

SUPPLEMENTARY MATERIAL

For robustness, we re-performed the ANOVA and regression analyses to include cigarette smoking and/or alcohol use disorder as covariates of no interest.

ANOVA: Interactions Effects

Including cigarette smoking and alcohol use disorder as covariates to the 2 x 2 ANOVA, the diagnosis \times gender interaction remained significant in both the left anterior insula ($x=-32$, $y=23$, $z=8$, $k=221$, $Z= 4.31$, $p_{FWE}=0.024$) and the left lingual gyrus ($x=-3$, $y=-86$, $z=-8$, $k= 246$, $Z=4.31$, $p_{FWE}=0.014$) with the former still driven by a diagnosis difference within the women (CDW<CTLW) ($x=-33$, $y=23$, $z=8$, $k=226$, $Z= 4.35$, $p_{FWE}=0.02$). As in the main results, no post-hoc differences were significant for the left lingual gyrus.

We also reran this analysis including cigarette smoking and alcohol use disorders as covariates one at a time. Including only cigarette smoking as a covariate, the diagnosis \times gender interaction remained significant in both the left anterior insula ($x=-30$, $y=24$, $z=9$, $k=220$, $Z= 4.24$, $p_{FWE}=0.024$) and the left lingual gyrus ($x=-3$, $y=-86$, $z=-8$, $k= 217$, $Z=4.23$, $p_{FWE}=0.026$) with the former still driven by a diagnosis difference within the women (CDW<CTLW) ($x=-33$, $y=23$, $z=8$, $k=279$, $Z= 4.40$, $p_{FWE}=0.007$). As in the main results, no post-hoc differences were significant for the left lingual gyrus.

Including only alcohol use disorders as a covariate, the diagnosis \times gender interaction remained significant in both the left anterior insula ($x=-32$, $y=23$, $z=8$, $k=218$, $Z= 4.19$, $p_{FWE}=0.025$) and the left lingual gyrus ($x=-3$, $y=-86$, $z=-8$, $k= 272$, $Z=4.29$, $p_{FWE}=0.008$) with the former still driven by a diagnosis difference within the women (CDW<CTLW) ($x=-35$, $y=23$, $z=6$, $k=307$, $Z= 4.49$, $p_{FWE}=0.004$). As in the main results, no post-hoc differences were significant for the left lingual gyrus.

Regression Analysis

Including cigarette smoking and alcohol use disorder as covariates in the whole-brain regression analysis did not alter the significant effects for the CDM. A negative relationship between duration of cocaine use and GMV in the right hippocampus remained significant ($x=36$, $y=-36$, $z=-12$, $k=277$, $Z=4.28$; $p_{FWE}=0.003$) in CDM.

Table S1: Characteristics and Scan Parameters of Included Study Sample

PI	CD (Women)	Controls (Women)	Diagnostic Instrument	Scan Parameters
Garavan/Foxe	16 (1)	9 (2)	SCID	3T, MPRAGE, TR=11.6ms, TE=4.9ms, flip angle=8°, matrix=256×256×72, voxel size=0.937×0.938×1.0mm
Goldstein	9 (7)	18 (8)	SCID	3T, MPRAGE, TR=2400ms, TE=2.07ms, flip angle=8°, matrix=256×256×179, voxel size=0.8×0.8×0.8mm
Li	37 (26)	0 (0)	SCID	3T, MPRAGE, TR=300ms, TE=2.5ms, flip angle=60°, matrix=256×256, voxel size=1.0×1.0×1.0mm
Pearlson	25 (14)	25 (3)	SCID	3T, MPRAGE, TR=2300ms, TE=2.74ms, flip angle=8°, matrix=176×256×176, voxel size=1.0×1.0×1.0mm
Schmaal/Veltman	6 (0)	0 (0)	MINI	3T, TR=9ms, TE=3.5ms, flip angle=8°, matrix=256×256×170, voxel size=1.0×1.0×1.0mm,
Sinha	13 (16)	13 (22)	SCID	3T, MPRAGE, TR=2530ms, TE=3.34ms, flip angle=7°, matrix=256×256×176, voxel size=1.0×1.0×1.0mm
Stein	34 (6)	75 (35)	Computerized SCID	3T, MPRAGE, TR=1900ms, TE=3.51ms, flip angle=9°, matrix=256×192×208, voxel size=1.0×1.0×1.0mm
Total	140 (70)	140 (70)		

Table S2. Diagnosis Main Effect: Brain Regions with Significant Gray Matter Volume Differences in the CD Group Compared to Controls

Region	R/L	MNI coordinates	Z-score	Cluster size	p _{FWE-corr}
CTL>CD					
Frontal Pole	L	-8, 65, 3	5.08	1265	<0.001
Orbitofrontal Cortex	R	8, 35,-21	4.39	778	0.005
Superior Frontal Gyrus	L	-8, 50, 45	4.84	227	0.016
Superior Frontal Gyrus	R	27, 57, 12	4.84	548	<0.001
Anterior Cingulate Gyrus	L	0, 36, -14	4.22	177	0.049
Supplementary Motor Cortex	R	5, 23, 44	4.61	196	0.032
Inferior Temporal Gyrus	L	-47, -12, -41	4.77	272	0.006
CTL<CD					
No significant clusters					

CTL, control; CD, cocaine-dependent; FWE, family-wise error L, left; MNI, Montreal Neurological Institute; R, right

Table S3. Gender Main Effect: Brain Regions with Significant Gray Matter Volume Differences in Men Compared to Women

Region	R/L	MNI coordinates	Z-score	Cluster size	p _{FWE-corr}
Men>Women					
Cerebellar Vermis	R	2, -71, -15	5.83	1368	<0.001
Men<Women					
Superior Frontal Gyrus	L	-23, 9, 62	4.84	361	0.001
Middle Frontal Gyrus	L	-36, 36, 39	4.65	300	0.003
Middle Frontal Gyrus	R	32, 50, 26	4.06	219	0.019
Supplementary Motor Cortex	R	2, 21, -29	6.41	2913	<0.001
Superior Temporal Gyrus	R	47, -33, 3	4.60	369	0.001
Middle Temporal Gyrus	L	-63, -30, -6	4.80	239	0.012
Inferior Temporal Gyrus	R	62, -35, -20	4.49	202	0.028
Postcentral Gyrus	R	39, -15, 42	6.71	5763	<0.001
Thalamus	L	-8, 18, 11	Inf	3883	<0.001
Entorhinal Area	R	26, 9, -24	7.39	13720	<0.001
Caudate	R	9, 5, 8	5.19	220	0.019
Parahippocampal Gyrus	L	-20, -20, -30	7.06	466	<0.001
Parahippocampal Gyrus	R	20, -21, -29	6.52	426	0.000
Lateral Cerebellum	L	-42, -51, -45	7.19	3674	<0.001
Lateral Cerebellum	R	45, -48, -27	4.06	215	0.021

FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; R, right

Table S4. Demographic Characteristics of Matched Study Sample (N=280)

	CDM (n=70)	CDW (n=70)	CTLM (n=70)	CTLW (n=70)	p- Value
Age	37.54 (6.4)	39.56 (7.6)	37.96 (8.2)	37.15 (9.8)	0.24
Education	12.61 (1.5) ^{c,d}	12.24 (1.6) ^{c,d}	14.51 (2.5) ^{a,b}	14.51 (2.1) ^{a,b}	<0.01
Race (AA/White/Asian/O)	38/17/5/10 ^{b,d}	36/11/9/14 ^{a,c,d}	30/21/4/15 ^{b,d}	40/22/0/8 ^{a,b,c}	0.04
TIV (mL)	1529.61 (128.44) ^{b,d}	1368.52(135.35) ^{a,c}	1515.56 (121.53) ^{b,d}	1391.68 (121.53) ^{a,c}	<0.01
Duration of Use (years)	15.63 (9.4)	17.82 (8.9)	n/a	n/a	0.23

Data are presented as frequencies or means with standard deviations in parentheses; p-value is for the main effect of the ANOVA, for race p value is for the main effect of the Chi-squared test

a, mean differs from CDM; b, mean differs from CDW; c, mean differs from CTLM; d, mean differs from CTLW
n=12 missing data for education (CDM, n=7; CDW, n=4; CTLM, n=1)
n=38 missing data for duration of use (CDM, n=19; CDW, n=19)

AA, African American; CTLM, control men; CTLW, control women; CDM, cocaine-dependent men; CDW, cocaine-dependent women; O, other/missing; TIV, total intracranial volume

Table S5. Diagnosis Main Effect: Brain Regions with Significant Gray Matter Volume Differences in Individuals with CD Compared to Controls in Matched Study Sample (N=280)

Region	R/L	MNI coordinates	Z-score	Cluster size	p_{FWE-corr}
CTL>CD					
Orbitofrontal Cortex	R	8, 33, -21	3.99	839	0.018
Superior Frontal Gyrus	R	15, 35, 54	4.57	4183	<0.001
Inferior Frontal Gyrus	L	-45, 38, -11	4.20	1566	<0.001
CTL<CD					
No significance					

CTL, control; CD, cocaine-dependent; FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; R, right

Table S6. Gender Main Effect: Brain Regions with Significant Gray Matter Volume Differences in Men Compared to Women in Matched Study Sample (N=280)

Region	R/L	MNI Coordinates	Z-score	Cluster size	p_{FWE-corr}
Men>Women					
Cerebellar Vermis	R	2, -69, -11	4.95	2800	<0.001
Men<Women					
Middle Cingulate Gyrus	L	0, -20, 45	4.28	890	0.013
Thalamus	L	-8, -18, 11	Inf	4438	<0.001
Middle Temporal Gyrus	L	-65, -30,-6	3.98	793	0.026
Parahippocampal Gyrus	L	-18, -20, -30	6.15	954	0.008
Parahippocampal Gyrus	R	18, -20, -24	5.32	955	0.008
Lateral Cerebellum	L	-42, -50, -45	6.37	5200	<0.001
Lateral Cerebellum	R	8, -80, -33	4.47	2631	<0.001

FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; R, right

Table S7. Interaction Effects: Brain Regions with Significant Diagnosis by Gender Interactions in Gray Matter Volume in Matched Study Sample (N=280)

Region	R/L	MNI coordinates	Z-score	Cluster size	p_{FWE-corr}	Significant Post-Hoc Comparison
Anterior Insula	L	-33, 23, 6	3.98	947	0.009	CTLW>CDW, p _{FWE} <0.001
Lingual Gyrus	L	-3, -77, -2	4.26	3133	<0.001	----

CDW, cocaine-dependent women; CTLW, control women; FWE, family-wise error; L, left; MNI, Montreal Neurological Institute

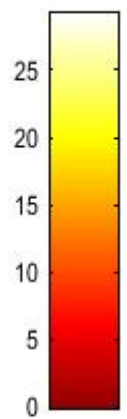
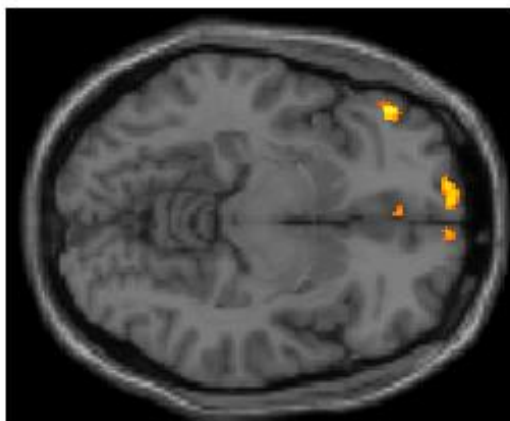
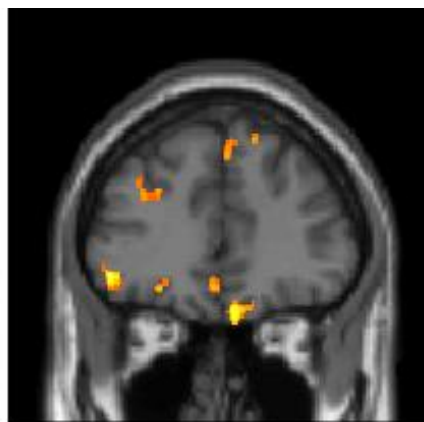
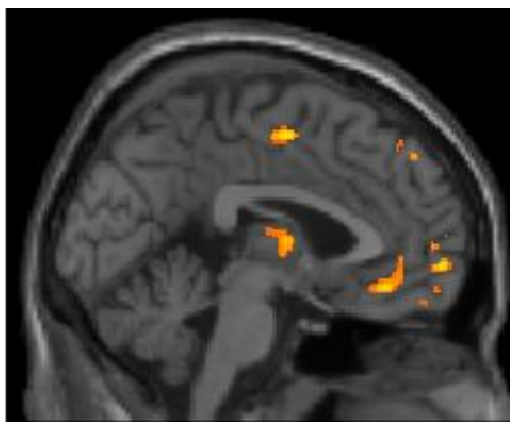
No other group comparison was significant for the anterior insula (i.e., CDM-CTLM; CDM-CDW; CTLM-CTLW) or the lingual gyrus (i.e., CDM-CTLM; CDW-CTLW; CDM-CDW; CTLM-CTLW).

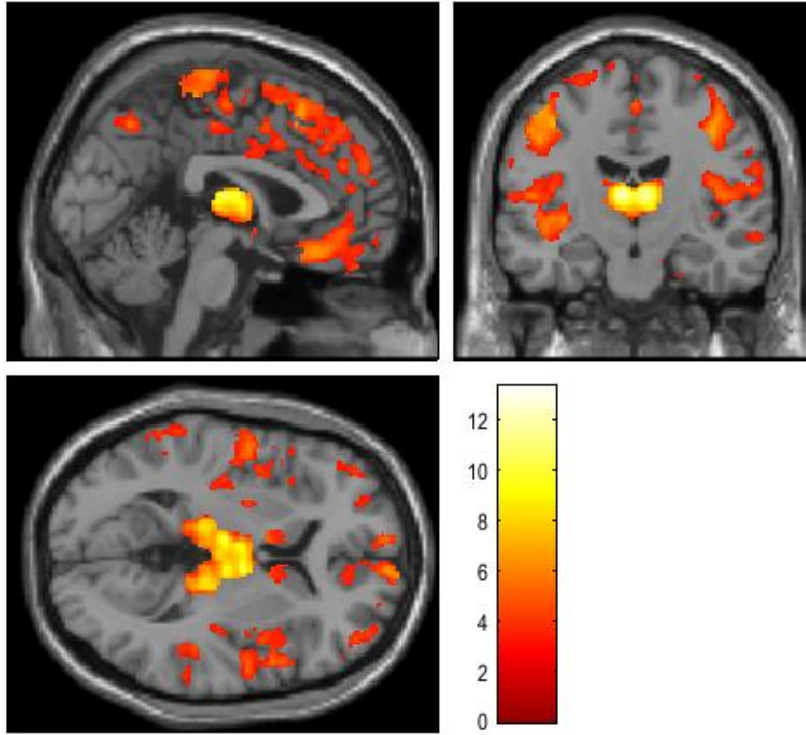
Figure S1. Main Effect of Diagnosis

Structural images demonstrate significant main effects of diagnosis in an axial, coronal, and sagittal view. CD individuals had lower GMV in the left frontal pole, right orbitofrontal cortex, bilateral superior frontal gyrus, and left anterior cingulate, inferior temporal gyrus, and supplementary motor cortex compared to CTL. No regions demonstrated greater GMV among CD individuals compared to CTL. The color bar represents the corresponding F -values. See Table S2 for statistics.

Figure S2. Main Effect of Gender

Structural images demonstrate significant main effects of gender in an axial, coronal, and sagittal view. Women had greater GMV in the superior and middle frontal gyrus, supplementary motor cortex, superior and middle temporal gyrus, post central gyrus, thalamus, entorhinal area, caudate, parahippocampal gyrus and lateral cerebellum (A), while GMV of the cerebellar vermis was greater in men than women (B). The color bar represents the corresponding F -values. See Table S3 for statistics.



A**B**