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Short communication

Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol

Traute Demirakca[a], Alexander Sartorius[c], Gabriele Ende[a], Nadja Meyer[a], Helga Welzel[a], Gisela Skopp[d], Karl Mann[b], Derik Hermann[b,*]

[a] Department of Neuroimaging, Central Institute of Mental Health, J 5, 68159 Mannheim, Germany
[b] Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, J 5, 68159 Mannheim, Germany
[c] Department of Psychiatry, Central Institute of Mental Health, J 5, 68159 Mannheim, Germany
[d] Institute of Forensic and Traffic Medicine, University Hospital, Voßstr. 2, 69115 Heidelberg, Germany

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ABSTRACT

Background: Chronic cannabis use has been associated with memory deficits and a volume reduction of the hippocampus, but none of the studies accounted for different effects of tetrahydrocannabinol (THC) and cannabidiol (CBD).
Methods: Using a voxel based morphometry approach optimized for small subcortical structures (DARTEL) gray matter (GM) concentration and volume of the hippocampus were measured in 11 chronic recreational cannabis users and 13 healthy controls, and correlated with THC and CBD from hair analyses. GM volume was calculated by modulating VBM using Jacobian determinants derived from the spatial normalization.
Results: Cannabis users showed lower GM volume located in a cluster of the right anterior hippocampus ($P_{uncorr} = 0.002$; effect size Cohen's $d = 1.34$). In a regression analysis an inverse correlation of the ratio THC/CBD with the volume of the right hippocampus (P_{uncorr} $p < 0.001$, Cohen's $d = 3.43$) was observed. Furthermore Cannabidiol correlated positively with GM concentration (unmodulated VBM data), but not with GM volume (modulated VBM) in the bilateral hippocampus ($P = 0.03$ after correction for hippocampal volume; left hippocampus Cohen's $d = 4.37$ and right hippocampus 4.65).
Conclusions: Lower volume in the right hippocampus in chronic cannabis users was corroborated. Higher THC and lower CBD was associated with this volume reduction indicating neurotoxic effects of THC and neuroprotective effects of CBD. This confirms existing preclinical and clinical results. As a possible mechanism the influence of cannabinoids on hippocampal neurogenesis is suggested.
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1. Introduction

A long lasting debate accompanies the use of cannabis. The contra-arguments are impairment of attention, memory and motivation, risk for psychosis and addiction, whereas the pro-arguments emphasize that neuropsychological deficits are transient, and the addictive potential is low (Murray et al., 2007). Neurobiological research is challenged to objectify the debate. The main ingredients of cannabis are delta-9-tetrahydrocannabinol (THC) and the non-psychogenic cannabidiol (CBD). Preclinical research gave evidence that THC acts as a partial agonist of cannabinoid (CB) receptors and CBD as an antagonist of CB-receptor agonists (Pertwee, 2008). Recently a series of fMRI studies with an experimental application of THC and CBD in humans confirmed different and partly opposite effects on brain activation during tasks involving verbal learning, viewing fearful faces, and response inhibition (summarized in Bhattacharyya et al., 2010). THC showed unfavorable effects, but a pretreatment with CBD was able to prevent THC effect, indicating beneficial effects of CBD (Bhattacharyya et al., 2010). Furthermore, especially high THC containing cannabis was associated with psychosis, and hair analyses revealed that cannabis users with high THC and low CBD concentration were more likely to exhibit schizophrenia-like symptoms (Di Forti et al., 2009; Morgan and Curran, 2008).

In search for an explanation of cannabis associated memory alterations, a recent MRI study using manual delineation of hippocampal and amygdala volumes showed decreased bilateral volumes correlating negatively with the self-reported amount of cannabis consumption (Yücel et al., 2008). Of four other studies investigating the hippocampus three failed to show differences

* Corresponding author at: Central Institute of Mental Health, Department of Addictive Behaviour and Addiction Medicine, P.O. Box 12 21 20, D-68072 Mannheim, Germany. Tel.: +49 621 17033541; fax: +49 621 17033505.
E-mail address: derik.hermann@zi-mannheim.de (D. Hermann).

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between control subjects and cannabis users, even with very heavy and long-term cannabis use (Block et al., 2000; Tzilos et al., 2005; Jager et al., 2007), whereas one study showed lower gray matter density in the right parahippocampal gyrus (Matochik et al., 2005). A methodological limitation of the latter study (Matochik et al., 2005) using VBM was that for group comparison different shapes of the head had to be normalised to the MNI–template. This process stretches or compresses the brain to fit it into a standard intracranial vault size and thereby alters volumes. Resulting unmodulated VBM data indicate the proportion of gray and white matter in each voxel, but do not account for volume changes. To obtain data about the volume, unmodulated VBM data have to be modified using the Jacobian determinants derived from the spatial normalization process, resulting in modulated VBM data allowing the comparison of volume differences.

Based on previous studies mentioned above we hypothesize diminished hippocampal volume in cannabis users and positive effects of CBD and negative effects of THC onto hippocampal volume. In our study, unmodulated and modulated VBM data are presented for comparability with earlier unmodulated VBM studies, and to assess hippocampal volume. For VBM analyses we use a method recently optimized for subcortical structures: the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra registration (DARTEL) (Ashburner, 2007; Yassa and Stark, 2009).

2. Methods

Eleven healthy male cannabis users (19–25 years old) and 13 age- and IQ- matched male control subjects, all students, were recruited by advertisement at the University of Mannheim. Cannabis was used for 5.4 years in an average daily dose of 0.27 g. Detailed clinical data of the study participants have been published previously (Hermann et al., 2007). The use of other illegal drugs in the previous 3–4 days was excluded by an immunochromatographic urine test. Cannabis users were more likely to smoke tobacco cigarettes ($n = 6$ versus $n = 1$) and consumed more alcohol (21.4 g/day = about 1.5 drinks/day) than controls (4.2 g/day). The concentration of cannabinoids in hair samples was determined by gas chromatography/mass spectrometry (detection limit: 0.025 ng/mg hair; for details see Skopp et al., 2007), and was 0.31 ± 0.2 ng THC/mg hair and 0.13 ± 0.12 ng CBD/mg hair (reflecting the cumulative dose of the previous 4.7 months). The 5 cannabis users solely using marijuana showed a higher THC/CBD ratio of 8.28 (THC: 0.3 ± 0.25 ng/mg hair; CBD: 0.036 ± 0.02 ng/mg hair) than the three cannabis users using at least 50% hashish resin (THC: 0.35 ± 0.23 ng/mg hair; CBD: 0.24 ± 0.16 ng/mg hair; THC/CBD = 1.46). Amount of alcohol and nicotine consumption was not correlated with CBD, THC or CBD/THC ratio in cannabis users but due to the group difference alcohol and nicotine were used as covariates in the VBM analysis.

The study was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg, Germany. Fully informed written consent was obtained from all participants.

2.1. VBM acquisition and analysis:

Isotropic T1-weighted MR images were obtained on a 1.5 T Siemens Vision System (Erlangen, Germany) with a standard circular polarized head coil (162 slices, 1 mm slice thickness, 256 mm field of view, 1 mm^3 resolution) and analysed with SPM8. After segmenting the images in gray (GM) and white (WM) matter and CSF, a GM template was generated out of 24 images through an iteratively nonlinear registration (DARTEL Toolbox, http://www.fil.ion.ucl.ac.uk/spm/software/spm8; Ashburner, 2007; Good et al., 2001) and an affine registration of this template to the MNI template (http://www.loni.ucla.edu/ICBM/ICBM/TissueProb.html). Individual images were normalised to the template, this gave the possibility of region of interest (ROI) analysis of the hippocampus using the WFU PIC Atlas (http://www.fmri.wfubmc.edu). After smoothing with an 8 mm^3 isotropic Gaussian kernel, unmodulated and modulated GM images were used for group comparison and regression analysis. Unmodulated data indicate the proportion of gray matter in each voxel and do not account for volume changes. Modulated VBM data are generated using the Jacobian determinants derived from the spatial normalization, thus allowing the comparison of volume differences. Total intracranial volume (TIV) and hippocampal volume were estimated through an integration of all voxels of the segmented tissue and within the hippocampal ROI (Smith et al., 2007; Lüders et al., 2002). To analyze only voxels with sufficient GM and to avoid possible edge effects around the borders between GM and WM as well as between GM and CSF, we included only voxels with a GM value >0.1. A general linear model approach was used to determine the relative differences in volume by an analysis of covariance (ANCOVA). A multiple regression analysis of GM concentration and volume with the ratio of THC/CBD as independent variable was performed within the group of cannabis users ($n = 11$). Total intracranial volume (TIV), alcohol and nicotine consumption were used as covariates to control their influence. Age was not included because the range was relatively close (19–25 years). Both analyses yielded statistical parametric maps based on a voxel level threshold of $P = 0.005$ (uncorrected, P_{uncorr}). In order to report meaningful results, the minimal size of the differences shown was defined as 0.1 ml or 30 voxel. To avoid false positive results due to multiple testing a small volume correction for multiple comparisons (family wise error, FWE (http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf page 218); P_{FWE}) on voxel level was applied using a mask of left and right hippocampus as region of interest.

3. Results

Group comparison of GM tissue composition or concentration (unmodulated data) revealed no differences between healthy controls and cannabis users in whole brain or in hippocampal ROI. Concerning the GM volume (modulated data) cannabis users showed lower volume of the anterior part of the right hippocampus in comparison to healthy controls (cluster size: 41 voxel = 138 mm^3, $P_{uncorr} = 0.002$, $P_{FWE} = 0.28$, $T = 3.3$, $Z = 2.9$, MNI: 36,−9,−27). Cohen's $d = 1.34$ for the volume difference (estimated from t-value ($d = t/\mathrm{sqrt}(1/n1 + 1/n2)$) showed a large effect size although the sample size was small.

Regression analyses of the ratio of THC/CBD with hippocampal GM volume (modulated data) revealed a significant inverse correlation of the ratio THC/CBD and GM volume only in the right hippocampus (right: cluster size 94 voxel = 317 mm^3, $P_{uncorr} < 0.001$, $P_{FWE} = 0.12$, $T = 8.4$, $Z = 3.8$, MNI: 29,−28,−12; beta = −0.0046). For hippocampal GM concentrations significant inverse correlations were found bilaterally (right: cluster size 95 voxel = 321 mm^3, $P_{uncorr} < 0.001$, $P_{FWE} = 0.27$, $T = 6.1$, $Z = 3.5$, MNI: 30,−34,−6; left: cluster size 211 voxel = 712 mm^3, $P_{uncorr} < 0.001$, $P_{FWE} = 0.11$, $T = 7.9$, $Z = 3.9$, MNI: −30,−19,−18; beta = −0.0061: Fig. 1B blue). This result was confirmed by a second analysis using mean GM concentration extracted from the hippocampal ROI (correlation of GM concentration with THC/CBD ratio: right: $r = 0.835$, $P = 0.003$; left: $r = 0.646$, $P = 0.044$; see Fig. 1A).

Restricting the correlation analysis to CBD, a correlation with GM volume could not be observed. But for hippocampal GM concentration a positive correlation was observed bilaterally, which survived a correction for multiple testing (=P_{FWE}) based on the number of voxels in the hippocampus (right: cluster size 196

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