The Impact of Regular Cannabis Use on Human Brain Structure

V Lorenzetti [1,2], N Solowij [3,4], A Fornito [1], DI Lubman [5], M Takagi [1,2], IH Harding [1,2], C Pantelis [1,2], M Seal [1,2], M Yücel [1,2]

[1] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Australia; [2] Orygen Youth Health Research Centre, The University of Melbourne, VIC, Australia; [4] School of Psychology, University of Wollongong; [5] Schizophrenia Research Institute, Sydney, NSW. Australia; [6] Turning Point Alcohol and Drug Centre, Eastern Health Clinical School, Monash University, Melbourne, Australia

Introduction

Regular cannabis use is associated with adverse mental health and neurocognitive outcomes [1]. To date, there is limited and inconclusive evidence on whether regular cannabis use is associated with brain abnormalities [3] and on the variables that may be associated with such abnormalities. This study seeks to achieve **three main objectives**, including to examine whether:

I. Regular cannabis exposure is associated with **volumetric alterations** in brain regions high in cannabinoid receptors and mediating psychopathology/cognitive processes that are altered in regular CB users;

II. Cannabis use patterns are associated with regional brain volumes in CB users;

III. Selected **'clinical' variables** exert a confounding or an independent impact on regional brain volumes from that of cannabis use patterns.

Hypotheses

I. CB users would exhibit altered brain volumes in key brain regions (ROIs) compared to HC. Specifically, CB users would have smaller hippocampi and amygdalae, and larger pituitary, nucleus accumbens (Nacc) and caudate volumes.

II. More chronic cannabis use patterns (i.e., frequency, dose; duration and age of regular use) will be associated with altered ROI volumes in CB users.
Chronicity of use will be negatively associated with hippocampal/amygdala, positively associated with PGV, Nacc and caudate.

III. Clinical measures (i.e., anxiety; positive, negative psychotic and depressive symptoms, global functioning) will also be associated to altered ROI volumes in CB users.

Method

Sample

We investigated the largest sample of CB users and age and sex-matched HC (**Tables 1-2**). All subjects were recruited from the general community and were medically and psychiatrically healthy. CB users had limited exposure to substances other than cannabis.

Table 1. Sample Characteristics (M±SD)

		HC	CB users
N (males)		37 (19)	46 (23)
Age		30 ± 11	33 ± 11
Education *		14 ± 2	13 ± 2
WASI IQ *		112 ± 13	103 ± 12
AUDIT		10 ± 5	12 ± 6
CB	**Dependence (SDS)**	-	5 ± 4 (moderate)
	Craving (MWCL)	-	5± 6 (not craving)

Table 2. Key Cannabis Use and Clinical Data

Cannabis Use Patterns M ± SD, Range			
Frequency (days/mo)	**Past Year**	25 ± 9	3-30
	Life	24 ± 7	8-30
Dose (cones*)	**Past Year**	4834 ± 4014	96-19,917
	Life	75,076 ± 82,852	720-459,000
Duration (yrs)		16 ± 9.9	1-38
Age Reg Use		17 ± 3	11-25
Clinical Data M ± SD			
		HC	**CB users**
Trait Anxiety*		34 ± 8	40 ± 13
Depression (CAPE) *		12 ± 3	14 ± 3
Psychotic Symptoms	**Positive ***	24 ± 3	27 ± 6
	Negative *	22 ± 6	25 ± 7
Global Function*		86 ± 4	75 ± 10

* 3 cones= 1joint, 12 cones=1gram

Imaging

Acquisition - of imaging data was performed on a 3-T Siemens Trio scanner, with a 3D MPRAGE sequence and a 32-channel head coil.

Analysis - Selection of key brain regions (ROI) that:

- Have a a high concentration of CB_1 receptors
- Are linked to behaviors altered in regular CB users

Examined ROI:

- **Hippocampus** (learning and memory)
- **Amygdala** (emotion regulation)
- **Pituitary** gland (stress regulation)

Traced manually (Analyze 11, Mayo)

- **Nucleus accumbens** (reward sensitivity)
- **Caudate nucleus** (repetitive behaviors)

Segmented automatically (FreeSurfer v.4)

Statistical analyses

We run **2 levels of analyses**

i) Repeated measures ANCOVAs
*to investigate **group differences in ROI volumes***

ii) 2-block regression models (CB users only)
to examine which key variables predict ROI alterations

a) Major confounders (age, ICV) effects on ROI volumes were controlled for.
b) Predictors of ROI volumes were examined.

Block I - CB Use
- Duration
- Frequency
- Dosage
- Age Onset

Block II - Clinical
- Anxiety
- Depression
- Psychotic symptoms
- Global functioning
- IQ

c) Confounders correlated with significant predictors were controlled for.

Results

i) Group comparisons

Volumetric **alterations** were observed in the **hippocampus and amygdala only** [see **Table 3** and **Figures 2a-b**].

CB users relative to HC, showed a **reduction** in hippocampal [F(1,78) =13.97, Effect size= 0.87, Cohen's d=.66] and amygdala volumes [F(1,78)=4.11, Effect size=0.35, Cohen's d=.40] **by 10% and 7%, respectively**.

Table 3. ROI volumes by group

Volume (mm^3)	HC	CB	p
Hippocampus *	2,694 ± 353	2,462 ± 342	<0.001
Amygdala *	1,607 ± 285	1,499 ± 250	.046
Pituitary	571 ± 114	568 ± 111	n.s.
NAcc	508 ± 74	520 ± 112	n.s.
Caudate	3,545 ± 458	3,556 ± 556	n.s.
ICV	1,514,617 ± 146,494	1,429,625 ± 132,469	n.s.

*= significant; **Nacc**= nucleus accumbens; **ICV**= Intra-Cranial Volume

ii) Cannabis use Patterns (Linear Regression, Block I)

- **Age of Regular Use** negatively predicted hippocampal volume [right, p=.005 & left, p=.019, **Figure 3a**].

*This effect **persisted** after controlling for clinical [right, p=.007, left, p=.019] and correlated confounders [right, p=.003, left, p=.008].*

- **Past year cannabis dosage** was associated with smaller amygdala [left, p=.010, **Figure 3b**] but larger Nacc [right, p=.018, left, p=.038] and caudate [right, p=.035].
- **Life cannabis dosage** predicted smaller NAcc [left, p=.019].

*These effects **persisted** after controlling for clinical variables, but **not** correlated **confounders**.*

- Instead, **age of onset** emerged as a negative predictor of **caudate** volumes after controlling for confounding variables [right, p=.018, **Figure 3c**].

iii) Clinical Variables (Linear Regression, Block II)

- No significant effect.

Figure 2a. Hippocampi across groups.

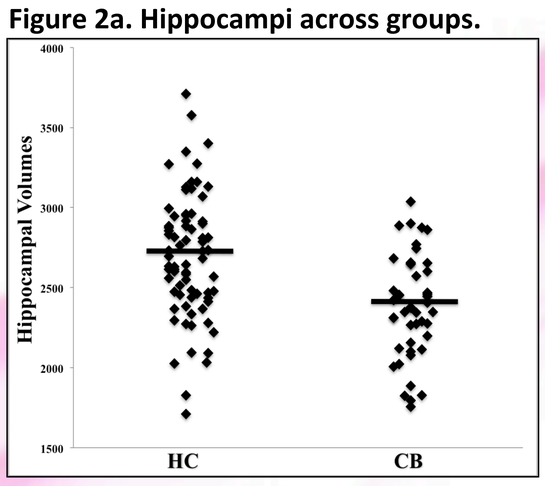


Figure 2b. Amygdala across groups

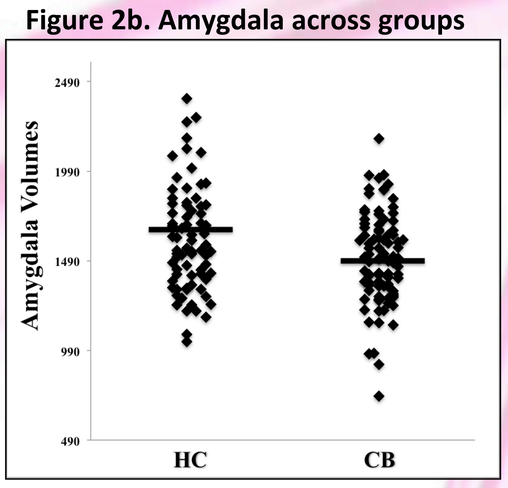


Figure 3a. Hippocampus-Age onset

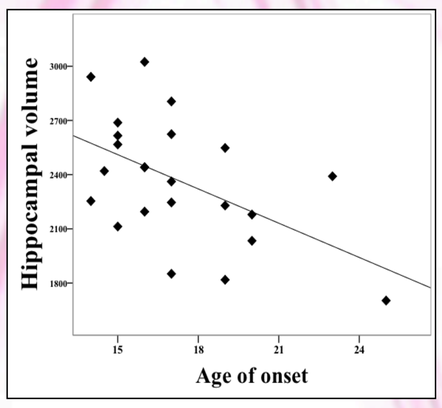


Figure 3b. Amygdala-Dosage

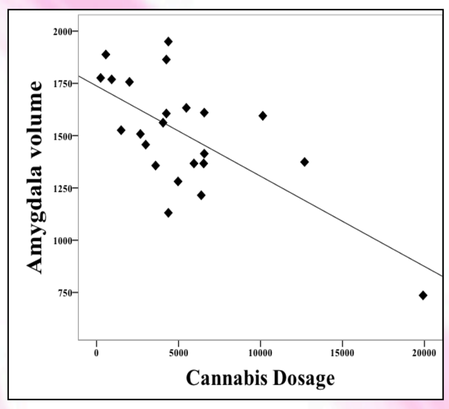
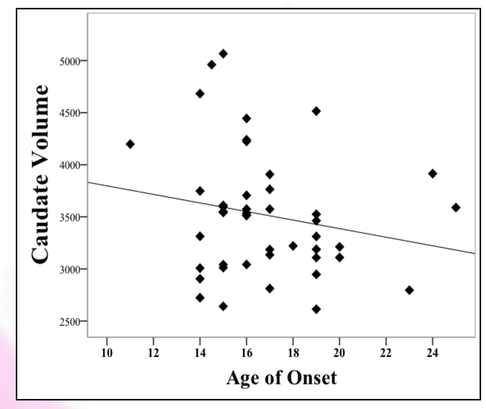


Figure 3c. Caudate-Age onset



Conclusions

Consistent previous research **[2]**, these data suggest that regular cannabis exposure is associated with altered brain morphology in key areas that are high in CB_1 receptors and that mediate psychopathology/ cognitive processes that are altered in CB users.

Importantly, there was a regional-dependent association between regular cannabis exposure, cannabis use patterns and brain abnormalities. The reported alterations appeared to occur independently from the impact of 'clinical' variables.

Thus, alteration of cannabinoid receptor mediated mechanisms may drive the reported findings as a function of the biochemical and functional specificity of the examined brain region.

The emerging association between age of onset and specific brain regions in CB users suggest that cannabinoids may trigger alteration of brain neurotrophic factors (NGF, BDNF) **[3,4]** and thus mediate those volumetric abnormalities that were apparent in the hippocampus and subtle in the caudate.

Conversely, the associations observed between cannabis dosage and other brain regions suggest that THC-mediated neurotoxic mechanisms **[5]** may drive subtle volumetric alterations in the amygdala, NAcc and caudate.

Overall, these data suggest that there are complex associations between regular cannabis use, cannabis use patterns and brain morphological alterations.

Nevertheless, the mechanisms underlying these findings remain unclear, and further analyses will be conducted to explore this issue.

References

[1] UNODC (2010): World Drug Report.

[2] Lorenzetti et al (2010), Substance Use and Misuse.

[3] D'Souza et al (2009), Psycho-pharmacology.

[4] Angelucci et al (2008), European Neuropsychopharmacology.

[5] Scallet (1987), Brain Research.

Conflict of Interest: None

Valentina Lorenzetti - **vlor@unimelb.edu.au**