Addiction Biology | SSA | **WILEY**

Sex differences in brain regional homogeneity during acute abstinence in cocaine use disorder

Breno Sanvicente-Vieira[1,2] | Leonardo Melo Rothmann[1] |
Nathalia Bianchini Esper[1] | Lucca Pizzato Tondo[1] | Pedro Eugênio Ferreira[1] |
Augusto Buchweitz[1,3] | Alexandre Rosa Franco[4,5,6] | Rodrigo Grassi-Oliveira[1,7]

[1]Brain Institute, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

[2]Laboratory of Individual Differences and Psychopathology, Pontifical Catholic University of Rio de Janeiro (PUC-Rio), Rio de Janeiro, Brazil

[3]Department of Psychology, University of Connecticut, Stamford, USA

[4]Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute for Psychiatric Research, Orangeburg, New York, USA

[5]Center for the Developing Brain, Child Mind Institute, New York, New York, USA

[6]Department of Psychiatry, NYU Grossman School of Medicine, New York, New York, USA

[7]Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence
Rodrigo Grassi-Oliveira, Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Universitetsbyen 13, Building 2b, 8000 Aarhus, Denmark.
Email: rogo@clin.au.dk

Funding information
NIDA and Fogarty Foundation (NIH), Grant/Award Number: R01DA044859; Secretaria Nacional de Cuidados e Prevenção às Drogas, Grant/Award Number: 822647/2015; CNPq, Grant/Award Number: 466802/2014-5

Abstract

There are significant sex differences in the clinical characteristics of cocaine use disorder (CUD). As this is a brain disorder that involves changes in functional connectivity, we investigated the existence of sex differences among people with CUD and controls. We used a data-driven method comparing males ($n = 20$, CK-M) and females with CUD ($n = 20$, CK-F) and healthy controls (20 males, HC-M and 20 females, HC-F). The participants undertook a resting-state functional magnetic resonance imaging exam. Regional homogeneity (ReHo) was performed to identify group and sex differences. Persons with CUD of both sexes presented lower ReHo parameters than controls, especially within the parietal lobule. Males with CUD showed higher ReHo than females in three right-side brain areas: postcentral gyrus, putamen and fusiform gyrus. It was found that abstinence symptoms severity was associated with lower ReHo values in the right postcentral gyrus and the right fusiform gyrus. Participants with CUD exhibited altered ReHo parameters compared to controls, similar to what is found in ageing-related disorders. Our data also indicate that cocaine has sex-specific effects on brain functioning when analysing ReHo.

KEYWORDS
cocaine sex differences, substance use and related disorders, resting-state

1 | INTRODUCTION

Cocaine use disorder (CUD) is a chronic relapsing disorder of the brain characterized by changes in reward and inhibitory systems.[1,2]

Resting-state fMRI (rs-fMRI) studies of persons with CUD have identified alterations in mesocorticolimbic functional connectivity (FC),[3–5] particularly between limbic areas and the default mode network.[6] Moreover, some evidence has shown that brain

dysfunctions in premotor and supplementary motor areas associated with cocaine use are distributed across large-scale brain networks, including the intraparietal sulcus and the orbitofrontal, the anterior cingulate insular cortices.[7]

Regional homogeneity (ReHo) evaluates the similarities or coherence of intra-regional spontaneous low-frequency BOLD signal fluctuations in voxel-wise analysis across the entire brain.[8] ReHo is based on the assumption that when the brain is activated, it is in the form of a cluster rather than a single voxel. It represents the most efficient, reliable and widely used index of network centrality for characterizing the FC relationships between a given node in the human brain connectome regarding its local functional interactions.[9] Despite that, the few studies on FC during resting state in CUD did not include such an approach.[7,10]

Sex-related differences in brain function are critical for rs-fMRI studies. For example, sex-related differences in default mode and dorsal attention network connectivity are associated with reward and punishment,[11] and resting-state studies show significant sex-related differences in connectivity between the frontoparietal and sensory-motor networks.[12–14] However, few studies have investigated sex differences in rs-fMRI alterations associated with CUD and, even less so, such modifications in populations from Latin America.[7,15]

Therefore, considering that females advance faster from recreational cocaine use to CUD in comparison to males[16] and the adverse outcomes are more severe within females with CUD,[17–19] including higher subjective cravings[20] and higher drug consumption,[21] this study aimed to explore sex differences among persons with CUD and healthy controls using rs-fMRI. The central hypothesis was that persons with CUD might experience unique modulation of neural activity with sex-dependent alterations in brain ReHo during resting state. To test this hypothesis, we first used rs-fMRI to explore differences in ReHo between males and females with CUD and healthy controls. Second, we examined possible relationships between areas with significant differences in ReHo and clinical characteristics of cocaine addiction.

2 | METHODS

2.1 | Participants

Eighty participants took part in this cross-sectional study—a group of 40 people with CUD (CK), divided into a male (CK-M, $n = 20$) and a female (CK-F, $n = 20$) groups. Given our interest in investigating possible sex differences in FC that would be specific to CUD, we chose to include 40 healthy controls (HC), divided into males (HC-M, $n = 20$) and females (HC-F, $n = 20$) to check if possible differences between CK-M and CK-F would be a specific effect within cocaine users.

We recruited participants with CUD from public drug-treatment facilities in the local area. During hospitalization, they followed a standardized cocaine detoxification protocol. As inpatients, they were in an abstinence-controlled situation with no access to drugs, including alcohol and cigarettes. We recruited the control participants from the community through local advertisements. The original

sample was 23 individuals for CK-M, 23 for CK-F, 22 for HC-M and 21 for HC-F. Still, some participants were excluded due to problems with MRI acquisition (e.g., excessive motion or claustrophobia).

For inclusion, all participants had to (a) be right-handed, (b) self-declare as being of low or middle socio-economic status, (c) be 18–50 years old, (d) have >8 years of formal education and (e) have an IQ >80. Additionally, (f) the participants with CUD should have tested positive for cocaine in urine screening test during the first three days of hospitalization (indicating that there had been less than 1 week since their last cocaine consumption). They also (g) should have CUD as the primary diagnosis, and (h) their preferred method of cocaine consumption should be by smoking a rock (i.e., crack), as the route of use could impact the clinical response.[22] Aside from restrictions related to MRI procedures, the exclusion criteria included the presence of neurologic disorders, HIV or syphilis. For the last two, the participants took a fast-test blood exam. For participants with CUD, concurrent severe mental disorders were also an exclusion criterion; we included only patients who had other substance use disorders or who had depressive and anxiety disorders with no painful symptoms. For the HC, the exclusion criteria also considered any mental disorder aside from tobacco use disorders. The HC should not have used any medication with neuropharmacological effects in the last 6 months before assessment and should not have drunk alcohol in the week before the exam. All participants should have tested negative for cocaine, cannabis, amphetamines, opioids and benzodiazepines in a urine screening on the MRI exam. The ethics committees from the institutions involved in the study approved this work, and all participants gave informed consent before beginning the procedures.

2.2 | Measures

The presence/absence of mental disorders, including the confirmation of CUD, were assessed by *The Structured Clinical Interview for DSM-IV Axis I Disorders*.[23] IQ was assessed with the *Wechsler Abbreviated Scale of Intelligence-II* (WASI-II), an IQ score in vocabulary and matrix reasoning.[24] Because even subclinical symptoms can impact FC measures,[25] on the day of the fMRI exam, we assessed depressive symptoms using a self-assessment measure—the Beck Depression Inventory-II.[26] We investigated symptoms related to crack cocaine abstinence with the Cocaine Selective Severity Assessment (CSSA),[27] which considers various abstinence symptoms of at least 24 h. It uses a 0–7 visual analogue scale, and the sum of all items returns a total score. Participants were assessed by CSSA 60 min before the MRI exam.

All participants also completed an interview regarding other medical conditions and sociodemographic characteristics. To better characterize the CK sample and investigate the severity of drug use, the participants completed the Addiction Severity Index (ASI-6). This interview evaluates drug use and the related adverse psychosocial outcomes. The ASI-6 computes composite scores of negative impact in nine domains: drugs, alcohol, family/children, psychiatric symptoms,

medical issues, legal problems, employment, social support and social problems. Higher scores mean more severe problems.[28,29]

We also assessed childhood maltreatment history with the Childhood Trauma Questionnaire (CTQ[30]), as childhood maltreatment is documented to have sex-dependent effects on cocaine users.[31] The CTQ is a self-answered 5-point Likert-type questionnaire with 28 items and evaluates the severity of negative life experiences. The results include a global score and subscores for various types of maltreatment. Standard cut-offs can classify the presence or absence of each type of maltreatment.[30,32]

2.3 | Procedures

As soon as each crack cocaine user entered the drug-treatment facility and fulfilled the inclusion criteria, we invited them to participate in the study. After 1 week of hospitalization, professional psychiatrists interviewed each participant using the SCID-V. Psychologists gave them the WASI subtests to test their IQs; on the day of the cognitive assessment, medications were suspended for 24 h. Participants also answered the ASI-6 during the second week of hospitalization and underwent an MRI exam between the eighth and 15th day of hospitalization.

HC was invited through advertisements that expressed voluntary interest and fulfilled the inclusion criteria. Afterward, we scheduled two assessment sessions for each participant before the exam. In each ~1-h session, the participants answered the same questions as the CK participants. We planned the MRI exams after finishing all these assessments.

On the day of their MRI exams, all participants had to test negative for drugs in a urine screening. Moreover, the participants had to answer the BDI-II questions. The CK participants also completed the CSSA. All psychiatric medications were suspended for the CK participants 36 h before the exam.

2.3.1 | Imaging data acquisition

Data were collected on a GE HDxt 3T scanner using an eight-channel radio-frequency head coil. At the beginning of the scanning session, a single, high-resolution T1-weighted anatomic image was collected (echo time = 2.18 ms; repetition time = 6.1 ms; flip angle = 11°; number of excitations = 1; slice thickness = 1 mm; field of view = 256 mm; resolution = 256 × 256). The rs-fMRI exams were conducted while participants were still and looked at a white cross centred on a black screen; participants were instructed not to think about anything. As a result, 210 echo-planar images were acquired using a single-shot, gradient-echo planar-pulse sequence (echo time = 30 ms; repetition time = 2000 ms; flip angle = 90°; field of view = 240 mm; matrix size = 64 × 64). Twenty-nine interleaved, sagittal, 4.4-mm-thick slices were selected to provide whole-brain coverage (at a plane resolution of 3.75 × 3.75 mm^2). The first three volumes were eliminated to account for T1 equilibrium effects, leaving 207 images.

2.3.2 | Preprocess of the fMRI data

All preprocessing and statistical analyses were carried out using the Analysis of Functional NeuroImages[33] toolbox. The preprocessing was performed using the afni_proc.py function, including slice-time and motion corrections.[34] The motion-corrected fMRI images were co-registered with the individual anatomical images (T1).[35] The T1 images were segmented into grey matter, white matter and cerebrospinal fluid; they were then spatially normalized using a nonlinear registration to standard space (the MNI152 template).[36] Using the same registration parameters for the T1 images, the fMRI images were registered to the MNI152 space and then smoothed using a 6-mm FWHM Gaussian filter. Censoring was performed on all-time points with a more than 0.3 mm motion. Nuisance regression was performed using the average time-sequence signal of the white matter and cerebrospinal fluid and the six motion parameters.[37]

2.4 | Data analysis

2.4.1 | Group characteristics

One-way analysis of variances (ANOVAs) compared groups for sociodemographic, childhood maltreatment and depression factors. For the CK-M and CK-F, the drug use characteristics and abstinence were computed using independent two-sample t tests.

2.4.2 | Motion

We used a one-way ANOVA to assess the differences in average head motion between groups. In the case of significant differences, we investigated specific group-by-group head motion differences for further control.

2.4.3 | Regional homogeneity

We used a whole-brain investigation approach to investigate crack use and sex differences in FC, using ReHo analysis. ReHo assesses the synchrony in BOLD fluctuations within clusters of voxels.[38] Since ReHo measures temporal synchrony among close neighborhoods, it has been considered an index of network centrality.[9,38] After preprocessing the resting-state fMRI data, we calculated ReHo using a 27-voxel neighbourhood for each subject. Higher ReHo values mean a higher degree of localized temporal synchronization within a neighbouring cluster. We computed a 2 × 2 (Group × Sex) ANCOVA with 3dMVM[39] for comparing ReHo across groups. Based on the comparisons of sample characteristics, we included depressive symptoms (from BDI-II scores), childhood maltreatment (from CTQ total scores), head motion, alcohol and cannabis years of frequent use as covariates due to their significant group differences. Further post hoc tests with Bonferroni correction explored specific group differences.

2.4.4 | Multiple comparison adjustments

To correct multiple comparisons, the *3dClustSim* programme was used to calculate a corrected *p* score of <0.05. Following the calculation, the analyses were carried out for a cluster of $p < 0.005$ with a minimum cluster size = 45 voxels (1926 µl).

2.4.5 | Correlation analyses

We first located brain regions using a data-driven approach based on ReHo values identified significant differences between groups. To check possible interrelationship between ReHo values from these brain regions and clinical variables such as addiction severity (ASI-6 drugs score), abstinence symptoms severity (CSSA total score), years of cocaine use and age of cocaine use onset, Pearson correlations were applied followed by Bonferroni multiple comparison adjustments.

3 | RESULTS

3.1 | Sample characteristics

Demographic and clinical characteristics are shown in Table 1. The CK-F group reported more severe childhood maltreatment histories than the HC groups. Since we found the main group effect in the severity of depressive symptoms, we included BDI-II and CTQ scores as covariates in all comparative analyses of brain functioning. Regular tobacco use was also more common in CK groups than in HC groups, which was expected.

Within CK groups, we found significant differences in drug use characteristics. In terms of alcohol use, CK-M reported higher years of frequent use and earlier age of first use. On the other hand, in terms of cannabis use, no significant sex differences were found regarding the frequency of cannabis use and age of first use. CK-F users reported higher rates of frequent tobacco smoking. There were no sex differences regarding years of regular cocaine use and age of first cocaine use. Still, the CK-F group reported more severe cocaine abstinence symptoms, higher addiction severity, and more serious medical problems. CK-M reported the highest negative impact on family and social support.

3.2 | Motion

A one-way ANOVA showed significant differences in average head motion between groups. The post hoc test showed that CK-F had more head motion than both HC groups. Descriptive results are detailed in Table 1. Hence, we adjusted all imaging analyses, including average head motion as a covariate.

3.3 | ReHo

Figure 1 illustrates the two-way ANCOVA results. Table 2 shows ReHo post hoc comparisons analyses. All results were controlled for depressive symptoms, childhood trauma, head motion, alcohol and cannabis use.

When contrasting with CK-F, CK-M showed higher ReHo in three brain regions: right postcentral gyrus, right putamen and right fusiform gyrus. CK-M showed higher ReHo in the left superior parietal lobule and left precuneus when contrasting with HC-M.

Among female groups, CK-F showed lower ReHo than HC-F in the left inferior parietal lobule, right superior temporal gyrus and left superior parietal lobule. No differences between HC-M and HC-F were found.

3.4 | Association between clinical variables and ReHo measures

We found that abstinence symptoms severity was associated with lower ReHo values in the Right Postcentral Gyrus ($r = -0.48$, $p = 0.002$; $p_{adj} = 0.014$) (Figure 2A) and Right Fusiform Gyrus ($r = -0.45$, $p = 0.003$, $p_{adj} = 0.021$) (Figure 2B). We also found that earlier onset of cocaine use was related with lower ReHo in the Right Postcentral Gyrus ($r = -0.32$, $p = 0.048$; $p_{adj} = 0.33$), Right Putamen ($r = -0.33$, $p = 0.038$; $p_{adj} = 0.26$), Right Cuneus ($r = -0.33$, $p = 0.036$; $p_{adj} = 0.25$), but those correlations did not survive multiple comparison adjustments. When we analysed the relationship between years of cocaine use and ReHo parameters we found that it was associated with higher values in Left Precuneus ($r = 0.37$, $p = 0.019$; $p_{adj} = 0.13$), but it did not survive p adjustment.

4 | DISCUSSION

Despite the main effect of biological sex in ReHo values of resting-state functional magnetic resonance imaging data, post hoc analysis only indicated such effect in persons with CUD, probably because it was much larger within CK groups. We also found that both CK groups presented lower ReHo parameters than HC groups, especially within the parietal lobule. Males with CUD (CK-M) had higher ReHo in three areas on the right side of the brain compared to females with CUD (CK-F). In addition, Moreover, after adjusting for multiple comparisons, it was found that the severity of abstinence symptoms was associated with lower ReHo values in the regions related to the ventral temporal and visual cortex within persons with CUD.

Although the ReHo method cannot directly measure the intensity of the local neuron activity, abnormal ReHo signals are related to fluctuations in neuronal activity because they reflect the synchronization of neuronal activity in the local brain region.[8,40] ReHo is a measure of similarity of the BOLD time series of a given voxel to those of its nearest neighbors. It has been shown to explain the variance in

TABLE 1 Sample characteristics

	CK-M (n = 20)		CK-F (n = 20)		HC-M (n = 20)		HC-F (n = 20)		Statistics	p
	M/n	SD/%	M/n	SD/%	M/n	SD/%	M/n	SD/%		
Sociodemographic										
Age (years)	29.85	6.50	34.2	7.24	29.05	7.59	29.10	5.33	$F(3, 76) = 2.678$	0.055
Income ($)	770.96	281.78	700.80	264.12	851.61	394.57	802.58	362.96	$F(3, 76) = 1.102$	0.338
Years of education	9.85	2.36	9.85	2.51	10.25	1.80	10.00	2.12	$H(3, 76) = 2.144$	0.543
Ethnicity (white/n, %)	13	65	10	50	13	65	9	45	$\chi^2 = 2.590$	0.459
IQ	97.60	7.37	95.25	8.69	99.20	8.27	98.85	7.40	$F(3,76) = 1.367$	0.261
CTQ score	45.45	18.28	47.20	16.21	32.45	9.25	34.25	10.60	$F(3, 76) = 5.242$[a]	0.002
Psychiatric										
Depressive symptoms (BDI-II)	10.00	5.60	11.40	6.28	7.20	6.80	6.70	5.40	$F(3,76) = 2.764$[b]	0.048
No comorbidity (n, %)	10	50	8	40	—	—	—	—	$\chi^2 = 0.404$	0.751
Depressive disorders	5	25	3	15	—	—	—	—	$\chi^2 = 0.625$	0.695
Anxiety disorders	5	25	5	25	—	—	—	—	$r = 0.000$	1.000
ASI-6 Scores										
Drugs	50.05	5.67	53.75	4.10	—	—	—	—	$t(38) = 2.362$	0.023
Alcohol	49.40	8.78	50.50	7.70	—	—	—	—	$t(38) = -0.421$	0.676
Family/Child	54.05	10.17	56.05	10.92	—	—	—	—	$t(26) = -0.681$	0.502
Psychiatric	52.05	7.91	50.25	7.08	—	—	—	—	$t(38) = 0.758$	0.453
Medical	38.60	4.79	47.40	10.08	—	—	—	—	$t(27.17) = -3.524$	0.002
Legal	53.15	7.03	50.50	5.53	—	—	—	—	$U = 153.000$	0.166
Employment	39.30	3.13	39.20	3.15	—	—	—	—	$U = 195.000$	0.904
Family/social support	54.88	11.79	46.60	10.37	—	—	—	—	$t(35) = 2.27$	0.029
Family/social problem	50.65	6.27	51.35	11.59	—	—	—	—	$t(38) = -0.237$	0.814
CSSA										
Cocaine/crack abstinence symptoms (CSSA score)	15.80	8.12	23.35	8.38	—	—	—	—	$t(38) = -2.892$	0.006
Drug Use Characteristics										
Frequent smoker (n, %)	14	70	18	90	9	45	8	40	$\chi^2 = 13.641$[c]	0.003
Age of first alcohol use	13.38	2.65	16.10	4.48	—	—	—	—	$t(36) = -2.234$	0.032
Frequent use of alcohol (years)	7.00	7.32	4.05	7.54	—	—	—	—	$U = 119.500$	0.028
Age of first cannabis use	13.85	2.66	15.25	4.99	—	—	—	—	$t(38) = -1.107$	0.275
Frequent use of cannabis (years)	9.30	7.88	5.85	6.24	—	—	—	—	$U = 138.500$	0.096

(Continues)

TABLE 1 (Continued)

	CK-M (n = 20)		CK-F (n = 20)		HC-M (n = 20)		HC-F (n = 20)		Statistics	p
	M/n	SD/%	M/n	SD/%	M/n	SD/%	M/n	SD/%		
Age of first cocaine/crack use	19.60	6.09	19.35	6.97	–	–	–	–	$t_{(38)} = 0.121$	0.905
Frequent use of cocaine/crack (years)	10.55	5.24	9.75	7.18	–	–	–	–	$t_{(38)} = 0.402$	0.690
Head motion during exam (millimeters)	0.05	0.01	0.08	0.03	0.05	0.01	0.04	0.01	$F_{(79)} = 5.787$[d]	<0.001

[a]Tukey's post hoc analyses showed CK-F > HC-F and HC-M.

[b]Tukey's post hoc analyses showed no significant differences.

[c]Independent chi-square analyses showed CK groups with significantly more tobacco regular use than HC groups ($\chi^2 = 11.850$, $p = 0.001$).

[d]Post hoc analyses of head motion revealed CK-F > CG-F ($t = 4.374$, $p < 0.001$) and CK-F > CG-M ($t = 3.067$, $p = 0.004$).

neurovascular coupling and task activations.[41] Therefore the decreased ReHo parameters identified in persons with CUD compared with controls could reflect less internal consistency in (a) left precuneus and left superior parietal lobule in males and (b) right superior temporal gyrus and left superior and inferior parietal lobules in females.

A decreased ReHo in precuneus has been found in cognitively normal older adults but with higher beta-amyloid retention[42] and within Alzheimer's Disorder (AD) and Mild Cognitive Impairment (MCI) patients.[43] In addition, reduced ReHo in parietal lobules was identified in participants with MCI.[44] This is intriguing because recently, we demonstrated white matter deficits in cocaine users by integrating in vivo DTI findings and ex vivo proteomic analysis, suggesting an ageing-like effect associated with CUD.[45]

Assuming ReHo as an index of centrality within brain networks, persons with CUD may have decreased regional connectivity in brain areas related to facial emotion recognition,[41] visuospatial imagery, episodic memory retrieval, self-consciousness, and the ability to be engaged in self-related mental representations during rest.[46] This is corroborated by previous findings showing that CUD individuals exhibited significant impairments in recognizing facial expressions of fear and anger[47] and lower levels of emotional self-awareness.[48]

We also found that sex differences in ReHo values were only detected among CK groups, with CK-M exhibiting higher ReHo within the right hemisphere in the postcentral gyrus, putamen, and the fusiform gyrus when compared with CK-M. Thus, this prominent rightward brain lateralization in males with CUD needs further investigation. Nonetheless, abstinence symptoms severity was associated with lower ReHo values in the right postcentral gyrus and the right fusiform gyrus.

Despite the lack of information about lower connectivity in those areas within CUD, the magnitude of connectivity reduction in sensorimotor and visual regions was significantly associated with the severity of harmful or hazardous drinking behaviours in a previous study.[49] The authors suggest dysfunction in a brain network in charge of sensory awareness and attention providing important information necessary for decision-making and assessment. Despite our findings being associated with resting-state conditions, a recent meta-analysis of regional differences for task-evoked activation during loss anticipation for participants with addictions showed hyperactivation in the postcentral gyrus.[50] The role of the fusiform gyrus in CUD is still largely unknown, but dopamine was considered to be related to its neural activity and emotion recognition.[51]

The present study has limitations that must be kept in mind when interpreting its results. First, the menstrual cycle affects resting-state fMRI,[12] but this was not controlled. Second, although we noted the sex differences in tobacco use disorders in Beltz et al.,[52] we did not control for this in our models. Third, even though, as far as we know, this is the first experiment to study differences between males and females regarding the effect of cocaine use, the sample size is limited. Forth, we used stringent criteria to control false positives, but more extensive imaging studies must be conducted to validate these results. Fifth, these results should be interpreted in the context of subacute withdrawal (2–3 weeks).[53] Since a linear improvement in negative affect, cocaine craving, and cognitive skills is expected over the first
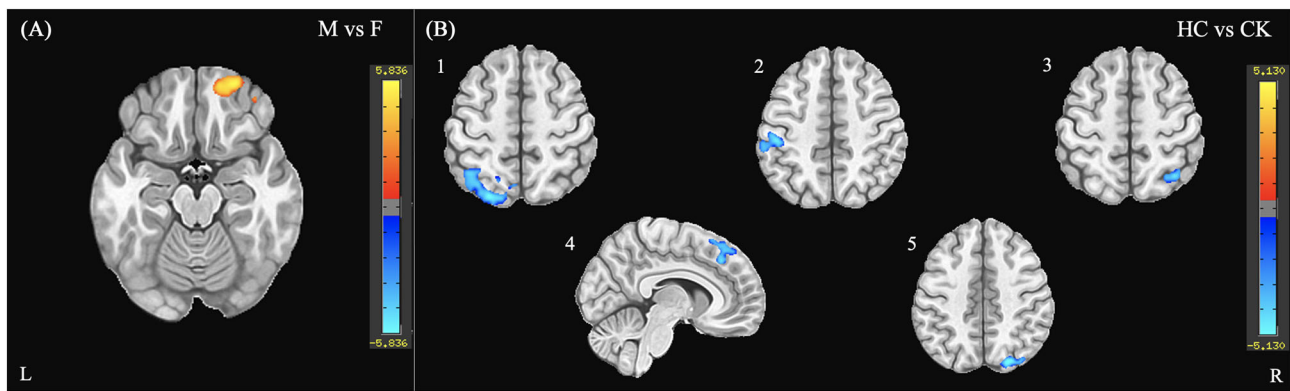
FIGURE 1 Analysis of covariance (ANCOVA) map of regional homogeneity (ReHo) in participants with cocaine use disorder (CUD) and healthy controls (HC) ($P < 0.05$). The image shows the peak signal of each brain region—using MNI152 template. The color bar shown on the bottom represents Fscore. (A) The main SEX effect with higher ReHo on Right Superior Frontal Gyrus in male participants. (B) The main GROUP effects, with HC having lower ReHo in 1: Left Superior Parietal Lobule; 2 Left Postcentral Gyrus; 3: Right Superior Parietal Lobule; 4: Right Superior Medial Gyrus; 5: Right Cuneus

TABLE 2 ReHo diferences

Post hoc							Peak MNI coordinates		
Brain region	Contrast CK-M versus CK-F	CK-M M (SD)	CK-F M (SD)	HC-M M (SD)	HC-F M (SD)	CS (µl)	x	y	z
Right postcentral gyrus	CK-M > CK-F**	0.63 (0.07)	0.51 (0.11)	0.60 (0.06)	0.59 (0.05)	3087.0	45	−19	34
Right putamen	CK-M > CK-F**	0.56 (0.04)	0.45 (0.10)	0.53 (0.05)	0.53 (0.05)	2186.6	35	−8	3
Right fusiform gyrus	CK-M > CK-F**	0.46 (0.05)	0.36 (0.08)	0.43 (0.04)	0.40 (0.06)	1972.2	35	−26	−25
	CK-M versus HC-M								
Left superior parietal lobule	CK-M < HC-M**	0.44 (0.06)	0.43 (0.09)	0.51 (0.04)	0.48 (0.06)	3258.5	−24	−72	56
Left precuneus	CK-M < HC-M**	0.49 (0.08)	0.56 (0.13)	0.60 (0.07)	0.5 (0.06)	2786.8	−4	−65	28
	CK-F versus HC-F								
Left inferior parietal lobule	CK-F < HC-F**	0.55 (0.08)	0.48 (0.11)	0.56 (0.06)	0.58 (0.06)	4459.0	−46	−26	49
Right superior temporal gyrus	CK-F < HC-F**	0.57 (0.04)	0.48 (0.11)	0.60 (0.05)	0.58 (0.07)	2015.1	59	−26	7
Left superior parietal lobule	CK-F < HC-F**	0.47 (0.06)	0.42 (0.09)	0.52 (0.05)	0.51 (0.07)	1929.3	−35	−65	59

Note: CS: Cluster size. Values for all groups were extracted only for representation; analyses were computed using whole brain functional connectivity (FC). **$p < 0.001$.
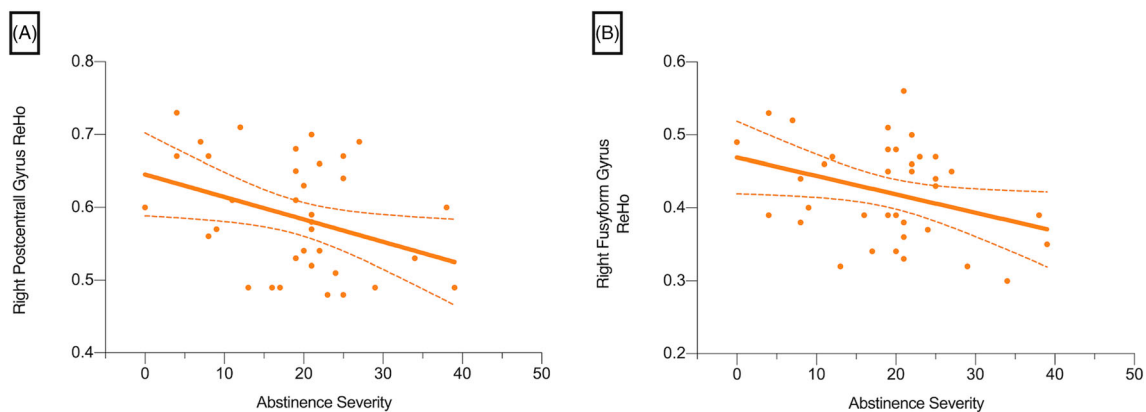
FIGURE 2 Regional homogeneity (ReHo) parameters association with severity of cocaine abstinence and addiction. (A) Abstinence symptoms severity was associated with lower ReHo values in the Right Postcentral Gyrus. (B) Abstinence symptoms severity was associated with lower ReHo values in the Right Fusiform Gyrus

month of cocaine withdrawal,[53] we don't know if ReHo findings would be the same in persons with current use or long-term recovery.

Participants with CUD exhibited altered ReHo parameters compared to controls, similar to those found in AD and MC samples. Specific sex differences were identified within CK groups, where men show higher rates of ReHo in brain regions related to sensory awareness, memory, and emotion recognition. Finally, we described the role of the right postcentral gyrus and right fusiform gyrus in cocaine withdrawal severity.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTION

RGO and BSV conceived and planned the experiments. BSV, LMR and PEF carried out the experiments. AB, NBE, ARF and BSV planned and carried out the neuroimaging protocol and analyses. RGO, BSV, LMR and LPT contributed to the interpretation of the results. RGO took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

ORCID

Breno Sanvicente-Vieira https://orcid.org/0000-0002-9922-966X
Leonardo Melo Rothmann https://orcid.org/0000-0001-5988-2368
Nathalia Bianchini Esper https://orcid.org/0000-0003-3218-9226
Lucca Pizzato Tondo https://orcid.org/0000-0002-0086-4875
Augusto Buchweitz https://orcid.org/0000-0003-3791-7472
Alexandre Rosa Franco https://orcid.org/0000-0002-1552-1090
Rodrigo Grassi-Oliveira https://orcid.org/0000-0001-9911-5921

REFERENCES

1. Dackis CA, O'Brien CP. Cocaine dependence: a disease of the brain's reward centers. *J Subst Abuse Treat*. 2001;21(3):111-117. doi:10.1016/S0740-5472(01)00192-1
2. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med*. 2016;374(4):363-371. doi:10.1056/NEJMra1511480
3. Contreras-Rodríguez O, Albein-Urios N, Vilar-López R, et al. Increased corticolimbic connectivity in cocaine dependence versus pathological gambling is associated with drug severity and emotion-related impulsivity. *Addict Biol*. 2016;21(3):709-718. doi:10.1111/adb.12242
4. Konova AB, Moeller SJ, Tomasi D, Volkow ND, Goldstein RZ. Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction. *JAMA Psychiatry*. 2013;70(8):857-868. doi:10.1001/jamapsychiatry.2013.1129
5. Ray S, Di X, Biswal BB. Effective connectivity within the mesocorticolimbic system during resting-state in cocaine users. *Front Hum Neurosci*. 2016;10(563). doi:10.3389/fnhum.2016.00563
6. Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A*. 2006;103(37):13848-13853. doi:10.1073/pnas.0601417103
7. Kelly C, Zuo XN, Gotimer K, et al. Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biol Psychiatry*. 2011;69(7):684-692. doi:10.1016/j.biopsych.2010.11.022
8. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. *Neuroimage*. 2004;22(1):394-400. doi:10.1016/j.neuroimage.2003.12.030
9. Jiang L, Zuo XN. Regional homogeneity: a multimodal, multiscale neuroimaging marker of the human connectome. *Neuroscientist*. 2016;22(5):486-505. doi:10.1177/1073858415595004
10. Berlingeri M, Losasso D, Girolo A, et al. Resting state brain connectivity patterns before eventual relapse into cocaine abuse. *Behav Brain Res*. 2017;327:121-132. doi:10.1016/j.bbr.2017.01.002
11. Dumais KM, Chernyak S, Nickerson LD, Janes AC. Sex differences in default mode and dorsal attention network engagement. *PLoS One*. 2018;13(6):e0199049. doi:10.1371/journal.pone.0199049
12. Hjelmervik H, Hausmann M, Osnes B, Westerhausen R, Specht K. Resting states are resting traits—an FMRI study of sex differences and menstrual cycle effects in resting state cognitive control networks. *PLoS One*. 2014;9(7):e103492. doi:10.1371/journal.pone.0103492
13. Allen EA, Erhardt EB, Damaraju E, et al. A baseline for the multivariate comparison of resting-state networks. *Front Syst Neurosci*. 2011;5(2). doi:10.3389/fnsys.2011.00002
14. Filippi M, Valsasina P, Misci P, Falini A, Comi G, Rocca MA. The organization of intrinsic brain activity differs between genders: a resting-state fMRI study in a large cohort of young healthy subjects. *Hum Brain Mapp*. 2013;34(6):1330-1343. doi:10.1002/hbm.21514
15. Hu Y, Salmeron BJ, Gu H, Stein EA, Yang Y. Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction. *JAMA Psychiatry*. 2015;72(6):584-592. doi:10.1001/jamapsychiatry.2015.1
16. Vsevolozhskaya OA, Anthony JC. Transitioning from first drug use to dependence onset: illustration of a multiparametric approach for comparative epidemiology. *Neuropsychopharmacology*. 2016;41(3):869-876. doi:10.1038/npp.2015.213
17. Keutmann MK, Gonzalez R, Maki PM, Rubin LH, Vassileva J, Martin EM. Sex differences in HIV effects on visual memory among substance-dependent individuals. *J Clin Exp Neuropsychol*. 2017;39(6):574-586. doi:10.1080/13803395.2016.1250869
18. Vernaglia TVC, Leite TH, Faller S, et al. The female crack users: higher rates of social vulnerability in Brazil. *Health Care Women Int*. 2017;38(11):0-1187. doi:10.1080/07399332.2017.1367001
19. Lejuez CW, Bornovalova MA, Reynolds EK, Daughters SB, Curtin JJ. Risk factors in the relationship between gender and crack/cocaine. *Exp Clin Psychopharmacol*. 2007;15(2):165-175. doi:10.1037/1064-1297.15.2.165
20. Elman I, Karlsgodt KH, Gastfriend DR. Gender differences in cocaine craving among non-treatment-seeking individuals with cocaine dependence. *Am J Drug Alcohol Abuse*. 2001;27(2):193-202. doi:10.1081/ADA-100103705
21. Bertoni N, Burnett C, Cruz MS, et al. Exploring sex differences in drug use, health and service use characteristics among young urban crack users in Brazil. *Int J Equity Health*. 2014;13(70). doi:10.1186/s12939-014-0070-x
22. Kiluk BD, Babuscio TA, Nich C, Carroll KM. Smokers versus snorters: do treatment outcomes differ according to route of cocaine administration? *Exp Clin Psychopharmacol*. 2013;21(6):490-498.
23. First M, Williams J, Karg R, Spitzer R. *Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV)*. Arlington, VA: American Psychiatric Association (APA); 2015.
24. Wechsler D. *Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)*. San Antoni, TX: NCS, Pearson; 2011.
25. Wang L, Hermens DF, Hickie IB, Lagopoulos J. A systematic review of resting-state functional-MRI studies in major depression. *J Affect Disord*. 2012;142(1-3):6-12. doi:10.1016/j.jad.2012.04.013

26. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *Journal of Personality Assessment*. 1996;67(3):588-597. doi:10.1207/s15327752jpa6703_13

27. Kampman KM, Volpicelli JR, McGinnis DE, et al. Reliability and validity of the cocaine selective severity assessment. *Addict Behav*. 1998;23(4):449-461. doi:10.1016/S0306-4603(98)00011-2

28. McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *J Nerv Ment Dis*. 1980;168(1):26-33. doi:10.1097/00005053-198001000-00006

29. Cacciola JS, Alterman AI, Habing B, McLellan AT. Recent status scores for version 6 of the Addiction Severity Index (ASI-6). *Addiction*. 2011;106(9):1588-1602. doi:10.1111/j.1360-0443.2011.03482.x

30. Bernstein DP, Fink L. *Childhood Trauma Questionnaire: A Retrospective Self-report*. San Antonio, TX: Harcourt Brace & Co; 1998.

31. Hyman SM, Paliwal P, Chaplin TM, Mazure CM, Rounsaville BJ, Sinha R. Severity of childhood trauma is predictive of cocaine relapse outcomes in women but not men. *Drug and Alcohol Dependence*. 2008;92(1-3):208-216. doi:10.1016/j.drugalcdep.2007.08.006

32. Grassi-Oliveira R, Cogo-Moreira H, Salum GA, et al. Childhood Trauma Questionnaire (CTQ) in Brazilian samples of different age groups: findings from confirmatory factor analysis. *PLoS One*. 2014;9(1):e87118. doi:10.1371/journal.pone.0087118

33. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996;29(3):162-173. doi:10.1006/cbmr.1996.0014

34. Sladky R, Friston KJ, Tröstl J, Cunnington R, Moser E, Windischberger C. Slice-timing effects and their correction in functional MRI. *Neuroimage*. 2011;58(2):588-594. doi:10.1016/j.neuroimage.2011.06.078

35. Ashburner J, Friston K. Multimodal image coregistration and partitioning--a unified framework. *Neuroimage*. 1997;6(3):209-217. doi:10.1006/nimg.1997.0290

36. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839-851. doi:10.1016/j.neuroimage.2005.02.018

37. Jo HJ, Saad ZS, Simmons WK, Milbury LA, Cox RW. Mapping sources of correlation in resting state FMRI, with artifact detection and removal. *Neuroimage*. 2010;52(2):571-582. doi:10.1016/j.neuroimage.2010.04.246

38. Liu D, Yan C, Ren J, Yao L, Kiviniemi VJ, Zang Y. Using coherence to measure regional homogeneity of resting-state FMRI signal. *Front Syst Neurosci*. 2010;4(24). doi:10.3389/fnsys.2010.00024

39. Chen G, Adleman NE, Saad ZS, Leibenluft E, Cox RW. Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. *Neuroimage*. 2014;99:571-588. doi:10.1016/j.neuroimage.2014.06.027

40. Xu Z, Lai J, Zhang H, et al. Regional homogeneity and functional connectivity analysis of resting-state magnetic resonance in patients with bipolar II disorder. *Medicine (Baltimore)*. 2019;98(47):e17962. doi:10.1097/MD.0000000000017962

41. Sarkheil P, Goebel R, Schneider F, Mathiak K. Emotion unfolded by motion: a role for parietal lobe in decoding dynamic facial expressions. *Soc Cogn Affect Neurosci*. 2013;8(8):950-957. doi:10.1093/scan/nss092

42. Kang DW, Choi WH, Jung WS, Um YH, Lee CU, Lim HK. Impact of amyloid burden on regional functional synchronization in the cognitively normal older adults. *Sci Rep*. 2017;7(1):14690. doi:10.1038/s41598-017-15001-8

43. Zhang Z, Liu Y, Jiang T, et al. Altered spontaneous activity in Alzheimer's disease and mild cognitive impairment revealed by regional homogeneity. *Neuroimage*. 2012;59(2):1429-1440. doi:10.1016/j.neuroimage.2011.08.049

44. Yuan Q, Qi W, Xue C, et al. Convergent functional changes of default mode network in mild cognitive impairment using activation likelihood estimation. *Front Aging Neurosci*. 2021;13:708687. doi:10.3389/fnagi.2021.708687

45. Tondo LP, Viola TW, Fries GR, et al. White matter deficits in cocaine use disorder: convergent evidence from in vivo diffusion tensor imaging and ex vivo proteomic analysis. *Transl Psychiatry*. 2021;11(252). doi:10.1038/s41398-021-01367-x

46. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006;129(3):564-583. doi:10.1093/brain/awl004

47. Ersche KD, Hagan CC, Smith DG, Jones PS, Calder AJ, Williams GB. In the face of threat: neural and endocrine correlates of impaired facial emotion recognition in cocaine dependence. *Transl Psychiatry*. 2015;5:e570. doi:10.1038/tp.2015.58

48. Moeller SJ, Konova AB, Parvaz MA, et al. Functional, structural, and emotional correlates of impaired insight in cocaine addiction. *JAMA Psychiatry*. 2014;71(1):61-70. doi:10.1001/jamapsychiatry.2013.2833

49. Vergara VM, Liu J, Claus ED, Hutchison K, Calhoun V. Alterations of resting state functional network connectivity in the brain of nicotine and alcohol users. *Neuroimage*. 2017;151:45-54. doi:10.1016/j.neuroimage.2016.11.012

50. Qiu Z, Wang J. A voxel-wise meta-analysis of task-based functional MRI studies on impaired gain and loss processing in adults with addiction. *J Psychiatry Neurosci*. 2021;46(1):E128-E146. doi:10.1503/jpn.200047

51. Rypma B, Fischer H, Rieckmann A, Hubbard NA, Nyberg L, Backman L. Dopamine D1 binding potential predicts fusiform BOLD activity during face-recognition performance. *J Neurosci*. 2015;35(44):14702-14707. doi:10.1523/JNEUROSCI.1298-15.2015

52. Beltz AM, Berenbaum SA, Wilson SJ. Sex differences in resting state brain function of cigarette smokers and links to nicotine dependence. *Exp Clin Psychopharmacol*. 2015;23(4):247-254. doi:10.1037/pha0000033

53. Coffey SF, Dansky BS, Carrigan MH, Brady KT. Acute and protracted cocaine abstinence in an outpatient population: a prospective study of mood, sleep and withdrawal symptoms. *Drug Alcohol Depend*. 2000;59(3):277-286. doi:10.1016/S0376-8716(99)00126-X