Supplementary Online Content

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eAppendix 1. Family Structure Information and Sibling Pair Creation

173 families contributed multiple siblings to the current analysis; 11 families had data available from all four siblings, data from three siblings was available from 79 families, data from two siblings was available from 83 families, and 36 individuals were the only member of their family at the time of the June 2014 data release. This included 48 monozygotic and 45 dizygotic twin pairs where both twins had participated by this data release.

For the discordant sibling analyses, all possible pairings of siblings were drawn from the data (N=368 pairs from 173 families). For example, if all four siblings recruited from a given family had already participated by the current data release, six sibling pairs were created (sib1-sib2, sib1-sib3, sib1-sib4, sib2-sib3, sib2-sib4, sib3-sib4). Thus, any one individual could contributed to multiple paired observations. Sibling pairs were grouped as concordant exposed (both siblings ever used cannabis; N=123), concordant unexposed (both siblings never used cannabis; N=114), or discordant (one sibling reported use while their sibling never used cannabis; N=149). For ease of analysis and interpretability, the cannabis-exposed sibling in a discordant pair was always ordered first in the pair; the order of siblings was pseudo-randomized for concordant pairs to balance the sex and cannabis use distributions across siblings.

Given the confounds noted in the main text, we excluded 145 opposite-sex pairs, resulting in 241 sibling pairs (50 MZ, 45 DZ, and 146 non-twin siblings) of which 89 pairs were discordant for cannabis exposure, 81 were concordant for cannabis exposure, and 71 pairs were concordantly unexposed.

eAppendix 2. MRI Pre-Processing Information

Relevant steps from the HCP processing pipeline included: (1) Down-sampling of the 0.7mm T1w image to 1mm using splines, (2) Intensity normalization and Talairach transformation (-autorecon1), (3) Skull registration, (4) FreeSurfer skull stripping, (5) FreeSurfer subcortical segmentation (-autorecon2), and (6) Extraction of volume statistics (-segstats).

eAppendix 3. Variable Coding Information

Age of onset (1=≤14years old, 2=15-17, 3=18-20, 4=≥21)
Lifetime frequency of use (1=1-5 times used, 2=6-10, 3=11-100, 4=101-999, 5=≥1000)
Total Household Income (1=<$10,000, 2=10,000-19,999, 3=20,000-29,999, 4=30,000-39,999, 5=40,000-49,999, 6=50,000-74,999, 7=75,000-99,999, 8= >=100,000)
Alcohol use (drinks per day during the 12-month heaviest period of use 0=0, 1=1, 2=2, 3=3, 4=4, 5=5-6, 7=6+ drinks)
Non-cannabis illicit drug use (times used across the lifetime; 0=never, 1=1-2 times, 2=3-10, 3=11-25, 4= males 26-100; females ≥26, 5=males ≥100)
Childhood conduct problems (0=0, 1=1, 2=2 for males, ≥2 for females, 3=≥3 problem behaviors for males)
These variables were all available as ordinal as part of the HCP data release (none were made ordinal as part of the current analyses).
For further information see, http://www.humanconnectome.org/documentation/
https://wiki.humanconnectome.org/display/PublicData/HCP+Data+Dictionary+Public-+500+Subject+Release

eAppendix 4. Picture Vocabulary

Age-Adjusted Scale Scores from the NIH Toolbox Picture Vocabulary Test were included as a covariate in all analyses. The test was administered in a computerized adaptive format. Participants were presented with an audio recording of a word and four images on the computer screen and were asked to select the picture that most closely matched the meaning of the word. Scores are considered to be a measure of receptive vocabulary and a strong proxy of crystallized intelligence abilities. An age-adjusted score of 100 is considered average for one's age based on the NIH Toolbox normative data. Scores around 115 indicate above-average ability while individuals scoring around 130 are in the top ~2% nationally for their age. A score of 85 indicates below-average ability, while a score of 70 or below suggests significant impairment.

eAppendix 5. Additional Covariates

(a) Tobacco, alcohol, and other illicit drug use are highly comorbid with cannabis use[1], thus these were included a additional covariates to control for potential confounds between substance use and brain volumes: The SSAGA was used to assess alcohol use (drinks per day during the 12-month heaviest period of use), cigarette use (heaviness of smoking index[2], with those who had smoked <100 cigarettes lifetime coded as 0), and non-cannabis illicit drug use (times used across the lifetime).

(b) To account for increased cannabis use in individuals with certain psychopathology[3,4], which have been occasionally linked to structural variation[5,6]: Lifetime histories of DSM-IV major depressive disorder diagnosis and childhood conduct problems were also assessed by the SSAGA (see eMethods S3 for variable codings).

(c) Personality measures have been implicated as correlates of cannabis use[7] and structural variation[8]: Personality measures included neuroticism, extraversion, openness, agreeableness and conscientiousness scores (from the revised 60-item NEO five factor inventory [NEO-FFI][9] completed as part of the Penn Computerized Cognitive Battery[10,11]).

(d) Impulsivity underlies cannabis use[12] and may be an index of predisposition to onset of use and may be related to volumetric alterations: A relatively coarse measure of impulsivity was computed from the ADHD subscale of the Achenbach Adult Self-Report (ASR) for Ages 18-59[13]. Specifically, we summed responses to the items: “I am impulsive or act without thinking”, “I am too impatient”, and “I rush into things without considering the risks”. Higher sum scores indicate a higher liability to impulsive behaviors. In addition, scores on a delay discounting task were used as an additional measure of impulsivity/self-regulation. Participants made six economic decisions between a larger, delayed reward ($200) and a smaller, immediate reward to determine an ‘indifference point’ where a participant was equally likely to chose the immediate or delayed amount (for details, see [14-16]). We calculated area under the curve (AUC), a validated and reliable index of delay discounting[17]; smaller AUC indicates steeper discounting i.e. more impulsivity/less self-regulation.

eTable 1. Sibling Pairs by Cannabis Exposure, Zygosity, and Sex

Concordant Never Pairs	Sibling Pairs	DZ Pairs	MZ Pairs	Total	Mean Age Difference for Sibling Pairs (years)
Both Female	24	9	21	54	3.54
Both Male	10	4	3	17	4.40
Opposite Sex	43	0	0	43	3.60
Total	77	13	24	114	3.68
Concordant Ever Pairs	**Sibling Pairs**	**DZ Pairs**	**MZ Pairs**	**Total**	
Both Female	19	9	11	39	4.74
Both Male	28	8	6	42	3.25
Opposite Sex	42	0	0	42	3.62
Total	89	17	17	123	3.74
Discordant Pairs	**Sibling Pairs**	**DZ Pairs**	**MZ Pairs**	**Total**	
Both Female	49	13	5	67	3.45
Both Male	16	2	4	22	3.81
Female User-Male Non-User	14	0	0	14	4.64
Male User-Female Non-User	46	0	0	46	4.02
Total	125	15	9	149	3.84

A breakdown of sibling pairs (total N=386) is presented by concordance for cannabis use, pair zygosity, and sex. Pairs consisted of monozygotic twins (MZ, total N= 50 pairs), dizygotic twins (DZ, total N=45), or non-twin siblings (total N=291). Pairs were either same-sex (both female or both male) or opposite sex. All twin pairs were same-sex. The ordering of opposite sex pairs was randomized across concordant pairs, but was fixed for discordant pairs based on use. The count of pairs discordant for use and sex is presented split by female user-male non-user vs. male user-female non-user pairs. The final column presents mean age differences between individuals in non-twin sibling pairs, split by sex concordance, as well as overall mean values for each cannabis use discordance group.

eTable 2. Summary of Regression Results Controlling for Additional Covariates

	Cannabis Exposure - Ever vs. Never Used (N=483)			Lifetime Amount of Use Among Exposed Individuals (N=262)			Age of Onset Among Exposed Individuals (N=262)		
Volume (mm^3)	**b**	**t**	**p**	**b**	**t**	**p**	**b**	**t**	**p**
Whole Brain	-1807.514	-0.216	0.829	**-9438.681**	**-2.236**	**0.026**	-1646.645	-0.289	0.773
Left Amygdala	**-34.056**	**-2.369**	**0.018**	-0.512	-0.068	0.946	-0.046	-0.005	0.996
Right Amygdala	-22.143	-1.463	0.144	-8.728	-1.148	0.252	1.716	0.170	0.865
Left Hippocampus	-38.097	-1.028	0.304	**-46.840**	**-2.293**	**0.023**	24.257	0.891	0.374
Right Hippocampus	9.156	0.277	0.782	-22.543	-1.290	0.198	28.763	1.246	0.214
Left Ventral Striatum	-5.459	-0.683	0.495	-1.006	-0.233	0.816	1.986	0.349	0.728
Right Ventral Striatum	**-20.355**	**-2.428**	**0.016**	-3.910	-0.878	0.381	0.908	0.154	0.878
Left Orbitofrontal Cortex	-20.214	-0.239	0.811	9.775	0.218	0.828	-50.560	-0.855	0.393
Right Orbitofrontal Cortex	22.907	0.295	0.768	1.026	0.025	0.980	-15.913	-0.289	0.773

Unstandardized (b) regression coefficients and their associated t- and p-values for the effects of cannabis exposiure, age of onset, and lifetime quantity of use from separate linear regression models predicting whole brain or regional volume. Regressions controlled for sex, age, ethnicity (White vs. not; African American vs. not), zygosity (Monozygotic vs. not; Dizygotic vs. not), alcohol use, cigarette use, non-cannabis illicit drug use, self-reported impulsivity, NEO-FFI scores, delay discounting, major depressive disorder history, childhood conduct problems, and whole brain volume (when predicting regional volumes). Negative regression coefficients indicate smaller volumes for exposed vs. unexposed individuals, with later age of onset, or greater lifetime quantity of use. Effects significant at p<0.05 are in bold.

eTable 3. Helmert Contrast Coding

	Contrast 1 Causal Hypothesis	Contrast 2 Graded Liability Hypothesis	Contrast 3 Predispositional Hypothesis
Unexposed Individual from Discordant Pair	-1	-1	-1
Exposed Individual from Discordant Pair	1	-1	-1
Concordant Exposed Pairs	0	2	-1
Concordant Unexposed Pairs	0	0	3

The Helmert contrast coding scheme for the linear mixed model analyses is presented here. Contrast 1 compares exposed and unexposed siblings from discordant pairs. Contrast 2 compares individuals from concordant exposed pairs to individuals from discordant pairs. Contrast 3 compares individuals from concordant unexposed pairs to all other groups.

eTable 4. Relationships Between Covariates and Cannabis Use Variables

Variable	Test	Cannabis Age of Onset	Cannabis Times Used
Sex (F>M)	t-test	2.36*	-5.39***
Age (years)	Correlation	0.05	-.122*
White or Not	t-test	0.05	-2.19*
African American or Not	t-test	1.27	2.17*
Monozygotic or Not	t-test	-0.83	-0.30
Dizygotic or Not	t-test	0.55	-0.58
Total Household Income	Correlation	0.11	-0.23***
Age-Adjusted Picture Vocabulary	Correlation	0.08	-0.05
NEO Contentiousness	Correlation	0.04	-0.04
NEO Extraversion	Correlation	-0.01	-0.03
NEO Neuroticism	Correlation	0.02	-0.04
NEO Openness	Correlation	-0.07	0.28**
NEO Agreeableness	Correlation	0.16**	-.017**
Delay Discounting	Correlation	-0.04	0.09
Impulsivity	Correlation	-0.11	0.09
Alcohol Use	Correlation	-0.22**	0.30**
Cigarette Use	Correlation	-0.35**	0.36**
Illicit Drug Use	Correlation	-.034**	0.53**
Depression History	t-test	-1.20	2.03*
Childhood Conduct Problems	Correlation	-0.20**	0.24**

Ordinal variables for age of onset of cannabis use and lifetime times using cannabis were related to all covariates of interest by either t-test (for binary covariates) or correlation. Thus, values represent t-statistics for t-test results and Pearson's r for correlations. Note that earlier age of onset relates to more lifetime use (r(260)= -0.42, p<0.001), so observed relationships with covariates tend to be in opposite directions for these two variables, i.e. females begin using cannabis at a later age and use less over their lifetime.
** p<0.05, ** p<0.01, *** p<0.001*

eTable 5. Descriptive Statistics and Intercorrelations Among Brain Volumes

			Inter-Correlations							
	Mean	**SD**	**Left Amyg**	**Right Amyg**	**Left HC**	**Right HC**	**Left VS**	**Right VS**	**Left OFC**	**Right OFC**
Whole Brain Volume	1116835.18	112422.14	0.71	0.72	0.67	0.71	0.55	0.57	0.83	0.84
Left Amygdala (Amyg)	1526.22	192.22		0.81	0.68	0.67	0.42	0.44	0.57	0.60
Right Amygdala (Amyg)	1610.18	204.61			0.65	0.66	0.42	0.41	0.57	0.60
Left Hippocampus (HC)	4344.16	465.88				0.78	0.39	0.34	0.46	0.53
Right Hippocampus (HC)	4406.23	439.93					0.44	0.44	0.48	0.57
Left Ventral Striatum (VS)	557.04	92.45						0.70	0.53	0.55
Right Ventral Striatum (VS)	597.09	98.02							0.57	0.59
Left Orbitofrontal Cortex (OFC)	12369.45	1417.05								0.82
Right Orbitofrontal Cortex (OFC)	12233.55	1339.60								

Mean and standard deviation (SD) values are presented for each brain volume of interest (N=483). Pearson's correlation between all volumes of interest were also presented. All correlations were significant p<0.001.

eTable 6. Interrelationships Among Covariates

	Age	White	African Am.	MZ Twin	DZ Twin	NEO-C	NEO-E	NEO-N	NEO-O	NEO-A	Delay Disc.	Impuls.	Alcohol	Cig.	Illicit	MDD	Conduct
Sex (F>M)	0.63	0.06	0.06	13.81***	1.54	2.52*	0.37	3.02**	-2.21*	3.32**	-1.01	-2.54*	-2.64**	-2.58*	-4.20***	0.00	-0.29**
Age (years)		2.03*	-1.70	3.33**	2.97**	0.07	0.00	-0.03	-0.12*	0.11*	0.03	-0.15**	0.02	0.11*	0.02	-0.64	0.03
White or Not			-	11.55**	0.72	-1.12	1.60	0.29	-1.11	3.93***	7.09***	-1.12	3.43**	-0.49	0.77	2.81	-0.12**
African Am. or Not				7.02*	0.33	2.02*	-1.05	-1.09	0.57	-2.89**	-7.31***	0.44	-3.83***	0.92	-1.92	1.43	0.09
Monozygotic or Not					-	4.65***	3.86***	-2.37*	-2.38*	4.78***	0.42	-4.18***	0.63	-0.07	-0.85	2.41	-0.10*
Dizygotic or Not						-1.42	-1.05	0.14	-1.55	0.81	-1.23	-2.22*	-0.60	1.24	0.34	0.63	-0.07
NEO Contentiousness							0.35**	-0.42**	-0.06	0.24**	-0.04	-0.26**	0.03	-0.02	-0.11*	-2.26*	-0.03
NEO Extraversion								-.379**	0.06	0.34**	-0.01	-0.02	0.14**	-0.01	0.01	-4.49***	-0.03
NEO Neuroticism									0.01	-0.29**	-0.03	0.24**	-0.06	-0.01	-0.01	5.20***	0.07
NEO Openness										0.13**	0.08	0.00	0.05	0.03	0.19**	2.70**	0.11*
NEO Agreeableness											.090*	-.031**	-0.11*	-0.17**	-0.10*	-2.20*	-0.27**
Delay Discounting												-0.08	-0.07	-0.13**	0.03	1.79	0.00
Impulsivity													0.06	0.01*	0.02	1.94	0.12**
Alcohol Use														0.28**	0.31**	-0.31	0.14**
Cigarette Use															0.36**	0.61	0.11*
Illicit Drug Use																0.89	0.27**
Depression History																	0.21**

Values represent t-statistics when comparing a binary and a continuous variable by independent-samples t-test, chi^2 statistics when comparing two binary variables, or Pearson's r coefficients relating two continuous variables. Sex, ethnicity, zygosity, and depression history are binary variables.
** p<0.05, ** p<0.01, *** p<0.001*

eTable 7. Full Cannabis Exposure Regression Results

	WBV	L. Amyg.	R. Amyg.	L. Hipp.	R. Hipp.	L. Accumb.	R. Accumb.	L. OFC	R. OFC
Intercept	**1114080.197***	**523.688***	**405.275**	**1426.197***	**1540.894***	50.159	**163.683***	**1555.591***	**1918.633**
Cannabis Use	-6684.224	**-34.676**	-20.644	-29.514	14.900	-0.585	**-20.866**	-88.716	-21.509
Whole Brain Volume	-	**0.001***	**0.001***	**0.002***	**0.002***	**0.001***	**0.001***	**0.01***	**0.01***
Sex (F>M)	**-145402.729***	**-71.587***	**-51.932**	-45.333	-62.71	10.119	-3.252	-46.98	21.655
White or Not	**39478.07***	-4.96	13.682	138.584	**252.801***	-27.226	-11.341	-55.404	-13.105
African American or Not	-2721.389	-11.602	-1.853	65.114	**220.602**	-1.623	8.176	-108.448	-86.000
Age (years)	-1684.557	-1.357	-0.442	1.997	0.798	-2.031.	**-3.129**	-16.84	**-34.557**
Monozygotic or Not	-9596.319	-3.394	-11.872	**-113.456**	-47.686	-9.438	-10.208	-174.268.	-144.654
Dizygotic or Not	3431.441	17.936	16.554	-61.935	-56.675	**-18.192***	-3.469	-69.531	-69.696
Income	**6715.404***	3.38	2.41	-2.55	-2.55	13.368	-1.80	-1.75	29.65
Picture Vocabulary	**937.851***	-0.44	-0.41	1.62	1.62	1.22	0.38	0.00	0.08

Unstandardized regression coefficients for cannabis exposure (ever vs. never used cannabis) and all covariates predicting whole brain volume and left and right amygdala, hippocampus, ventral striatum, and orbitofrontal cortex volumes are presented. Significant effects are in bold.
** p<0.05, ** p<0.01, *** p<0.001*

eTable 8. Full Times Used Regression Results

	WBV	L. Amyg.	R. Amyg.	L. Hipp.	R. Hipp.	L. Accumb.	R. Accumb.	L. OFC	R. OFC
Intercept	**1148775.959*** **	**487.155** **	**487.577** **	**2035.91*** **	**2147.548*** **	126.569	**220.057***	1724.505	**3044.788*** **
Cannabis Use	-6568.307	-4.723	-10.497	-31.834	-15.578	0.256	-2.834	-26.001	-39.727
Whole Brain Volume	-	**0.001*** **	**0.001*** **	**0.002*** **	**0.002*** **	**0.001*** **	**0.001*** **	**0.010*** **	**0.009*** **
Sex (F>M)	**-162659.104*** **	**-71.631** **	**-67.823** **	-78.05	-94.895	3.584	-18.274	-88.973	-211.221
White or Not	32149.864	-13.079	-5.416	103.305	154.803.	-21.465	-3.088	-40.713	67.811
African American or Not	242.661	-16.501	-16.268	11.313	52.563	1.856	12.643	-165.457	29.456
Age (years)	-2452.965	0.308	-0.261	-9.220	-6.608	-2.129	-2.825	-27.889	**-32.023***
Monozygotic or Not	-4965.48	-34.71	-29.256	-92.885	-57.716	-9.393	-12.469	-192.975	**-276.029***
Dizygotic or Not	1123.352	-8.526	-9.297	-83.447	-67.827	-11.714	-2.038	-128.261	-208.752.
Income	**6034.039***	7.27	1.72	14.93	14.93	**32.772** **	-2.03	-1.55	29.66
Picture Vocabulary	**1054.727** **	-1.053.	-0.56	-0.92	-0.92	-0.30	-0.09	-0.12	3.64

Unstandardized regression coefficients for times using cannabis among exposed individuas (N=262) and all covariates predicting whole brain volume and left and right amygdala, hippocampus, ventral striatum, and orbitofrontal cortex volumes are presented. Significant effects are in bold.
** p<0.05, ** p<0.01, *** p<0.001*

eTable 9. Full Age at Onset Regression Results

	WBV	L. Amyg.	R. Amyg.	L. Hipp.	R. Hipp.	L. Accumb.	R. Accumb.	L. OFC	R. OFC
Intercept	**1119521.438*** **	**453.069** **	**411.452***	**1799.812*** **	**2012.669*** **	126.42	**198.645***	1566.643	**2753.595** **
Cannabis Use	721.671	2.347	5.578	21.933	29.314	1.792	2.33	-15.677	24.066
Whole Brain Volume	-	**0.001*** **	**0.001*** **	**0.003*** **	**0.002*** **	**0.001*** **	**0.001*** **	**0.010*** **	**0.009*** **
Sex (F>M)	**-155918.707*** **	**-65.874** **	**-55.155***	-41.383	-83.441	2.601	-15.141	-47.293	-164.308
White or Not	32644.176	-13.826	-7.229	95.681	143.199	-22.237	-3.926	-32.708	59.696
African American or Not	-1758.147	-19.233	-22.599	-11.475	28.134	0.632	10.345	-160.066	3.381
Age (years)	-2343.358	0.391	-0.08	-8.724	-6.559	-2.153	-2.785	-27.134.	**-31.369***
Monozygotic or Not	-6841.627	-35.534	-30.996	-96.912	-55.055	-8.869	-12.734	-204.637	**-281.879***
Dizygotic or Not	580.846	-8.853	-10.01	-85.421	-68.094	-11.624	-2.2	-131.135	-211.34
Income	**6936.764***	7.747	2.76	17.79	17.79	**33.118** **	-2.16	-1.32	33.90
Picture Vocabulary	**1047.632** **	-1.083	-0.63	-1.16	-1.16	-0.56	-0.11	-0.14	3.69

Unstandardized regression coefficients for cannabis age of onset among exposed individuals (N=262) and all covariates predicting whole brain volume and left and right amygdala, hippocampus, ventral striatum, and orbitofrontal cortex volumes are presented. Significant effects are in bold.
** p<0.05, ** p<0.01, *** p<0.001*

eTable 10. Volume Relationships With Cannabis Use by Light vs Heavier Use

	Left Amygdala			Right Ventral Striatum		
	Robust Coefficient	**t**	**p**	**Robust Coefficient**	**t**	**p**
Intercept	**533.252**	**3.71**	**<0.001**	**170.499**	**2.38**	**0.018**
Cannabis Use <100 times	**-32.479**	**-2.37**	**0.019**	**-19.549**	**-2.30**	**0.023**
Cannabis Use ≥100 times	**-43.323**	**-2.25**	**0.026**	**-26.663**	**-2.25**	**0.025**
Whole Brain Volume	**0.001**	**9.25**	**<0.001**	**.0004**	**10.94**	**<0.001**
Sex (F>M)	**-74.784**	**-3.47**	**0.001**	-5.629	-0.52	0.603
White or Not	-5.592	-0.21	0.832	-11.907	-0.69	0.489
African American or Not	-12.950	-0.45	0.657	6.916	0.36	0.721
Age (years)	-1.472	-0.74	0.460	**-3.218**	**-2.42**	**0.017**
Monozygotic or Not	-2.062	-0.12	0.908	-9.192	-0.85	0.395
Dizygotic or Not	18.900	1.25	0.214	-2.675	-0.26	0.792
Income	3.350	1.02	0.307	-1.714	-0.77	0.444
Picture Vocabulary	-0.410	-0.75	0.454	0.023	0.07	0.943
Test comparing coefficients for cannabis use <100 vs. ≥100 times	F(1, 204)=0.32, p=0.574			F(1, 204)=0.35, p=0.553		

Analyses conducted in STATA with dummy coded variables representing lifetime cannabis use of <100 and ≥100 times, with never use as the reference group. Individual estimates indicate that both dummy codes (<100 and ≥100 times) are significantly associated with brain volumes. Post-hoc comparisons between the estimates for each dummy tested whether the difference between the coefficients for <100 and ≥100 times could be equated to zero (i.e. not statistically different from each other). A non-significant result indicates that there are no significant differences in the magnitude of association between brain volumes and using cannabis <100 and ≥100 times. A robust sandwich variance estimator was used to adjust standard errors for familial clustering.

eTable 11. Linear Mixed Model Results for Same-Sex Sibling Pairs

Effect	**WBV**	**L. Amyg**	**R. Amyg**	**L. HC**	**R. HC**	**L. VS**	**R. VS**	**L. OFC**	**R. OFC**
Intercept	**1055403.1*** **	**338.80** **	**140.70**	**872.60** **	**895.00*** **	78.020	**169.30***	93.330	**2333.00*** **
Whole Brain Volume	-	**0.001*** **	**0.001*** **	**0.003*** **	**0.003*** **	**0.001*** **	**0.001*** **	**0.011*** **	**0.01*** **
Sex (F>M)	-142727***	-43.98#	-5.431	-0.151	-3.560	16.720	5.454	173.000	44.490
White or Not	17771.10	37.350	14.390	117.700	125.900	**-47.07***	-6.592	-126.200	-27.990
African American or Not	-11327.00	39.860	-13.710	73.310	139.700	-21.000	11.850	-32.470	-83.420
Age (years)	188.800	-0.496	-0.139	5.345	2.868	-2.082#	**-3.011***	-15.490	**-48.78*** **
Monozygotic vs. Sibling Pair	-918.800	-14.990	-14.400	**-87.49***	-7.614	-5.892	-14.580	-22.470	-28.920
Dizygotic vs. Sibling Pair	2714.000	7.459	15.390	-40.200	-35.670	-12.690	-6.443	85.380	-12.800
Income	**4799.9** **	1.779	-2.542	-6.074	0.951	-1.479	**-4.572***	-15.140	-13.730
Picture Vocabulary	**970.5*** **	0.691	0.388	**4.373*** **	**4.914*** **	-0.225	-0.399	1.090	-0.808
Contrast 1	-6274.600	-7.431	-1.961	16.430	23.810	-1.221	-1.628	59.520	-30.180
Contrast 2	-3523.900	4.312	-0.902	1.098	4.899	-1.785	-2.151	-12.600	-10.380
Contrast 3	1803.400	**12.56** **	7.743#	6.028	-9.214	-2.088	2.731	8.593	4.190

*Estimates of fixed effects from the linear mixed model analyses examining same-sex sibling pairs are presented. Effects significant at p<0.05 are in bold; significant effects of the Helmert contrasts (eTable 2) are shaded gray. #p<0.10, *p<0.05, **p<0.01, ***p<0.001*

eTable 12. Linear Mixed Model Results for All Sibling Pairs

Effect	**WBV**	**L. Amyg**	**R. Amyg**	**L. HC**	**R. HC**	**L. VS**	**R. VS**	**L. OFC**	**R. OFC**
Intercept	**1067574.5*** **	**386.7*** **	184.50#	**803.10** **	**1049.00*** **	96.57#	**159.00** **	**1135.00* **	**1607.00*** **
Whole Brain Volume	-	**0.001*** **	**0.001*** **	**0.003*** **	**0.003*** **	**0.001*** **	**0.001*** **	**0.011*** **	**0.01*** **
Sex (F>M)	**-144400.3*** **	**-66.01*** **	-23.940	-33.350	-22.730	5.597	-0.770	33.540	24.190
White or Not	25077.000	32.560	-12.320	98.530	**233.9*** **	**-41.03* **	-9.898	-208.200	19.730
African American or Not	-8892.600	31.870	-25.930	83.030	**239** **	-15.070	8.002	-261.000	-103.300
Age (years)	-791.700	1.110	1.003	6.062	2.494	**-1.928* **	**-2.957** **	-17.97#	**-29.68*** **
Monozygotic vs. Sibling Pair	-2823.200	-6.607	-6.625	-72.07#	1.103	-1.335	-14.45#	-30.890	-62.370
Dizygotic vs. Sibling Pair	1026.700	11.490	23.890	-34.360	-45.630	-10.670	-6.308	78.370	-34.870
Income	**4836.3*** **	2.815	-1.324	-2.121	8.665	-2.441#	**-3.082* **	-12.320	-22.43#
Picture Vocabulary	**1237*** **	0.454	0.534	**3.789*** **	**3.003** **	-0.093	-0.312	-0.488	1.959
Sex Concordant vs. Discordant Pair	-9268.400	-7.066	-9.236	29.120	5.840	-1.617	4.582	-101.700	-71.410
Contrast 1	8125.200	**-25.88** **	-13.440	-18.530	-25.090	-5.044	**-16.2** **	0.867	-39.630
Contrast 2	-2892.900	0.103	-0.294	-5.580	4.891	-3.060	-4.179#	-26.590	-10.590
Contrast 3	1665.000	**9.511** **	5.800	7.149	-3.367	-0.767	3.414#	-2.388	7.950
Contrast 1 x Sex Concordance	**-14930.5* **	19.280	11.830	37.120	50.81#	3.517	**14.91* **	53.590	17.340

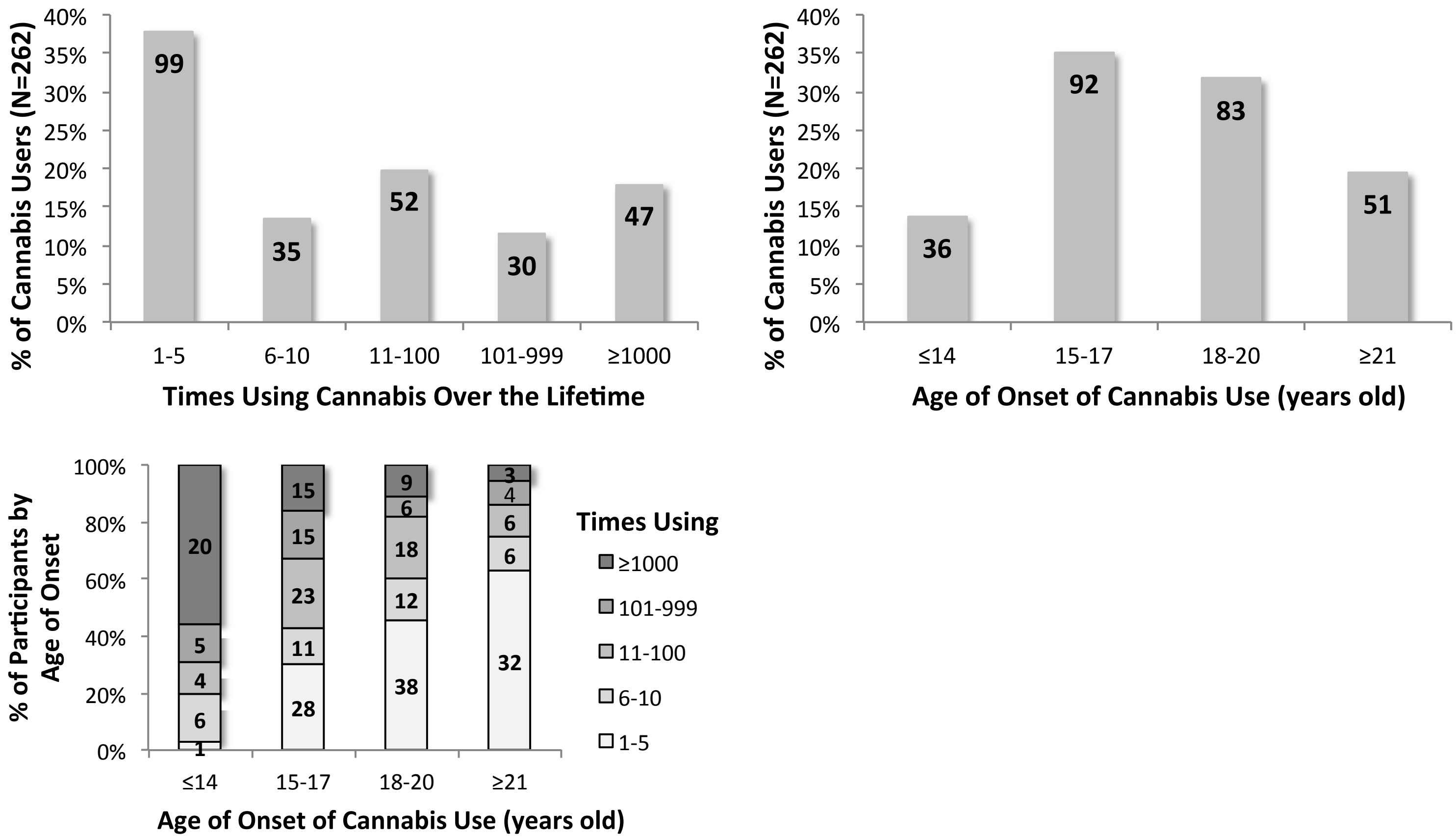
*Estimates of fixed effects from the linear mixed model analyses examining all sibling pairs are presented. Effects significant at p<0.05 are in bold; significant effects of the Helmert contrasts (eTable 2) are shaded gray. #p<0.10, *p<0.05, **p<0.01, ***p<0.001*

eTable 13. Control Analysis Results

	Discordant Users vs. Unrelated Individuals	
	t	**p-value**
Whole Brain Volume	-1.69	0.09
Left Amygdala	**-3.44**	**0.001**
Right Amygdala	-1.69	0.09
Left Hippocampus	-0.99	0.33
Right Hippocampus	-0.41	0.68
Left Ventral Striatum	0.34	0.74
Right Ventral Striatum	-1.24	0.22
Left Orbitofrontal Cortex	-1.72	0.09
Right Orbitofrontal Cortex	-1.98	0.05

We compared the cannabis-exposed individuals from same-sex discordant pairs (N=89) with unrelated *but sex-matched unexposed individuals using a pair t-test. T-statistics and their associated p-value for the paired t-test are presented.*

eFigure. Histogram of Age at Onset and Times Using Cannabis



eReferences

1. Kandel D, Yamaguchi K. From beer to crack: developmental patterns of drug involvement. *American Journal of Public …*. 1993;83(6):851–855. doi:10.2105/AJPH.83.6.851.

2. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict*. 1989;84(7):791–799.

3. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: cohort study. *BMJ*. 2002;325(7374):1195–1198.

4. Elkins IJ, McGue M, Iacono WG. Prospective Effects of Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Sex on Adolescent Substance Use and Abuse. 2007;64(10):1145–1152. doi:10.1001/archpsyc.64.10.1145.

5. Hajek T, Kopecek M, Kozeny J, Gunde E, Alda M, Höschl C. Amygdala volumes in mood disorders — Meta-analysis of magnetic resonance volumetry studies. *Journal of Affective Disorders*. 2009;115(3):395–410. doi:10.1016/j.jad.2008.10.007.

6. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-Analysis of Structural Imaging Findings in Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*. 2007;61(12):1361–1369. doi:10.1016/j.biopsych.2006.06.011.

7. Vink JM, Nawijn L, Boomsma DI, Willemsen G. Personality differences in monozygotic twins discordant for cannabis use. *Addiction*. 2007;102(12):1942–1946. doi:10.1111/j.1360-0443.2007.02008.x.

8. Lewis GJ, Panizzon MS, Eyler L, et al. Heritable influences on amygdala and orbitofrontal cortex contribute to genetic variation in core dimensions of personality. *NeuroImage*. 2014;103:309–315. doi:10.1016/j.neuroimage.2014.09.043.

9. McCrae RR, Costa PT Jr. A contemplated revision of the NEO Five-Factor Inventory. *Personality and Individual Differences*. 2004;36(3):587–596. doi:10.1016/S0191-8869(03)00118-1.

10. Gur R. Computerized Neurocognitive Scanning: I. Methodology and Validation in Healthy People. *Neuropsychopharmacology*. 2001;25(5):766–776. doi:10.1016/S0893-133X(01)00278-0.

11. Gur RC, Richard J, Hughett P, et al. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: Standardization and initial construct validation. *Journal of Neuroscience Methods*. 2010;187(2):254–262. doi:10.1016/j.jneumeth.2009.11.017.

12. Wrege J, Schmidt A, Walter A, et al. Effects of Cannabis on Impulsivity: A Systematic Review of Neuroimaging Findings. *Curr Pharm Des*. 2014;20(13):2126–2137. doi:10.2174/13816128113199990428.

13. Achenbach TM. *Achenbach System of Empirically Based Assessment (ASEBA)*. University of Vermont Research Center of Children Youth & Families; 2009.

14. Estle SJ, Green L, Myerson J, Holt DD. Differential effects of amount on temporal and probability discounting of gains and losses. *Memory & Cognition*. 2006;34(4):914–928.

15. Green L, Myerson J, Shah AK, Estle SJ, Holt DD. Do adjusting-amount and adjusting-delay procedures produce equivalent estimates of subjective value in pigeons? *J Exp Anal Behav*. 2007;87(3):337–347.

16. Barch DM, Burgess GC, Harms MP, et al. Function in the human connectome: Task-fMRI and individual differences in behavior. *NeuroImage*. 2013;80(C):169–189. doi:10.1016/j.neuroimage.2013.05.033.

17. Myerson J, Green L, Warusawitharana M. Area under the curve as a measure of discounting. *J Exp Anal Behav*. 2001;76(2):235–243. doi:10.1901/jeab.2001.76-235.