Nonacute (Residual) Neuropsychological Effects of Cannabis Use: A Qualitative Analysis and Systematic Review

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Because there is a possibility that cannabis or cannabis-like molecules might be used as treatments for certain conditions in the future, it becomes important to consider the possible adverse effects of these compounds. In this paper, the authors review the evidence for persisting effects of nonacute cannabis use on the central nervous system, as reflected by alteration in neuropsychological performance. From the 40 articles that met criteria for inclusion in this review, the authors could not detect consistent evidence for persisting neuropsychological deficits in cannabis users; however, 22 of the 40 studies reported at least some subtle impairments. The inability to reach a firm conclusion results largely from methodological limitations inherent in most studies. These are considered in detail to inform future studies on (nonacute) consequences of cannabis consumption on cognitive abilities.

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The general climate toward medicinal and recreational use of cannabis, both in Europe and the United States, has changed in recent years. According to several national and statewide surveys conducted in the United States, approximately 60% to 70% of respondents are in favor of allowing patient access to cannabis for medicinal purposes.1,2 Paralleling public opinion, changes in legislation have emerged to facilitate patient access to cannabis when deemed appropriate. Even though U.S. federal law continues to view cannabis as a Schedule I drug, eight U.S. states have enacted medical marijuana laws. In Europe, several countries have taken an approach toward drug policies that focus on “harm reduction” rather than prohibition. Switzerland has recently begun regulation of marijuana sales, and several other countries (e.g., Germany, Spain, Portugal, Belgium, and the Netherlands) have made permissive changes to their policies regarding cannabis consumption.

Anecdotal and limited scientific observations suggest that constituents of cannabis may improve appetite and facilitate weight gain,3,5 as well as alleviate muscular spasticity, tremor, and neuropathic pain.6 Thus, cannabis may be helpful in managing the symptoms of several debilitating diseases, including AIDS, cancer, diabetic neuropathy, and multiple sclerosis.7-9 These claims have been raised and reviewed in some detail by recent expert panels, including the NIH Expert Panel Report,10 and by the Institute of Medicine,11 both of which concluded that cannabis and its constituents may have some clinical utility. Furthermore, the potential therapeutic value of synthetic and endogenous cannabinoids, as well as those naturally found in cannabis, appears to show promise in the treatment of poststroke patients.12 Several animal studies have documented the ability of some cannabis constituents and their analogs to function as potent antioxidants,13 reduce glutamate-mediated excitotoxic injury to the brain,13,14 and reduce experimentally induced infarct volume both in vitro15 and in vivo.16

It is evident that if social, political, and scientific trends regarding medical uses for cannabis continue in the current direction, the possibility exists that decisions will need to be made whether to treat patients with cannabis or synthetic cannabis-like substances. Because of this possibility, it is imperative that the potential dangers of cannabis be assessed as carefully as
its benefits. Of particular concern are the effects of cannabis on brain functions, as reflected by neuropsychological abilities, such as attention, memory, and executive functions. Ample literature and anecdotal information document the detrimental effects that acute intoxication with cannabis can have on some of these abilities. However, investigations examining the presence, nature, and duration of longer term nonacute effects of cannabis on neuropsychological performance present equivocal findings.

The goal of this paper is to present a systematic assessment of the existing literature on the nonacute persisting effects of cannabis use on neuropsychological performance. In a review conducted by Pope and colleagues, the question of nonacute effects was divided into two subcategories: “residual” and “CNS alterations.” Residual meant slowly reversible alterations, consistent with gradual elimination of cannabis, or withdrawal phenomenon. CNS alterations connoted permanent brain changes. The current review will encompass studies that have investigated the presence of either residual effects or CNS alterations due to cannabis consumption. However, rather than focusing primarily on the outcome of such studies, our review examines the quality of their methodology and research design in an attempt to document research standards in the field and to explore how they may affect study results. In a separate manuscript, we will report on the use of a meta-analytic approach in an effort to quantitatively assess outcome through the estimation of effect sizes of the persisting nonacute effects of cannabis consumption on neuropsychological performance.

METHOD

Two investigators (CC & RG) conducted preliminary literature searches to establish a set of keywords that would produce the maximum number of studies pertaining to the question of nonacute neuropsychological effects of cannabis in adult humans. After deciding on the optimal keywords, both investigators independently searched the literature using 11 separate online databases. Keywords and Boolean operators were modified as necessary to comply with specific database requirements. Results from each database were compiled by each investigator, and duplicate entries were deleted. The combined search results yielded 1014 unique citations, the titles and abstracts of which were examined to identify empirical studies relevant to this review. When abstracts were not available or the information provided was insufficient to determine the relevance of an article, the decision to include the article was postponed until the full manuscript was obtained.

If a study empirically investigated the nonacute neuropsychological effects of cannabis in adult humans, it was deemed eligible for inclusion in this review. In addition, due to the language limitations of the investigators, only studies written in English were examined in detail. A second consensus meeting was held between both investigators to agree on the final set of studies for review. After resolving the status of 7 articles on which authors’ classifications disagreed, a total of 38 articles were ultimately identified. Two more articles, published after the literature searches were completed, were added to this review, bringing the total number of articles reviewed in this article to 40.

Due to the limited scope of this review, many articles that examined the general issue of nonacute effects of cannabis on the brain were not included. The largest proportion of these studies included nonhuman samples and did not assess neuropsychological functioning. Investigations examining psychiatric/psychological issues (including prevention) constituted the second largest proportion of studies that were not included in our final analysis. The third largest subset of studies focused on nonadult human subjects (e.g., children, adolescents, or infants). The remainder of excluded studies focused primarily on medical factors, neuroimaging results, effects of acute intoxication, or polydrug abuse.

In investigating the nonacute effects of cannabis on neuropsychological performance, it is imperative that certain critical issues be addressed by investigators. The neuropsychological performance of a cannabis-using group could differ from that of a control group for many reasons aside from the group’s history of cannabis consumption. Therefore, necessary steps must be taken so that between-group differences can be more confidently attributed to differences in history of cannabis use. Prior to conducting the literature search, a set of criteria was established, representing the minimum requirements a study must fulfill to adequately address confounds and establish a cannabis effect. Table I presents these “minimal criteria.”

RESULTS

Increasing Number of Studies Published

The literature on the effects of cannabis on the brain has grown dramatically over the past decade. Using all of the citations retrieved in our literature search that provided a year of publication, we tabulated the number of unique studies published during several epochs from 1968 through 2001. With the exception of the early 1980s, the number of citations retrieved increased...
steadily across epochs, showing 56% growth from the late 1980s to the early 1990s and an additional 59% growth from the late 1990s to 2001. More new studies were published in the past 6 years than in the entire period from 1969 to 1985. A similar trend was observed for articles that focused specifically on the nonacute effects of cannabis on neuropsychological abilities. Of the 40 articles reviewed in this article, 13 were published prior to 1980. Only 5 of the 40 articles were published during the period between 1980 and 1989. Not surprisingly, the vast majority of articles pertaining to this specific question appeared after 1990 (n = 22).

Tables II through IV provide summaries of reviewed studies, including sample characteristics, cognitive domains assessed, and authors' conclusions. Studies were grouped into one of three tables, depending on the number of "minimal criteria" not met. The most widely assessed cognitive domain across all studies was attention/working memory (n = 31), followed by learning (n = 28), perceptual motor (n = 25), forgetting (n = 23), abstraction/executive (n = 22), verbal (n = 15), simple reaction time (n = 11), and motor (n = 8).

Neuropsychological Findings

Fifty-five percent of studies reported at least some subtle impairment in a given cognitive ability as a result of nonacute cannabis use. Poorer performance by cannabis users was most frequently reported for the attention/working memory domain (45%). Thirty-eight percent of studies that investigated performance in the motor domain and 35% of the studies that looked at the forgetting domain reported significantly poorer performance for the cannabis groups relative to controls. Less than one-third of studies concluded a detrimental effect of cannabis when assessing the perceptual/motor (28%), abstraction/executive (27%), simple reaction time (27%), learning (7%), and verbal (7%) domains. It is important to note that these tabulations are based on the conclusions provided by the studies' authors and are therefore subject to some bias (see Discussion).

Quality of Studies Based on "Minimal Criteria"

Detailed investigation of the study designs revealed that any overall conclusion based on the results of these 40 studies should be interpreted with caution. Only a few studies adequately met all of the a priori criteria that we established (i.e., the minimum requirements for controlling confounds and confidently establishing the presence of an effect from cannabis consumption) [see Table I]. It is important to note that we were lenient in establishing whether a study violated our criteria. For example, the control group and cannabis-using group did not have to be matched on the prevalence of psychiatric or neurological problems, nor did the investigators have to control statistically for such factors. Rather, a study was deemed to comply with criterion 7 if the presence of neurological or psychiatric disorders in the cannabis-using group was addressed by investigators or if study participants were screened for such factors. Even though we were permissive when determining if the criteria were adequately addressed, only one-third (n = 13) of the studies were in full accord with these standards, and more than half violated at least two criteria.

To examine if the overall quality of publications in this area has improved in recent years, we examined if studies published more than two decades ago (those prior to 1989) differed from studies published in or after 1990 on the number of criteria violations. On average, studies prior to 1990 had 1.9 criteria violations, whereas those published in or after 1990 violated an average of 1.4 criteria. A Wilcoxon rank sum test did not reveal statistically significant differences in the number of criteria violations between these two groups (z = 1.45, p = 0.14). Although some might consider this result to suggest a trend toward significantly less criteria violations in studies published in the past decade, the magnitude of this difference is very small (1.4 vs. 1.9).
<table>
<thead>
<tr>
<th>Study</th>
<th>Users (n)</th>
<th>Control (n)</th>
<th>Characteristics of Marijuana Users</th>
<th>Frequency/Amount of Use</th>
<th>Duration of Use (years)</th>
<th>Length of Abstinence (h)</th>
<th>Cognitive Domains Assessed</th>
<th>Cognitive Impairment Concluded?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block and Ghoneim, 1993</td>
<td>144</td>
<td>72</td>
<td>Volunteers recruited through advertisements</td>
<td>1 to 7+ times/wk</td>
<td>5.6 (M)</td>
<td>≥ 24</td>
<td>AE, L, PM, SRT</td>
<td>No; only on achievement tests</td>
</tr>
<tr>
<td>Carlin and Trupin, 1977</td>
<td>10</td>
<td>10</td>
<td>Recruited by participants in previous MJ studies</td>
<td>NR</td>
<td>4.1 (SD)</td>
<td>≥ 24</td>
<td>A, AE, L, M, PM, V</td>
<td>No</td>
</tr>
<tr>
<td>Croft et al., 2001</td>
<td>18</td>
<td>31</td>
<td>Recruited through London magazine</td>
<td>Lifetime joints: 5309.8 (M) 6517.5 (SD)</td>
<td>NR</td>
<td>66.5 (M) 42.4 (SD)</td>
<td>A, AE, F, L, M, V</td>
<td>Yes; attention</td>
</tr>
<tr>
<td>Ehrenreich et al., 1999</td>
<td>99</td>
<td>40</td>
<td>Recruited by advertising in a German university town newspaper</td>
<td>Use in past 6 months: 3.5 days/wk (M) 1.9 (SD)</td>
<td>4.2 (M) 3.4 (SD)</td>
<td>29.8 (M) 29.5 (SD)</td>
<td>A, SRT</td>
<td>Yes; attention</td>
</tr>
<tr>
<td>Fletcher et al., 1996</td>
<td>41</td>
<td>41</td>
<td>Subjects recruited from Costa Rican neighborhoods</td>
<td>9.6 joints/day (M) 16.9 (M)</td>
<td>16.9 (M)</td>
<td>≥ 72</td>
<td>A, AE, F, L, SRT</td>
<td>Yes; attention, short-term memory</td>
</tr>
<tr>
<td>Gouzoulis-Mayfrank et al., 2000</td>
<td>28</td>
<td>28</td>
<td>Recruited in the German dance scene by word of mouth</td>
<td>20.9 days/month (M) 10.2 (SD)</td>
<td>2.9 (M) 2.0 (SD)</td>
<td>96 (M) 372 (SD)</td>
<td>A, AE, F, L, PM, SRT, T, V</td>
<td>No</td>
</tr>
<tr>
<td>Hamil, 1996</td>
<td>19</td>
<td>19</td>
<td>Archival data set of male Vietnam veterans</td>
<td>NR</td>
<td>NR</td>
<td>≥ 336</td>
<td>F, V</td>
<td>No</td>
</tr>
<tr>
<td>Pope and Yurgelon-Todd, 1996</td>
<td>65 (H)</td>
<td>64 (L)</td>
<td>Undergraduates recruited by advertisements in student newspapers</td>
<td>22-30 days/past month (H); 0-9 days/past month (L)</td>
<td>≥ 2</td>
<td>≥ 19</td>
<td>A, AE, F, L, V</td>
<td>Yes; attention/executive and learning in (H)</td>
</tr>
<tr>
<td>Pope et al., 2001</td>
<td>63 (CH)</td>
<td>72</td>
<td>Recruited individuals ages 30 to 55 years</td>
<td>≥ 5000 lifetime episodes and ≥ 7 times/week (CH) or &lt; 12 times/last 3 months (FH)</td>
<td>≥ 13 years</td>
<td>0, 24, 168, and 672</td>
<td>A, AE, F, L, PM, V</td>
<td>No</td>
</tr>
<tr>
<td>Rodgers, 2000</td>
<td>15</td>
<td>15</td>
<td>Individuals who had decided to stop using cannabis</td>
<td>4 days/wk (M) 11 (M)</td>
<td>11 (M)</td>
<td>≥ 720</td>
<td>A, F, L, SRT, V</td>
<td>Yes; verbal memory</td>
</tr>
<tr>
<td>Solowij, 1995</td>
<td>28 (Ex)</td>
<td>16</td>
<td>Recruited from community in Sydney, Australia</td>
<td>19.1 days/month (M) 10.9 (SD) (Ex); 13.7 days/month (M) 9.0 (SD) (CLD); 10.3 days/month (M) 6.5 (SD) (CSD)</td>
<td>≥ 1008</td>
<td></td>
<td>A, SRT</td>
<td>Yes; “hit rate”</td>
</tr>
<tr>
<td>Solowij et al., 1995</td>
<td>16 (H)</td>
<td>16 (L)</td>
<td>Subset from Solowij 1995 study</td>
<td>17.9 days/month (M) 6.0 (SD) (H); 6.0 days/month (M) 2.8 (SD) (L)</td>
<td>6.7 (M) 5.6 (SD) (H); 6.7 (M) 6.3 (SD) (L)</td>
<td>≥ 24</td>
<td>A, SRT</td>
<td>Yes; focused attention and reaction time</td>
</tr>
<tr>
<td>Solowij et al., 2002</td>
<td>51 (ST)</td>
<td>33</td>
<td>Treatment-seeking, cannabis-dependent users, or recruited through the Marijuana Treatment Project</td>
<td>28.3 days/month (median) (ST); 27.4 days/month (median) (LT)</td>
<td>10.2 (M) 3.8 (SD) (ST); 23.9 (M) 4.1 (SD) (LT)</td>
<td>17 (median) 7-240 (range)</td>
<td>A, AE, F, L, PM, SRT</td>
<td>Yes; attention, learning, and memory (LT) &lt; (ST) and controls</td>
</tr>
</tbody>
</table>

MJ user descriptions: (H) heavy; (L) light; (CH) current heavy; (FH) former heavy; (Ex) ex-users; (CLD) current users, long duration; (CSD) current users, short duration; (ST) short-term users; (LT) long-term users. NR, not reported.

a. A, attention; AE, abstraction/executive; F, forgetting/retrieval; L, learning; M, motor; PM, perceptual motor; SRT, simple reaction time; V, verbal/language.

b. Dissertation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Users (n)</th>
<th>Control (n)</th>
<th>Characteristics of Marijuana (MJ Users)</th>
<th>Frequency or Amount of Use</th>
<th>Duration of Use (years)</th>
<th>Length of Abstinence (h)</th>
<th>Cognitive Domains Assessed&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cognitive Impairment Concluded?</th>
<th>Criteria Not Met&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al., 1975&lt;sup&gt;34&lt;/sup&gt;</td>
<td>40</td>
<td>0</td>
<td>Clients of an Indian Bhang shop</td>
<td>Almost daily, 2-3 (Raw Bhang)/dose</td>
<td>5-29</td>
<td>≥ 8</td>
<td>F, L, PM</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Block et al., 1990&lt;sup&gt;35&lt;/sup&gt;</td>
<td>61 (H)</td>
<td>89</td>
<td>Paid volunteers recruited through local news media</td>
<td>≥ 7 times/wk (H); 1-4 times/wk (L)</td>
<td>6.5 [M (H)]; 6.2 [M (L)]</td>
<td>NR</td>
<td>L, F, V</td>
<td>Yes: language expression, (H) &lt; (L) users and controls</td>
<td>4, 5</td>
</tr>
<tr>
<td>Cohen, 1976&lt;sup&gt;36&lt;/sup&gt;</td>
<td>30</td>
<td>0</td>
<td>Males (21-35 years) recruited by advertisements, employment agencies, and word of mouth</td>
<td>NR</td>
<td>NR</td>
<td>≥ 264</td>
<td>A, AE, L, F, PM</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Culver and King, 1974&lt;sup&gt;37&lt;/sup&gt;</td>
<td>28</td>
<td>28</td>
<td>Students at Dartmouth College recruited through questionnaire</td>
<td>≥ once/month</td>
<td>≥ 1</td>
<td>≥ 168</td>
<td>A, AE, L, M, PM, V, A</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>Deif et al., 1993&lt;sup&gt;38&lt;/sup&gt;</td>
<td>15</td>
<td>10</td>
<td>Fifteen male subjects</td>
<td>1.1 gm/day (M); 0.5 (SD)</td>
<td>7.5 [M 2.2 (SD)]</td>
<td>NR</td>
<td>A, AE, L, PM</td>
<td>No</td>
<td>4, 5</td>
</tr>
<tr>
<td>Grant et al., 1973&lt;sup&gt;39&lt;/sup&gt;</td>
<td>29</td>
<td>29</td>
<td>Medical students recruited by questionnaire</td>
<td>3 times/month (median)</td>
<td>4 [median]</td>
<td>NR</td>
<td>A, AE, L, PM</td>
<td>No</td>
<td>4, 5</td>
</tr>
<tr>
<td>Mendhiratta et al., 1978&lt;sup&gt;40&lt;/sup&gt;</td>
<td>50</td>
<td>25</td>
<td>Chronic Bhang and Charas/Ganja users</td>
<td>150 mg THC/average daily dose</td>
<td>4-21+</td>
<td>≥ 12</td>
<td>A, M, PM, SRT</td>
<td>Yes: attention, motor skills, perceptuomotor, reaction time</td>
<td>4, 5</td>
</tr>
<tr>
<td>Mendhiratta et al., 1988&lt;sup&gt;41&lt;/sup&gt;</td>
<td>30</td>
<td>15</td>
<td>Indian males from 31 to 40 years of age recruited from earlier study</td>
<td>10-15 g charms/day and 3-30 g Bhang/day</td>
<td>NR</td>
<td>≥ 12</td>
<td>A, M, PM, SRT</td>
<td>Yes: attention, motor skills, perceptuomotor, reaction time</td>
<td>6, 7</td>
</tr>
<tr>
<td>Page et al., 1988&lt;sup&gt;42&lt;/sup&gt;</td>
<td>27</td>
<td>30</td>
<td>Follow-up on sample used in previous research</td>
<td>9.6 joints/day (M)</td>
<td>30 [M]</td>
<td>24</td>
<td>A, AE, L, F, M, PM, V</td>
<td>Yes: retrieval, sustained attention, and concentration</td>
<td>6, 7</td>
</tr>
<tr>
<td>Pope et al., 1997&lt;sup&gt;43&lt;/sup&gt;</td>
<td>25</td>
<td>30</td>
<td>College students</td>
<td>29 days/last month (Median)</td>
<td>NR</td>
<td>≥ 19</td>
<td>A, AE, F, L, SRT</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Rochford et al., 1977&lt;sup&gt;44&lt;/sup&gt;</td>
<td>26</td>
<td>25</td>
<td>Medical students</td>
<td>NR</td>
<td>3.7 [M]</td>
<td>NR</td>
<td>L, PM</td>
<td>Yes: verbal, abstraction, perceptuomotor</td>
<td>5</td>
</tr>
<tr>
<td>Stefanis, 1978&lt;sup&gt;45&lt;/sup&gt;</td>
<td>47</td>
<td>40</td>
<td>Refugees from Asia Minor residing in Athens</td>
<td>7.48 g/day (M) 5.98 (SD)</td>
<td>23.10 [M] 4.12 [SD]</td>
<td>NR</td>
<td>AE, PM</td>
<td>Yes: motor and perceptuomotor</td>
<td>4, 5</td>
</tr>
<tr>
<td>Varma et al., 1988&lt;sup&gt;46&lt;/sup&gt;</td>
<td>26</td>
<td>26</td>
<td>Recruited from common gathering places in India</td>
<td>150 mg THC/daily, 20 or more times/month</td>
<td>5</td>
<td>≥ 12</td>
<td>A, AE, L, F, M, PM, SRT, V</td>
<td>Yes: moderate memory, perceptuomotor</td>
<td>6, 7</td>
</tr>
<tr>
<td>Vos and Burch, 1986&lt;sup&gt;47&lt;/sup&gt;</td>
<td>30</td>
<td>0</td>
<td>Male inpatients admitted to a mental hospital</td>
<td>NR</td>
<td>5-24</td>
<td>≥ 96</td>
<td>L, F, PM</td>
<td>Yes: memory, concentration</td>
<td>2, 6</td>
</tr>
<tr>
<td>Weckowicz and Janssen, 1973&lt;sup&gt;48&lt;/sup&gt;</td>
<td>11</td>
<td>11</td>
<td>Male volunteers</td>
<td>3-5 times/wk</td>
<td>4 [median]</td>
<td>NR</td>
<td>A, AE, PM</td>
<td>No</td>
<td>4, 5</td>
</tr>
<tr>
<td>Wig and Varma, 1977&lt;sup&gt;49&lt;/sup&gt;</td>
<td>11</td>
<td>11</td>
<td>Indian “caste-IV” individuals</td>
<td>NR</td>
<td>NR</td>
<td>≥ 24</td>
<td>A, F, L, PM</td>
<td>Yes: memory, concentration</td>
<td>6, 7</td>
</tr>
</tbody>
</table>

<sup>a</sup> M: motor; PM, perceptual motor; SRT, simple reaction time; V, verbal/language.
<sup>b</sup> See Table I.
<sup>c</sup> Book chapter.
<table>
<thead>
<tr>
<th>Study</th>
<th>Users (n)</th>
<th>Control (n)</th>
<th>Characteristics of Marijuana (MJ) Users</th>
<th>Frequency or Amount of Use</th>
<th>Duration of Use (years)</th>
<th>Length of Abstinence (h)</th>
<th>Cognitive Domains Assessed</th>
<th>Cognitive Impairment Concluded?</th>
<th>Criteria Not Met&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bannarjee et al., 1997&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>22</td>
<td>30</td>
<td>Male cannabis addicts undergoing drug treatment</td>
<td>NR</td>
<td>≥ 1</td>
<td>NR</td>
<td>A, AE, F, L, PM</td>
<td>Yes; forgetting, perceptuomotor, executive skills</td>
<td>4, 5, 6, 7</td>
</tr>
<tr>
<td>Brignell et al., 2000&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>15</td>
<td>NR</td>
<td>Males (18-30 years)</td>
<td>NR</td>
<td>NR</td>
<td>≥ 24</td>
<td>A, F, L, PM</td>
<td>No</td>
<td>3, 4, 5, 6, 7</td>
</tr>
<tr>
<td>Easton and Bauer, 1996&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>14</td>
<td>21</td>
<td>Recruited from other study, newspapers, and treatment centers</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>A, AE, PM, V</td>
<td>No</td>
<td>4, 5, 6</td>
</tr>
<tr>
<td>Elwan et al., 1997&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>37</td>
<td>120</td>
<td>Egyptian volunteers</td>
<td>NR</td>
<td>≥ 6</td>
<td>NR</td>
<td>A, PM</td>
<td>Yes; attention</td>
<td>4, 5, 6</td>
</tr>
<tr>
<td>Gruber and Yurgeiun-Todd, 1996&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>65</td>
<td>64</td>
<td>27.8 (M)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>A, AE, F, L, PM, V</td>
<td>Yes; attention, executive functioning</td>
<td>2, 4, 5, 7</td>
</tr>
<tr>
<td>Hall et al., 1975&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>20</td>
<td>20</td>
<td>College students</td>
<td>NR</td>
<td>≥ 1 year</td>
<td>NR</td>
<td>A, PM</td>
<td>No</td>
<td>4, 5, 7</td>
</tr>
<tr>
<td>Lyketsos et al., 1999&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>511</td>
<td>806</td>
<td>Participants from the Epidemiologic Catchment Area Study</td>
<td>NR</td>
<td>6 or more times/month</td>
<td>NR</td>
<td>A, F</td>
<td>No</td>
<td>4, 5, 7</td>
</tr>
<tr>
<td>Satz et al., 1976&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>41</td>
<td>41</td>
<td>Costa Rican males</td>
<td>NR</td>
<td>7.7 joints/day (median)</td>
<td>NR</td>
<td>A, AE, F, L, M, PM, V</td>
<td>No</td>
<td>4, 5, 7</td>
</tr>
<tr>
<td>Sethi et al., 1981&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>50</td>
<td>0</td>
<td>Subjects from India</td>
<td>Daily</td>
<td>11-15</td>
<td>NR</td>
<td>F, L, PM</td>
<td>No</td>
<td>2, 4, 5</td>
</tr>
<tr>
<td>Souef, 1976&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>850</td>
<td>839</td>
<td>Egyptian male prison inmates</td>
<td>NR</td>
<td>&lt; 5-20+</td>
<td>NR</td>
<td>A, PM</td>
<td>Yes; attention and perceptuomotor in younger users</td>
<td>4, 5, 6</td>
</tr>
<tr>
<td>Spalletta et al., 1999&lt;sup&gt;aa&lt;/sup&gt;</td>
<td>88</td>
<td>0</td>
<td>Military personnel positive for cannabinoid derivatives in random urine testing</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>AE</td>
<td>Yes; WCST categories achieved and perseverative errors</td>
<td>2, 4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values in parentheses are median or range of means. Data reported in the text should be considered as a minimum estimate.  Data reported in the text should be considered as a minimum estimate.

<sup>b</sup> a. A, attention; AE, abstraction/executive; F, forgetting/retrieval; L, learning; M, motor; PM, perceptual motor; V, verbal/language.

<sup>c</sup> See Table I.

<sup>d</sup> Abstract.
We further examined the studies to determine which criteria were most commonly violated. Because the criteria established to rate study quality are not equally important, Table I ranks them from most essential (i.e., includes a group with history of cannabis use) to those considered less critical (i.e., study addresses potential neurologic and/or psychiatric confounds). Although considered less critical, the latter criteria are still essential to confidently establish a cannabis effect. Because the focus of this review was limited to studies that investigated the nonacute effects of cannabis on neuropsychological functioning, all studies met the first criterion (i.e., included a group with history of cannabis use). Our third criterion (i.e., use of valid neuropsychological tests) was violated by only one study. The high compliance to this criterion was also influenced by our search strategy, as a study was immediately discarded from review if it was clear upon first examination that it did not use neuropsychological outcome measures. Examination of compliance for the remaining criteria across studies reveals important information on some of the specific limitations encountered in many of the studies reviewed.

Of the remaining five criteria, the one least likely to be violated was the inclusion of an appropriate control group. Only seven (18%) of the studies failed to comply with this standard. It is important to underscore the lenient approach used to determine if a study violated any criterion. For example, a control group was determined to be appropriate if it consisted of non-drug-using individuals or individuals with minimal histories of drug use (including marijuana). Therefore, it was often the case that a study would meet this requirement without actually matching groups on important factors, such as other drug use, educational history, and pertinent demographic factors (i.e., age, sex, ethnicity), all of which could have ultimately affected a study’s conclusion.

Most studies attempted to quantify or address other drug use, as well as the presence of neurologic or psychiatric disorders in the cannabis group. Thus, criteria 6 and 7 were violated by only 25% (n = 10) and 28% (n = 11) of studies, respectively. We determined that a study successfully complied with these criteria if there was mention in the manuscript of any instrument, questionnaire, or interview used for establishing the presence of psychiatric and/or neurologic disorders or other substance use. Because of the leniency of these criteria, there were some studies that employed suboptimal means for assessing these potential confounds. Furthermore, when differences between groups on these confounds were discovered, the investigators either opted to statistically covary for these differences or did nothing at all. In cases where a study did not comply with either of these criteria or did not control for their potential effects on neuropsychological functioning, concluding that group differences were based solely on history of cannabis use cannot be justified.

The aforementioned criteria can be applied to any study using neuropsychological outcome measures. They include using appropriate control and experimental groups, using valid outcome measures, and controlling for important confounds. The remaining criteria we examined are specific to studies on the nonacute effects of cannabis on neuropsychological performance. Criteria 4 and 5 are imperative in determining if there is a residual effect or CNS alteration associated with cannabis consumption rather than an acute effect. Criterion 4 requires that participants are determined to be drug free (i.e., not intoxicated) on the day they complete their neuropsychological evaluation. In keeping with our lenient determination of criterion compliance, investigators (at a minimum) needed to mention that participants did not appear intoxicated at the time of testing. Criterion 5 requires that an attempt be made by investigators to assess the recency of last cannabis use to determine how long a participant has been abstinent from cannabis. Forty-three percent (n = 17) of studies violated criterion 4, and an even larger proportion (45%, n = 18) failed to be in accordance with criterion 5. Although both criteria are clearly essential in establishing a persistent, nonacute effect of cannabis on neuropsychological performance, almost half of the studies examined in this review did not explicitly address this issue in their research design.

**DISCUSSION**

Overall, the most important and consistent finding revealed by our review of the literature examining the nonacute effects of cannabis on neuropsychological function was that most studies to date do not meet desired research standards. Few studies met all of our a priori criteria, which were developed to indicate the minimum requirements necessary to confidently establish an effect of cannabis on neuropsychological functioning. This observation was particularly troublesome, given the propensity for conclusions from individual studies to be quickly disseminated in popular (and scientific) culture. Complex and equivocal findings are generally distilled and summarized in a dichotomous manner, which fail to accurately represent the actual results. As an illustration, consider a study that finds poorer performance on a measure of atten-
tion for a group of individuals with a history of heavy cannabis use relative to a control group. This same study may have used several measures of attention but discovered statistically significant differences on only one of these measures. Nevertheless, the study may conclude that a history of heavy cannabis use is associated with deficits in attention and ultimately summarize its findings to suggest that a history of cannabis use is detrimental to cognitive functioning, when in reality the study’s findings could be easily explained by other factors, including Type I error. Because of this, the summary of study results presented in this review, or any review that summarizes investigators’ conclusions, is severely limited. Regardless, our review found that only 55% of studies concluded that nonacute cannabis use is associated with poorer neuropsychological performance. When examining all studies that assessed a given cognitive domain, we found that most failed to find between-group differences. A better way to address this question and more accurately quantify the presence, if any, of a nonacute cannabis effect is by using meta-analytic procedures. Between-group differences on individual neuropsychological tests can be computed, averaged within ability areas, and then combined across studies to determine the overall “cannabis effect” for each ability area. This approach benefits from its ability to generate a quantitative estimate of an effect and its confidence limits, which more closely approximates a “real effect” than a dichotomous conclusion. We recently conducted a meta-analysis of the studies in this review that violated only a few of our “minimal criteria.”

Following a thorough examination of the studies included in this review, additional methodological concerns surfaced that were not directly addressed by our a priori “minimal criteria.” Of particular concern was the possibility that the control and cannabis groups in several studies differed on influential factors not directly related to cannabis consumption. For example, demographic factors such as age, sex, ethnicity, and years of education are known to affect neuropsychological performance. Therefore, if groups differed on any of these factors, observed between-group differences on neuropsychological performance could not have been confidently attributed solely to cannabis use. The effects of these factors can be reduced by using demographically corrected normative data for neuropsychological outcome measures or by using demographic factors as covariates in statistical analyses; however, few studies took advantage of these approaches. Nevertheless, both of these methods have limitations. Specifically, comprehensive normative data that adjust for all pertinent demographic factors are not available for most neuropsychological instruments. Covariates may reduce the effects of demographic differences between groups, but their use does not equate groups on these factors, nor does it completely eliminate their influence and is subject to other limitations.22

Another related issue affecting most studies was that the premorbid neuropsychological abilities of these subjects were largely unknown because subjects’ neuropsychological performance prior to the onset of regular marijuana use was not documented. Some studies attempted to estimate premorbid intelligence through consideration of performance on tests that are not likely to be affected by subtle brain injury (e.g., scores on the Vocabulary subtest of the Wechsler Adult Intelligence Scale [WAIS] series). Although the use of these methods is better than doing nothing at all, they do not effectively equate groups on all important influential factors and cannot ensure that subjects come from the same population. As a result, they are often inadequate. It is important that the groups examined are sampled from the same population and resemble each other on as many factors as possible, with the exception of cannabis use. Some of the most elegant and sophisticated studies reviewed in this article suffered from some of these methodological problems despite meeting our “minimal criteria.” Furthermore, the characteristics of their sample (i.e., only cannabis-dependent individuals, patients from recovery homes, etc.), some studies obtained results that are not generalizable to the entire population of individuals with histories of cannabis use.

We acknowledge the difficulties inherent in studying this topic, given the vast array of potential confounds that could affect results. It is because of these difficulties that we strongly believe it is inaccurate to conclude the presence of a “cannabis effect” when employing suboptimal designs. Stronger research designs can be implemented to more accurately determine the presence of a cannabis effect. For example, studying children and young adolescents prior to entering a period for risk to cannabis exposure can reduce the influence of several confounds. An alternative strategy would be to examine monozygotic twins discordant for marijuana 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 and colleagues19 represents the next best alternative. By examining regular active users who were instructed to abstain and then were 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 marijuana use while simultaneously minimizing important confounds.

The results from this article should present a clearer picture of the research methodology commonly used in studies investigating the nonacute effects of cannabis on neuropsychological performance. Some of the most important methodological shortcomings and confounds in these studies were highlighted, and techniques to eliminate or minimize their influence were discussed. Future studies that attempt to establish a nonacute effect of cannabis on neuropsychological functioning should take special care to ensure that these issues are addressed. In this way, misinterpretation of study results can be minimized, thus revealing the true impact of cannabis use on cognitive abilities.

REFERENCES

NEUROPSYCHOLOGICAL EFFECTS OF CANNABIS USE


