The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis

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ABSTRACT

Patients with schizophrenia frequently report cannabis use, yet its effects on neurocognitive functioning in this population are still unclear. This meta-analysis was conducted to determine the magnitude of effect of cannabis consumption on cognition in schizophrenia without the confounding effects of other co-morbid substance use disorders. Eight studies met inclusion criteria yielding a total sample of 942. Three hundred and fifty-six of these participants were cannabis users with schizophrenia, and 586 were patients with no cannabis use. Neuropsychological tests were grouped into seven domains (general cognitive ability and intelligence; selective, sustained and divided attention; executive abilities; working memory and learning; retrieval and recognition; receptive and expressive language abilities and visuo-spatial and construction abilities). Effect sizes were computed for each cognitive domain between cannabis-using patients and patients with no history of cannabis use. Effect size differences in cognitive performance in the schizophrenia group as a function of cannabis use were in the small to medium range, denoting superior performance in cannabis-using patients. Explanations for these findings are discussed and suggestions for future research in this area are recommended.

1. Introduction

With lifetime use reported to be as high as 64.4%, cannabis is the most commonly used illicit drug among patients with schizophrenia (Barnes et al., 2006). Further, approximately 25% of individuals with the illness have been diagnosed with a comorbid cannabis use disorder (CUD) (Koskinen et al., 2010). While cognitive impairment is common in this disorder, wherein approximately 80% of patients will present with global, rather than specific, deficits across cognitive domains (Keefe et al., 2005), the moderating role of cannabis use on intelligence, attention, learning and memory, executive functioning, and spatial abilities remains unclear (Keefe et al., 2005).

While research reliably illustrates cognitive impairment in schizophrenia, very little is known about the cognitive function of patients suffering from the combined effects of schizophrenia and cannabis use. Intuitively, one may expect cannabis to have a deteriorating effect on cognitive performance as cannabis use has been associated with higher rates of psychotic symptoms (Fergusson et al., 2003), aberrant brain functioning (D’Souza et al., 2004) and is thought to hinder prognosis (Linszen et al., 1994). Nevertheless, to date inconsistent findings of the effects of cannabis on neurocognition have been reported. While the majority of studies examining the effects of cannabis on cognition in schizophrenia report superior neuropsychological functioning (Schnell et al., 2009), others have observed poorer cognitive performance (Mata et al., 2008), or fail to find a difference in some cognitive tasks when comparing patterns of cannabis use (Jockers-Scherubl et al., 2007; Sevy et al., 2007). Furthermore, studies conducted in otherwise healthy cannabis users report either poorer neuropsychological functioning (Bolla et al., 2002) or observe comparable cognitive performance between users and non users (Pope et al., 2001). These findings suggest that cannabis may have differential effects on a vulnerable schizophrenia brain as compared to a healthy brain.

In 2008, Potvin and colleagues conducted a meta-analysis to determine to which extent better neuropsychological functioning might be found among patients with schizophrenia and substance use disorders (Potvin et al., 2008). Their findings are in support of superior cognitive capacities in substance using patients compared to schizophrenia patients without an SUD. They further concluded that these schizophrenia patients do not represent a homogeneous group and that future investigations should consider intermediate factors to define subgroups such as preferred drug of abuse.

Recently, Yucel et al. (2010) published a meta-analysis focusing on the effects of cannabis on cognition in patients with established schizophrenia. Studies were included as long as cannabis was the...
most preferred substance of the sample. As such, their analyses included studies where not all patients in the substance-using group were abusing cannabis, and as a result the cannabis-using subgroup contained patients who did not use cannabis (e.g. Potvin et al., 2005). Moreover, the effects of cannabis use were confounded by concurrent drug use, as patients with current comorbid diagnoses of drug abuse and dependence other than cannabis were not excluded (e.g. Loborg and Hugdahl, 2009; Sevy et al., 2007).

Thus, in the present meta-analysis, our goal was to conduct a further refined analysis to emphasize the direct effects of cannabis on cognition in schizophrenia without the confounding influence of other comorbid substance use disorders. More specifically, we wanted to determine the magnitude of effect of cannabis consumption on neuropsychological performance in schizophrenia.

2. Methods

2.1. Meta-analysis

We employed standard meta-analytic techniques to our review of the literature (Cooper and Hedges, 1994; Hedges and Olkin, 1985; Rosenthal, 1991, 1995). In addition to solving problems with traditional narrative reviews (Wolf, 1986), meta-analysis provides tools for the analysis of magnitude. Magnitude can be indexed with the effect size estimate $d$ that is meant to reflect the degree to which the dependent variable is present in the sample group or the degree to which the null hypothesis is false (Cohen, 1988). In mathematical terms, $d$ is the difference between two group means calibrated in pooled standard deviation units. Eligible research studies comprising a common dependent variable as well as statistics that can be transformed into effect sizes are viewed as a population to be systematically sampled and surveyed. Individual study results (typically means and standard deviations from each group) and relevant moderator variables can be abstracted, quantified and coded, and assembled into a database that is statistically analyzed (Lipsey and Wilson, 1993). The main statistic presented in a meta-analysis is the mean effect size, which is meant to reflect the average individual effect across the sample of studies included in the synthesis. Given the small sample size of studies available, we were unable to correlate moderator variables to the effect size. As a result subject characteristics that may have influenced the magnitude of the effect size could not be teased out. However, to ascertain how robust our findings were, Orwin's fail safe N formula was also utilized so to provide an index of how many studies would be theoretically needed to overturn the obtained effect size and yield an insignificant effect (i.e., $d = 0.1$) (Orwin, 1983). The effect sizes were also transformed into a non-overlap percentage using (Cohen, 1988) idealized distributions, which can be further transformed into an overlap percentage (OL%) to articulate the meaningfulness of an effect size (Zakzanis, 1998, 2001). The OL% statistic represents the degree of overlap by subtracting the non-overlap from 100. In the present context, the hypothetical overlap statistic used represents cognitive test sensitivity, or the percentage of patients who perform unlike any normal control participant in terms of cognitive impairment on a given cognitive test measure.

2.2. Search strategy, selection criteria, and effect size analysis

Articles for consideration were identified through extensive literature searches using online databases, which included PsychINFO, Medline, and PubMed. The search was limited to published English-language articles with human participants. The keywords used were schizophrenia, psychosis, cannabis, tetrahydrocannabinol (or THC), marijuana, in combination with a number of neuropsychology-related terms including; neuropsych", "neurocog", and "cognitive impairment. A secondary search involved checking the reference sections of relevant review and meta-analytic papers for articles that may have been missed in the computerized search. Studies meeting the following criteria were included: (i) Studies had to compare a schizophrenia (or schizophrenia spectrum disorder) cannabis-using group to an appropriate control group i.e. schizophrenia nonusers, control users or healthy controls; (ii) Each study had to provide sufficient information in which effect sizes could be calculated, which implies that sample size, means and standard deviations, and exact p-values, t-values, or exact should be reported; (iii) The use of validated measures of neuropsychological performance must have been used; (iv) Participants must not have any other concurrent drug or alcohol use disorders. A description of included studies is presented in Table 1.

This analysis focused on studies that have either looked solely at the association between cannabis and cognition or those who have properly parsed out the effects of cannabis from other drugs of abuse and/or dependence. Given that other substances including alcohol, cocaine, and stimulants are associated with altered cognitive performance, studies in which participants met for poly-substance use disorders, even if there was preferential use towards cannabis, were excluded.

To this end specifically, effect sizes were derived whenever means and standard deviations were reported. Effect sizes were calculated from inferential statistics based on formulas provided by Wolf (1986) when primary studies did not report central tendency and dispersion data. The statistical software Meta-Analysis 5.3 was used to calculate effect sizes.

2.3. Recorded variables

Recorded variables from each study used in our meta-analysis included the full study reference and any moderator variables reported (e.g. age, duration of illness, and psychotic symptoms). Effect sizes were calculated for each neuropsychological test that measured some aspect of cognitive functioning. To this end, a total of 75 neuropsychological test variables were categorized into 7 cognitive domains. Table 2 illustrates the specific neuropsychological tests that were aggregated into each neurocognitive category. Individual effect sizes for each reported cognitive test score in the literature were calculated and placed under the appropriate domain. If multiple scores were reported for the same measure (e.g., WCST) an aggregate effect size was computed so to not bias the weight that each individual study had on the final average effect size.

3. Results

A total of 8 studies, published between 2005 and 2010, met inclusion criteria and were incorporated into the meta-analysis. These studies yielded a total sample of 942 of which 356 were cannabis-using patients (mean age 28.7 years, 81.9% male, mean education 11.4 years), and 586 were patients with no cannabis use or current substance use disorders (SUD) (mean age 32.4 years, 65.8% male, mean education 12.2 years).

The schizophrenia cannabis-using patients had mean PANSS positive and negative scores of 18.66 (5.6) and 17.97 (5.0) respectively, while the schizophrenia non-using comparison group achieved a mean positive score of 14.61 (6.2) and mean negative score of 17.97 (5.0). While schizophrenia cannabis-using patients had higher positive symptom scores than nonusers [t (1, 191) = 4.73, p < .05], there were no differences in the negative symptoms profile between the two groups [t (1, 191) = 0.82, p > .05].

The effect sizes and related statistics of differences in performance between cannabis-using patients and non-using patients on several neurocognitive domains are presented in Table 3. Most effect sizes were in the small to medium range (Cohen's d = 0.06–0.48), and all suggest superior cognitive functioning in cannabis-using patients as compared to non-using patient. Due to the limited presentation of data on control samples, relevant effect size between schizophrenia...
cannabis users and healthy controls, schizophrenia non-users and healthy controls, and between patient users and cannabis-using controls could not be computed.

4. Discussion

To our knowledge, this is the first quantitative synthesis of neurocognition in patients with schizophrenia with lifetime cannabis use and no other current comorbid substance use disorder. While deficits in various domains of cognition in schizophrenia compared to healthy controls have been reported (Heinrichs and Zakzanis, 1998), our main findings demonstrate superior neurocognitive performance in cannabis-using patients compared to non-using patients.

In clinical neuropsychology effect sizes of 0.50 or greater are considered to be of clinical significance (Lezak et al., 2004). The magnitudes of these effect sizes were only in the small to medium range, which calls into question the clinical significance of the effects of cannabis on neurocognition in this sample of patients with schizophrenia. Our findings are in line with those of Yucel et al. (2010), who observed similar magnitudes of effect, ranging from 0.00 to 0.47.

Given that all studies that met inclusion criteria employed a cross-sectional methodological design, poses a challenge and limits the interpretation of our findings. That is, it is difficult to determine whether...
it is cannabis itself that triggers alterations in neuropsychological functioning or if drug-using patients represent a subset of the schizophrenia population who exhibit better cognitive performance. Longitudinal designs studying the effects of cannabis abstinence or acute challenges are needed to parse the effects of cannabis per se on cognition in schizophrenia.

It has been proposed that the endocannabinoid system serves to regulate neuronal circuits and pathways involved in neurocognition (Gerdenman et al., 2003). Research suggests that exposure to cannabinoids can result in functional changes in CB1-rich brain regions, such as dopamine, GABA, and glutamate (Cohen et al., 2008). The neurochemical mechanisms by which cannabis may ameliorate cognitive dysfunction in schizophrenia have recently been reviewed (Coulston et al., 2011).

Alternatively, patients with comorbid cannabis use disorders may belong to a subgroup of schizophrenia whereby they encompass better premorbid adjustment, social skills and prognosis (Dixon et al., 1991). Drug-seeking individuals may possess social skills that enable them to socialize in drug scenes and allow them to facilitate the purchase and acquisition of illegal substances. These characteristics have been associated with higher cognitive capacities among persons with schizophrenia (Silverstein et al., 2002).

While not included in the analysis due to its methodological study design, it is important to comment on the work of D’Souza et al. (2005). They characterized the dose-related effects of intravenous THC in13 patients with no history of a CUD and controls. Both patients and control participants demonstrated impairments in verbal memory and attention compared to those on placebo. Moreover, the schizophrenia group performed worse than controls in these domains, demonstrating an enhanced sensitivity to the effects of THC on cognition in schizophrenia (D’Souza et al., 2005). It is important to note that the patient sample of the study was comprised of schizophrenia subjects with at least one exposure to cannabis but no lifetime CUD, a divergence from the sample examined in this study. In keeping with the results of our analyses, one would expect such individuals to perform worse than healthy controls and patient users.

While our findings lend support for better cognitive functioning in cannabis-using patients, it must be stressed that this does not imply that cannabis improves cognition in schizophrenia. Cannabis may very well impair cognition in a dose-related fashion in both healthy controls and those with a diagnosis of schizophrenia. In lieu of this, patients who use cannabis who then achieve abstinence may then demonstrate even further improvements in their cognitive functioning. Future research may opt to include an additional comparison group of patients with former CUDs in order to help determine and clarify cannabis’ role and neurobiological mechanism of action in the brain.

The current study has several limitations. First, as this is a relatively understudied area of research, only 8 studies met inclusion criteria and were able to be incorporated into our analyses. Thus, these findings are preliminary and will need to be replicated with larger number of studies to help articulate the nature of this relationship as well as to determine the influence of any potential moderating variables. The low fail safe Ns are supportive of our general findings that cannabis use has little to no detrimental effect on most aspects of cognition in schizophrenia. And while the fail safe N is to be taken to articulate the robustness of an obtained effect as a function of sample size, other meta-analyses have demonstrated that in the instance of a large effect size based on a similar very few number of studies, results in very high fail safe N (e.g. McKay and Zakzanis, 2010; Zakzanis et al., 2010).

Second, while we were able to compute effect sizes as a function of cannabis use in schizophrenia (Scz+ vs Scz−), we were unable to calculate effect size differences due to psychotic diagnosis (Scz− vs Ctrl−), the combined effects of cannabis use and schizophrenia (Scz+ vs Ctrl+) nor the effects of cannabis use alone (Scz+ vs Ctrl−). Not enough data was presented to isolate these more specific effects of cannabis use as only 3 of the 8 studies included a healthy control sample, and only 2 studies had a non-psychiatric cannabis comparison group. The inclusion of a control group with CUDs would allow for a more comprehensive understanding of the effects of cannabis on the brain, and determine whether it acts similarly in healthy users vs patient users.

Third, only a subgroup of studies reported moderator data regarding variables like age of illness onset, duration of illness and cannabis use disorder and affective and psychiatric symptoms. This information is critical in order to precisely examine the influence of potential moderators on effect size as a number of authors have emphasized the role of symptom severity, and chronicity in the cognitive functioning of patients with schizophrenia (Bornschein et al., 1990; Stip, 1996).

Fourth, a meta-analysis is only as good as the studies it includes. Limitations and lack of control over potential confounding variables exemplified in the 8 studies are likely responsible for the inconsistent findings reported in the literature. While our study excluded cannabis-using patients with other concurrent substance use disorders, future studies may benefit from examining the cognitive effects of cannabis with very limited lifetime use of any other drug. This may help

### Table 2
Neurocognitive and tests used in meta-analysis.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Recorded test variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cognitive ability and intelligence</td>
<td>MWT-B (IQ), NART, Full-scale IQ WAIS, Verbal score (WAIS), Performance score (WAIS), WAIS Picture</td>
</tr>
<tr>
<td>Selective, sustained and divided attention</td>
<td>WAIS Digits Symbol, Trailmaking A, CPT d’ symbol, CPT digit, CPT samples Loght, Dual Tasking (auditory hits, auditory false alarms, auditory misses, visual hits, visual false alarms, and visual misses), CogState</td>
</tr>
<tr>
<td>Executive abilities</td>
<td>WCST (total correct, total errors, trials to complete first category, perseverative errors, perseverative responses, nonperseverative errors, conceptual level response, other errors, categories completed, failure to maintain set), Tower of London, Trailmaking B, Color–Word Interference Test, Color–Word Set Shifting</td>
</tr>
</tbody>
</table>

### Table 3
Results of meta-analysis of cannabis use vs no use in schizophrenia.

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Mean d</th>
<th>SD</th>
<th># of studies used in ES</th>
<th>Overlap %</th>
<th>Nfs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General cognitive ability and intelligence</td>
<td>0.48</td>
<td>0.51</td>
<td>4</td>
<td>64</td>
<td>15</td>
</tr>
<tr>
<td>2. Selective, sustained and divided attention</td>
<td>0.35</td>
<td>0.23</td>
<td>6</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>3. Executive abilities</td>
<td>0.14</td>
<td>0.49</td>
<td>7</td>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>4. Working memory and learning</td>
<td>0.07</td>
<td>0.40</td>
<td>5</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>5. Retrieval and recognition</td>
<td>0.12</td>
<td>0.50</td>
<td>6</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>6. Receptive and expressive language abilities</td>
<td>0.06</td>
<td>0.30</td>
<td>4</td>
<td>95</td>
<td>1</td>
</tr>
<tr>
<td>7. Visuo-spatial and constructional abilities</td>
<td>0.33</td>
<td>0.27</td>
<td>3</td>
<td>76</td>
<td>7</td>
</tr>
</tbody>
</table>

ES, effect size; Nfs, Orwin’s fail safe N formula.
to further clarify the role of cannabis in cognitive performance as lifetime alcohol and drug use has been associated with altered cognition (Allen et al., 1999; Lilaud and Verdoux, 2002; Pencer and Addington, 2003; Serper et al., 2000). Several other caveats to note are a heterogeneous sample population, varying cannabis abstinence period before neurocognitive testing, and failure to control for smoking status.

Finally, in addition to confounds, methodological variability between the studies presents itself as another source of discrepancy. For example, the approach in which cannabis users vs non-users were characterized differed greatly between studies. While some researchers defined it according to diagnostic standards of cannabis abuse or dependence using the Structured Clinical Interview for the DSM-IV (SCID-IV), (DeRosse et al., 2010; Kumra et al., 2005; Schnell et al., 2009) others declared a minimum arbitrary amount and duration (Jockers-Scherubl et al., 2007; Yucel et al., 2010), whereas other investigators failed to provide any diagnostic criteria whatsoever (Ringen et al., 2010; Scholes and Martin-Iverson, 2009). The comparative cannabis-naïve group is more uniform across studies, mostly defined as the absence of a SCID CUD diagnosis. Employing this binary classification system can be misleading as it is apt to include occasional cannabis users or more frequent and heavy users whose functioning is unaffected to the extent in which an SUD diagnosis is made. Jockers-Scherubl et al. (2007) overcame this inadequacy by defining abuse as lifetime consumption of at least 5 times; others have followed and adopted this criteria as well (Schnell et al., 2009).

The importance of clearly assessing and defining comparison groups cannot be stressed enough, as the way in which one proposes to characterize a “cannabis user” or “non-user” can significantly influence results. For example Scholes and Martin-Iverson, 2009 and Ringen et al. (2010) defined the cannabis-using group according to a binary system, classifying participants as either users or non-users. No other criteria such as impact on functioning, amount, frequency or duration was taken into account. Interestingly, it was these studies that reported null findings or observed cannabis use to have a detrimental effect on cognition. In contrast, studies which mandated a diagnosis of a CUD or stipulated a minimum amount and duration of use reported superior neuropsychological functioning among the cannabis-using group. This highlights the importance of patterns of cannabis consumption, rather than bisecting a spectrum of use. Further support for this is found in studies that report higher frequency of cannabis use is associated with even better cognitive performance (Coulston et al., 2007; Schnell et al., 2009). Moreover, it should be noted that a CUD often encompasses both current diagnosis of abuse and/or dependence as well as those with a history or who are now in remission. Partitioning these participants into former and current abusers may further eradicate discrepancies in the literature.

In conclusion, cannabis use likely has modest and possible clinically insignificant effects on neurocognitive function in schizophrenia. We propose that future studies asserting the effects of cannabis on cognition in schizophrenia may benefit from the introduction of standardized approaches in research methodology, such as the use of homogeneous definitions, as well as the inclusion of appropriate comparison groups (i.e. non-psychiatric healthy controls and control participants diagnosed with CUDs). Additional research should consider employing longitudinal designs and ensure to control for potential confounding factors. Implementing these suggestions will allow for a more comprehensive interpretation of results and ultimately culminate in better understanding the effects of cannabis use on cognition in schizophrenia.

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Contributors
Miss Rachel Rabin performed the literature search and analyses, as well as wrote the manuscript. Dr. Zakzanis helped with analyses and methods section and Dr. George assisted with the preparation of the manuscript. All authors contributed to and have approved the final manuscript for submission.

Conflict of interest
The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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