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# Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study

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**Abstract**

The possible medicinal use of cannabinoids for chronic diseases emphasizes the need to understand the long-term effects of these compounds on the central nervous system. We provide a quantitative synthesis of empirical research pertaining to the non-acute (residual) effects of cannabis on the neurocognitive performance of adult human subjects. Out of 1,014 studies retrieved using a thorough search strategy, only 11 studies met essential *a priori* inclusion criteria, providing data for a total of 623 cannabis users and 409 non- or minimal users. Neuropsychological results were grouped into 8 ability domains, and effect sizes were calculated by domain for each study individually, and combined for the full set of studies. Using slightly liberalized criteria, an additional four studies were included in a second analysis, bringing the total number of subjects to 1,188 (i.e., 704 cannabis users and 484 non-users). With the exception of both the learning and forgetting domains, effect size confidence intervals for the remaining 6 domains included zero, suggesting a lack of effect. Few studies on the non-acute neurocognitive effects of cannabis meet current research standards; nevertheless, our results indicate that there might be decrements in the ability to learn and remember new information in chronic users, whereas other cognitive abilities are unaffected. However, from a neurocognitive standpoint, the small magnitude of these effect sizes suggests that if cannabis compounds are found to have therapeutic value, they may have an acceptable margin of safety under the more limited conditions of exposure that would likely obtain in a medical setting. (*JINS*, 2003, 9, 679–689.)

**Keywords:** Cannabis, Cannabinoids, Marijuana, THC, Cognitive effects, Neuropsychology, Meta-analysis

## INTRODUCTION

Recent developments in the scientific and public sectors have reawakened the possibility that cannabis compounds or their synthetic analogues may be proposed as treatments for several medical conditions. At the research level, the discovery of the first cannabinoid receptor (CB1) in 1986, and a second receptor (CB2) in 1992, paved the way to the identification of endocannabinoid-signaling molecules including anandamide and glyceryl-anandamide (Devane et al., 1992; Herkenham, 1992; Herkenham et al., 1990; Howlett et al., 1990; Matsuda et al., 1990; Munro et al., 1993; Pertwee, 1993, 1997).

The CB receptor system is widely distributed in the body, with CB1 primarily localized in the central nervous system. The highest concentrations are found in deep brain structures and the cerebellum (Childers & Breivogel, 1998; Herkenham et al., 1991a, 1991b). Receptors are also found in other organ systems including the uterus, pancreas, and testes (Pertwee, 1997). The CB2 receptor appears to be primarily localized in the spleen and immune cells (Kaminski et al., 1992). Although the biological functions of the endocannabinoid system remain unclear at this time, it is

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likely that the CB1 receptor system is important in a number of neurobehavioral events, including dampening of neuro-excitability (Sanudo-Pena & Walker, 1997), and perhaps in the initiation and maintenance of complex feeding behaviors, including suckling (Fride et al., 2001; Hao et al., 2000).

From the public health standpoint, there have been increasing anecdotal and limited scientific observations to suggest that cannabinoids may have utility in the management of severe pain, especially neuropathic pain (Noyes et al., 1975), muscular spasticity, tremor in conditions such as multiple sclerosis (Baker et al., 2000, 2001), and improved appetite and weight gain in patients with chronic inanition (Gorter et al., 1992; Nelson et al., 1994; Plasse et al., 1991). The possibility that cannabis might have a benefit in conditions such as AIDS or diabetic neuropathy, muscle spasm in multiple sclerosis, and severe weight loss, nausea, and vomiting related to cancer and its treatments, has been raised and reviewed in some detail by recent expert panels, including the NIH Expert Panel Report (U.S. National Institute of Health, 1997) and by the Institute of Medicine (1999).

These developments have converged with an increasing public sense that cannabis might be beneficial to some patients with severe chronic illnesses, and therefore should be made available to them. Evidence of this mood comes from the passing of initiative laws seeking to facilitate access to cannabis by medical patients in nine states in the United States. Therefore, it seems reasonable to expect that the convergence of scientific evidence and public pressure may result in increasing use of cannabis products by patients with certain severe chronic illnesses in the future. If this were to happen, it would naturally raise the concern that cannabis may have certain long-term undesirable effects, particularly with respect to the central nervous system. Although the acute neurobehavioral effects of cannabis intoxication have been characterized and reviewed in some detail (e.g., Solowij, 1998), the very long-term effects of cannabis on brain function are not well understood. In order to assess the state of current knowledge on persisting CNS consequences of cannabis use, we have performed a meta-analysis of the existing literature on neuropsychological evaluation of persons who have been exposed to regular, long-term use of cannabis. Previous reviews have provided excellent summaries of investigations on this topic and their findings (Grant & Mohns, 1975; Pope et al., 1995; Solowij, 1998). In order to avoid duplication of previous efforts and provide new information, we have approached this task with a view of arriving at a quantitative estimate of the potential effects of long-term cannabis consumption on various neurocognitive functions. In this way, we have attempted to estimate effect sizes for each of eight neurocognitive domains, as well as a global indicator of overall neurocognitive functioning as it relates to history of cannabis consumption. Thus, the overall objective of this study was to provide a quantitative synthesis of the research investigating the non-acute (residual) effects of cannabis use on the neurocognitive performance of long-term users. Readers interested in more detailed descriptions of studies on this topic are encouraged to examine the aforementioned reviews. In addition, we have recently published a companion paper (Gonzalez et al., 2002) that qualitatively examines the research methodologies of studies included in this meta-analysis.

## METHODS

### Literature Search and Study Identification Strategy

Two of the investigators (RG and CC) conducted independent literature searches through several online databases, including Medline/HealthSTAR, PsychInfo, BioSys, Current Contents, Dissertation Abstracts International, Article First, Eric, Science Citation Index Expanded, and Social Science Citation Index. The key words used were (marijuana or marihuana or tetra-hydrocannabinol or THC or cannabis) with the Boolean operator "and" connecting (neuro* or cognitive or assessment or ability or effects or processes or impairment or cognition or drug effects). Boolean operators were slightly modified and tailored to each database, in order to comply with specific database guidelines and to ensure a valid search. The search criteria were liberal, purposely so, in order to avoid missing any potentially relevant citations. The results of the two independent searches are presented in Figure 1. The first investigator identified 824 citations (Data Set A) and the second investigator identified 1,006 citations (Data Set B). After a consensus meeting, both databases were combined, and the investigators agreed that there were 1,014 unique citations.

The two investigators then independently rated each citation by title and abstract (if available) and classified these references into one of four relevance categories: CORE, REVIEW, UNKNOWN, and NOT RELEVANT. An article

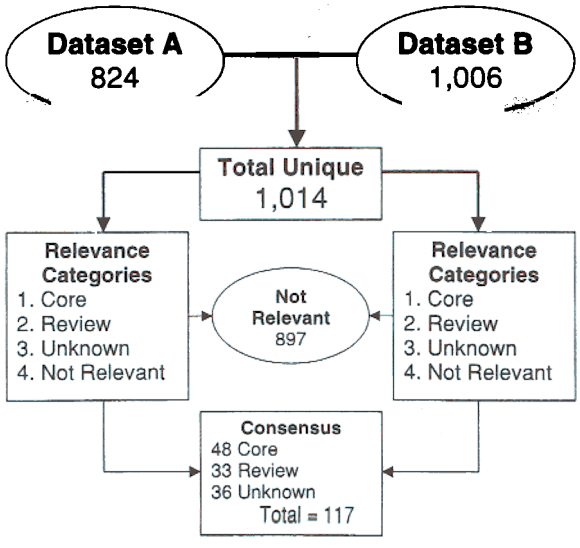



**Fig. 1.** Literature search process.

was categorized as CORE if, based on title and abstract, the study was highly likely to contain information relevant to the question of persisting, non-acute effects of cannabis exposure on neurocognitive functioning. An article was identified as REVIEW if the title or abstract indicated it was a literature review or an editorial. An UNKNOWN classification was given to an article if there was insufficient information based on an examination of the title or abstract, to confidently place it in one of the other categories. An article was categorized as NOT RELEVANT if it was clear from the title or abstract that it did not address the question of long-term, non-acute effects of cannabis on neurocognitive functioning.

Once these independent classifications were achieved, the two investigators had a second set of meetings to arrive at a consensus classification, resolving the status of the small number of articles upon which their original classification did not agree (seven articles). Figure 1 shows the results of this process. From 1,014 articles, 897 articles were classified as not relevant. Table 1 provides a summary of the major topics represented by articles deemed NOT RELEVANT. The majority of articles were excluded because they either did not deal with human subjects, or they involved studies of children and adolescents who were prenatally exposed or whose exposure to cannabis was not sufficient in duration to explore long-term persisting effects. Another large group of studies concerned psychiatric and other behavioral issues but not neurocognitive functioning *per se*.

After excluding the 33 review articles, the remaining 84 articles originally classified as CORE and UNKNOWN were examined in detail. From these, 38 were ultimately selected for coding as they met the inclusion criteria for this analysis as outlined below. The 38 included 35 of the 48 articles originally classified as CORE. Three additional studies, originally classified as UNKNOWN, were added after being reclassified as CORE upon thorough examination of the complete manuscript.

Before the literature search began, the authors identified a set of criteria that a study should have met in order to adequately answer the principal research question: "Is regular, long-term use of cannabis associated with non-acute (residual) neurocognitive dysfunction, suggestive of brain injury?" The criteria, presented in Table 2, emphasized the necessity of including an appropriate control group (i.e., non-drug using or very lightly drug using), indicating that subjects were drug free (i.e., not acutely intoxicated) at the time of evaluation, addressing potential confounds (e.g., history of heavy use of other substances, presence of other neurological conditions or traumatic brain injury, psychiatric confounds, other neuromedical risks), providing information on cannabis abstinence, and collecting data of sufficient detail to calculate effect sizes for each test administered.

**Table 1.** Classification of non-relevant studies omitted after initial search ($n$ = 897)

| | |
|---|---|
| Neurobiology/Pharmacology/Animal | = 314 |
| Psychiatric/Psychological/Prevention | = 231 |
| Prenatal/Infant/Children/Adolescents | = 155 |
| Neurological/Medical/Neuroimaging | = 89 |
| Acute cannabis use or misc. exclusions | = 66 |
| Polydrug/Other drugs | = 24 |
| Completely irrelevant | = 18 |

**Table 2.** Original inclusion criteria for studies entering meta-analysis

1. Includes a group of "cannabis only" users
2. Includes an appropriate control group (i.e., non drug-using or very limited cannabis use)
3. Provides sufficient information to calculate effect size
4. Outcome measures include valid neuropsychological tests
5. Cannabis-using group is drug-free on day of neuropsychological testing
6. Study addresses other potential substance use in cannabis group
7. Study addresses potential history of neurological or psychiatric problems
8. Study reports length of abstinence from cannabis before testing

We were surprised to discover that only nine studies ultimately met all original inclusion criteria. In a companion review paper (Gonzalez et al., 2002) we provide a more thorough analysis of the methodological limitations that affected many of the studies that we examined. To the nine studies that met all original inclusion criteria, two additional studies were added. One of these studies was brought to the authors' attention during a conference on cannabis organized by the National Institute on Drug Abuse on August 13–14, 2001 in Rockville, Maryland. This article by Pope et al. (2001), in press at the time our analyses were being conducted, met all of the inclusion criteria, and was therefore added to the original meta-analysis of the nine studies. The other manuscript added to our original meta-analysis was authored by Solowij et al. (2002) and was published while this manuscript was under review. Because this study met all of our original inclusion criteria, we felt our analyses would be incomplete without its inclusion. These 11 articles are briefly summarized in Table 3a. The meta-analysis of the 11 studies that met all original inclusion criteria involved data from 1,032 subjects, of whom 623 were regular, moderate, or heavy cannabis users and 409 were either non-users or persons whose exposure to cannabis was extremely limited.

In order to ensure that we were not rejecting potentially informative studies, we reexamined the 38 coded studies with a slightly relaxed set of criteria. We chose to accept a study if it violated no more than one of our *a priori* inclusion criteria (Table 2), as long as neither of two absolutely essential criteria were violated; that is, the study had to have an appropriate non-cannabis using (or extremely limited cannabis using) contrast group, and it had to have enough detail in the presentation of results to permit computation of effect sizes. For example, an often cited investigation by

Table 3a. Description of original 11 studies

| Study | Users (*n*) | Control (*n*) | Frequency or amount of use | Duration of use (yrs) | Length of abstinence (hr) | Cognitive domains assessed* |
|---|---|---|---|---|---|---|
| [1]Block & Ghoneim (1993) | 144 | 72 | 1 to 7+ times/wk | 5.8 (*M*) 4.1 (*SD*) | ≥24 | AE, L, PM, SRT |
| [2]Carlin & Trupin (1977) | 10 | 10 | NR | 5 (*M*) range: 2.5–8 | ≥24 | A, AE, L, M, PM, V |
| [3]Croft et al. (2001) | 18 | 31 | lifetime joints: 5309.8 (*M*) 6517.5 (*SD*) | NR | 66.5 (*M*) 42.4 (*SD*) | A, AE, F, L, M, V |
| [4]Ehrenreich et al. (1999) | 99 | 49 | use in last 6 mo: 3.5 dys/wk (*M*) 1.9 (*SD*) | 4.2 (*M*) 3.4 (*SD*) | 29.8 (*M*) 29.5 (*SD*) | A, SRT |
| [5]Gouzoulis-Mayfrank et al. (2000) | 28 | 28 | 20.9 dys/mo (*M*) 10.2 (*SD*) | 2.9 (*M*) 2.0 (*SD*) | 96 (*M*) 372 (*SD*) | A, AE, F, L, PM, SRT, V |
| [6]Hamil (1996) | 19 | 19 | NR | NR | ≥336 | F, L |
| [7]Pope & Yurgelun-Todd (1996) | 65 | 64 | ≥22 days of the past 30 days | ≥2 | ≥19 | A, AE, F, L, V |
| [8]Pope et al. (2001) | 63 | 72 | ≥5000 lifetime episodes ≥7 times/week | ≥13 years | ~672 | A, AE, F, L, PM, V |
| [9]Rodgers (2000) | 15 | 15 | 4 dys/wk (*M*) | 11 (*M*) | ≥720 | A, F, L, SRT |
| [10]Solowij (1995) | 60 | 16 | 15.3 dys/mo (*M*) 10 (*SD*) | 7.8 (*M*) 5.1 (*SD*) | ≥1008 | A, SRT |
| [11]Solowij et al. (2002) | 102 | 33 | median: 2 joints/day 27.9 dys/mo in past 14 wks | 17.1 (*M*) 7.9 (*SD*) | 17 (median) | A, AE, F, L, PM, V |

*Note.* Numeric superscripts refer to the data presented in Figures 2A and 2B.
*A study may have "assessed" a given domain, but their data may not have been included in our analyses if it was presented in a format that was incompatible with our methods for effect size calculations.
A, Attention; AE, Abstraction/Executive; F, Forgetting/Retrieval; L, Learning; M, Motor; PM, Perceptual Motor; SRT, Simple Reaction Time; V, Verbal/Language; NR, not reported.

Fletcher and colleagues (1996), which examined the cognitive correlates of long-term cannabis use in Costa Rican men, did not meet the latter criterion and was therefore excluded. In addition, a study was also included if criterion items #5 and #8 (see Table 2) were the only two criteria not met. This decision was made based on the interdependence of these two items (i.e., studies that did not quantify length of abstinence from cannabis, also did not confirm if subjects were drug-free at time of testing).

As a result of re-inspecting the 38 studies, an additional four studies met the revised criteria necessary for inclusion. These particular studies were initially excluded due to the lack of abstinence information in all but one instance. Nevertheless, based on the totality of the study design, it appeared unlikely that the authors included acutely intoxicated individuals in their analyses. Thus, this expanded meta-analysis based on 15 studies (the 11 original plus the four added) now included 1,188 subjects (i.e., 484 controls and 704 cannabis users). In terms of the meta-analytic methodology, the analysis of the 15 studies was identical in all respects to that of the original 11 studies described above. A brief description of the four additional studies is provided in Table 3b, along with the original inclusion criteria that were not met.

## Statistical Methodology

Using the techniques described by Hedges and Olkin (1985) to combine continuous outcome measures, a standardized mean difference (effect size) $d$, and its variance were calculated for each neuropsychological test that was administered within each of the 11 studies. In particular, $d = (M_e - M_c)/S$, where $M_e$ and $M_c$ were the mean scores on a neuropsychological test for the cannabis using and control groups respectively and $S$ was the standard deviation for the pooled sample. The expression for variance ($v$), is $v = (n_e + n_c)/(n_e n_c) + d^2/(2(n_e + n_c))$, with $n_e$ and $n_c$ representing the sample sizes for the cannabis users and controls, respectively. Then, within each of the studies, the individual effect sizes were linearly combined by subsets into one of eight neurocognitive ability domains. Thus, if $d_1, d_2, \ldots d_k$ represented the effect sizes for $k$ tests from a particular study all deemed to measure the same neurocognitive ability, a pooled estimate ($d'$), $d' = \Sigma(w_i d_i)$, was obtained. The decision to group individual tests into domains was necessary due to the lack of overlap between tests across studies. We acknowledge that individual neuropsychological tests assess multiple cognitive abilities; nevertheless, each test was assigned to the cognitive domain it was determined to

Table 3b. Study characteristics for four additional studies

| Study | Users ($n$) | Control ($n$) | Frequency or amount of use | Duration of use (years) | Cognitive domains assessed* | Cognitive impairment concluded? | Criteria not met† |
|---|---|---|---|---|---|---|---|
| [12]Deif et al. (1993) | 15 | 10 | 1.1 gm/dy ($M$) 0.5 ($SD$) | 7.5 ($M$) 2.2 ($SD$) | A | No | 5, 8 |
| [13]Grant et al. (1973) | 29 | 29 | 3 times/mo (median) | 4 (median) | A, AE, L, PM | No | 5, 8 |
| [14]Rochford et al. (1977) | 26 | 25 | NR | 3.7 ($M$) | L, PM | No | 5, 8 |
| [15]Wig & Varma (1977) | 11 | 11 | NR | NR | A, AE, F, L, PM | Yes; memory, concentration | 6 |

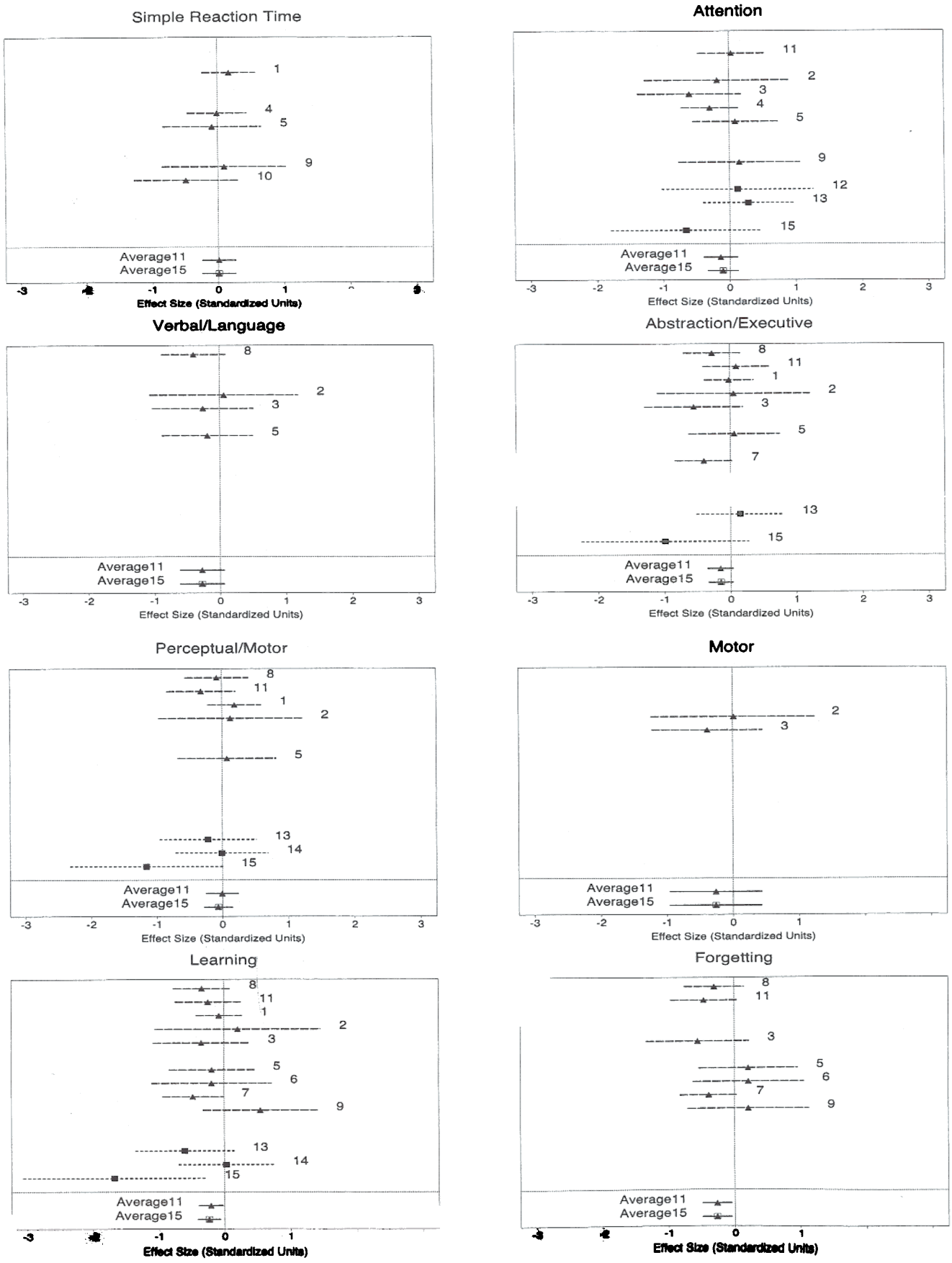
*Note.* Numeric superscripts refer to the data presented in Figures 2A and 2B.
*A study may have "assessed" a given domain, but their data may not have been included in our analyses if it was presented in a format that was incompatible with our methods for effect size calculations.
A, Attention; AE, Abstraction/Executive; F, Forgetting/Retrieval; L, Learning; PM, Perceptual Motor; NR, not reported.
†See Table 2.

best assess. These domains were simple reaction time, attention (e.g., WAIS–R Digit Span, Digit Vigilance), verbal/language (e.g., WAIS–R Vocabulary, Verbal Fluency), abstraction/executive functioning (e.g., Wisconsin Card Sorting Test, Raven's Progressive Matrices), perceptual motor (e.g., WAIS–R Block Design, WAIS-R Object Assembly), simple motor (e.g., Grooved Pegboard, Finger Tapping), learning (e.g., California Verbal Learning Test–Learning Trials, Rey Auditory Verbal Learning Test–Learning Trials), and forgetting/retrieval (e.g., California Verbal Learning Test–Delayed Recall, Rey Auditory Verbal Learning Test–Delayed Recall). As different tests measuring the same neurocognitive domain would be expected to be correlated, the method prescribed by Hedges and Olkin (1985; Chapter 10) was adopted, whereby, the vector of weights $(w_1, \ldots w_k)$ above was chosen to be proportional to the inverse of the covariance matrix of the vector $(d_1, d_2, \ldots d_k)$, thus reflecting the dependence between the tests. We assumed a correlation of .7 between any two tests that were purported to measure the same neurocognitive domain. The assumption of this value had to be made because we did not have individual test results for each subject from each study. However, based on extensive experience in the conduct of neuropsychological studies employing comprehensive neuropsychological test batteries with many thousands of subjects over the years (Grant, et al., 1978, 1979, 1982, 1987; Heaton et al., 1981, 1991, 1995), it has been our experience that tests grouped into a particular domain share about 50% of common variance, with a range of 30% to 70%. Using a correlation of .7 ensures a conservative estimate of the variance of the pooled effect size.

A heterogeneity statistic, $Q$, was calculated in order to assess whether the effect sizes that were pooled within each study could in fact be said to be measuring the same underlying population effect, representing a particular neurocognitive domain. In a few instances, this exploration indicated a large amount of heterogeneity between tests within a given domain, suggesting that a test may have been incorrectly assigned to a particular domain or would better fit classification under a different cognitive domain. In these cases, the tests within a domain were reexamined, and redistributed to another neurocognitive domain if deemed appropriate based on logical grounds and previous experience (e.g., a computer-assisted test which was assigned to the domain of learning *a priori*, better fit the attention domain).

A fixed effects model was used in our computations. Our choice of using fixed effects rather than random effects, was guided by the judgment that in investigating the potential toxic effects of a substance such as cannabis, it was important to be more "permissive" rather than "conservative" in our modeling of the information due to the likelihood of heterogeneity in data across studies. If a subtle signal were present in a heterogeneous data field, it would be more readily detected using a fixed effects model. Thus, the fixed effects approach was expected to produce somewhat smaller confidence intervals around the effect sizes than would a random effects model, thus increasing the likelihood of detecting a cannabis effect.

The above analysis yielded for each study a vector of effect sizes with variances for each of the neurocognitive domains (with the possibility of missing values if the study in question did not measure a particular neuropsychological domain). Effect sizes were again linearly combined (with weights inversely proportional to the variance) across studies to obtain an overall effect size and a variance for each domain. An across study heterogeneity statistic $Q$ was also computed for each domain. Finally, an overall or global neurocognitive effect size and its variance were computed by pooling the effect sizes across domains. The methodology for this final combination mirrored the methods described above for the within study pooling. As it might be expected that scores on tests corresponding to different neuropsychological domains might be (weakly) correlated, the correlation between separate domains was assumed to be .3. Again, this estimate was based on the authors' experience of the likely correlation of tests from separate domains. Because the overall determination of the association between cannabis use and neuropsychological impairment was based


Simple Reaction Time
1
4
5
9
10
Average11
Average15
Effect Size (Standardized Units)
Attention
11
2
3
4
5
9
12
13
15
Average11
Average15
Effect Size (Standardized Units)
Verbal/Language
8
2
3
5
Average11
Average15
Effect Size (Standardized Units)
Abstraction/Executive
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Average11
Average15
Effect Size (Standardized Units)
Perceptual/Motor
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Average15
Effect Size (Standardized Units)
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8
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Average15
Effect Size (Standardized Units)

**Fig. 2a & 2b.**

on a large number of test scores measuring eight different neuropsychological domains, 99% confidence intervals were calculated to allow adjustment for multiple comparisons.

## RESULTS

The effect sizes for each neurocognitive domain from each study are presented in Figures 2a and 2b. The effect sizes for each domain across the 11 original studies ranged from +.0086 for the perceptual motor domain, to −.28 for the verbal/language domain. In most instances, the 99% confidence interval surrounding the mean effect size for each domain included zero; therefore, the possibility that the effect size observed was indeed zero could not be discounted. However, in the case of the learning [−.21 99%CI (−.39, −.022)] and forgetting [−.27 99%CI (−.49, −.044)] domains the average effect sizes were found to be significant, albeit of small magnitudes. Comparable results were obtained when all 15 studies were considered.

The global measure of neurocognitive performance was determined through a linear combination of effect sizes across all domains. Data from the 11 studies included under the original criteria indicated an average effect size of −.15 99%CI (−.29, −.019) on the global measure of neurocognitive performance. When all 15 studies were considered, the average global neurocognitive effect size was −.16 99% CI (−.29, −.033). Thus, the results of both sets of analyses suggest a small detrimental cannabis effect on overall neurocognitive performance.

Inspecting the effect sizes for neurocognitive domains by study, we noted that one study examining users in India (class-IV caste) of bhang and charas appeared to be a distant outlier. Due to the fact that this study was based on a population very unlike that of other studies in our pool, we repeated the analysis omitting this study from the pool. Eliminating this study had a negligible influence on effect sizes, but did reduce heterogeneity so that none of the domain-specific $Q$ statistics were statistically significant. Table 4 presents the values of $Q$ for each domain across studies, as well as observed effect sizes, both before and after the removal of the outlier study.

### Meta-Regression

To determine whether several study and subject characteristics influenced the observed effect sizes, we performed a set of univariate regressions. These analyses were limited to four of the eight domains (attention, abstraction/executive functioning, perceptual motor, and learning) that contained data from a sufficient number of studies. Variables included whether the cannabis-using and control groups were adequately matched with regard to education or intelligence, as well as the extent to which cannabis users and controls were excluded due to other significant drug use. Furthermore, with respect to cannabis using subjects, variables of interest included whether individuals were ascertained to be abstinent from cannabis for at least 24 hr at time of testing, and their duration of cannabis use. Because of the possibility that sex and years of education might moderate neurocognitive performance in the cannabis group, these variables were also examined. For each of the univariate meta-regressions, years of cannabis use, percent female in the cannabis group, and years of education in the cannabis group, were coded as continuous variables. Dichotomous variables were used to represent whether subjects were known to be abstinent from cannabis for 24 hr, were excluded for other significant drug use, and were matched with the control group on education and/or IQ. The meta-regression results indicated that none of the examined covariates significantly moderated the effect size in any of the regressions.

## DISCUSSION

The results of our meta-analytic study failed to reveal a substantial, systematic effect of long-term, regular cannabis consumption on the neurocognitive functioning of users who were not acutely intoxicated. For six of the eight neurocognitive ability areas that were surveyed, the confidence intervals for the average effect sizes across studies overlapped zero in each instance, indicating that the effect size could not be distinguished from zero. The two exceptions were in the domains of learning and forgetting. Here when we averaged across the 11 studies that had the most rigorous inclusion/exclusion criteria and the best designs, the effect size for learning was −.21 99%CI (−.39, −.022) indicating a very small but discernible negative effect. This effect was slightly larger when all 15 studies were included [−.24 99%CI (−.41, −.064)]. Similarly, in the domain of forgetting (failure to recall or recognize) the average effect size was −.27 99%CI (−.49, −.044), again suggesting a very small but measurable decrement.

**Fig. 2a & 2b.** Effect sizes for each neurocognitive domain. Effect sizes derived from the 11 studies included under the original set of criteria are depicted with solid triangles and long-dashed confidence intervals; data for the four studies added under the relaxed criteria are displayed with solid squares and small-dashed confidence intervals. Each effect size and confidence interval is shown with a number that references the study as presented in Table 3a and 3b. The average effect sizes across studies for each domain, are presented at the base of each of the specific domain related figures. A negative effect size represents poorer performance by the cannabis using groups. "Average 11" refers to the average effect size of the studies included under the original criteria; "Average 15" presents effect sizes for the entire set of studies.

**Table 4.** Effect sizes and estimate of heterogeneity within domains, across studies

| Domain | Effect size (99% CI) | $Q$-statistic | $df$ for $Q$ | $p$-value for $Q$ |
|---|---|---|---|---|
| Attention | −.11 (−.34, .12) | 11.26 | 8 | .19 |
| | −.083 (−.32, .15) | 9.30 | 7 | .23 |
| Abstraction/Executive | −.15 (−.34, .032) | 14.24 | 8 | .08 |
| | −.13 (−.32, .052) | 10.73 | 7 | .15 |
| Forgetting/Retrieval* | −.27 (−.49, −.044) | 10.81 | 6 | .09 |
| Learning* | −.24 (−.41, −.064) | 23.09 | 11 | .02 |
| | −.21 (−.39, −.040) | 14.60 | 10 | .15 |
| Motor | −.26 (−.96, .43) | .55 | 1 | .46 |
| Perceptual–Motor | −.065 (−.28, .15) | 12.80 | 7 | .15 |
| | −.026 (−.25, .20) | 5.57 | 6 | .47 |
| Simple Reaction Time | .0086 (−.25, .26) | 4.54 | 4 | .34 |
| Verbal/Language | −.28 (−.62, .060) | 1.30 | 3 | .73 |

*Note.* * denotes a significant effect size; Rows with two sets of numbers contain the values obtained before and after the removal of an outlier study (i.e., Wig & Varma), in the respective order; $df$ = degrees of freedom.

These results can be interpreted in several ways. A statistically reliable negative effect was observed in the domain of learning and forgetting, suggesting that chronic long-term cannabis use results in a selective memory defect. While the results are compatible with this conclusion, the effect size for both domains was of a very small magnitude. The "real life" impact of such a small and selective effect is questionable. In addition, it is important to note that most users across studies had histories of heavy long-term cannabis consumption. Therefore, these findings are not likely to generalize to more limited administration of cannabis compounds, as would be seen in a medical setting.

Some of the studies included in our analyses tested cannabis users with less than 24 hr of abstinence, and others reported no information on abstinence at all. As a result, another factor that may have contributed to the small tendency towards worse performance in the cannabis-using group might be attributable to what Pope et al. have called "residual effects." In a recent study by Pope et al. (2001), three groups of subjects were repeatedly examined over a period of 28 days. They included a group of current heavy cannabis users, a group of persons who had heavy histories of past cannabis use but had not used in the recent past, and a group of controls who had very limited experience with cannabis. The active cannabis users were tested on Days zero, 1, 7, and 28 after ceasing active cannabis use. Abstinence was confirmed through regular urinalysis, which detected declining concentrations of THC in the urines of the active users, and demonstrated that all had undetectable THC levels by 28 days. Pope and colleagues noted subtle impairments on several neurocognitive tests in the active cannabis users who had just become abstinent. However, by 28 days, the active cannabis users who had abstained for almost a month were indistinguishable from former heavy users or non-using controls. Pope et al. suggested that the subtle cognitive impairments observed in the active users during the first week of cessation might represent residual effects (i.e., effects of persisting low levels of THC in the system), abstinence phenomena, or both. The Pope et al. data have direct relevance on the interpretation of results obtained in this study. In nearly all instances, heavier cannabis users were asked to abstain for a period of hours or days before testing. Therefore, many of them could have been at risk for "residual effects" or "abstinence phenomena," which might have contributed to slight decrements in their performance. Given this likelihood, it is even more surprising that our meta-analytic study revealed so few effects.

In interpreting the results of this meta-analytic study, several caveats need to be considered. First, many of the studies examined had significant limitations. For example, several studies had small numbers of subjects, reducing our confidence in the individual study's results and creating concerns about generalizability. Second, many studies had insufficient information about potential confounding factors. These factors included recency of last cannabis exposure, extent of exposure to other drugs of abuse, presence of confounding neuropsychiatric factors (e.g., depression, anxiety, personality disorders, etc.), or other neuromedical risks that can independently affect brain function. As an example, the most recent study by Solowij et al. (2002) focused on patients receiving treatment for cannabis dependence, and the controls were non-patients. This study found negative effects on memory. An unanswered question is whether the cannabis users in that study, being persons who sought or were referred to treatment, might consist of a highly selected group that either were experiencing cannabis related cognitive problems, or who had such difficulties as a function of comorbid psychiatric disorders. No data were presented on mood disorders, which can contribute

both to subtle memory difficulties and account for treatment seeking. In this particular study, the long term using group was, on average, 8 years older than the controls. Although the authors attempted to adjust for age in some of their analyses, there is reason to believe that such covariance adjustments often under-correct, and therefore are not an appropriate substitute for proper age matching, especially when interpreting neuropsychological tests which are influenced by age (Adams et al., 1985).

A general issue affecting most studies was that the premorbid neurocognitive abilities of these subjects were largely unknown, as the studies did not document neurocognitive performance before subjects' onset of regular cannabis use. Although methods are available to estimate premorbid intelligence through consideration of performance on tests that are not likely to be impacted by subtle brain injury (e.g., scores on the Vocabulary subtest of the WAIS series), these techniques are often inadequate. For example, we can never be absolutely certain whether the cannabis users might have been brighter than controls to begin with, and then lost some measure of their cognitive function. Nevertheless, many of the confounds discussed would most likely result in poorer scores in the cannabis group, thus increasing the likelihood and magnitude of observed effects. Only studies that begin with the examination of children and young adolescents before they enter the period of risk to cannabis exposure, can sufficiently reduce the influence of confounds, thus answering this question most effectively. An alternative strategy would be to examine monozygotic twins discordant for cannabis and other substance use. In such studies, one can be more confident of controlling for "native endowment." In the absence of such designs, which can be costly to implement, the approach developed by Pope et al. represents the next best alternative. By examining regular active users who were instructed to abstain, and then repeatedly tested during a lengthy supervised abstinence period, studies such as those designed by Pope et al. bring us closer to understanding the persisting effects of cannabis use, while simultaneously tracking the potential confounds of a "residual effect" and "abstinence phenomena."

In addition to the limitations posed by suboptimal study designs, limiting aspects of the statistical methodology necessarily employed when conducting a meta-analysis should also be considered. It is important to recognize that noise and interpretability, inherent in such analyses, present an additional challenge. To compute the average effect size, as discussed in the statistical methodology section, three types of linear combinations were performed. First, within studies, different tests (from study to study) were combined into the eight neuropsychological domains. Then, across studies, domain effect sizes were linearly combined into eight domain effect size estimates. Finally, the eight effect sizes were linearly combined across domains, yielding a highly processed overall effect size that should be subject to caution in interpretation. In regards to the lack of findings when considering the influence of covariates on observed effect sizes, it is important to note that the meta-regressions were performed on data matrices with as many rows as there were studies testing a particular domain (no more than 10). With less than 10 data points per regression, it is necessarily difficult to make any conclusions about the significance of the model.

Finally, it is important not to generalize these findings to special populations. Many of the studies included in our analyses were conducted with better-educated, younger individuals. We do not know if these mostly negative findings would apply to individuals who have other risk factors for neurocognitive impairment and are then exposed to chronic heavy cannabis use. For example, we cannot be certain if individuals with mild head injuries, attention deficit/hyperactivity disorder, or other neuropsychiatric conditions that may affect cognitive capacity, might be equally resistant to the chronic effects of cannabis. In addition, the fact that cannabinoids appear to be well tolerated by healthy adults does not mean that children and adolescents, who are continuing to undergo neurobiological and cognitive development, will be similarly unaffected. Data from several human studies, as well as animal studies examining the effects on the offspring of cannabis-exposed mothers, suggest that neurodevelopmental difficulties can occur. For example, Fried et al. (2001) have noted executive dysfunction in older children and adolescents of mothers who were substantial cannabis users in the Ottawa cohort. Similar findings were noted in the Pittsburgh longitudinal study (Goldschmidt et al., 2000). Thus, it remains entirely possible that exposure of the developing nervous system to cannabinoids may cause alterations that affect cognitive function in the future.

In conclusion, our meta-analysis of studies that have attempted to address the question of longer term neurocognitive disturbance in moderate and heavy cannabis users has failed to demonstrate a substantial, systematic, and detrimental effect of cannabis use on neuropsychological performance. It was surprising to find such few and small effects given that most of the potential biases inherent in our analyses actually increased the likelihood of finding a cannabis effect. Specifically, our use of a fixed effects model resulted in smaller confidence intervals for the effect sizes we computed, thus facilitating the discovery of statistically significant between-group differences. Moreover, many of the confounds inherent in the studies included in our analyses made it more likely for the cannabis using group to demonstrate poorer performance on neuropsychological tests than controls, irrespective of cannabis consumption. Finally, meta-analytic studies are generally criticized for including only investigations that have been published in peer-reviewed journals, because studies that report statistically significant findings are more likely to be published. This "file-drawer" bias can result in an underrepresentation of studies that did not find statistically significant results, therefore also increasing the likelihood of generating statistically significant effect sizes. Nevertheless, when considering all 15 studies (i.e., those that met both strict and more relaxed criteria) we only noted that regular cannabis users per-

formed worse on memory tests, but that the magnitude of the effect was very small. The small magnitude of effect sizes from observations of chronic users of cannabis suggests that cannabis compounds, if found to have therapeutic value, should have a good margin of safety from a neurocognitive standpoint under the more limited conditions of exposure that would likely obtain in a medical setting.

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