

CEREBELLAR ABNORMALITIES IN ADOLESCENTS WITH MARIJUANA DEPENDENCE

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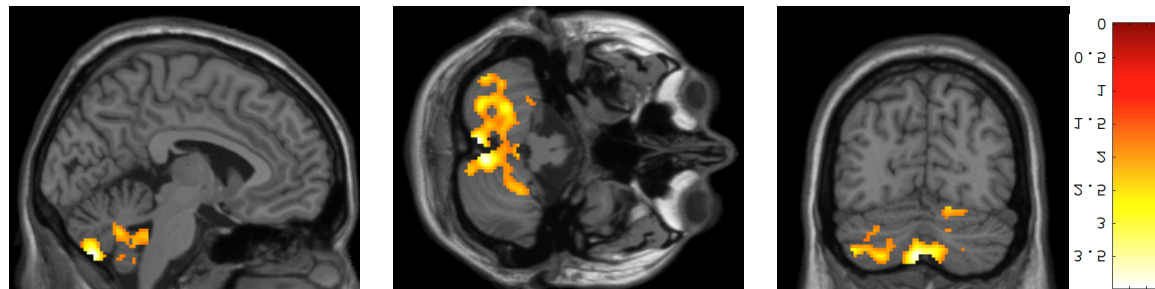
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Objectives: Despite the widespread abuse of marijuana (MJ), knowledge about its effects in the human brain, particularly during development, is limited. To date, the majority of studies examining the acute effects of MJ administration used Positron Emission Tomography (PET) methods and reported increased activation in frontal and paralimbic regions and the cerebellum.¹ In addition, a PET study found that at baseline, marijuana abusers showed lower relative cerebellar metabolism than normal subjects.² One of the only fMRI studies to evaluate the finger-tapping task, found that adult MJ users had reduced activation in Brodmann's area (BA) 4 (primary motor cortex) and BA6 (supplementary motor area) compared to healthy controls (HC).³ However, this study did not assess the cerebellum. The cerebellum contains the highest density of cannabinoid receptors in the brain, and MJ use has been found to interfere with visual tracking, balance and coordination. This study will evaluate whether there are activation differences in the cerebellum in addition to previously reported motor cortices between MJ using adolescents and HC on a fMRI bilateral finger-tapping task.

Methods: Nineteen older adolescents (aged 17.9±1.0 years; females: n=2), with DSM-IV MJ Dependence and no current or prior psychiatric history or psychotropic medication use and 19 healthy controls, matched for age (17.6±1.3 years; females, n=8), had MRI scans on a 3T Siemens Trio scanner, including a standard bilateral fMRI finger tapping sequence (A BOLD EPI sequence was used with TR=2 seconds, TE=28 ms to central K-space, 64 x 64 matrix, parallel imaging with GRAPPA acceleration factor of 2). Image data were analyzed using general linear model and the SPM5 software package in Matlab. Functional MRI data were realigned, normalized and smoothed with an isotropic Gaussian filter (FWHM = 6 mm). High-pass temporal filtering with a cut-off of 80 s was applied, serial autocorrelations were modeled with an AR(1) model, and global scaling was not used. Statistical analysis for individual subjects was performed by applying the framework of the general linear model using a box-car reference function convolved with the hemodynamic response function. Multisubject activation maps were created using within group and between group second-level analyses. Group maps by diagnostic group showed significant activation in regions of the cerebellum when thresholded at FWE <0.001, with a minimum cluster-size threshold k set at 20 contiguous voxels. Using the two-sample t-test, we made direct comparisons between data from the HC group and the data from the MJ group. These data were thresholded at p<0.005, and k= 20. A priori region of interest (ROI) group maps were set to a threshold of p <.005, uncorrected, with a minimum cluster-size threshold k set at 20 contiguous voxels. The ROIs (BA4, BA6, and cerebellum) were selected using WFU Pickatlas utility⁴ and significant clusters of activity were determined according to the statistical threshold of p<0.05, corrected, and k=20. Linear regressions were performed for age of MJ onset and lifetime MJ use (p< 0.001, k=20). (p< 0.001, k=20).

Results: Marijuana users reported their age of first and regular MJ use was 14.9 ±1.3 and 15.7±0.9, respectively; and the average frequency of MJ use was 10.4±8 times/week. HC were found to have greater activation than MJ for BA 4 (154 voxels, max T =2.89), BA 6 (49 voxels, Tmax=3.12), and cerebellum (3263 voxels, Tmax=3.96). Activation of the cerebellum (Tmax=5.45) and BA6 (Tmax=5.64) were found to negatively correlate with age of onset in MJ users. Activation of the cerebellum (Tmax=4.54) was correlated with total number of lifetime MJ smokes.

Figure 1. fMRI results of a bilateral finger tapping task showing increased activation in the cerebellum ROI in HC compared to MJ.



Conclusion: This is one of the first studies to evaluate cortico-cerebellar circuits in a group of adolescents with heavy MJ use utilizing a bilateral finger tapping fMRI task. Our findings are consistent with our prior study that found reduced activation of BA 4, 6 and the cingulate in MJ using adults compared to HC.³ The BA 4 comprises of the primary motor cortex and BA6, is composed of the premotor cortex, laterally, and the supplementary motor area, medially. Together these cortical areas play a role in the selection and execution of movements. Furthermore, the cerebellum is thought to play a significant role in coordination and motor control. Our findings suggest that age of first use and amount of MJ used may have an impact on functioning in the developing brain. The decrease in cerebellar activation in MJ users could account for the motor deficits previously reported in these subjects.⁵ Additional studies of the cortico-cerebellar networks in cannabis dependence during development are warranted.

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