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Cannabis use, cognition and brain structure in first-episode psychosis ☆

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ABSTRACT

Cannabis use is highly prevalent worldwide and it is associated with psychosis, but its effects on brain structure and cognition are still controversial. The aim of this paper is to investigate cognitive functioning and brain structure in patients with their first episode of psychosis who used *Cannabis*. We examined gray matter and lateral ventricle volumes in 28 patients with first-episode psychosis and a history of *Cannabis* use, 78 patients without a history of *Cannabis* use and 80 healthy controls who had not used *Cannabis*. Cognition was assessed using forward and backwards digit span tests, from the Wechsler Memory Scale-Third Edition (WMS-III) and the Controlled Oral Word Association Test (COWAT). Patients with a history of *Cannabis* use had less brain abnormalities, characterized by gray matter and lateral ventricle volume preservation, as well as less attentional and executive impairments compared to patients without a history of *Cannabis* use. *Cannabis*-using patients who develop psychosis have less neurodevelopmental impairment and better cognitive reserve than other psychotic patients; perhaps reflecting different etiological processes.

1. Introduction

Cannabis is the most widely used illegal substance worldwide and its use is associated with increased risk of psychosis (Moore et al., 2007; Murray et al., 2007; Koskinen et al., 2010; UNODCP, 2011). However, studies about *Cannabis* effects on human brain structure have provided heterogeneous and inconclusive data (Block et al., 2000; Matochik et al., 2005; Tzilos et al., 2005; Jager et al., 2007; Szeszko et al., 2007; Yücel et al., 2008; Wobrock et al., 2009; Lorenzetti et al., 2010; Martín-Santos et al., 2010; Cousijn et al., 2012; Malchow et al., 2012; Rapp et al., 2012).

Our previous data from a population-based voxel-based morphometry (VBM) study examining patients with first-episode psychosis (FEP), including *Cannabis* users and non-users, showed significant regional gray matter (GM) deficits, lateral ventricle (LV) enlargement, midline brain abnormalities and poorer cognitive functioning in patients (Ayres et al., 2007; Schaufelberger et al., 2007; Minatogawa-Chang et al., 2009; Ayres et al., 2010; Rosa et al., 2010; Trzesniak et al., 2012; Schaufelberger et al., 2011). Although *Cannabis* use is known to be associated with cognitive dysfunction and brain abnormalities in non-psychotic people (Hester et al., 2009; Cunha et al., 2010; Fontes et al., 2011a,b; Solowij et al., 2012), there is evidence that *Cannabis* is associated with better premorbid cognitive functioning in people with schizophrenia (Rodríguez-Sánchez et al., 2010; Yücel et al., 2012) and bipolar disorder (Braga et al., 2012). However, only one study (without a control group) has investigated the relationship between *Cannabis* use, brain structure and cognitive functioning in patients with FEP to date (Schnell et al., 2012).

In the present study, we investigated GM and LV volumes, as well as cognitive performance in patients with FEP and a history of *Cannabis* use (FEP C+), FEP without any history of *Cannabis* use (FEP C−), and healthy controls (HC). Based on previous neuropsychological findings, we hypothesized that subjects with FEP C+ would present less structural brain abnormalities and a more preserved pattern of cognitive functioning than patients with FEP C−.

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2. Methods

2.1. Participants

Patients were selected from a sample of 200 people with FEP identified for an epidemiological study of the incidence of psychotic disorders in São Paulo, Brazil. People presenting with a psychotic illness were recruited from a population who had been living for a period of at least 6 months in a circumscribed geographical area of São Paulo. Participants were identified by active surveillance of all people that made contact for the first time with the mental healthcare services for that region between 2002 and 2005 (see Menezes et al., 2007). Inclusion criteria for the present study were: (a) age between 18 and 50 years and (b) diagnosis of psychosis (affective or non-affective) according to DSM-IV 295–298 codes (APA, 2000) assessed by the Structured Clinical Interview for DSM (SCID) (Spitzer et al., 1992). As the sample was followed up by the same epidemiological team, the diagnoses reported here are those confirmed by the SCID administered at the one-year follow-up. People with psychotic disorders due to a general medical condition or substance-induced psychosis were excluded.

Next-door neighbors were contacted as potential controls and screened to exclude the presence of psychotic symptoms using the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995). The absence of psychotic or mood disorders in controls was also confirmed with the SCID (Spitzer et al., 1992).

Additional exclusion criteria for each participant were: (a) head injury with loss of consciousness; (b) organic disorders that could affect the central nervous system; and (c) contraindications for MRI scanning. Additional exclusion criteria for the control group were: personal history of psychosis or other Axis I disorders, except substance misuse or mild anxiety disorders.

From the above 200 people with psychosis included in the incidence study, 50 did not meet the inclusion criteria for the neuroimaging study because of contraindication for MRI, age above 50 years, presence of organic disorders, or subtle brain lesions identified by the MRI scans. Of the remaining 150 people, we lost contact with 15; 23 refused to participate and five had to be excluded owing to artifacts during image acquisition, resulting in a total of 107 patients from the incidence investigation included in the MRI study. There were no differences between those included in the present study ($n = 107$) and those that were lost ($n = 43$) in terms of their clinical and demographic profile except for a trend towards greater mean current age for those lost to the MRI study ($p = 0.06$, two-tailed t test). additionally, fifteen people with first-episode psychosis, identified at the same mental healthcare services for the region, but excluded from the incidence investigation as they lived outside the catchment area, were also included in the MRI study, resulting in a sample of 122 people with FEP. There were no significant differences between those from the original epidemiological study ($n = 107$) and those living outside the catchment area ($n = 15$) in regard to clinical and demographic data.

For the present investigation, from the 122 patients, we excluded 16 patients with alcohol and/or cocaine abuse without a history of *Cannabis* use, resulting in a final sample of 106 FEP. Patients with a lifetime history of *Cannabis* use (with a frequency of at least 3 times/month for at least one year), regardless of a diagnosis of abuse or dependence and regardless of other concomitant substance use as assessed by the SCID were included in the FEP C+ group ($n = 28$). The remaining 78 patients who had no history of *Cannabis* use were included in the FEP C− group.

For the control group, a total of 114 people from the same catchment area were recruited for MRI scanning, but 11 were excluded owing to the presence of silent gross brain lesions and 9 owing to artifacts during image acquisition, resulting in a sample of 94 controls. From this control sample, four individuals fulfilled DSM-IV criteria for alcohol dependence and ten participants had a previous history of *Cannabis* use, which led to their exclusion. In sum, we analyzed MRI data from 28 FEP C+, 78 FEP C− and 80 HC.

2.2. Clinical measures

Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and substance use was assessed using the SCID (Spitzer et al., 1992). The local Institutional Review Board (IRB) approved the protocol and we obtained written informed consent from all participants.

2.3. MRI acquisition

Neuroimaging data were acquired by two 1.5 T MRI GE Signa scanners (General Electric, Milwaukee Wisconsin, USA) with the same acquisition protocols (a T1-SPGR sequence providing 124 contiguous slices, voxel size $0.86 \times 0.86 \times 1.5$ mm, echo time 5.2 ms, repetition time 21.7 ms, flip angle 20, field of view 22, matrix 256×192). We verified the reliability of the scanners by intraclass correlation coefficients (ICCs). Briefly, six healthy volunteers were scanned twice on each scanner on the same day. Images were spatially normalized and segmented using voxel-based morphometry, and GM images from the two scanners were compared. Intraclass correlation coefficients (ICCs) were obtained for frontal, temporal, parietal and occipital neocortical regions, medial temporal structures (hippocampus, amygdala and parahippocampal gyrus), and subcortical nuclei (caudate, putamen and thalamus). These regions were circumscribed using the spatially normalized volumes of interest within the AAL SPM toolbox; gray matter estimates were given by the mean voxel intensity values obtained within each volume of interest, calculated using the MRIcro program. As an exception, the LVs were measured by the manual tracing region-of-interest (ROI), as already published (Rosa et al., 2010). We obtained between-scanners ICC values >0.90 for all neocortical and medial temporal regions, as well as for the LVs (Schaufelberger et al., 2007; Rosa et al., 2010).

2.4. Image processing

We conducted the VBM analyses using the Statistical Parametric Mapping package (SPM2) in Matlab (http://www.fil.ion.ucl.ac.uk/spm/software/SMP2) and detailed processing is described elsewhere (Schaufelberger et al., 2007).

The LVs were measured by a manual tracing ROI approach with the MRIcro 1.40 software (http://www.sph.sc.edu/comd/rorden/mricro.html). Automatic skull striping produced total brain volumes, and then four ventricle-to-brain ratios (VBRs) were calculated for each participant. Further details on the LV measurement in this sample can be found elsewhere (Rosa et al., 2010).

2.5. Neuropsychological functioning

Participants underwent cognitive testing composed by a brief neuropsychological battery, with the following instruments:

2.5.1 Forward digits (FD) and backward digits (BD), from the Wechsler Memory Scale (WMS-III) (Wechsler, 1997), measures of attention and working memory (executive functioning), respectively. Both tests consist of seven pairs of random sequences of numbers that the examiner reads aloud at the rate of one per second. FD consists of repeating series of numbers in the same order that was presented and BD in the reverse order.

2.5.2 Controlled Oral Word Association Test (COWAT) (Lezak et al., 2004), a measure of verbal fluency (language) and executive functioning. Participants must recall as many words as they can, beginning with the letters “F”, “A”, and “S” in a one-minute trial each. The main measure of COWAT represents the sum of all correct words recalled.