

Appendix 1 to Koenders L, Machielsen M, Van der Meer FJ, et al. Brain volume in male patients with recent onset schizophrenia with and without cannabis use disorders. *J Psychiatry Neurosci* 2014.

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Table S1: Results of the linear regression analysis of age at onset of regular cannabis use and brain volume, calculated in the CUD group (n = 74), adjusted for age, slice thickness and intracranial volume

Brain region	β	SE _{β}	p value*
Total grey matter†‡	-2580.3	1674.92	0.13
Hippocampus†	-21.1	15.3	0.17
Amygdala†	10.0	9.8	0.31
Thalamus†‡	-67.0	31.1	0.04
Caudate†	2.0	20.8	0.91
Putamen†	63.2	35.4	0.08
OFC§	-75.9	53.3	0.16
ACC§	-26.3	27.4	0.34
Insula§	-20.3	28.7	0.48
Parahippocampal gyrus§	12.7	13.7	0.36
Fusiform gyrus§	80.1	63.3	0.21

ACC=anterior cingulate cortex; OFC=orbitofrontal gyrus; SE = standard error.

*Significant from $p < 0.01$.

†Based on the FreeSurfer segmentation output.

‡Significant interaction between age at onset and intracranial volume.

§Brain region based on the FreeSurfer Desikan-Killiany Atlas.

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Table S2: Results of the linear regression analysis of frequency of use and brain volume, calculated in the CUD group. All results are adjusted for age, slice thickness and intracranial volume (ICV).

Brain region	Frequency, mean ± SD		F	p value*
	Daily (n = 57)	Weekly or less (n = 22)		
Total grey matter†‡	475973 ± 43173	488121 ± 58969	0.12	0.73
Hippocampus†	4273 ± 377	4118 ± 601	0.00	0.99
Amygdala†	1768 ± 209	1720 ± 278	0.58	0.57
Thalamus†	7246 ± 721	7516 ± 890	1.91	0.17
Caudate†	4005 ± 447	4310 ± 518	5.70	0.019
Putamen†	6407 ± 776	6259 ± 909	0.24	0.63
OFC§¶	13126 ± 1401	13538 ± 1736	2.63	0.11
ACC§	4689 ± 687	4866 ± 800	0.59	0.45
Insula§**	7104 ± 680	7043 ± 846	0.40	0.53
Parahippocampal gyrus§	2335 ± 318	2305 ± 322	0.45	0.51
Fusiform gyrus§	10349 ± 1355	10324 ± 1723	0.36	0.55

ACC=anterior cingulate cortex; OFC=orbitofrontal cortex; SE = standard error.

*Significant from $p < 0.01$.

†Based on the FreeSurfer segmentation output.

‡Significant interaction between the frequency of drug use and age.

§Based on the FreeSurfer Desikan-Killiany Atlas.

¶Significant interaction between the frequency of drug use and intracranial volume.

**Significant interaction between slice thickness and intracranial volume.

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Table S3: Results of the mixed model analyses of the effect of group on brain volume, with exclusion of patients with polysubstance use*

Brain region	Group, mean ± SD						CUD v. control				NCUD v. control				CUD v. NCUD					
	CUD, n = 50		NCUD, n = 33		Control, n = 84		F	p value	β	SE _β	p value	d	β	SE _β	p value	d	β	SE _β	p value	d
total GM ^a	472895	49413	506359	48802	496952	44090	1.53	.22												
hippocampus ^a	4277	445	4331	478	4337	417	.70	.50												
amygdala ^a	1763	225	1678	199	2042	224	30.07	<.001	-313.0	62.5	<.001	1.45	-372.0	50.3	<.001	1.55	-58.9	63.3	.35	
thalamus ^a	7259	669	7460	784	7157	639	1.76	.18												
caudate ^a	4043	480	4018	436	4197	420	1.93	.15												
putamen ^{a,c}	6364	818	5942	742	6885	687	21.18	<.001	-1505.8	433.4	.001	1.00	-1141.5	185.7	<.001	1.33	364.3	431.1	.40	.53
OFC ^b	13099	1570	14340	1614	13511	1361	3.26	.04												
ACC ^b	4597	681	4819	740	4908	880	.35	.70												
insula ^a	6994	703	7485	771	7551	879	5.17	.007	-557.5	174.0	.002	.58	-139.6	140.2	.32		417.9	176.3	.02	
parahip. ^{b,c}	2320	298	2188	260	2566	321	28.16	<.001	-783.4	177.8	<.001	.79	-526.9	76.2	<.001	1.24	256.6	176.9	.15	
fus. gyrus ^b	10276	1492	10263	1130	11415	1191	14.7	<.001	-1520.9	346.7	<.001	.80	-1296.4	279.3	<.001	.87	224.7	351.3	.53	

Note: CUD=Cannabis Use Disorder; NCUD=Non-Cannabis Use Disorder; HC=Healthy Controls; M=Mean; SD=Standard Deviation; SEβ=Standard Error of beta; p=p-value, significant from p<.01; d=Cohen's d, measure of effect size, only calculated for significant areas; Total GM= total cortical grey matter; OFC=orbitofrontal gyrus; ACC=anterior cingulate gyrus; parahip=parahippocampal gyrus; fus. gyrus=fusiform gyrus; abased on the FreeSurfer segmentation output; bbased on the FreeSurfer Desikan-Killiany Atlas; csignificant interaction between group status (i.e. CUD, NCUD or HC).

*Pair-wise comparisons are only reported for ROIs with a significant effect of group status on brain volume. All results are adjusted for age, slice thickness and intracranial volume (ICV).

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Table S4: Results adjusted for nicotine use. Means, standard deviations and the results of the mixed model analyses of the effect of group (i.e. CUD, NCUD, HC) on brain volume. Pair-wise comparisons are only reported for ROIs with a significant effect of group status on brain volume. All results are adjusted for age; slice thickness, intracranial volume (ICV) and nicotine use (y/n).

Brain region	CUD (n = 50)		NCUD (n = 33)		HC (n = 84)		CUD v. HC				NCUD v. HC				CUD v. NCUD						
	M	SD	M	SD	M	SD	F	p	β	SE _β	p	d	β	SE _β	p	d	β	SE _β	p	d	
total GMa	472895	49413	506359	48802	496952	44090	1.69	.19													
hippocampus	4277	445	4331	478	4337	417	.75	.48													
amygdalaa	1763	225	1678	199	2042	224	26.47	<.001	-270.5	59.8	<.001	1.24	-363.5	51.6	<.001	1.73	-93.0	61.0	.13		
thalamusa	7259	669	7460	784	7157	639	2.66	.07													
caudatea	4043	480	4018	436	4197	420	1.46	.24													
putamena,c	6364	818	5942	742	6885	687	13.65	<.001	-482.6	202.9	.02		-912.3	174.8	<.001	1.33	-429.7	206.9	.04		
OFCb	13099	1570	14340	1614	13511	1361	3.73	.03													
ACCb	4597	681	4819	740	4908	880	3.73	.03													
insulab	6994	703	7485	771	7551	879	3.73	.03	-115.3	142.5	.42		407.3	168.7	.02		-115.3	142.5	.42		
parahip.b,c	2320	298	2188	260	2566	321	23.87	<.001	-473.3	69.2	<.001	1.23	-177.9	81.9	.03		-473.3	69.2	<.001	1.23	
fus. gyrusb	10276	1492	10263	1130	11415	1191	13.93	<.001	-1374.9	328.7	<.001	.80	-1315.5	283.2	<.001	.87	-59.5	335.3	.86		

Note: CUD=Cannabis Use Disorder; NCUD=Non-Cannabis Use Disorder; HC=Healthy Controls; M=Mean; SD=Standard Deviation; SE_β=Standard Error of beta; p=p-value, significant from p<.01; d=Cohen's d, measure of effect size, only calculated for significant areas; Total GM= total cortical grey matter; OFC=orbitofrontal gyrus; ACC=anterior cingulate gyrus; parahip=parahippocampal gyrus; fus. gyrus=fusiform gyrus; ^abased on the FreeSurfer segmentation output; ^bbased on the FreeSurfer Desikan-Killiany Atlas; ^csignificant interaction between group status (i.e. CUD, NCUD or HC) and nicotine use (i.e. yes/no).

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Table S5: Pair-wise comparisons of the ROIs with a significant effect of group status (i.e. CUD, NCUD or HC) on cortical thickness (ACC, insula, parahippocampus and fusiform gyrus; see Table 5). All results are adjusted for age, slice thickness and mean cortical thickness, weighted by surface area. All ROIs are based on the FreeSurfer Desikan-Killiany Atlas.

Brain region	CUD v. HC				NCUD v. HC				CUD v. NCUD			
	β	SE $_{\beta}$	<i>p</i>	<i>d</i>	β	SE $_{\beta}$	<i>p</i>	<i>d</i>	β	SE $_{\beta}$	<i>p</i>	<i>d</i>
ACC	-.0919	.0287	.002	.42	-.0838	.0934	.023		.0081	.0382	.83	
insula	-.1591	.0201	<.001	.93	-.1817	.0274	<.001	.95	-.0226	.0267	.57	
parahip	-.2066	.0402	<.001	.76	-.3549	.0549	<.001	1.22	-.1483	.0560	.03	
fus. gyrus	-.1749	.0220	<.001	1.01	-.2019	.0299	<.001	1.10	-.0271	.0292	.57	

Note: CUD=Cannabis Use Disorder; NCUD=Non-Cannabis Use Disorder; HC=Healthy Controls; *d*=Cohen's *d*, measure of effect size, only calculated for significant ROIs; SE $_{\beta}$ =Standard Error of beta; *p*=*p*-value, significant from *p*<.02; ACC = anterior cingulate gyrus; parahip= parahippocampal gyrus; fus. gyrus=fusiform gyrus.

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Table S6: Pair-wise comparisons of the ROIs with a significant effect of group status (i.e. CUD, NCUD or HC) on cortical surface area (orbitofrontal cortex and insula; see Table 5). All results are adjusted for age, slice thickness and total surface area. Both ROIs are based on the FreeSurfer Desikan-Killiany Atlas.

Brain region	CUD v. HC				NCUD v. HC				CUD v. NCUD			
	β	SE $_{\beta}$	p	d	β	SE $_{\beta}$	p	d	β	SE $_{\beta}$	p	d
OFC	-64.9	46.1	.16		212.2	58.8	<.001	.31	147.4	58.1	.01	.54
insula	80.4	32.9	.02	.01	165.8	41.9	<.001	.53	85.4	41.5	.04	

Note: CUD=Cannabis Use Disorder; NCUD=Non-Cannabis Use Disorder; HC=Healthy Controls; d =Cohen's d , measure of effect size, only calculated for significant ROIs; SE $_{\beta}$ =Standard Error of beta; p = p -value, significant from p <.03; OFC=orbitofrontal gyrus.

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Table S7: Asymmetry analyses. Cortical symmetry was assessed in all three groups separately with a paired t-test between the raw cortical thickness data of left and right hemisphere per ROI. Mean values more than 0 signify greater cortical thickness in the left hemisphere, and mean values less than 0 signify greater cortical thickness in the right hemisphere.

	CUD (n = 80)				NCUD (n = 33)				HC (n = 84)			
	M	SD	T (df = 79)	p	M	SD	t (df = 32)	p	M	SD	t (df = 83)	p
OFC	.06	.33	1.71	.91	-.86	.22	-2.23	.33	.24	.30	7.26	.00
ACC	.11	.38	2.58	.01	.07	.48	.82	.42	.09	.42	2.02	.05
insula	-.04	.16	-2.40	.02	.00	.14	-.02	.99	-.12	.14	-8.09	.00
parahip	.13	.23	5.11	.00	-.03	.24	-.74	.47	.04	.25	1.48	.14
fus. gyrus	-.01	.10	-.78	.44	.03	.12	1.26	.22	-.01	.14	-.95	.34

Note: CUD=Cannabis Use Disorder; NCUD=Non-Cannabis Use Disorder; HC=Healthy Controls; M=Mean; SD=Standard Deviation; df=degrees of freedom; p=p-value, significant from p<.05; OFC=orbitofrontal gyrus; ACC=anterior cingulate gyrus; parahip=parahippocampal gyrus; fus. gyrus=fusiform gyrus.