Schizophrenia Research 143 (2013) 179–184

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Alteration to hippocampal shape in cannabis users with and without schizophrenia

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ARTICLE INFO

Article history:
Received 20 June 2012
Received in revised form 27 August 2012
Accepted 7 October 2012
Available online 30 November 2012

Keywords:
Cannabis
Schizophrenia
Hippocampus
Shape analysis
Neuroimaging

ABSTRACT

Abnormalities in hippocampal morphology are characteristic of schizophrenia and have also been reported in chronic cannabis users. There is a paucity of research investigating potential additive effects of cannabis use on brain pathology associated with schizophrenia. In this study, we performed hippocampal shape analysis in cannabis-using and non-using patients with schizophrenia, healthy cannabis users and healthy non-using controls. Hippocampal shape changes were observed in each group relative to controls, with the greatest degree of alterations (i.e., deflations across the hippocampus, and with an anterior predisposition), in cannabis-using schizophrenia patients. These alterations were associated with cannabis use patterns and psychotic symptoms.

1. Introduction

Cannabis use is highly comorbid with schizophrenia (Koskinen et al., 2010) and considered a component cause of the disorder (Murray et al., 2007; D'Souza et al., 2009). There is growing evidence that long-term or heavy cannabis use impacts upon brain structure and function, particularly in regions known to be affected in schizophrenia, such as the hippocampus (Solowij and Michie, 2007; Lorenzetti et al., 2010; Ashtari et al., 2011; Solowij et al., 2012). We have previously reported dose-related reductions in hippocampal volume in otherwise healthy chronic cannabis users that were associated with subclinical positive psychotic symptoms (Yücel et al., 2008), and were of a magnitude similar to that observed in schizophrenia (e.g. Velakoulis et al., 1999). A key question is whether effects associated with comorbid chronic cannabis use and schizophrenia exceed those associated with either condition occurring in isolation.

We sought to address this question by assessing hippocampal volume and performing hippocampal shape analysis to inform regional specificity in healthy cannabis users and in cannabis using and non-using patients with schizophrenia. In line with a recent study that reported greater hippocampal shape alterations in patients with schizophrenia and prior comorbid alcohol use disorders (Smith et al., 2011), we hypothesised that cannabis use would exert an additional effect on the hippocampal pathology typically observed in schizophrenia, particularly in the anterior hippocampus (Csernansky et al., 2002; Tamminga et al., 2010; Small et al., 2011).

2. Experimental/Materials and methods

2.1. Participants, substance use and clinical measures

Seventeen medicated patients with schizophrenia, 15 long-term heavy cannabis users (THC) and 16 healthy controls (CON), all right handed males, were recruited from the general community, by referral from psychiatrists or through the Australian Schizophrenia Research Bank register, and provided written informed consent. Eight of the patient group were long-term cannabis users (SZ + THC), with similar extensive levels of use as the healthy THC group (near daily for 10–32 years), while nine patients had never used cannabis regularly (SZ − THC). No participant had used any other illicit substance >10 times and alcohol use was limited to <24 standard drinks per week. All groups were matched on age (range 21–60 years), premorbid IQ (National Adult Reading Test) and education, but alcohol and tobacco use differed between groups. Demographic, clinical and substance use characteristics (elicited by structured interview) are provided in Table 1 (see also Solowij et al., 2011).

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http://dx.doi.org/10.1016/j.schres.2012.10.040

Table 1
Demographic, clinical, drug use and MRI volumetric measures: mean (SD) or median [range].

	THC n = 15	CON n = 16	SZ + THC n = 8	SZ − THC n = 9	*p*-value[a]
Age	39.8 (8.9)	36.4 (9.8)	37.5 (6.6)	44.1 (8.6)	0.21
IQ	109.2 (6.3)	113.9 (8.1)	110.6 (9.2)	105.5 (11.8)	0.14
Years of education	13.5 (3.2)	14.8 (3.7)	13.4 (3.0)	14.9 (3.8)	0.58
SAPS composite score	6.0 [0–28]	0.0 [0–4]	30.0 [12–43]	16.0 [3–43]	<0.001
SANS composite score	12.0 [0–25]	1.5 [0–4]	31.0 [16–43]	24.0 [12–35]	<0.001
Duration of illness	–	–	14.1 (5.9)	23.6 (11.2)	0.049
Age at diagnosis	–	–	20.5 [17–37]	20.0 [16–27]	0.56
Cannabis					
Years of regular use[b]	19.7 (7.3), range 10–32	–	17.9 (6.5), range 11–29	–	0.57
Age started regular use[b]	20.1 (5.4), range 12–34	–	19.6 (6.2), range 13–29	–	0.84
Current use (days/month)[c]	28 (4.6)	–	25 (8.1)	–	0.34
Current use (cones/month)[c]	636 (565)	–	644 (344)	–	0.97
Cumulative exposure (past 10 years)[c]	77816 (66542)	–	62925 (25756)	–	0.55
Alcohol (stand. drinks/week)	7.0 [0–24]	4.0 [0–16]	7.0 [0–21]	0 [0–10]	0.028
Tobacco (cigarettes/day)	20 [1–35]	0 [0–14]	20 [0–35]	7 [0–35]	<0.001
Intracranial cavity[d]	1 546 237 (94 018)	1 607 590 (126 386)	1 539 072 (157 846)	1 486 687 (164 022)	0.17
Whole brain volume[c]	1 310 780 (90 779)	1 374 123 (105 673)	1 293 879 (145 199)	1 239 308 (155 894)	0.063
Left hippocampal volume[c]	2849 (270)	3240 (423)	3036 (374)	3044 (300)	0.03
Right hippocampal volume[c]	2949 (244)	3348 (400)	3144 (383)	3003 (264)	0.01

[a] Difference between the 4 groups or 2 groups depicted in each row from ANOVA, Kruskal–Wallis or Mann–Whitney tests.
[b] Regular use was defined as at least twice a month.
[c] Cannabis users had used at this level for the majority of their drug-using careers. A 'cone' is a small funnel into which cannabis is packed to be consumed through a water pipe in a single inhalation. Without the loss of sidestream smoke, the quantity of THC delivered by this method is estimated as equating three cones to one cigarette-sized joint. Thus, the cannabis users with and without schizophrenia smoked the equivalent of 213 joints per month, or approximately 7 joints per day. Estimates of lifetime dose beyond 10 years in these very long-term users became skewed and unreliable, hence the 10-year estimate was used in correlational analyses.
[d] Measures of brain volumes corrected for intracranial cavity are in units of mm^3.

The Structured Clinical Interview for DSM-IV Axis I Disorders was used to exclude psychiatric disorders among healthy participants and to confirm a schizophrenia diagnosis in patients. Psychotic symptoms were assessed using the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS; Andreasen, 1983). Healthy cannabis users had significantly higher SAPS ($z = 3.57$, $p < .0005$) and SANS ($z = 3.66$, $p < .0005$) scores than controls. The two patient groups (SZ + THC and SZ − THC) did not differ in symptom scores (SAPS: $p > .19$; SANS: $p > .09$), which were higher than those observed in the healthy cannabis users (THC vs. SZ + THC, SAPS: $z = 3.07$, $p = .002$; SANS: $z = 3.39$, $p = .001$; THC vs. SZ − THC, SAPS: $z = 1.88$, $p = .060$, SANS: $z = 2.69$, $p = .007$). All protocols were approved by university and regional health ethics committees.

2.2. Neuroimaging procedures, measurements and statistical analyses

MRI data were acquired from a 3-Tesla scanner using a volumetric SPGR sequence with 180 contiguous coronal slices (TE, 2.9 ms; TR, 6.4 ms; flip-angle, 8°; matrix-size, 256 × 256; 1 mm^3 voxels).

Hippocampal volumes were measured using established protocols (Velakoulis et al., 1999) and delineated by a trained rater blind to group information (see Yücel et al., 2008). Left and right hippocampal volumes were compared between groups by ANOVA. Shape analysis was undertaken in a semi-automated fashion using the University of North Carolina shape analysis toolkit — spherical harmonic shape description (SPHARM-PDM; Brechbuhler et al., 1995); a detailed description of the methodology is available in Styner et al. (2004, 2006). We utilised MANCOVA within SPHARM-PDM to control for alcohol and tobacco use in between-group analyses, while controlling for multiple comparisons using the false discovery rate (FDR) correction procedure (Pantazis et al., 2004; Styner et al., 2004; Paniagua et al., 2009), and the toolkit's correlational analysis to calculate Spearman's correlations with cannabis use parameters and psychotic symptoms.

3. Results

3.1. Hippocampal volume

Neither tobacco nor alcohol use correlated with hippocampal volumes in the entire sample (cigarettes/day: left: −.09, $p = .66$; right: −.13, $p = .52$; standard drinks/day: left: −.18, $p = .29$; right: −.14, $p = .42$) or in any subgroup, and were therefore not included as covariates. The overall difference between the 4 groups was significant for both the left and right hippocampus (Table 1) with the THC group having smaller hippocampi bilaterally than CON (left: $F_{1,29} = 9.25$, $p = .005$; right: $F_{1,29} = 11.05$, $p = .002$). The THC group did not differ from either of the schizophrenia groups (SZ + THC: left $p = .18$, right $p = .15$; SZ − THC: left $p = .11$, right $p = .62$). The SZ + THC group did not differ significantly from controls (left $p = .26$, right $p = .25$), whereas SZ − THC had smaller right ($F_{1,23} = 5.33$, $p = .03$) but not left ($p = .23$) hippocampi than CON. Combining the two schizophrenia groups confirmed a significant difference from CON for the right ($F_{1,31} = 4.88$, $p = .035$) but not left ($p = .14$) hippocampus. SZ + THC and SZ − THC did not differ in volume (left $p = .96$, right $p = .39$).

3.2. Between-group shape comparisons

Fig. 1 shows the raw and FDR-corrected *p*-value and difference maps from between-group comparisons of hippocampal shape, with each clinical group compared against CON. Regional shape alterations were observed in each group, but only the large reductions (areas of deflation up to 4 mm) in the left hippocampus of the SZ + THC group survived the conservative FDR correction. The overall shape change in the left hippocampus was significant between SZ + THC and CON ($p = .003$), falling just short of significance on the right ($p = .058$) (with areas of deflation up to 2 mm). SZ − THC showed shape alterations in regions of the head and body of the hippocampus, with areas of deflation of approximately 2 mm in the left and 1.5 mm