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Inferior performance on selected neuropsychological tests in abstinent schizophrenia patients who have used cannabis

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
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Background:

Summary

A substantial proportion of patients with schizophrenia have co-morbid psychoactive substance use, which can influence their cognitive functions. The aim of this study was to assess cognitive functioning in abstinent schizophrenia patients with various previous patterns of psychoactive substance use.

Material/Methods:

The study was performed on a group of 80 schizophrenia patients (74 men, 6 women), aged 18–40 (mean 25) years, of whom in 40 a co-morbid psychoactive substance abuse was diagnosed. The latter group was subdivided, based on their predominant type of substance (opioid, amphetamine, or cannabis). All patients were examined during clinical improvement, and patients with comorbid substance use were also examined after a 6-week period of detoxification in a therapeutic community. A battery of neuropsychiatric tests was used, which included subtests of Trail Making test, Stroop test and Verbal Fluency test.

Results:

No significant differences in clinical factors and cognitive functioning between the 2 examined groups were found. However, when the patients were divided according to their pattern of substance use, it turned out that the group of patients who used cannabis, despite the shortest duration of disease and that of addiction, and highest percentage of using atypical antipsychotics, performed worse on all cognitive tests, significantly so on Stroop and Fluency tests, compared to the groups with predominant opioid or amphetamine use.

Conclusions:

Abstinent schizophrenic patients who previously used cannabis have worse cognitive functioning compared to other schizophrenic patients with comorbid substance use. The possible role of previous cannabis use or cannabis withdrawal in this phenomenon is discussed.

key words:

schizophrenia • psychoactive substance • cognitive functions • cannabis

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BACKGROUND

Various factors (eg, duration of untreated psychosis, prodromal functioning, employment, social and family network) have an impact on the course of schizophrenia [1]. Among those, a history of substance use disorder is associated with worse clinical functioning of patients with schizophrenia [2]. Psychoactive substances exert a negative impact on cognitive functions; therefore, their use in schizophrenia could further deteriorate cognition in these patients. However, studies evaluating the influence of the substance use on cognitive functioning in schizophrenia patients have greatly differed in methodology, research strategies, and the focus on used substances. Therefore, the comparison of cognitive functions between schizophrenia patients with or without concomitant substance abuse has brought about highly heterogeneous results. Schizophrenia patients with comorbid substance use compared to their non-abusing counterparts were found to have cognitive functions that were either similar [3–6], inferior [7–9] or superior [10–14].

Potvin et al. (2008), in their recent meta-analysis, suggest that type of preferred substance and mean age of participants [15] are important intermediate factors that could influence the results. Concerning the first issue, they found that chronic use of cocaine is usually associated with worse neuropsychological performance [7–9], while the use of amphetamine is associated with a better one [16]. On the other hand, the experiences with cannabis, which is the drug most commonly used by schizophrenia patients [17], yielded inconsistent results, suggesting either improvement [18] or deterioration of neuropsychological performance [19]. Furthermore, most studies showed that neuropsychological performance significantly deteriorated with age.

In our previous study we found no difference in cognitive functioning between matched schizophrenia patients with or without substance use [20]. The aim of the present study was, therefore, to compare cognitive functions between matched groups of schizophrenia patients with or without history of substance use, when various patterns of substance use were taken into account. Three patterns of substance abuse were established according to the results of epidemiological studies among Polish youth in Poznan [21]: 1) opiate use as the main drug used is the most traditional and probably the most destructive pattern; 2) amphetamines as the main drug used, accompanied by hallucinogens, cannabis and hypnotics; and 3) cannabis as the main drug used.

MATERIAL AND METHODS

Schizophrenia subjects

The study was performed on 80 patients with schizophrenia (74 male, 6 female), aged 18–40 years. The exclusion criteria included organic disorders of the central nervous system and somatic conditions, which can influence cognitive functioning (hypertension, cardiovascular, metabolic, neoplastic diseases, infections with HIV, HBV and HCV). The patients were divided into 2 groups of 40 patients each (with and without comorbid substance use) matched on age, gender, duration of illness and percent taking atypical antipsychotic

drugs. The diagnosis of schizophrenia and schizophrenia with comorbid substance use/dependence was done by a psychiatrist, according to DSM-IV (1994) criteria [22].

The sample of patients with schizophrenia and comorbid substance abuse/dependence was recruited from the “Familia” Addiction Center in Gliwice, which at the time of the study was the only center in Poland with a specialized program for dual diagnosis patients. Each year about 30 patients complete the program. Out of these, only about 2/3 meet the criteria to be enrolled into the study. Therefore, it took almost 2 years to recruit 40 patients. In order to have a larger study group, the data collection would have to last 3–4 years.

For further analysis, the group of schizophrenia patients with comorbid substance use/dependence was divided into 3 groups: 1) opiate use as the main drug used is the most traditional and probably the most destructive pattern (9 patients); 2) amphetamines as the main drug used, accompanied by hallucinogens, cannabis and hypnotics (19 patients); and 3) cannabis as the main drug used (12 patients) [21].

The psychopathological symptoms were measured with the use of the PANSS scale [24]. The assessment of cognitive functions was performed by a psychologist specializing in neuropsychology. Each examination of a patient was done in a single session, during the afternoon break between the patients' activities, and lasted about 1 hour.

The group of patients with schizophrenia without comorbid drug use was examined after 4–6 weeks of hospitalization, when a stabilization of acute psychotic symptoms was achieved.

The examination of patients with drug use comorbidity was done after 4–6 weeks of detoxification and after stabilization of acute psychotic symptoms. This timing for examination was chosen according to the guidelines for psychological examination of dual diagnosis patients [23]. The ward where the examination was performed had a therapeutic community character, where the basic rule was abstinence. The abstinence was controlled in the following way. On admission, all personal belongings were checked. The program was in-patient, and all the contacts with the external environment were monitored by staff, which was a part of the contract. The basic medical and neurological examination was done daily, with a special focus on body temperature, papillae reaction, and state and color of the skin, oral mucosa, and tongue. In case of any doubt, a urine screening test was performed.

The study was approved by the Bioethics Committee of the Medical University of Silesia. Written consent was obtained from all patients after the study had been explained to them.

Neuropsychological methods

Cognitive functioning of the patients was assessed with the use of following methods:

1. Trail Making test – consisting of Part A, measuring psychomotor speed, and Part B, measuring visuospatial working memory;
2. Stroop test – consisting of part RCNb (Reading Color Names in Black), measuring the reading speed, and the

Table 1. Demographic and clinical factors and the results of neuropsychological tests in schizophrenic patients with or without comorbid substance addiction.

	Schizophrenia without comorbid substance addiction	Schizophrenia with comorbid substance addiction	Difference (U Mann-Whitney test)
No of patients	40	40	–
Age [\bar{x} (SD)]	24.6 (4.3)	26.5 (5.3)	p=0.076
% of males	5%	7.5%	–
Duration of illness	3.0 (2.3)	2.7 (2.2)	p=0.582
Duration of addiction		2.9 (2.3)	–
% taking atypicals	75.0	75.0	–
PANSS [\bar{x} (SD)]	69.8 (11.5)	66.5 (10.1)	p=0.177
TMT A [\bar{x} (SD)]	35.5 (11.5)	32.5 (9.5)	p=0.233
TMT B [\bar{x} (SD)]	83.5 (32.7)	84.3 (37.1)	p=0.852
RCNb [\bar{x} (SD)]	24.2 (3.9)	22.9 (4.4)	p=0.143
NCWd [\bar{x} (SD)]	68.5 (20.6)	62.5 (16.5)	p=0.244
PF [\bar{x} (SD)]	37.8 (10.2)	35.1 (8.9)	p=0.429
CF [\bar{x} (SD)]	40.0 (9.2)	39.1 (8.0)	p=0.705

TMT A – Trail Making Test, Part A; TMT B – Trail Making Test, Part B; RCNb – Stroop Test, Part RCNb; NCWd – Stroop Test, Part NCWd; PF – Phonological fluency; CF – Categorical fluency.

part NCWd (Naming Color of Word-Different), measuring verbal working memory;

3. Verbal Fluency test – consisting of phonological and category fluency parts.

Statistical methods

Calculations were performed using the Statistica version 7.1 statistical package. Comparison of 2 groups was performed by Mann-Whitney test. Comparisons of 3 groups were done with one-way analysis of variance (ANOVA) with post-hoc test comparing individual groups. When the ANOVA test was positive ($P < 0.05$), then MedCalc performed a Student-Newman-Keuls test for pairwise comparison of subgroups. Comparisons of percentages were done by chi-squared test. The level of statistical significance was determined at $p < 0.05$. For comparisons within drug use, the effect size was also calculated.

RESULTS

Demographic and clinical factors and the results of neuropsychological tests in the matched group of schizophrenic patients with or without co-morbid substance use are shown in Table 1.

Both groups did not differ on such clinical factors as mean age, duration of illness, duration of drug use and percent of patients taking atypical antipsychotic drugs, as well as mean PANSS score during the time of study. The mean PANSS score was below 70 points, which means a mild intensity of schizophrenic symptoms. Also, no difference in performance of any neuropsychological tests was observed if both groups were taken as a whole.

Demographic and clinical factors and the results of neuropsychological tests in schizophrenic patients with various patterns of comorbid substance use are shown in Table 2.

Significant clinical differences between subgroups of patients with different patterns of substance use are observed. Patients with predominant opioid use were older than other groups and had significantly longer duration of illness and duration of substance use. The percentage of subjects taking atypical antipsychotic drugs was highest in the cannabis user group and lowest in the opioid group, although the differences were not significant.

Comparing neuropsychological results in these 3 subgroups of patients, it became clear that the performance of the cannabis group was worse as compared with the others. This difference achieved statistical significance in the Stroop tests and the Fluency tests. A statistically significant effect for the Stroop RCNb test was found when comparing the 3 groups with ANOVA ($p < 0.05$), as well as in individual comparisons between the cannabis and opiates group ($p = 0.03$) and between the cannabis and stimulants group ($p < 0.05$). A statistically significant effect for the Stroop NCWd test was obtained in the comparison of the 3 groups with ANOVA ($p = 0.018$) and in individual comparisons between the cannabis and opiates groups ($p = 0.009$) and between the cannabis and stimulants groups ($p = 0.02$). A statistically significant effect for the Phonological Fluency test was obtained in the comparison of the 3 groups with ANOVA ($p < 0.05$) and in individual comparison between the cannabis and amphetamine groups ($p = 0.013$). Finally, a significant individual difference in the Categorical Fluency test was obtained between the cannabis and opiates groups ($p < 0.05$).

Table 2. The results of neuropsychological tests in schizophrenic patients with various predominant comorbid substance addiction.

	Schizophrenia predominant opioids (group 1)	Schizophrenia predominant amphetamines (group 2)	Schizophrenia predominant cannabis (group 3)	Difference (ANOVA and post-hoc tests)
No of patients	9	19	12	
Age (years) [\bar{x} (SD)]	29.1 (5.1)	22.3 (2.7)	25.0 (3.1)	ANOVA: $p=0.001$ (1) vs. (2): $p=0.001$ (1) vs. (3): $p=0.010$ (2) vs. (3): $p=0.055$
Duration of illness (years)	5.2 (2.8)	2.2 (1.3)	1.7 (1.1)	ANOVA: $p=0.001$ (1) vs. (2): $p=0.001$ (1) vs. (3): $p=0.001$ (2) vs. (3): $p=0.526$
Duration of addiction (years)	5.4 (3.2)	2.2 (1.3)	2.0 (1.1)	ANOVA: $p=0.001$ (1) vs. (2): $p=0.001$ (1) vs. (3): $p=0.001$ (2) vs. (3): $p=0.758$
% taking atypicals	55.6	73.7	91.7	Chi square test: $p=0.164$
TMT A [\bar{x} (SD)]	30.9 (8.9)	32.0 (11.0)	34.5 (7.7)	ANOVA: $p=0.673$ (1) vs. (2): $p=0.768$ (1) vs. (3): $p=0.403$ (2) vs. (3): $p=0.497$
TMT B [\bar{x} (SD)]	88.9 (13.5)	75.6 (35.5)	94.8 (36.9)	ANOVA: $p=0.350$ (1) vs. (2): $p=0.380$ (1) vs. (3): $p=0.718$ (2) vs. (3): $p=0.167$
RCNb [\bar{x} (SD)]	21.2 (2.3)	22.21 (4.2)	25.42 (5.2)	ANOVA: $p=0.047$ (1) vs. (2): $p=0.566$ (1) vs. (3): $p=0.030$ (2) vs. (3): $p=0.046$
NCWd [\bar{x} (SD)]	54.8 (8.8)	59.5 (15.0)	73.2 (18.7)	ANOVA: $p=0.018$ (1) vs. (2): $p=0.444$ (1) vs. (3): $p=0.009$ (2) vs. (3): $p=0.020$
PF [\bar{x} (SD)]	36.0 (9.9)	38.0 (8.1)	30.0 (7.5)	ANOVA: $p=0.042$ (1) vs. (2): $p=0.557$ (1) vs. (3): $p=0.111$ (2) vs. (3): $p=0.013$
CF [\bar{x} (SD)]	41.8 (9.6)	40.4 (6.3)	35.2 (8.5)	ANOVA: $p=0.119$ (1) vs. (2): $p=0.657$ (1) vs. (3): $p=0.045$ (2) vs. (3): $p=0.083$

TMT A – Trail Making Test, Part A; TMT B – Trail Making Test, Part B; RCNb – Stroop Test, Part RCNb; NCWd – Stroop Test, Part NCWd; PF – Phonological fluency; CF – Categorical fluency.

The groups of patients with predominant opioid and amphetamine use did not significantly differ on any neuropsychological test.

DISCUSSION

The main finding of our study is that abstinent schizophrenic patients who previously abused cannabis displayed inferior cognitive performance on selected neuropsychological tests. Patients with previous cannabis use, despite the

shorter duration of disease and duration of addiction, performed significantly worse on Stroop and Fluency tests, compared to the remaining groups with predominant opioid or amphetamine abuse. Patients with history of cannabis use were also more likely to have used atypical antipsychotics, although recently a clear advantage of atypical antipsychotics over conventional ones for functioning of patients with schizophrenia has been questioned [25]. The results of cannabis patients on TMT were numerically worse compared to other groups, but did not obtain statistical significance.

The Stroop test measures some aspects of executive functions and the Fluency test focuses mostly on verbal memory. The performance on both these tests is impaired in schizophrenia patients [26,27]. It is possible that these selective neuropsychological functions are the most sensitive to previous cannabis use or/cannabis withdrawal compared to the effect of other substances such as opioids and amphetamines.

In this study, the neuropsychological assessment was done after 4–6 weeks of detoxification and treatment in the protective environment of a therapeutic community in order to avoid a direct influence of illicit drug use on the results of the examination. The moment of examination was chosen according to the guidelines for diagnosing dual diagnosis patients [23]. Patients were also studied during the period of clinical improvement in order to minimize the effect of schizophrenia symptoms on cognitive functioning.

Two meta-analyses have recently studied the effect of cannabis use on cognitive functioning in patients with schizophrenia. Yucel et al. (2010) included 10 studies comprising 572 schizophrenia patients with or without comorbid cannabis use in the first part of their review. Information regarding abstinence preceding the investigation was provided (it was 3 or 4 weeks in only 2 of them). They concluded that patients with a history of cannabis use, but not necessarily with current or recent use, may have superior neuropsychological functioning compared to their non-using counterparts. In the second part they compared 85 patients with first-episode schizophrenia, among them 59 were using cannabis, with 43 healthy control subjects. All schizophrenia patients had a substantial intensity of clinical symptoms. Patients with cannabis use had various periods of cannabis abstinence, with more than half being abstinent for > 1 month. They found that co-morbid patients had only selective neuropsychological impairments, while patients without a history of cannabis use displayed generalized neuropsychological impairments [28].

The second analysis was done by Rabin et al. (2011) and included 8 studies with 942 schizophrenia patients, among them 356 with concomitant cannabis use [29]. Four studies overlapped with that of Yucel et al. (2010) [28]. The abstinence period exceeded 3 weeks in only 2 studies. Generally, cognitive performance was slightly better in patients with concomitant cannabis use; however, the size effects were in the small-to-medium range (0.06–0.48) [29].

The analyses mentioned above draw our attention to the issue of differences in sample sizes and methodology in the interpretation of the results. This problem is widely discussed in the review by Coulston et al. (2007). The authors emphasize that in most analyzed studies on cannabis and schizophrenia, the numbers of patients are too small to determine which indices of cannabis use are associated with better or worse cognitive performance. The interpretations of results are also influenced by methodological variability between studies. For example, in some reviewed studies only the acute effects of cannabis were examined, and in other studies examined only the longer-term effects of cannabis in participants who had been abstinent for a few weeks [30].

The results of our study are in accord with others showing an impairment on selective cognitive functions (eg,

decision-making) related to cannabis abuse in schizophrenia patients [9,19]. We demonstrated that schizophrenia patients that have used cannabis may have deficits in neuropsychological tests of executive functions and verbal memory. However, the causal interpretation of our results is difficult. An inferior performance could be due to the previous effect of cannabis (mean duration of 2 years) or, alternatively, it could be related to a 6-week cessation of cannabis use and a possible rebound effect.

The most important limitation of the study is a relatively small sample of examined patients within the cannabis users group – only 30% of the co-morbid group with substance abuse. However, this 30% may reflect a specificity of concomitant substance abuse in Polish schizophrenia patients. The other 2 subgroups of patients taking different drugs, especially opiates, are small, which makes the analysis still more difficult. The problem of recruiting larger samples of patients to this type of study, considering all accepted exclusion criteria, has been described above. A possible solution could be development of a multi-center study including centers where these dual diagnosis patients are treated in a similar program and which is following similar rules. Also, the period of data collection could be prolonged. The second limitation is using only selected neuropsychological tests. The use of a wider battery of test could make it possible to diagnose more precise, and perhaps more specific, effects of cannabis use on different cognitive domains. Another factor that can influence the results is gender differences. In our study the female patients are only a small minority; the problem of recruiting women to this type of study has also been mentioned by other authors, as well as other methodological difficulties and limitations commonly faced by researchers in this field [30,31]. The strengths of our study is its careful matching of schizophrenia patients with or without substance use, and performance of neuropsychological tests in standard conditions such as 6 weeks of abstinence, which was regularly controlled during the treatment process, and a state of clinical improvement in schizophrenia symptoms.

CONCLUSIONS

Abstinent schizophrenia patients who had previously used cannabis may have worse cognitive functioning compared to other schizophrenic patients with co-morbid substance use, which may be related either to previous cannabis use or cannabis withdrawal. We believe that the results of our study may add to the ongoing controversy concerning the effect of cannabis use on cognitive functions in schizophrenia.

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