

# Sex and dependence related neuroanatomical differences in regular cannabis users: findings from the ENIGMA Addiction

## Working Group

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### **Assessment instrument by imaging site**

Supplementary Table S1 shows differences in behavioral, mental health, substance use and MRI assessment tools by imaging site. Cannabis use was measured as grams, joints and cones or as occasions of use. Grams and joints were converted to ‘cones’ as cones is a standardized unit for comparisons (e.g., 1g = 12 cones, 1 paper joint = 3 cones; see guidelines provided at <https://cannabissupport.com.au/media/1593/timeline-followback.pdf>). Alcohol and tobacco use was quantified as standard drinks and number of cigarettes respectively, as well as days/occasions of use. For statistical analyses we adopted the measures that were more consistently used across sites including, age of onset of use and monthly cones for cannabis; monthly standard drinks for alcohol and monthly cigarettes for tobacco (measures expressed in days/weeks were previously converted to months). The Intelligent Quotient (IQ) was estimated using the Dutch version of the National Adult Reading Test (DART) (1) (site 1); the National Adult Reading Test (NART) (2) (site 3) and The Wechsler Abbreviated Scale of Intelligence (WASI) (3) (site 4). The vocabulary subscale score of the Wechsler Adult Intelligence Scale, 3<sup>rd</sup> ed. (WAIS-III) (4) from the site 2 was converted to an estimated full scale IQ by standardizing to the average IQ of cannabis users and controls respectively of the remaining sites (5).

**Supplementary Table S1. Assessment instruments by imaging site**

	<i>Site 1 Amsterdam</i> <sup>(6)</sup> (N =73)	<i>Site 2 Barcelona</i> <sup>(7)</sup> (N=59)	<i>Site 3 Wollongong</i> <sup>(8)</sup> (N=34)	<i>Site 4 Melbourne</i> <sup>(9)</sup> (N=101)
<b>Inclusion criteria</b>				
Cannabis group	≥ 10 days/mo, ≥ 240 days over last 2 yrs	First use age < 16, 14-28 joints/week over last 2 yrs	≥ 3-4 times/wk	≥ 2 days/mo for at least 2 yrs
Control group	< 50 joints/lifetime, did not use in last mo	< 15 lifetime experiences with cannabis	No lifetime history of regular cannabis use, did not use in last yr	<= 10 times/lifetime, did not use in last yr
<b>Exclusion criteria, all participants</b>				
IQ	< 80	< 90		< 70
Axis I psychiatric disorders	MINI	PRISM	SCID	SCID
Illicit substance use other than cannabis	> 100 times/lifetime	> 5 times/lifetime	√	> 50 times/past 10 yrs
Positive toxicology (urine) test	√	√	√	√
Female		√		
MR contraindication	√	√	√	√
Use of psychoactive medication	√	√	√	√
Left-handed		√	√	
<b>Assessment tools</b>				
IQ	DART	WAIS-III vocabulary subscore	NART	WASI
<b>Cannabis use</b>				
Onset of use, yrs	√	√	√	√
Frequency	Days/wk		Days/mo	Days/mo
Dosage	Grams/wk,	Joints/day	Cones/mo	Cones/mo
Dependence	MINI – score >= 3 as dependent	SDS – score >= 4 as dependent	SCID	SDS – score >= 4 as dependent
<b>Alcohol use</b>				
Frequency				
Dosage	StDr/mo	StDr/wk	StDr/wk	StDr/mo
<b>Tobacco use</b>				
Frequency				
Dosage	Cig/day	Cig/day	Cig/day	Cig/mo

Wk = week, mo = month, yrs = years, occ= occasions, StDr = standard drinks, cig = cigarettes, MINI = Mini Neuropsychiatry International Interview (10), PRISM = Psychiatric Research Interview for Substance and Mental Disorders (<http://www.columbia.edu/~dsh2/prism/>) (11), SCID = Structured Clinical Interview for DSM Disorders (12), DART = Dutch version of the National Adult Reading Test (1), WAIS-III = Wechsler Adult Intelligence Scale – Third Edition (4), NART = National Adult Reading Test (2), WASI = Wechsler Abbreviated Scale of Intelligence (3), SDS = Severity of Dependence Scale (13)

**Supplementary Table S2. Scanners parameters by imaging site**

	<b>Site 1 Amsterdam (N =73)</b>		<b>Site2 Barcelona (N=59)</b>	<b>Site 3 Wollongong (N=34)</b>		<b>Site 4 Melbourne (N=101)</b>
Manufacturer and Model	Phillips Intera	GE Signa Ecite		Phillips Intera		Siemens Trio
Field Strength (Tesla, T)	3	1.5		3		3
Number of Channels	8	8		8		32
Repetition Time, TR (ms)	9600	11.8		6.4		1900
Echo Time, TE (ms)	4.6	4.2		2.9		2.15
Sequence	Turbo field echo	3D inversion recovery prepared fast spoiled gradient		3D spoiled gradient-recalled echo		MPRAGE

**Supplementary Table S3. Demographic and substance use characteristics of participants from the three-site subsample with data for cannabis dependence status (Mean (SD))**

	HC		Recreational CB		Dependent CB		<i>Group</i> (dependent CB vs recreational CB)		<i>Group</i> (dependent CB vs HC)		<i>recreational CB vs HC)</i>		<i>Sex</i> (Males vs Females)		<i>Group-by-Sex</i>		Site <sup>§</sup>
	Males	Females	Males	Females	Males	Females	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>	Var
	Sex, N	65	33	29	20	42	17	-	-	-	-	-	-	-	-	-	-
Age, yrs	24.02 (7.20)	25.50 (9.06)	23.74 (8.62)	31.75 (11.20)	24.91 (8.07)	26.46 (9.12)	-3.32 (- 6.20, 0.46)	.023*	1.08 (-3.62, 1.45)	.401	2.24 (-0.27, 4.75)	.080	-0.11 (- 2.45, 2.23)	.924	1.24	.624	.30
IQ	108.18 (12.57)	106.21 (11.70)	99.66 (14.02)	104.15 (9.32)	99.83 (12.00)	98.53 (11.08)	-2.66 (- 7.41, -2.08)	.271	-8.42 (- 12.60, 4.23)	<.001***	-5.75 (-9.91, 1.59)	<.007**	1.71 (-2.09, 5.52)	.377	-0.27 (-8.51, 7.97)	.948	.06
Alcohol, StDr/mo	19.72 (22.98)	17.60 (23.10)	28.21 (37.38)	17.05 (23.06)	32.93 (40.01)	20.82 (14.81)	4.30 (-7.10, 15.70)	.460	7.28 (-2.77, 17.32)	.156	2.98 (-7.01, 12.96)	.559	13.04 (3.93, 22.16)	.005	10.89 (- 8.911, 30.69)	.281	.04
Tobacco, Cig/mo	25.50 (94.69)	51.09 (110.03)	207.65 (236.98)	289.97 (266.93)	220.98 (207.70)	242.00 (211.00)	-17.71 (- 52.82, 88.23)	.623	192.19 (- 130.32, 254.06)	<.001***	209.90 (147.75, 272.04)	<.001***	-40.08 (- 93.65, 13.50)	.143	5.34 (- 118.04, 128.73)	.932	.00
Cannabis Onset of use, yrs	-	-	14.97 (1.88)	15.70 (2.47)	15.19 (1.71)	14.41 (1.66)	-0.68 (- 1.82, 0.46)	.245	-	-	-	-	0.73 (-0.26, 1.71)	.149	0.07 (-2.19, 2.34)	.949	.05
Dosage, cones/mo	-	-	252.66 (191.88)	200.90 (228.56)	334.76 (317.09)	318.12 (191.10)	84.44 (13.17, 155.16)	.019*	-	-	-	-	52.22 (- 4.71, 109.17)	.072	29.84 (- 92.87, 152.56)	.634	.07
ICV, 10 <sup>6</sup>	1.60 (0.15)	1.40 (0.17)	1.54 (0.14)	1.34 (0.19)	1.57 (0.15)	1.48 (0.14)	0.05 (-0.00, 0.11)	.059	-0.01 (-0.06, 0.04)	.763	-0.06 (-0.11, 0.01)	.014	0.17 (-0.22, 0.13)	<.001***	-0.09 (-0.18, 0.01)	.079	.19

$\beta$  = beta; CB = cannabis users; CI = confidence interval; Cig = cigarettes; Cones = standardized measure of cannabis dosage, see <https://cannabissupport.com.au/media/1593/timeline-followback.pdf>; HC = controls; ICV = Intracranial volume; IQ = Intelligence quotient; mo = monthly; StDr = Standard drinks; Var = Variation, yrs = years. § Site level variation based on intraclass correlation (ICC). Differences between groups for sex distribution were measured with chi<sup>2</sup> test ( $\chi^2=1.73, p = 0.42$ ).

\*  $p(unc) < .05$ , \*\* $p(unc) < .01$ , \*\*\*  $p(unc) < .001$ .

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