Schizophrenia Research xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

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ARTICLE INFO

Article history:
Received 24 December 2012
Received in revised form 8 April 2013
Accepted 10 April 2013
Available online xxxx

Keywords:
Cannabis
First-episode psychosis (FEP)
Schizophrenia
Cognition
Magnetic resonance imaging
Substance use

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−.

☆ Presented at the 1st Schizophrenia International Research Society (SIRS) South America Meeting, 5–7 Aug, 2011, and at the SIRS 3rd Biennial Schizophrenia International Research Society Conference, 14–18 Apr, 2012 Florence, Italy (abstract).

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http://dx.doi.org/10.1016/j.schres.2013.04.009

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.

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2.6. Statistical analysis

Comparisons of sociodemographic characteristics among groups were performed with chi-square test and Analysis of Variance (ANOVA). Clinical variables were analyzed among FEP participants (FEP C+ vs. FEP C−) using independent *t* test. The normal distribution of each cognitive variable was confirmed by the Kolmogorov–Smirnov test. Between-group analysis of cognitive functioning was conducted using Analysis of Covariance (ANCOVA) with gender and age as covariates and Bonferroni post hoc testing.

Between-group analyses of VBRs were performed using Multivariate Analysis of Covariance (MANCOVA), with gender and age as covariates. A logarithmic transformation was conducted on each of the four VBRs (when they were not normally distributed) to convert the data to a normal distribution. We also performed correlation analysis between neuropsychological scores, *Cannabis* use variables, and VBRs measures. In this case, we restricted the analyses to patients with history of *Cannabis* use (FEP C+). Here, when variables were normally distributed, group associations between two variables (e.g., years of *Cannabis* use and neuropsychological measures) were calculated using the Pearson correlation. When variables were not normally distributed, group correlations were performed using the Spearman's rho correlation. The analyses regarding sociodemographic, clinical and neuropsychological data, as well as VBR measures were performed with the Statistical Package for the Social Science (SPSS) software, version 14.0 and were reported as statistically significant at a threshold of $p < 0.05$.

Regional GM volumes were compared among the three groups within a General Linear Model approach using the SPM2. Gender, age and a measure of the total amount of GM were included as covariates. We used the small volume correction (SVC) tool to restrict comparisons to voxels in areas where we have previously found GM deficits: the frontal cortex and distinct left and right ROIs for the superior temporal cortices, the hippocampi and parahipocampal gyri, and the insuli. Any cluster of voxels showing significant findings within each of those ROIs was reported only if surviving family-wise error (FWE) correction for multiple comparisons ($p < 0.05$) over that region. Additionally, exploratory analyses were conducted to identify significant findings in other unpredicted regions across the entire brain. Such findings were reported as statistically significant at $p < 0.05$ only if surviving FWE correction for multiple comparisons over the whole brain. Localization of GM clusters of significant findings was provided in MNI space coordinate system.

3. Results

3.1. Demographic and clinical characteristics

Socio-demographic and clinical characteristics of the groups are described in Table 1.

The three groups did not differ in educational level, monthly income, or handedness (data of these last two variables not shown). FEP C+ patients were younger and more frequently male and single in comparison to both FEP C− and HC (Table 1).

The groups of patients were not different in terms of diagnosis of psychotic disorder (schizophrenia/schizophreniform disorder and affective psychosis; $p = 0.34$). Patients were similar in regard to severity of psychotic symptoms and treatment history. Patients with

Table 1
Sociodemographic, clinical and neuropsychological variables for FEP C+, FEP C− and HC.

Variables[a]	FEP C+ (n = 28)	FEP C− (n = 78)	HC (n = 80)	Statistics (p value)
Age, years	24.1 (6.5)	29.3 (8.6)	30.4 (8.3)	0.003[b]
Gender (Male/female), n	21/7	31/47	41/39	0.006[c]
Education, years	9.2 (4.1)	8.7 (4.2)	10 (4.2)	0.14
Living with a partner, n	6	32	42	0.15[d]
Diagnosis[e]				
Schizophrenia/schizophreniform disorder	17	36	–	–
Affective psychosis	10	33		
Other psychosis	01	9		
Psychosis, age at onset	23 (6.6)	28.6 (8.6)		0.002
Current treatment with antipsychotics (yes/no), n	15/13	48/30		0.46
Type of antipsychotic (typical/atypical), n	7/8	19/29	–	0.35
Antipsychotic exposure, days	121 (122)	105 (112)	–	0.63
PANSS, total score	45.6 (12.7)	44.9 (11)	–	0.78
COWAT, verbal fluency[f]	27.8 (8.0)	23.2 (10.0)	26.6 (10.3)	0.093[g]
FD (WMS-III), Forward Digits[f]	6.1 (2.2)	4.7 (2.0)	5.9 (2.6)	0.019[h]
BD (WMS-III), Backward Digits[f]	5.6 (2.1)	3.7 (1.5)	5.1 (1.9)	<0.001[i]
Cannabis use, age at onset	15.9 (3.1)	–	–	–
Cannabis, duration of exposure, years	6.5 (4.9)	–	–	–
Cannabis, pattern of use, n				
daily	18	–	–	–
2–3 times/week	06			
1–3 times/month	04			
Current *Cannabis* use (within two weeks before MRI scanning).	04	–	–	–
Previous *Cannabis* use, washout period, n				
2 weeks–6 months	14	–	–	–
>6 months	10			
Other substances (misuse, lifetime), n				
Alcohol	02			
Cocaine	04			
Alcohol + Cocaine	03			

FEP C+, patients with first-episode psychosis with *Cannabis* use; FEP C−, patients with first-episode psychosis with no history of *Cannabis* use; HC, healthy controls; PANSS (Positive and Negative Syndrome Scale); COWAT = Controlled Oral Word Association Test; FD = Forward Digits; BD = Backward Digits; WMS-III = Wechsler Memory Scale, Third Edition; a. Continuous variables are expressed in means (s.d.). Categorical variables are expressed as absolute number of participants; b. FEP C+ < FEP C− ($p = 0.014$); FEP C+ < HC ($p = 0.002$); c. Male gender FEP C+ > FEP C− ($p = 0.003$); d. FEP C+ (21.4%) < HC (52.5%) ($p = 0.012$); e. Psychiatric diagnosis according to DSM-IV: FEP C+ (schizophrenia = 15, schizophreniform = 02, bipolar disorder = 06, unipolar psychotic depression = 04, delusional disorder = 01); FEP C− (schizophrenia = 24, schizophreniform disorder = 12, bipolar disorder = 17, unipolar psychotic depression = 16, brief psychotic disorder = 6, schizoaffective disorder = 3); f. Not available for all participants (see text for details); g. COWAT: FEP C+ vs. FEP C− ($p = 0.25$); FEP C+ vs. HC ($p = 1.0$); FEP C− vs. HC ($p = 0.178$) (adjusted for multiple comparisons (Bonferroni)); h. FEP C+ vs. FEP C− ($p = 0.315$); FEP C+ vs. HC ($p = 1.0$); FEP C− < HC ($p = 0.019$) (adjusted for multiple comparisons (Bonferroni)); i. FEP C+ > FEP C− ($p = 0.002$); FEP C+ vs. HC ($p = 1.0$); FEP C− < HC ($p < 0.001$) (adjusted for multiple comparisons (Bonferroni)).

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Table 2
Voxel-based morphometry (VBM): gray matter differences between FEP C+ (n = 28), FEP C− (n = 78) and HC (n = 80).

Comparison	Anatomic location	Cluster size[a]	Peak z score[b]	p value[c]	MNI[d] x, y, z
FEP C− < HC	L inferior frontal gyrus (BA 9/45)/ L middle frontal gyrus (BA 46)	401	5.53	<0.001	−48 18 28
	L hippocampus	40	3.54	0.024	−20 −22 −14
	R parahipocampal gyrus (BA 28)/ R parahippocampal gyrus (BA 34)	133	4.96	<0.001	24–20 −12
			3.82	0.010	16–10 −16
FEP C− < FEP C+	L middle frontal gyrus (BA 9)	73	4.36	0.025	−34 24 30
	L hippocampus/	82	3.65	0.017	−30 −26 −8
	L parahipocampal gyrus (BA 35)/		3.45	0.032	−24 −22 −14
	L parahipocampal gyrus (BA 35)		3.36	0.042	−22 −26 −16

FEP C+, patients with first-episode psychosis with *Cannabis* use; FEP C−, patients with first-episode psychosis with no history of *Cannabis* use; HC, healthy controls; MNI, Montreal Neurological Institute; L, left; R, right; BA, Brodmann Area; a. Total number of contiguous voxels in each region above an initial cutoff of z > 3.09; b. z scores for the voxels of maximal statistical significance; c. Statistical significance after correction for multiple comparisons (FEW, family wise error, voxel level); d. Montreal Neurological Institute coordinates of the voxel of maximal significance within each region.

Cannabis use had a significantly earlier onset of psychosis. Among patients with FEP C+ (n = 28), *Cannabis* use preceded the onset of psychosis in all patients. Their mean age at onset of *Cannabis* use was 15.9 (SD = 3.1) years old, the mean lifetime duration of *Cannabis* exposure was 6.5 years (SD = 4.9) and 64.3% (n = 18) had a history of daily use. At the time of the MRI scan, ten patients (35.71%) were abstinent from *Cannabis* for more than 6 months, 14 had been abstinent from 2 weeks to 6 months, and four were current users (were using *Cannabis* within the last two weeks), but they were not intoxicated at the time of the clinical and MRI evaluation. From the 28 FEP C+ patients, nine had a lifetime history of regular use of other substances (cocaine = two, alcohol = four, cocaine plus alcohol = three). Details of *Cannabis* use are given in Table 1.

3.2. Neuropsychological findings

The ANCOVA including gender and age as covariates did not show any statistically significant difference among groups in COWAT ($p = 0.093$), but groups differed in attention (FD, $p = 0.019$) and in working memory (BD, $p = 0.001$) tests (Table 1). Post hoc comparisons showed that the difference in FD was due to worse performance of FEP C− in comparison to HC ($p = 0.019$) while the difference in BD was due to poorer results of FEP C− when directly compared to FEP C+ ($p = 0.002$) and HC ($p = 0.001$). In order to investigate whether these neuropsychological findings could be biased by exposure of patients to other substances rather than *Cannabis* itself, we compared the 19 patients with exposure to *Cannabis* only with those who were exposed to *Cannabis* plus other substances (n = 9). This analysis did not reveal any significant findings.

3.3. Neuroimaging findings

3.3.1. VBM analysis

We found statistically significant GM differences in two clusters in the left prefrontal cortex (PFC) ($p = 0.001$ and $p = 0.0039$) and in the left and right hippocampus/parahipocampus ($p = 0.024$ and $p < 0.001$, respectively). Post hoc analyses showed that FEP C− patients had significantly less GM in the left middle and inferior frontal gyrus (MFG and IFG), in the left hippocampus and in the right parahipocampal gyrus relative to HC and less GM in the left MFG and in the left hippocampus/parahippocampal gyrus in relation to FEP C+ (Table 2). The main clusters of GM differences are displayed in Fig. 1(A and B).

In order to investigate whether these neuroimaging findings could be biased by exposure of patients to other substances rather than *Cannabis* itself, we also compared the 19 patients with exposure to *Cannabis* only with those who were exposed to *Cannabis* plus other substances, but this analysis did not reveal any significant findings.

Correlation analysis within each diagnostic group revealed statistically significant correlation between GM and both COWAT and BD scores (Table 3). COWAT scores were positively associated with GM in the right superior temporal gyrus for FEP C+ ($r = 0.34$, $p = 0.003$), in the left MFG in FEP C− ($r = 0.51$, $p = 0.03$) and in the right insula for the control group ($r = 0.38$, $p = 0.027$). Also, BD scores were positively correlated with GM in left superior frontal gyrus in FEP C− ($r = 0.50$, $p = 0.049$).

3.3.2. VBR analysis

We found significant differences among groups in the right and left LV ($p = 0.035$ and $p = 0.002$, respectively) as well as in the right TH ($p = 0.009$). Post hoc Bonferroni tests revealed that the FEP C− group, when compared to HC, had significant larger left LV and right TH (Table 4). Correlation analysis between VBRs and neuropsychological scores did not reveal any statistically significant correlations.

3.4. Association of Cannabis use variables with brain structure and cognition

Additional analyses were conducted in order to investigate the influence of the following variables associated with *Cannabis* use on brain structure and cognition: duration of exposure to *Cannabis* (in years), washout period from *Cannabis* use, and age at onset of *Cannabis* use.

3.4.1. Cannabis washout

Patients with a washout period of at least 6 months (N = 10) had greater GM than recent users (n = 18, including current users and patients with less than 6 months of washout) in the left hippocampus/parahippocampal gyrus (21 voxels, $x = -22$, $y = -40$, $z = 6$, Broadmann Area, BA, 30, $p = 0.027$; 49 voxels, $x = -36$, $y = -16$, $z = -12$, $p = 0.028$) and in the right hippocampus/parahippocampal gyrus (220 voxels, $x = 22$, $y = -30$, $z = -16$, BA 35, $p = 0.039$; $x = 30$, $y = -36$, $z = -2$, $p = 0.005$). We did not find differences between these groups in regard to LVs or neuropsychological data.

3.4.2. Duration of Cannabis exposure and age at first Cannabis use

Gray matter, VBRs or neuropsychological data were not correlated with lifetime duration of *Cannabis* exposure or with age at onset of *Cannabis* use. We also categorized the patients according to the mean age at first *Cannabis* use (<16 and ≥16 years), and these two groups were not different in terms of GM, VBRs or neuropsychological data.

4. Discussion

This study found GM deficits in medial temporal structures (hippocampus and parahipocampal gyrus) and in the PFC, as well as LV

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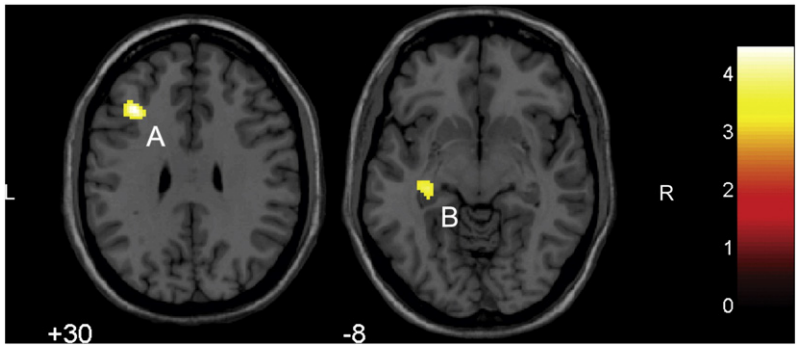

Fig. 1. VBM analysis: main clusters of GM differences between FEP C+ and FEP C−. Legend: Axial slices displaying clusters of significant increased GM volume in FEP C+ in relation to FEP C− in the left PFC (left panel, A) and in the left hippocampus (right panel, B). For display purposes only, clusters are overlaid on a T1 weighted template at $p < 0.001$, uncorrected for multiple comparisons. Numbers refer to z axis on MNI coordinate system. Abbreviations: VBM, voxel-based morphometry; GM, gray matter; FEP C+, patients with first-episode psychosis and *Cannabis* use; FEP C−, patients with first episode psychosis and no history of *Cannabis* use; PFC, prefrontal cortex; L, left; R, right.

enlargement and cognitive impairments, in patients with FEP C−, but not in subjects with FEP C+. In fact, those abnormalities were found in patients without *Cannabis* use when directly compared to patients with a history of *Cannabis* use, confirming that FEP C+ have less structural brain abnormalities and less cognitive impairments when compared with the group of FEPs without a history of *Cannabis* use. No difference in neuropsychological performance was seen between FEP C+ and controls.

These data are in accordance with studies suggesting that those individuals who develop psychosis in the context of *Cannabis* use have better premorbid cognitive functioning (Joyal et al., 2003; Rodríguez-Sánchez et al., 2010; Yücel et al., 2012). Indeed, executive abilities are necessary to find, acquire, and sustain illegal drug use (Joyal et al., 2003), so FEP C+ would be composed of patients with relatively better premorbid cognitive functions and premorbid social adjustment (Rodríguez-Sánchez et al., 2010) who had early contact with *Cannabis*, followed by a psychotic disorder emerging in a more structurally preserved brain. This is consistent with recent data showing an association between high premorbid IQ and *Cannabis* use (White and Batty, 2012).

A recent study also reported less severe cognitive impairments and GM deficits in the PFC in patients with schizophrenia and *Cannabis* use (Schnell et al., 2012), although that study was different in terms of methodological issues (e.g., lack of a healthy control group and limited number of inspected brain regions).

In our study, we cannot attribute the between group differences in brain volumes to differences in clinical symptoms, because the FEP C− and FEP C+ groups were similar in terms of psychopathology. Differences in other sociodemographic variables were found but we included them as covariates in each analysis (e.g., gender and age). Also, a younger age of psychosis onset in FEP C+ is in accordance with the literature on schizophrenia and bipolar disorder (De Hert et al., 2011; Lagerberg et al., 2011), which gives support to the notion that such disorders, when associated with *Cannabis* use might have specific characteristics, develop at different stages of brain maturation and might be associated with different neurobiological aspects.

Finally, it should be mentioned that less brain abnormalities and less cognitive deficits exhibited by FEP patients with a lifetime exposure to *Cannabis* in comparison to FEP patients without history of *Cannabis* exposure do not mean that these patients will not develop some degree of deficits. For example, in a 5-year prospective study, *Cannabis*-using schizophrenia patients presented progressive alterations in the dorsolateral PFC and in the anterior cingulate cortex, possibly because patients with FEP who continue to use *Cannabis* after illness onset are particularly vulnerable to brain alterations in areas rich in CB1 receptors, related to negative symptoms and to poorer cognitive functioning (Rais et al., 2010). Indeed, additional investigation considering the recent or past use of *Cannabis* in our subgroup of FEPC+ revealed that recent exposure to *Cannabis* (investigated by the comparison between current users/or patients who had stopped the use less than six months before the MRI session and those patients who were abstinent from *Cannabis* for more than six months) was associated with GM deficits in the left and right hippocampus/parahipocampal gyrus. Therefore, less GM abnormalities were related to any history of *Cannabis* exposure (including previous and current use), in comparison to no exposure, but we must have in mind that patients were scanned after approximately one year after the first episode of psychosis, and within the *Cannabis* users, those

Table 3
Voxel-based morphometry (VBM): significant direct correlations between gray matter and neuropsychological testing.

Neuropsychological testing within groups	Anatomic location	Cluster size[a]	Peak z score[b]	Correlation coefficients (r)[c]	p value[d]	MNI[e] x, y, z
FEP C+ (n = 25)						
COWAT	R superior temporal gyrus	246	4.40	0.34	0.003	48 −28 8
			3.68	0.44	0.034	66 −30 14
FEP C− (n = 64)						
BD	L superior frontal gyrus (BA 10)	424	4.21	0.50	0.049	−26 52 26
COWAT	L medial frontal gyrus (BA 10)	405	4.34	0.51	0.03	−8 58 18
HC (n = 80)						
COWAT	R insula	07	3.52	0.38	0.027	40 −8 22

FEP C+, patients with first-episode psychosis and history of *Cannabis* use; FEP C−, patients with first-episode psychosis with no history of *Cannabis* use; HC, healthy controls; MNI, Montreal Neurological Institute; L, left; R, right; BA, Brodmann Area; COWAT, Controlled Oral word Association Test; BD, Backward digits; a. Total number of contiguous voxels in each region above an initial cutoff of $z > 3.09$; b. z scores for the voxels of maximal statistical significance; c. Pearson Correlation Coefficients (r); d. Statistical significance after correction for multiple comparisons (FWE, family wise error, voxel level); e. Montreal Neurological Institute coordinates of the voxel of maximal significance within each region.

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Table 4
Comparison of ventricle-to-brain ratios (VBRs) between FEP C+, FEP C− and HC[a].

VBR[b]	FEP C+ (n = 28)	FEP C− (n = 78)	HC (n = 80)	Statistics (p value)	
				FEP C− vs. HC	FEP C− vs. FEP C+
Right LV	0.0041 (0.0015)	0.0047 (0.0021)	0.0041 (0.0026)	0.082	0.727
Left LV	0.0042 (0.0017)	0.0054 (0.0026)	0.0045 (0.0026)	0.016	0.06
Right TH	0.00032 (0.00008)	0.00039 (0.00017)	0.00032 (0.0001)	0.015	0.126
Left TH	0.0003 (0.0001)	0.00036 (0.0002)	0.0003 (0.0001)	0.145	0.549

FEP C+, patients with first-episode psychosis with *Cannabis* use; FEP C–, patients with first-episode psychosis with no history of *Cannabis* use; HC, healthy controls; VBR, ventricle-to-brain ratio; R, right, L, left; LV, lateral ventricle; TH, temporal horn; a. MANOVA (Multivariate Analysis of Variance) with post hoc Bonferroni test; b. VBR is expressed as a percentage (%) of the brain volume that is occupied by the region of interest; numbers are expressed by means (s.d.).

with a recent use had decreased, rather than increased GM in amygdale and hippocampal region.

These results suggest that exposure to *Cannabis* has an effect on the development of psychosis in a structurally "preserved" brain, but after the illness onset, the effects of *Cannabis* might be associated with GM deficits. It should be noticed, however, that the performance in the neuropsychological tests did not differ between recent users and long-term abstinent patients.

Our study has several strengths. We selected a sample from a large population-based study, including not only patients with schizophrenia, but also patients with "affective psychosis", such as bipolar disorder and major depressive disorder with psychotic features, and other forms of psychosis (e.g. schizoaffective disorder and schizophreniform disorder). This is a reflection of the variety of psychotic disorders we observed in the community. Also, there is a scarcity of MRI studies investigating *Cannabis* effects on brain structure in patients with affective psychosis, and there were no studies examining brain structure and cognition simultaneously in those patients. Also, frequency of *Cannabis* users among affective patients was the same as in the non-affective group.

The VBM and the ROI methods employed in this study, although technically different, are well validated methods to assess GM and LVs respectively. We applied a specific method to measure the lateral ventricles based on a manual tracing of ROIs, which is considered as the gold-standard approach for measurements of such structures (Job et al., 2002). The use of VBM was an additional strength of our study because it allowed the investigation of regional GM across the whole brain, while other studies focused on particular structures or global measures (Cahn et al., 2004; Bangalore et al., 2008; Schnell et al., 2012). This is important when studying psychosis and mood disorders, which are associated with abnormalities in several brain regions (Schaufelberger et al., 2007; Rosa et al., 2010; Périco et al., 2011). Furthermore, CB1 receptors are present in many brain regions (e.g. basal ganglia, cerebellum, frontal cortex, hippocampus, amygdala), thus, restricting the analysis to only a few regions of interest would limit the study. Finally, the use of control participants was necessary and useful, because they were representative of the general population.

We must acknowledge that our study has some limitations. First, we performed only 2 cognitive tests (Digits and COWAT) and neuropsychological data were not available for all participants. We only have premorbid IQ data from less than a half of the sample, which precluded us from including this variable in the volumetric and cognitive analyses. But it should be noticed that we observed, in an exploratory analysis with this subset of participants, that the FEP C− patients had significant lower mean IQ scores than FEP C+ and HC (data not shown), which is another limitation, given that a lower premorbid IQ could influence brain structure and neuropsychological measures (Bolla et al., 2002). Second, we relied on retrospective information about *Cannabis* consumption given to us by patients or family members. We did not have objective information about the *Cannabis* use, such as measures of *Cannabis* exposure (e.g., estimated THC/cannabidiol ratios and potency, confirmation of use by biologic tests). Third, we included patients who had used other substances in our FEP C+ group. However, we do not believe that this fact biased our findings, because we compared cognitive functioning, GM and LV volumes between FEP C+ patients with exclusive use of *Cannabis* and FEP C+ patients with additional substance use and found no between-group differences. Fourth, another issue that could be raised is the possible influence of antipsychotics use on our results. However, groups did not differ in terms of duration of exposure or types of antipsychotics used. Fifth, despite our relatively large FEP sample, the final sample was limited to allow additional investigations in subgroups of patients (for example, comparisons among affective and non-affective). Finally, although we had patients who reported daily use of *Cannabis* at some moment (n = 18), while others were less frequent users (n = 10), a direct comparison between them would not provide reliable results, since they could not be matched in terms of current/past use. We tried to investigate a dose-related effect by conducting correlation analysis between duration of exposure to *Cannabis* use and the neuroimaging and neuropsychological data but the results did not show such relationship. We also failed to find an association between a younger age at first use of *Cannabis* and structural brain and cognitive deficits. While *Cannabis* use has been associated with cognitive and brain abnormalities in volunteers without psychosis (Hester et al., 2009; Cunha et al., 2010; Fontes et al., 2011a,b; Solowij et al., 2012), our study suggest that this does not apply for FEP C+, suggesting a role for interactions between biological aspects of psychotic disorder and the exposure to cannabinoids.

Our results also suggest that psychosis is not associated with a homogeneous pattern of brain structure and cognitive functioning. From a neurodevelopmental perspective, it is possible that FEP C+ and FEP C− represent distinct subgroups of patients with psychosis. While FEP C− patients would have a particular history of neurodevelopment impairment, probably including cognitive abnormalities before the first psychotic episode, it is possible that FEP C+ patients would have a more preserved pattern of cognitive functioning (cognitive reserve), at least until this initial period of the first psychotic episode. *Cannabis* use would be, then, a crucial factor for the development or for the precipitation of psychosis in an otherwise not so compromised brain. In sum, subjects with FEP C− may have more developmental factors involved in the etiology of their psychoses, whereas patients with FEP C+ may have more 'environmental' and relatively recent factors, such as *Cannabis*, in their causal chain.

Future longitudinal studies evaluating neuroimaging, neuropsychological, life-events (e.g., exposure to maltreatment, early emotional stress, and others), and genetic parameters with larger sample sizes would be useful to elucidate the complex specific interactions between *Cannabis*, cognition, and brain morphology in psychosis.

Role of the funding source

This study was carried out with data previously collected using Wellcome Trust (UK) funds. Sir Robin Murray has received honoraria for lectures from Janssen, AstraZeneca, Lilly, Novartis and Bristol-Myers Squibb. Dr. Maristela Schaufelberger, Paulo Menezes, José Crippa and Geraldo Busatto are partly funded by the CNPq-Brazil. Paulo Cunha and Geraldo Busatto are partly funded by FAPESP (Grant Numbers: 2010/15786-1 to Dr. Geraldo Busatto e 2010/15604-0 to Dr. Paulo Cunha).

Contributors

The authors contributed equally to this work and all of them have approved the final manuscript.

Please cite this article as: Cunha, P.J., et al., *Cannabis* use, cognition and brain structure in first-episode psychosis, Schizophr. Res. (2013), http://dx.doi.org/10.1016/j.schres.2013.04.009

Conflict of interest

None of the authors have any conflict of interest which might inappropriately influence the development or the results of this work.

Acknowledgements

We thank Claudio Campi de Castro for assistance in the collection of MRI data.

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Please cite this article as: Cunha, P.J., et al., *Cannabis* use, cognition and brain structure in first-episode psychosis, Schizophr. Res. (2013), http://dx.doi.org/10.1016/j.schres.2013.04.009