Decreased BOLD Activation during Visual Attention Tasks in Marijuana Abusers

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INTRODUCTION: Prior positron emission tomography studies have demonstrated altered regional brain metabolism and blood flow in marijuana users, especially in the cerebellum [1-4]. Neurophysiological and cognitive tests also found deficits in attention and memory in heavy marijuana users [5], but these effects may be reversible after abstinence [6]. It is unknown whether the reversible cognitive deficits indicate that marijuana does not alter brain networks or that such changes occur but the brain adapts to the drug-induced changes. Therefore, we performed fMRI in a group of heavy marijuana users during tasks that required visual attention, and further compared those with active cannabinoid (THC) metabolites in their urine to those with prolonged abstinence.

METHODS: Thirty-one right-handed subjects [13 marijuana users (age 30±3 yrs, 7 men and 6 women) and 18 controls without a history of drug abuse (age 30±1.8 years; 9 men and 9 women)] were enrolled after fulfilling study criteria, assessed by neuropsychiatric examination, neuropsychological tests, blood and urine tests (including drug screen). Entry criteria for marijuana users: smoked at least 5 joints per week for at least two years. Subjects completed fMRI during a set of visual-attention tasks that required mental tracking of multiple targets (2, 3, or 4 balls) amongst 10 moving balls[7, 8]. After a brief training session, subjects had fMRI in a 4 T whole-body MRI scanner, using single-shot gradient-echo EPI (TE/TR 25/3000, 4 mm slices, 1 mm gap, typically 33 coronal slices, 64^2 matrix, 20cm FOV, 124 time points). Task performance and subject motion were monitored online during fMRI [9], to assure accuracy>80%, motion<1mm-translations and <1°-rotations. After motion correction, spatial normalization to the Talairach frame, and spatial smoothing, activation maps for the drug users and controls, as well as the contrasts (Controls>Drug users, and Drug users>controls) were calculated with SPM99. Regional % BOLD signals were extracted using a customized ROI program.

RESULTS: Clinical:. The marijuana users smoked 23.3±1.6 joints/month, for 156.5±30.8 months, which yielded an estimated cumulative lifetime exposure of 156±45 g of THC. These subjects had relatively normal mental function (Mini-Mental State examination=28.7±0.2) and minimal depressive symptoms (CES-Depression score=11.8±2.2). Hematocrit was similar in the drug users (42.5±1.2%) and controls (41.5±0.8%). **fMRI:** These tasks produced robust and characteristic activation in the visual attention network (Figure, left). Despite similar performance accuracies [Drug users (2-balls:97.4±2%; 3-balls:95.9±1.5%; 4-balls:90.3±3%); Controls (2-balls:95.5±2%; 3-balls:94.1±2.3%; 4-balls: 89.9±2%)], the marijuana users had less activation in the cerebellar vermis and the dorsal parietal region (Figure) compared to Controls. Active marijuana users (positive urine for THC, n=7) had greater activation than abstinent users (negative urine for THC, n=6) in the lateral prefrontal and parietal regions (not shown). ANOVA showed a significant drug effect in the dorsal parietal cortex (p=0.004; Figure, middle) and cerebellar vermis (p=0.05). Cumulative marijuana exposure inversely correlated with % BOLD signal change in the cerebellar vermis (Figure, right).

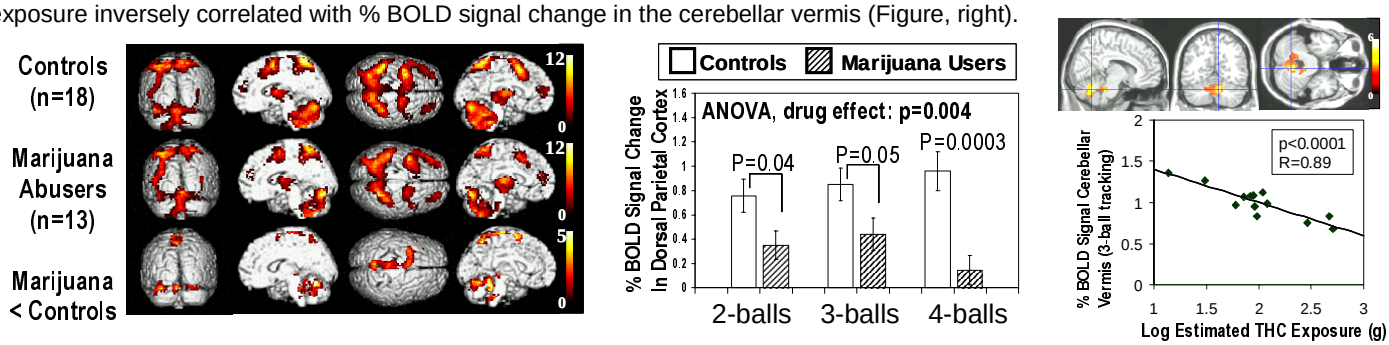

Figure: SPM results for 3-ball tracking. *Left*: Surface maps for brain regions activated in controls and marijuana users (one-sample t-test, random effects analyses; T ≥ 1.7, p<0.05, k=100), and the contrast: "Marijuana users>Controls" using ANCOVA (random effects, co-varied for hematocrit; cerebellar and parietal clusters: p(corrected)<0.0001); *Middle:* Bar graphs showing mean %BOLD signal in dorsal parietal ROIs of THC users and controls. *Right*: Cumulative THC exposure is inversely associated with cerebellar BOLD signal.

CONCLUSIONS: Compared to control subjects, marijuana users had decreased brain activation in cerebellar vermis and dorsal parietal cortex, while performing tasks that required visual attention. Consistent with prior studies that found decreased baseline blood flow but increased blood flow after acute THC administration [1], those who were active THC users had greater activation than those who were abstinent. Furthermore, marijuana users showed exposure-dependent decreases in % BOLD signal in the cerebellar vermis. The decreased BOLD activation may be due to marijuana -induced alteration in resting cerebral perfusion and/or neurochemical abnormalities. Future perfusion and receptor binding studies are needed to evaluate the relationship between blood flow, specific receptors (e.g. dopaminergic, cannabinoid) and BOLD signals.

ACKNOWLEDGEMENTS: Studies were supported partially by NIDA (K24-DA16170; K02-DA16991; T32 DA07316) and DOE(OBER).

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