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RESEARCH ARTICLE

Common and gender-specific associations with cocaine use on gray matter volume: Data from the ENIGMA addiction working group

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Abstract

Gray matter volume (GMV) in frontal cortical and limbic regions is susceptible to cocaine-associated reductions in cocaine-dependent individuals (CD) and is negatively associated with duration of cocaine use. Gender differences in CD individuals have been reported clinically and in the context of neural responses to cue-induced craving and stress reactivity. The variability of GMV in select brain areas between men and women (e.g., limbic regions) underscores the importance of exploring interaction effects between gender and cocaine dependence on brain structure. Therefore, voxel-based morphometry data derived from the ENIGMA Addiction Consortium were used to investigate potential gender differences in GMV in CD individuals compared to matched controls (CTL). T1-weighted MRI scans and clinical data were pooled from seven sites yielding 420 gender- and age-matched participants: CD men (CDM, n = 140); CD women (CDW, n = 70); control men (CTLM, n = 140); and control women (CTLW, n = 70). Differences in GMV were assessed using a 2×2 ANCOVA, and voxelwise whole-brain linear regressions were conducted to explore

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relationships between GMV and duration of cocaine use. All analyses were corrected for age, total intracranial volume, and site. Diagnostic differences were predominantly found in frontal regions (CD < CTL). Interestingly, gender × diagnosis interactions in the left anterior insula and left lingual gyrus were also documented, driven by differences in women (CDW < CTLW). Further, lower right hippocampal GMV was associated with greater cocaine duration in CDM. Given the importance of the anterior insula to interoception and the hippocampus to learning contextual associations, results may point to gender-specific mechanisms in cocaine addiction.

KEYWORDS

addiction, cocaine, gender differences, gray matter volume, hippocampus, insula, lingual gyrus

1 | INTRODUCTION

Despite higher rates of lifetime cocaine dependence among men (3%) compared to women (1.8%) (Grant et al., 2016), women are at a greater risk for developing and maintaining problematic cocaine use (SAMHSA, 2016). For example, women tend to experience a more severe course of the disorder, have greater difficulty quitting, and are at higher risk for relapse following abstinence as compared to men (Back, Brady, Jackson, Salstrom, & Zinzow, 2005; Bobzean, DeNobrega, & Perrotti, 2014; Gallop et al., 2007; Hernandez-Avila, Rounsaville, & Kranzler, 2004). These reports parallel preclinical models demonstrating that females may be more vulnerable than males to the addictive properties of cocaine (Becker & Koob, 2016; Cosgrove, Mazure, & Staley, 2007). Gender differences in addiction have also been reported in the context of neural responses to stress reactivity, cue-induced craving, and rewarding stimuli. In one study, compared to control women, cocaine-dependent (CD) women showed greater brain activation in the amygdala, striatum, and insula in response to stress cues (Potenza et al., 2012). Similarly, compared to CD men, CD women exhibited greater brain activation in the insula, left middle and inferior frontal cortices, and the cingulate cortex while viewing stress-related imagery (Li, Kosten, & Sinha, 2005). In contrast, CD men demonstrated greater activations in similar limbic regions (e.g., insula, amygdala) but in response to drug-related cues (rather than stress cues) compared to control men (Potenza et al., 2012) and CD women (Kilts, 2001). Last, a recent study from our own lab showed that compared to CD men and control women, CD women exhibited lower activation in the precentral gyrus and greater activation in the inferior frontal gyrus to a monetary stimulus (Konova et al., 2016), suggesting that gender differences in brain function may also extend to processing positive reinforcers (i.e., rewarding stimuli). Collectively, this body of research suggests gender-dependent influences on neural reactivity to salient stimuli in individuals with cocaine dependence, particularly in frontal cortical regions and the limbic system. However, the underlying anatomical characteristics of these functional differences remain unknown, partly because gender differences in the behavioral and neurobiological aspects of addiction have largely been overlooked, at least until the last decade (Lind et al., 2017).

Voxel-based morphometry (VBM) uses magnetic resonance imaging (MRI) to investigate focal differences in gray matter volume (GMV) on a whole-brain voxel-by-voxel basis (Ashburner & Friston, 2000). Studies employing this method have revealed neuroanatomical gender differences in various frontal and limbic regions, beginning in young children and extending through the adult years (Durston et al., 2001; Luders, Gaser, Narr, & Toga, 2009; Pruessner, Collins, Pruessner, & Evans, 2001). Specifically, after correcting for total brain volume, in men, greater GMV is most consistently reported in the amygdala, hippocampus, and parahippocampal gyri, while in women, greater GMV is most pronounced in the insula as well as in many frontal regions, including the anterior cingulate cortex (Lotze et al., 2019; Ruigrok et al., 2014) (although note also negative results for hippocampal GMV (Tan, Ma, Vira, Marwha, & Eliot, 2016)). Frontal cortical (e.g., orbitofrontal cortex) and limbic (e.g., insula, amygdala, and hippocampus) regions may be particularly vulnerable to cocaine-associated brain volume reductions in CD individuals as compared to controls (Alia-Klein et al., 2011; Ersche et al., 2011; Franklin et al., 2002; Hall et al., 2015; Moreno-Lopez et al., 2012; Parvaz et al., 2017) as further associated with duration of cumulative/lifetime cocaine use (Alia-Klein et al., 2011; Barros-Loscertales et al., 2011; Ersche et al., 2011; Hall et al., 2015). Taken together, these findings underscore the importance of exploring interaction effects between gender and cocaine dependence on the integrity of brain structure. Notably, to date only a handful of studies have examined such a potential interaction. In one, compared to control women (n = 22), CD women (n = 18) had lower GMV in the left inferior frontal gyrus, left anterior insula, and left hippocampus, while compared to control men (n = 28), CD men (n = 18) had lower GMV in the precentral gyrus and mid cingulate gyrus (Rando, Tuit, Hannestad, Guarnaccia, & Sinha, 2013). Further, compared to control women (n = 28), women with stimulant-dependence (n = 28) had lower GMV in widespread brain regions that included the orbitofrontal cortex, insula, amygdala, hippocampus, and inferior parietal lobule while GMV did not differ between men with stimulant-dependence (n = 31) and control men (n = 40) (Regner et al., 2015). Interestingly, while diagnosis by gender interaction effects did not reach significance, compared to CD men (n = 55), CD women (n = 29) showed a significantly steeper negative association

between GMV in the right superior frontal gyrus and duration of cocaine use (Ide et al., 2014). A recent meta-analysis assessed how gender may moderate the relationship between cocaine use and regional GMV in CD participants; findings revealed that compared to CD men (*n* = 185), CD women (*n* = 28) were more likely to show greater GMV in the left superior frontal gyrus and lower GMV in the cerebellum (Hall et al., 2015) (note we refer to the cocaine and not the methamphetamine studies in this meta-analysis). Divergent findings across these studies may be attributable to small sample sizes, which may also impact the generalizability of results.

The ENIGMA Addiction consortium, which has 52 member sites around the world, leverages the ENIGMA protocols for multi-site neuroimaging analyses to study the neurobiological basis of addiction. The combination of data from multiple sites allows the consortium to overcome issues related to small sample sizes and low statistical power that limit most single site studies. Therefore, the objective of the current study was to use data from the ENIGMA Addiction Consortium to investigate gender differences in VBM-derived GMV in CD individuals compared to individuals without CD/matched controls. We also assessed whether gender moderates the association between duration of cocaine use and GMV. Pooling data across sites is an important step toward providing information that might lead to a better understanding of the neuroanatomical substrates of cocaine use disorder with potential implications for the care of these individuals.

2 | METHODS

2.1 | Participants

The total sample (*n* = 666) was pooled from seven member sites within the ENIGMA Addiction Consortium that had demographic and clinical data and T1-weighted brain MRI scans for CD individuals (*n* = 294) and non-CD controls (CTL, *n* = 372). Participating sites obtained approval from local institutional review boards and ethics committees and all study participants provided written informed consent. Procedures were performed in accordance with the Declaration of Helsinki.

All participants were interviewed ascertaining DSM-IV diagnoses using the Structured Clinical Interview (First, Spitzer, Gibbon, & Williams, 2002) or Mini International Neuropsychiatric Interview (Sheehan et al., 1998). All cocaine-using participants met criteria for cocaine dependence and were excluded if they met criteria for current dependence for another substance (excluding nicotine, caffeine, and alcohol) or had a lifetime diagnosis of a psychotic illness. Controls were excluded if they met criteria for any Axis I disorder (except for nicotine and caffeine dependence). Additionally, any participant with a lifetime neurological disease or any contraindication for MRI was excluded. Current tobacco use was collected as a categorical variable to index whether a participant was a current cigarette smoker.

Demographic information for the four groups, CD men (CDM, *n* = 140), CD women (CDW, *n* = 70), control men (CTLM, *n* = 140), and control women (CTLW, *n* = 70), is provided in Table 1. It is important to note that in the present manuscript the term gender, rather than sex, was used as participants self-identified/reported themselves as men or women. Gender identity was not a focus of this study.

2.2 | Neuroimaging data acquisition, processing, and analysis

Neuroimaging scans were acquired at each site. Site-specific image acquisition parameters are outlined in Table S1. After data aggregation, manual visual inspection was performed for gross morphological pathology and quality of each scan locally, blind to both gender and diagnosis, following the ENIGMA protocols for quality control (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Controls were then gender- and age-matched to individuals with CD resulting in a final sample of 420 (CD, *n* = 210 and CTL, *n* = 210).

TABLE 1 Demographic characteristics of the study sample

	CDM (*n* = 140)	CDW (*n* = 70)	CTLM (*n* = 140)	CTLW (*n* = 70)	*p*-value
Age	37.79 (6.7)	39.56 (7.6)	37.02 (8.5)	37.15 (9.8)	.17
Education	12.48 (1.4)[c,d]	12.24 (1.6)[c,d]	14.71 (2.6)[a,b]	14.51 (2.1)[a,b]	<.01
Race (AA/White/Asian/O)	76/24/13/27	36/11/9/14[d]	70/38/5/27	40/22/0/8[b]	<.01
TIV (mL)	1,519.67 (129.90)[b,d]	1,368.52(135.35)[a,c]	1,506.44 (129.82)[b,d]	1,391.68 (121.53)[a,c]	<.01
Duration of cocaine use (years)	15.24 (8.8)	17.82 (9.0)	n/a	n/a	.09
Current cigarette smoker (Y/N)	54/86[c,d]	31/39 [c,d]	10/130[a,b]	5/65[a,b]	<.01
Presence of an alcohol use disorder (Y/N)	14/126	6/64	n/a	n/a	.42

Note: Data are presented as frequencies or means with standard deviations in parentheses; p-value is for the main effect of the ANOVA, for categorical variables, the p value is for the main effect of the Chi-squared test. *n* = 24 missing data for education (CDM, *n* = 16; CDW, *n* = 4; CTLM, *n* = 3; CTLW, *n* = 1). *n* = 62 missing data for duration of use (CDM, *n* = 43; CDW, *n* = 19). Abbreviations: AA, African American; CDM, cocaine-dependent men; CDW, cocaine-dependent women; CTLM, control men; CTLW, control women; O, other/missing; TIV, total intracranial volume.

[a]Mean differs from CDM.

[b]Mean differs from CDW.

[c]Mean differs from CTLM.

[d]Mean differs from CTLW.

VBM is a whole-brain, fully automated, unbiased, MRI analysis technique used to detect regionally specific differences in brain tissue composition using a voxelwise comparison across participants (Ashburner & Friston, 2000). Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology, University of London, London, UK) and the Computational Anatomy Toolbox (CAT12, Christian Gaser, Department of Psychiatry, University of Jena, Jena, Germany) running on MATLAB 2018b (MathWorks, MA) were used to process the structural T1 MRI scans using CAT12 default parameters as per previous studies (Kaag et al., 2018; Lotze et al., 2019). For better registration, each scan was manually reoriented so that the origin was set to the anterior–posterior commissure. Scans from all participants were then resampled to a 1 mm isotropic voxel size.

The preprocessing of images involved the following steps: (a) T1 images were spatially normalized to the Montreal Neurological Institute space; (b) whole brain structural data were segmented into gray matter, white matter, and cerebrospinal fluid; (c) for further quality assurance, the resulting images were checked for homogeneity; (d) gray matter tissues were modulated by multiplying by the Jacobian determinants generated during spatial normalization to compensate for expansion or contraction due to the nonlinear part of the transformation; (e) modulated images were then smoothed using a 4-mm full width at half maximum Gaussian kernel to compensate for potential inaccuracies during the normalization step. Total intracranial volume was then computed as the sum of the extracted total gray matter and white matter volume and cerebrospinal fluid for each participant. This measure was calculated as an adjustment factor used in all analyses to account for overall head size on regional GMV.

2.3 | Statistical analyses

For group comparisons of demographic variables, chi-squared tests were used to analyze categorical variables and ANOVA was employed for continuous variables in SPSS 23. Gray matter spatial maps were pooled across sites to examine whole-brain voxelwise differences in GMV. Differences were assessed in SPM 12 using a 2×2 (diagnosis × gender) ANCOVA model that included age, total intracranial volume, and site as covariates of no interest. Variables that differed between groups and correlated with GMV were also included as covariates in the model (e.g., education, race; subgroup means were used to substitute missing values for education; note that, collapsed across subgroups, GMV did not differ between smokers and nonsmokers, and therefore this variable was not a priori included as a covariate in our analyses. Nevertheless, for completeness, we conducted sensitivity analyses that controlled for both current cigarette smoking status and alcohol use disorder as reported in Supporting Information). *F*-contrasts were employed to test for main effects as well as interaction effects. To pinpoint the source of any observed interaction effects, the following six post hoc comparisons were tested: (a) CTLW versus CDW; (b) CTLM versus CDM; (c) CDM versus CDW; (d) CTLM versus CTLW; (e) CTLW versus CDM; and (f) CTLM versus CDW. Analyses were re-run in groups that were equated for sample size between men and women to ensure that the higher sample size of men was not driving the effects; this was accomplished by randomly excluding half of the men from each diagnostic group (-Tables S4-S7). Last, the Marsbar tool in SPM (http://marsbar.sourceforge.net) was used to extract GMV from clusters of voxels that showed significant whole-brain diagnosis × gender interactions for display purposes and to inspect potential associations with demographic variables.

Further, within CD, whole-brain voxelwise linear regression analyses were conducted to explore relationships between duration of cocaine use (i.e., subjective report of lifetime use in years) and GMV in the total sample, and then separately in only CDM and CDW while controlling for age, total intracranial volume, and site. An interaction model testing for different regression slopes between GMV and cocaine duration in men versus women was also assessed using Student's *t* test (Zar, 1999). We conducted similar analyses for all extracted GMV clusters that showed significant diagnosis × gender effects. For sensitivity purposes, we reran both the ANOVA and the regression models to include the presence of current cigarette smoking and current alcohol use disorder as covariates of no interest.

Statistical maps for all analyses (group comparisons and regression analyses) were set at a threshold of $p < .001$ ($p < .015$ for supplementary analyses) voxel-level uncorrected. AFNI MonteCarlo simulation (3dClustSim) identified a minimum significant cluster size of 75 voxels using a voxel wise probability threshold of $p < .001$ and a posteriori family-wise error (FWE) cluster-level correction of $p < .05$. Thus, results are reported with a FWE of $p < .05$ cluster-level corrected for multiple comparisons. Post hoc tests were also corrected for multiple comparisons using a Bonferroni correction (at $p < .004$ [$p < .05/12$ (group comparisons in both directions)]).

3 | RESULTS

3.1 | Group comparisons

3.1.1 | Main effects

Controls had greater GMV compared to the group of individuals with CD in several frontal brain regions including the bilateral superior frontal gyrus, left frontal pole, right orbitofrontal cortex, left anterior cingulate gyrus, right supplementary motor cortex, and the left inferior temporal gyrus (see Table S2, Figure S1). There were no significant differences in the opposite direction (CD > CTL). Significant differences in GMV between the genders were also found, such that men demonstrated greater GMV in the cerebellar vermis, while women demonstrated greater GMV in several cortical and subcortical regions including the frontal gyrus, thalamus, parahippocampal gyrus, caudate, and lateral cerebellum as compared to men (see Table S3, Figure S2). When the sample sizes were matched, diagnostic differences in frontal regions were preserved and many of the gender effects remained statistically significant (see Tables S5 and S6).

3.1.2 | Interactions effects

The diagnosis × gender interaction revealed significant results in two regions, the left anterior insula (x = −32, y = 23, z = 8, k = 236, Z = 4.32, p_{FWE} = .013) and the left lingual gyrus (x = −2, y = −84, z = −8, k = 266, Z = 4.15, p_{FWE} = .007), with the former driven by a diagnosis difference within the women (CDW < CTLW) (Table 2; Figure 1). No post hoc differences were significant for the left lingual gyrus. Adding current cigarette smoking and alcohol use disorder as covariates did not change these results; see Supporting Information. Even when groups were equated for sample size, these interaction effects were preserved (Table S7). Notably, for all of the analyses, when the cluster size threshold was set to zero, there were no additional brain regions that achieved significance (i.e., no regions were significant and < 75 clusters).

3.2 | Regression analyses

Collapsed across all CD participants, a whole-brain regression analysis did not show any significant effects for an association between duration of cocaine use and GMV. However, separate whole-brain regression analyses within CDM and CDW revealed a negative relationship between duration of cocaine use and GMV in the right hippocampus (x = 36, y = −35, z = −12, k = 234, Z = 4.30; p_{FWE} = .008) in CDM but not CDW (extracted values from this region showed the expected

TABLE 2 Interaction effects: brain regions with significant diagnosis by gender interactions in gray matter volume

Region	R/L	MNI coordinates	Z-score	Cluster size	$p_{FWE\text{-}corr}$	Significant post hoc comparison
Anterior insula	L	−32, 23, 8	4.32	236	.013	CTLW>CDW, p_{FWE} < .001
Lingual gyrus	L	−2, −84, −8	4.15	266	.007	—

Note: 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).
Abbreviations: CDW, cocaine-dependent women; CTLW, control women; FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; R, right.

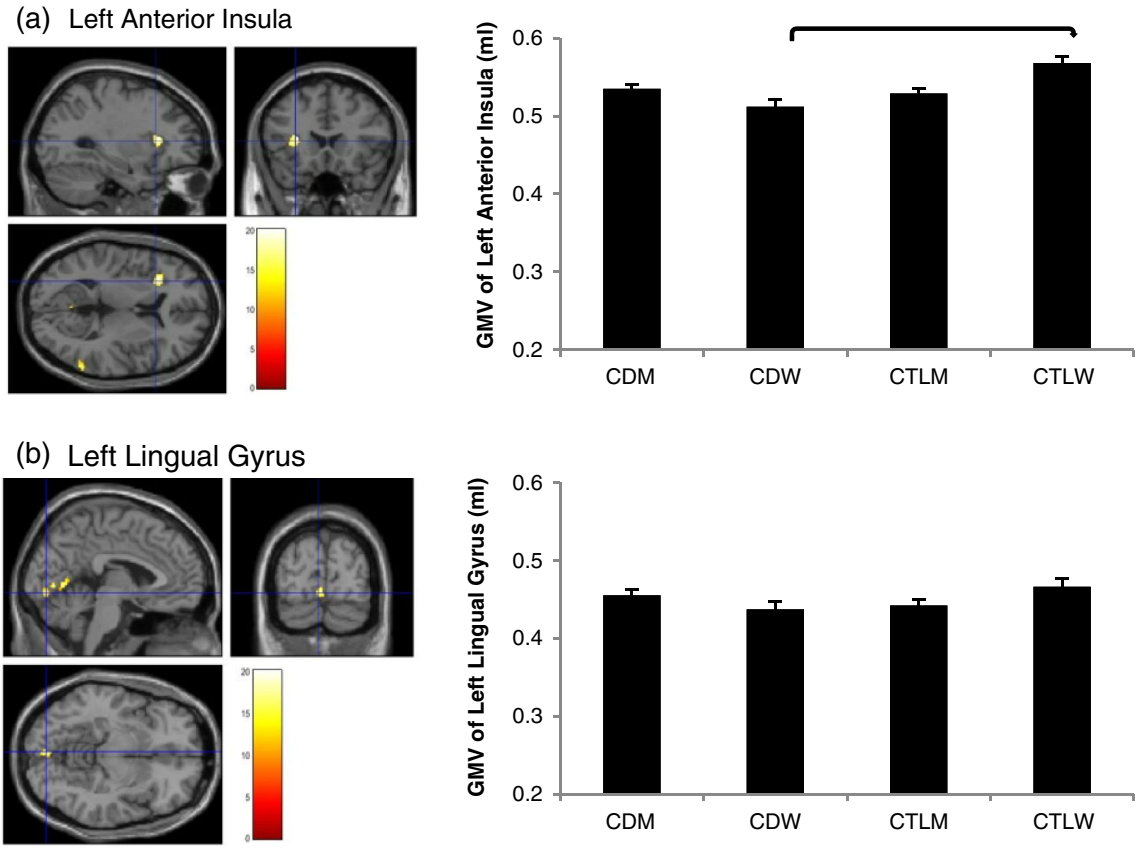


FIGURE 1 Diagnosis × gender interactions in gray matter volume. Structural images demonstrate significant diagnosis × gender interactions in the (a) left anterior insula (x = −32, y = 23, z = 8) and (b) left lingual gyrus (x = −2, y = −84, z = −8). Axial, coronal, and sagittal views are shown. The color bar represents the corresponding F-values. The bar graph on the right demonstrates post hoc group differences for the left anterior insula. See Table 2 for statistics

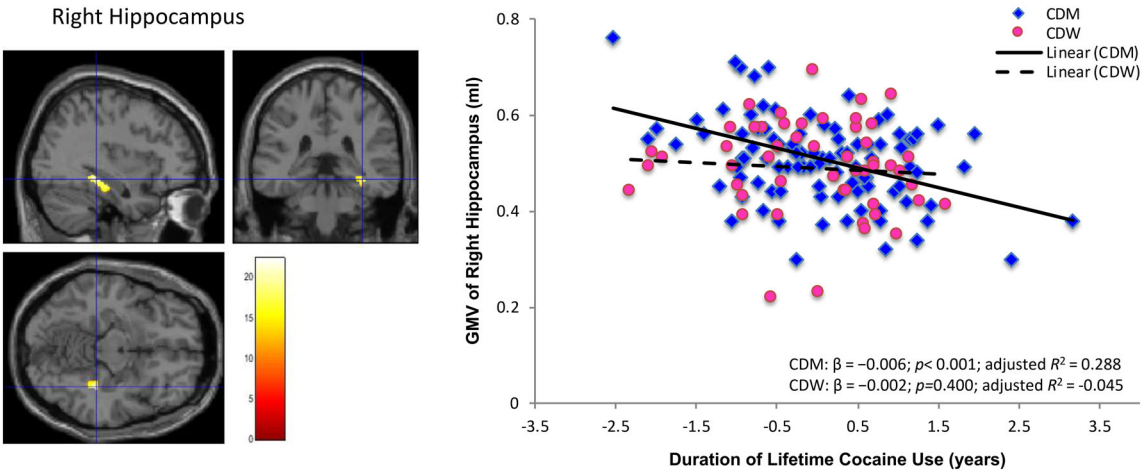


FIGURE 2 Partial regression plot of the relationship between duration of cocaine use and gray matter volume of the right hippocampus. In CDM, longer duration of cocaine use was associated with lower GMV in the right hippocampus (x = 36, y = −36, z = −12). This relationship was not observed in CDW or across all CD participants. Standardized residuals are plotted to account for all controlled covariates (age, total intracranial volume, and site). Structural images (on the left) show the right hippocampus in an axial, coronal and sagittal view. The color bar represents the corresponding T-value

correlation in the CDM, β = −.006, p < .001, but did not show a similar correlation in the CDW, β = −.002, p = .400; Figure 2). While showing the expected trend, the difference between regression coefficients in CDM compared to CDW did not reach significance (t = 1.78 [144], p = .07). Similarly, whole-brain gender × duration of cocaine use interactions did not reach statistical significance. Notably, results remained significant when adding current cigarette smoking and alcohol use disorder as covariates to the regression model; see Supporting Information.

3.2.1 | Post-hoc analyses

While there were no significant relationships between duration of cocaine use and the left anterior insula using a whole-brain regression approach, a significant relationship was observed across all CD participants with the extracted left anterior insula regional values (β = −.002, p = .003). However, when covariates were included (age, total intracranial volume, and site), the relationship was no longer significant (p = .062). This relationship was also not significant in the CD subgroups (CDM or CDW) both with and without covariates.

4 | DISCUSSION

Replicating prior findings, compared to controls, the group of CD individuals demonstrated lower GMV in several frontal regions including the left frontal pole, right orbitofrontal cortex, bilateral superior frontal gyrus, and left anterior cingulate (Alia-Klein et al., 2011; Ersche et al., 2011; Franklin et al., 2002; He et al., 2018; Matochik, London, Eldreth, Cadet, & Bolla, 2003; Moreno-Lopez et al., 2012; Rando et al., 2013; Sim et al., 2007). We also confirmed previous reports of lower GMV in CD individuals compared to controls in the temporal cortex, specifically in the inferior temporal gyrus (Alia-Klein et al., 2011; Moreno-Lopez et al., 2012; Sim et al., 2007). While GMV of the supplementary motor cortex has previously been shown to correlate with duration of cocaine use in individuals with CD (Ersche et al., 2011), to our knowledge we are the first to report a difference between CD individuals and controls in this region (CD < CTL). Notably, these results differ from previous findings using the ENIGMA Addiction consortium data, where we reported no difference in GMV (in regions defined by Freesurfer) in CD users compared to controls (Mackey et al., 2019). However, cocaine users were still discernable from controls in cortical thickness of the supramarginal gyrus, suggesting that group differences indeed exist. Discrepancies between findings from the two studies may be attributed to the following: (a) sample specific variability (in order to age- and gender-match controls to CD participants we only used a subset of the previous ENIGMA data, with data from three additional ENIGMA sites incorporated only into the current analysis) and (b) the analytic approach used (the previous study used a region of interest approach defined by FreeSurfer, while the current study employed a voxelwise GMV approach, which might have greater sensitivity for detecting small regional group differences effects that may be averaged out when measured over a larger area such as in Freesurfer).

With respect to gender differences and in line with previously reported findings, women had greater GMV in many frontal and temporal regions as well as in the thalamus, caudate, parahippocampal gyrus, and the lateral cerebellum compared to men (Lotze et al., 2019; Ruigrok et al., 2014; Wei, Chen, Dong, & Zhou, 2016). However, unlike other studies, we also found greater GMV in the supplementary motor cortex in women compared to men. While a large study reported that men tend to have greater GMV in subcortical regions (Lotze et al., 2019), our study only showed one region, the cerebellar vermis, with greater GMV in men than women.

Importantly, an interaction between diagnosis and gender emerged in two regions such that compared to control women, CD

women had lower GMV in the left anterior insula and left lingual gyrus. No such effect was observed in men. The insula result parallels (Rando et al., 2013; Regner et al., 2015) and replicates (Li et al., 2005) prior findings in smaller sample sizes of women (but not men) with cocaine- or stimulant-dependence compared to control women. A similar pattern of results was found in the left lingual gyrus, with CD women showing lower GMV compared to control women, although post hoc tests did not reach significance, hence, the source of this interaction cannot be statistically determined.

The insula has extensive connections with frontal, sensory, and other limbic regions of the brain (Ture, Yasargil, Al-Mefty, & Yasargil, 1999) and has consistently been implicated in a host of functions related to addiction (Droutman, Read, & Bechara, 2015; Rotge et al., 2017). The anterior insula, specifically, is thought to play a role in the perception of one's internal bodily states, emotional awareness, cognitive processing, and regulatory functions (Cole et al., 2013; Craig, 2009; Gasquoine, 2014; Gu, Hof, Friston, & Fan, 2013; Wang et al., 2019; Zaki, Davis, & Ochsner, 2012) as a means to maintain physiological homeostasis (Craig, 2002; Harrison, Gray, Gianaros, & Critchley, 2010). Both GMV and neural activity within the anterior insula predicted objective measures of interoceptive performance and subjective ratings of visceral awareness in healthy volunteers, suggesting that the insula is indeed a neuroanatomical substrate for feeling states (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Accordingly, it is plausible that insular abnormalities, namely GMV loss, may contribute to a desensitized interoceptive system and failure to properly engage in self-reflection/awareness and behavioral control in drug addicted individuals (Goldstein et al., 2009; Noel, Brevers, & Bechara, 2013). Importantly, these feeling states may be central to the conscious experience of motivational states that contribute to drug urges and cravings (Garavan, 2010). As such, there is evidence to suggest that structural abnormalities of the insula are associated with greater craving severity and dependence severity in addicted individuals (Morales, Ghahremani, Kohno, Hellemann, & London, 2014). Our finding of decreased GMV in the insula in CD women (but not men) needs to be taken into account also with a previous result whereby gender differences in interoception were driven by greater sensitivity and attentiveness to internal signals in women as compared to men (Grabauskaite, Baranauskas, & Griskova-Bulanova, 2017). In this respect, women may become motivated to engage in drug use to alleviate cravings and/or withdrawal symptoms and to restore equilibrium (Naqvi & Bechara, 2010), overpowering the intent to attain other nondrug related goals (Paulus, Tapert, & Schulteis, 2009). However, given that the association with duration of cocaine use did not survive corrections for whole-brain analyses or for covariates, lower insular GMV in CD women may reflect a neuroanatomical endophenotype that predisposes women to cocaine dependence; this speculation remains to be tested. Of note, prior studies that reported negative associations between duration of cocaine use and GMV of the insula included either all men (Barros-Loscertales et al., 2011) or predominantly (~90%) CD men (Ersche et al., 2011) with the largest sample size for any group in these studies of $n = 53$.

The lingual gyrus is directly connected to the insula as well as to other regions within the limbic system (Conrad & Stumpf, 1975; Ghaziri et al., 2017) and is a key region of the visual cognitive network supporting processes such as visual memory (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987) and vivid visual imagery (Olivetti Belardinelli et al., 2009). Numerous investigations have described a role for the visual cortex in the pathophysiology of addiction. For example, a meta-analysis reported that 86% of addiction-related neuroimaging studies demonstrated significant visual cortex activity in response to drug cues in comparison to neutral cues (Hanlon, Dowdle, Naselaris, Canterberry, & Cortese, 2014), suggesting a potential role for the lingual gyrus in discriminating salient stimuli (Vollstadt-Klein et al., 2012). Further, in a normative sample, greater GMV of the lingual gyrus was associated with enhanced cognitive fluency, defined as the ability to inhibit strong preferences by shifting attention to other nonrelated mental activities (Jauk, Neubauer, Dunst, Fink, & Benedek, 2015), a function compromised in stimulant-dependent individuals (van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009). Thus, although post hoc tests did not reach significance, the significant interaction in this region and the pattern of results suggests that lower GMV in the lingual gyrus in CD women compared to control women may contribute to a heightened attentional bias to drug-related stimuli.

A significant relationship between duration of cocaine use and lower GMV in the right hippocampus was significant in CD men (but not women). This association replicates results from a previous study by our group that exclusively assessed CD men (Alia-Klein et al., 2011) and a meta-analysis that predominantly included men with cocaine dependence (~90%) (Hall et al., 2015). The high degree of plasticity of the hippocampus (Leuner & Gould, 2010) and its role in learning contextual associations (Smith & Mizumori, 2006) play an important role in drug-seeking and relapse (Bossert, Marchant, Calu, & Shaham, 2013). Specifically, preclinical evidence suggests that the hippocampus is implicated in the formation and maintenance of long-term memories that support cocaine-cue/context associations (Burgdorf et al., 2017; Castilla-Ortega et al., 2016). The harmful nature of these associative memories can be attributed to their robust resistance to extinction (i.e., forgetting) (Kutlu & Gould, 2016), which may in part be due to cocaine's deleterious effects on hippocampal neurogenesis (Garcia-Fuster, Perez, Clinton, Watson, & Akil, 2010; Noonan, Bulin, Fuller, & Eisch, 2010; Sudai et al., 2011). Hippocampal dopamine release following exposure to drug cues in CD individuals (Fotros et al., 2013) may potentiate drug memories (Everitt & Robbins, 2016; Q. S. Liu, Pu, & Poo, 2005), resulting in an inability to effectively extinguish the motivational salience of drug-associated cues and contexts (Havermans & Jansen, 2003; Martin, LaRowe, & Malcolm, 2010). In our study, although the direct comparison of slopes by gender did not reach significance, the stronger association with duration of cocaine use in CD men may reflect differential susceptibility to the morphological and physiological changes to the hippocampus. One such mechanism may be conferred by the protective effects of estrogen on hippocampal neurogenesis in women (Barker & Galea, 2008). Another mechanism may invoke chronic stress (Andreano & Cahill, 2009), which may also extend to drug use. In partial support is a recent study of a predominantly male sample of CD

individuals showing that increased cerebral blood flow to the posterior hippocampus at rest, a measure of enhanced resting-state activity (Thomason, Tocco, Quednau, Bedway, & Carre, 2013), was associated with an increased relapse risk to cocaine (Adinoff et al., 2015).

Contrary to previous research (Rando et al., 2013; Regner et al., 2015), we did not observe a GMV interaction in frontal cortical structures (e.g., anterior cingulate cortex, orbitofrontal cortex) or limbic-related structures other than the insula and hippocampus, such as the amygdala. Notably, previous studies that reported GMV gender differences in these other brain regions examined mostly participants with stimulant-dependence rather than samples restricted to cocaine users (Regner et al., 2015). Future research is needed to directly compare women with stimulant use disorders (to amphetamines, and/or methamphetamines, and/or 3,4-methylenedioxymethamphetamine, with or without cocaine) to CD women exclusively. In addition, our analyses showed that the interaction effects were not driven by men, which contrasts with previous reports that showed lower GMV in the precentral and midcingulate gyrus in men with cocaine dependence compared to control men (Rando et al., 2013). In general, our more circumscribed results may reflect our focus on cocaine dependence and the inclusion of a large sample size.

While results from this large multi-site sample support the presence of gender differences in GMV in cocaine dependence, we had limited data pertaining to the additional potential influence of comorbid and/or polysubstance use (nicotine, alcohol, cannabis, etc.) that commonly accompanies cocaine use (Liu, Williamson, Setlow, Cottler, & Knackstedt, 2018). Although our results suggest that current nicotine smoking and alcohol use disorder did not contribute to results, future studies should include more detailed and quantitative measures ascertaining the patterns of co-substance use (e.g., frequency/amount and duration of use). A related limitation, and common characteristic of numerous multi-site retrospective studies, pertains to our inability to examine the impact of numerous other clinical (e.g., affective symptoms/diagnoses such as depression and anxiety), drug-use (e.g., age of onset, amount of use, abstinence length, treatment history and other environmental factors, route/type of cocaine administration), and behavioral variables in our sample. The contribution of other factors, such as race (Chee, Zheng, Goh, Park, & Sutton, 2011; Tang et al., 2010) and genetic markers (Petrella, Mattay, & Doraiswamy, 2008) to our results also remains to be studied. It is plausible that these other factors contributed to the GMV differences reported here as remains to be tested to enhance the translational impact of our structural findings. Moreover, differences in pharmacological sensitivity to cocaine (Evans, 2007; Soutschek et al., 2017), variations in stress reactivity (Back et al., 2005; Fox et al., 2009; Waldrop et al., 2010), and hormonal factors (Quinones-Jenab et al., 2001; Ramoa, Doyle, Naim, & Lynch, 2013) should be considered as they also may mediate sexually dimorphic effects related to addiction. It would be advantageous if future studies could incorporate assessments of these dynamic measures to better understand their putative contributions to the neuroanatomical gender differences reported here. Nevertheless, a clear strength of this study is the sample size, being the largest analysis of gender-based differences in GMV in cocaine use disorder to date, with enough power to detect even small effects.

The current results add to the fledgling literature documenting gender differences in the development, course, and pattern of GMV atrophy associated with cocaine dependence in humans. More research is needed to better understand their underlying mechanisms in order to improve upon currently available treatment options for this difficult to treat disorder. Targeted deployment of gender-specialized interventions may offer help for CD individuals. For example, treatment for women may emphasize targeting interoceptive processes, such as self-awareness and greater attention to body sensations as well as retraining attentional bias. In contrast, treatment for CD men may benefit from interventions that focus on extinguishing conditioned responses to drugs and their cues.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Rachel A. Rabin: Provided substantial contributions to the conception, analysis, and interpretation of data for the work. Rachel A. Rabin also wrote the manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Scott Mackey: Prepared data for multi-site analysis and helped with data analysis. Scott Mackey also provided final approval of the manuscript to be published. Muhammad A. Parvaz: Helped with data analysis and provided final approval of the manuscript to be published. Janna Cousijn: Helped with editing of the manuscript and provided final approval of the manuscript to be published. Chiang-shan Li: Contributed to the acquisition of the data and provided final approval of the manuscript to be published. Godfrey Pearlson: Contributed to data acquisition and final approval of the manuscript to be published. Lianne Schmaal: Contributed to data acquisition and final approval of the manuscript to be published. Rajita Sinha: Contributed to data acquisition and final approval of the manuscript to be published. Elliot Stein: Contributed to data acquisition and final approval of the manuscript to be published. Dick Veltman: Provided final approval of the manuscript to be published. Paul M. Thompson: Provided final

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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