Associations Between Plasma Δ9-THC Metabolites and Brain Metabolite Concentrations in PWH Using Whole-Brain Magnetic Resonance Spectroscopic Imaging

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Background

Delta-9-tetrahydrocannabinol (Δ9-THC), one of the main psychoactive components in cannabis, acts on the central nervous system through interaction with cannabinoid receptors that are densely distributed within brain networks, altering brain chemistry. However, despite increasing cannabis use, especially among people with HIV (PWH), few studies have investigated the direct influence of cannabis on brain metabolites.

Aim

This study aims to associate plasma Δ9-THC, 11-hydroxy-Δ9-THC (11-OH-THC), and carboxy-Δ9-THC (THC-COOH) metabolites concentrations with brain metabolite concentrations in PWH and people without HIV (PWoH). Brain metabolites were evaluated using our whole-brain magnetic resonance spectroscopic imaging (MRSI) technique for measuring N-acetyl aspartate (NAA; neuronal viability), creatine (Cre; cellular energy), choline (Cho; membrane turnover), glutamate+glutamine (Glx; neurotransmitters) and myo-inositol (MI; inflammation).

Methods

Recruitment Site: UM/JMH HIV Clinic & Herbal Heart Study

Eligibility Criteria:

- Age between 18 and 50 years
- No MRI contraindications
- No primary psychiatric or neurological conditions
- Cannabis use (CB+) within the past month

Total Sample Size: 93 participants

- Males: n=47
- Females: n=46
- Mean age: 36 years (SD = 7.7)
- HIV status: HIV+ (n=48) HIV- (n=45)

Group Classification: (CB+ only)

- *PWH* (n=16; 38±7.5 y.o.)
- *PWoH* (n=17; 37.4±7.8 y.o.)

MRI Scan:

- The 60-minute MRI protocol included our unique whole-brain short-TE magnetic resonance spectroscopic imaging (MRSI: TE = 17.6 ms; 17min) acquired at 3-Tesla (Siemens Vida) (**Figure 1**).
- MRSI data were processed using MIDAS software[1] to estimate neurometabolite concentrations at 47 brain anatomical regions-of-interest (ROI) from the AAL47 atlas,[2] using appropriate data quality criteria (**Figure 2**).

Blood samples:

- Plasma samples were extracted using a solid phase extraction (SPE) technique and analyzed using a Gas Chromatography Tandem Mass Spectrometry (GC-MS/MS) to quantify Δ9-THC, 11-OH-THC, and THC-COOH.[3] (**Figure 3**)

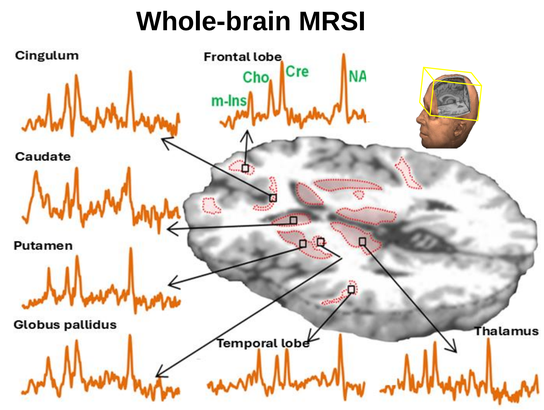
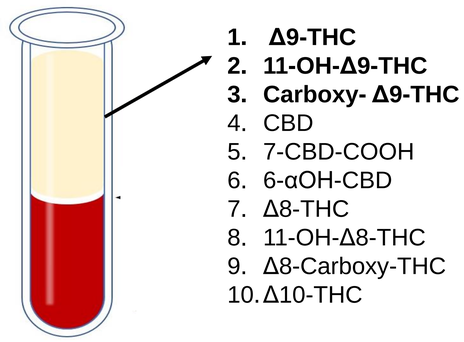


Figure 1: Spectra shown are from a voxel in the cingulum, caudate, putamen, globus pallidus, frontal lobe, temporal lobe, and thalamus.



1. **Δ9-THC**
2. **11-OH-Δ9-THC**
3. **Carboxy- Δ9-THC**
4. CBD
5. 7-CBD-COOH
6. 6-αOH-CBD
7. Δ8-THC
8. 11-OH-Δ8-THC
9. Δ8-Carboxy-THC
10. Δ10-THC

Figure 2: Quantified cannabinoid metabolites from plasma using a method established by Lisa Jayne Reidy, M.D., at the Pathology and Laboratory Medicine Laboratory (Miller School of Medicine, University of Miami).

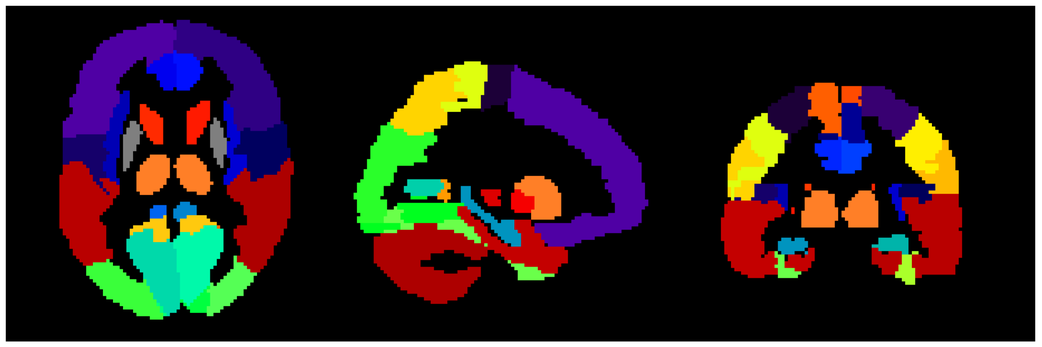


Figure 3: Axial, Sagittal, and coronal view of the AAL47 brain atlas showing the location of the 47 ROIs used in our analysis.

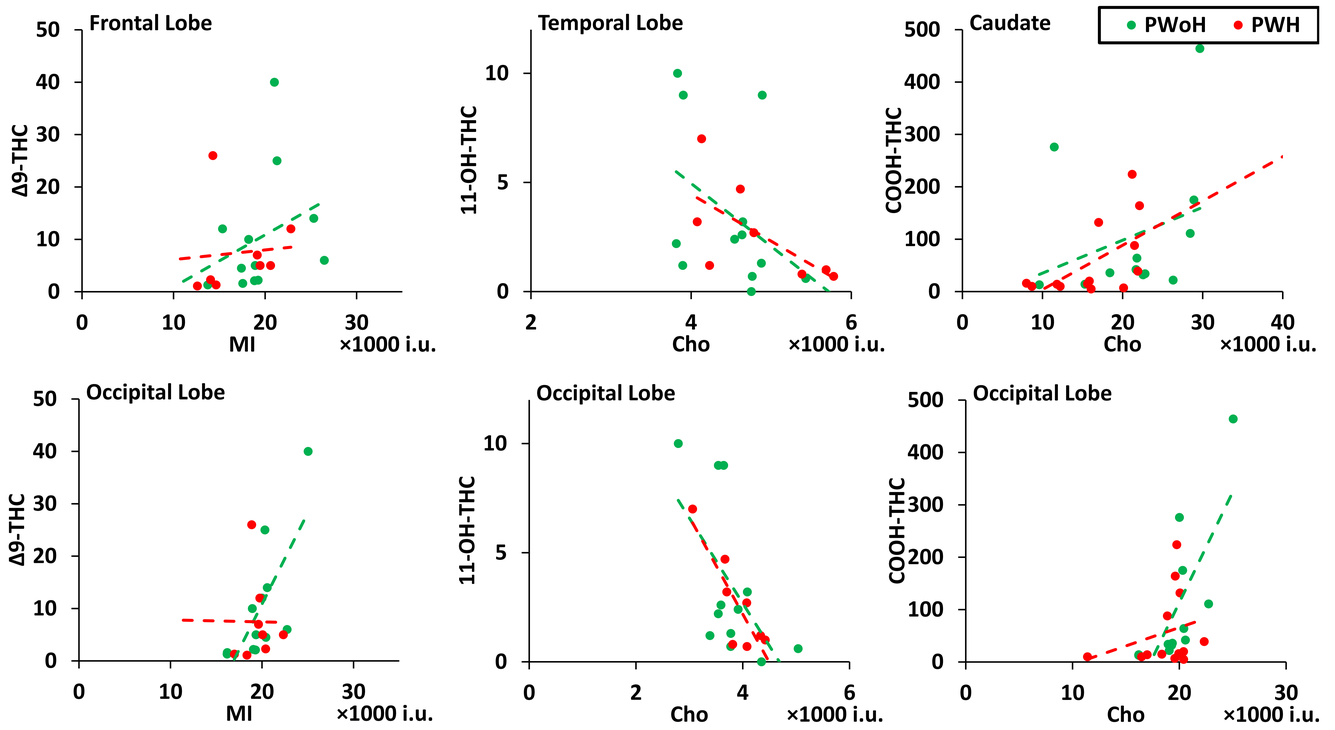


Figure 4: Results of the Spearman correlation analyses between Δ9-THC, 11-hydroxy-Δ9-THC (11-OH-THC), and carboxy-Δ9-THC (THC-COOH) metabolite concentrations with MRSI-derived brain metabolites. The 6 plots show the 6 regions with the most significant correlations out of the 47 ROIs from the AAL47 atlas.

Analysis

At each ROI, we performed Spearman correlations to associate plasma THC with neurometabolite levels, and tested for homogeneity of variance between PWH and PWoH (significance at $p<0.05$ in this preliminary analysis).

Results

- 11-OH-THC negatively correlated with Cho in the hippocampus (rho=-0.59, p=0.008), cuneus (rho=-0.59, p=0.008), and occipital lobe (rho=-0.63, p=0.004). While no difference in variance (p>0.05) was observed, this effect with stronger among PWH.
- COOH-THC positively correlated with MI in multiple brain ROIs including caudate (rho=0.53, p=0.007), cuneus (rho=0.62, p=<0.001), occipital lobe (rho=0.55, p=0.004), and lingual gyrus (rho=0.43, p=0.03) with no differences between PWH and PWoH.
- Δ9-THC correlated positively with MI among PWoH, but negatively (or no significant correlation) in PWH at the same ROIs.
- We also see a differential effect of COOH-THC between PWH and PWoH in the occipital lobe.

Conclusions

- Higher 11-OH-THC and COOH-THC associated with lower Cho and higher m-Ins, respectively, reflecting impaired myelinization and increased inflammation.
- However, Δ9-THC and 11-OH-THC had differential effects on MI with higher inflammation in PWoH and lower inflammation in PWH.

Future Analysis

Further analysis should investigate whether plasma cannabinoid metabolite levels are associated with overall systemic inflammation, measured by plasma biomarkers, and how this relates to other brain outcomes. Specifically, we will associate the plasma cannabinoid metabolite levels with brain microstructural changes (from DTI) and with neuromelanin MRI.

We will also evaluate the effect of co-variates such as BMI, sex, frequency/duration and mode of administration.

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