The long-term effects of marijuana use on the brain

Sina Aslan[1,2], Vince Calhoun[3], Jeffrey Spence[2], and Francesca Filbey[2]

[1]Advance MRI, LLC, Frisco, Texas, United States, [2]University of Texas at Dallas, Dallas, TX, United States, [3]The Mind Research Network, Albuquerque, New Mexico, United States

Introduction: The rate of marijuana use has had a steady increase since 2007. Questions surrounding the effects of chronic marijuana use on brain structure continue to increase. To date, however, findings remain inconclusive. In this comprehensive study that aimed to characterize brain alterations associated with chronic marijuana use, we measured gray matter (GM) volume via structural MRI (high resolution T1 or MPRAGE) across the whole brain using voxel-based morphology (VBM), synchrony among abnormal GM regions during resting state via functional connectivity MRI (fcMRI) and white matter integrity (i.e. structural connectivity) between the abnormal GM regions via diffusion tensor imaging (DTI) MRI.

Methods: A total of 110 participants consisting of 62 non-using controls and 48 marijuana users were recruited. Marijuana users were included if they currently use marijuana regularly (at least four times per week) over the last six months (confirmed via positive THC-COOH urinalysis). Normal controls (control group) had no self-reported regular use of marijuana and had a negative urine drug screen at baseline. MRI scans (MPRAGE, fcMRI and DTI) were performed on a Siemens 3 Tesla Trio scanner using the standard 12-channel phased array head coil. The T1 structural images were processed using DARTEL of SPM8 by segmenting the images into modulated, spatially normalized GM images. fcMRI data were also routinely preprocessed by choosing bilateral orbitofrontal gyri clusters from VBM analysis, [+26 +54 -8] and [-16 +58 -10] in MNI template. Last, DTI data were preprocessed using FMRIB of FSL and tensor images were calculated. Because the orbitofrontal cortex is innervated by the forceps minor, and, therefore, plays a role in decision-making processes, the forceps minor tract was delineated via two techniques: manual and automatic tractography whereas forceps major tract was delineated only manually as a control in DTI Studio.

Results: The IQ of the marijuana users was significantly lower than the control group ($p<0.05$) and was used as a covariate comparing marijuana and control groups. Voxelwise comparison of the high-resolution T1 images showed a significant lower gray matter volume in marijuana users in the right middle orbitofrontal (MNI Coordinates: [+26 +54 -8]; t-score=3.37) and left superior orbitofrontal gyri (MNI Coordinates: [-16 +58 -10]; t-score=3.19) ($p<0.01$[FWE Corrected] and cluster ≥ 15,936 mm3) per anatomical automatic labeling (AAL), shown in Figure 1. We then characterized the functional connectivity of the orbitofrontal network; consist of bilateral orbitofrontal and bilateral temporal gyri. Figure 2A show qualitative differences between the groups such that the cannabis group had higher functional connectivity compared to the control group. Figure 2B shows that, quantitatively, marijuana users had significantly higher connectivity in all four nodes (i.e. bilateral OFC and bilateral temporal lobe) compared the control group. We also measured the structural connectivity of the forceps minor tract, which connects the orbitofrontal regions, both manually and automatically (shown in Figure 3). We found that the forceps minor's FA of the cannabis group was significantly higher than the control group in both automatic and manual methods, $p=0.003$ and $p<0.001$, respectively. As a manipulation check, we also measured the FA of the forceps major, which did not show any significant difference between control and cannabis groups. Additionally, we examined which component of FA may be driving this effect. We found that radial diffusivity (RD) of the cannabis users was significantly lower than that of the controls in both automatic and manual tractography, $p=0.05$ and $p=0.004$, respectively. Differences between axial diffusivity (AD) and mean diffusivity (MD) were not significant between the groups. Brain-behavior correlations showed that the forceps minor's FA and RD showed gains with initial heavy usage but declined after chronic usage, as shown in Figure 4.

Discussions: Long term changes of human brain when exposed to marijuana have been equivocal. Our findings provide evidence that heavy, chronic marijuana users have lower OFC gray matter volumes compared to non-using controls. This effect on the OFC are not surprising given that the OFC is a primary region in the reward network, is enriched with CB1 receptors, and, is highly implicated in addictive behavior. We also evaluated OFC functional (fcMRI) and structural connectivity (DTI). Functional connectivity analysis revealed greater connectivity within OFC network in marijuana users compared to controls. This may suggest a compensatory mechanism whereby greater network recruitment is engaged to compensate for OFC liability. OFC, a network hub, observed increase in OFC functional connectivity concomitant with reductions in OFC gray matter may suggest neuroadaptive plasticity. The findings of greater functional connectivity in OFC network in marijuana users were echoed by increased structural connectivity (i.e. FA) of forceps minor in marijuana users relative to controls. Based on RD and AD measurements, it appears that the FA difference between the groups in forceps minor was driven by lower RD, suggesting greater myelination in the marijuana users. Among possible explanations for these findings of greater FA in marijuana users include differential effects of cannabis depending on the specific fiber tract. Others have also reported anti-inflammatory properties of cannabis constituents such as cannabidiol (CBD). Lastly, a quadratic trend was observed suggesting that the FA of forceps minor initially increased following regular marijuana use but decreased with protracted regular use. This pattern may indicate differential effects of initial and chronic marijuana use that may reflect complex neuroadaptive processes in response to marijuana use.

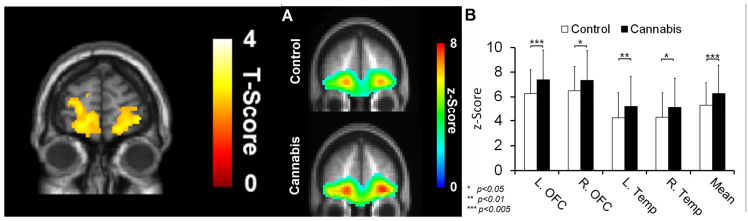

Fig 1. Group comparison of the gray matter volume shows reduction of gray matter volume in bilateral orbitofrontal gyri in marijuana users compared to controls.

Fig 2. A) The average OFC functional connectivity maps of the control and marijuana groups are superimposed on their average T1-weighted image. **B)** Mean fcMRI z-scores are shown for the OFC network for marijuana and controls groups.

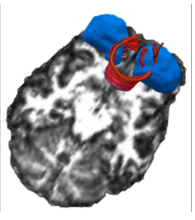

Fig 3. A representative participant's forceps minor tract (in red) and gray matter nodes (in blue) is overlaid on its corresponding FA map.

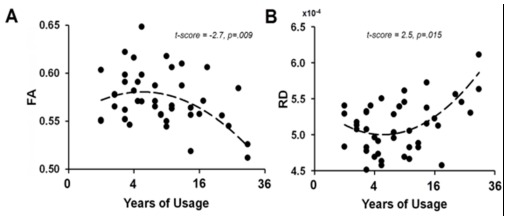

Fig 4. The quadratic relationship between duration of marijuana use and forceps minor's **A)** FA and **B)** RD are shown.