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Cocaine-related alterations in fronto-parietal gray matter volume correlate with trait and behavioral impulsivity

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Abstract

Background: Chronic cocaine use is associated with structural brain abnormalities within prefrontal regions implicated in impulsivity. Despite high levels of impulsivity among persons who use cocaine, it is not known how reductions in gray matter volume (GMV) may relate to trait and behavioral measures of impulsivity.

Methods: The sample included 39 active cocaine users (COC+) and 40 controls with no history of cocaine use (COC-). Participants had a brain scan on a 3T MRI machine and completed out-of-scanner measures of trait impulsivity and delayed reward discounting. Whole-brain voxel-based morphometry was used to compare GMV between COC+ and COC-. Within regions that differed between groups, voxelwise correlations were conducted to examine the relationship between GMV and impulsivity.

Results: In a whole-brain analysis, COC+ had broad reductions in GMV compared to COC- in bilateral frontal, parietal, occipital, and cerebellar regions. Lower GMV correlated with trait impulsivity in lateral prefrontal regions and with delayed reward discounting in medial prefrontal regions, while lower GMV correlated with both measures in the posterior parietal cortex. COC+ demonstrated significantly higher impulsivity than COC- on all measures, but the nature of the correlation with GMV was similar in both groups.

Conclusions: Reflecting the multi-faceted nature of impulsivity, these results show that trait and behavioral measures of impulsivity map differentially onto altered brain morphology. While the brain-behavior patterns were similar in COC+ and COC-, suggesting that impulsivity varies on a

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Contributors

Meade conceptualized the study and secured grant funding; Meade, Towe, and Bell conducted the analyses; all authors contributed to interpretation of findings; Meade drafted the manuscript and Bell, Towe, and Hall wrote additional sections; and all authors reviewed the manuscript and approved the final version.

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CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

continuous spectrum, cocaine-related abnormalities in frontal-parietal brain systems may contribute to heightened impulsivity.

Keywords

Cocaine; Impulsivity; delayed reward discounting; MRI; voxel-based morphometry; gray matter volume

1. INTRODUCTION

Cocaine use remains a significant public health problem, with multiple indicators suggesting that it is on the rise globally. After a sustained decrease, cocaine manufacture rose by 56% from 2013 to 2016, reaching its highest level in recorded history (UNODC, 2018). In 2016, approximately 18.2 million people worldwide used cocaine, a nearly 7% increase from 2015 (UNODC, 2018). The prevalence of cocaine use is highest in the United States, with an estimated 1.9 million current users (Ahrnsbrak et al., 2017). Chronic cocaine use is associated with deficits in reward-based decision making that are often associated with impulsive behaviors (Spronk et al., 2013). Many of the negative consequences of cocaine use, such as sexually transmitted infections, criminal behaviors, and violence (Butler et al., 2017; Enns et al., 2017), likely stem from impulsivity.

Impulsivity is a multidimensional construct that describes a propensity toward rapid, unplanned reactions without regard for possible undesirable consequences (de Wit, 2009; Robbins et al., 2012). Most commonly, impulsivity is measured as a personality trait using self-report questionnaires that require introspection. As a personality trait, there are three distinct substrates of impulsivity – attentional, non-planning, and motor (Stanford et al., 2009). In contrast, behavioral measures provide a direct assessment of specific processes involved in impulsivity. Among these, delayed reward discounting describes the subjective devaluing of rewards that are delayed in time (Mazur, 1987; Rachlin and Green, 1972). Delayed reward discounting can be estimated using decision-making tasks that ask participants to choose between smaller, immediate rewards and larger, delayed rewards. Together, trait and behavioral measures of impulsivity may provide complementary information related to the neural mechanisms underlying the expression of impulsive behavior.

Cocaine users consistently demonstrate greater trait impulsivity and delayed reward discounting compared to non-cocaine users (Dalley et al., 2011; MacKillop et al., 2011; J. L. Smith et al., 2014). Impulsivity is thought to be related to abnormalities in the mesocorticolimbic system, including lower gray matter volume (GMV). In healthy adults, trait impulsivity is most consistently associated with reduced GMV in medial frontal regions, specifically orbitofrontal cortex (OFC) and medial prefrontal cortex (MPFC) (Fuentes et al., 2012; Korponay et al., 2017; Matsuo et al., 2009). In contrast, delayed reward discounting appears to be associated with reduced GMV in the lateral prefrontal cortex, including dorsal (DLPFC) and ventral (VLPFC) regions, as well as abnormalities in the OFC (Bjork et al., 2009; Mohammadi et al., 2016; Owens et al., 2017; Wang et al., 2016).

Many studies have identified cocaine-related abnormalities in the mesocorticolimbic system (Mackey and Paulus, 2013), largely overlapping with the regions implicated in impulsivity. The most consistent finding is reduced GMV in lateral and medial prefrontal cortices, including DLPFC, VLPFC, and OFC, among cocaine users compared to healthy controls, although broader reductions in temporal, hippocampal, and cerebellar regions have also been reported (Alia-Klein et al., 2011; Crunelle et al., 2014; Ersche et al., 2011; Moreno-Lopez et al., 2012; Sim et al., 2007; Yip et al., 2018). The largest of these studies also demonstrated cocaine-related increases in striatal volume (Ersche et al., 2011).

Only three of the aforementioned studies examined the link between brain morphology and impulsivity in cocaine users. Two studies correlated whole-brain GMV to trait impulsivity. In the first, which included only cocaine users, attentional impulsivity correlated negatively with GMV in the OFC and precentral gyrus (Crunelle et al., 2014). Unexpectedly, there were also positive correlations between motor impulsivity and GMV in the DLPFC and between non-planning impulsivity and GMV in the posterior parietal cortex (PPC) (Crunelle et al., 2014). In the second study, which included cocaine users, gamblers, and healthy controls, trait impulsivity correlated negatively with GMV in insular, limbic, and temporo-parietal regions (Yip et al., 2018). A third study combined trait measures with behavioral measures of inhibitory control and sustained attention (Ersche et al., 2011). Restricting the analyses to regions that differed between cocaine users and controls, greater impairment in attentional control, as measured primarily by a stop-signal task, was negatively correlated with GMV in the insula and middle temporal area, and positively with GMV in the striatum (Ersche et al., 2011). These studies suggest that brain morphology may contribute to impulsivity in cocaine users, but findings are inconsistent. Moreover, prior studies have not examined the relationship between GMV and delayed reward discounting, a signature of drug addiction, in persons who use cocaine.

Building upon this foundational research, the present study investigated the relationship of GMV to impulsivity in a community-recruited sample of cocaine users. Using voxel-based morphometry, we expected to find reduced GMV in lateral and medial PFC and increased GMV in the striatum among cocaine users compared to a closely matched comparison group of non-cocaine users. To investigate the potential implications of cocaine-related abnormalities in brain structure, we examined the relationship of GMV to both trait impulsivity and delayed reward discounting. We hypothesized that prefrontal GMV would be negatively correlated with both measures, and that the strength of the correlation would be strongest in cocaine users.

2. METHODS

2.1. Participants

The study was open to adults aged 18–55 years who were active cocaine users (COC+) or non-cocaine users (COC–). The COC+ groups met the following criteria: lifetime cocaine dependence as defined by the DSM-IV-TR, regular cocaine use for 1 year, repeated use in the past month (defined as 2 days or positive drug screen), and cocaine as a principal drug of abuse (as determined by structured clinical interviews). The COC– groups had no history of cocaine abuse and met the following criteria: no lifetime cocaine use disorder (abuse or

dependence), no history of regular cocaine use, no cocaine use in the past year, and a cocaine-negative drug screen. Alcohol and marijuana use were permitted in all groups. For other drugs, individuals were excluded for any history of dependence, lifetime regular use for >2 years, and regular use in the past year. Additional exclusion criteria were: English non-fluency or illiteracy; <8th grade education; severe learning disability; serious neurological disorders or history of neuroinfections; severe head trauma with loss of consciousness >30 minutes and persistent functional decline; severe mental illness; current use of antipsychotic or mood stabilizing medications; MRI contraindications; and/or impaired mental status.

2.2. Procedures

Participants were recruited via advertisements in local newspapers, websites, and community-based organizations. After a brief pre-screener conducted over the telephone, individuals completed an in-person screening. Eligible participants returned for the MRI scan and additional assessments. All participants provided written informed consent, and procedures were approved by the institutional review board at Duke University Health System. Participants were compensated up to \$180 for their participation.

2.3. Screening measures

All participants had a confirmed blood alcohol level of 0.00 prior to engaging in any study activities. Participants completed clinical interviews, computerized surveys, urine drug screening, and pregnancy testing. Module E of the Structured Clinical Interview for DSM-IV-TR identified substance use disorders (First et al., 1996), and the Addiction Severity Index-Lite assessed current and lifetime substance use and associated impairments (McLellan et al., 1992). This comprehensive substance abuse assessment covered cocaine, marijuana, alcohol, opioids, amphetamines, benzodiazepines, and other illicit drugs. Participants reported on demographic characteristics, including age, gender, race, and education. HIV status was verified using an OraQuick© rapid test; all participants were negative. Healthcare records were reviewed to ensure no exclusionary medical history, including substance abuse.

2.4. Behavioral assessments

Substance abuse.—On the day of the MRI scan, participants had another breathalyzer test, which had to be 0.00 before proceeding with the visit. Timeline follow-back methodology was used to assess substance use in the past 30 days (Robinson et al., 2014). Participants also completed another urine toxicology screen for cocaine, cannabis, methamphetamine, opioids, and benzodiazepines.

Trait impulsivity.—Trait impulsivity was assessed with the widely-used the Barratt Impulsivity Scale (BSI-11) (Patton et al., 1995). This 30-item self-report measure includes three factors that capture non-planning, attentional, and motor impulsivity. Non-planning impulsivity describes a present orientation without consideration of the future (e.g., “I plan tasks carefully.” “I am self-controlled.” “I am more interested in the present than the future.”). Attentional impulsivity is characterized by an inability to focus or concentrate (e.g., “I don’t pay attention.” “I concentrate easily.” “I have racing thoughts.”). Motor

impulsivity involves acting without thinking (e.g., “I do things without thinking.” “I act on the spur of the moment.” “I can only think about one thing at a time.”). Participants rate the frequency with which each item applies to them using a 4-point scale.

Delayed reward discounting.—The Monetary Choice Questionnaire (MCQ) is a commonly used delayed reward discounting task that asks participants to choose between a series of smaller, immediate rewards and larger, delayed rewards (e.g., “Would you prefer \$33 today or \$80 in 14 days?”) (Kirby et al., 1999). To accommodate for extreme discounting among cocaine users, we used the extended version (MCQ-36), which includes a fixed set of 36 items (Towe et al., 2015). Immediate rewards ranged from \$7-\$80 and delayed rewards ranged from \$25-\$85 with a delay of 1–186 days. The task was programmed using ePrime (Psychology Software Tools, Inc., <http://www.pstnet.com>), and choices were presented in random order. Participant k-values were estimated using standard scoring procedures (Towe et al., 2015). Since the range of possible k-values increases exponentially from 0.00016 to 4.00, the data was normalized using a natural logarithm transformation.

2.5. MRI data acquisition

MRI data was acquired with a 3.0T GE Discovery MR750 whole-body scanner. All scans occurred on the same scanner at the Brain Imaging and Analysis Center at Duke University using an eight-channel head coil. High-resolution T1-weighted structural images were acquired with the following parameters: TR = 8.10 ms, TE = 3.18 ms, FOV = 25.6 cm, flip angle = 12°, in-plane matrix = 256*256; slice thickness = 1 mm, and number of slices = 166.

2.6. Data Analysis

Case-specific pre-processing steps were implemented to improve data quality. The images were first visually checked to ensure full coverage and identify significant motion-related artifacts that could affect processing. Structural data was analyzed with FSL-VBM (Douaud et al., 2007, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted and segmented for maximum gray matter (GM) inclusion before being registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template that contained equal representation from both groups. Second, all native GM images were non-linearly registered to this study-specific template and “modulated” to correct for local expansion/contraction due to the non-linear component of the spatial transformation. The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. Finally, a voxelwise GLM was performed between groups using permutation-based non-parametric testing ($p < .05$; 10,000 permutations), correcting for multiple comparisons across space using FSL’s Threshold-Free Cluster Enhancement (TFCE) (S. M. Smith and Nichols, 2009). Age (in years) and other substance use (alcohol use, marijuana use, and daily cigarette use; each yes/no) were included as covariates. Analyses were restricted to a mean GM mask created from the study sample. Any significant regional differences between groups in the whole-brain analysis were then masked, and the mean GMV within each cluster was extracted using `fslmeans`. Cortical regions were defined using the Human Connectome Project’s multi-modal cortical

parcellation (HCP_MMP1.0) that delineates 180 regions per hemisphere (Glasser et al., 2016), while sub-cortical regions and cerebellum were identified using the Harvard-Oxford Atlas (Desikan et al., 2006). Among COC+, in regions that differed between groups, we examined the relationships between GMV to years of regular cocaine use and days of use in the past 30 days (log 10 transformed) while controlling for age utilizing a voxelwise correlation analysis.

These regional volumes were then examined across the entire sample for any relationship to trait impulsivity (BIS-11 factors) and delayed reward discounting (MCQ In k-value) utilizing voxelwise correlations restricted to a mask of significant results from the whole-brain analyses with age and other substance use included as covariates. These voxelwise correlations were conducted using permutation testing ($p < .05$; 10,000 permutations) with TFCE correction. Scatter plots were used to visualize the partial correlations between GMV and impulsivity controlling for age and other substance use. To test whether COC status moderated the relationship between GMV and impulsivity scores, step-wise multiple regression models were conducted in SPSS Statistics 26. For each significant cluster, variables were entered in blocks as follows: (1) age and other substance abuse, (2) COC status and impulsivity measure, and (3) interaction product of COC status and impulsivity measure.

3. RESULTS

3.1. Sample characteristics

The sample included 39 COC+ and 40 COC- participants (Table 1). Participants were primarily male (61%) and African-American (77%), ranging in age from 28 to 55 ($M = 44.43$, $SD = 6.87$), and had a mean of 13.16 years of education ($SD = 2.36$). Participants were well matched on gender, race, and age, but COC+ had significantly fewer years of education than COC-.

Participants in the COC+ group had been using cocaine regularly for an average of 17.87 years ($SD = 8.20$), with the majority (92%) reporting smoking as their primary route of administration. In the 30 days prior to screening, they had used on an average of 10.69 days ($SD = 7.66$). On the day of the scan, 76% of participants had a urine toxicology screen positive for cocaine. The mean number of days since last use was 4.31 ($SD = 5.67$), with 69% reporting use within the past 3 days.

Polysubstance use was common (Table 1). In the past 30 days, 71% used alcohol, 35% used cannabis, and 49% smoked cigarettes daily, with COC+ more likely than COC- to use each substance. Among users of each substance, COC+ had used alcohol on more days, while COC- had used cannabis on more days.

As expected, COC+ had significantly higher scores than COC- on each subscale of the BIS-11, indicating higher trait impulsivity. They also demonstrated steeper delayed reward discounting on the MCQ, with higher k-value estimates.

3.2. Group differences in GM volume

In the whole-brain analysis, voxel-wise group comparisons revealed significant group differences in seven clusters that spanned bilateral regions throughout frontal, parietal, and occipital lobes and the cerebellum (Figure 1, Table 2). In each cluster, COC+ had significantly reduced GMV compared to COC-. The largest cluster of $>110,000 \text{ mm}^3$ included bilateral DLPFC, VLPFC, OFC, MPFC, frontopolar cortex, anterior cingulate cortex, and motor cortices. Additional clusters included bilateral cerebellum, right and left PPC, right and left visual cortices, and left insula. Among COC+, years of regular cocaine use and days of cocaine use in the past 30 days was unrelated to GMV in all clusters ($p > .05$).

3.3. Correlation with impulsivity measures

Within the clusters that differed significantly between COC+ and COC-, there were significant voxel-wise correlations of GMV with BIS attention, BIS non-planning, and MCQ In k-value, but not BIS motor (Figure 2). In each case, reduced GMV correlated with increased impulsivity. Table 3 describes the clusters that correlated with each measure, including the overlap across measures. Reduced volume in the left DLPFC and VLPFC correlated with greater attentional and non-planning impulsivity. For non-planning, this correlation was present in a larger area of the DLPFC and VLPFC. Reduced volume in the PPC correlated with greater non-planning and delayed reward discounting, with substantial overlap for the two measures. Delayed reward discounting was also uniquely correlated with reduced volume in the MPFC and OFC.

Figure 2 shows the scatterplots for each significant correlation. Moderator analyses confirmed that the strength of the correlations were similar between COC+ and COC- for each impulsivity measure. The COC*impulsivity interaction term was non-significant for attentional impulsivity in the left DLPFC ($\beta = .24, p = .58$), for non-planning impulsivity in the left DLPFC ($\beta = -.74, p = .25$) and left PPC ($\beta = -.32, p = .64$), and for delayed reward discounting in the bilateral OFC ($\beta = -.22, p = .33$) and left PPC ($\beta = -.31, p = .13$).

4. DISCUSSION

Our key finding is that cocaine-related alterations in fronto-parietal GMV are associated with both trait and behavioral measures of impulsivity. Consistent with prior studies, cocaine users had reduced GMV compared to non-cocaine users broadly in the bilateral PFC, including DLPFC, VLPFC, OFC, and MPFC, and throughout occipital, parietal, and cerebellar regions. As expected, cocaine users also had higher trait impulsivity and steeper delayed reward discounting, which were associated with morphological differences in the PFC and PPC. Specifically, lower GMV correlated with trait impulsivity in the lateral PFC and with delayed reward discounting in the medial PFC, while lower GMV correlated with both measures in the PPC. The nature of these correlations was similar for cocaine users and non-users, underscoring the relevance of brain structure for understanding both normal personality differences and more extreme impulsivity in clinical populations.

Self-reported measures of trait impulsivity capture an individual's self-perception of behavior, and thus rely heavily on regions of the cognitive control system. Specifically, both non-planning and attentional impulsivity correlated with GMV in the left DLPFC/VLPFC. The lateral PFC plays a key role in cognitive and inhibitory control processes across multiple domains (Miller and Cohen, 2001). Specifically, the DLPFC is associated with impulsive choice, attention, and planning, while the VLPFC is activated during response inhibition (Bari and Robbins, 2013; Dalley and Robbins, 2017; Morein-Zamir and Robbins, 2015; Zhang et al., 2017). The non-planning cluster extended into a larger area of the lateral PFC, suggesting that this is a more complex component of impulsivity that draws on broader set of neural substrates. Moreover, non-planning also correlated with GMV in the PPC, which is involved in decision making processes that require cognitive flexibility or abstraction, including the evaluation of reward magnitude and probability (Dorris and Glimcher, 2004; Zhou and Freedman, 2019). These regions map onto the lateralized fronto-parietal network that is critical for planning and other complex attentional tasks (Huettel et al., 2005; Laird et al., 2011; Majdandzic et al., 2007; Newman et al., 2003; Reyna and Huettel, 2014).

In contrast, delayed reward discounting correlated with GMV in the OFC and MPFC, suggesting that discrete regions of the PFC are involved in different aspects of impulsivity. Medial prefrontal activation is associated with a preference for immediate rewards (Dalley and Robbins, 2017; Hariri et al., 2006). Specifically, the OFC is thought to guide behavior based on the represented value of expected outcomes (Lucantonio et al., 2012), and has been shown to be involved in delayed reward discounting tasks (Mobini et al., 2002; Winstanley et al., 2004). In functional MRI studies, the medial OFC shows greater activation when choosing the smaller, sooner reward (McClure et al., 2007; McClure et al., 2004), while the PPC encodes the subjective value of the delayed option (Essex et al., 2012; Louie and Glimcher, 2010; Massar et al., 2015). In sum, structural abnormalities in the OFC/MPFC and PPC may disrupt reward processing and top-down control over impulses, leading to an exaggerated preference for immediate rewards.

While multiple studies have examined brain volume differences associated with cocaine addiction, there is considerable inconsistency in results (Mackey and Paulus, 2013). This could stem from differences in methodologies, such as alternate software packages and variations in smoothing kernel size. In addition, some of the earlier studies had relatively small sample sizes (Button et al., 2013). Given the current crisis of reproducibility in neuroscience, including a lack of attention to reproducing well-powered studies (Poldrack et al., 2017), we report whole-brain GMV analyses. The most robust study to date included a sample of 60 cocaine users and 60 healthy controls (Ersche, 2011). We reproduced most of their findings, including reduced GMV in prefrontal, parietal, temporal, and cerebellar cortices, but did not find increases in striatum or cerebellum. We also found more extensive reductions in GMV in the lateral PFC, including DLPFC. These differences may relate to our use of TFCE, rather than cluster-based probability thresholding, which minimizes problems associated with defining the arbitrary initial cluster-forming threshold and amount of spatial smoothing (S. M. Smith and Nichols, 2009). Despite these inconsistencies, collectively these studies indicate that cocaine addiction is associated with broad reductions in GMV.

Several biological mechanisms are believed to drive neuronal loss in cocaine users. Vasoconstriction following cocaine intake decreases blood flow in the cortex that can result in “mini-strokes” or cell death (Siniscalchi et al., 2015). In addition, increases in dopamine following cocaine use can lead to cell death via oxidative stress (Pereira et al., 2015). Chronic cocaine use is associated with neuroinflammation resulting from microglial activation, which can lead to tissue damage (Kohn 2019; Ersche 2017). While it might be expected that longer duration of cocaine use would be associated with greater neuronal loss, we did not find a correlation between years of regular use and GMV. However, the COC+ sample was relatively homogenous in regard to cocaine use, with all participants reporting a chronic history of use and meeting diagnostic criteria for dependence. Therefore, this study was not well-suited to test the effects of varying duration of cocaine exposure.

Poly-substance use is highly prevalent among persons who use cocaine (John and Wu, 2017). A strength of this study is the comprehensive assessment of lifetime cocaine and other substance use, and the exclusion of participants with any regular use of “hard” drugs such as opioids and amphetamines. However, we permitted the use of alcohol, marijuana, and nicotine to ensure generalizability of results. Importantly, use of these substances was represented in both groups, although they were more common in the COC+ group. To control for potential effects of these other substances, our analyses controlled for concurrent use of alcohol, marijuana, and cigarettes. As our sample was comprised of persons with cocaine as their principal drug of abuse, additional studies are needed to distinguish the effects of polysubstance abuse on brain morphology.

This is the first MRI study conducted among cocaine users to examine the relationship of GMV to both trait and behavioral measures of impulsivity. Additional strengths of our study include a robust sample size with demographically-matched groups and subject-specific skull stripping parameters to optimize the amount of GM included in the analyses. Nevertheless, there are several limitations to consider. First, due to the cross-sectional design, it is unknown whether reductions in GMV are due to chronic exposure to cocaine or whether individual differences in brain morphology predispose individuals to drug abuse. Longitudinal studies that begin assessments prior to the onset of cocaine use disorder are needed to determine this. Second, our study included only a single behavioral measure that taps delayed reward discounting. Future studies should examine additional processes such as inhibitory control and sustained attention. Finally, while impulsivity is a robust predictor of risk behaviors (Bickel et al., 2012; Hayaki et al., 2006; Stanford et al., 2009), additional research is needed to determine whether cocaine-related abnormalities in GMV relate to real-world outcomes, such as sexual risk behavior.

4.1. Conclusion

Impulsive behaviors in cocaine users are associated with a variety of adverse outcomes, such as use addiction severity (Moeller, Dougherty, et al., 2001), poor treatment adherence (Winhusen et al., 2013), and the development of persistent, compulsive drug-taking (Belin, Mar, Dalley, Robbins, & Everitt, 2008). Consistent with the broader literature, our study suggests that cocaine-related alterations in PFC and PPC structures may contribute to heightened impulsivity. However, trait and behavioral measures mapped differentially onto

brain morphology in the PFC, such that self-reported non-planning and attentional impulsivity were linked to the left DLPFC/VLPFC, while delayed reward discounting was linked to the OFC and MPFC. Our results support the multifaceted nature of impulsivity and the importance of supplementing trait measures with behavioral task data, particularly in clinical populations characterized by elevated impulsivity. Interestingly, the brain-behavior patterns were similar between cocaine users and non-users, suggesting that impulsivity varies along a continuous spectrum, rather than there being a quantitative distinction. While cocaine-related structural abnormalities in fronto-parietal brain systems appear to contribute to impulsive behaviors, longitudinal research is critical to elucidate the mechanisms driving this link.

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Highlights

- Cocaine users had broad reductions in gray matter volume in the brain.
- Reduced volume in prefrontal and posterior parietal cortices correlated with impulsivity.
- Trait impulsivity correlated with left lateral prefrontal and posterior parietal regions.
- Behavioral impulsivity mapped onto left medial prefrontal and posterior parietal regions.
- The link between brain structure and impulsivity is similar in non-cocaine users.

Figure 1.

Whole-brain maps of significant differences in gray matter volume (GMV) between groups. Regions in blue denote lower GMV in COC+ relative to COC- participants. Results were generated through permutation testing of voxel cluster statistics with cluster-wise $p < .05$ using TFCE to correct for multiple comparisons. Clusters are described in Table 2. Statistical results are overlaid on the MNI152 2mm standard-space T1-weighted structural template. The numbers below the images indicate the Z coordinate for each axial slice. Images are in radiological orientation (left = right, right = left).

L. Dorsolateral and ventrolateral cortices **L. Posterior parietal cortex** **B. Medial prefrontal and orbitofrontal cortices** **Figure 2.**

Images on the left show clusters in which gray matter volume (GMV) correlated with impulsivity measures. Voxelwise correlations were conducted using permutation testing with TFCE at $p < .05$ to correct for multiple comparisons. Each impulsivity measure and their overlap is coded with a different color. Clusters are described in Table 3. Statistical results are overlaid on the MNI152 2mm standard-space T1-weighted structural template. The numbers below the images indicate the appropriate coordinate for each slice. Images are in radiological orientation (left = right, right = left). Scatterplots on the right show the correlation between GMV and impulsivity within each significant cluster. The standardized residuals from the partial correlations controlling for age and other substance use are plotted. The r -values represent the partial correlation coefficients. $^*p < .005$, $^{**}p < .001$.

Table 1.

Sample characteristics by cocaine status

	COC+ (N = 39)	COC- (N = 40)	Statistic	P-value
Demographic characteristics				
Male, N (%)	24 (61.5%)	24 (60.0%)	$\chi^2(1) = .020$	.889
Age in years, M (SD)	45.44 (6.21)	43.45 (7.40)	$t(77) = 1.29$	.201
Race, N (%)			$\chi^2(2) = 1.28$	.528
African American	32 (82.1%)	29 (72.5%)		
White	5 (12.8%)	9 (22.5%)		
Other or mixed	2 (5.1%)	2 (5.0%)		
Education in years, M (SD)	12.56 (2.46)	13.75 (2.12)	$t(77) = -2.30$	.024
Impulsivity				
BIS-11 non-planning, M (SD)	28.03 (4.73)	21.50 (4.28)	$t(77) = 6.43$	< .001
BIS-11 attention, M (SD)	15.10 (3.75)	13.23 (3.45)	$t(77) = 2.31$	.023
BIS-11 motor, M (SD)	23.74 (4.99)	19.93 (3.52)	$t(77) = 3.94$	< .001
MCQ ln(k), M (SD) ^I	-2.52 (1.19)	-3.51 (1.83)	$t(74) = 2.77$	.007
Other substance use in past 30 days				
Any alcohol use, n (%)	34 (87.2%)	22 (55.0%)	$\chi^2(1) = 9.91$	.002
Days of alcohol use, M (SD)	12.38 (9.39)	5.09 (6.51)	$t(54) = 3.18$	.002
Any cannabis use, n (%)	18 (46.2%)	10 (25.0%)	$\chi^2(1) = 3.86$	.049
Days of cannabis use, M (SD)	12.00 (11.25)	24.20 (9.16)	$t(26) = -2.93$	.007
Daily cigarette use, N (%)	25 (64.1%)	14 (35.0%)	$\chi^2(1) = 6.69$	.010

^IThree participants had MCQ scores that did not pass the standard QA checks.

Table 2:

Description of clusters that differed between COC groups in a whole-brain analysis

Anatomical regions in cluster	HCP_MMP1.9 area name	Volume in mm ³	X Y Z at max	COC+ M (SE)	COC- M (SE)
B. Dorsolateral prefrontal cortex	L/R_p9-46v *, L/R_46, L/R_8Ad, L/R_s6-8, L/R_SFL, L/R_9p, L_a9-46v, L_9-46d, R_8Av, R_8C, R_8BL, R_i6-8	110,832	-44, 42, 16	.383 (.005)	.425 (.005)
B. Orbitofrontal cortex	L/R_OFC, L/R_13l, L/R_11l, L_a47r				
B. Medial prefrontal cortex	L/R_8BM, L/R_10r, L/R_10v				
B. Ventrolateral prefrontal cortex	L/R_44, L/R_p47r, L/R_IFSa, L_IFJp,				
B. Frontopolar cortex	L/R_a10p, L/R_10pp				
B. Motor cortices	L/R_4, L/R_6mp, L/R_6ma, L/R_SCEF, L_PEF				
B. Anterior and mid cingulate cortices	L/R_s32, R_p32pr, R_24dv, R_24dd				
L. Primary somatosensory cortex	L_3a				
B. Cerebellum *	n/a	21,784	-16, -94, -32	.384 (.011)	.441 (.011)
L. Ventral stream visual cortex	L_PIT				
L. Early visual cortex	L_V2, L_V3, L_V4				
L. Lateral occipital cortex	L_LO2				
R. Posterior parietal cortex *	R_7PC *, R_7AL, R_PGs, R_IP1, R_LIPv	13,960	32, -52, 66	.352 (.007)	.395 (.007)
R. Somatosensory cortices	R_2				
R. Posterior cingulate cortex	R_POS2, R_31pd, R_7m				
L. Posterior parietal cortex *	L_PFm *, L_PGs, L_PGp, L_PF, L_7PC, L_IP2, L_LIPv, L_7AL	12,616	-44, -72, 46	.360 (.006)	.403 (.006)
L. Temporal parietal occipital junction	L_TPOJ3				
R. Lateral temporal cortex	R_TE1p *, R_TE2p, R_PHT	6,112	62, -64, -12	.380 (.008)	.432 (.008)
R. Cerebellum	n/a				
R. Primary and early visual cortices	R_V3 *, R_V2, R_V4, R_V1	4,736	28, -86, -2	.394 (.010)	.450 (.010)
R. Lateral occipital cortex	R_LO2				
L. Insula *	L_PI *, L_PoI1	280	-42, -2, -22	.383 (.007)	.430 (.007)
L. Auditory association cortex	L_STGa				

* Region at maximum value. Mean values are estimated marginal means controlling for age and other substance use.

Table 3:

Description of clusters that correlated with impulsivity measures in regions with volumetric differences between COC+ and COC– groups

Anatomical regions in cluster	HCP_MMP1.9 area name	Volume (mm ³)	X Y Z at max
Primary clusters			
BIS-11 attention			
L. Dorsolateral and ventrolateral prefrontal cortices	L_a9-46v *, L_46, L_IFSa	1,352	–44 40 16
BIS-11 non-planning			
L. Dorsolateral and ventrolateral prefrontal cortices	L_a9-46v *, L_p9-46v, L_46, L_8C, L_p47r, L_IFJa, L_IFSp, L_IFSa	7,496	–42 38 14
L. Posterior parietal cortex	L_PFm *, L_PGs, L_IP1	568	–34 –66 54
MCQ discounting			
B. Medial prefrontal and orbitofrontal cortices	L/R_10v *, L_10r, L_OFC	2,104	0 54 –18
L. Posterior parietal cortex	L_PFm *, L_IP1	648	–36 –68 58
Overlap of clusters			
BIS-11 non-planning and BIS-11 attention			
L. Dorsolateral prefrontal cortex	L_a9-46v *, L_46, L_IFSa	792	–40 40 12
BIS-11 non-planning and MCQ discounting			
L. Posterior parietal cortex	L_PFm *, L_IP1	464	–36 –60 52
BIS-11 attention and MCQ discounting			
None			

* Region at maximum value. Only clusters with >25 voxels are presented.