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Research paper

Does cannabis affect cognitive functioning in patients with schizophrenia?

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ABSTRACT

Introduction: Cannabis use impairs cognitive performance in healthy subjects; several studies have shown improved cognitive outcomes in schizophrenic patients using cannabis. The aim of this study was to evaluate the effects of cannabis use on cognitive function in Moroccan patients with schizophrenia who were cannabis users.
Method: Two groups were recruited in a Moroccan University Psychiatric Centre. Fifty patients diagnosed with schizophrenia according to the DSM-V who were cannabis users (SZ CANN +) and forty-nine patients diagnosed with schizophrenia according to DSM-V who do not use cannabis (SZ CANN-). Cognitive functioning was assessed using the CogState neuropsychological battery.
Results: The results of the study suggest that SZ CANN- patients performed better in the test of psychomotor function, attention and verbal memory. While SZ CANN+ patients performed better in the test of working memory, visual memory and emotional recognition. We found no relationship between SZ CANN+ patients and SZ CANN- patients concerning executive function.
Conclusions: Our results suggest that cannabis use may have different effects on neurocognitive functioning. It is associated with disorders of psychomotor function, attention and verbal memory. So, it is associated with an improvement in working memory, visual memory and emotion recognition.

1. Introduction

Cannabis is the most commonly used illicit drug by patients with schizophrenia (Cantwell et al., 1999). Cannabis contains a mixture of cannabinoids that may have effects that are not necessarily harmful to mental health (Morgan and Curran, 2008).

Cannabis use in patients with schizophrenia has been associated with an increase in auditory hallucinations and a strong decrease in negative affectivity (Henquet et al., 2006). Heavy cannabis users show temporary cognitive deficits several hours or days after cannabis withdrawal (Pope et al., 2001). These cognitive deficits are common signs of schizophrenia (Green, 1996; Palmer et al., 2009; Green et al., 2004), and are detected by neuropsychological tests assessing cognitive functions, including attention, working memory and executive functions (Heinrichs and Zakzanis, 1998; Keefe and Fenton, 2007).

Cannabis use is associated with a higher risk of developing schizophrenia (Andréasson et al., 1987; Arseneault et al., 2007; Zammit et al., 2002). It has been suggested that cannabis use in healthy individuals can lead to cognitive impairment similar to schizophrenia (Andréasson et al., 1987; Arseneault et al., 2007; Zammit et al., 2002).

Pope et al. (2001) and Jager et al. (2006) found no difference between cannabis users and non-users concerning attention, learning and verbal memory, visual memory and executive functions. In contrast, Bolla et al. (2002) reported that heavy cannabis users showed persistent dose-related deficits in tests of verbal memory, visual memory, executive functions and psychomotor speed. The authors identified risk factors for cognitive impairment, namely specific patterns of cannabis use, early onset, long-term use and higher frequency of use (Bolla et al., 2002; Harvey et al., 2007). A recent meta-analysis indicates that cannabis use is generally not associated with neurocognitive functioning (attention, executive functions, processing speed, learning and verbal memory, visual memory and working memory) in patients with a first episode of psychosis (Sánchez-Gutiérrez et al., 2020).

Therefore, the present study was designed to assess the effects of

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cannabis use on cognitive function in Moroccan schizophrenia patients who are cannabis users or non-users using the computerized neuropsychological Cogstate battery, measuring seven domains most prevalent in schizophrenia patients, including processing speed, attention, working memory, visual memory, verbal memory, executive functions and emotional recognition.

Two hypotheses were put forward: first, those cannabis-using patients would have worse neurocognitive functioning than non-cannabis-using patients, and second, that age and gender influence the relationship between cannabis use and neurocognitive functioning.

2. Methods

2.1. Subjects

Recruitment for the study was carried out from January to August 2019 in the Ibn Rochd University Psychiatric Centre, Casablanca, Morocco.

The study included two groups (sample modest):

- The first group: included 50 patients with DSM-V schizophrenia who were cannabis users (SZ CANN+).
- The second group: included 49 patients with DSM-V schizophrenia who were not cannabis users (SZ CANN-). This group is exclusively composed of patients who have never used cannabis and does not include patients with past use.

The patients included in the study were aged between 18 and 45 years, with no history of neurological disorders or significant central nervous system trauma.

Subjects were excluded if they had reported regular use of alcohol (more than three drinks per week) or drugs other than cannabis on more than four times in their lifetime (according to Jockers-Scherubl et al., 2007). Thus, patients were excluded if they tested positive for amphetamines, methamphetamines, cocaine, barbiturates, benzodiazepines or opiates in daytime urine using immunochromatography.

All patients were in a stable psychopathological state, according to the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). SZ CANN- patients never used cannabis, while SZ CANN+ patients used at least twice a week.

The study was approved by the Ethics Committee of the Faculty of Medicine and Pharmacy Casablanca (ref: 2001/20:CE). Written consent was obtained from the patients' families. Confidentiality and anonymity were maintained during data collection, analysis and reporting.

Prior to inclusion in the study, each treating psychiatrist contacted the patient to determine his or her capacity to give informed consent.

2.2. Procedures

Each subject participated in two sessions that took between 2 and 4 days interval. In the first session, a structured clinical interview using DSM 5 criteria was used. Information was collected regarding demographic data: age of onset of schizophrenia, duration of illness. Psychiatric symptoms were assessed using the PANSS scale (Kay et al., 1987). In the second session, we performed a cognitive test and a urine sample in order to ascertain cannabis use.

Cannabis use was assessed by asking participants about their lifetime use, current or past: if yes, age of onset of use, withdrawal period longer than 6 months and use in the last 4 weeks.

Cogstate is a computerized battery that measures cognitive function with good validity and reliability.

The CogState cognitive test battery required a maximum of 40 min, with patients completing the test battery in one session. It consisted of a test of psychomotor function (De tection Test), a test of attention (Identification Test), and executive functions (Groton Maze Learning Test). For these three tests a lower score means a better performance. Two tests of working memory (One Rewind Test, Two Rewind Test), a test of visual memory (Map Learning Test), a test of verbal memory (International Shopping List Task) and a test of emotional recognition (Socio-emotional Cognition Test) (https://www.cogstate.com). For these five tests a higher score means better performance. The tests were displayed on a green screen, complete with standardized instructions given by trained researchers before the start of each test, to ensure that patients fully understood and followed the rules. The results were uploaded to a secure account on the Cogstate website, where the data was calculated and standardized.

2.3. Statistical analysis

All analyses were performed using Jamovi software version 1.6.15.0. Statistical significance was determined using the 0.05 level.

All analyses were performed comparing SZ CANN- patients with SZ CANN+ patients. Age and gender have been analyzed using chi-square. Analysis of variance (ANOVA) was used to compare other demographic variables, positive and negative symptoms and general psychopathology. For the comparison of groups on cognitive functions, a student (t) test was performed when the variables followed the normal distribution and a Mann-Whitney test (U) when the variables do not follow the normal distribution. Differences in cognitive functions between groups were analyzed using an ANCOVA test adjusted for age and gender.

3. Results

3.1. Demographic characteristics

As shown in Table 1, the two groups SZ CANN+ and SZ CANN- were similar in terms of age, with a higher proportion of males in the SZ CANN + group compared with the SZ CANN- group. The number of years of education was comparable in both groups. The age of onset of psychotic symptoms in both patients was similar. The SZ CANN+ group had a shorter duration of illness than the SZ CANN- group. The average number of hospitalizations was about the same among the two groups.

3.2. Cognitive performance

The SZ CANN-group of patients performed well in the tests of psychomotor function ($U = 81.00$, $P = 0.003$), attention ($U = 53.00$, $P = 0.001$) and verbal memory ($T = -2.103$, $P = 0.043$) compared to the SZ CANN+ group. While the SZ CANN+ group of patients performed better in both tests of working memory ($U = 82.00$, $P = 0.020$; $U = 77.5$, $P = 0.023$), visual memory ($T = 3.846$, $P < 0.001$) and emotional recognition ($T = 2.229$, $P = 0.033$).

The SZ CANN+ group performed better in the executive function test ($U = 145.00$, $P = 0.804$) but the p-value remained insignificant (Fig. 1).

After adjustment for age and sex, we found that there was no association between age and sex and cognitive performance in patients with schizophrenia. The results suggest that age and gender did not affect the

Table 1
Comparison of cannabis users (SZ CANN+) and non-users cannabis (SZ CANN-) patients on demographic information.

	SZ CANN+(mean ± standard deviation)	SZ CANN-(mean ± standard deviation)	p
Age	29.95 ± 10.86	32.45 ± 10.31	0.540
Gender (% men/women)	62/38	34.4/56.7	0.020
Education of patients	7.53 ± 2.98	7.00 ± 2.72	0.576
Age of onset of schizophrenia	18.74 ± 6.72	20.18 ± 3.73	0.519
Disease duration	10.16 ± 6.36	12.91 ± 8.37	0.318
Number of hospitalizations in psychiatric hospital	1.68 ± 0.67	1.45 ± 0.82	0.412

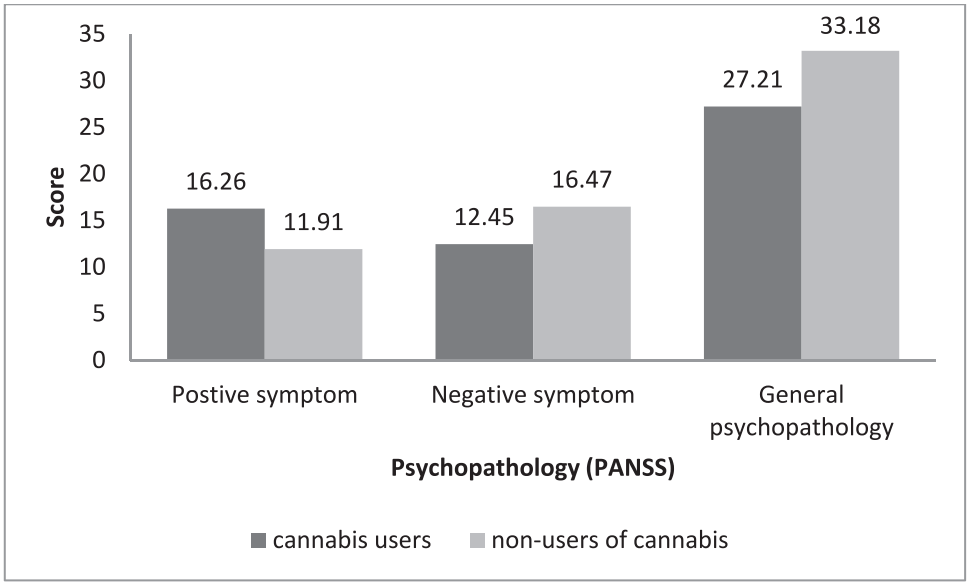

Fig. 1. Comparison of users cannabis (SZ CANN +) and non-users of cannabis (SZ CANN-) patients on measures of cognitive function.

cognitive performance of SZ CANN+ and SZ CANN- patients (Table 2).

4. Discussion

Our study was designed to assess the effect of cannabis use on cognitive functioning in Moroccan patients with schizophrenia. We administered the Cogstate neuropsychological test battery to 49 schizophrenic patients who did not use cannabis (SZ CANN-) and to 50 schizophrenic patients who did use cannabis (SZ CANN+).

Our results suggest that cannabis use improves visual memory, working memory and emotion recognition in schizophrenia, which is consistent with several studies that have found that cannabis improves cognitive function in schizophrenic patients (Schnell et al., 2009). These results are consistent with other studies that have found improved neuropsychological functioning in cannabis-using patients with schizophrenia compared with non-using patients (Sevy et al., 2001; Carey et al., 2003; Joyal et al., 2003; Løberg et al., 2003, 2008; Herman, 2004; Kumra et al., 2005; Potvin et al., 2005; Stirling et al., 2005; McCleery et al., 2006; Coulston et al., 2007; Jockers-Scherubl et al., 2007), while others have observed a deterioration in cognitive performance (Mata et al., 2008).

In addition, some studies found no significant difference in certain cognitive tasks when comparing cannabis use in patients with schizophrenia (Sevy et al., 2007). There was no difference between cannabis users and non-users who had experienced a first episode of psychosis in the neurocognitive tasks of memory, verbal fluency and attention (De Vos et al., 2020). Bosia et al., 2019 examined the relationship between cannabis use and cognitive measures; no significant differences were found between cannabis users and non-users.

Bogaty et al., 2019 found no cognitive differences in psychomotor speed, mental flexibility, verbal learning, verbal memory and attention in patients with psychosis who used cannabis and those who were abstinent at the time of illness onset. As a result, Bogaty et al., 2018 demonstrated that psychotic patients who currently use cannabis show deficits in tests of verbal learning, verbal working memory and motor inhibition, compared with those who do not use cannabis. Moderate and heavy cannabis use was associated with less impairment in neurocognition and metacognition compared with non-users (Schnakenberg Martin et al., 2016). Cannabis users use the substance to alleviate some of the symptoms associated with the disease, such as anxiety, hallucinations or sleep disorders (Dixon, 1999).

Cannabis use is not only linked to psychotic patients (Ringen et al., 2008), it also increases the risk of schizophrenia (Moore et al., 2007; Manrique-Garcia et al., 2012). Furthermore, some of the neurocognitive deficits observed in cannabis users are similar to those observed in patients with schizophrenia (Solowij and Michie, 2007; Cohen et al., 2008). There is increasing evidence that cannabis use in patients with schizophrenia improves cognitive function (Segev and Levkovitz, 2012). Two main explanations have been proposed to explain why cannabis use does not impair cognitive performance in people with psychosis, unlike in healthy subjects. One of them suggests that certain cannabinoids present in cannabis may have a favourable effect on cognition (Riedel and Davies, 2005). Previous studies have shown that cannabis use in adolescents can affect areas of the brain involved in neurocognitive functions (Parolaro et al., 2010) and can impair neurocognitive functions in adolescents (Crews et al., 2007). The parts of the brain most affected by cannabinoids are the prefrontal cortex, hippocampus, amygdala, nucleus accumbens and hypothalamus (Sowell et al., 1999, 2002). However, the two main cannabinoids in cannabis, delta-9tetrahydrocannabinol (D9-THC) and cannabidiol (CBD) can have opposite effects on cognition. Delta 9-tetrahydrocannabinol (D9-THC) is responsible for many of the psychotomimetic effects of the drug. It has been linked to increased levels of anxiety and psychotic symptoms in healthy subjects (D'Souza et al., 2004). In schizophrenic patients and their healthy siblings, acute administration of the main psychoactive

Table 2
ANCOVA results for cognitive data.

Cognitive performance	Group (users cannabis / non-users cannabis)	Gender	Age
Psychomotor function	$F = 1.166$, $p = 0.288$	$F = 0.828$, $p = 0.378$	$F = 0.148$, $p = 0.703$
Attention	$F = 0.039$, $p = 0.843$	$F = 0.015$, $p = 0.902$	$F = 1.430$, $p = 0.241$
Visual memory	$F = 1.21$, $p = 0.280$	$F = 2.309$, $p = 0.139$	$F = 0.184$, $p = 0.084$
Working memory	$F = 0.546$, $p = 0.465$	$F = 0.561$, $p = 0.459$	$F = 0.084$, $p = 0.774$
Working memory	$F = 0.214$, $p = 0.646$	$F = 1.405$, $p = 0.245$	$F = 0.029$, $p = 0.886$
verbal memory	$F = 0.964$, $p = 0.334$	$F = 0.132$, $p = 0.718$	$F = 1.319$, $p = 0.260$
Executive function	$F = 2.309$, $p = 0.139$	$F = 0.964$, $p = 0.334$	$F = 2.829$, $p = 0.103$
Emotional recognition	$F = 0.985$, $p = 0.329$	$F = 1.002$, $p = 0.325$	$F = 1.006$, $p = 0.324$

component of cannabis (D9-tetrahydrocannabinol; THC) led to various neuro-cognitive difficulties in attention, executive function and memory (D'Souza et al.2005, Henquet et al., 2006). D9-THC transiently increases learning deficits, positive and negative symptoms of schizophrenia, perceptual impairments and vigilance deficits (D'Souza et al., 2005). D9-THC acts as an exogenous agonist for endogenous presynaptic cannabinoid receptors. These endogenous cannabinoids have an important function in the control of neural structures and circuits involved in attention, executive functions and memory. D9-THC is deposited in fatty tissue, liver, lungs, spleen and myelin in the brain. It is then released and metabolized in the bloodstream, which can last from 5 to 95 days in heavy users (Musshoff et al., 2006).

The cannabidiol (CBD), another major compound in cannabis, has been shown to be anxiolytic and has antipsychotic characteristics, and may be neuro-protective in humans (Zuardi et al., 2006; Leweke et al., 2000; Hermann et al., 2007). There is preliminary evidence that CBD may improve cognition in healthy individuals (Colizzi and Bhattacharyya, 2017). Therefore, the ratio of D9-THC to CBD in cannabis may represent a significant confounding factor when studying the association between cannabis use and cognition.

CBD offers a degree of protection against the cognitive effects of THC (Oreja-Guevara, 2012). A higher CBD to THC ratio reduces cognitive impairment and the effects generated by THC (Wade et al., 2004). Researchers suggest that using cannabis containing CBD in addition to D9-THC may be protective against psychotic-like symptoms induced by D9-THC alone (Morgan and Curran, 2008).

It is important to note that cannabis is neither a sufficient nor an obligatory cause of psychosis; it interacts with neurobiological vulnerability and facilitates the onset of illness in vulnerable individuals (Caspi et al., 2005; Linszen and van Amelsvoort, 2007). Therefore, early and frequent cannabis use increases the likelihood of becoming psychotic, and it is possible that some patients would not be psychotic if they had not used cannabis. Moore et al. (2007) estimate that cannabis use may be the primary cause of psychosis in approximately 10 % of patients with schizophrenia.

This article highlights the significant difference in cognitive performance between SZ CANN + and SZ CANN- patients, suggesting that cannabis use may have a role in the indices of neurocognitive performance assessed in the current study. As mentioned previously, we were unable to collect information on the kind of cannabis that individuals prefer, as the content of D9-THC and CBD varies considerably between strains, although it is difficult to interpret the results due to the unknown ratio of 9D-THC to CBD contained in the cannabis consumed. Cannabis contains different amounts of 9D-THC and CBD, and these two cannabinoids influence the potency of cannabis. We must consider that CBD can improve cognitive performance.

It would be interesting to compare the patient data with data from a third group of healthy cannabis users and a fourth healthy control group not cannabis users. Larger sample of respondents are needed to scientifically determine cannabis potential in improving cognitive performance among male and female schizophrenic patients. Unfortunately, we were not able to recruit subjects meeting this criterion because the recruitment of these people will probably take a long time.

5. Conclusions

In conclusion, our results show that cannabis use can impair cognitive domains of psychomotor function and attention, and can improve the cognitive domains of working memory, visual memory, verbal memory, emotional recognition and executive functions studied here.

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CRediT authorship contribution statement

Hajar Rachid: Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. **Zineb Saif:** Formal analysis. **Salma Raoui:** Investigation. **Zineb Serhier:** Software. **Mohamed Agoub:** Methodology, Project administration, Software, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Andréasson, S., Allebeck, P., Engstrom, A., Rydberg, U., 1987. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet 2, 1483–1486. https://doi.org/10.1016/s0140-6736(87)92620-1.

Arseneault, L., Cannon, M., Witton, J., Murray, M., 2007. Causal association between cannabis and psychosis: examination of the evidence. Focus 5, 137–278. https://doi.org/10.1176/foc.5.2.foc270.

Bogaty, S.E.R., Lee, R.S., Hickie, I., Hermens, D.F., 2018. Meta-analysis of neurocognition in young psychosis patients with current cannabis use. J. Psychiatr. Res. 99, 22–32. https://doi.org/10.1016/j.jpsychires.2018.01.010.

Bogaty, S.E.R., Crouse, J.J., Hickie, I.B., Hermens, D.F., 2019. The neuropsychological profiles of young psychosis patients with and without current cannabis use. Cogn. Neuropsychiatry 24, 40–53. https://doi.org/10.1080/13546805.2018.1562887.

Bolla, K.I., Brown, K., Eldreth, D., Tate, K., Cadet, J.L., 2002. Dose-related neurocognitive effects of marijuana use. Neurology 59, 1337–1343. https://doi.org/10.1212/01.wnl.0000031422.66442.49.

Bosia, M., Buonocore, M., Bechi, M., Stere, L.M., Silvestri, M.P., Inguscio, E., Cavallaro, R., 2019. Schizophrenia, cannabis use and catechol-O-methyltransferase (COMT): modeling the interplay on cognition. Progress in Neuro-Psychopharmacology Biological Psychiatry 92, 363–368. https://doi.org/10.1016/j.pnpbp.2019.02.009.

Cantwell, R., Brewin, J., Glazebrook, C., Dalkin, T., Fox, R., Medley, I., Harrison, G., 1999. Prevalence of substance misuse in first-episode psychosis. Br. J. Psychiatry 174, 150–153. https://doi.org/10.1192/bjp.174.2.150.

Carey, K.B., Carey, M.P., Simons, J.S., 2003. Correlates of substance use disorder among psychiatric out patients: focus on cognition, social role functioning, and psychiatric status. J. Nerv. Ment. Dis. 191, 300–308. https://doi.org/10.1097/01.NMD.0000066152.87832.A9.

Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., Craiq, I.W., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol. Psychiatry 57, 1117–1127. https://doi.org/10.1016/j.biopsych.2005.01.026.

Cohen, M., Solowij, N., Carr, V., 2008. Cannabis, cannabinoids and schizophrenia: integration of the evidence. Aust. NZ J. Psychiatry 42, 357–368. https://doi.org/10.1080/00048670801961156.

Colizzi, M., Bhattacharyya, S., 2017. Does cannabis composition matter? Differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition. Curr. Addict. Rep. 4, 62–74. https://doi.org/10.1007/s40429-017-0142-2.

Coulston, C.M., Perdices, M., Tennant, C.C., 2007. The neuropsychological correlates of cannabis use in schizophrenia: lifetime abuse/ dependence, frequency of use, and recency of use. Schizophr. Res. 96, 169–184. https://doi.org/10.1007/s40429-017-0142-2.

Crews, F., He, J., Hodge, C., 2007. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol.Biochem.Behav 86, 189–199. https://doi.org/10.1016/j.pbb.2006.12.001.

De Vos, C., Leopold, K., Blanke, E.S., Siebert, S., Baumgardt, J., Burkhardt, E., Bechdolf, A., 2020. The relationship between cannabis use and cognition in people diagnosed with first-episode psychosis. Psychiatry Res. 293, 113424 https://doi.org/10.1016/j.psychres.2020.113424.

Dixon, L., 1999. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr. Res. 35 (Suppl), S93–100.

D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y.T., Braley, G., Gueorguieva, R., Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29, 1558–1572. https://doi.org/10.1038/sj.npp.1300496.

D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T.B., Krystal, J.H., 2005. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol. Psychiatry 57 (6), 594–608. https://doi.org/10.1016/j.biopsych.2004.12.006.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J.Psychiatry 153 (3), 321–330. https://doi.org/10.1176/ajp.153.3.321.

Green, A.I., Tohen, M.F., Hamer, R.M., Strakowski, S.M., Lieberman, J.A., Glick, I., Clark, W.S., 2004. First episode schizophrenia related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr. Res. 66, 125–135. https://doi.org/10.1016/j.schres.2003.08.001.

Harvey, M.A., Sellan, J.D., Porter, R.J., Frampton, C.M., 2007. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev. 26 (3), 309–319. https://doi.org/10.1080/09595230701247772.

Heinrichs, W, Zakzanis, K, 1998. *Déficit neurocognitif dans la schizophrénie : un examen quantitatif des preuves*. Neuropsychologie 12 (3), 426–445. https://doi.org/10.1037/0894-4105.12.3.426.

Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Fananas, L., Drukker, M., Ramaekers, J.G., van Os, J., 2006. An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacol 31 (12), 2748–2757. https://doi.org/10.1038/sj.npp.1301197.

Herman, M., 2004. Neurocognitive functioning and quality of life among dually diagnosed and non-substance abusing schizophrenia inpatients. Int. J. Ment. Health Nurs. 13, 282–291. https://doi.org/10.1111/j.1440-0979.2004.00346.x.

Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., 2007. Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. BiolPsychiatry 61, 1281–1289. https://doi.org/10.1016/j.biopsych.2006.08.027.

Jager, G., Kahn, R.S., Van Den Brink, W., Van Ree, J.M., Ramsey, N.F., 2006. Long-term effects of frequent cannabis use on working memory and attention : an fMRI study. Psychopharmacology 185, 358–368. https://doi.org/10.1007/s00213-005-0298-7.

Jockers-Scherubl, M.C., Wolf, T., Radzei, N., Schlattmann, P., Rentzsch, J., Gomez-Carrillo de Castro, A., and. Kuhl KP., 2007. Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. Prog.Neuropsychopharm. Biol. Psychiatry 31 (5), 1054–1063. https://doi.org/10.1016/j.pnpbp.2007.03.006.

Joyal, C.C., Hallé, P., Lapierre, D., Hodgins, S., 2003. Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. Schizophr. Res. 63 (3), 297–299.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–277. https://doi.org/10.1093/schbul/13.2.261.

Keefe, R.S.E., Fenton, W.S., 2007. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr. Bull. 33 (4), 912–920. https://doi.org/10.1093/schbul/sbm046.

Kumra, S., Thaden, E., DeThomas, C., Kranzler, H., 2005. Correlates of substance abuse in adolescents with treatment-refractory schizophrenia and schizoaffective disorder. Schizophr. Res. 73, 369–371. https://doi.org/10.1016/j.schres.2004.08.006.

Leweke, F.M., Schneider, U., Radwan, M., Schmidt, E., Enrich, H.M., 2000. Different effects of nabilone and cannabidiol on binocular depth inversion in man. Pharmacol. Biochem. Behav. 66 (1), 175–181. https://doi.org/10.1016/s0091-3057(00)00201-x.

Linszen, D., van Amelsvoort, T., 2007. Cannabis and psychosis: an update on course and biological plausible mechanisms. CurrOpin Psychiatry 20 (2), 116–120. https://doi.org/10.1097/YCO.0b013e32803577fb.

Løberg, E.M., Jørgensen, H.A., Hugdahl, K., 2003. The effects of previous drug abuse on neurocognition in schizophrenia. Abstract. J. Int. Neuropsychol. Soc. 9, 172.

Løberg, E.M., Hugdahl, K., Jørgensen, H.A., 2008. Lower neurocognitive vulnerability in schizophrenia with a history of cannabis abuse? Abstract. Schizophr. Res. 98 (Suppl. S), 73. https://doi.org/10.1016/j.schres.2007.12.164.

Manrique-Garcia, E., Zammit, S., Dalman, C., Hemmingsson, T., Allebeck, P., 2012. Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts. BMC Psychiatry 12, 112. https://doi.org/10.1186/1471-244X-12-112.

Mata, I., Rodríguez-Sánchez, J.M., Pelayo-Terán, J.M., Pérez-Iglesias, R., González-Blanch, C., Ramírez-Bonilla, M., Martínez-García, O., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2008. Cannabis abuse is associated with decision-making impairment among first-episode patients with schizophrenia-spectrum psychosis. Psychol. Med. 38 (9), 1257–1266. https://doi.org/10.1017/S0033291707002218.

McCleery, A., Addington, J., Addington, D., 2006. Substance misuse and cognitive functioning in early psychosis: a 2 year follow-up. Schizophr. Res. 88, 187–191. https://doi.org/10.1016/j.schres.2006.06.040.

Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., Lewis, G., 2007. Cannabis use and risk of psychotic or affective mental outcomes: a systematic review. Lancet 370, 319–328. https://doi.org/10.1016/S0140-6736(07)61162-3.

Morgan, C.J.A., Curran, H.V., 2008. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br. J. Psychiatry 192 (04), 306–307. https://doi.org/10.1192/bjp.bp.107.046649.

Musshoff, F., Driever, F., Lachenmeier, K., Lachenmeier, D.W., Banger, M., Madea, B., 2006. Results of hair analyses for drugs of abuse and comparison with self-reports and urine tests. Forensic Sci. Int. 156 (2–3), 118–123. https://doi.org/10.1016/j.forsciint.2004.07.024.

Oreja-Guevara, C., 2012. Clinical efficacy and effectiveness of Sativex, a combined cannabinoid medicine, in multiple sclerosis-related spasticity. Expert Rev. Neurother. 12 (4 Suppl), 3–8. https://doi.org/10.1586/ern.12.11.

Palmer, B.W., Dawes, S.E., Heaton, R.K., 2009. What do we know about neuropsychological aspects of schizophrenia? Neuropsychol. Rev. 19 (3), 365–384. https://doi.org/10.1007/s11065-009-9109-y.

Parolaro, D., Realini, N., Vigano, D., Guidali, C., Rubino, T., 2010. The endocannabinoid system and psychiatric disorders. Exp. Neurol. 224 (1), 3–14. https://doi.org/10.1016/j.expneurol.2010.03.018.

Pope, H.G., Gruber, A.J., Hudson, J.I., Huestis, M.A., Yurgelun-Todd, D., 2001. Neuropsychological performance in long-term cannabis users. Arch. Gen. Psychiatry 58 (10), 909–915. https://doi.org/10.1001/archpsyc.58.10.909.

Potvin, S., Briand, C., Prouteau, A., Bouchard, R.H., Lipp, O., Lalonde, P., Nicole, L., Lesage, A., Stip, E., 2005. CANTAB explicit memory is less impaired in addicted schizophrenia patients. Brain Cogn. 59 (1), 38–42. https://doi.org/10.1016/j.bandc.2005.04.002.

Riedel, G., Davies, S.N., 2005. Cannabinoid function in learning, memory and plasticity. Cannabinoids. Handb Exp Pharmacol 168, 445–477. https://doi.org/10.1007/3-540-26573-2_15.

Ringen, P.A., Melle, I., Birkenaes, A.B., Engh, J.A., Faerden, A., Jonsdottir, H., Nesvag, R., Vaskinn, A., Friis, S., Larsen, F., Opjordsmoen, S., Sundet, K., Andreassen, O.A., 2008. Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study. Acta Psychiatr. Scand. 117 (2), 133–138. https://doi.org/10.1111/j.1600-0447.2007.01135.x.

Sánchez-Gutiérrez, T., Fernandez-Castilla, B., Barbeito, S., González-Pinto, A., Becerra-García, J.A., Calvo, A., 2020. Cannabis use and non use in patients with first-episode psychosis: a systematic review and meta-analysis of studies comparing neurocognitive functioning. Eur. Psychiatry 63, 1. https://doi.org/10.1192/j.eurpsy.2019.9.

Schnakenberg Martin, A.M., Bonfils, K.A., Davis, B.J., Smith, E.A., Schuder, K., Lysaker, P.H., 2016. Compared to high and low cannabis use, moderate use is associated with fewer cognitive deficits in psychosis. Schizophrenia Research: Cognition 6, 15–21. https://doi.org/10.1016/j.scog.2016.09.001.

Schnell, T., Koethe, D., Daumann, J., Gouzoulis-Mayfrank, E., 2009. The role of cannabis in cognitive functioning of patients with schizophrenia. Psychopharmacology 205, 45–52. https://doi.org/10.1007/s00213-009-1512-9.

Segev, A., Levkovitz, Y., 2012. Neurocognitive functions of heavy cannabis using schizophrenia patients. Eur. Psychiatry 27 (5), 365–368. https://doi.org/10.1016/j.eurpsy.2011.04.010.

Sevy, S., Robinson, D.G., Holloway, S., Woerner, M.G., Bilder, R., Goldman, R., Lieberman, J., Kane, J., 2001. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder. Acta Psychiatr. Scand. 104, 367–374.

Sevy, S., Burdick, K.E., Visweswaraiah, H., Abdelmessih, S., Lukin, M., Yechiam, E., Bechara, A., 2007. Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. Schizophr. Res. 92 (1–3), 74–84. https://doi.org/10.1016/j.schres.2007.01.005.

Solowij, N., Michie, P.T., 2007. Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? J. Psychiatry Neurosci. 32 (1), 30–52.

Sowell, E.R., Thompson, P.M., Holmes, C.J., Jernigan, T.L., Toga, A.W., 1999. In vivo evidence for post adolescent brain maturation in frontal and striatal regions. Nat. Neurosci. 2, 859–861.

Sowell, E.R., Trauner, D.A., Gamst, A., Jernigan, T.L., 2002. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev. Med. Child Neurol. 44, 4–16.

Stirling, J., Lewis, S., Hopkins, R., White, C., 2005. Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow up. Schizophr. Res. 75 (1), 135–137. https://doi.org/10.1016/j.schres.2004.10.006.

Wade, D.T., Makela, P., Robson, P., House, H., Bateman, C., 2004. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult. Scler. 10 (4), 434–441. https://doi.org/10.1191/1352458504ms1082oa.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., Lewis, G., 2002. Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 325 (7374), 1199. https://doi.org/10.1136/bmj.325.7374.1199.

Zuardi, A.W., Crippa, J.A., Hallak, J.E., Moreira, F.A., Guimaraes, F.S., 2006. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz. J. Med. Biol. Res. 39 (4), 421–429. https://doi.org/10.1590/s0100-879x2006000400001.