as well as executive functions, were most impaired in studies examining the residual effects of cannabis in cannabis users. Though, it is encouraging that some evidence indicates that residual effects may probably be remediated with prolonged abstinence, as it suggests that the effects may be somewhat reversible after abstinence. It is, nevertheless, worth mentioning that although some regular cannabis users may attempt to quit, most have begun to use the substance early on in their life and may have already obtained reduced educational attainment, thereby reducing their options in adulthood [73–75]. Moreover, the meta-analysis by Scott *et al.* [53] reported that help-seeking cannabis users in treatment displayed moderate deficits in cognition, which suggests lasting residual effects of cannabis use in specific sub-samples that should not be overlooked.

Despite the findings provided in this meta-review, several elements need to be discussed when interpreting results. First and foremost, the meta-analyses discussed comprised cross-sectional data with several analyses having relatively small sample sizes, which limits the inference of a causal relationship between cannabis use and cognition as well as the generalizability of results. When considering the sample, some analyses were conducted solely on youths or solely on adults, whereas some mixed age groups together. This is important, as the magnitude of cognitive dysfunction may be dependent upon the particular age groups being analyzed. For instance, this meta-review showed that the effects of cannabis use on working memory and complex attention were evident when considering studies on youths alone and not those that comprised of larger age ranges. Age of onset is correspondingly an important issue to consider, with some evidence showing larger effects for earlier cannabis use onset, which is not surprising given that prior reviews have also concluded that frequent use of cannabis impairs cognitive functioning in several domains, with greater deficits associated with adolescent versus adult onset of use [40, 76–78]. Furthermore, although sex differences in cannabinoid metabolism and action have been recognized, these differences were not systematically accounted for in studies [39], a point that was addressed in the meta-analysis by Zhornitsky *et al.* [58]. Secondly, these meta-analyses are hampered by inconsistencies in the tests administered among included studies, which creates challenges in assigning outcomes into specific cognitive domains. Analyses presented should be interpreted cautiously due to the heterogenous tests used to analyze the same cognitive function, which may vary in complexity and sensitivity. Thirdly, research has also been limited by variation in how cannabis exposure data have been collected. With the increase in the potency of cannabis contributing to a great variability regarding cannabis ingredients and concentrations consumed by users, it is essential to promptly report cannabis use parameters, such as dose, frequency of use, duration of use and route of administration, as they may interact to mediate the neurocognitive impairments of the substance [51–53, 56, 58, 59]. Also, many studies have not reported cannabis dependence and withdrawal, which should be documented; these factors can influence cognitive outcomes and neural correlates [51]. The varying ratios of THC and CBD need to be similarly considered, as these compounds appear to have different and opposing pharmacological effects [79]. Overall, studies should adhere to recommendations on minimum reporting criteria for cannabis use research [80]. This variability is notably observed in the heterogeneous criteria used when classifying subjects as cannabis users versus non-users (e.g. arbitrary minimal amount, once a life-time) or heavy versus light users leading to unavoidable comparator issues that can influence results, and therefore the results of meta-analyses. For some meta-analyses on residual effects, the definition for the comparison groups were more explicit (e.g. individuals who had never used cannabis or who had minimal use during their life-time (e.g. fewer than 50 times [55]), whereas this was not the case for other meta-analyses

(e.g. [38, 53]). To exclude possible confounding factors related to acute effects of the substance on the day of testing and to focus upon the residual effects of cannabis use, some authors have set a threshold of abstinence period before testing (e.g. strict period of at least 12 hours without using cannabis [55]). Lastly, the possibility that the adverse neurocognitive effects of cannabis use are attributed to confounding factors (e.g. other substance use) cannot be dismissed [31].

Although most of the evidence on the cognitive sequelae of cannabis use has been provided by cross-sectional data associated with methodological limitations, a growing number of longitudinal studies, which are useful to address causal inferences, have emerged. This has led to several reviews examining, among others, evidence provided by prospective designed studies [20, 27, 31, 81]. For instance, Bourque *et al*. [27] noted similar findings to those observed in cross-sectional data. Indeed, most studies showed declines in both executive functioning and verbal learning/memory [82–95], while results were less consistent for processing speed [82, 85, 88, 90, 94–96]. Furthermore, longitudinal data have similarly shed light on the hypotheses that have been put forth to explain the association between cannabis use and cognitive functions (see Bourque *et al*. [27] for an overview). A first hypothesis, that has received mixed evidence, specifies that cannabis use leads to persistent cognitive impairments. These neurotoxic effects last although cannabis users reduce their intake or quit altogether. While some longitudinal studies suggest that cognitive deficits resolve following abstinence [92, 94], other studies have confirmed that cannabis use frequency led to subsequent long-term cognitive decline (i.e. executive function) regardless of prolonged cannabis intake, while adjusting for covariates [84, 87, 97]. Following, the premorbid cognitive vulnerability hypothesis proposes that individuals at increased risk of using the substance more regularly already presented cognitive deficits before cannabis use onset. Several studies have shown that specific cognitive impairments (i.e. memory and executive functions) seemed to incline individuals to earlier onset of use in addition to more frequent use in comparison to non-using individuals [83–86, 98]. However, such findings were not evident in all studies [82, 87, 97, 99, 100] and some studies more probably support the common antecedent hypothesis [86, 98], which postulates that common factors (e.g. externalizing behaviour) may predispose individuals to both cannabis use and cognitive deficits in users. Hence, results from longitudinal co-twin studies have suggested that cannabis use may not necessarily cause neurocognitive decline, but rather that factors related to family background, such as genetic and shared environmental factors, may more clearly explain worse cognitive performances amid cannabis users [86, 98]. Lastly, the concurrent model postulates that the use of cannabis is associated with worse cognitive performances in the short term when controlling for pre-morbid cognitive function and that reduction in use or abstinence may relieve these impairments. While only a few studies reported no concurrent effect [85, 100], several studies adjusting for several factors, including premorbid cognitive performances, other mental health comorbidities, substance use, academic achievement and socio-economic status, have indeed shown that cannabis use is associated with cognitive impairments (e.g. executive function, memory, processing speed) both in the short and long term after cannabis use onset [82, 84, 88, 92, 94, 97, 99, 101]. Moreover, increases in the frequency of cannabis use are associated with lower performances in executive function for the same assessment period [83–85]. Taken together, better-quality evidence provided from longitudinal studies is in accordance with cross-sectional data and has shown varying levels of supports for the different non-mutually exclusive hypotheses.

CONCLUSION

To conclude, meta-analytical data on the acute effects of cannabis use on neurocognitive function have shown that cannabis intoxication leads to small to moderate deficits in numerous cognitive domains, most notably executive functions, verbal learning and memory and processing speed. These acute impairments are in accordance with the residual effects that have been documented in several meta-analyses suggesting that the detrimental effects of cannabis persist beyond the period of acute intake. Several measures may be taken to mitigate the cognitive risks of cannabis in the general population. For instance, health professionals should be informed of the potential cognitive risks associated with cannabis use and further diffuse their knowledge to their treating clientele through psychoeducation, while screening for problematic patterns of use. In those with problematic use, there are several evidence-based treatments, including motivational interviewing, that may be offered [102]. Conversely, it may also be potentially useful to implement cognitive remediation programs in cannabis users with more severe patterns of use to improve cognition. Additionally, as youths remain particularly susceptible to the effects of cannabis, school settings should put in place prevention and intervention measures to educate students on cannabis use and discourage them from using the substance in a chronic manner. Nevertheless, in practical terms more research is needed to examine whether observed deficits in performances are also expressed in impairments in daily life (i.e. forgetting to carry through intended tasks, academic difficulties or work-related errors, car accidents). Therefore, several questions remain to be addressed to more clearly understand the association between cannabis and cognition. Future research into the effects of cannabis use on neurocognitive performance should focus upon continuing to control for important confounds. While some meta-analyses investigating the residual cognitive effects in cannabis users have found that deficits do not persist following prolonged abstinence, additional high-quality prospective study designs following cognitive functioning from current use through cessation of use during long periods of abstinence are required [31]. Moreover, withdrawal symptoms need to be assessed for and included in subsequent analyses. As age of onset has been inconsistently associated to cognition functioning, more studies need to further investigate whether earlier age of onset predicts worse cognitive function in adulthood, whether pre-existing cognitive profiles may predict earlier age of onset or whether there is a bidirectional relationship altogether [20]. Studies of the effects of cannabis use in late adulthood and the elderly population have been limited and require further attention, mainly as cannabis

use in the population has been increasing [103]. The effects of cannabis use on cognition in older populations may be more complicated by several factors related to ageing, such as an increased selection of cannabis with high-CBD content as well as age-related changes in the dopamine system, for instance, in addition to brain morphology and function that are also affected by cannabis use [104, 105]. Additionally, future studies should continue to examine the cognitive effects of different cannabis compositions and potencies, as studies on the acute effects have yielded inconsistent findings and studies on residual effects have rarely examined these important elements. Because cannabis potency has been rising [106], further understanding the effects of different cannabis compositions or potencies is increasingly critical. Similarly, there are not enough studies on the cognitive deficits associated with cannabis in people with a cannabis use disorder. Often, studies are conducted in the general population. Besides, although there are increasing studies where oral cannabinoids or sublingual cannabinoids, for instance, are offered to patients with chronic pain and other health problems, there remains little to no knowledge of the cognitive effects of these cannabinoids. Also, different areas of cognition not listed in the current meta-analysis that have been less investigated, such as social cognition, require more research [107]. In all, refinements in future methodologies would allow the performance of rigorous meta-analyses on the effects of cannabis on various cognitive domains that may ultimately inform clinicians and policymakers.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

Laura Dellazizzo: Conceptualization; data curation; methodology. **Stephane Potvin:** Conceptualization; methodology; supervision. **Sabrina Giguère:** Conceptualization; data curation; methodology; validation. **Alexandre Dumais:** Conceptualization; methodology; supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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