University of Roehampton London

COMBINED UNIVERSITIES BRAIN IMAGING CENTRE CUBIC

Prefrontal Cortex and Putamen Grey Matter Alterations in Cannabis and Tobacco Users

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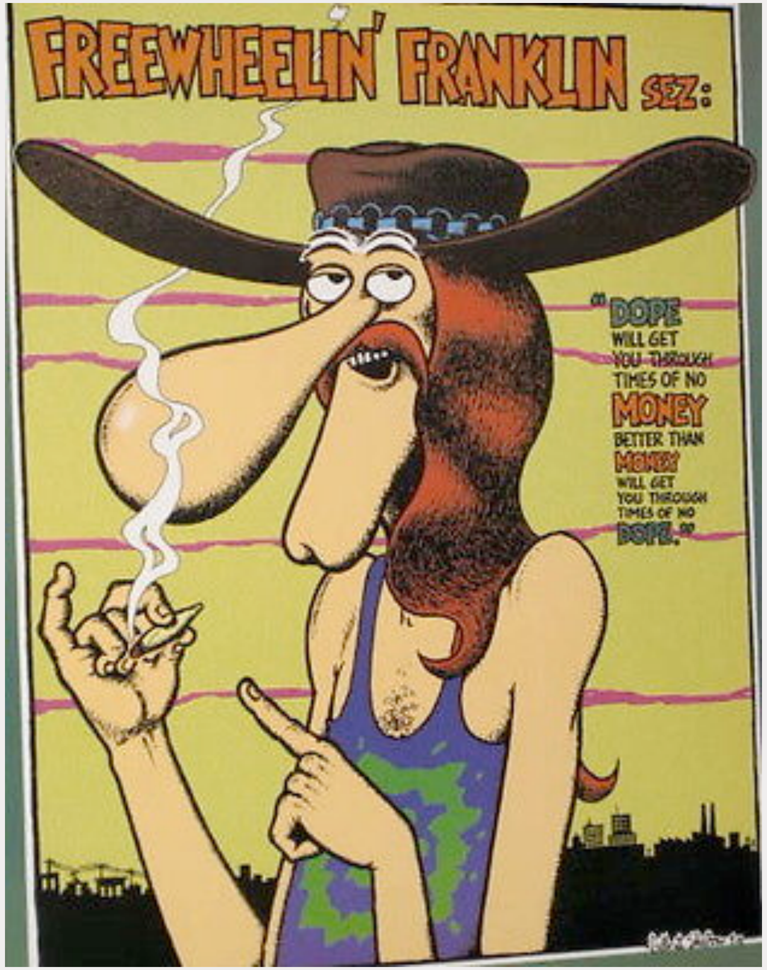
Cannabis – The Cultural Journey



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A clear danger from cannabis

Robin Murray

Classification isn't all-important. What's crucial is that we recognise cannabis does increase the risk of schizophrenia

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Comments
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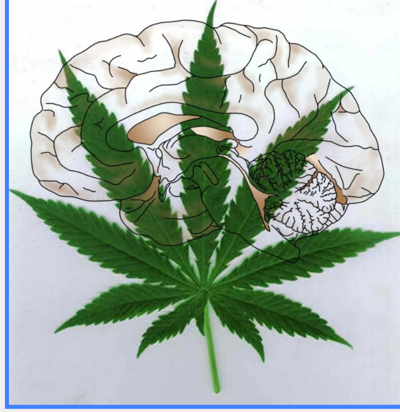
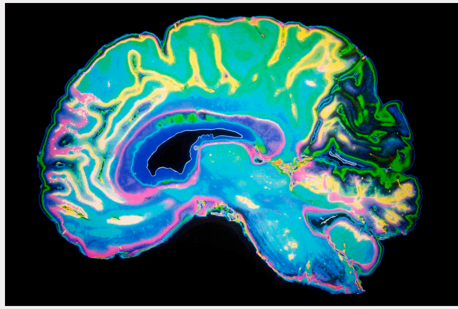
The Advisory Council on the Misuse of Drugs (ACMD), on which Professor David Nutt sits, has an unfortunate history in relation to cannabis. In 2002, it boobed by advising David Blunkett, then home secretary, that there were no serious mental health consequences of cannabis use; the council had done a sloppy job of reviewing the evidence. Since that time, they have been trying to regain credibility, and now accept that heavy use of cannabis is a risk



Background: Cannabis Use

- Approximately 200 million regular cannabis users worldwide (UNODC, 2021) & recreational use is likely to increase as cannabis use is decriminalised in many regions of the world
- Animal studies investigating Δ^9 tetrahydrocannabinol (THC) demonstrate dose-dependent neurotoxicity in cannabinoid receptor-rich regions of the brain *(Chan et al. 1998; Heath et al. 1980; Lawston et al. 2000)*
- Over recent decades there has been a trend for recreational users to use stronger and more potent strains of cannabis that have increased concentrations of THC to around 14% *(Potter et al. 2018)*

Background: Cannabis and brain volume



- Voxel based morphometry (VBM) studies in humans report lower grey matter volume (GMV) in regular cannabis users compared to non-cannabis using controls – particularly in **prefrontal cortex (PFC), hippocampus, and putamen** *(Ashtari et al. 2011; Battistella et al. 2014; Demirakca et al. 2011; Filbey et al. 2015; Lorenzetti et al. 2015; Yücel et al. 2008)*

- These cannabis-related GMV decreases may also be cognitively and clinically significant as regular cannabis use associated with cognitive impairments *(Crean et al. 2011; Meier et al. 2012)* and adverse mental health outcomes *(Henquet et al. 2004; Moore et al. 2007)*

Background: Cannabis and tobacco use

- A confounding factor is that the majority of previous VBM studies did not control for tobacco use across cannabis using and non-cannabis using groups *(e.g., Cousijn et al. 2012; Yücel et al. 2008)*

- Tobacco is often used with cannabis *(Banbury et al. 2013; US Department of Health and Human Services and Substance Abuse and Mental Health Services Administration, 2011)*

- Problematic because tobacco use is also associated with altered GMV in PFC and putamen regions *(Brody et al. 2004; Faulkner et al. 2020; Franklin et al. 2014; Fritz et al. 2014; Gallinat et al. 2006)*

Aims

- Compare GMV in regular cannabis users that also used tobacco (CT), non-cannabis using tobacco cigarette smokers (T), and controls who do not use cannabis or tobacco (C)

- By recruiting a non-cannabis using tobacco-smoking group (T) we were able to examine whether similar volumetric patterns were observable in tobacco users only

- We recruited recreational cannabis users reporting a wide variety of cannabis use to obtain a more representative sample of recreational users than those examined in some previous studies *(e.g. Filbey et al. 2015; Wetherill et al. 2015; Yücel et al. 2008)*

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Predictions

- Relative to the C group, the CT and T groups would show lower GMV in prefrontal cortex and hippocampal regions, and greater putamen GMV.

- Given the link between cannabis use, adverse mental health, and intellectual function *(Crean et al. 2011; Meier et al. 2012)*, we also explored the relationship between GMV, IQ, and levels of depression, anxiety and stress in CT and T groups

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Methods: Participants

- Cannabis and Tobacco users (CT: n= 31)
- Tobacco users (T: n = 19)
- Non-smoking controls (C: n =35)
- Groups matched for sex, age, and IQ

- Using VBM, groups compared across bilateral hippocampal, putamen and PFC regions of interest (ROI)

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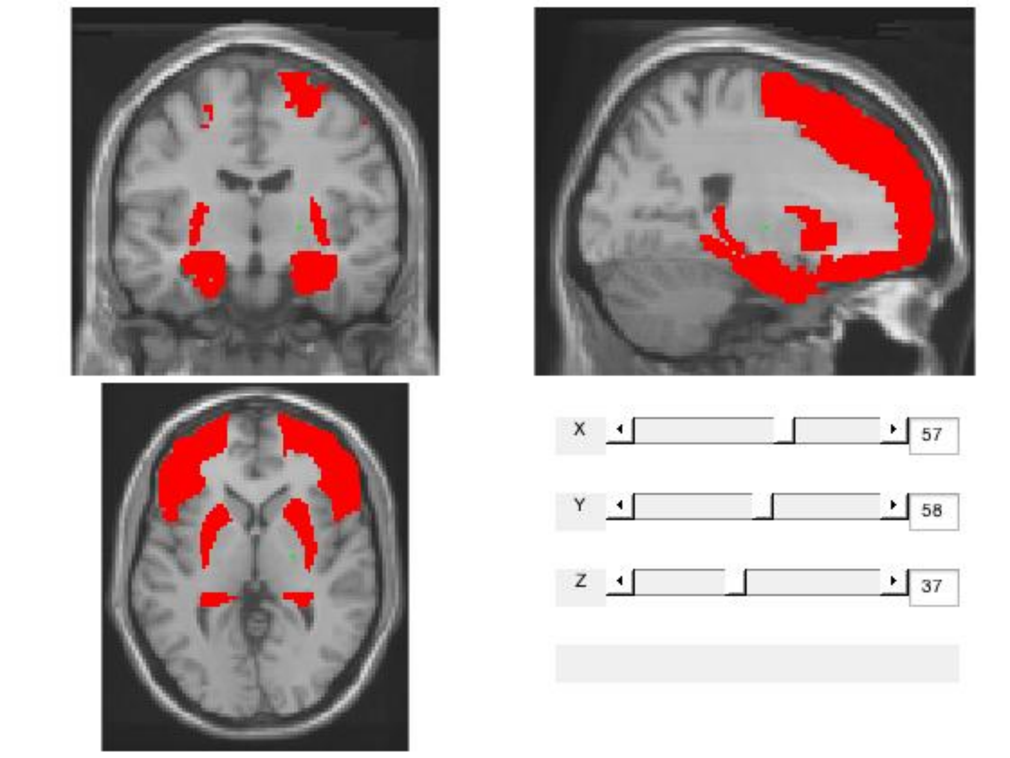
Methods: Voxel based morphometry (VBM)

Volumetric data preprocessed using the Computational Anatomy Toolbox, (CAT12; http://www.neuro.uni-jena.de/cat/)

Age, sex, and total intracranial volume were included as regressors of no interest to control for effects on regional grey matter volume.

Statistical thresholds were applied at a $p<0.05$ after Family Wise Error (FWE) correction level for multiple comparisons within bilateral hippocampal, PFC and putamen ROI using WFU Pickatlas Toolbox (https://www.nitrc.org/projects/wfu_pickatlas)



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Methods: Participants' cannabis and tobacco use

	Tobacco users (T) *N*= 19	Cannabis and tobacco users (CT) *N*= 31	Non-smoking Controls (C) *N*= 35	*Analysis*
Daily cigarettes smoked	6.6 (5.3)	4.8 (5.5)	0	$t(45)= 1.58$, $p= 0.12$ [b]
Years of tobacco use	6.2 (4.2)	5.3 (4.3)	0	$t(45) =1.95$ $p = 0.35$ [b]
Pack Years	2.7 (3.65)	2.1 (4.07)	0	$t(45)= 1.02$ $p = 0.31$ [b]
Total lifetime joints	25.1 (43.0)	3703 (4465)	0	$t(45)=12.10$ $p = 0.001$
Years of cannabis use	0	8.2 (4.4)	0	*n/a*

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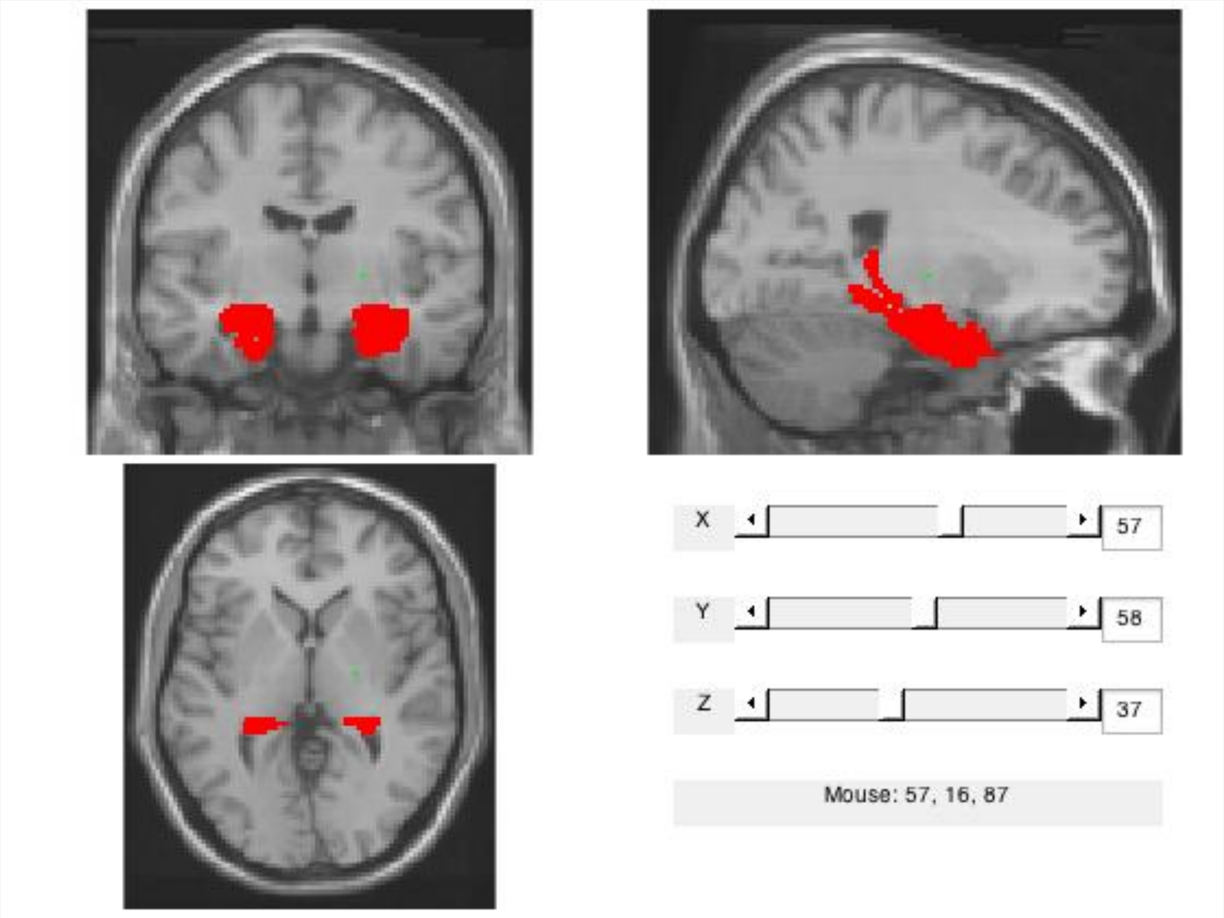
Results: Hippocampal ROI



No supra threshold result

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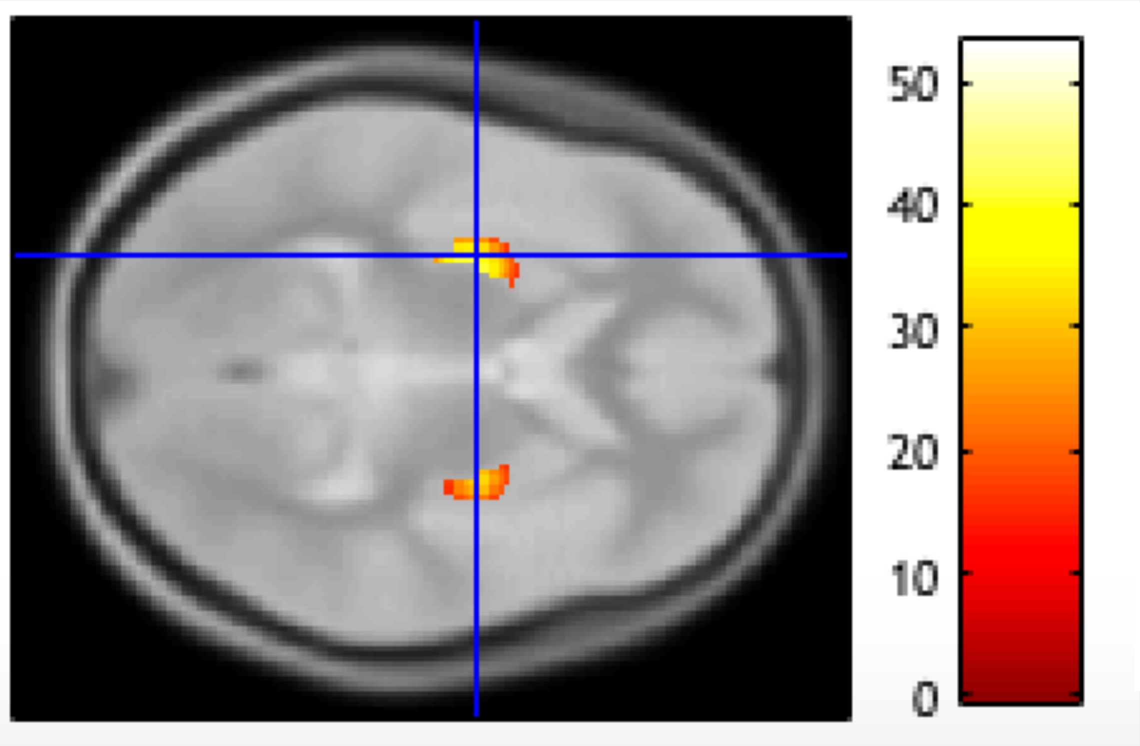
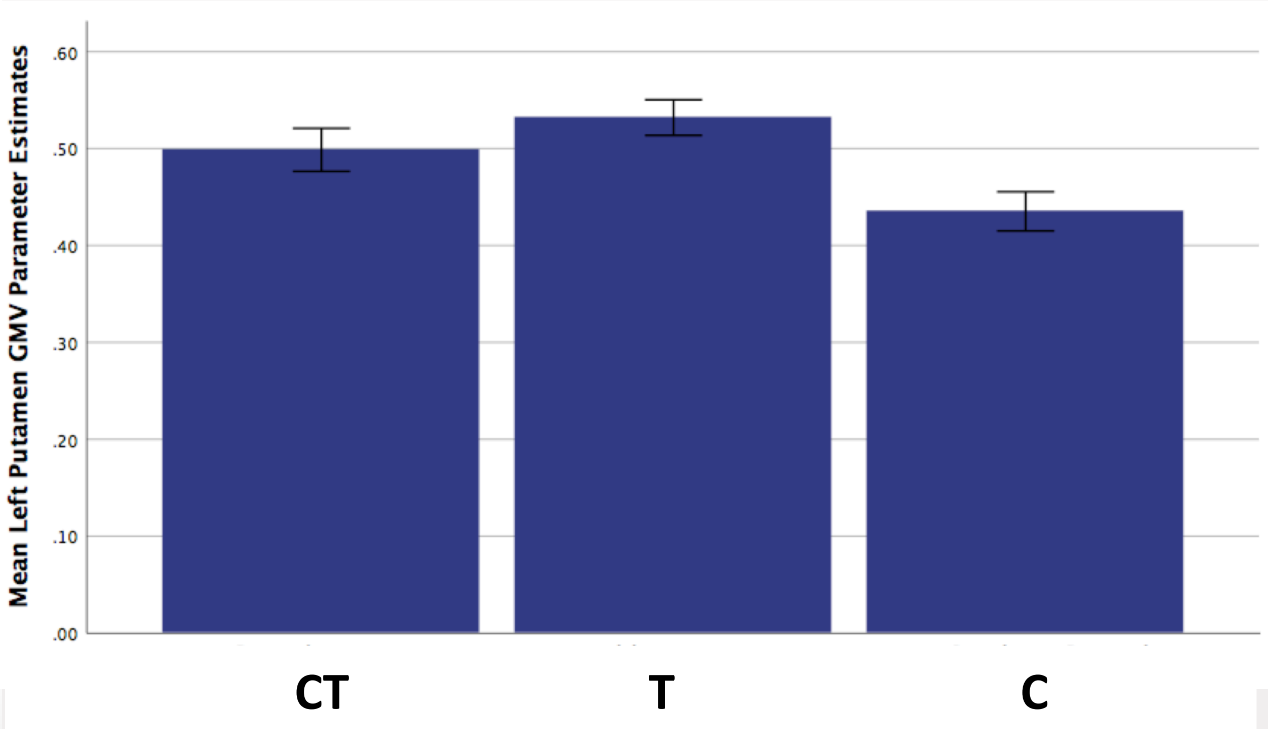
Results: Putamen ROI: Group Effects (x = -28, y = -9, z = 8, Z = 7.8, *k* =927, ***p FWE (peak) < .01,*** and x = 30, y = -6, z = 3, Z = 6.54, *k* = 444, ***p FWE (peak) < .01***)





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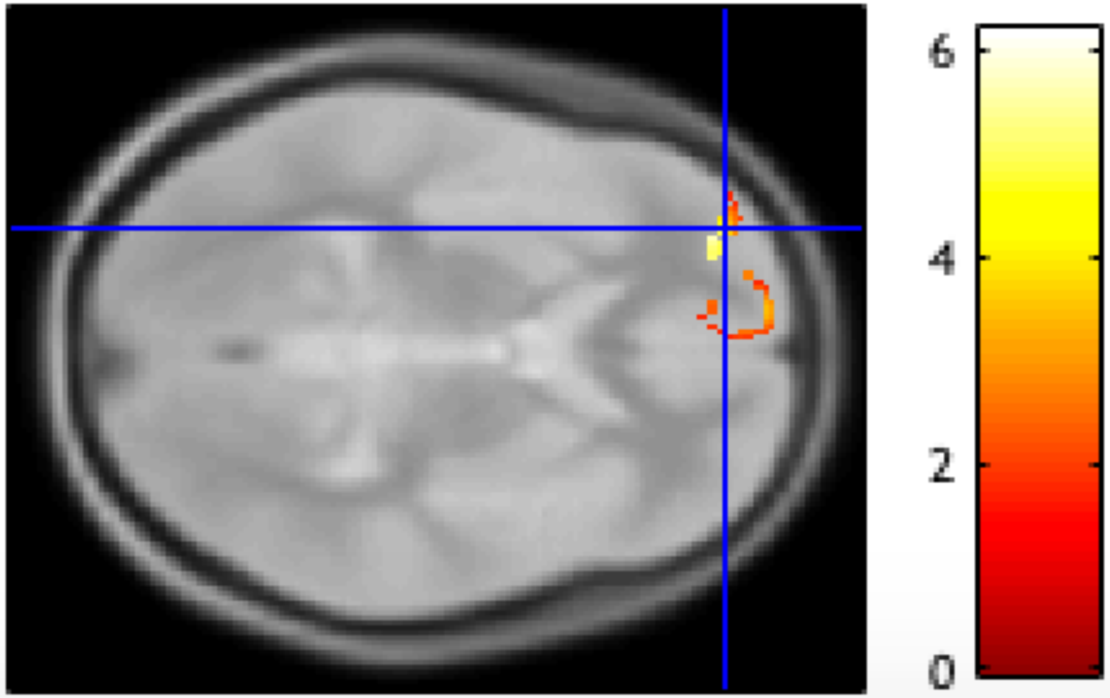
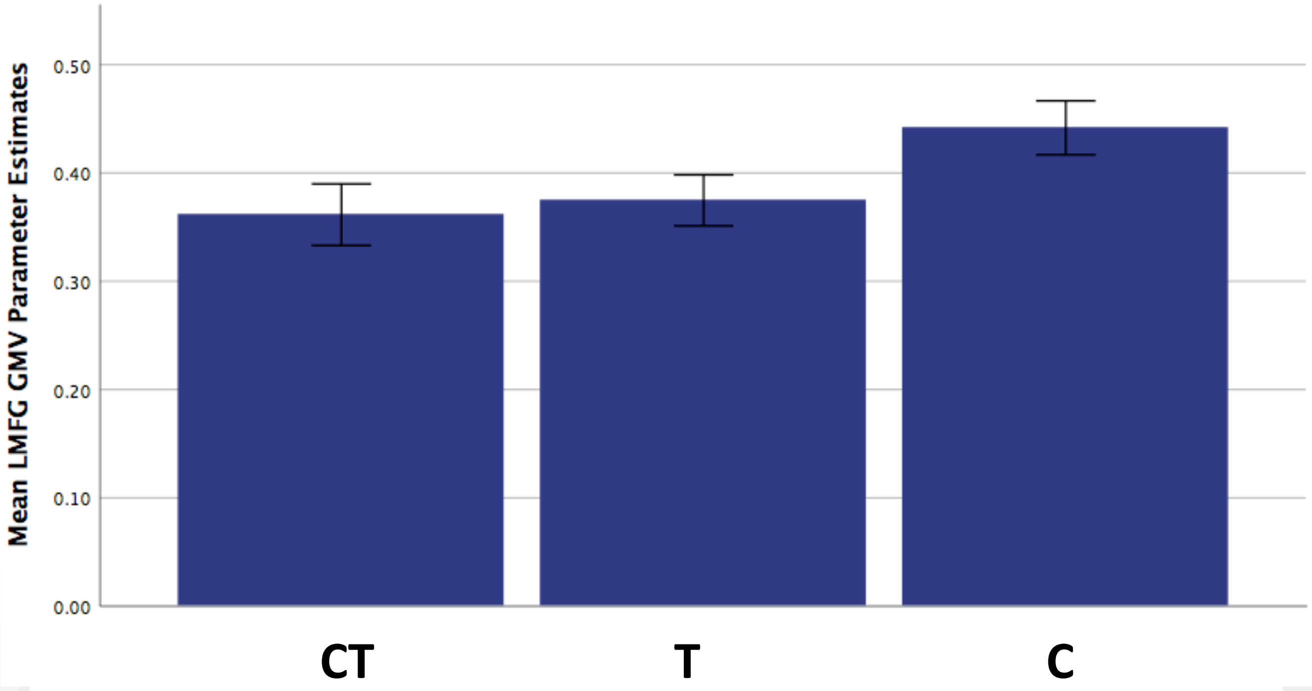
Results: **PFC ROI** Group Effect left inferior frontal gyrus (x = -30, y = 51, z = 0, Z = 5.54, *k* = 77, *p FWE (peak) = .01)*





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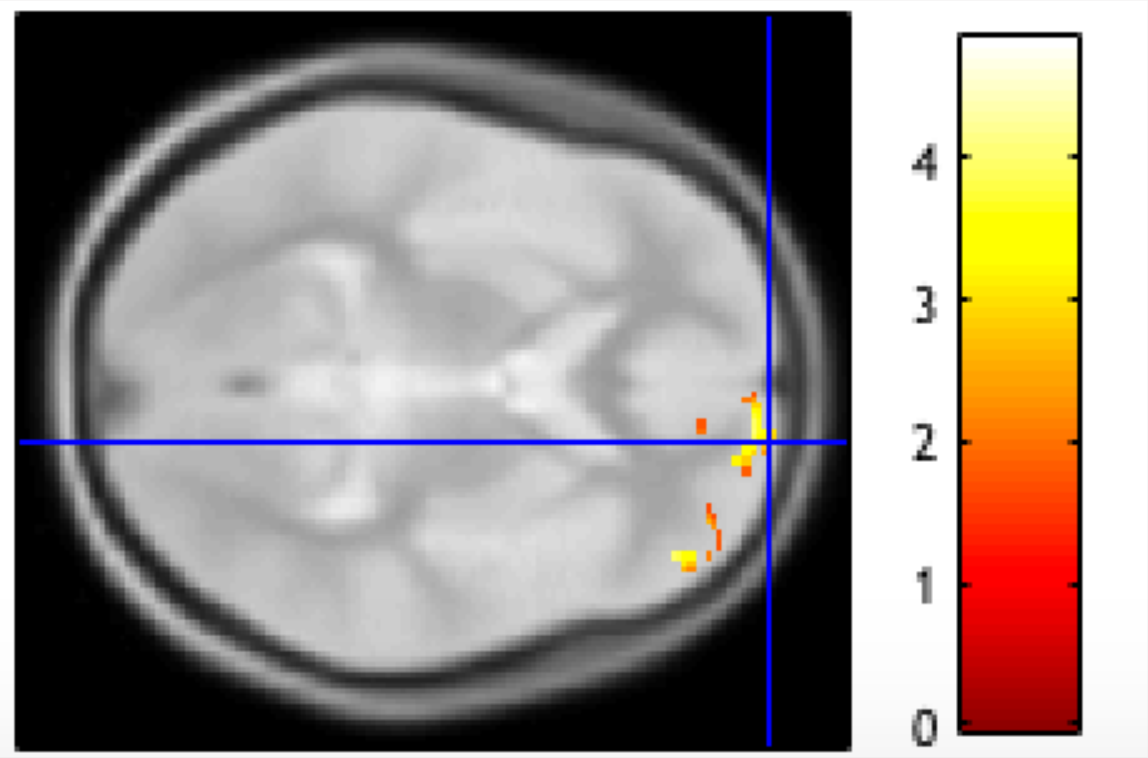
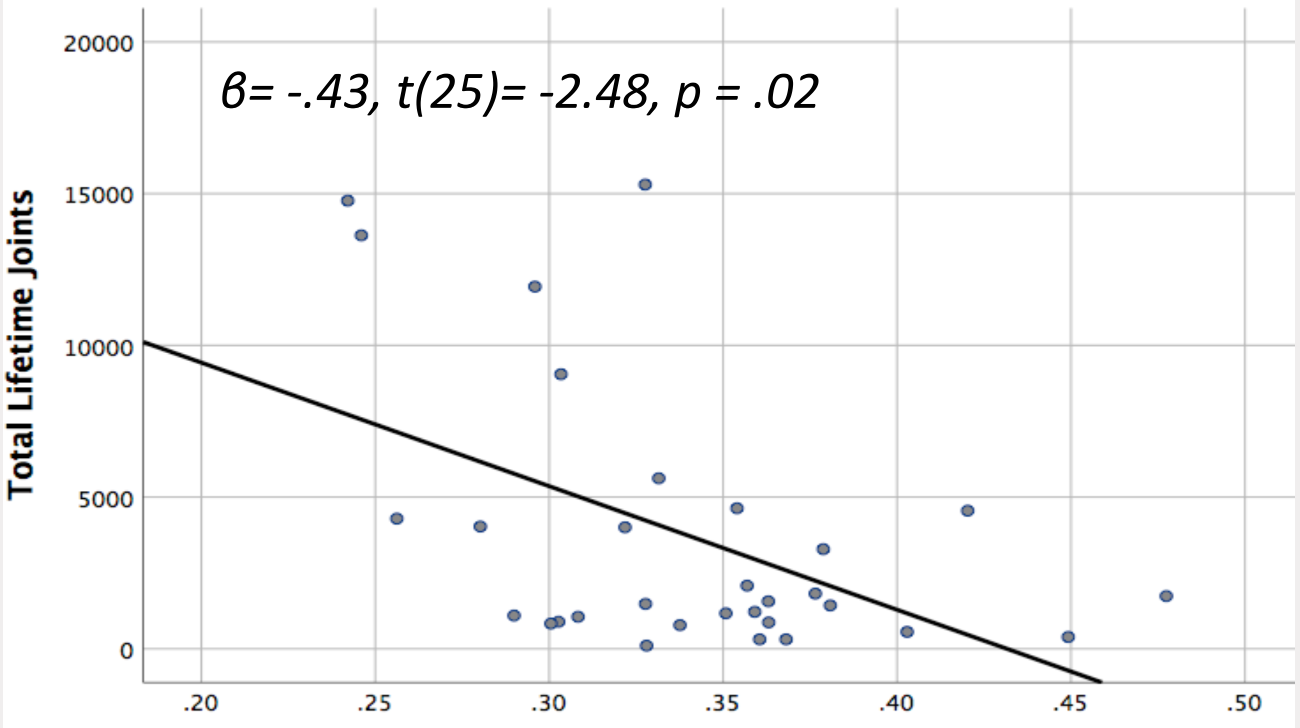
Results PFC ROI (CT vs. C): right frontal pole (x = 15, y= 63, z =-3, Z =3.90, k = 13, *p FWE (peak) =.02)*





Mean GMV Parameter Estimates in in Right Frontal Pole

Results: IQ, Depression, Anxiety, Stress

DASS Subscale	CT Group		T Group		C Group		Analysis
	M	SD	M	SD	M	SD	
Depression	7.61	(5.95)	8.05	(8.84)	6.64	(8.50)	$F\ (2, 82) = .29$ $p = 0.75$
Anxiety	6.10	(5.05)	6.26	(5.30)	6.17	(7.00)	$F\ (2,82) = .005$ $p = 0.99$
Stress	9.71	(7.24)	9.74	(7.87)	11.17	(9.60)	$F\ (2,84) = .306$ $p = 0.74$

Significant positive correlation between GMV in the right frontal pole cluster and IQ scores in the CT group $(r = .401, p = .02)$; not statistically significant after Bonferroni correction for multiple tests $(p > .01)$. All other tests were non-significant.

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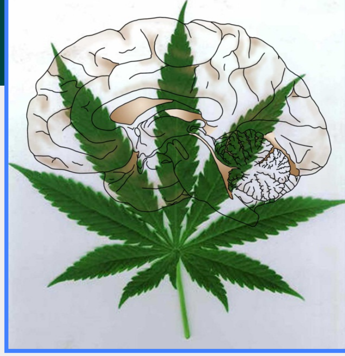

Summary and Conclusions

- In a young adult population of regular cannabis and tobacco users - exhibiting a range of recreational cannabis use patterns – we observed lower than normal GMV within the PFC and increased GMV in the putamen – but not in hippocampus.

- No significant associations between GMV alterations and clinical or IQ measures (after correction)

- GMV findings broadly in line with a previous study that reports volumetric changes in young people with limited exposure to cannabis *(Orr et al. 2019)*

- Similar volumetric alterations were also observed in non-cannabis using tobacco smokers - thus further work is needed to better understand the differential effects of regular cannabis and tobacco use on brain volume.