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ORIGINAL PAPER

Combined Grey Matter VBM and White Matter TBSS Analysis in Young First Episode Psychosis Patients With and Without Cannabis Consumption

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Abstract Cannabis consumption is temporally associated with the development of first episode psychosis (FEP). Whether or not the chronic use of this substance induces structural brain changes that may be responsible for the cognitive and psychological disturbances in this disorder is still matter of debate. To address this issue, we compared the magnetic resonance imaging (MRI)-assessed grey (GM) and white matter (WM) changes in young FEP patients between users versus non-users of cannabis. This prospective study included 50 consecutive FEP subjects: 33 users (22.7 ± 4.1 years, 4 women) and 17 non-users (23.9 ± 4.2 years, 10 women). Users were further divided into 15 heavy (23.3 ± 4.5 years, 2 women) and 18 light users (22.2 ± 3.8 years, 2 women) according to their lifetime cannabis use. Voxel-based-morphometry (VBM) analysis of GM and tract-based-spatial-statistics (TBSS) analysis of WM were performed. Age and gender were used as non-explanatory co-regressors. There were no supra-threshold differences between user and non-user groups for both GM and WM parameters. This was also the case when only heavy users were compared to non-users. Multivariate models controlling for age and gender confirmed these findings. We found no evidence for cannabis consumption related alterations in GM or WM in FEP subjects. Due to the strict correction for multiple comparisons and sample size, we cannot formally exclude subtle morphometric changes associated with cannabis consumption. However, even if present, such potential alterations would be of low magnitude.

Keywords Psychosis · Cannabis · VBM · TBSS

Abbreviations

BPRS	Brief psychiatric rating scale
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FEP	First episode psychosis
GAF	Global assessment of functioning
GM	Grey matter
LD	Longitudinal diffusivity
MD	Mean diffusivity
RD	Radial diffusivity
TAP	Test of attentional performance
TBSS	Tract-based-spatial-statistics
TFCE	Threshold-free cluster enhancement
VBM	Voxel-based-morphometry
WM	White matter
WMS-R	Wechsler memory scale: revised

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Introduction

First episode psychosis (FEP) is a major health problem in young adults with a reported incidence rate of at least 1.5 % per year in urban areas (Amminger et al. 2006). Cannabis use is very frequent in all stages of psychosis (Regier et al. 1990) and represents one of its main risk factors (Semple et al. 2005; Henquet et al. 2005; Moore et al. 2007). Previous

studies have demonstrated alterations in both grey matter (GM) [review see e.g. (Honea et al. 2005; Glahn et al. 2008; Fornito et al. 2009; Fusar-Poli et al. 2011)] and white matter (WM) [review see e.g. (Kyriakopoulos and Frangou 2009)] in at-risk individuals and patients with early stages of psychosis. Given the frequency of moderate to heavy cannabis use in these groups, it has been thought that the chronic use of this substance partly contributes to these structural changes by affecting both GM densities and WM microstructure. Most previous studies focused on FEP or early psychosis in line with the hypothesis of an early toxic effect of cannabis on brain maturation. Cross-sectional comparisons revealed decreased GM densities in cannabinoid receptor rich areas (i.e. temporal fusiform gyrus, parahippocampal gyrus, insular cortex, precuneus, paracingulate gyrus, dorsolateral prefrontal cortex, cerebellum) of these patients (Szeszko et al. 2007; Bangalore et al. 2008; Cohen et al. 2011; James et al. 2011). Volume loss and cortical thinning were also described upon follow-up in FEP patients with heavy cannabis consumption (Rais et al. 2008, 2010; Habets et al. 2011). However, negative data were reported both in original articles (Schnell et al. 2012; Wobrock et al. 2009) and a systematic review (Malchow et al. 2012). Diffusion tensor imaging (DTI) data on WM are not less conflicting. Chronic cannabis use in FEP patients was associated with altered WM microstructure, increased WM directional coherence or no significant changes (Peters et al. 2009; Dekker et al. 2010; Ho et al. 2011; James et al. 2011). Several methodological limitations render difficult the interpretation of these data. First, most of the previous studies explored either GM or WM changes in limited series of FEP patients. Second, positive data may reflect the concomitant presence of cognitive deficits that have not been excluded in most of these contributions. In the current investigation, we combined neuropsychological assessment of attention and memory performances, GM volumetry with voxel-based-morphometry (VBM) (Ashburner and Friston 2000) and WM microstructure with tract-based-spatial-statistics (TBSS) (Smith et al. 2006) in 50 young FEP patients with heavy, light or no cannabis consumption. The main aim of this work is to provide a detailed analysis of the cannabis-related structural changes in FEP patients after controlling for the confounding effect of cognitive status.

Materials and methods

Subjects

Fifty patients with a FEP were recruited from a specialized inpatient service for young adults. A FEP was considered on the presence of any DSM-IV diagnosis of a psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, manic or depressive episode with psychotic symptoms and delusional disorder) with a total duration of illness less than 1 year. For each patient, the diagnosis at time of MRI was established by combining information gathered from several sources (clinical presentation, relatives, staff members, and previous medical records when available). All diagnoses were confirmed by at least two independent psychiatrists blind to their respective assessment (LC, FC and/or MM). In order to cover the wide spectrum of psychosis, three diagnostic categories were considered (Table 1): I, schizophrenia; II, Other psychotic diagnosis (including schizoaffective disorder, schizophreniform disorder and delusional disorder); III, Mood disorder with psychotic symptoms (including manic or depressive episode with psychotic symptoms). At the time of MRI, all patients had been receiving atypical antipsychotic treatment (aripiprazole, clozapine, olanzapine, quetiapine or risperidone) for at least 2 weeks. Lifetime cannabis and substance use at time of MRI was determined using the cannabis experience questionnaire that was administrated by the clinical psychologist of the care team (MA) (Di Forti et al. 2009). Subjects were not included if they presented with a history of substance use other than cannabis, nicotine or alcohol (use defined as more than four separate occasions). Heavy cannabis use was defined as near daily or more cannabis consumption for at least 1 year prior to clinical presentation. Patients consuming at lower frequencies prior to presentation were categorized as light cannabis users, whereas patients with ten lifetime cannabis consumptions or less were considered as non-users.

Subjects were grouped as 33 users (22.7 ± 4.1 years, 4 women) and 17 non-users (23.9 ± 4.2 years, 10 women) of cannabis. Users were further divided into 15 heavy (23.3 ± 4.5 years, 2 women) and 18 light users (22.2 ± 3.8 years, 2 women). The mean age at onset of cannabis consumption was at age 15.5 ± 1.9 (age range: 13–20 years). We further divided the users according to the age at onset in early (age 15 or less at onset) and late (age 16 or above at onset) groups. For two cases this information was not available.

All subjects underwent neuropsychological testing of attention and working memory performances within 2 months of MRI testing (MB or SB, fully certified neuropsychologists). Attentional functions were tested using the French computerized version of the test of attentional performance (TAP) (Zimmerman and Fimm 1994). Visuospatial and auditory working memory was evaluated with the French version of the WMS-R span tasks (Wechsler 1981). Additional assessments included the global assessment of functioning score (GAF) (Dufton and Siddique 1992) and Edinburgh handedness inventory (Oldfield 1971).

Table 1 Demographic and clinical characteristics

Variables	Cannabis users		Non-users	Statistical analysis
	High dose	Low dose		
N	15	18	17	
Age (years)	23.3 ± 4.5	22.2 ± 3.8	23.9 ± 4.2	NS
Gender (f/m)	2/13	2/16	10/7	Group**
				high vs non*
				low vs non**
GAF score	28.9 ± 10.4	33.5 ± 11.7	31.6 ± 12.1	NS
Medication type (ap/ap+ad/ap+ms)	11/2/2	15/3/0	13/3/1	NS
Medication CPZ equivalent (mg)	426.5 ± 281.5	296.2 ± 202.9	283.3 ± 262.2	NS
Diagnosis (I/II/II, see below)	9/3/3	11/1/6	6/4/7	NS
Handedness (EHI)	18.5 ± 1.7	18.6 ± 1.6	14.8 ± 7.4	NS
Visuospatial working memory (score)	17.2 ± 2.6	14.3 ± 7.9	12.0 ± 7.7	NS
Auditory working memory (score)	11.7 ± 3.4	8.9 ± 6.2	9.1 ± 6.0	NS
Attentional inhibition response time (ms)	570.0 ± 124.4	560.3 ± 91.1	556.0 ± 59.5	NS
Attentional flexibility response time (ms)	1166.0 ± 532.2	890.1 ± 202.8	1058 ± 273.1	NS

Essential demographic and clinical characteristics of the three study groups FEP subjects with high dose cannabis consumption, low dose cannabis consumption and without concomitant cannabis consumption. Diagnoses are grouped into three categories according to DSM-IV criteria: I, schizophrenia; II, other psychotic diagnosis (including schizoaffective disorder, schizophreniform disorder and delusional disorder); III, mood disorder with psychotic symptoms (including manic or depressive episode with psychotic symptoms)

GAF global assessment of functioning, *Ap* 2nd generation antipsychotic, *Ad* antidepressant, *Ms* mood stabilizer, *EHI* edinburgh handedness inventory

NS non significant ($p > 0.05$); * $p < 0.05$; ** $p < 0.01$

The normal distribution of the demographic and clinical data was tested by D'Agostino and Pearson omnibus normality tests. Normally distributed variables (age, visuospatial and auditory working memory, attentional flexibility) were analyzed using ANOVA group tests and post-hoc pair-wise Bonferroni's multiple comparison tests. Variables without normal distribution (gender, handedness, attentional inhibition) were analyzed using Kruskal–Wallis group statistics and post-hoc pair-wise Dunn's multiple comparison tests.

MR Imaging

MR imaging was performed with a 1.5 T clinical routine whole body scanner (Achieva, Philips Medical Systems, Best, The Netherlands). 3D T1 MPRAGE: coronal acquisition, 124 slices, matrix 256 × 256, voxel size 0.94 × 0.94 × 1.5 mm^3, TE 6 ms, TR 35 ms, 1 average. DTI: 30 diffusion directions, b = 1,000 s/mm^2 isotropically distributed on a sphere, 1 reference b = 0 s/mm^2 image with no diffusion-weighting, axial acquisition, 70 slices, matrix 112 × 112, voxel size 2.0 × 2.0 × 2.0 mm^3, TE 71.2 ms, TR 13469.4 ms, 1 average. Additional sequences (T2w, FLAIR) were acquired and analyzed to exclude other brain pathology.

GM VBM Analysis of T1 Data

The VBM analysis was analyzed using the FSL software package (http://www.fmrib.ox.ac.uk/fsl/, Version 4.1). Standard processing steps were used, as described in detail before (Smith et al. 2006, 2007). The essential processing steps included brain extraction using BET (brain extraction tool, part of FSL), tissue-type segmentation using FAST4 (part of FSL), non-linear transformation into MNI (Montreal Neurological Institute) reference space and creation of a study-specific GM template, to which the native GM images were then non-linearly re-registered. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. Finally, voxel-wise general linear model (GLM) was applied using permutation-based non-parametric testing (RANDOMISE, part of FSL), correcting for multiple comparisons implementing threshold-free cluster enhancement (TFCE) (Smith and Nichols 2009). Because of the significant difference in gender between the two groups, all calculations were performed twice, once without and once with age and gender as non-explanatory co-regressors. Fully corrected p values <0.05 are considered as significant. Additionally, the analysis was repeated with respect to the GAF score using and age and gender as non-explanatory co-regressors.

WM TBSS Analysis of DTI Data

The TBSS analysis of the DTI data was again done implementing the FSL software package (http://www.fmrib.ox.ac.uk/fsl/, Version 4.1), according to the standard procedure described in details (Smith et al. 2004). In principle, TBSS projects all subjects' FA data onto a mean FA tract skeleton using non-linear registration. The tract skeleton is the basis for voxel-wise cross-subject statistics and reduces potential misregistrations as the source for false-positive or negative results. The other DTI derived parameters longitudinal (LD, also known as axial diffusivity AD), radial (RD) and mean (MD) diffusivity were analyzed in the same way re-using the spatial transformation parameters that were estimated in the initial FA analysis. Similar to the VBM analysis discussed above, voxel-wise statistical analysis was performed with TFCE (Smith and Nichols 2009) correction for multiple comparisons, considering fully corrected p values <0.05 as significant. As for the VBM analysis, all calculations were performed twice with and without age and gender as non-explanatory co-regressors due to the difference in gender between groups. Equivalent to the VBM analysis, an additional analysis was performed with respect to the GAF score using and age and gender as non-explanatory co-regressors.

Results

Demographic and clinical data are summarized in Table 1. There was a clear predominance of women among non-users (12 % of users and 59 % of non-users, $p < 0.05$). Symptomatology at initial presentation as measured by GAF (DSM-IV) scores was consistent with clinically significant acute psychosis (overall average score 31.5, range 15–55). There were no significant differences in age, clinical symptom severity at initial presentation, diagnosis, medication type and dose (chlorpromazine equivalents), handedness, attention and memory performance between the two groups. The average neurocognitive performance of all groups falls within the normal age-adjusted range (i.e. within one standard deviation of age-adjusted normal means).

No supra-threshold differences at $p < 0.05$ TFCE corrected for multiple comparisons (VBM; TBSS FA, LD, RD, MD) were found for the comparison of all users versus non-users (see Fig. 1). In the same line, we separately compared the groups of heavy users versus light users, heavy users versus non-users and light users versus non-users again yielding no supra-threshold difference (VBM; TBSS FA, LD, RD, MD). The comparison between early onset versus late onset, early onset versus controls and late onset versus controls also showed no supra-threshold differences for all MRI variables (VBM; TBSS FA, LD, RD, MD). The inclusion of age and gender as non-explanatory co-regressors led to similar results. The analysis with respect to the GAF score also resulted in no supra-threshold results.

Discussion

The present study did not identify changes in GM volume and WM microstructure in FEP subjects with versus without concomitant cannabis consumption. These negative data concerned not only light users but also young patients with long-standing heavy consumption and do not support the idea of cannabis-mediated neurotoxicity during brain maturation in FEP.

The impact of cannabis consumption on brain structure remains a highly controversial issue. Some lines of evidence indicated that cannabis use in itself and in the absence of psychosis can be deleterious for brain structure. However, recent reviews on this subject have concluded that overall, cannabis use has minimal or no effect on brain structure in the general population (Martin-Santos et al. 2010; Quickfall and Crockford 2006). In respect to

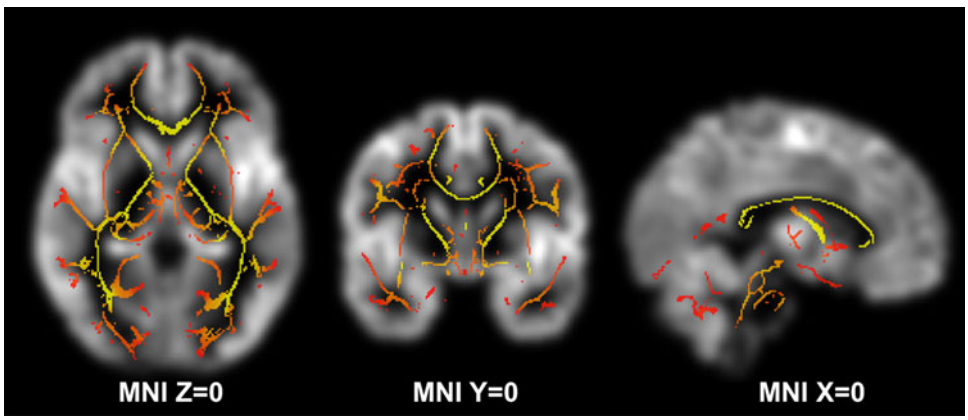

Fig. 1 Illustrates the group average grey matter (*greyscale*) and white matter FA skeleton (*red–yellow*) in MNI standard space centered at MNI X = 0, Y = 0, Z = 0. There were no supra-threshold differences between cannabis users and non-users, nor between heavy users versus light users, nor between early onset versus late onset

cannabis use in psychosis, previous VBM studies in at risk individuals, FEP and early stages of schizophrenia led to discrepant data [for recent reviews see (Rapp et al. 2012) (Hermann and Schneider 2012)]. The review by Rapp et al. (2012) includes eleven studies identifying a decrease in global or specific brain structures associated with cannabis consumption in psychosis patients or at risk subjects. These morphometric effects were particularly strong in brain regions rich on cannabinoid receptors, including the cingulum, the dorsolateral prefrontal cortex and the cerebellum. The authors further conclude that psychosis patients and at risk subjects might be particularly vulnerable as similar brain volume loss is not consistently reported in nonpsychotic and healthy samples. This vulnerability is further supported by the recent review of Hermann and Schneider (2012) concluding that brain alterations were especially pronounced in schizophrenic patients with cannabis consumption. Furthermore, close relatives of schizophrenic patients showed greater cannabis-associated brain tissue loss. Nevertheless, this review also points out that different components of cannabis might have differential effects, notably pointing to a potentially protective effect of cannabidiol. Intriguingly, Schnell et al. found increased GM in middle frontal gray matter in FEP patients (Schnell et al. 2012). An increase of striatal GM density was also reported by Potvin and coworkers in cannabis users with psychotic symptoms (not only FEP) and concomitant alcohol abuse (Potvin et al. 2007). In the only study that combined assessment of GM densities and WM microstructure in adolescent-onset schizophrenia with cannabis use, James et al. (2011) reported GM density loss in the temporal fusiform gyrus, the parahippocampal gyrus, the ventral striatum, the right middle temporal gyrus, the insular cortex, the precuneus, the right paracingulate gyrus, the dorsolateral prefrontal cortex, the left postcentral gyrus, the lateral occipital cortex and the cerebellum.

DTI data in the field of cannabis use in psychosis were not less discrepant. Supporting the idea of hyperconnectivity in FEP, one recent study assessed young men with FEP with or without cannabis consumption (Peters et al. 2009) and revealed increased directional coherence in the bilateral uncinate fasciculus, the anterior internal capsule and frontal WM in cannabis users. In the same line, Dekker and collaborators reported increased vulnerability of corpus callosum fibers in cannabis naïve patients (Dekker et al. 2010). In contrast to these results, decreased FA in several brain regions including the brain stem, the internal capsule, the corona radiata, and the superior and inferior longitudinal fasciculus in cannabis users was reported in adolescent-onset schizophrenia and FEP patients with early cannabis use (Ho et al. 2011). Several methodological differences may explain these striking discrepancies. Firstly, most of the studies included a limited number of cases and attempted three groups (controls, psychosis with and without cannabis use) comparisons that limit their statistical power. Secondly, age differences as well as clinical parameters may further explain these discrepancies. For instance, our FEP patients were older than those of James et al. (average of 16 years) (James et al. 2011). Diagnostic considerations may also be relevant in this context. The majority of previous studies limited recruitment to subjects diagnosed with schizophrenia. However, in line with epidemiological evidence that cannabis consumption is a risk factor for broadly defined psychosis (James et al. 2011), our results include several forms of psychosis. One other study (Wobrock et al. 2009) assessed brain morphology for cannabis users and non-users amongst subjects with more broadly defined psychosis (schizophrenia and schizoaffective disorder) and also found no significant structural differences. It is thus possible that decreased GM densities and altered WM microstructure may characterize a subgroup of very young FEP patients with increased vulnerability to cannabis consumption. One additional parameter to take into account here is the dose and duration of cannabis consumption that is highly variable among the previously cited studies. In the present series, both dose and duration of cannabis consumption were not related to MRI parameters. Moreover, all of our cases were cognitively preserved at least for attention and working memory. It is thus likely that our FEP cannabis users had a less aggressive form of their disease not associated with cognitive deficits in early life.

Strengths and Limitations

Since the main issue to address concerns the deleterious effects of cannabis in FEP, this investigation includes only clinically overt cases without comparisons with an ad hoc control group. The present study has two main strengths. Firstly, it combines GM densities and WM microstructure investigation using a strict correction for multiple comparisons. Secondly, cannabis users and non-users did not differ in terms of cognitive performances precluding the presence of MRI differences that could be attributed to this confounding factor. However, several limitations should also be considered. The major limitation of the current investigation is the relatively small sample size of 50 FEP subjects. One should, however, consider that this sample size of prospectively assessed FEP subjects with high MRI data quality without for example motion artifacts is comparable to that of previous studies in this field. Despite the comparable medication load at inclusion, we cannot formally exclude that the chronic administration of these agents may alter the quality of our observations. In fact, previous studies showed that both typical and atypical antipsychotics often display contradictory impacts on both

GM and WM volumes (Ho et al. 2011; Smieskova et al. 2009; Navari and Dazzan 2009). However, this is an unlikely scenario given the young age of the present cohort.

The inverse conclusion, notably the absence of cannabis-related alterations in FEP subjects, is not warranted by the current investigation for two main reasons. Firstly, the TFCE multiple comparison correction compensates for false positive but not false negative results since the sample size of 50 consecutive subjects might have insufficient statistical power to detect subtle yet significant group differences in MRI parameters. However, even if present, it is highly unlikely that such subtle cannabis-related alterations in GM and WM would have a major effect on the long-term evolution of FEP. Future longitudinal studies on young and adult FEP patients combining structural and functional MRI imaging, neuropsychological evaluation including activation paradigms and quantitative assessment of cannabis use are needed to explore the effect of the long-term consumption of this drug on brain structure and reactivity across the age spectrum of this disorder.

Conflict of interest The authors declare that they have no conflict of interest.

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