Cannabis effects on microglia, astroglia and synaptic density

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Conflict of Interest/Disclosures

Nothing to disclose other than….

I will be representing our own work, in the context of great work from colleagues…

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Outline: From TSPO to SV2A

Molecular imaging in Youth–(selected)

I. Da Silva T, Hafizi S, Watts J, Weickert CS, Meyer JH, Houle S, Rusjan PM, Mizrahi R. (2019). In vivo imaging of translocator protein in long-term cannabis users. JAMA Psychiatry, 76(12):1305-1313.

II. Nisha Aji, K., Lalang, N., Ramos-Jiménez, C. et al. Evidence of altered monoamine oxidase B, an astroglia marker, in early psychosis and high-risk state. Mol Psychiatry (2024).

III. Blasco MB, Nisha Aji K, Ramos-Jiménez C, et al. Synaptic Density in Early Stages of Psychosis and Clinical High Risk. JAMA Psychiatry (2024)

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GLIA

Microglia

(Michael W Salter., et al. 2017)

Immune Response

- Monitor brain for pathogens/damage.
- Phagocytosis of debris and pathogens.
- Release cytokines to regulate immune response.

Synap

- Elim napses during development.
- Maintain synaptic plasticity and circuit refinement.

Neuroprotection

- Programmed cell death.
- Modulate inflammation to prevent excessive damage from stress or injury.

TSPO

Astroglia

(Verkhratsky, A., et al. 2018; Notter T. et al. 2021)

Homeostasis

- Balance extracellular ion (K^+ CA^+) and pH
- Citoarquitecture, including neuronal glial vascular interface and control of BBB.

Metabolic Support

- Supply te) to neuron
- Regula tabolic waste clearance including ROS.

Neurotransmitter levels via Clearance

- Uptake and recycling of neurotransmitters, including glutamate (via EAAT) and DA (via MAO-B/VMAT2).

Synaptic Function

- Influence synaptic strength and neuronal connectivity (myelination).

MAO-B

Imaging TSPO as a neuroimmune marker (mostly microglia) with [^{18}F]FEPPA PET in long term cannabis users

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Immune response and cannabis

- Regular cannabis use has been associated with long-term changes in the brain.
- Cannabinoid signaling plays a critical role in the modulation of inflammatory responses; however clinical evidence remains sparse.
- Preclinical studies have reported anti-inflammatory and immunosuppressant effects of cannabinoids by inhibiting microglial activation, inhibiting release of ROS, decreasing proinflammatory cytokine secretion, and increasing anti-inflammatory cytokine release from microglia (Mecha et al. 2016; Suarez-Pinilla et al. 2014).
- THC and cannabidiol, are also currently being investigated as potential therapeutic agents for several inflammatory and/or immune diseases, including schizophrenia and putative CHR participants.

Demographics & PET parameters (CU vs HV)

Demographics		HV (n=27)	CU (n=24)	Results	*p*
	Age(years)	23.6 ± 4.2	23.1 ± 3.8	t=0.4	0.68
Gender	Male	9	15	X^2=4.3	0.04
	Female	18	9		
Genotype	HAB	19	18	X^2=0.1	0.71
	MAB	8	6		
PET measures	Amount injected (mCi)	4.9 ± 0.4	5.0 ± 0.3	t= -0.7	0.49
Cannabis use and behaviour	Age at first use (years)	--	16.4 ± 3.4		
	Estimated lifetime cannabis use (grams)	--	2163.6 ± 1641.9		
	CUD	--	15		
Tobacco		0	7		

(Da Silva et al. 2019, *JAMA Psychiatry*)

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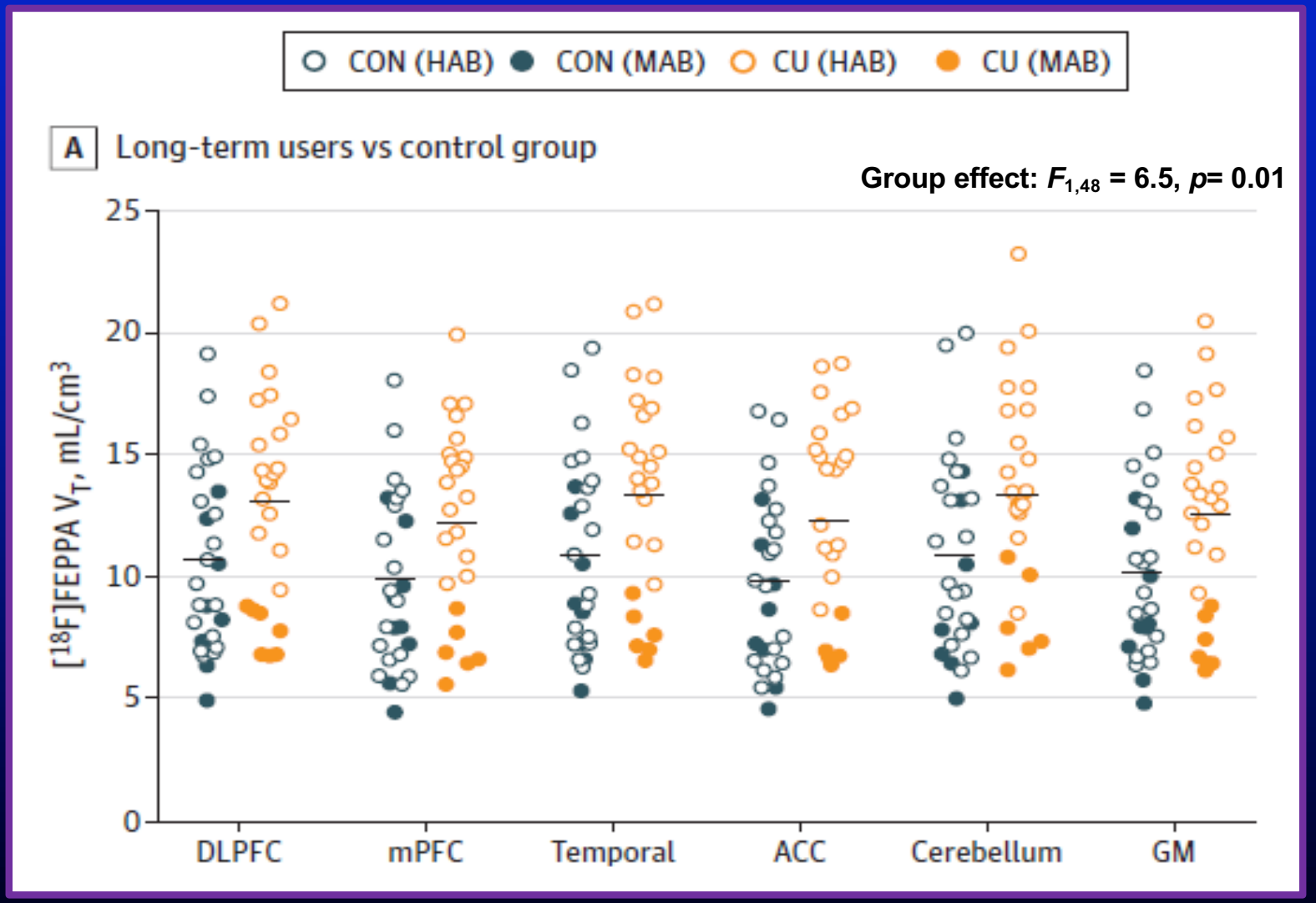
Higher TSPO in long-term cannabis users compared to controls



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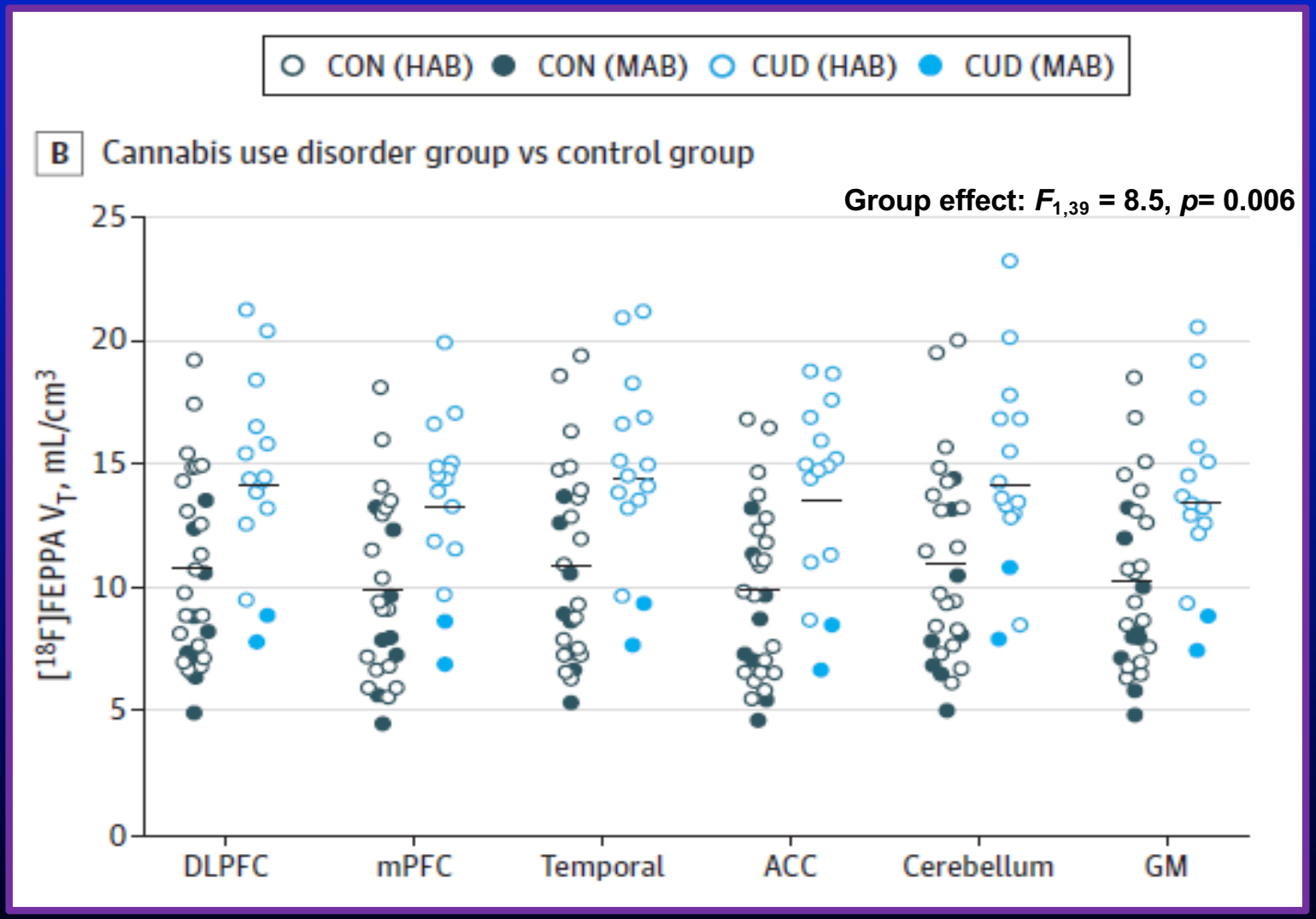
(Da Silva et al. 2019, *JAMA Psychiatry*)

Higher TSPO levels in CUD compared to non-cannabis using controls



(Da Silva et al. 2019, *JAMA Psychiatry*)

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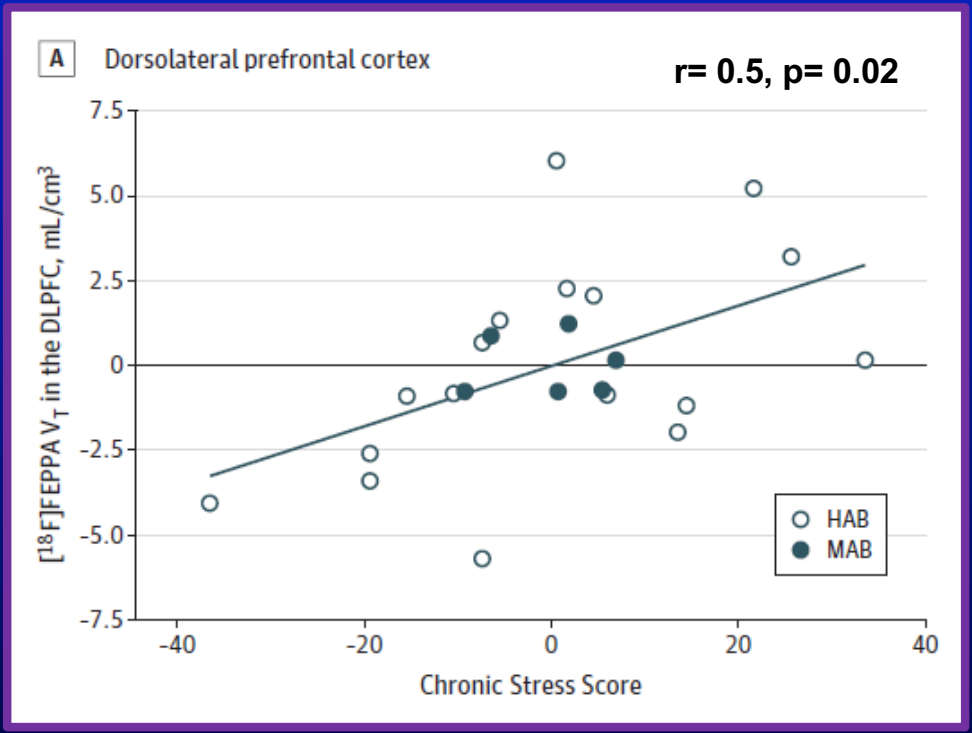
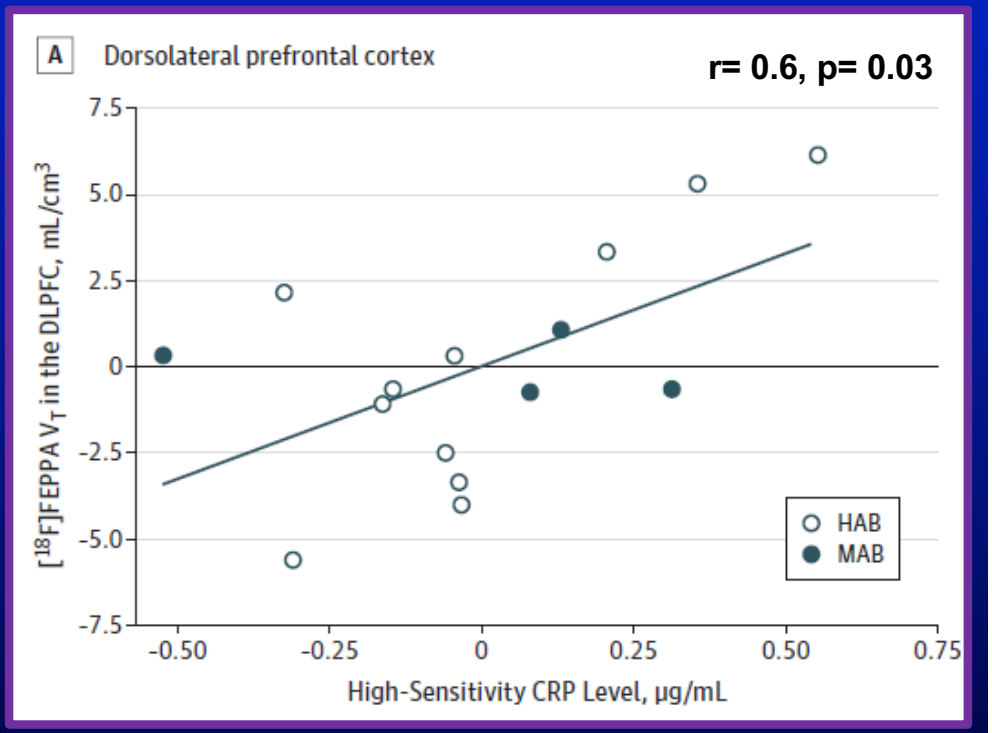
Higher TSPO was associated with higher behavioral measures of stress and anxiety scores, and higher circulating CRP levels in CU





(Da Silva et al. 2019, *JAMA Psychiatry*)

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Imaging Monoamine Oxidase B (MAO-B), an Astroglia Marker, in Early Psychosis with Cannabis Use with [^{11}C]SL25.1188 a valid PET radioligand to quantify MAO-B in brain

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MAO-B and its role in psychosis and CUD

- Post-mortem (Owen, F., et al. 1987),
- Peripheral studies (Bortolato M, et al. 2011)
- Preclinical findings (Berrettini WH. et.al 1978)

variable results across studies

- Regular cigarette smokers - ↓ brain MAO-B (**Post-mortem**: Berlin, I., et al. (1995) Biol. Psychiatry; **PET Study** - Karolewicz, B., et al. (2005). Brain Res)

Cannabis

- ↓ MAO-B gene expression after acute low-dose cannabis exposure (***In vitro* study)**
- ↓ GFAP expression and astrocytic alterations (pre-clinical)

No in vivo study investigated MAO-B in the brain of psychosis patients or Cannabis use.

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CaTS Clinical & Translational Sciences

Aim and Hypothesis

Aims	Primary hypotheses
Examine the effect of study group (HV, CHR, and FEP) on [^{11}C]SL25.1188 binding (V_T).	[^{11}C]SL25.1188 binding (V_T) will be significantly different between study groups (HV>CHR>FEP).
Examine the effect of cannabis use (cannabis vs no-cannabis) on [^{11}C]SL25.1188 V_T.	MAO-B will be lower in cannabis users.
Examine the group by cannabis interaction.	Effect of cannabis will be significantly different in the CHR and FEP groups as compared to the HVs.

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Study protocol

Participants

- 17 healthy volunteers
- 7 CHR patients
- 14 FEP patients

Assessments

- FEP - DSM5 diagnosis using SCID, PANSS
- CHR -SIPS
- Cannabis users – Urine drug screen and Drug History Questionnaire (DHQ)
- Record tobacco use

[^{11}C]SL25.1188 PET Scan

PET scan (3D HRRT) – 90 minutes
Blood data

- *Arterial blood sampling* - Automatic blood sampling system (ABSS)
- *Manual blood sampling*

MRI Scan

MRI scan (3T)

- proton density (PD)-weighted brain MR images

Analysis

- MRI co-registration to [^{11}C]SL25.1188 PET images
- Generate the Time activity curves (TACs)
- A full kinetic model of the TACs - Logan graphical method with arterial input function - **outcome measure V_T**

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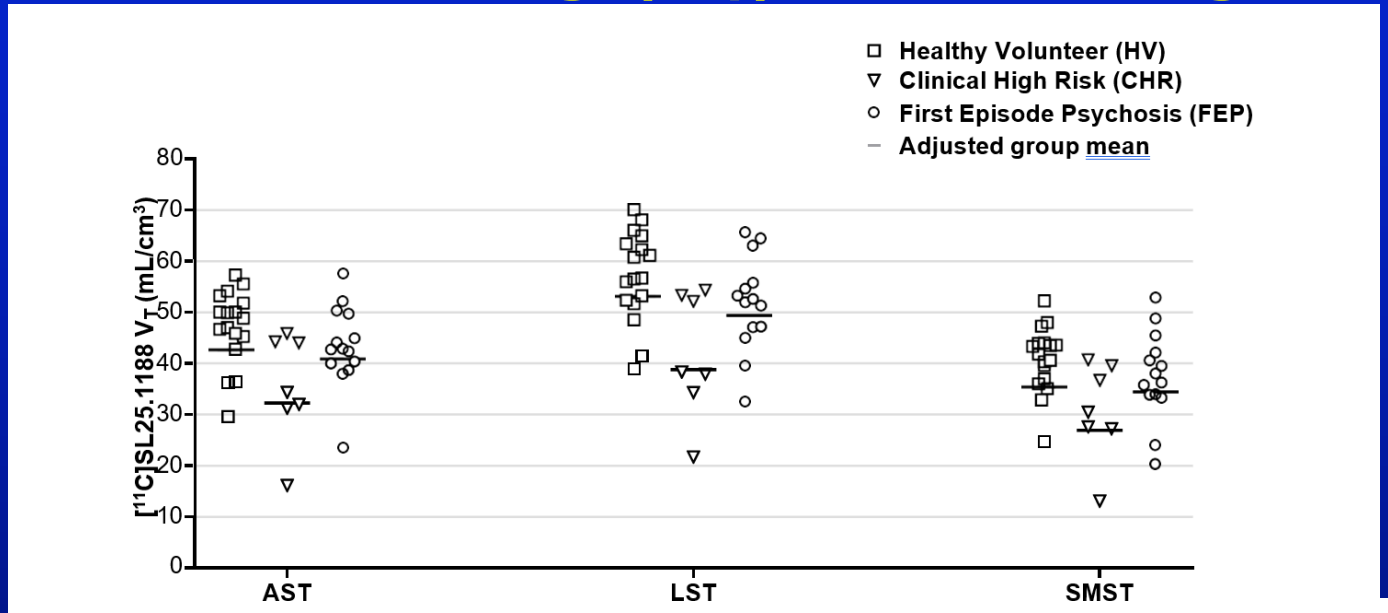
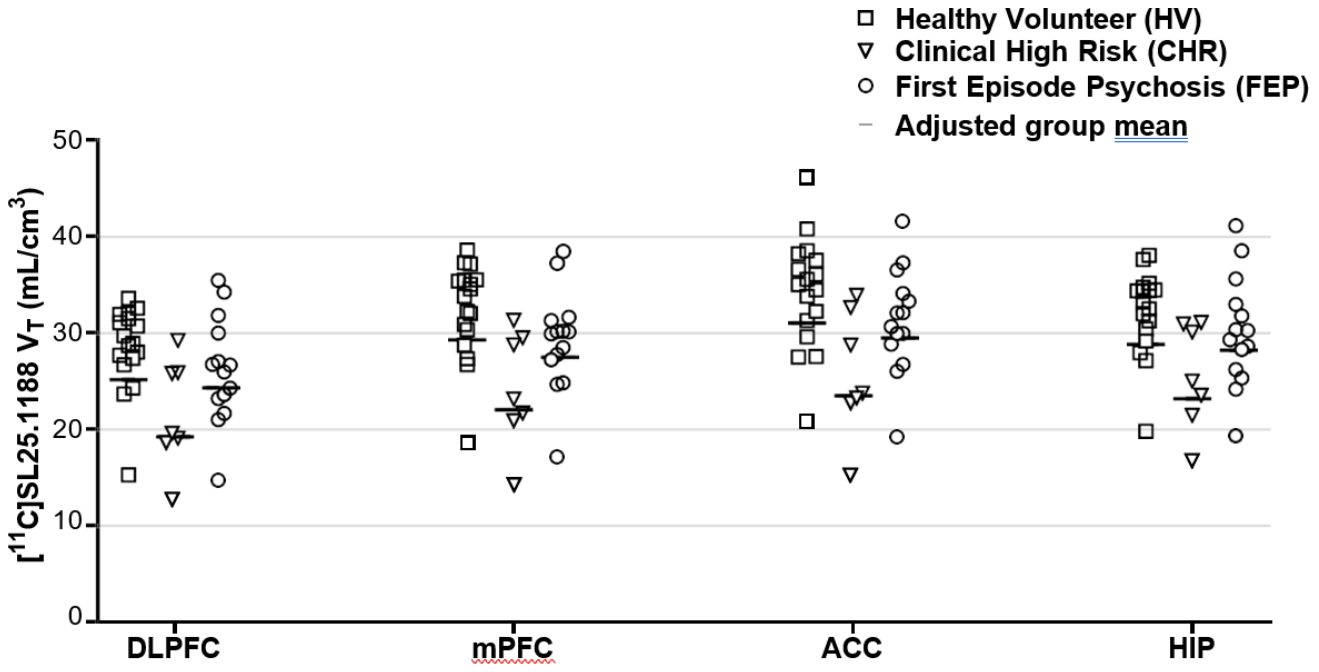
Demographic and variables		HV (n=17)	CHR (n=7)	FEP (n=14)	χ^2 Test or F-value or t-Test	*p* value
Age, y		31.24 ±13.99	20.86 ±3.67	25.71 ± 5.68	F = 2.83	0.07
Male/Female, n		8/9	3/4	8/6	X^2 = 0.38	0.54
BMI, Mean ± SD		23.41 ±2.87	22.32 ±4.54	24.78 ±3.89	t = 1.21	0.31
Non-smoker/smoker, n		17/0	6/1	11/3	X^2 = 0.15	0.69
Non-cannabis users/Cannabis users, n		15/2	5/2	13/1	X^2 = 1.92	0.21
Antipsychotic-free/AP-current, n		N/A	6/1	5/9	X^2 = 4.68	**0.03**
PET Parameters	**Amount injected (mCi)**	10.09 ± 0.71	9.75 ± 0.52	9.75 ± 0.65	F = 1.26	0.29
	Specific activity (mCi/μmol)	1804.99 ± 815.25	1849.93 ± 1170.70	1983.41 ± 902.34	F = 0.15	0.86
	Mass injected (μg)	2.65 ± 1.36	4.03 ± 4.48	2.26 ± 1.17	F = 1.58	0.22
Total PANSS Score		NA	NA	52.14 ± 15.58	NA	NA
SOPS Total Symptom Severity Score		NA	28.43 ± 16.06	NA	NA	NA
Total RBANS Score		N/A	95.14 ± 17.85	81.50 ± 16.74	t = -1.48	0.16

Significant difference in [^{11}C]SL25.1188 binding (V_T) between groups

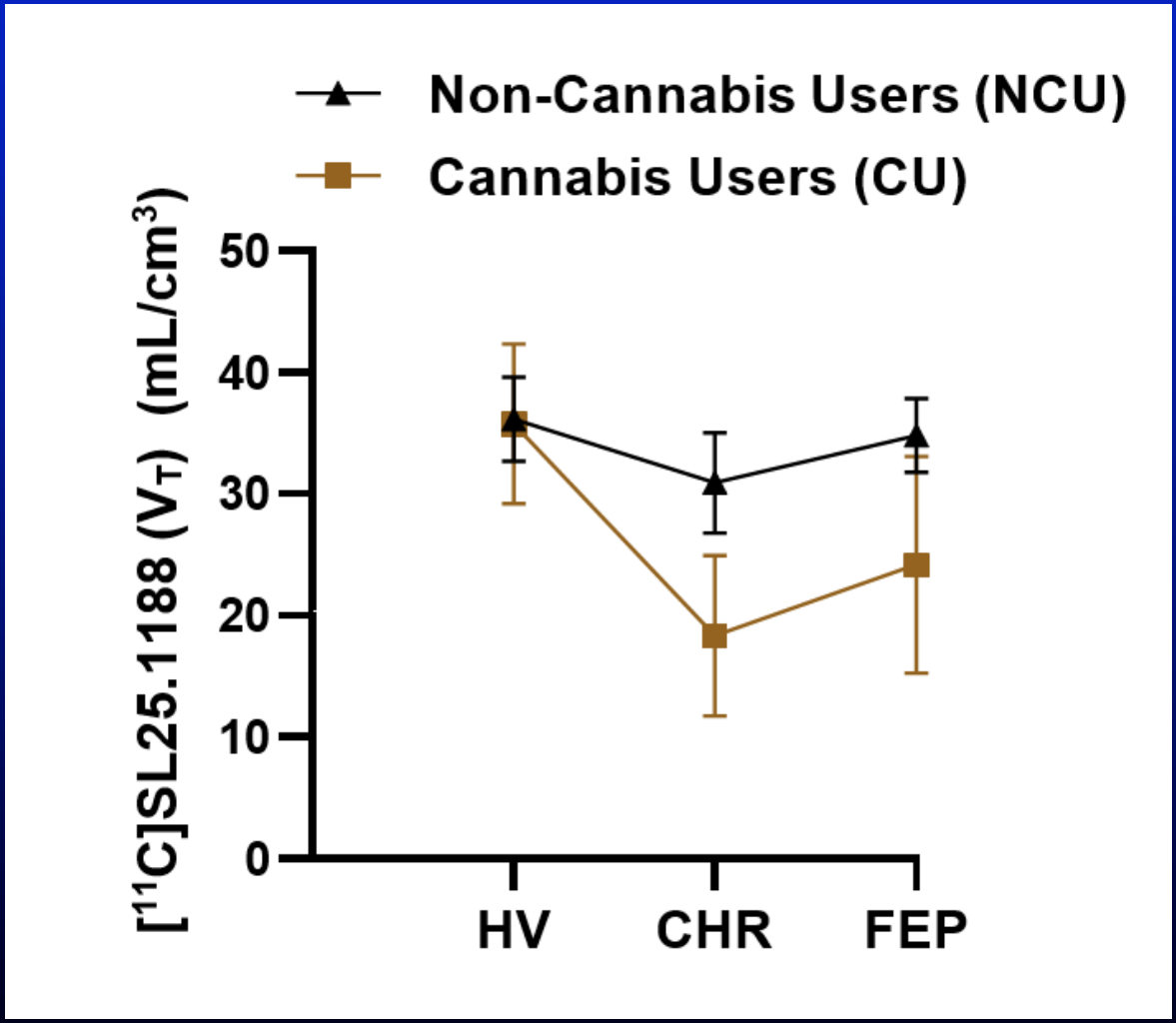




$F_{(2, 37.46)} = 4.56$, **p = 0.02**, **Cohen's f = 0.49**, ROI: ($F_{(6, 50.41)} = 264.62$, $p < 0.001$), controlling for **tobacco** ($F_{(1,37.46)} = 5.50$ p = 0.02) and **cannabis use** ($F_{(1,37.46)} = 5.05$ p = 0.03)

⬇ CHR vs. HVs (**p = 0.01**, **Cohen's d = 0.99**)

Significant effect of cannabis use on MAO-B *VT* and larger cannabis effects in Clinical groups vs. HV



Cannabis: F(1, 39.47) = 12.45, **p=0.001, Cohen's f = 0.56**, group effect: *F*(2, 38.47) = 11.29, p < 0.001

Group-by-cannabis interaction: F(2, 37.35) = 3.81, **p=0.03, Cohen's f = 0.45**, group effect: *F*(2, 38.47) = 11.29, p < 0.001

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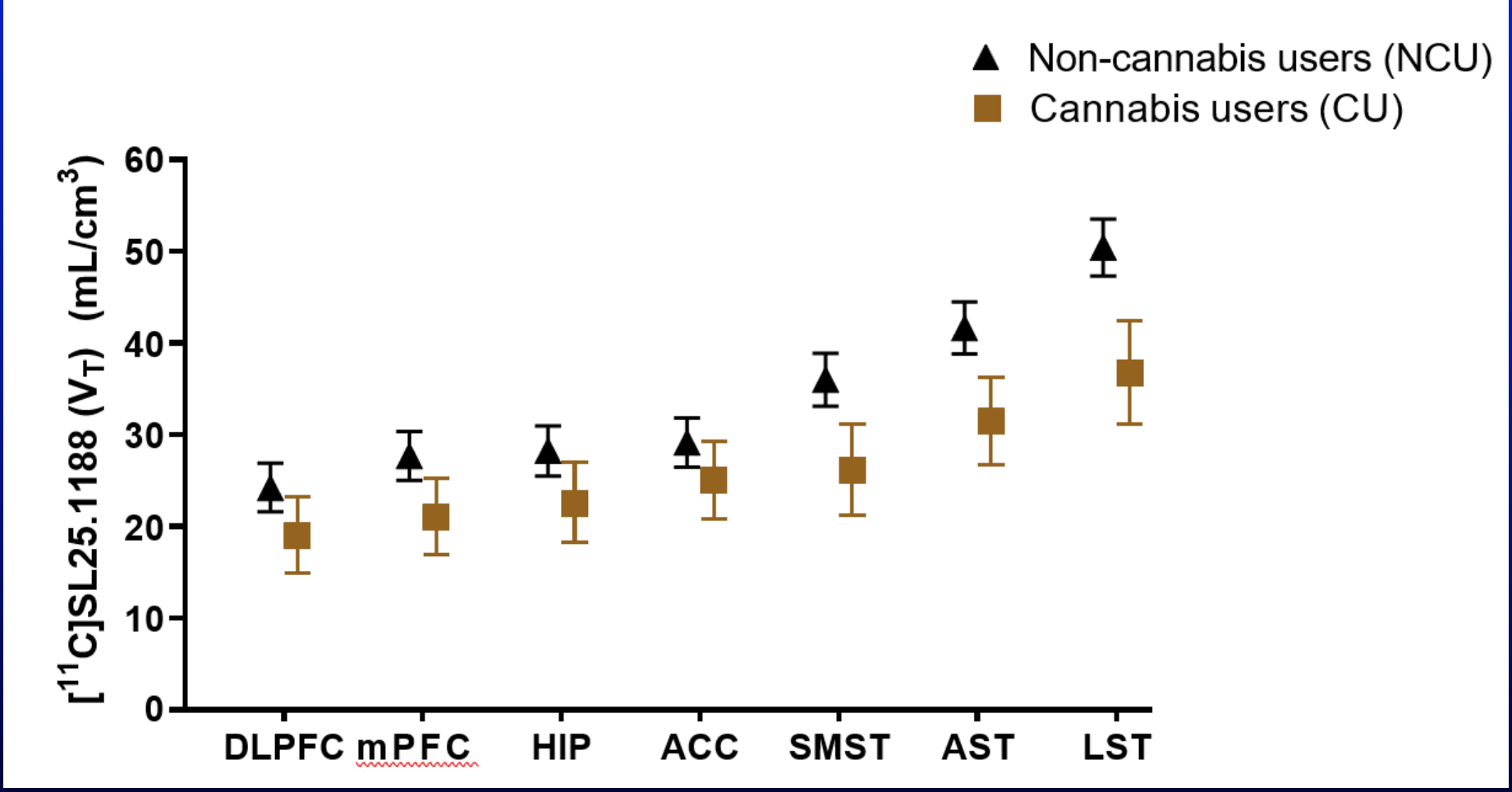
Larger cannabis effects on MAO-B *VT* in the striatal vs. cortical ROIs



Cannabis-by-ROI interaction ($F(6, 46.07) = 6.01$, **$p < 0.001$, Cohen's $f = 0.89$**; group effect: $F(2, 38.47) = 11.29$, $p < 0.001$)

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Altered MAO-B, an Astroglia Marker, in Early Psychosis with Cannabis Use

- We showed reduced MAO-B in cannabis-using CHR and FEP patients.
- Reduced MAO-B is consistent with the replicated striatal dopamine elevation in psychosis.
- Reduced MAO-B supports the involvement of astrocytes in glutamatergic processes, including psychosis and cannabis use.

Brain investigations beyond dopamine highlight the need to identify new targets to guide the development of novel treatments

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Imaging synaptic density with [^{11}F]SynVesT-1 PET in early stages of psychosis, critical effect of cannabis

Dr. M. Belen Blasco MD, PhD student

Blasco MB, Nisha Aji K, Ramos-Jiménez C, et al. Synaptic Density in Early Stages of Psychosis and Clinical High Risk. JAMA Psychiatry (2024)

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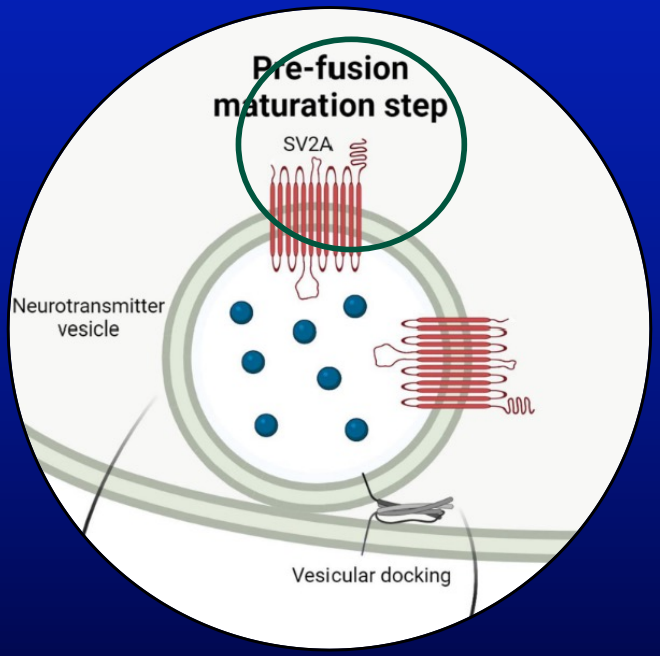
Synaptic vesicle glycoprotein 2A (SV2A) can be used to quantify synaptic density



Located in synaptic vesicles

The participation in key mechanisms of the vesicular processes is widely accepted (Rossi et al. 2022, *Front Neurosci*)

Ubiquitous distribution

Unlike SV2B and SV2C that are expressed mainly in cortical and subcortical structures respectively (Rossi et al. 2022, *Front Neurosci*)

Correlation with synaptic markers

It correlates highly with presynaptic markers considered gold standards in postmortem studies (e.g., synaptophysin) (Finnema et al. 2016, *Sci Transl Med*)

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Background - *PET Studies (SV2A)*

	Sample	n	Radiotracer	Duration of illness	Regions of Interest	Outcome
Onwordi, 2021[1]	SCZ	18	[^{11}C] UCB-J	17.4 ± 11.3	PFC, ACC, Hipp	SV2A V_T
Radhakrishnan, 2021[2]	SCZ	13	[^{11}C] UCB-J	17.3 ± 12.6	PFC, ACC, Hipp, Occ, Par, Temp	SV2A V_T
Yoon, 2023[3]	EP	9	[^{11}C] UCB-J	3.36 ± 2.38	Hipp, Put, STG, MFG	SV2A BP_{ND}
Onwordi, 2023[4]	EP	21	[^{11}C] UCB-J	2.67 ± 0.46	PFC, ACC, Hipp	SV2A V_T / DVR

EP: early psychosis, SCZ: schizophrenia, ACC, anterior cingulate cortex, Hipp: hippocampus, Put: Putamen, MFG = medial frontal gyrus, STG: superior temporal gyrus, Occ: occipital cortex, Par: parietal cortex, Temp: temporal cortex

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1. Onwordi EC, et al. Nat Commun. 2020 Jan 14;11(1):246.
2. Radhakrishnan R, et al. Mol Psychiatry. 2021 Dec;26(12):7690–8
3. Yoon JH, , et al. J Psychiatr Res. 2023 May;161:213–7.
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Objectives

- Investigate whether synaptic density (SV2A BP_{ND}) is reduced in FEP and CHR.
- Examine the relationship between synaptic density (SV2A BP_{ND}) and the severity of psychotic symptoms
- Investigate the effect of cannabis use on synaptic density

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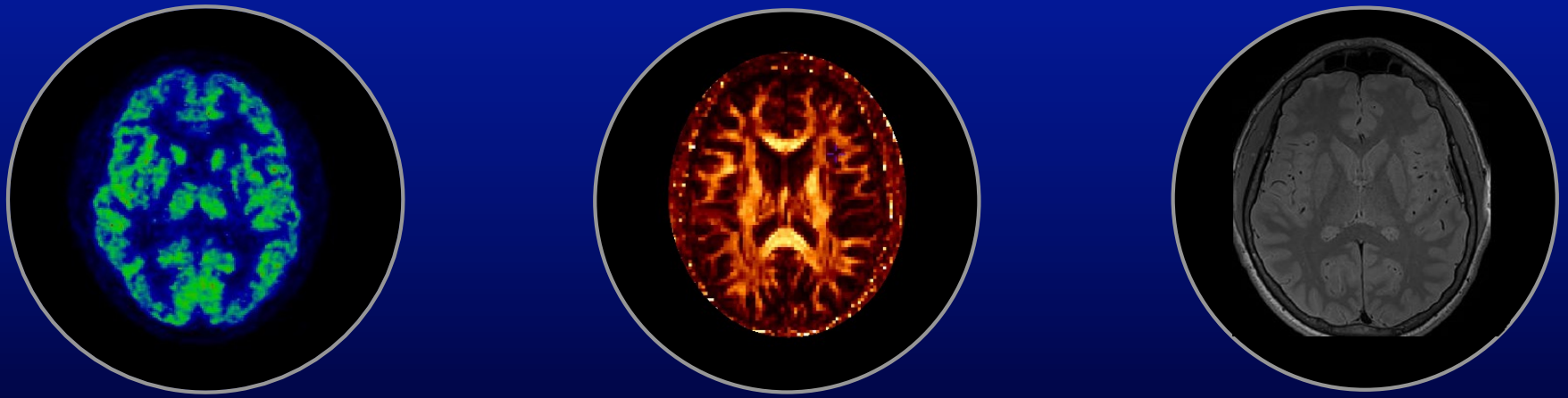
General methods – *Image acquisition*

MRI

[^{11}F]SynVesT-1 PET

Diffusion Weighted (DW)-MRI

Proton density weighted-MRI



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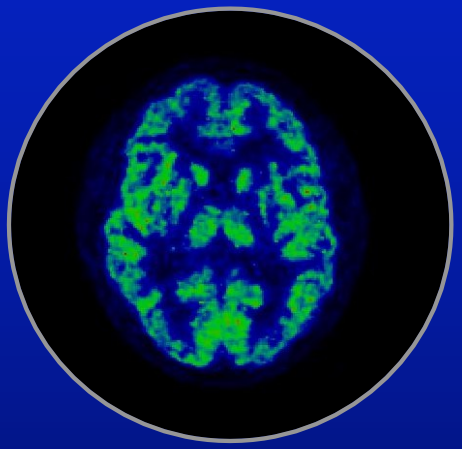
General methods – *Image acquisition*

[^{11}F]SynVesT-1 PET



MRI

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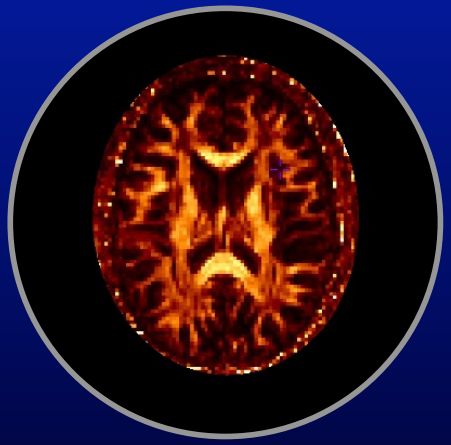
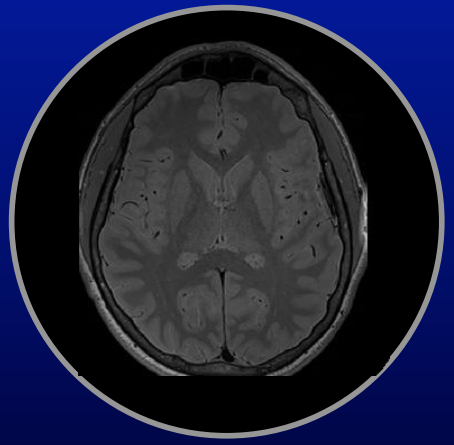


Proton density weighted-MRI



- 90-min [^{18}F]SynVesT-1 PET scan (205.07 ± 19.39 MBq).
- Simplified Reference Tissue Model (SRTM) using white matter as reference region
- SynVesT-1 BP_{ND}

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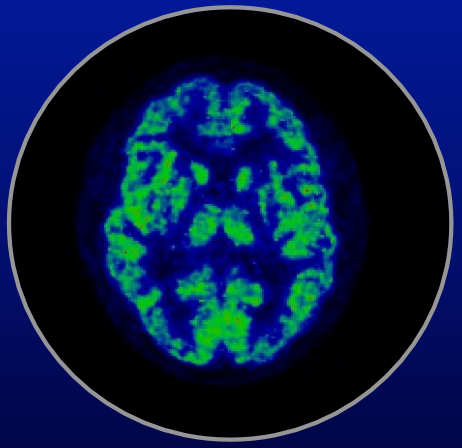
General methods – *Image acquisition*

[^{11}F]SynVesT-1 PET



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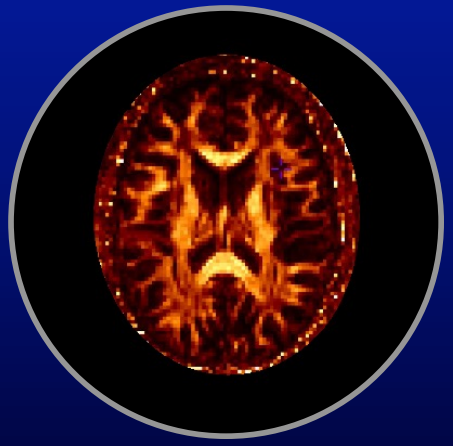

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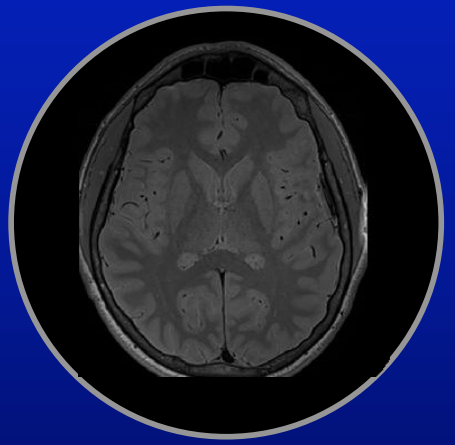

- Anatomical delineation of the regions of interest (ROIs) and co-registration with PET scans

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Table 1. Participants' demographic and clinical characteristics

Variable		HC (n=16)	CHR (n=17)	FEP (n=16)	Test statistic	p value
Age, Mean (SD), years		23.4 (3.6)	21.2 (3.4)	26.1 (4.6)	6.68[a]	<0.01
Male/Female, n		7/9	8/9	9/7	0.54[b]	0.76
BMI, Mean (SD), kg/m²		24.0 (3.5)	26.9 (8.5)	26.6 (4.9)	1.12[a]	0.34
Current substance use	Non-tobacco smokers/smokers, n	15/1	9/8	11/5	6.81[b]	0.03
	Non-cannabis users/cannabis users, n	14/2	10/7	11/5	3.40[b]	0.18
Antipsychotic use, AP-free/AP-current, n		N/A	11/6	1/15	12.17[b]	<0.01
PET Parameters, Mean (SD)	Amount injected, mCi	5.5 (0.44)	5.5 (0.33)	5.6 (0.74)	0.34[a]	0.71
	Specific activity, mCi/µmol	3482.3 (2215.3)	3729.6 (3193.8)	4087.1 (2232.5)	0.22[a]	0.80
	Mass injected, µg	0.72 (0.47)	0.79 (0.61)	0.56 (0.33)	0.93[a]	0.40
Total PANSS Score, Mean (SD)		N/A	N/A	62.9 (15.1)	N/A	N/A
SOPS Total Symptom Severity Score, Mean (SD)		N/A	38.2 (9.4)	N/A	N/A	N/A
Age at onset, Mean (SD), years		N/A	N/A	22.9 (4.6)	N/A	N/A
Duration of illness, Mean (SD), months		N/A	N/A	10.4 (11.4)	N/A	N/A

AP – Antipsychotic; BMI – Body Mass Index; CHR – Clinical high risk; N/A – Not applicable NA – Not Available; HC – Healthy controls, HRSD - Hamilton Depression Rating Scale; FEP – first episode psychosis; PANSS - Positive and Negative Syndrome Scale; SOPS - Scale of Prodromal Syndromes
Statistical analysis was performed using - [a]ANOVA F-test; [b]χ^2 test

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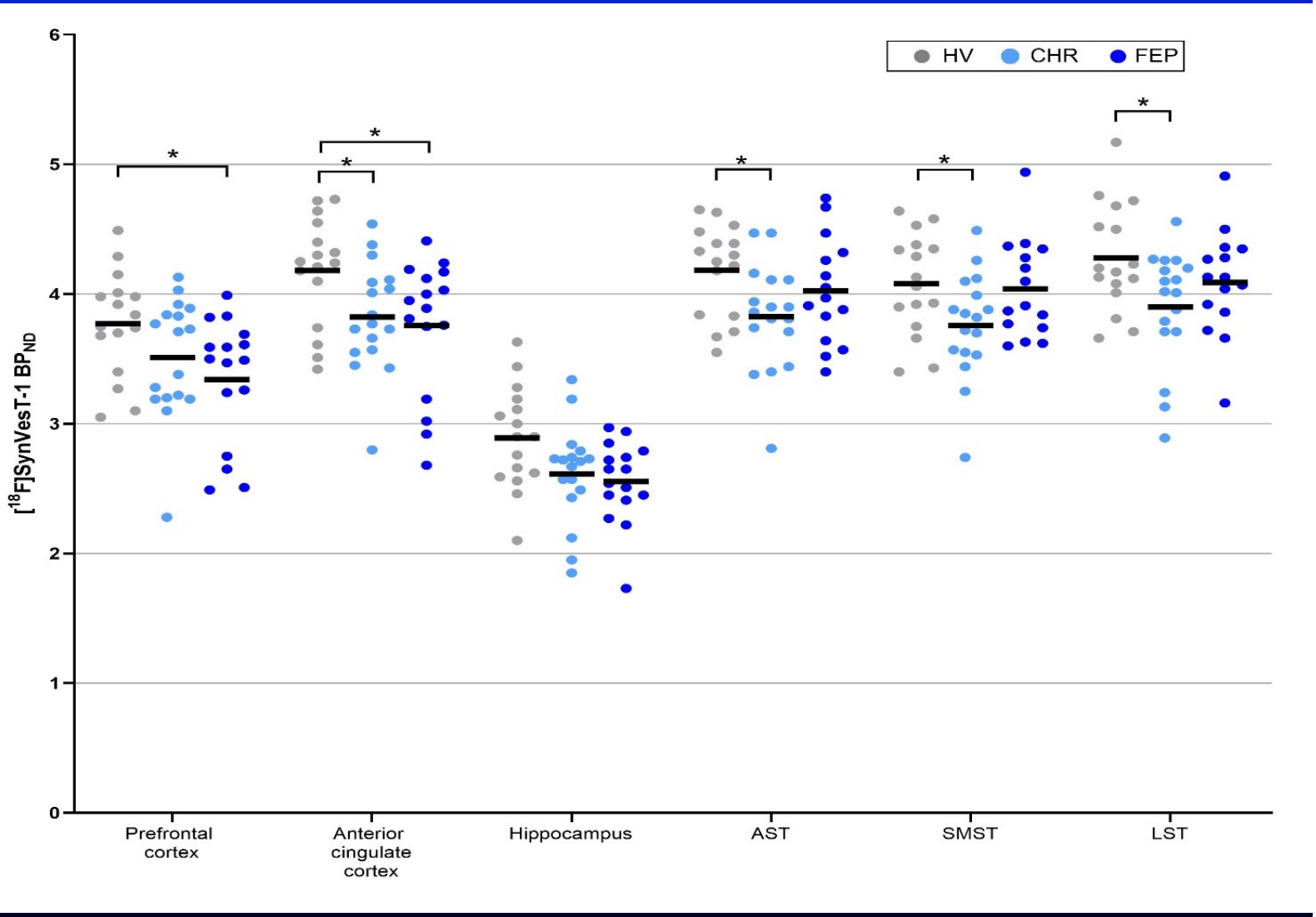
Synaptic density ([^{18}F]SynVesT-1 BP_{ND}) is different between groups

Group ($F_{2,273}$=4.02, p=0.02, Cohen's F=0.17);

ROI: $F_{5,273}$=360.18, p<0.01, Cohen's F=2.55) with a significant ROI by group interaction (Group*ROI: $F_{10,273}$=2.67, p<0.01 Cohen's F=0.32).



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Effect of group and covariates on synaptic density ([^{18}F]SynVesT-1 BP_{ND})

	Effects on all ROIs (SV2A)[1]								Effects on cortical ROIs (SV2A)[2]							
	Model fit		Group			Covariate			Model fit		Group			Covariate		
	AIC	BIC	F	p	Cohen's F	F	p	Cohen's F	AIC	BIC	F	p	Cohen's F	F	p	Cohen's F
No covariates	104.9	196.7	4.02	**0.02**	0.17	NA	NA	NA	52.6	79.5	4.22	**0.02**	0.24	NA	NA	NA
Anti-psychotics	106.9	228.4	3.41	**0.03**	0.16	<0.01	0.99	<0.01	53.2	83.1	1.83	0.16	0.16	1.39	0.24	0.10
Age	106.8	202.3	4.02	**0.02**	0.17	<0.01	0.94	<0.01	52.8	82.7	3.99	**0.02**	0.24	1.84	0.18	0.11
Sex	105.1	200.6	4.42	**0.01**	0.18	1.83	0.18	0.08	54.1	84.0	4.43	**0.01**	0.25	0.51	0.47	0.06
BMI	103.2	198.7	3.02	**0.05**	0.15	3.79	>0.05	0.12	52.6	82.5	3.43	**0.03**	0.22	2.01	0.16	0.12
Nicotine	105.3	200.8	2.54	0.21	0.14	1.56	0.08	0.08	54.5	84.4	3.69	**0.03**	0.23	0.05	0.82	0.02
Cannabis	101.8	197.3	2.66	0.07	0.14	5.31	**0.02**	0.14	51.8	81.7	3.31	**0.04**	0.22	2.88	0.09	0.14

[1]All models included ROI by Group interaction given that it showed a significant effect on synaptic density (SV2A BP_{ND}) with a large effect size ($F_{(4,138)}$=2.67, p<0.01, Cohen's F = 0.31).

[2]ROI by Group interaction was tested and removed after proven non-significant ($F_{(4,138)}$=1.53, p=0.20, AIC=54.9, BIC=93.5).

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The severity of negative symptoms is associated with synaptic density ([^{18}F]SynVesT-1 BP_{ND})

PANSS-Negative score: F(1,81)=4.31, *p*=0.04, Cohen's F=0.23

SANS score: F(1,81)=5.75 *p*=0.02, Cohen's F=0.27;

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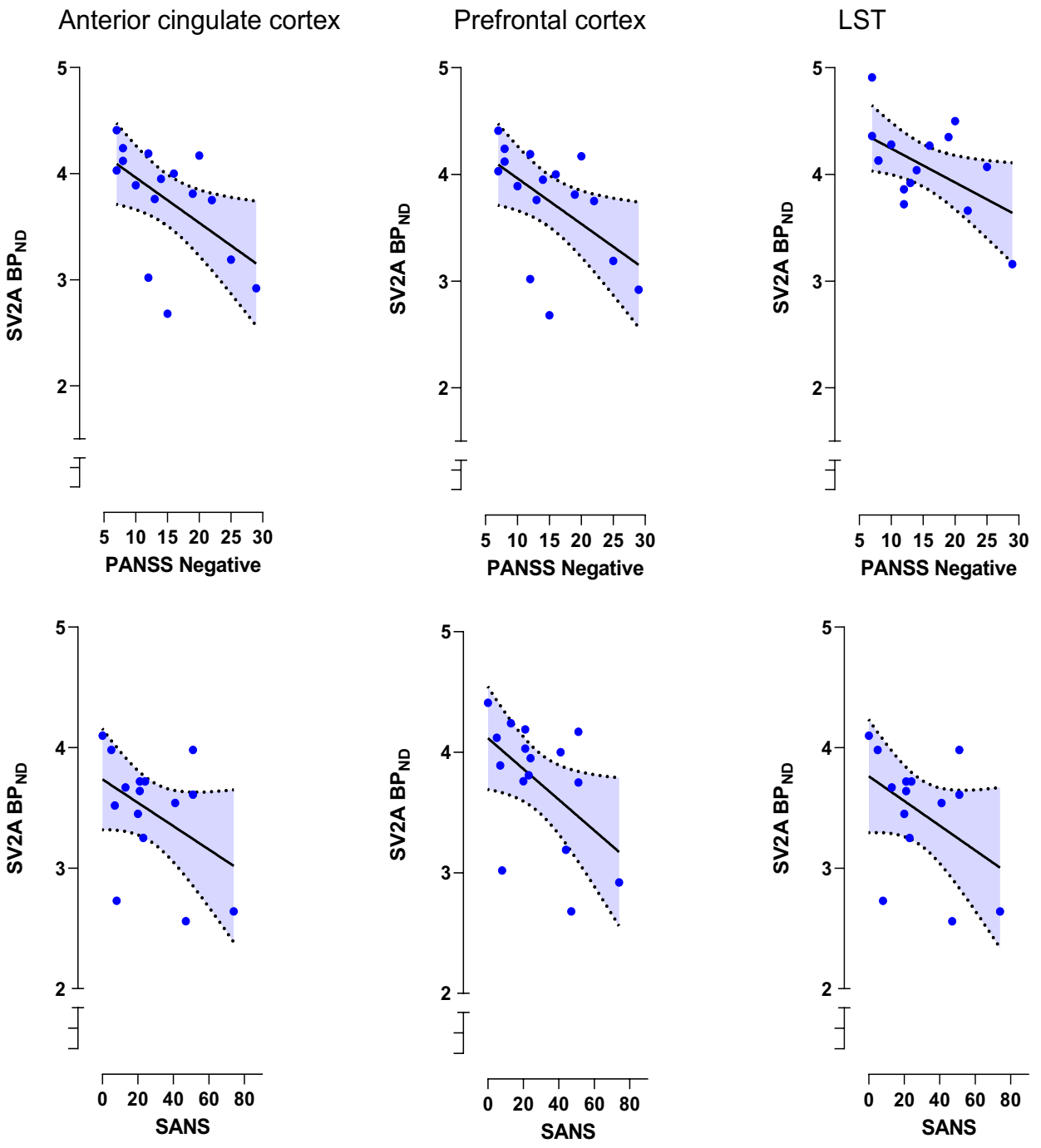
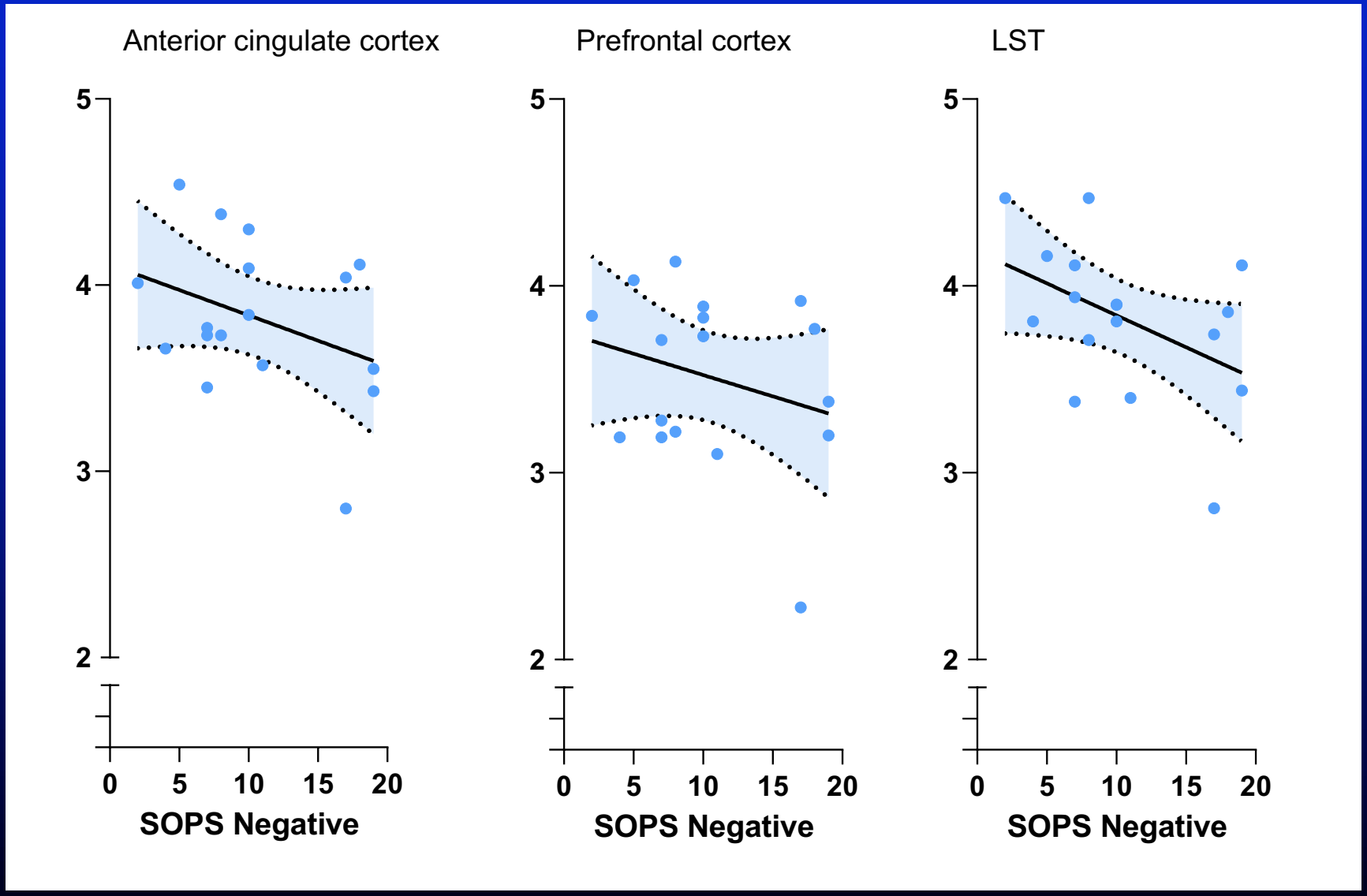


The severity of negative symptoms is associated with synaptic density ([18F]SynVesT-1 BP_{ND})



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SOPS- Negative score: F(1,90)=4.12, *p*=0.04, Cohen's F=0.21

Discussion

Lower synaptic density in FEP and CHR, with a significant effect of cannabis use (in striatal regions)

FEP cohort with a mean duration of illness three times shorter than previously investigated (<1 vs 3 years)

Evidence of synaptic alterations during CHR states (ACC, striatum)

Significant association between synaptic density and negative symptoms (both in CHR and FEP)

SV2A may serve as a molecular target in intervention trials in CHR and FEP, especially for negative symptoms.

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Trainees: E-mail me, if you want to come to Montreal for a postdoc or PhD!

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C4A -> microglia -> pruning -> Synapses

Given the role of complement proteins in mediating microglial engulfment of synaptic material, it is possible that genetically predicted brain C4A expression relates to TSPO and brain morphology in-vivo.

AIM 1: To investigate the association between genetically predicted brain C4A expression and a) TSPO and b) Cannabis use

We hypothesized that C4A will be associated with TSPO and brain morphology. We also hypothesized higher C4A in patient populations

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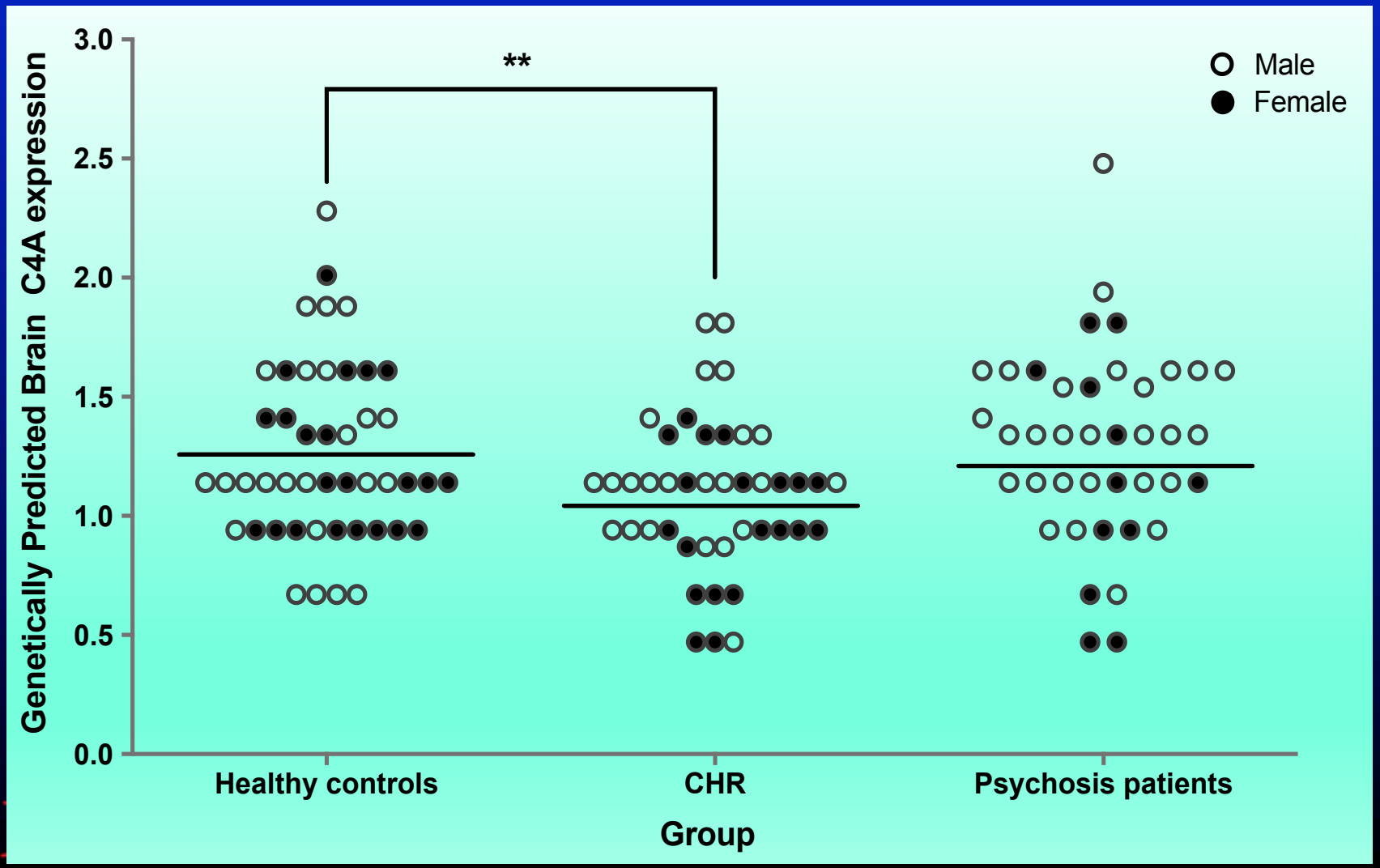
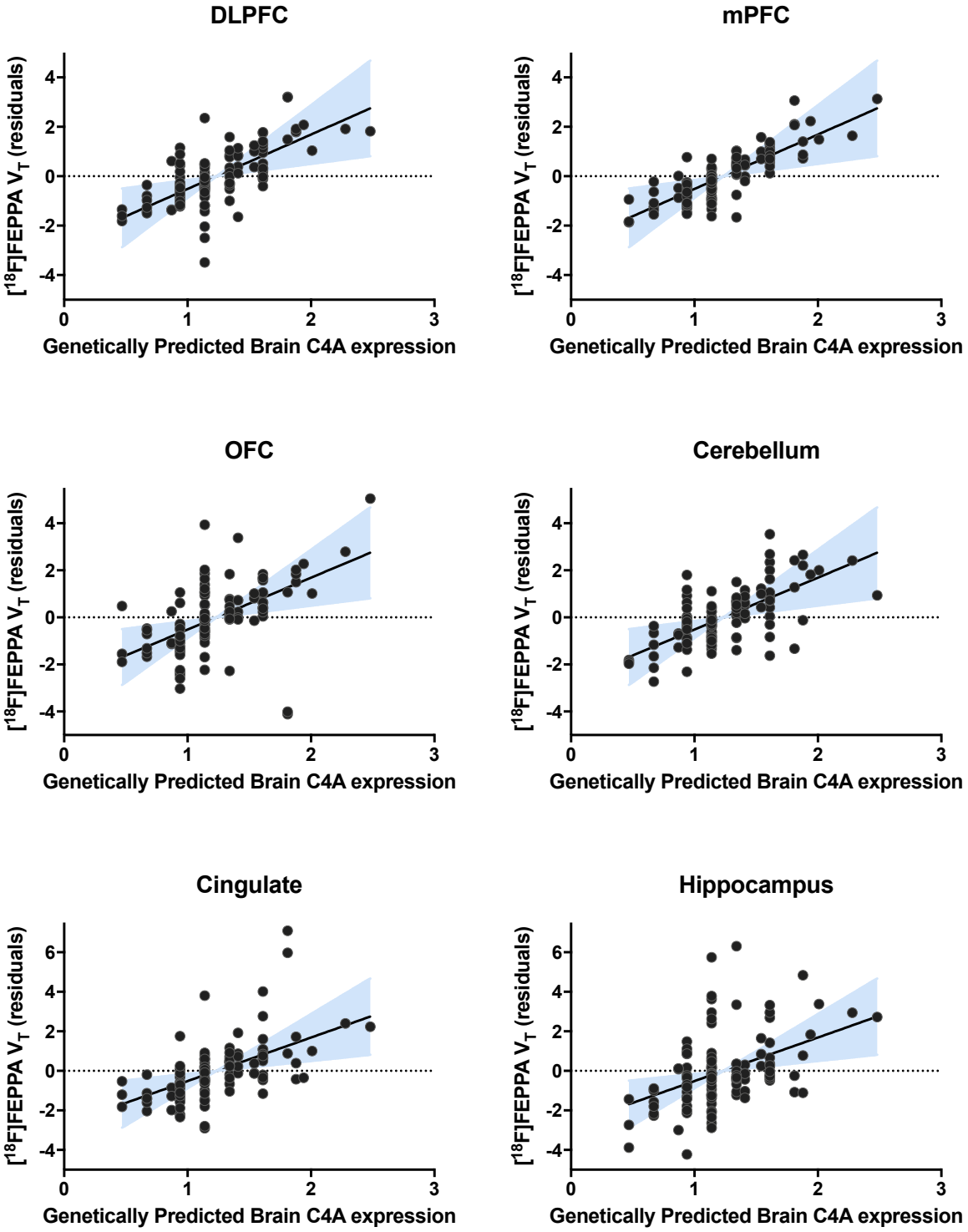
Da Silva et al, Biol Psychiatry 2021

Demographics and Clinical Variables		Healthy Controls (n=46)	Clinical High Risk for Psychosis (n=43)	Psychosis Patients (n=40)	
Age (years)		23.00 ± 4.20	20.81 ± 2.13	31.78 ± 12.27	F=25.34, p<0.001
Sex	Male/female	24/22	23/20	28/12	χ^2=3.37, p=0.19
TSPO Genotype[1]	HAB/MAB	32/10	21/16	25/9	χ^2=3.94, p=0.14
PET parameters[1]	Amount injected (mCi)	4.96 ± 0.34	5.08 ± 0.23	4.94 ± 0.62	F=1.16, p=0.32
	Specific activity (mCi/μmol)	1973.44 ± 2055.18	1639.08 ± 1112.41	2703.55 ± 2301.43	F=2.93, p=0.06
	Mass injected (μg)	1.61 ± 1.12	1.84 ± 1.50	1.07 ± 0.63	F=4.20, p=0.02
Antipsychotics	Current	—	7	17	
	<250 mg/day CPZ equivalents	—	7/7	10/17	
Drug use (current)	Nicotine	9	11	16	
	Cannabis	27	8	2	
PANSS		—	—	65.00 ± 12.17	
SOPS		—	35.84 ± 11.60	—	
AES[2]	Apathy scores	30.02 ± 7.48	40.24 ± 9.33	33.68 ± 8.43	
SHAPS[2]	Anhedonia scores	1.13 ± 1.80	3.15 ± 3.05	1.75 ± 2.82	

Significant effect of clinical group on genetically predicted brain C4A ($F(2,124)=4.25$, $p=0.016$), such that CHR had lower C4A compared with healthy controls (post hoc $p=0.028$).





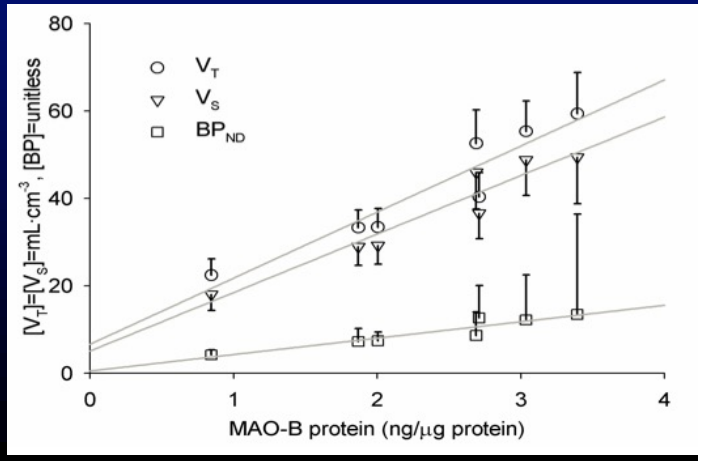
- Genetically predicted brain C4A expression was significantly associated with TSPO levels (n=111, main effect of C4A expression: $F_{(1,111)=}$ 7.91, p=0.006)
- There was a significant sex effect (main effect of sex: $F_{(1,111)=}$ 11.96, p=0.001), and current cannabis use (main effect of cannabis use: $F_{(1,111)=}$ 6.89, p=0.01) → males and cannabis users had higher TSPO levels, with no clinical group effect.

Monoamine oxidase B (MAO-B)

- Confined to the outer mitochondria within astrocytes and serotonergic neuronal cell bodies.
- Catalyze the oxidative deamination of monoamine neurotransmitters, including dopamine, norepinephrine (etc).
- MAO-B is critically engaged in hydrogen peroxide synthesis, thus involved in mitochondrial dysfunction and/or oxidative stress also described in psychosis pathophysiology.
- MAO-B expression is significantly increased in reactive astrocytes (hippocampus and frontal cortex in AD), and MAO-B inhibitors can reduce astrogliosis (neuroprotective).
- Glial fibrillary acidic protein (GFAP), a sensitive and reliable marker for astrogliosis demonstrate high correlations with MAO-B (Tong J et al. 2017)

[^{11}C]SL25.1188 a valid radioligand to quantify MAO-B in brain

- Increased MAO-B selectivity & sensitivity as compared to previous MAO-B radioligands.
- Good reproducibility (*mean regional absolute difference in MAO-B V_T of 11 to 13%*) and identifiability (COV(V_T)<8%)
- MAO-B can be used as a reliable reactive astroglial marker, supported by the significant increase in MAO-B levels in autopsied striatums of patients with multiple system atrophy, a disease characterized by marked increase in astrogliosis.
- **Very high correlation between regional MAO-B V_T and MAO-B density in autopsied brain (r^2=0.9).**



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