TITLE: LIFETIME CANNABIS USE AND COGNITION IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS AND THEIR UNAFFECTED SIBLINGS

AUTHORS: Ana M. Sánchez-Torres[1], Virginia Basterra[1], Araceli Rosa[2], Lourdes Fañanás[2], Amalia Zarzuela[1], Berta Ibáñez[3], Víctor Peralta[1], Manuel J. Cuesta[1]*

[1]*Psychiatric Unit B, Complejo Hospitalario de Navarra, Irunlarrea, 4, 31008 Pamplona (Spain)*

[2] *Unitat d'Antropologia, Facultat de Biologia, Universitat de Barcelona, Avinguda Diagonal 645, 08028 Barcelona, Spain*

[3] *Methodology Unit, Biomedical Research Center, Fundación Miguel Servet, Irunlarrea, 4, 31008 Pamplona (Spain)*

* Correspondence:

Dr. Manuel J. Cuesta

Psychiatric Unit B, Complejo Hospitalario de Navarra

c/ Irunlarrea 4, E-31008 Pamplona, Spain

Tel/Fax: +34 848 422488

Email: mcuestaz@cfnavarra.es

ABSTRACT

The relationship between cannabis and cognitive performance is controversial. While both acute administration and long-term cannabis use impair cognitive performance in healthy subjects, several studies have shown improved cognitive outcomes in patients with schizophrenia spectrum disorders who use cannabis. The aim of this study was to determine the relationship between lifetime cannabis use, as assessed longitudinally over 10 years of follow-up in a sample of 42 patients and 35 of their unaffected siblings, and current cognitive performance. Forty-two healthy control subjects were assessed at follow-up with the same instruments. Stepwise linear regression revealed a negative effect of longitudinal cannabis use on performance in a social cognition task in the patient group. In the sibling group, lifetime cannabis use had a negative effect on processing speed and declarative memory performance. In the control group, cannabis use per se did not predict cognitive performance; however, when adding lifetime tobacco use to the model, we found a negative association between lifetime cannabis and tobacco use and processing speed and social cognition performance. Moreover, a lower IQ associated with current cannabis use predicted worse attentional performance in the control group. The differential pattern of associations between cannabis use and cognitive performance in patients compared with siblings and controls can be explained by the negative impact of illness on cognition.

KEYWORDS: *schizophrenia spectrum disorders, cognition, cannabis, longitudinal*

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1. Introduction

The relationship between cannabis use and neuropsychological impairment in patients with psychosis remains unclear. Most studies have reported improved cognitive performance among psychotic patients who usually use cannabis compared with those who do not. In a meta-analysis, Yücel et al. [1] reported improved cognitive performance in schizophrenic patients using cannabis with regard to measures of global cognition, visual memory, processing speed, working memory, planning and reasoning. More specifically, a lifetime history of cannabis use resulted in higher effect sizes in the differences in cognitive performance compared to those schizophrenic patients who reported only recent use and those who had never used cannabis. Stirling et al [2] reported data from a sample of patients with first-episode psychosis that was followed for 10-12 years. They found that those patients with a history of cannabis use performed better than those without a history of cannabis use with regard to measures of memory, verbal fluency, visuospatial construction, sequencing and face recognition. Jöckers-Scherübl et al [3] examined the residual effects of long-term cannabis abuse on cognitive performance following 28 days of abstinence in schizophrenic patients and healthy controls. Again, patients with schizophrenia who used cannabis outperformed non-users on measures of psychomotor speed. In addition, the authors found that starting cannabis use before 17 years of age resulted in better cognitive functioning compared with patients who began abusing cannabis after the age of 17.

Several hypotheses have been proposed to explain the improvements in cognitive performance in psychotic patients who use cannabis. Some authors propose that substance-abusing patients require better cognitive functioning and higher social skills to maintain their substance use [4, 5]. Others argue that substance-using patients represent a subgroup of patients with a relatively lower genetic vulnerability to psychosis [6, 1, 7]. Moreover, it has been suggested that cannabis improves cognition, either by counteracting the neurotoxic process related to psychosis or by stimulating prefrontal neurotransmission [8, 9].

However, based on the findings noted in healthy subjects, these results in psychotic patients are paradoxical. In healthy subjects, cannabis use has been associated with cognitive deficits, such as memory and attention underperformance. In a review regarding the effects of drugs of abuse on cognitive performance, Fernandez-Serrano et al. [10] reported consistent effects of acute cannabis administration and sustained consumption. Specifically, acute cannabis administration is related to impairments in episodic memory, working memory, response inhibition and decision making in healthy subjects. Fried et al. [11] reported in a prospective longitudinal study that current cannabis users showed impairments in episodic memory and visual processing speed and had a lower IQ compared with non-users and former users. The prospective design is a strength of this study, because they assessed cognition years before the onset of consumption. Meier et al. [12] investigated the association between persistent cannabis use and cognitive functioning. They reported data of the Dunedin Study, a prospective study of a birth cohort of 1037 subjects followed from birth to 38 years old. In this study, cognitive functioning was assessed before cannabis use onset and then longitudinally assessed at each follow-up wave. Meier et al reported

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an association between persistent cannabis use over 20 years and neuropsychological decline, with worse results among adolescent-onset cannabis users, which showed persistent impairments after cessation of use of 1 year or more. They showed that cognitive impairment was global, represented a decline in IQ and was independent of other drugs use and educational level. Moreover, they reported that these cognitive impairments had an impact on everyday functioning. The authors propose that these findings support the hypothesis of the toxic effects of cannabis in the pubertal brain, which results in persistent neuropsychological impairments. Tait et al [13] assessed a cohort of 1439 young healthy subjects in three occasions every 4 years. They made groups according the longitudinal patterns of cannabis consumption over the follow-up and they found improved performance in an immediate recall task associated with sustained abstinence. Grant et al. [14] found that cannabis use was associated with impaired executive planning and more risky decisions in a gambling task in a sample of young cannabis users, compared to non-users. However, Fernandez-Serrano et al. [10] concluded that only episodic memory and planning deficits seem to persist after mid-term abstinence, and no cognitive impairments remain after long periods of abstinence. These authors highlight the fact that methodological differences between studies make it difficult to establish a correspondence between results. Also Pope et al. [15] came to the conclusion that cannabis effects are reversible. They assessed changes in cognitive performance by heavy cannabis users over time, and found that after 28 days there were few differences compared to former heavy users and controls.

There is little research concerning the relationship between cannabis use and the cognitive performance of the users' siblings. The Genetic Risk and Outcome of Psychosis (GROUP) investigators reported an increased psychotomimetic effect of cannabis in unaffected siblings of schizophrenia patients who reported lifetime and current use, suggesting that the genetic risk for psychosis is associated with sensitivity to cannabis [16, 17]. Acute administration of cannabis has been shown to cause larger impairments in the attention and memory of unaffected siblings of patients with schizophrenia than those in healthy controls [18, 19].

Other substance use must be taken into account when interpreting the results of the relationship between cannabis and cognition. For instance, tobacco smoking has an important impact on cognitive function. It has been well documented that the prevalence of cigarette smoking among psychotic patients is higher than that in the general population [20]. One of the hypotheses proposed for this high prevalence is the "self-medication hypothesis", which concerns that nicotine has positive effects on the side effects of antipsychotic medications, on negative symptoms and on cognitive function, [21-24]. Tobacco smoking has been related to an enhancement of attention, working memory and information processing [21, 25, 26], but also it has been suggested that nicotine may interact with genes related to the risk to develop schizophrenia and the cognitive deficits associated to the illness [27]. Stimulant use has also been shown to have an effect on cognitive function in psychotic patients. Some studies have reported that patients with schizophrenia who use cocaine exhibit greater impairments on memory tasks [28,29] and motor functioning [30] compared to non-using schizophrenia patients. However, some studies have not found differences between users and non-users with regard to other cognitive functions, such as attention

and executive functions [29, 31]. Moreover, some studies have noted improved cognitive functioning in schizophrenic patients who use stimulants compared with non-users with respect to some tasks of motor speed and executive function [30, 32]. Therefore, it is important to account for the effects of the consumption of other substances when assessing the relationship between cannabis and cognition.

The present study was a longitudinal study in which a sample of psychotic patients and their unaffected siblings were followed for up to 10 years following the patients' admission due to a psychotic exacerbation. Our main goal was to determine the relationship between lifetime cannabis use, as assessed by the pattern of consumption at three time points (previous to the episode that required admission 10 years ago, predominant use over 10 years and current use) and current cognitive performance in a sample of patients with a psychotic disorder diagnosis, their unaffected siblings and a healthy control group. Based on the data that have been reported in the literature, we hypothesised that cannabis use would have a differential effect on cognitive performance in patients, siblings and controls. Cannabis use in patients should be related to improved cognitive performance [1,33], while siblings should show a stronger relationship between cannabis use and impairments in cognitive function compared with controls, due to a higher sensitivity to cannabis effects related to genetic risk for psychosis [16,17].

2. Methods

2.1. Subjects

The initial sample population included 89 nuclear families. Between 1999 and 2001, 89 patients who were affected by DSM-IV schizophrenia spectrum disorders [34] were recruited from consecutive admissions to the Psychiatric Unit of Virgen del Camino Hospital in Pamplona, Spain; admissions were due to psychotic exacerbations. We interviewed the patients' parents and one of their unaffected siblings (sample described elsewhere [35]) using a comprehensive evaluation that included psychopathological, motor, and neuropsychological assessments.

For the purposes of the present study, only the patients and their siblings were invited to participate in the second study in 2009. The mean time between the two evaluations was 9 years and 6 months (range, 7 to 11 years). At follow-up, the sample population consisted of a total of 42 patients and 35 of their siblings (43% of the initial sample). The reasons for participant discontinuation were as follows: death of one of the siblings (8 pairs; 7 patients and 1 sibling); traumatic brain injury to the patient (1 pair); the patient moved or could not be contacted (11 pairs); or one of the siblings declined participation (27 patients and 34 siblings). The final patient sample at follow-up included the following diagnoses: schizophrenia (n=23), schizoaffective disorder (n=11), psychotic mood disorder (n=7) and brief psychotic disorder (n=1). The mean age at illness onset was 21.81±5.65 years. Patients had a mean of 15.07±5.47 years since illness onset, with a mean of 7.45±5.13 episodes and 7.34±9.9hospitalisations.

In addition, 42 healthy volunteers were included as a control group. Controls were recruited from the surrounding community according to the following inclusion criteria: the absence of major psychiatric

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disorders and drug or alcohol dependence disorders, the absence of first-degree relatives with major psychiatric illness, and the absence of any drug treatment.

All subjects provided written informed consent for participation in the study, and the study was approved by the local ethics committee.

2.2. Procedures

2.2.1. Clinical assessments

Demographic and clinical variables were assessed using the Comprehensive Assessment of Symptoms and History (CASH) [36]. The CASH is a semi-structured interview that assesses psychopathology, which allowed us to obtain a score on positive symptoms (mean rating of delusions and hallucinations), disorganisation (mean rating of positive formal thought disorder, bizarre behaviour, inappropriate affect and inattention), and negative symptoms (mean rating of affective flattening, alogia, avolition and anhedonia), which were rated at baseline and at follow-up. Patients and their siblings underwent psychopathological assessment to determine the presence of current or lifetime psychopathological symptoms.

Drug abuse was assessed longitudinally only in patients and siblings using a structured interview that was based on the Composite International Diagnostic Interview (CIDI) [37]. We recollected data concerning cannabis, alcohol, stimulants, other drugs (e.g. opioids) and tobacco use. Information regarding consumption habits was available for the following three time points: at baseline, predominant use over the 10-year follow-up period and at follow-up (current use). The controls, who were only assessed at follow-up, reported current consumption. A lifetime estimate of consumption was determined using the available sources of information (e.g., participants, family, and charts) for all participants. The ratings were classified from 0 (no consumption) to 5 (every-day consumption).

Clinical assessments were conducted by senior researchers (MJC and VP) at baseline and by a junior researcher at follow-up (VB), all of whom were blinded to the participants' cognitive status. Inter-rater reliabilities between the senior and junior researchers regarding the psychopathological assessments were good to excellent (Ks>0.80). At baseline, the assessments were performed during an index admission once the patients were clinically stable. At follow-up, the patients had been clinically stable for at least 6 months prior to assessment.

2.2.2. Neuropsychological assessments

The neuropsychological assessment was only carried out at follow-up. The cognitive assessment took approximately 2-2.5 hours. Subjects underwent 18 cognitive tasks, which targeted general intelligence, processing speed, attention/vigilance, visual and verbal memory, working memory, executive functioning and social cognition. These cognitive domains reflect the 7 dimensions proposed in

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the MATRICS battery [38,39]. Therefore, tests were assigned to a cognitive dimension to reduce the variables in the analyses.

General intelligence. To estimate premorbid IQ, the Vocabulary subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III [40]) was used. The current IQ was estimated using a short form of the WAIS-III, which is composed of Vocabulary, Block Design and Similarities subtests.

Processing speed. The Digit Symbol Coding and Symbol Search subtests of the WAIS-III and the Trail Making Test (form A) [41] were used as processing speed measures.

Attention/vigilance. The Continuous Performance Test-Identical pairs [38,42], Digits forward (WAIS-III) and Spatial Span forward items of the Wechsler Memory Scale-III (WMS-III [43]) were used as measures of vigilance and immediate attention.

Declarative memory. This domain was composed of verbal and visual memory. Verbal memory was assessed using the Spanish version of the California Verbal Learning Test, which in Spanish is the Test de Aprendizaje Verbal España-Complutense (TAVEC [44]). The following three measures in this test were used in the analysis: the sum of the first five trials, a short-term recall measure and a long-term recall measure. The Brief Visual Memory Test-Revised (BVMT-R [45]), included in the MATRICS battery, was chosen to assess visual memory.

Working memory. The Digits and Spatial Span backwards test, as well as the Letter-number Sequencing subtest (WAIS-III) and N-Back paradigm [46], were used as measures of working memory.

Executive functioning. Form B of the Trail Making Test (TMT) [41], the Wisconsin Card Sorting Test-64 cards computerised version (WCST-64) [47] (total number of categories, total number of correct responses, total number of errors, number of perseverative responses and number of conceptual-level responses), the Iowa Gambling Task [48], the Tower of Hanoi test (three and four discs) and semantic (number of animal names produced in 1 minute) and phonological fluency (number of words starting with "p" produced in 1 minute) composed the executive functions dimension.

Social cognition. This domain was assessed using the Managing Emotions section of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT [49]). We used only the two tasks included in the managing emotions branch, as these are the tasks included in the MATRICS battery.

An experienced neuropsychologist (AMS), who was blinded to the clinical status information, assessed each of the participants.

2.3. Data analysis

The demographic characteristics of patients, siblings and controls were compared using t-tests and chi-square tests. A one-way ANOVA was applied to compare cognitive performance between patients, siblings and controls. In addition, we introduced age, gender and years of education as covariates, due to the differences between groups found in these variables. Post-hoc analyses were performed using the Bonferroni test.

To normalise the different scales of measurements used for the neuropsychological tests, we calculated derived z-scores based on the means and standard deviations of the control group. Composite scores for cognitive domains which were represented by more than one measure (general intelligence, processing speed, attention, declarative memory, working memory and executive functioning), were calculated by taking the mean of all the z-scores included in each cognitive domain. Cronbach's alpha was calculated to assess the internal consistency of the composite scores.

Pearson correlations were used to analyse the relationship between drug use at each of the three time points, cognitive performance and clinical measures. Drug use variables were interpreted as continuous variables. Moreover, the relationships between positive, negative and disorganised symptom dimensions and cognitive performance were ascertained using Pearson correlations.

Hierarchical linear regression was performed to better characterise the relationship between cannabis use and cognitive performance. Premorbid IQ, age at cannabis use onset and lifetime tobacco exposure were introduced as control variables in the model for the three groups. In addition, age at illness onset was introduced as a control variable in the patient group.

All analyses were conducted using the Statistical Package for Social Sciences 17.0. [50]

3. RESULTS

There were no significant differences between patients who agreed and patients who declined to participate in terms of age (27.33±5.37 vs. 26.40±6.08; t=-0.78, p=0.44), years of education (11.8±2.91 vs. 11.49±3.79; t=-0.44; p=0.66), years since onset of illness (5.52±5.59 vs. 4.46±5.17; t=-0.96, p=0.34), number of episodes (3.88±5.47 vs. 3±2.71; t=-1, p=0.32), and level of functioning as measured by the Global Assessment of Functioning scale (GAF;[34] (86.78±10.15 vs. 83.19±12.23; t=-1.49, p=0.14). Likewise, the current and original sibling samples did not differ significantly in terms of age (28.29±5.99 vs. 27.16±7.06; t=-0.79, p=0.43), years of education (12.68±3.55 vs. 12.38±3.55; t=-0.32, p=0.75) or level of functioning (95.73±7.33 vs. 92.29±7.95; t=-1.64, p=0.11). The subsequent results refer to those subjects who participated in 2009 (42 patients and 35 siblings).

Table 1 shows the demographic data for the sample. Patients and siblings were not significantly different with respect to age and years of education (t=0.53, p=0.06). Controls were significantly younger than patients (t=3.03, p=0.003) and siblings (t=3.2, p=0.002) and were also more educated than the patients (t=2.93, p=0.004); however, they did not differ from the siblings with respect to years of education (t=-1.75, p=0.08). Males were overrepresented in the patient sample compared with siblings (z=-2.76, p=0.006) and controls (z=-2.84, p=0.005). The only significant difference in premorbid IQ (estimated using the Vocabulary subtest of the WAIS-III) was found between patients and controls (t=-2.34, p=0.02). We introduced age, gender and years of education as covariates in the univariate analysis, due to the differences found between groups.

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3.1. Relationship between drug use, cognition and clinical measures.

The Cronbach's alpha coefficients for the composite scores of the neuropsychological tests were as follows: 0.63 for the attention score, 0.84 for the processing speed score, 0.89 for the declarative memory score, 0.75 for the working memory score and 0.82 for the executive function score. All scores showed moderate to high reliability; thus, we used these composite scores to assess the relationship between drug use and cognitive performance.

The frequencies of consumption of cannabis, stimulants and alcohol for the three groups are reported in the Supplementary Table 1. Based on the total years of consumption and the frequencies of use, we calculated a measure of lifetime exposure to cannabis and tobacco for each participant. Ranges for the lifetime exposure to cannabis were from 0 to 125 in the patient group and from 0 to 100 in the sibling and control groups. Tobacco lifetime exposure ranged from 0 to 144 in the patient group, 0 to 112 in the sibling group and 0 to 81 in the control group.

The Pearson correlations showed no significant relationship between cannabis use in the patient group for the three time points and the composite scores for processing speed, attention, declarative memory, working memory and executive function. A significant negative correlation was found between longitudinal cannabis consumption and scores on the MSCEIT, and a trend toward significance was found for the relationship between current cannabis use and the MSCEIT. No significant correlations were found between the lifetime estimate of cannabis consumption and cognitive performance (Table 2).

With respect to the sibling group, significant negative correlations were found between the declarative memory composite scores and cannabis use at baseline 10 years prior to assessment and current use. Longitudinal cannabis use showed no significant correlation with the declarative memory composite score, although there was a trend toward significance. In addition, correlations between current cannabis use and processing speed composite scores showed a trend toward significance. No other significant correlations between cannabis use and cognitive performance were found in the sibling group (Table 2). When controlling for lifetime tobacco use, significant correlations between the declarative memory composite score and cannabis use at baseline and current use remained.

No significant correlations were found between current cannabis use or lifetime consumption and cognitive performance in the control group. However, correlations between lifetime cannabis consumption and MSCEIT scores showed a trend toward significance.

Stimulant and alcohol consumption showed no significant correlations with cognitive performance in any of the groups, so they were not included in further analyses.

Positive symptoms in the patient group at follow-up were significantly correlated with attention (r=-0.36, p=0.02), declarative memory (r=-0.34, p=0.03) and working memory (r=-0.31, p=0.05). Cannabis consumption at baseline (r=0.31, p=0.05) and the estimated lifetime cannabis consumption (r=0.37, p=0.02) were positively correlated with positive symptoms. Negative symptoms were correlated with attention (r=-0.32, p=0.04), declarative memory (r=-0.32, p=0.04), executive function (r=-0.34, p=0.04) and social cognition (r=-0.34, p=0.03). The predominant longitudinal cannabis use over the 10-year follow-up period (r=0.37, p=0.02) and current cannabis use (r=0.31, p=0.04) showed a significant positive

correlation with negative symptoms. Disorganised symptoms did not correlate significantly with cognitive performance, and no relationship was found between cannabis use and disorganised symptoms.

In addition, hierarchical linear regression analyses were performed to test for the effects of the following six additional variables on the relationship between cannabis use (in the three time periods and lifetime estimate of cannabis consumption) and cognitive performance: age at illness onset, positive and negative symptoms (only for the patient group), age at cannabis use onset, lifetime tobacco exposure and premorbid IQ estimate.

The significant results associated with the variables that met the criteria for use in the regression models are shown in Table 3. Regarding the relationship between cannabis use and cognition in the patient group, hierarchical regression demonstrated that performance on the social cognition task was negatively predicted by longitudinal cannabis use over the 10-year follow-up period. Premorbid IQ, current cannabis use and age at illness onset predicted performance on working memory tasks. In the sibling group, cannabis use (at baseline, longitudinal use and current use) and earlier age at cannabis use onset negatively predicted processing speed performance. Cannabis use at baseline and current use negatively predicted declarative memory performance.

In the control group, total exposure to cannabis and age at cannabis use onset predicted processing speed performance; premorbid IQ and current cannabis use predicted performance on attentional domain; current use and lifetime exposure to cannabis associated to tobacco, premorbid IQ and age at cannabis use onset predicted performance in declarative memory tasks. Finally, current and lifetime exposure to cannabis associated to tobacco use predicted social cognition performance.

3.2. Neuropsychological tests

Since there were found differences between groups in age, gender and years of education, we included these variables as covariates in the ANCOVAS. These analyses revealed that patients had significantly lower scores than siblings for all tests, with the exception of Digits forward, Spatial Span forward, Digits backward, Letter and number sequencing, N-Back, Tower of Hanoi and Iowa Gambling tasks. With respect to controls, patients exhibited lower scores for all measures except the CPT (4 digits), Digits forward, Spatial Span backward, Tower of Hanoi, Iowa Gambling task and the MSCEIT. Siblings and controls did not differ in any cognitive task. Patients exhibited a significantly lower IQ compared to controls, but they did not differ with siblings after controlling the covariates mentioned above. Siblings and controls did not differ with respect to IQ (Table 4). Figure 1 shows the plot for each cognitive scale by group, adjusted for age, gender and years of education.

4. DISCUSSION

The aim of this study was to determine whether there was a relationship between longitudinal patterns of cannabis use and cognition in patients with a psychotic disorder diagnosis, their unaffected

siblings and a control group. Moreover, we examined the role of tobacco smoking as a mediator of the relationship between cannabis use and cognitive performance.

Our main findings are as follows. First, cognitive performance was independent of the longitudinal patterns of cannabis use at baseline, use during the 10-year follow-up period and current use in the patient group. Second, the estimated lifetime cannabis consumption did not exhibit a relationship with cognitive outcomes in the patient group. Third, we found a negative relationship between longitudinal cannabis use and performance on social cognition in the patient group. Moreover, a worse premorbid IQ, current cannabis use and an earlier age at illness onset in the patient group predicted worse outcomes in the working memory domain. Fourth, we found a negative relationship between cannabis use and performance on processing speed and declarative memory tests in the sibling group. Cannabis use at baseline, longitudinal and current cannabis use associated to an earlier age at cannabis use onset were related to a worse cognitive performance on processing speed tests. Regarding declarative memory, the regression analyses revealed a relationship between cannabis consumption 10 years ago and current use and worse declarative memory performance. Finally, in the control group, cannabis use per se did not predict cognitive performance, but when adding other variables to the model, we found a negative association between lifetime cannabis use and an earlier age at cannabis use onset and processing speed. Besides, a lower IQ associated with current cannabis use was related to worse performance on attentional tasks; current cannabis use and lifetime estimation of consumption associated to tobacco use, earlier age at cannabis use onset and a lower IQ were related to worse declarative memory performance; and current cannabis use and lifetime estimation of consumption associated to tobacco use were related to lower scores on the social cognition task. Our initial hypotheses were only partially confirmed. There was a greater influence of cannabis on cognitive performance in siblings compared with controls. In the control group, the combination of cannabis and tobacco use, earlier age at cannabis use onset or lower IQ explained worsening processing speed, attention, declarative memory and social cognition performance, while cannabis demonstrated an influence specifically on declarative memory in the sibling group, and associated with an earlier age at onset of consumption cannabis use showed a negative influence on processing speed tasks. These results can be explained by the greater vulnerability to the cognitive effects of cannabis in siblings. Studies have shown that the genetic risk for psychosis may be associated with sensitivity to cannabis [16, 17]; thus, this increased sensitivity could lead to greater cognitive effects in siblings.

However, we did not find a positive association between cannabis use and cognition in the patient group. Most of the studies that have addressed the relationship between cannabis use and cognition in psychotic disorders have found that patients who use cannabis outperform those patients who do not use it [1, 7, 51]. Moreover, two studies found preserved cognitive performance in patients who began using cannabis before illness onset [33, 52], which contradicts those studies on healthy subjects that report worse cognitive functioning in adolescent-onset users [12]. These results suggest that the contribution of cannabis to illness onset explains the relationship between cannabis use and better cognitive performance, supporting the vulnerability hypothesis. This could mean that psychosis-prone individuals would be likely

to develop psychotic symptoms after cannabis consumption [53], and these individuals may be cognitively more preserved than psychotic patients who are genetically more vulnerable to psychosis. In contrast, our results did not support these findings, as we only found a relationship between longitudinal cannabis use and worsened performance on a social cognition task. In other words, not only did our patients fail to show improved cognitive performance associated with (past or present) cannabis consumption, but longitudinal cannabis consumption was associated with poorer social cognition. Furthermore, current cannabis use was related to worse working memory performance when adding a low premorbid IQ and an earlier age at illness onset to the explanatory model.

The differential pattern of associations between cannabis use and cognitive performance in patients compared with siblings and controls can be explained based on the negative effects of illness on cognition. Our patient sample showed cognitive function arrest in almost all of the domains assessed compared with healthy controls. Therefore, it is arguable that the effects of the illness per se were greater than the effects of cannabis consumption.

In addition, the counterintuitive results reported in the literature regarding improved cognitive performance in patients who use cannabis can also be partially explained by the instruments used to assess cognition. The complexity of the task is a variable that should be taken into account when assessing the effects of cannabis on cognition. For example, it has been reported in healthy subjects that acute delta-9-tetrahydrocannabinol (THC) administration reduced accuracy in a working memory task at a lower memory load than placebo; however, differences were not found at low levels of memory load [54]. Therefore, if cognitive tasks of low complexity are used in assessments, it may be that the effects of cannabis could be hidden. In this study, we used an extensive cognitive battery to prevent this possible confusion.

The exacerbation of psychotic symptoms in schizophrenic patients who used cannabis has been reported in the literature [18, 55-57]. In addition, clinical symptoms and cognitive performance are related in psychotic disorders [58-60]; thus, it is necessary to analyse the influence of symptoms on the relationship between cannabis consumption and cognitive outcomes. In our sample, cannabis use was related to increased positive and negative symptoms in the patient group at follow-up. Specifically, cannabis use 10 years previously and the estimated lifetime cannabis consumption were related to increased positive symptoms, and longitudinal use over the last 10 years, current use and lifetime estimate of consumption were related to increased negative symptoms. Regarding cognitive outcomes, there was not found any relationship between symptoms, cannabis use and cognition.

Strengths and limitations

The main strength of this study is the extended follow-up period used in the assessment of drug use, which is more reliable than collecting retrospective information. Moreover, the comprehensive neuropsychological battery used in the assessments enabled us to obtain a thorough cognitive profile of the patients, siblings and controls. However, the cognitive assessment was cross-sectional; thus, it is not

possible to infer the cognitive trajectories of the patients and their siblings related to cannabis consumption over time.

This study was part of a longitudinal study; thus, the lengthy follow-up period (nearly 10 years) resulted in high attrition rates.

In the original study [35], the DSM-IV diagnosis of cannabis dependence was an exclusion criterion of the study for the patients and siblings. Therefore, we included healthy participants who did not have a diagnosis of cannabis dependence as we wanted to compare the cognitive performance of patients and siblings with that of healthy controls. Therefore, most of the subjects included in this study were incidental cannabis users, showing patterns of use that ranged from sporadic to weekly use.

The clinical heterogeneity of the sample also represents a limitation. The reason was that the recruitment of the sample at baseline was naturalistic, according to the consecutive admissions in a psychiatric unit. Besides, research has demonstrated that cognitive differences across schizophrenia spectrum disorders are only quantitative [61].

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Table 1. Socio-demographic, clinical and diagnostic variables of patients, unaffected siblings and controls.

	Patients (n=42)	**Siblings (n=35)**	**Controls (n=42)**	***P. vs. S.***	***S. vs. C.***	***P. vs. C.***
Age: mean (s.d.)	37.02 (5.3)	37.71 (6.21)	32.10 (9.11)	t=-0.53 p=0.6	**t=3.2 p=0.002***	**t=3.03 p=0.003***
Gender (% males/females)	71.4/28.6	40/60	40.5/59.5	**z=-2.76 p=0.006***	z=-0.04 p=0.97	**z=-2.84 p=0.005***
Years of education: mean (s.d.)	12 (3.89)	12.89 (3.64)	14.19 (2.9)	t=-1.03 p=0.31	t=-1.75 p=0.08	**t=-2.93 p=0.004***
Premorbid IQ: mean (s.d.)	98.33 (11.41)	102.86 (11)	103.57 (8.92)	t=-1.76 p=0.08	t=-0.32 p=0.75	**t=-2.34 p=0.02***

P. = Patients; S. = Siblings; C. = Controls; IQ= intelligence quotient
***Significance, p<0.05**

Table 2. Pearson correlations between cannabis use and cognitive domains.

		Baseline	Predominant use in 10 years	Current	Lifetime
Processing speed	Patients	0.18	0.03	-0.13	0.04
	Siblings	-0.25	-0.23	-0.29	-0.20
	Controls			-0.08	-0.25
Attention	Patients	-0.08	-0.07	-0.21	-0.12
	Siblings	-0.06	-0.06	-0.18	0.13
	Controls			-0.24	-0.23
Declarative memory	Patients	0.06	-0.15	-0.18	-0.1
	Siblings	**-0.55****	-0.3	**-0.39***	-0.27
	Controls			-0.2	-0.25
Working memory	Patients	0.04	-0.08	-0.18	-0.17
	Siblings	-0.12	-0.03	-0.15	-0.001
	Controls			-0.05	-0.02
Executive functions	Patients	-0.08	0.06	0.02	0.04
	Siblings	-0.11	-0.14	-0.14	-0.07
	Controls			-0.01	-0.12
Social cognition	Patients	0.11	**-0.34***	-0.30	-016
	Siblings	-0.07	0.12	0.21	0.06
	Controls			-0.25	**-0.30***

p<0.05; **p<0.001

Table 3. Hierarchical linear regression between cannabis use and cognitive performance (with covariates).

		Variables in the model	β	t	R^2	p
PROCESSING SPEED	Siblings [a]	Age at cann use onset Cann baseline	0.40 -0.38	2.43 -2.29	0.21	0.024
	Siblings [a]	Age at cann use onset Cann long	0.4 -0.36	2.38 -2.15	0.2	0.031
	Siblings [a]	Current cann Age at cann use onset	-0.39 0.38	-2.39 2.33	0.22	0.019
	Controls [a]	Cann lifetime Age at cann use onset	-0.41 0.38	-2.55 2. 33	0.23	0.039
ATTENTION	Controls	Prem IQ Current cann	0.35 -0.35	2.42 -2.34	0.23	0.017
DECLARATIVE MEMORY	Siblings [a]	Cann baseline	-0.55	-3.78	0.3	0.001
	Siblings [a]	Current cann	-0.39	-2.4	0.15	0.022
	Controls [a]	Current cann Tobacco Prem IQ Age at cann use onset	-0.37 -0.35 0.33 0.34	-2.55 -2.45 2.44 2.29	0.34	0.003
	Controls [a]	Cann lifetime Tobacco Age at cann use onset Prem IQ	-0.4 -0.35 0.38 0.27	-2.74 -2.52 2.5 2.02	0.36	0.002
WORKING MEMORY	Patients [b]	Prem IQ Current cann Age at illness onset	0.79 -0.5 -0.45	4.56 -2.76 -2.71	0.64	0.008
SOCIAL COGNITION	Patients [b]	Cann long	-0.54	-2.79	0.28	0.012
	Controls [a]	Current cann Tobacco	-0.37 -0.32	-2.4 -2.12	0.24	0.032
	Controls [a]	Cann lifetime Tobacco	-0.41 -0.32	-261 -2.16	0.26	0.022

Cann baseline = cannabis use at baseline; Cann long = predominant longitudinal cannabis use over the 10-year follow-up period; Current cann = current cannabis use; Cann lifetime = lifetime estimate of cannabis consumption; Prem = premorbid

[a] Covariates included in the regression analyses: age at cannabis use onset, premorbid IQ and tobacco lifetime exposure

[b] Covariates included in the regression analyses: age at illness onset, positive and negative symptoms, age at cannabis use onset, premorbid IQ and tobacco lifetime exposure.

Table 4. Means and standard deviations of the direct scores on the neuropsychological tests. ANOVAS corrected by age, gender and years of education.

	Patients (n=42)	Siblings (n=35)	Controls (n=42)	*F (d.f.)*[a]	*P. vs. S*	*S. vs. C.*	*P. vs. C.*
General intelligence							
Current IQ	99.62(12.66)	105.83(11.35)	108(7.95)	**5.74 (2,116)****	**p=0.059**	n.s.	p=0.004
Processing speed							
Digit symbol coding	57.57(18.28)	79.17(16.13)	85.86(14.16)	**20.37 (2,116)****	**p<0.001**	n.s.	**p<0.001**
Symbol search	28.29(7.28)	36.20(7.82)	40.14(8.16)	**13.35 (2,116)****	**p<0.001**	n.s.	**p<0.001**
TMT-A (seconds)	41.55(18.31)	30.14(9.48)	29.05(8.63)	**8.73 (2,116)****	**p=0.001**	n.s.	**p<0.003**
Attention							
d' CPT-4 digits	1.27(0.76)	1.96(0.89)	1.83(0.96)	**5.77 (2,116)****	**p=0.004**	n.s.	**n.s.**
Digits forward	8.05(2.01)	8.77(1.89)	9.4(2.4)	2.62 (2,116)	n.s	n.s	**n.s**
Spatial Span forward	8.17(2.04)	8.54(1.72)	9.19(1.73)	1.44 (2,116)	n.s	n.s	**n.s.**
Declarative memory							
TAVEC-Total recall (num. of words)	46.88 (11.4)	60.03(9.29)	58.88(8.41)	**15.19 (2,116)****	**p<0.001**	n.s	**p<0.001**
TAVEC-Short-term recall (num. of words)	9.95(3.07)	13.43(2.42)	12.43(2.74)	**12.04 (2,116)****	**p<0.001**	n.s	**p=0.016**
TAVEC-Long-term recall (num. of words)	10.24(3.37)	13.74(2.45)	12.64(2.61)	**11.15 (2,116)****	**p<0.001**	n.s	**p=0.035**
BVMT-R (total score)	21.52(7.95)	26.11(5.33)	28.71(5.28)	**6.15 (2,116)****	**p=0.0042**	n.s	**p=0.003**
Working memory							
Digits backward	5.69(1.8)	6.46(1.76)	7.62(2.48)	**7.88 (2,116)****	n.s.	**n.s.**	**p<0.001**
Spatial Span backward	7.33(1.83)	8.40(1.58)	8.02(1.59)	**5.2 (2,116)***	**p=0.007**	n.s.	n.s.
Letter and number sequencing	9.19(2.51)	10.54(1.92)	11.79(3.14)	**7.61 (2,116)****	n.s.	n.s.	**p=0.001**
N-Back total errors	7.4(3.15)	5.94(3.24)	4.10(2.22)	**8.81 (2,115)****	**n.s.**	**n.s.**	**p<0.001**

Executive function							
Tower of Hanoi-3 discs (num. of movements)	9.7(3.24)	8.79(2.51)	10.4(3.2)	2.22 (2,111)	n.s.	n.s.	n.s.
Tower of Hanoi-4 discs (num. of movements)	31.33(10.69)	27.19(9.79)	27.04(7.2)	2.39 (2,109)	n.s.	n.s.	n.s.
TMT-B (seconds)	101.33(46.5)	64.94(22.71)	60.29(16)	**14.95 (2,116)****	**p<0.001**	n.s.	**p<0.001**
WCST-Categories	2.55(1.63)	3.94(1.24)	3.9(1.12)	**10.22 (2,116)****	**p<0.001**	n.s.	**p=0.004**
WCST-Correct responses	41.50(12.76)	51.80(5.53)	50.9(6.96)	**13.3 (2,116)****	**p<0.001**	n.s.	**p=0.001**
WCST-Total errors	21.83(12.33)	12.20(5.53)	13.1(6.96)	**11.29 (2,116)****	**p<0.001**	n.s.	**p=0.002**
WCST-Perseverative responses	12.76(8.68)	6.63(3.25)	7.17(4.58)	**10.12 (2,116)****	**p<0.001**	n.s.	**p=0.004**
WCST-Conceptual level responses	35.83(17.29)	49.06(8.54)	47.9(9.94)	**10.12 (2,116)****	**p<0.001**	n.s.	**p=0.005**
Iowa Gambling Task (net score)	-0.81(26.33)	7.33(21.5)	-0.64(23.13)	1.64 (2,116)	n.s.	n.s.	n.s.
Phonological (num. of words with "p")	14.02(4.84)	18.26(5.12)	16.98(3.4)	**8.54 (2,116)****	**p<0.001**	n.s.	**p=0.01**
Semantic (num. of words "animals")	19.07(5)	23.91(5.07)	25.95(6.74)	**11.25 (2,116)****	**p=0.005**	n.s.	**p<0.001**
Social cognition							
MSCEIT (T-score)	87.69(9.67)	94.76(9.17)	94.1(8.14)	**4.16 (2,116)****	**p=0.024**	n.s.	**n.s.**

p<0.05; **p<0.001

[a] Adding age, gender and years of education as covariates.