Neurological soft signs in Tunisian patients with first-episode psychosis and relation with cannabis use

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Abstract
Background: Neurological soft signs (NSS) are minor non-localizing neurological abnormalities that are conceptualized as neurodevelopmental markers that mediate the biological risk for psychosis. We aimed to explore the relationship between NSS and cannabis use, an environmental risk factor of psychosis.

Methods: This was a cross-sectional study in consecutively admitted patients hospitalized for first-episode psychosis. NSS were assessed by the NSS scale (23 items exploring motor coordination, motor integrative function, sensory integration, involuntary movements or posture, quality of lateralization). Presence of NSS was defined as a NSS scale total score \( \geq 9.5 \). Cannabis use was ascertained with the cannabis subsection in the Composite International Diagnostic Interview.

Results: Among 61 first-episode psychosis patients (mean age \( = 28.9 \pm 9.4 \) years; male \( = 86.9\% \), antipsychotic-naive \( = 75.4\% \)), the prevalence of current cannabis use was 14.8% (heavy use \( = 8.2\% \), occasional use \( = 6.6\% \)). NSS were present in 83.6% of the sample (cannabis users \( = 66.7\% \) versus cannabis non-users \( = 85.5\% \), \( p = 0.16 \)). The mean total NSS score was 15.3 \( \pm 6.7 \), with a significant lower total NSS score in cannabis users (11.2 \( \pm 5.6 \) versus 16.0 \( \pm 6.7 \), \( p = 0.048 \)). Differences were strongest for the "motor coordination" \( (p = 0.06) \) and "involuntary movements" \( (p = 0.07) \) sub-scores.

Conclusions: This study demonstrated a negative association between cannabis use and NSS, especially regarding motor discoordination. This finding supports the hypothesis that a strong environmental risk factor, such as cannabis, may contribute to the onset of psychosis even in the presence of lower biological and genetic vulnerability, as reflected indirectly by lower NSS scores. Nevertheless, additional studies are needed that explore this interaction further in larger samples and considering additional neurobiological and environmental risk factors.

Keywords: Schizophrenia, First episode, Cannabis, Neurological soft signs

Introduction
Neurological soft signs (NSS) are minor non-localizing neurological abnormalities determined by clinical examination [1]. NSS concern four main areas of neurological functioning: motor coordination, sensory integration, sequencing of complex motor acts, and primitive developmental reflexes [2]. NSS have been conceptualized as neurodevelopmental markers that mediate the biological propensity for the development of psychosis. This conceptualization was established on the basis of many observations showing higher rates of NSS not only among people with schizophrenia, but also among treatment-naïve patients with first-episode psychosis (FEP) [3, 4], non-psychotic siblings, and subjects considered at high risk for psychosis [5–8]. The prevalence of NSS in patients with FEP has been reported to range from 20 to...
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don't develop psychosis after cannabis use, suggesting
onset of psychosis [28, 29]. However, most individuals
[25–27]. Cannabis consumption usually precedes the
vulnerable individuals on their pathway to the disorder
suggest that cannabis use only precipitates psychosis in
specific to schizophrenia, as compared to other mental
disorders [21, 22]. This relationship cannot be explained
by potentially confounding factors, such as premorbid
disorders, other types of drug use, intoxication effects,
personality traits, sociodemographic markers, or intellec-
tual ability [22]. Accordingly, several reviews conclude
that there is an increased risk for psychosis in individu-
als who have used cannabis, typically in the magnitude of
an odds ratio of 1.5–2 [22–24]. However, there are also
opposing views on cannabis as a risk factor for psycho-
sis. Some authors propose that there is a causal relation-
ship between cannabis use and psychosis [25, 26]. Others
suggest that cannabis use only precipitates psychosis in
vulnerable individuals on their pathway to the disorder
[25–27]. Cannabis consumption usually precedes the
onset of psychosis [28, 29]. However, most individuals
do not develop psychosis after cannabis use, suggesting
that risk of psychosis must be modulated by other fac-
tors. In line with this conceptualization, data from recent
comprehensive studies suggest that cannabis is an envi-
ronmental risk factor that interacts with genetic and bio-
logical vulnerabilities for psychosis [30, 31].

While different authors have studied the association
between NSS and perinatal factors, such as obstetric complica-
tions [32–34], few studies have investigated the interaction
between NSS and non-perinatal environ-
mental factors, such as cannabis use [35–37].

The aim of this study was to explore the relationship
between neurodevelopmental markers reflecting neuro-
biological vulnerability (NSS) and an environmen-
tal risk factor (cannabis use) in a sample of Tunisian
patients with FEP. The hypothesis was that the cannabis
pathway to psychosis may reflect less neurobiological
vulnerability.

Patients and methods
Study design
This was a cross-sectional study conducted over a period
of 14 months (from July 2012 to September 2013) in the
psychiatry department of Fattouma Bourguiba Hos-
pital in Monastir, Tunisia, in consecutively admitted
patients hospitalized for FEP according to Diagnostic and
Statistical Manual of Mental Disorders (DSM-IV) criteria
[38]. Patients had the diagnosis of schizophrenia, schiz-
ophreniform disorder, brief psychotic disorder, delu-
sional disorder, substance-induced psychotic disorder,
or psychotic disorder not otherwise specified. Exclusion
criteria were: age >55 years old, prior hospitalization or
consultation in a psychiatric unit, diagnosis of psychotic
disorder due to medical condition, mental retardation, a
history of major neurological disorder and unwillingness
to consent to participate in the study.

Measures and assessment tools
Sociodemographic and clinical data were collected both
with a pre-established questionnaire and based on medi-
cal record review. The premorbid functioning was evalu-
ated by the Premorbid Adjustment Scale (PAS) [39, 40]
based on patient interview, the duration of untreated
psychosis (DUP) was estimated by interviewing the car-
egiver/family and the patient, the psychometric assess-
ment was conducted by the Positive and Negative
Syndrome Scale (PANSS) [41], and the Global Assess-
ment of Functioning scale (GAF) [42] based on patient
interview.

The neurological evaluations were carried-out using
the neurological soft signs (NSS) scale by Krebs et al. The
NSS scale explores 23 minor neurological signs that are
rated from 0 to 3 and distributed in five main domains:
motor coordination, motor integration, sensory integra-
tion, involuntary movements or posture, and quality of
lateralization. The threshold value for this scale was fixed
at 9.5 as recommended in the original version [43]. Neu-
rological side effects of antipsychotics were evaluated by
the Simpson Angus (SA) scale [44].

The PANSS and the GAF scales were administered
within 72 h of the patient’s hospitalization. The NSS scale
and the Simpson Angus scale were completed within
seven days of hospitalization.

We ascertained the use of cannabis with the cannabis
subsection of the Composite International Diagnostic
Interview (CIDI), included within the section of sub-
stance use. According to the CIDI, patients were con-
sidered to be cannabis users if they had taken cannabis
on five or more occasions; patients were considered as
“heavy cannabis users” when the frequency of cannabis
use was daily or nearly every day.

Statistical analyses
All statistical analyses were performed with SPSS for
Windows, Version 21.0.

The independent factor was cannabis use, which
divided the study sample in two groups: in-patients with
current cannabis use versus in-patients without current
cannabis use. The Mann–Whitney non-parametric test,
the Chi-square test, the Fisher’s exact test and the Pearson correlation coefficient were used for the between-group analysis. The statistical significance was set at 5%. Additionally, for the presence/absence of NSS, defined by the threshold value of >9.5 on the NSS Scale, we performed a logistic regression with cannabis use as well as smoking, alcohol use, PANSS positive score, PANSS negative score, PANSS disorganization score, PAS total score, and Simpson Angus score as variables entered into the model. The variables included were the significant ones at the statistical threshold of 0.25. All tests were two-sided with \( \alpha = 0.05 \). Due to the exploratory nature of the analyses, we did not correct for multiple comparisons.

**Results**

**Sociodemographic, clinical, therapeutic use characteristics**

At the end of the study period, 71 consecutively enrolled patients met the inclusion and exclusion criteria. Of these, 10 were not recruited: 4 patients due to premature discharge against medical advice and 6 patients refused study participation. Altogether, 61 in-patients were included in this study.

The study sample contained 53 men (86.9%) and 8 women; the mean age was 28.9 \( \pm \) 9.4 year-old. The majority had a low educational level or was unschooled (70.5%) and single (75.4%). Family history of mental illness was present in 24.6% of the patients; consisting mainly of psychotic disorders in first-degree relatives (Table 1). The majority of the patients (67.2%) had never taken psychotropic treatment before the hospitalization; only 24.6% had received antipsychotic treatment, most often only for a few days before hospitalization and 8.2% had received antidepressant treatment. The main diagnosis was schizophreniform disorder (42.6%), the mean DUP was 39.6 \( \pm \) 63.7 weeks; and the majority of patients were treated with first-generation antipsychotics (68.8%) (Table 2).

**Cannabis use**

The prevalence of the current cannabis use in this population was 14.8%, with heavy use among 8.2% of the patients and occasional use among 6.6%.

**Neurological soft signs (NSS)**

**NSS evaluation**

The mean NSS score was 15.3 \( \pm \) 6.7 (ranging from 4 to 32.5). The highest sub-scores were noted in the domain of motor coordination (6.1 \( \pm \) 2.7) (Table 3). Using the threshold value of \( \geq 9.5 \) on the NSS scale, NSS were present in 83.6% of the total patient sample.

**NSS and clinical and therapeutic characteristics**

Correlations were found between the NSS total scores and the Poor Premorbid Functioning (\( r = 0.32, p = 0.04 \)), the PANSS total scores (\( r = 0.36, p = 0.005 \)), and the negative (\( r = 0.45, p < 0.001 \)) and disorganization sub-scores (\( r = 0.41, p = 0.001 \)), the CGI-severity scores (\( r = 0.30, p = 0.02 \)), the impairment functioning in the GAF (\( r = -0.26, p = 0.04 \)) and with extrapyramidal symptoms (\( r = 0.52, p < 0.001 \)) (Table 3).

**NSS and cannabis use**

Comparing NSS scores between patients with and without cannabis use demonstrated significantly lower total NSS scores of in patients with cannabis use: 11.2 \( \pm \) 5.6 versus 16.0 \( \pm \) 6.7 (\( p = 0.048 \)) (Table 4). The linear regression model showed that this association remained significant after adjustment for two potentially confounding factors that have been associated with NSS: negative symptoms and neurological side effects of antipsychotics (Table 5).

There was also an inverse, but not significant relationship between the use of cannabis and the motor coordination and the involuntary movements sub-scores (Table 3).

| Table 1 | Sociodemographic characteristics |
|---------|----------------------------------|
| **Variables** | **Total number of patients** | **Cannabis users** | **Cannabis non-users** | **p** |
| **(n = 61)** | | **(n = 9)** | **(n = 52)** |
| Age | 28.9 \( \pm \) 9.4 | 274 \( \pm \) 7.8 | 29.2 \( \pm \) 10 | 0.81 |
| Male sex | 53 (86.9%) | 9 (100%) | 44 (84.6%) | 0.61 |
| Psychiatric family history | 15 (24.6%) | 2 (22.2%) | 13 (25.0%) | 0.33 |
| University studies | 18 (29.5%) | 3 (33.3%) | 15 (28.8%) | 0.57 |
| Marital status | 46 (75.4%) | 7 (77.8%) | 39 (75%) | 0.72 |
| Single | 11 (18%) | 1 (11.1%) | 10 (19.2%) | 0.91 |
| Married | 4 (6.6%) | 1 (11.1%) | 3 (5.8%) | 0.32 |
| Divorced | 27 (44.3%) | 8 (88.9%) | 6 (11.5%) | 0.23 |
| Currently employed | 19.2 \( \pm \) 7.9 | 18.7 \( \pm \) 8.5 | 22.6 \( \pm \) 7.6 | 0.23 |
There was also a significant association between heavy cannabis use and lower total NSS scores ($p = 0.048$).

Altogether, 66.7% of the patients with cannabis use exceeded the threshold value of 9.5 versus 85.5% of the non-users ($p = 0.16$). Similarly, a logistic regression analysis, with the presence of NSS as dependant variable and cannabis use, smoking, alcohol use, PANSS positive score, PANSS negative score, PANSS disorganization score, PAS total score and Simpson Angus score as covariates, did not show a significant association between presence of NSS and current cannabis use ($p = 0.12$).

**Discussion**

In this study, the prevalence of NSS was 83.6%, given the threshold score of 9.5 suggested by the NSS scale authors [43]. Studies that evaluated patients with first-episode psychosis reported a high prevalence of NSS, ranging from 20% for the Scottish Schizophrenia Research Group [9] to 97.1% for Browne et al. [4] (Table 6).

In this study, we examined the relationship between cannabis use and NSS in FEP patients; cannabis users had significantly fewer NSS than patients without a history of cannabis use. This findings were similar to those reported by Ruiz-Veguilla et al. [36] who studied cannabis use and NSS among 92 patients with FEP (64% males, mean age: 26.9 ± 10.1 years old). The authors found that heavy cannabis users (55% of the sample of the study) had significantly less NSS assesses with the Neurological Evaluation Scale independent of potential confounders, such as sex, age, family history of psychosis, and negative symptoms [36]. A similar association was also found by Stirling et al. [37] in a sample of 112 non-depressed FEP patients (56.2% males, mean age: 26.3 years old) with 38% of cannabis users. Other studies demonstrated a lower NSS scores for patients with chronic schizophrenia and

| Table 2 Clinical and therapeutic characteristics |
|-----------------------------------------------|
| Variables                                      | Total number of patients (n = 61) | Cannabis users (n = 9) | Cannabis non-users (n = 52) | p     |
| Psychiatric diagnosis                          |                                |                        |                           |       |
| Schizophrenia                                  | 20 (32.9%)                     | 5 (55.5%)              | 15 (28.8%)                |       |
| Schizophreniform disorder                      | 26 (42.6%)                     | 1 (11.1%)              | 25 (48.1%)                |       |
| Brief psychotic disorder                       | 10 (16.4%)                     | 1 (11.1%)              | 9 (17.2%)                 | 0.10  |
| Cannabis-induced psychosis                     | 3 (4.9%)                       | 2 (22.2%)              | 1 (1.9%)                  |       |
| Delusional psychosis                           | 1 (1.6%)                       | 0 (0%)                 | 1 (1.9%)                  |       |
| Psychotic disorder not otherwise specified     | 1 (1.6%)                       | 0 (0%)                 | 1 (1.9%)                  |       |
| PANSS total score                              | 99.5 ± 20.6                    | 101.6 ± 20.5           | 99.1 ± 20.8               | 0.65  |
| PANSS positive score                           | 25.1 ± 6                       | 27 ± 6.3               | 24.8 ± 6                  | 0.43  |
| PANSS negative score                           | 24.3 ± 9.3                     | 25.7 ± 9.8             | 24 ± 9.3                  | 0.56  |
| GAF score                                      | 32.4 ± 8                       | 30 ± 5.6               | 33.5 ± 8.3                | 0.28  |
| Duration of untreated psychosis (weeks)        | 39.6 ± 63.7                    | 28.6 ± 35.2            | 41.5 ± 87.4               | 0.45  |
| Antipsychotic treatment                        |                                |                        |                           |       |
| First-generation antipsychotic                 | 25(41%)                        | 4 (44.4%)              | 21 (40.4%)                |       |
| Second-generation antipsychotic                | 19 (31.1%)                     | 2 (22.2%)              | 17 (32.7%)                | 0.84  |
| Co-treatment of first- and second-generation antipsychotics | 17 (27.8%) | 3 (33.3%) | 14 (26.9%) |       |
| Chlorpromazine equivalent                      | 619.8 ± 419.8 mg               | 914.0 ± 629.8 mg       | 568.8 ± 356.6 mg          | 0.16  |
| Simpson Angus scale score                      | 3.8 ± 3.2                      | 4.3 ± 2.6              | 3.7 ± 3.                  | 0.37  |
| Duration of hospitalization (days)             | 29.1 ± 16.6                    | 43.3 ± 15.5            | 26.7 ± 15.6               | 0.005 |

| Table 3 Correlations between NSS and clinical and therapeutic characteristics |
|-----------------------------------------------|
| NSS total score                               |                                |                        |                           |       |
| PAS total score                                | r = 0.32, p = 0.04             |                        |                           |       |
| PANSS total score                              | r = 0.36, p = 0.005            |                        |                           |       |
| PANSS positive score                           | r = −0.06, p = 0.69            |                        |                           |       |
| PANSS negative score                           | r = 0.45, p < 0.001            |                        |                           |       |
| PANSS disorganization score                    | r = 0.41, p = 0.001            |                        |                           |       |
| CGI-severity score                             | r = 0.30, p = 0.02             |                        |                           |       |
| GAF score                                      | r = −0.26, p = 0.04            |                        |                           |       |
| SA score                                       | r = 0.52, p < 0.001            |                        |                           |       |

NSS, neurological soft signs, PAS, Premorbid Adjustment Scale, PANSS, Positive and Negative Syndrome Scale, GAF, Global Assessment of Functioning, CGI, Clinical Global Impression, SA, Simpson Angus
a history of cannabis use than for those without cannabis use. For example, Bersani et al. [45] investigated NSS in 25 male cannabis-consuming and 25 male non-consum- ing schizophrenia patients, using the Neurological Evalu - ation Scale and concluded that non-consuming patients showed a higher incidence of NSS. Joyal et al. [35], in a study of 16 men with and 14 men without a dual diagno- sis of drug abuse and schizophrenia, reported that drug abuse was associated to fewer frontal soft signs.

Three possible explanations are suggested for this seemingly paradoxical relationship between cannabis use and NSS in FEP. First, some cannabis components may have neuroprotective effects by inhibiting the glutamatergic excitotoxicity system [46, 47]. Second, this association could be explained by the fact that canna- bis would act more directly on the onset of psychosis in genetically less vulnerable individuals [19, 48] since NSS are shown to reflect a genetic liability to psychosis. In this context, cannabis use may be the environmental factor that reveals or potentiates the vulnerability to psycho- sis. Accordingly, it is likely that cannabis could increase the effects of genetic risk factors for psychosis. Thus, cannabis users may follow a different pathway (with less neurobiological vulnerability factors) in developing psy- chotic disorders compared to patients without a history of cannabis use [36, 48]. Third, the inverse association between NSS and cannabis use could be explained by a relationship between severe NSS with other clinical char- acteristics that would limit a subject’s personal access to cannabis [47]. In fact, most studies that examined NSS in FEP, in concordance with the results of this study, con- cluded that NSS were associated with more negative symptoms [2, 49, 50], disorganization symptoms [2, 49, 50] and illness severity [2]. These illness dimensions can limit the patients’ social interaction abilities and diminish their motivation or ability to obtain cannabis.

This study also showed an inverse, but not significant relationship between the use of cannabis and both “motor coordination” ($p = 0.06$) and “involuntary movements”

| Neurological soft signs scale scores: median, (interquartile range) | Total number of patients (n = 61) | Cannabis use | Statistic tests |
|---------------------------------------------------------------|----------------------------------|--------------|----------------|
|                                                               |                                  | Yes (n = 9)  | No (n = 52)    |                |
| Motor coordination sub-score                                   | 6.0 (4.3, 9.0)                   | 3.5 (2.3,8.0) | 6 (4.5, 9.0)   | $p = 0.06$     |
| Motor integration sub-score                                    | 3.0 (1.5, 5.3)                   | 2.5 (1.3,4.0) | 3(1.5, 5.5)    | $p = 0.51$     |
| Sensory integration sub-score                                  | 3.5 (1.5, 4.8)                   | 2.0 (1.0,4.0) | 3.5 (1.5, 5.4) | $p = 0.20$     |
| Involuntary movements or posture sub-score                     | 0 (0, 0)                         | 0 (0,0.3)    | 0.3 (0, 0.3)   | $p = 0.07$     |
| Quality of laterization sub-score                              | 1.0 (0,1.0)                      | 1 (0, 1.5)   | 1.0 (0, 3.0)   | $p = 0.20$     |
| Total score                                                    | 13.5 (11.0, 19.5)                | 11.5 (6.0,14.3) | 14.5 (11.5, 20.75) | $p = 0.048$ |
| Total score >9.5 (N, %)                                        | 51 (83.6%)                       | 6 (66.6%)    | 45 (86.5%)     | $p = 0.16$     |

| Table 5 Linear regression NSS total scores, PANSS negative scores and Simpson Angus scores |
|------------------------------------------------------------------------------------------|
| Standardized coefficient beta | CI | p value |
| Cannabis use | -0.315 | (-9.41, -2.41) | 0.001 |
| PANSS negative score | 0.402 | (0.15, 0.42) | <0.001 |
| Simpson Angus score | 0.476 | (0.59, 1.36) | <0.001 |

PANSS Positive and Negative Symptom Scale

Table 6 Prevalence of neurological soft signs in first-episode psychosis

| Authors (year)                        | N  | Study population                                   | Instrument to assess NSS | Prevalence of NSS (%) |
|---------------------------------------|----|---------------------------------------------------|--------------------------|-----------------------|
| The Scottish Schizophrenia Research Group [9] | 49 | First-episode schizophrenia                        | NES scale                | 20                    |
| Flyckt et al. [59]                    | 31 | First-episode psychosis                            | NES scale                | 78                    |
| Browne et al. [4]                     | 35 | First-episode schizophrenia or schizophreniform disorder | NES scale CNE scale | 97                    |
| Emsley et al. [60]                    | 66 | First-episode psychosis, schizophreniform disorder or schizoaffective disorder | NES scale                | 68                    |
| Ruiz-Veguilla et al. [36]             | 92 | First-episode psychosis                            | NES scale                | 45                    |
| Our study                            | 61 | First-episode psychosis                            | NES scale                | 84                    |

CNE Condensed Neurological Examination, NES Neurological Evaluation Scale, NSS neurological soft signs, NSS scale Neurological Soft Signs scale
(p = 0.07) sub-scores. To our knowledge, no other study explored the interaction between cannabis use and the different sub-groups of NSS in FEP patients. The available data about this topic are restricted to studies with non-psychotic populations that showed greater impairment of motor functioning in patients with cannabis use. Dervaux et al. [51] compared the impact of cannabis use on NSS among patients with cannabis dependence and healthy controls and demonstrated that higher NSS scores were associated especially with motor coordination difficulties in cannabis users. Roser et al. [52] reported impairment in motor speed after cannabis use. These results could be explained by the important role of the endocannabinoid system in the control of movements. In fact, a prominent distribution of the cannabinoid 1 (CB1) receptors in the basal ganglia has been described in patients with movements disorders [53, 54], and cannabis, when interacting with CB1 receptors, induces dopamine release and an increase in motor response [55]. Heavy cannabis consumption may also lead to deterioration in the control system balance and thereby contribute to motor inhibition [56]. The dose-dependent response of motor coordination to cannabis may be due to the involvement of GABAergic and glutamatergic systems as a target of cannabis and its psychoactive component Delta-(9)-tetrahydrocannabinol (THC) [56], or the development of sensitization and adaptive process, which leads to dopamine decrease in prefrontal regions after repeated use [57, 58]. This finding may explain the impairment of motor skills reported over non-psychotic patients. Conversely, however, higher cannabis consumption may produce a different response, which consists of a motor stimulation instead of inhibition depending on the adaptive mechanism put in place [47]. It is possible that this stimulatory effect could explain the inverse relation between motor coordination and cannabis in this study. Additionally, we investigated in-patients without any access to cannabis at the time of investigation. Hence, acute cannabis effects would not have been influenced our results and we assessed cannabis use more as a trait marker or risk factor for FEP. The fact that we found less motor coordination in patients with cannabis use and FEP strengthens our hypothesis that cannabis use might bring out psychosis risk in those individuals with less other neurobiological risk factors, as motor dysfunction, together with low intellectual quotient, was identified as one of the two strongest biological markers for schizophrenia risk in a recent meta-analysis [15].

There are several limitations to this study. First, the study was not based on a sample size calculation; the sample size, especially of the cannabis users, is small, although it lies within the range of similar FEP studies on this topic. Second, we did not confirm absence of cannabis use by urine screening and we did not have data regarding the exact time between the NSS evaluation and last cannabis consumption. Third, in view of the need for urgent treatment, it hasn’t been always possible to assess NSS before antipsychotic administration, which would have been better for NSS evaluation. Finally, we did not collect data on the amount of cannabis use.

This study demonstrated a negative association between cannabis use and NSS, especially regarding motor coordination. This finding supports the hypothesis that a strong environmental risk factor, such as cannabis, may contribute to the onset of psychosis even in the presence of lower biological and genetic vulnerability, as reflected indirectly by lower NSS scores. Nevertheless, due to the limitations of our study and its exploratory nature, this question remains open, and additional studies are needed to explore this interaction further. Such studies should have sufficiently large samples of cannabis users and non-users and consider cannabis and NSS in the context of additional neurobiological and environmental risk factors.

**Conclusions**

Our study demonstrated a negative association between cannabis use and NSS, especially regarding motor discoordination. This finding supports the hypothesis that a strong environmental risk factor, such as cannabis, may contribute to the onset of psychosis even in the presence of lower biological and genetic vulnerability, as reflected indirectly by lower NSS scores. Nevertheless, additional studies are needed that explore this interaction further in larger samples and considering additional neurobiological and environmental risk factors.

**Abbreviations**

NSS: neurological soft signs; FEP: first-episode psychosis; DSM: Diagnostic and Statistical Manual of Mental Disorders; PAS: Premorbid Adjustment Scale; DUP: duration of untreated psychosis; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning scale; CIDI: Composite International Diagnostic Interview; CB1: cannabinoid 1; THC: Delta-(9)-tetrahydrocannabinol.

**Authors’ contributions**

AM, BBM have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; have been involved in drafting the manuscript and have given final approval of the version to be published. CUC has made substantial contributions to analysis and interpretation of data; has been involved in drafting the manuscript; has revising the manuscript critically for important intellectual content; and has given final approval of the version to be published. BA has made substantial contributions to acquisition of data; has been involved in drafting the manuscript; and has given final approval of the version to be published. AM has made substantial contributions to conception and design, acquisition of data; analysis and interpretation of data; has been involved in drafting the manuscript; has revising the manuscript critically for important intellectual content; and has given final approval of the version to be published. LG has made substantial contributions to analysis and interpretation of data; has revising the manuscript critically for important intellectual content; and has given final approval of the version to be published. All authors read and approved the final manuscript.
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Competing interests
Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Bristol-Myers Squibb, Forum, Gerson Lehman Group, Intra Cellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Mediscape, Neurocrista, Otsuka, Pfizer, ProPhase, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck and Pfizer. He received grant support from Takeda. The other authors report no competing interests.

Availability of data and materials
The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Ethical approval
The ethics committee and the thesis committee of the faculty of medicine of Monastir have approved the protocol of this study. Informed consent to participate in the study was obtained from both participants and their parent or legal guardian.

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