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# Distance disintegration characterizes node-level topological dysfunctions in cocaine addiction

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## Abstract

Previous investigations have used global graph theory measures in order to disentangle the complexity of the neural reorganizations occurring in cocaine use disorder (CUD). However, how these global topological alterations map into individual brain network areas remains unknown. In this study, we used resting state functional magnetic resonance imaging (fMRI) data to investigate node-level topological dysfunctions in CUD. The sample was composed of 32 individuals with CUD and 32 healthy controls, matched in age, years of education and intellectual functioning. Graph theory measures of optimal connectivity distance, node strength, nodal efficiency and clustering coefficient were estimated in each participant using voxel-wise functional connectivity connectomes. CUD individuals as compared with healthy controls showed higher optimal connectivity distances in ventral striatum, insula, cerebellum, temporal cortex, lateral orbitofrontal cortex, middle frontal cortex and left hippocampus. Furthermore, clinical measures quantifying severity of dependence were positively related with optimal connectivity distances in the right rolandic operculum and the right lateral orbitofrontal cortex, whereas length of abstinence was negatively associated with optimal connectivity distances in the right temporal pole and the left insula. Our results reveal a topological distancing of cognitive and affective related areas in addiction, suggesting an overall reduction in the communication capacity of these regions.

**KEYWORDS**
addiction, cocaine, functional connectivity, graph theory, optimal connectivity distance, resting state

## 1 | INTRODUCTION

Neuroimaging evidence from structural and functional studies suggest that drug addiction involves the impairment of multiple brain areas,[1] with an especial disruptive effect on specific functional connectivity (FC) networks.[2] For example, increased FC on areas within the default mode network (DMN), such as posterior cingulate, medial frontal cortex and hippocampus, has been described in individuals with cocaine

use disorder (CUD) and adolescents with prenatal cocaine exposure.[3,4] Furthermore, CUD individuals as compared with healthy controls (HC) have shown increased internetwork FC in the left frontoparietal network (FPN) during resting state.[5] Our work has also highlighted that CUD individuals exhibit central alterations in the activity of the FPN network while performing motivational tasks.[6–8] Other studies have reported compelling evidence about the implication of salience network (SN) areas[9–11] and subcortical partnered areas such as amygdala, caudate, putamen and nucleus accumbens, as consistently reorganized in CUD.[3,12–17] Thus, our current knowledge of the brain connectivity effects in drug addiction shows a complex scenario in which many cerebral networks interdigitate and restructure to create prototypical alterations in cognitive and affective systems.

We believe that a proper understanding of such multisystem rearrangement of brain circuits requires adequate analytical approaches able to disentangle network complexity, such as graph theory (GT). GT is a branch of mathematics used to abstract macroscopic features of complex systems, helping thus to its simplification and quantification. In the past, previous investigations have focused on the study of GT topological properties and have found that CUD individuals show disrupted modularity of the SN and DMN.[18] From a global viewpoint of brain GT metrics, CUD individuals have shown an increase in global connectivity—also known as mean degree centrality—as well as decrease in global efficiency (i.e., a measure of network integration or the capacity of rapidly combine information from distributed regions), local efficiency (i.e., a measure of network segregation or the capacity for specialized processing to occur within densely interconnected subregions) and small world properties (i.e., a ratio between normalized segregation and integration characteristics) than matched HC.[19] Interestingly, GT investigations have shed light on how CUD produces network dynamics changes affecting the temporal flexibility (a measure of how often a network region interacts with other networks) and spatio-temporal diversity (a measure of how uniformly a brain region interacts with regions in other networks) of networks—including the DMN and SN.[20] Most recently, other GT studies have shown potential pharmacological treatment targets in CUD[21] and the effects of prenatal cocaine exposure in adolescents.[22]

Despite these advances, how global connectivity changes—such as those observed with global GT metrics—map into individual brain network areas at the node- or voxel-level remains largely elusive. A previous study has investigated voxel-wise connections in CUD individuals using FC density analysis (an analysis analogous to degree centrality in GT).[23] The results showed increased connectivity in CUD individuals (particularly in subcortical areas and regions of DMN), which was reduced after administration of methylphenidate. Nonetheless, how other network properties different from degree are locally characterized in CUD individuals remains unknown. Furthermore, in the past years, novel GT measures that characterize network information transfer as a diffusion process have been developed.[24,25] These metrics have successfully revealed FC reorganizations in clinical conditions such as Alzheimer's disease[26] and blindness.[27] However, our current knowledge about CUD-related alterations in network

information processing is limited to metrics based on shortest paths, which involve a restrictive model of information flow.[28] Thus, the study of metrics based on diffusion models might provide novel insights into the neural basis of cocaine addiction.

In this study, we investigated the topological network dysfunctions associated with CUD at high resolution and brain node level. To this aim, we used a diffusion-based GT measure called optimal connectivity distance,[24] which measures the relative distance between nodes in terms of communication capacity through all the possible routes in the graph. Besides optimal connectivity distance, we also investigated CUD-related alterations in node-level topological properties of centrality (strength), integration (nodal efficiency) and segregation (clustering coefficient). Moreover, we also explore associations between clinical variables and GT measures in CUD individuals. Given the revised bibliography, we expect to find CUD-related topological alterations in regions of the DMN, SN and striatum.

## 2 | METHODS AND MATERIALS

### 2.1 | Participants

Thirty-two individuals (29 men and 3 women) with CUD and 32 (27 men and 5 women) HC matching in age, years of education and intellectual functioning were selected for this study (see Table 1). CUD participants were recruited through the Addictive Behaviors Unit San Agustín clinic of Castellón (Spain) from people who met the DSM-V criteria for CUD. History of use or abuse of other substances

**TABLE 1** Demographic characteristics and clinical variables

| | CUD (N = 32) | HC (N = 32) |
| --- | --- | --- |
| Sociodemographic variables[a] | | |
| Sex | M/F = 29/3 | M/F = 27/5 |
| Age | 36.41 (6.45) | 36.16 (9.31) |
| Years of education | 10.72 (3.79) | 11.78 (2.86) |
| Intellectual functioning[b] | 9.84 (3.17) | 10.53 (2.57) |
| Clinical variables | | |
| CSSA | 46.58 (23.21) | - |
| SDS | 9.68 (2.85) | - |
| CCQ-G | 31.55 (15.48) | - |
| Length of abstinence (months) | 13.76 (17.84) | - |
| Age of first use of cocaine (years) | 19.31 (4.22) | - |
| Years of cocaine use | 15.25 (6.23) | - |

*Note:* One participant did not complete CSSA, SDS, CCQ-G and matrix reasoning test; therefore, statistics for these variables involve a sample size of 31 CUD individuals.
Abbreviations: CCQ-G, Cocaine Craving Questionnaire-General; CSSA, Cocaine Selective Severity Assessment; CUD, cocaine use disorder; F, female; HC, healthy control; M, male; SDS, Severity Dependence Scale.
[a]Mean and standard deviation (in parentheses) are shown for quantitative variables.
[b]Standard score in the matrix reasoning test (Wechsler Adult Intelligence Scale-III).

different from cocaine was not an exclusion criterion whenever did not exist suspicious of dependence. Nonetheless, participants were excluded if the abuse had taken place during the cocaine abstinence period. CUD individuals reported to be free of drug the day of the scan and were asked about their last consumption. The reported abstinence cocaine period ranged from 11 days to 59 months. Furthermore, a urine toxicology test ensured that they had not consumed cocaine neither the scan day nor in the 2/4 days before. HC group was recruited by placing posters in public places and through word of mouth. The inclusion criteria for this group were the absence of diagnosis of any type of substance abuse or dependence. The exclusion criteria for all participants included major medical or neurological illnesses, head trauma resulting in loss of consciousness for longer than 30 min and presence of any contraindications to a magnetic resonance imaging (MRI) environment. Participants were informed of the nature of the research and provided written informed consent prior to their participation in the study. All the study procedures conformed to the Code of Ethics of the World Medical Association and were approved by the Institutional Review Board of the Universitat Jaume I.

## 2.2 | Clinical measures

In order to characterize the clinical profiles, CUD individuals were interviewed in order to determine three clinical variables: (1) length of abstinence, which was calculated as the number of months without lapses or relapses at the time of the scanning session; (2) age of first use of cocaine; and (3) years of cocaine use, which indicated the time between the first intake and the beginning of the abstinence period. In addition, CUD individuals completed the Cocaine Selective Severity Assessment (CSSA),[29] the Spanish version of the Severity Dependence Scale (SDS)[30] and the Spanish version of the Cocaine Craving Questionnaire-General (CCQ-G).[31] Descriptive statistics for all the variables recorded are reported in Table 1. One CUD participant did not complete CSSA, SDS and CCQ-G questionnaires; therefore, statistics and analyses for these variables involve a sample of 31 CUD individuals.

## 2.3 | Image acquisition

Participants were instructed to simply rest with their eyes closed and not to sleep or think about anything in particular during the resting state functional magnetic resonance imaging (fMRI) acquisition. Images were acquired on a 1.5-T Siemens Avanto scanner. We acquired 24 interleaved axial slices parallel to the anterior–posterior commissure using a gradient-echo T2*-weighted EPI sequence (200 volumes; TR, 2000 ms; TE, 48 ms; matrix, 64 × 64; voxel size, 3.5 mm × 3.5 mm; flip angle, 90°; slice thickness, 4 mm; slice gap, 0.8 mm). Also, a T1-weighted MPRAGE sequence (TR/TE = 2200/3.79 ms, flip angle 15°, voxel size = 1 mm × 1 mm × 1 mm) was acquired.

## 2.4 | Image preprocessing

We used the DPABI v4 toolbox for image analyses (http://rfmri.org/dpabi). Preprocessing included the following steps: (1) removal of the first five volumes; (2) slice timing correction; (3) head motion correction using a six-parameter (rigid body) linear transformation; (4) T1 skull stripping; (5) individual T1 coregistration with the mean functional image; (6) T1 segmentation using DARTEL; (7) removal of spurious variance through linear regression: 24 parameters from the head motion correction, scrubbing within regression at framewise displacement (FD) > 0.5 mm, linear and quadratic trends and the first five principal components associated to white matter and cerebrospinal fluid; (8) spatial normalization to the MNI space (voxel size: 3 × 3 × 3 mm$^3$); (9) spatial smoothing with a 4-mm full width at half maximum (FWHM) Gaussian kernel; and (10) band-pass temporal filtering (0.01–0.1 Hz). No participant showed more than 1.5 mm/degree of movement in any of the six directions or less than 150 volumes with FD < 0.5 mm (ensuring at least 5 min of rest with low FD).

## 2.5 | Matrix construction

Association matrices for each participant were computed by calculating the Pearson correlation between each voxel time course and every other voxel time course. For computational purposes, the preprocessed resting state images were first down sampled to a voxel size of 4 × 4 × 4 mm$^3$ and then masked with a binary template of 15 821 voxels covering cortical and subcortical grey matter. The resulting r values were normalized using the Fisher z transformation. Furthermore, we excluded positive correlations that did not reach a false discovery rate (FDR) correction threshold of $p < 0.05$ in order to remove spurious associations. Prior to FDR correction, negative correlations were excluded to avoid ambiguity in the interpretation of topological measures.[32] Given that most graph theoretic measures are sensitive to variations in the number of edges in a graph, we replicated our analyses using density-based thresholding with a sparsity range from 5% to 25%.

## 2.6 | GT measures

GT analyses were performed using MATLAB and Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/). Optimal connectivity distance was estimated by

$$OD_{ij} = \mathrm{argmax}_l \left( \frac{W_{ij}^l - \min\left(\mathbf{W}_{i.}^l\right)}{\max\left(\mathbf{W}_{i.}^l\right) - \min\left(\mathbf{W}_{i.}^l\right)} \right),$$

where $\mathbf{W}^l$ is the weighted association matrix to the $l$ power. We set $l$ to range from 1 to 7 in base to previous studies showing that seven steps are enough for the characterization of connectivity patterns in healthy young adults.[25] Then, we estimated the averaged optimal

connectivity distance for each node in order to characterize its communication capacity through the brain. Thus, the averaged optimal connectivity distance for a node $i$ was estimated by

$$\bar{OD}_i = \frac{1}{N-1} \sum_j OD_{ij}.$$

Besides optimal connectivity distance, we investigated GT measures of centrality, integration and segregation. As a measure of centrality, we estimated node strength by

$$k_i^w = \sum_j w_{ij},$$

where $w_{ij}$ is the strength or weight of the edge linking nodes $i$ and $j$. Furthermore, we estimated nodal efficiency as a measure of integration by

$$E_{nodal}(j) = \frac{1}{N-1} \sum_i \frac{1}{l_{ij}^w},$$

where $l_{ij}^w$ is the shortest weighted path between $i$ and $j$ estimated with the Floyd–Warshall algorithm as implemented in Brain Connectivity Toolbox. Finally, weighted clustering coefficient was estimated as a measure of segregation by

$$C_i^w = \frac{2}{k_i(k_i-1)} \sum_{j,h} (w_{ij} w_{jh} w_{hi})^{1/3},$$

where $k_i$ is the node degree.

## 2.7 | Statistical analysis

SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to identify specific nodes (i.e., voxels) showing between-group differences in GT measures. For each measure, voxel-wise two-sample $t$-test models comparing CUD individuals and HC were

**TABLE 2** Brain regions showing significant higher optimal connectivity distances in CUD as compared with HC (CUD > HC)

| | Hemisphere | MNI ($x$ $y$ $z$) | TFCE $p$ value[a] |
|---|---|---|---|
| Cluster 1 (308 voxels) | | | |
| Temporal pole superior | Right | 46 18 −16 | 0.007 |
| Orbitofrontal | Right | 50 26 −12 | 0.012 |
| Frontal middle | Right | 30 34 32 | 0.012 |
| Ventral striatum | Right | 6 6 −4 | 0.015 |
| Insula | Right | 30 22 −12 | 0.017 |
| Cluster 2 (112 voxels) | | | |
| Temporal superior | Left | −62 −38 12 | 0.008 |
| Cluster 3 (226 voxels) | | | |
| Cerebellum VI | Left | −10 −66 −12 | 0.009 |
| Cerebellum vermis | Right | 2 −62 −8 | 0.012 |
| Calcarine | Right | 6 −70 8 | 0.013 |
| Cluster 4 (28 voxels) | | | |
| Precentral | Right | 46 −6 48 | 0.011 |
| Cluster 5 (134 voxels) | | | |
| Orbitofrontal | Left | −38 30 −4 | 0.013 |
| Ventral striatum | Left | −22 10 −8 | 0.013 |
| Temporal pole superior | Left | −54 10 −12 | 0.013 |
| Insula | Left | −38 2 −4 | 0.014 |
| Cluster 6 (38 voxels) | | | |
| Rolandic operculum | Right | 50 −22 16 | 0.015 |
| Cluster 7 (43 voxels) | | | |
| Temporal superior | Right | 62 −26 0 | 0.015 |
| Cluster 8 (24 voxels) | | | |
| Hippocampus | Left | −18 −34 −4 | 0.019 |

Abbreviations: CUD, cocaine use disorder; FWE, family-wise error; HC, healthy control; TFCE, threshold-free cluster enhancement.
[a]FWE corrected.

estimated. Then, statistical inference was performed using the threshold-free cluster enhancement method as implemented in the Computational Anatomy Toolbox 12 (CAT12, http://www.neuro.uni-jena.de/cat/). Non-parametric permutation testing (5000 permutations) was used to detect statistically significant differences at $p < 0.05$, family-wise error (FWE) corrected. In secondary analyses, we investigated how clinical variables were related to the alterations shown in GT measures. Specifically, for each region showing a significant difference in group analyses, we defined a 5-mm-radius sphere mask centred in the local maxima (see MNI coordinates in Table 2). Then we averaged the specific GT values of the voxels within the mask in each CUD participant separately. These averaged values were used to perform linear regression models with each clinical variable. Statistically significance was determined with non-parametric permutation testing (5000 permutations) at $p < 0.05$ FWE corrected.

## 3 | RESULTS

### 3.1 | Between-group comparisons

The results of the two-sample $t$-test analyses comparing CUD individuals and HC showed significant differences in optimal connectivity distance. Specifically, CUD individuals showed higher optimal connectivity distances than HC in bilateral regions of insula, temporal pole, lateral orbitofrontal cortex, superior temporal cortex and ventral striatum, as well as in right middle frontal cortex, right rolandic operculum, right precentral cortex, left hippocampus and a cluster located in the cerebellum and extended to occipital cortex (see Figure 1A and Table 2). A similar pattern of results was found using density-based thresholding in matrices with sparsity of 5% and 10% (see Figure S1). Figure 1B shows group differences (descriptive values) in the optimal connectivity distance maps of specific regions relevant for addiction,
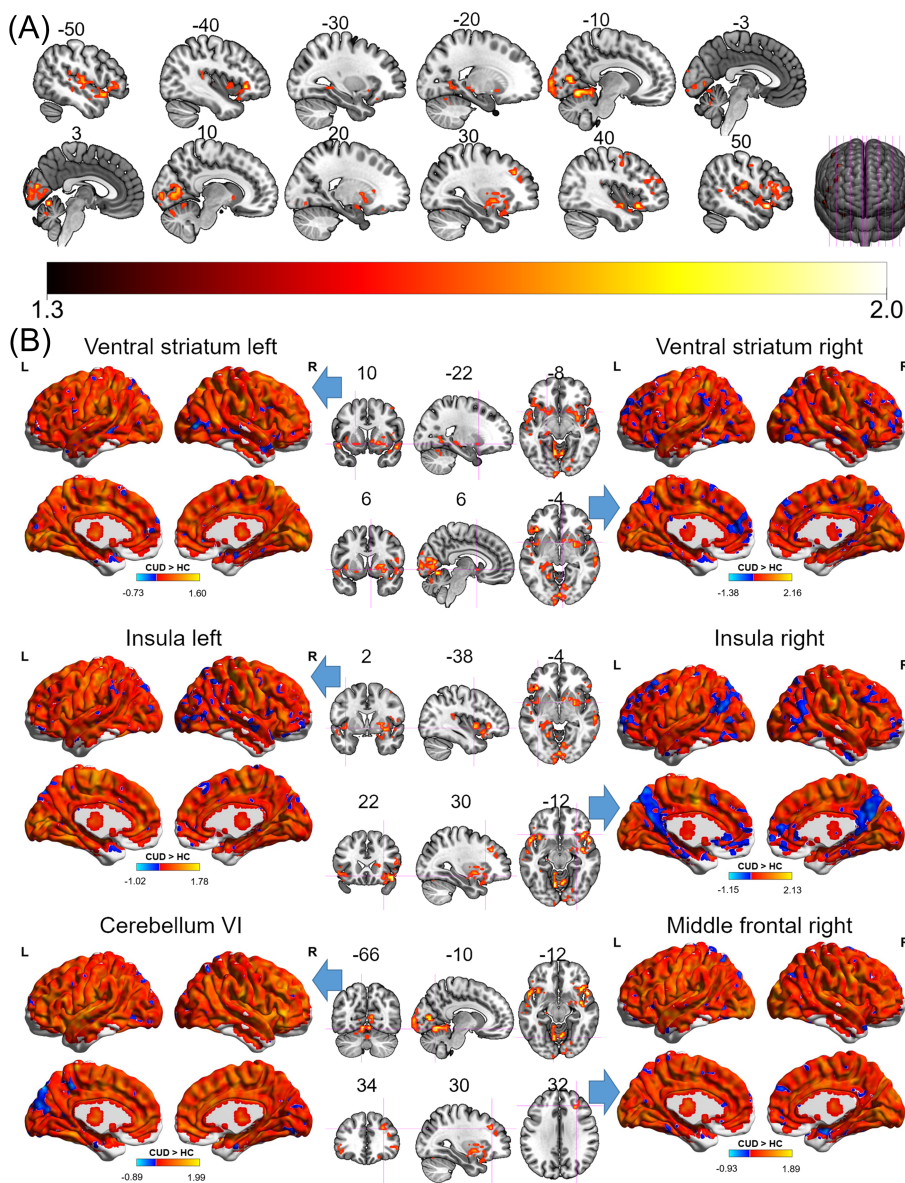


**FIGURE 1** Results using optimal connectivity distance. (A) Optimal connectivity distance differences between CUD and HC individuals. The colour bar shows the log-scale $p$ value applicable to the image. (B) Spatial distribution of the distance differences of specific ROIs. ROIs were defined as 5-mm-radius spheres centred on the local maxima of the regions showing significant differences in the between-group comparisons (middle column). Voxel-specific optimal distance maps were averaged across the voxels within the ROI and across participants, separately for each group. Lateral columns show the difference (CUD minus HC; descriptive values) between groups in the ROI-specific optimal distance maps. Warm colours show voxels where the distance from the ROI is higher in CUD than in HC. Cold colours show voxels where the distance from the ROI is lower in CUD than in HC. Colour bars represent the differential optimal connectivity value. CUD, cocaine use disorder; HC, healthy control; ROI, region of interest

such as ventral striatum, insula, cerebellum lobule VI and middle frontal cortex. Group-averaged optimal connectivity distance maps for HC and CUD are shown in Figure S2. No significant differences were found using strength, nodal efficiency and clustering coefficient measures.

## 3.2 | Clinical characteristics and GT measures

Analyses investigating the relationship between clinical variables and GT measures showed a significant positive relationship between SDS and optimal connectivity distance in the right rolandic operculum ($t = 3.33$, $p = 0.015$ FWE corrected). Furthermore, a significant relationship between CSSA and optimal connectivity distance in the right lateral orbitofrontal cortex was found ($t = 3.31$, $p = 0.025$ FWE corrected). Thus, CUD individuals with higher severity of dependence showed higher distances in these regions (see Figure 2A). These results remained significant after including the length of abstinence as covariate (SDS—right rolandic operculum: $t = 2.93$, $p = 0.037$ FWE corrected; CSSA—right lateral orbitofrontal cortex: $t = 2.97$,
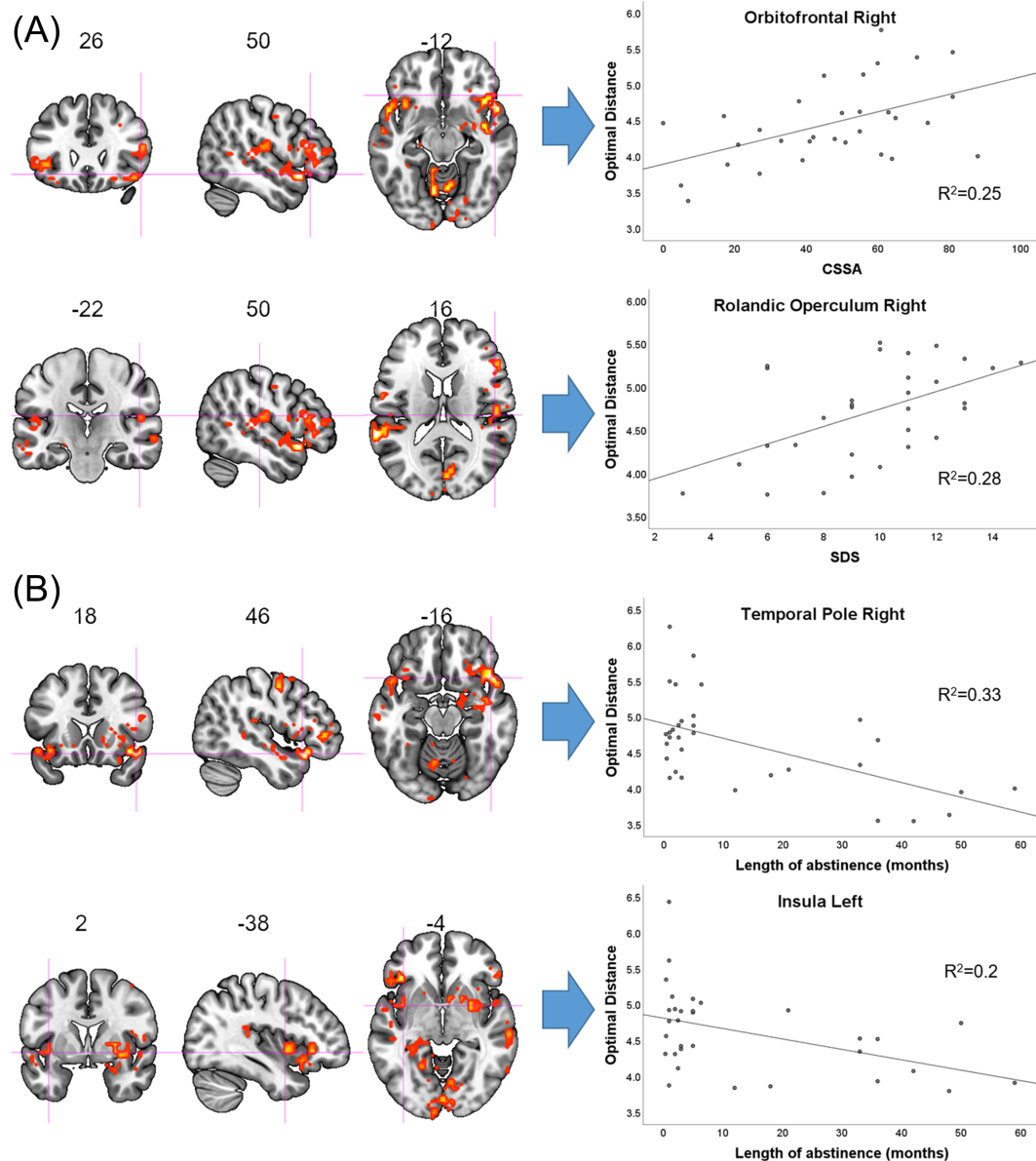


**FIGURE 2** Relationship between optimal connectivity distance and clinical variables. (A) Scatter plots showing the positive relationship between severity of dependence scales (CSSA and SDS) and optimal connectivity distances in the right lateral orbitofrontal cortex and right rolandic operculum. (B) Scatter plots showing how length of abstinence is positively related with optimal connectivity distance in the right temporal pole and the left insula. Values on the Y axes were obtained from the optimal connectivity distance average of voxels within a 5-mm-radius sphere centred on the local maxima obtained in the between-group comparison. The left side of the figure shows the location of these local maxima in the between-group comparison statistical map. Significance was determined with non-parametric permutation testing (5000 permutations) at $p < 0.05$ FWE corrected. CSSA, Cocaine Selective Severity Assessment; FWE, family-wise error; SDS, Severity Dependence Scale

$p = 0.036$ FWE corrected). Moreover, length of abstinence was negatively associated with optimal connectivity distance in the right temporal pole ($t = -3.88$, $p = 0.002$ FWE corrected) and the left insula ($t = -2.74$, $p = 0.049$ FWE corrected), indicating that participants with less abstinence period showed higher distances in these regions (see Figure 2B). The relationship between length of abstinence and optimal connectivity distance in the right temporal pole remained significant after controlling by SDS ($t = -3.49$, $p = 0.011$ FWE corrected) and CSSA ($t = -3.71$, $p = 0.004$ FWE corrected). However, the relationship between length of abstinence and optimal connectivity distance in the left insula only showed a trend when controlled by CSSA ($t = -2.58$, $p = 0.07$ FWE corrected) and was not significant when controlled by SDS ($p > 0.1$ FWE corrected). No other significant results were found.

## 4 | DISCUSSION

In this study, we investigated CUD-related alterations in voxel-wise connectomes using resting state fMRI. Specifically, we studied differences between a group of 32 individuals with CUD and a group of 32 HC individuals in optimal connectivity distance, node strength, nodal efficiency and clustering coefficient. From all these GT measures, only optimal connectivity distance revealed node-level differences between HC and CUD. Specifically, our results showed that CUD individuals presented higher distances than HC participants in temporal areas, insula, lateral orbitofrontal cortex, middle frontal cortex, cerebellum and subcortical areas, including ventral striatum and left hippocampus. Furthermore, regression analyses showed that the values of optimal distance in right lateral orbitofrontal, right rolandic operculum, right temporal pole and left insula were related with clinical measures. Optimal connectivity distance quantifies the distance at which the relative communication capacity between nodes is maximal. Thus, our results suggest that cocaine addiction is characterized by a topological distancing of the above regions.

An important finding in the current study was that CUD individuals showed higher optimal connectivity distances than HC in the ventral striatum. The ventral striatum has been related with the reinforcing effects of drugs.[33] This region is a central node of the mesocorticolimbic reward system, which is the major site of action of addictive drugs. It is suggested that drugs of abuse induce neuroplasticity by hijacking the reward system, contributing to a reorganization of neural circuits that eventually leads to addiction.[34] Specific neural reorganizations of ventral striatum in CUD have been investigated in seed-based resting state studies. These studies showed reduced coupling of ventral striatum with superior temporal gyrus, middle temporal gyrus, insula, middle cingulate, dorsal prefrontal cortex, lateral orbitofrontal cortex and ventral tegmental area[12,13,15] and increased coupling with anterior cingulate, medial orbitofrontal cortex and dorsal striatum.[15–17] These seed-based studies focused on studying direct connections of ventral striatum. In contrast with these studies, our results involve the whole pattern of ventral striatum connectivity and suggest that in average, the capacity of information transfer of this region across the brain is reduced in cocaine addiction. Crucially, a recent study showed that the ventral striatum can be parcelled in CUD according to distinctive patterns of FC,[35] suggesting that FC studies using the whole region as a seed might overlook relevant FC alterations. The differences in optimal connectivity distance shown in our study contribute to this literature by suggesting that not only direct but also indirect connections are relevant to understand ventral striatum connectivity impairments in CUD.

Another relevant finding in our study was that CUD individuals as compared with HC showed higher optimal connectivity distances in the bilateral insula. The insula has been related with the conscious representation of the interoceptive effects of drug taking.[36] Previous seed-based resting state studies showed increased FC of the insula with prefrontal areas[11] and reduced FC of this region with putamen, periaqueductal grey and anterior cingulate cortex.[10,12,14,37] A study using independent component analysis, however, showed greater mean network connectivity in a network comprising anterior insula and anterior cingulate in CUD individuals as compared with HC.[9] This study also showed CUD-related weaker internetwork connectivity between this network and striatum. Previous studies suggest that the insula could be divided in three subregions according with its FC and function: the posterior insula, related with sensorimotor processing; the ventral anterior insula, related with affective processes; and the dorsal anterior insula, which involves the insular part most related with the SN and is associated with cognitive control processes.[38] In our study, we found significant differences in voxels within the three regions. Previous studies showed that ventral anterior insula present strong FC with the lateral orbitofrontal cortex, the temporal pole, the superior temporal gyrus and the ventral striatum,[39–41] which are regions that also showed differences in optimal connectivity distance in our study. Furthermore, CUD individuals in our study also showed reduced distances in the right middle frontal cortex (Brodmann area 46), which is part of the SN.[42] These topological alterations in SN areas agree with a previous GT study showing that CUD is related to decreased intermodule connectivity of the SN and reduced connectivity of the bilateral insula.[18] Furthermore, our results add to this literature by showing that the affective network associated with ventral insula is also impaired in CUD.

In this study, we also found optimal connectivity distance differences in a cluster located on the cerebellum and extended to visual areas. Within the cerebellum, the lobule VI was the region showing the highest differences. There is evidence showing that addictive drugs, including cocaine, induce and modify plasticity mechanisms in the cerebellum.[43] Furthermore, previous literature suggests that cerebellar areas, including the lobule VI, play an influential role in maintaining the homeostatic balance of the brain circuits involved in addiction.[44] Alterations in these cerebellar regions thus would alter this balance. In particular, the lobule VI of the cerebellum has been related with the cingulo-opercular/ventral attention network,[45] which involves insular regions. Thus, our results using optimal connectivity distance revealed CUD-related alterations in both insular networks and its modulatory regions in the cerebellum. A recent model of cerebellar function highlights the relevance of this region in compulsive and impulsive

behaviours. Specifically, this model suggests that cerebellum is involved in restraining ongoing actions when environmental conditions change by adjusting prefrontal activity in response to the new external and internal stimuli.[46] Therefore, following this model, the topological distancing of cerebellar areas showed in our study might contribute to compulsive and impulsive behaviours in cocaine addiction.

Another important finding in our study was that optimal connectivity distances in CUD individuals were associated with clinical variables quantifying severity of dependence and abstinence. The correlations between clinical variables and GT measures may be interpreted as dynamic FC (e.g., across severity of dependence levels or time of abstinence) in contrast to static FC architectures of addiction when comparing cocaine addicts with a control group.[47] The variables we used to parameterized severity of dependence, the SDS and the CSSA, showed an associated increased optimal connectivity distance in the right rolandic operculum and the right lateral orbitofrontal cortex, respectively. That is, CUD individuals who reported higher scores in variables related to severity of dependence showed increased topological distance in these two regions, which in addiction had shown increased optimal connectivity distance in CUD participants when compared with HC. On the other hand, abstinence may be related to the downregulation of the optimal connectivity distances associated with severity of dependence. It is important to note that both severity of dependence measures (SDS and CSSA) were not related to the variable length of abstinence ($p > 0.1$). The length of abstinence was related to reductions in optimal connectivity distances in the left insula and right temporal pole, which do not overlap with those regions associated with SDS or CSSA, although they are directly and indirectly connected through structural connectivity and FC.[48] In fact, when severity of dependence measures were regressed out from abstinence-associated effects in the left insula, the association was reduced to non-significant. Therefore, downregulation effects of abstinence on optimal connectivity distance should be taken with caution, particularly in the left insula where progressive abstinence-related effects may be partially explained by severity of dependence. Thus, Prisciandaro et al. suggested two aspects of the severity of dependence: the 'state-like' facet of severity (e.g., abstinence) and the 'trait-like' facet of cocaine severity (e.g., years of use).[49] According to this differentiation, the results with CSSA may be interpreted as state-like facets and the results with SDS as trait-like facets, given that these scales evaluate dependence severity attending to the past 24 h and the past year, respectively. On the other hand, Prisciandaro et al. considered abstinence as a state-like facet of severity, but it may be a matter of discussion. In this sense, our sample of abstinent CUD participants showed a range from 11 days to 59 months of abstinence and not as a 'yes or no' abstinence condition. The abstinence-associated effects in the left insula may be considered dynamic as a state, rather than a trait, in cocaine addicts, which directly or indirectly seems to be affected by severity variables associated with longer periods of time and, therefore, related to less dynamic severity changes (e.g., SDS). Further studies may test whether these and other GT measures are sensitive or specific measures to state- or trait-like topological conditions in CUD affecting more dynamic or static FC.

A previous study investigating GT in cocaine addiction showed differences between HC and CUD in global measures of centrality, integration and segregation.[19] In this study, we aimed to characterize these differences at node level using a voxel-wise approach; however, we did not find significant results. Only the diffusion-based measure of optimal connectivity distance was able to show node-level reorganizations in CUD. Why this measure showed higher sensitivity in our study is a question that requires further consideration. One possibility relies on the quantity of information in which the different measures are based. Optimal connectivity distance considers all possible routes of connectivity between nodes across different link steps and is based on its relative distances. Thus, although it is a nodal measure, it is based on global network information. In contrast, strength, nodal efficiency and clustering coefficient are based on pieces of these possible routes of connectivity. Specifically, strength is based on direct connections, nodal efficiency is based on shortest paths and clustering coefficient is based on three-link cycles. Thus, it is possible that optimal connectivity distance would be more sensitive to detect brain connectivity alterations/reorganizations at the expense of being less specific about the nature of these changes. In relation with this, previous studies have shown that GT measures of strength, nodal efficiency and clustering coefficient are modulated by regional brain properties such as perfusion.[50] Thus, considering the global nature of optimal connectivity distance, we speculate that it could be less influenced by regional brain properties. Future studies should examine this possibility.

Finally, there are some limitations in our study that should be considered. First, our data were acquired in a 1.5-T scan, which involved relatively high susceptibility-induced loss of signal in regions with air–tissue interface and less advanced acquisition parameters. Second, CUD patients may show co-morbidity with alcohol and other drug abuse, but they were not excluded due to the high rates. Nonetheless, the abuse had to be restricted prior to the onset of their cocaine abstinence. Third, the region of interest (ROI) approach performed to study the relationship between clinical variables and optimal connectivity distance measure is limited in several ways. On the one hand, only the voxels within the ROI mask were considered. On the other hand, the features of the voxels within the ROIs were averaged. However, limiting the analyses to ROIs provides a better control for type I error by reducing the number of statistical tests, and averaging voxels within the ROI mask enhances homogeneity and reduces possible peak-voxel selection bias. Fourth, the optimal connectivity distance measure was calculated up to seven link steps based on previous findings.[25] However, these previous studies are based on healthy young adults. It is unknown if seven steps are also enough to characterize connectivity patterns in addicted populations. Future studies are necessary to overcome these limitations.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

ABL, VC and JCB created the experimental design and methodology. JCB, PRN, PFC, JJL and VC acquired the experimental data. VC, JAV, AMP and MPG performed the data analysis. JS, VC and ABL interpreted the results obtained in the study. VC, JS and ABL were the major contributors in writing the manuscript. ABL and VC supervised the whole process. All the authors read and approved the final manuscript.

## 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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