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Short report

Gross morphological brain changes with chronic, heavy cannabis use

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Summary
We investigated the morphology of multiple brain regions in a rare sample of 15 very heavy cannabis users with minimal psychiatric comorbidity or significant exposure to other substances (compared with 15 age- and IQ-matched non-cannabis-using controls) using manual techniques. Heavy cannabis users demonstrated smaller hippocampus and amygdala volumes, but no alterations of the orbitofrontal and anterior- and paracingulate cortices, or the pituitary gland. These findings indicate that chronic cannabis use has a selective and detrimental impact on the morphology of the mediotemporal lobe.

Declaration of interest
None.

There is growing evidence that long-term heavy cannabis use is associated with anatomical alterations across multiple brain regions.[1] Many studies employing structural magnetic resonance imaging (MRI) techniques have adopted automated parcellation techniques, which can be problematic when measuring brain areas that are highly variable across individuals and where the boundaries are not clear.[2,3] Our group has previously used manual tracing techniques, which are sensitive to interindividual neuroanatomical variability, to identify gross abnormalities in hippocampus and amygdala morphology in chronic cannabis users.[4] Whether these abnormalities occur in other brain areas is yet to be elucidated. Here, we investigate volumetric alterations of key brain regions that heavy cannabis use may have an impact on, namely the orbitofrontal and anterior cingulate cortices, as well as the pituitary gland, all of which are rich in cannabinoid receptors and are involved in cognition and the regulation of emotion and stress levels, the alteration of which is associated with cannabis exposure.[5–7] We report these data alongside our previously reported hippocampus and amygdala volumes in the same sample for comparative purposes.[4]

Method

We recruited 15 male heavy cannabis users with the highest level of cumulative cannabis exposure of all samples examined to date (21 years of regular use and lifetime 62 000 smoking episodes) and 16 male controls who were matched for age (mean 40 years (s.d. = 9) and 36 years (s.d. = 10), respectively), IQ (mean 109 (s.d. = 6) and 114 (s.d. = 8), respectively) and education years (mean 13 years (s.d. = 3) and 15 years (s.d. = 4), respectively).[4] Participants had very limited exposure to substances other than cannabis (< 10 episodes) and no history of medical, neurological or psychiatric conditions. Cannabis users were smoking at a rate of 28 days per month (s.d. = 3) and were consuming approximately 212 joints per month. Structural T_1-weighted MRI images were acquired with a 3T Phillips Intera scanner (Symbion Clinical Research Imaging Centre, Prince of Wales Medical Research Institute, Sydney, Australia), matrix size $256 \times 256 \times 180$, with an isotropic voxel size of 1 mm^3.

All regions of interest were manually delineated using ANALYZE 11.0 software for Unix. We examined the anatomy of functionally and anatomically distinct components for the orbitofrontal cortex (i.e. medial and lateral subregions), anterior cingulate and paracingulate cortices, both of which were parcelled into dorsal, rostral and ventral portions.[3] Inter- and intrarater reliabilities for manual tracings were assessed by intraclass correlation coefficients. The range was 0.80–0.98, indicating that the implemented tracing methods were reliable means to measure brain morphology, while considering interindividual variations in sulcal and gyral anatomy.

The impact of cannabis use on regional brain volumes was examined by performing separate ANOVAs on each primary brain region, with hemisphere (i.e. left or right) as repeated measure, group as between-participant factor and regional brain volumes as dependent variables. For the orbitofrontal cortex, region (i.e. lateral or medial) was entered as an additional within-participants factor. For the anterior cingulate cortex, region (dorsal, rostral, ventral) and cortex (cingulate and paracingulate cortex) were entered as an additional within-participants factor. Hemisphere was not included in the analysis of pituitary volume. Main effects and interactions were evaluated using Greenhouse–Geisser corrected degrees of freedom with $a = 0.0125$ (0.05 divided by the number of brain regions investigated). Significant effects were further investigated with *post hoc* pair-wise contrasts evaluated against a Bonferroni-adjusted a to correct for multiple comparisons. Statistical analyses were performed using SPSS version 20.0 for Mac OS.

Results

Cannabis users, compared with controls, demonstrated reduced hippocampus and amygdala volumes, as previously reported,[4] but no alteration in the orbitofrontal and anterior cingulate cortices, or the pituitary gland (online Fig. DS1). There was no significant interaction between group and hemisphere on the examined brain regions.

Discussion

Our findings suggest that chronic cannabis use is associated with localised neuroanatomical reductions in mediotemporal regions, largely hippocampal, with clear divergence between groups in distribution of hippocampal volumetric data relative to significant overlap for other regions. We failed to find any gross alteration in the orbitofrontal cortex, anterior cingulate cortex and pituitary gland. Our results accord with other studies showing effects of chronic cannabis use on mediotemporal (largely hippocampal) regions,[8] but are the only findings to date showing volumetric reductions in the amygdala, as previously reported.[4] Our results

contrast however, with previously reported prefrontal alterations in cannabis users who were smoking at lower rates than those of our present study.[1] Thus, regular exposure to cannabis may adversely have an impact on the hippocampus, whereas very heavy and prolonged exposure may be required for other brain regions (for example prefrontal cortex). As such, the small size of the investigated sample may also explain the lack of a detectable effect in these regions.

Although the distinct characteristics of our sample (i.e. no significant exposure to substances other than cannabis and no comorbid psychopathology) may limit the generalisability of our findings, this study offers a relatively pure insight into the neurobiological sequelae of prolonged, heavy cannabis use on multiple brain regions. Our findings support the notion that chronically high cannabinoid exposure has a selective and detrimental impact on mediotemporal brain regions. Combined multimodal neuroimaging techniques should be used in future studies to elucidate the pathophysiological mechanisms involving metabolic processes, functional and structural connectivity in brain regions that are high in cannabinoid receptors and may be vulnerable to the adverse impact of chronic cannabis exposure.[9,10]

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EXTRA CONTENT ONLINE

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