

**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	$\beta$	SE <sub><math>\beta</math></sub>	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 <sub>β</sub>	p value	d	β	SE <sub>β</sub>	p value	d	β	SE <sub>β</sub>	p value	d
total GM <sup>a</sup>	472895	49413	506359	48802	496952	44090	1.53	.22												
hippocampus <sup>a</sup>	4277	445	4331	478	4337	417	.70	.50												
amygdala <sup>a</sup>	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 <sup>a</sup>	7259	669	7460	784	7157	639	1.76	.18												
caudate <sup>a</sup>	4043	480	4018	436	4197	420	1.93	.15												
putamen <sup>a,c</sup>	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 <sup>b</sup>	13099	1570	14340	1614	13511	1361	3.26	.04												
ACC <sup>b</sup>	4597	681	4819	740	4908	880	.35	.70												
insula <sup>a</sup>	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. <sup>b,c</sup>	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 <sup>b</sup>	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; SE<sub>β</sub>=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 <sub>β</sub>	p	d	β	SE <sub>β</sub>	p	d	β	SE <sub>β</sub>	p	d	
total GMa	472895	49413	506359	48802	496952	44090	1.69	.19													
hippocampusa	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	<b>-429.7</b>	<b>206.9</b>	<b>.04</b>		
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<sub>β</sub>=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; <sup>a</sup>based on the FreeSurfer segmentation output; <sup>b</sup>based on the FreeSurfer Desikan-Killiany Atlas; <sup>c</sup>significant 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			
	$\beta$	SE $_{\beta}$	<i>p</i>	<i>d</i>	$\beta$	SE $_{\beta}$	<i>p</i>	<i>d</i>	$\beta$	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			
	$\beta$	SE $_{\beta}$	<i>p</i>	<i>d</i>	$\beta$	SE $_{\beta}$	<i>p</i>	<i>d</i>	$\beta$	SE $_{\beta}$	<i>p</i>	<i>d</i>
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
<b>OFC</b>	.06	.33	1.71	.91	-.86	.22	-2.23	.33	.24	.30	7.26	<b>.00</b>
<b>ACC</b>	.11	.38	2.58	<b>.01</b>	.07	.48	.82	.42	.09	.42	2.02	<b>.05</b>
<b>insula</b>	-.04	.16	-2.40	<b>.02</b>	.00	.14	-.02	.99	-.12	.14	-8.09	<b>.00</b>
<b>parahip</b>	.13	.23	5.11	<b>.00</b>	-.03	.24	-.74	.47	.04	.25	1.48	.14
<b>fus. gyrus</b>	-.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.