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# Functional connectivity of brain areas related to social cognition and anxiety in cervical dystonia

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**Introduction:** Recent studies highlighted the importance of non-motor symptoms, including emotional processing dysfunction, in individuals with cervical dystonia (CD). The resting state functional connectivity of areas involved in emotional processing, and the modulatory role of social anxiety on this connectivity, remain unexplored in CD. We hypothesized that CD patients would have altered functional connectivity between limbic areas involved in emotional processing as compared to healthy subjects and examined how variations in social anxiety affect connectivity.

**Methods:** 14 CD patients and 26 age- and sex-matched healthy controls completed a series of questionnaires and underwent functional magnetic resonance imaging (fMRI). Resting state functional connectivity was investigated between seeds (amygdala and insula) and whole brain ROIs, and in conventional functional networks. The modulatory role of social anxiety was investigated.

**Results:** CD patients showed reduced intra-regional connectivity in the insula, reduced connectivity between the right insula, left parietal operculum and left central opercular cortex. CD patients also showed clear reductions in connectivity in the salience, dorsal attention and sensorimotor resting state networks, as well as modest inter-network connections between language and fronto-parietal networks. In CD patients, higher anxiety scores and performance on affect naming tasks were associated with lower connectivity between right and left insula and between right insula and left central opercular cortex.

**Conclusion:** This study demonstrates that the previously observed deficits in emotional processing in CD patients may be underpinned by reduction in resting state functional connectivity in limbic areas and salience network with anxiety and social perception as a modulating factor.

KEYWORDS

**cervical dystonia, social cognition, anxiety, depression, resting state functional MRI**

# Introduction

Among the different types of isolated focal dystonia that emerge during adulthood, cervical dystonia (CD) is the most common [1]. It is characterized by involuntary posture of the neck and muscle spasms in the cervical region causing pain and discomfort. While the motor aspects have been widely investigated, in recent years more attention has been paid to the non-motor aspects of the condition and the impact that those have on patients' quality of life [2–4]. Anxiety and depression have been found comorbid with CD in 30%–50% of patients [5–7]. Psychiatric comorbidities seem to be present even before the onset of the motor symptoms [5], indicating that they are not merely due to the distress and stigma associated with motor features. Moreover, the presence of psychiatric comorbidities is typically not correlated to severity of motor features [8].

Social cognition encompasses all the cognitive processing of socially salient stimuli, from perception and understanding of emotions and social cues to the decisionmaking activity that can be relevant in a variety of social contexts. This complex spectrum of mental activities has a crucial role in guiding social communication and in regulating emotions and behaviours generated within social interactions. Previous literature has shown that anxiety in CD is often related to social contexts [7] and that depression impairs quality of life also in relation to social functioning [2]. Deficits in social cognition domains such as theory of mind (i.e., ability to understand someone else's thoughts and emotions and predict future behaviour [9]) and empathy [10] have been reported in CD patients. Furthermore, Burke and colleagues [11] showed deficits in social cognition in relation to recognition of emotional faces and prosody, but not mentalizing. The authors attributed these deficits to a collicular-pulvinar-amygdala pathway dysfunction that their group had reported in these patients. Our group has previously investigated the association between social cognition, anxiety, and depression in 46 patients with CD, 40 of whom were women [12]. Unexpectedly, we found that patients performed normally on social perception and social behaviour tests, and only a few patients had impairments on tests of theory of mind and empathy. However, a relationship emerged with individuals with greater anxiety, depression and social phobia performing better in social perception tasks, likely a compensatory mechanism to balance baseline increases in anxiety levels and lowered mood. Another recently published study [13] similarly tested the ability of patients with CD, compared to age- and sex-matched controls, to recognize auditory and visual emotional stimuli with the Cambridge Mindreading Face-Voice Battery (CAFMB) [14]. Patients performed worse than controls; however, in this case higher symptoms of depression were associated with poorer understanding of emotional facial expressions. The discrepancy in these findings is possibly due to the heterogeneity in CD populations in terms of comorbidities and disease presentation (*e.g.*, with/without tremor).

Several theories have been proposed to explain psychiatric comorbidities in CD. One is the presence of shared genetic underpinnings between mood disorders and dystonia [15]. Alternatively, dysfunction in brain connectivity between areas involved in emotional processing has been highlighted as potential underlying mechanism. A series of neuroimaging studies reported dysfunction in the prefrontal cortex (PFC) with decreased gray matter volume in primary dystonia [16], functional overactivity of the PFC and underactivity of the motor cortical areas in patients with idiopathic dystonia [17], altered connectivity between the PFC and basal ganglia [18], or more generally altered connectivity in the cortico-striato-thalamo-cortical loop [19, 20]. However, to our knowledge no study to date has investigated the direct neural mechanisms underlying the association between CD, anxiety (including social anxiety), depression, and performance on social cognition tasks.

In the present study, we collected resting state functional connectivity data from patients with CD and healthy individuals. We hypothesized that patients with CD would have reduced connectivity as compared to controls between subcortical and cortical areas involved in emotional processing, with specific focus on insula and amygdala. Furthermore, we explored group differences in intra-network connectivity across defined resting state brain networks between patients and controls. Finally, we investigated the modulating role of anxiety, depression, social perception, and empathy in the connectivity patterns observed in the patient population. The overarching aim of this analysis was to investigate the brain correlates of the previously described relationship between anxiety, depression, and social cognition domains in people with CD.

# Methods

## Participants

Participants were recruited from the Movement Disorders Clinic at the University of Calgary (patients with CD; n = 14, aged mean, standard deviation [M,SD] = 59.00 (8.47) years) while the healthy volunteers were staff or patients' friends or spouses (healthy volunteers, HV, all without history of neurologic disorders; n = 26, aged [M,SD] = 57.69 (8.19) years). The inclusion criterion for patients was a diagnosis of adult-onset idiopathic isolated CD according to international criteria [21], with onset in the neck. Exclusion criteria included history of other neurological manifestations (apart from tremor), positive genetic test for DYT1, DYT4, DYT6, DYT24 and DYT25 monogenic dystonia, and Montreal Cognitive Assessment [22] score <26, or psychotropic medication use.

## Clinical assessment

Participants with CD completed the Hospital Anxiety and Depression Scale (HADS) [23], the Liebowitz Social Anxiety Scale (LSAS) [24], and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [25], as part of previously published work [12]. The HADS scale includes two domain scores, a "Depression" score and an "Anxiety" score, each ranging from 0 to 21; for both, higher scores indicate a larger degree of the named trait. Similarly, we made use of two social anxiety subdomain scores from the LSAS: the "Fear & Anxiety" score and "Avoidance" score. Again, higher scores in each measure indicate a greater degree of the named trait. The TWSTRS scale includes three subdomain scores, quantifying levels of "Severity," "Disability," and "Pain" in individuals with CD. Social cognition measures tapped social perception and empathy. Social perception was assessed using three Social Cognition subtests from the Advanced Clinical Solutions (ACS) for the Wechsler Adult Intelligence Scale IV (WAIS-IV) and Wechsler Memory Scale IV (WMS-IV) [26]. In these subtests, participants matched emotion labels to 24 colour images of facial expressions (Affect Naming task); matched facial expressions to 12 audio-clips of single statements (Prosody Face Matching task); selected images or labels that best depicted the emotion expressed in 12 audio-clips of single statements, and determined whether the tone of voice influenced the meaning of these statements (Prosody Pair Matching task). Empathy was evaluated using the Empathy Quotient, a 60-item questionnaire which assesses cognitive and affective components of empathy [27]. Higher scores on this scale indicate greater empathic ability.

This study obtained ethical approval from the University of Calgary's Conjoint Health Research Ethics Board (CHREB #18-0645). Participants were assessed at the University of Calgary and provided written informed consent prior to testing.

## MRI acquisition

We collected MRI data on a GE Discovery 750 with an 8-channel head coil. Sequences included a 1 mm isotropic structural acquisition from a sagittal Fast Spoiled Gradient Echo (FSPGR) sequence, with a 2.252 ms echo time, 10° flip angle, 600 ms inversion time, and 7.176 ms repetition time. We also collected a 1 mm isotropic sagittal Fluid-Attenuated Inversion Recovery (FLAIR) image, with a 74.679 ms echo time, 90° flip angle, 1.379 s inversion time, and 4.2 s repetition time. For resting-state functional data acquisition, participants were instructed to keep their eyes fixated on a cross. For this, data were acquired using an axial Echo Planar Imaging (EPI) Blood Oxygen Level Dependent (BOLD) sequence, with a 28 ms echo time, 90° flip angle, 2.9 s repetition time, a 26 cm field of view, and a bottom-up sequential slice order. This functional sequence was acquired with a matrix size of 96, and reconstructed at a matrix size of 128, with a resultant voxel size of 2.03 × 2.03 × 2.7 mm.

## MRI preprocessing

We prepared each subject's MRI data for analysis with the following steps:

1) in SPM12 (version 7771) we independently brain-extracted the FSPGR and FLAIR data using the unified segmentation module. Default parameters were used, except bias-field-removed images were output, sampling distance was set to 2.5 mm, and n Gaussians for tissue classes 1 and 2 (*i.e.*, grey and white matter) were set to 2.
2) We generated brain masks for both FSPGR and FLAIR images from the segmentation results from (1) using *fslmaths*. We binarized the data from (1), then smoothed it with a 2 mm sigma gaussian kernel, and re-binarized at a threshold of 0.75.
3) We used the antsRegistration.sh script from ANTs version 2.4.2 to non-linearly warp the bias-field-corrected and non-brain-extracted FSPGR image from (1) to the bias-fieldcorrected and non-brain-extracted FLAIR image from (1). This registration included a rigid-body mutual information registration, followed by a heavily regularized SyN deformation [28] to ensure the resulting warps were spatially smooth. This was done to correct for deformations between the FSPGR and FLAIR images resulting from their differing receiver bandwidths. The FLAIR image was selected to define the resultant space because its higher bandwidth results in less geometric distortion. Both registrations were computed using masks from step (2).
4) We then performed a fine multimodal segmentation and normalization using SPM12's unified segmentation with the bias-field-corrected FLAIR from (1) and the warped and bias-field-corrected FSPGR from step (3). Default parameters were used, except additionally we outputted forward warps to Montreal Neurological Institute (MNI) space, used a sampling distance of 1 mm, and set the n Gaussians to 2, 2, 3, 4 and 5, for tissue classes 1 through 5, respectively.
5) We motion-corrected the functional MRI data from each run in SPM12 using the Realign module. Default parameters were used except estimation quality was set to 0.95, separation was set to 3 mm, and smoothing was set to 4 mm full width at half maximum (FWHM), using a 3rd degree B-spline for estimation interpolation. These data, as well as a mean image, were resliced using a 6th degree B-spline.
6) We slice-time corrected the motion corrected outputs from step (5) using SPM12 with the reference slice set at the first acquired slice of the acquisition volume.

7) We coregistered the mean volume from step (5) to the bias-field-corrected FLAIR image in SPM12's coregistration module. We used default parameters, except set the estimation separation to (3 mm, 1 mm). We carried slice-time-corrected outputs from step (6) along the computed transformation.
8) We moved the coregistered slice-time-corrected fMRI data from step (7) and the native space grey matter, white matter, and CSF tissue map from step (4) to 2 mm isotropic MNI space using SPM12's Normalize module with warps computed from step (4). Data from step (7) were interpolated with a 7th degree B-spline, and the tissue maps for classes grey matter, white matter, and CSF from step [3] were interpolated using trilinear interpolation.
9) We computed additional first-level fMRI noise regressors with an in-house python script. The resulting set of first-level fMRI regressors included 6 motion regressors, their temporal derivatives, framewise displacement, scrubbing regressors for global signal spikes calculated from step (8) that exceed Z-scores of 3, and 5 aCompCor [29] regressors each from eroded WM and CSF masks from step (8).
10) We smoothed the fMRI data from step (8) in SPM12 using an 8 mm FWHM Gaussian kernel.

## MRI analysis

We performed connectivity analyses using CONN 22.a [30]. Generally, region-to-region functional connectivity strengths are represented by Fisher-transformed Pearson correlation coefficients from a weighted general linear model, independently for each region pair. CONN's pre-analysis processing includes the following: a) individual scans are weighted using a step function that represents a sudden onset and offset of activity; b) the step function is then convolved with SPM's canonical hemodynamic response function; c) finally, a rectification is applied which involves taking the absolute value of the signal and effectively converting negative values to positive ones; this allows to focus on the positive fluctuations of the BOLD signal, which are indicative of neural activity. Group-level analyses for each connection are performed independently using general linear models with first-level connectivity estimates as dependent variables, and groups represented as independent variables.

## Hypothesis-driven group differences

We performed four *a priori* analyses building generalized linear models to examine differences in functional connectivity between participants with CD and controls using the left and right insula and amygdala in seedto-ROI analyses with whole brain target coverage. These analyses used CONN's default brain atlas, which is constituted by the FSL Harvard-Oxford atlas' cortical & subcortical areas and the AAL atlas cerebellar areas [29]. For each seed-to-target analysis, false discovery rate (FDR) correction (at $\alpha < 0.05$) for multiple comparisons was made at the connection level. We included both age and sex as demeaned covariates of no interest in these analyses, with effects of interest estimated at the study-wide average age of 57.35 years old. Where between-group connectivity differences were observed, we followed up with exploratory correlational analyses between anxiety, depression, and social cognition scores with functional connectivity measures to determine whether these factors modulated group differences in network connectivity.

## Exploratory group differences

We additionally performed an exploratory analysis of differences between participants with CD and controls by contrasting ROI-to-ROI functional connectivity between each pair of regions among 32 network ROIs identified using high performance computing-independent component analysis (HPC-ICA) [31]. Cluster-level inferences were based on parametric statistics within- and between- each pair of networks, with networks identified using the *a priori* HPC-ICA networks defined in CONN. Results were thresholded at the connection level with an $\alpha$ of 0.05 and an FDR corrected cluster-level threshold of $\alpha < 0.05$. We included both age and sex as demeaned covariates of no interest in these analyses, with effects of interest estimated at the study-wide average age of 57.35 years old.

# Results

Descriptive statistics and between-groups differences for demographic features in patients with CD and healthy volunteers, and clinical characteristics of patients with CD are summarized in Table 1.

## Group differences - Hypothesis driven

We first performed a series of seed-to-ROI analyses contrasting the resting state functional connectivity of the insula and amygdala between individuals with CD and controls, with whole-brain target ROI coverage, correcting for both age and sex. Individuals with CD displayed similar functional connectivity profiles of both left ($|t_{49}|$s $\leq$ 3.55, $p_{FDR}$s $\geq$ 0.111) and right ($|t_{49}|$s $\leq$ 3.25, $p_{FDR}$s $\geq$ 0.275) amygdala as compared to control subjects. However, individuals with CD displayed statistically significant ($p_{FDR} <$ 0.05) differences in functional connectivity relative to controls with the right insula seed (detailed in Table 2), with less positive

TABLE 1 Demographic and clinical characteristics of the study groups.

| | CD | Controls | Between groups difference *p* (or Fisher's exact test, as appropriate) |
|---|---|---|---|
| Count, *n* | 14 | 26 | |
| Age in years, *M* (*SD*) | 59 (8.5) | 57.7 (8.2) | 0.64 |
| Sex, Female/Male | 10/4 | 18/8 | 1 |
| Age at CD onset in years, *M* (*SD*) | 45.1 (11.6) | | |
| CD duration in years, *M* (*SD*)<br>Severity subscale<br>Disability subscale<br>Pain subscale | 14.2 (10.9)<br>17.3 (6.4)<br>8.9 (7.4)<br>6.2 (4.1) | | |
| HADS score, *M* (*SD*)<br>Depression subscale<br>Anxiety subscale | <br>6.6 (4.9)<br>7.6 (4.6) | | |
| LSAS score, *M* (*SD*)<br>Fear/Anxiety subscale<br>Avoidance subscale | <br>30.7 (14.3)<br>29.5 (16.1) | | |
| Affect naming task score, *M* (*SD*) | 11.1 (2.5) | | |

*M*, mean; *SD*, standard deviation; SSRI, serotonin selective reuptake inhibitors; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; HADS, Hospital Anxiety Depression Scale; LSAS, Lebowitz Social Anxiety Scale.

TABLE 2 Differences in resting state functional connectivity between participants with cervical dystonia (CD) and controls with the right insula as the seed region of interest.

| Right Insula Seed Target ROI | $\beta$ | Direction | $t_{49}$ | $p_{FDR}$ |
|---|---|---|---|---|
| L Insula | −0.34 | Control > CD | −3.74 | 0.0467 |
| L Parietal Operculum | −0.25 | Control > CD | −3.70 | 0.0467 |
| L Central Opercular Cortex | −0.26 | Control > CD | −3.54 | 0.0486 |

$N = 40$. Sex and Age, included as demeaned covariates, displayed differences with effects of interest estimated at the study-wide average age of 58 years old.

connectivity with the left insula, left parietal operculum, and left central opercular cortex.

## Group differences - exploratory in defined resting state networks only

Following the hypothesis-driven investigation of functional connectivity of the insula and amygdala in individuals with CD, we performed an exploratory analysis of functional connectivity perturbations in defined resting state networks. This analysis revealed widespread differences in resting state functional connectivity between controls and individuals with CD (detailed in Figure 1; Table 3). Clear intra-network reductions in functional connectivity in those with CD were detected in the salience network, including the insula, supramarginal gyrus, anterior cingulate cortex, and rostral prefrontal cortex. CD participants exhibited also intra-network reductions in functional connectivity in the dorsal attention network, involving the intraparietal sulcus, and in the sensorimotor network, involving the lateral sensorimotor cortex. Participants with CD additionally displayed more modest changes in inter-network connections between the language and the frontoparietal networks, expressed both as reductions (in the connectivity between the left posterior superior temporal gyrus and the left posterior parietal cortex, and between the right posterior parietal cortex and the right inferior frontal gyrus); and as increases (in the connectivity between the right posterior superior temporal gyrus and the left posterior parietal cortex).

## Correlational analyses with psychiatric and social cognition measures

To further investigate the insular functional connectivity differences seen in participants with CD, we performed

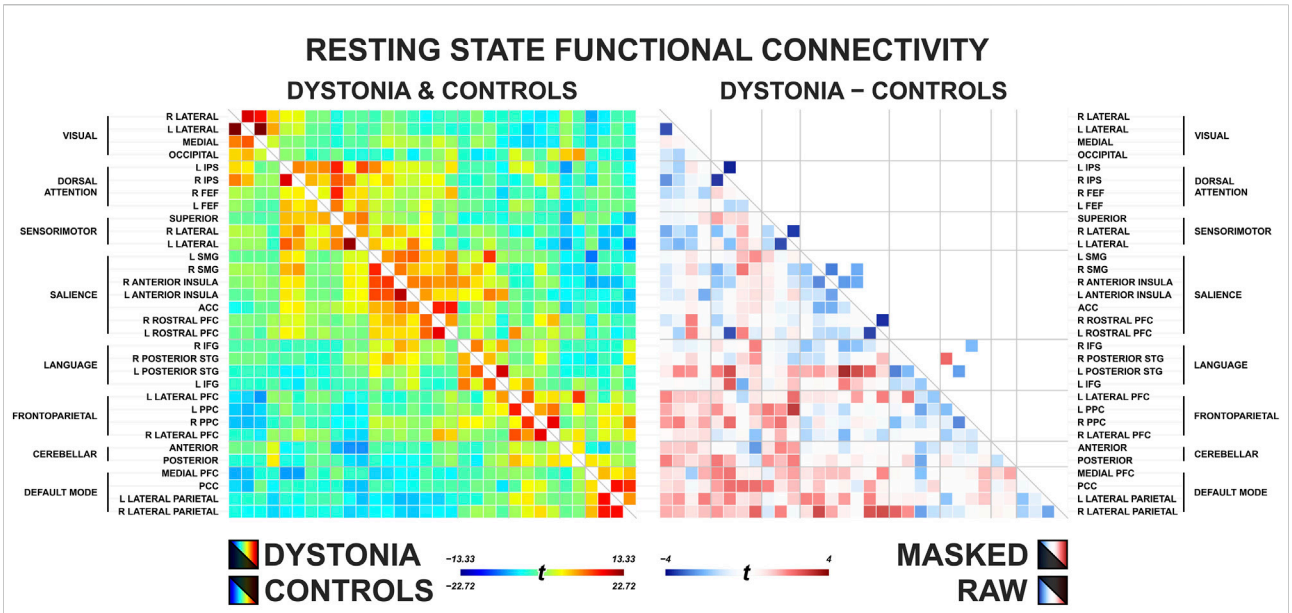


FIGURE 1
The panel on the left depicts the resting state functional connectivity in individuals with cervical dystonia (CD; upper right) and control subjects (bottom left). The panel on the right depicts significantly affected clusters ($p_{FDR} < 0.05$, as indicated in Table 2) of region-to-region functional connectivity between CD and control subjects (upper right), as well as all connectivity significances (bottom left). Red cells indicate more positive functional connectivity in CD relative to control subjects, whereas blue cells indicate more negative functional connectivity. Values depicted are *t* values. $N = 40$.

TABLE 3 Differences in resting state networks connectivity between participants with cervical dystonia (CD) and controls.

| ROI | Network | Direction | $t_{49}$ | $p_{FDR}$ |
|---|---|---|---|---|
| Cluster 1 $F_{2,35} = 7.92$ | | | | 0.0244 |
| L Posterior Superior Temporal Gyrus ↔ L Posterior Parietal Cortex | Lang, FP | Ctrl > Dys | −2.46 | 0.0833 |
| R Inferior Frontal Gyrus ↔ R Posterior Parietal Cortex | Lang, FP | Ctrl > Dys | −2.05 | 0.2657 |
| R Posterior Superior Temporal Gyrus ↔ L Posterior Parietal Cortex | Lang, FP | Dys > Ctrl | 2.38 | 0.5403 |
| Cluster 2 $F_{2,35} = 7.77$ | | | | 0.0244 |
| L Intraparietal Sulcus ↔ R Intraparietal Sulcus | DA | Ctrl > Dys | −3.7 | 0.0244 |
| Cluster 3 $F_{1,36} = 10.77$ | | | | 0.0244 |
| L Lateral Sensorimotor ↔ R Lateral Sensorimotor | SM | Ctrl > Dys | −3.51 | 0.0381 |
| Cluster 4 $F_{2,35} = 7.03$ | | | | 0.0244 |
| R Rostral Prefrontal Cortex ↔ L Rostral Prefrontal Cortex | Sal | Ctrl > Dys | −3.6 | 0.0296 |
| R Supramarginal Gyrus ↔ R Anterior Insula | Sal | Ctrl > Dys | −2.85 | 0.1124 |
| R Supramarginal Gyrus ↔ Anterior Cingulate Cortex | Sal | Ctrl > Dys | −2.27 | 0.2104 |
| R Anterior Insula ↔ L Anterior Insula | | | | |
| R Anterior Insula ↔ Anterior Cingulate Cortex | Sal | Ctrl > Dys | −2.5 | 0.2622 |
| | Sal | Ctrl > Dys | −2.27 | 0.3000 |

Networks include Cerebellar (Cer), Dorsal Attention (DA), Frontoparietal (FP), Language (Lang), Salience (Sal), Sensorimotor (SM), and Visual (Vis). $N = 40$. Sex and Age, included as demeaned covariates, displayed differences with effects of interest estimated at the study-wide average age of 58 years old.

exploratory correlational analyses between anxiety, depression, social anxiety and social cognition scores and functional connectivity measures within participants with CD. The functional connectivity between the right insula and the left central opercular cortex was inversely correlated with the HADS anxiety subscore ($r_{12} = -0.715$, p = 0.004), and the Affect naming

score ($r_{12}$ = −0.585, $p$ = 0.028). Similarly, the functional connectivity between left and right insula was inversely correlated with the HADS anxiety subscore ($r_{12}$ = −0.602, $p$ = 0.023), and the Affect naming score ($r_{12}$ = −0.543, $p$ = 0.045). We did not detect any significant correlation between the functional connectivity differences observed in CD patients from healthy volunteers and disease duration, TWSTRS scores (motor and pain sub-scores), HADS depression subscores, LSAS scores and scores on Prosody, Social Perception, and Empathy measures (all $p$ values >0.05).

## Discussion

In this study we assessed differences in resting state functional connectivity between patients with CD and controls. Amygdala and insula, regions known to be involved in emotional processing, were chosen as ROIs in these analyses as previous research showed mood disorders, including heightened social anxiety and depression, and deficits in emotional processing in this patient population [3–8, 32, 33]. We found no differences in the functional connectivity of the amygdala with other areas of the brain.

However, we found differences between patients and controls in the connectivity of the insula, with patients showing lower intra-regional connectivity (between left and right insula), as well as lower connectivity between right insula and left parietal and central opercular cortex.

Decreased intra-regional connectivity of the insula is in line with previous findings in CD. In fact, previous studies have identified structural and functional changes of the insula in CD, specifically reduced grey matter and cortical thickness [34, 35], and increased functional regional homogeneity between voxels indicative of reduced functional specialization [36]. Insula activity has been previously associated with detection and processing of internal states, a process otherwise known as interoception [37]. Functional activation changes of the right insula found in this study may be linked to the previously reported decrease in interoceptive sensitivity in CD [38]. Alternatively, and perhaps more importantly, the changes in functional connectivity of the right insula detected herein may be related to sensory and emotional regulation mechanisms that are relevant to process socially salient stimuli.

A relationship between changes in insular connectivity and somatosensory processing is supported by the observed decreased functional connectivity between the right insula and the central (rolandic) and parietal opercular cortical regions. Insular and opercular cortical regions are highly structurally inter-connected, primarily due to their anatomic contiguity. The connectivity changes involving the insula and the somatosensory cortices include secondary somatosensory areas encompassing the central and the parietal opercular sub-regions. This suggests that patients with CD exhibit alterations in the processing of different somato- and viscero-sensory experiences. Although these connectivity changes did not correlate with the pain subscore on the TWSTRS, their relationship to pain and combined sensory processing deserves further investigation, since the dorsal posterior insula oversees basic painful stimuli processing, and the dorsal middle insula regulates subjective sensory discriminatory properties [39–41].

The lack of significant changes in the connectivity of the amygdala in this analysis are different from recent results by Mahajan and colleagues [42]. The authors used correlational tractography to analyze the structural connectivity between the amygdala and motor and sensorimotor areas in patients with CD and increased state and trait anxiety. They found increased connectivity between the amygdala bilaterally and the motor and parietal cortex associated with increased trait anxiety. This discrepancy with our results may be explained by a few factors. First of all, we examined functional connectivity rather than white matter tracts. Furthermore, the focus of this study was on social anxiety rather than generalized anxiety. It is reasonable to consider that the amygdala *per se* plays a greater role in generalized anxiety and fear while the salience network may be more involved in more complex socio-emotional behavior. Finally, the patients in Mahajan et al.'s study were medicated with antidystonia and anti-anxiety medications while we decided to only include patients that were not taking any psychotropic medications that may impact brain connectivity.

Our exploratory analysis of resting state networks is consistent with previous studies showing a broad involvement of long cortico-cortical structural connections, but also changes in functional network connectivity in focal dystonia [19, 20]. Despite part of the findings of our seed-to-ROI analyses suggest potential compensatory gains in social cognition, the dysfunction detected within the salience network is consistent with the high burden of depressive and anxiety symptoms in CD. Defective salience network connectivity may represent a neurobiological substrate that CD and other forms of isolated dystonia share with psychiatric disorders, manifesting with emotional dysregulation and even accounting for the high prevalence of emotional symptoms in this movement disorder [32]. The decreased intra-network connectivity involving both dorsal attention and sensorimotor networks confirms the observation from Berman and colleagues [43] of reduced hemodynamic responses in cognitive/visual networks during rest, and in key nodes of the default mode, executive control and visual networks during a finger tapping task.

None of the specific functional connections explored in our seed-to-ROI analyses was clearly correlated to the severity of depressive symptoms, expressed by a rating scale (the HADS) that measures generic states of depression rather than specific types of mood disorders. This suggests that none of the functional connections explored is likely to contribute significantly more than others to clinical aspects of depression measured by the HADS in people with CD. Previous research [44] demonstrated

an association between the diagnosis of major depressive disorder or bipolar disorder and resting-state functional connectivity of the insula, in particular its ventral anterior subregion. Other reports have shown decreased resting-state functional connectivity between the anterior cingulate cortex and the anterior insula in more severely depressed individuals [45, 46]. Importantly, the activity within the insula showed a strong, negative correlation with depression severity during an interoceptive attention task, suggesting that this correlation could be stronger for task-related, compared to restingstate, functional connectivity of the insula [47]. It is of course also possible that our relatively small sample size, or the use of the HADS to measure depression severity, may have contributed to the lack of significant correlation between depression severity and our seed-to-ROI functional connectivity.

Conversely, a direct link between anxiety levels, processing of social stimuli namely the ability to name visually perceived affects represented by facial expressions- and insular connectivity is supported by our findings. We detected a negative correlation between severity of anxiety in CD patients and functional connectivity between right insula and left insular and opercular cortex, with lower connectivity between these areas in individuals reporting higher anxiety scores. At the same time, we observed that the lower the functional connectivity between these regions the better the performance on affect naming as a measure of the social perception cognitive domain. Contextualized with the changes in intra- and inter-network connectivity, this finding may be interpreted as an association between greater levels of anxiety and reduced recruitment of regulatory fronto-parietal networks linked to cognitive reappraisal of socially salient stimuli [48]. This reduced recruitment of fronto-parietal networks does not appear to have any functional effect on social perception abilities, since the latter were detected as higher in the presence of this functional connectivity change. Interesting insight on the relationship between interhemispheric projections from the insula to the contralateral insula and socio-emotional processing was recently provided by a mouse model focused on the role of $Insula^{Ins}$ neurons, that are functionally related to an efficient social discrimination [49]. When this neuronal subpopulation is stimulated, the inter-insular inter-hemispheric circuit is excited. At odds with this model, our observation suggests instead lower connectivity with greater social perception abilities, which may reflect some form of functional compensation in individuals with CD and better performance on facial affect recognition. This apparent discrepancy indicates that new studies are necessary to investigate in greater depth the relationship between inter-hemispheric insular connectivity in humans with special focus on insular sub-nuclei and its relationship to CD and social cognition.

This study has a few noteworthy limitations. Its sample size is small, especially for the CD group, and shows strong female predominance. Despite the general population of patients with CD consistently showing a 2.5-3-to-1 female-to-male ratio [50], and the lack of influence of sex on the associations between connectivity and CD group in our analyses, the overrepresentation of females might limit the generalizability of our findings. We adopted a naturalistic selection of our patient sample, including eligible patients following the order of enrollment and regardless of their psychiatric comorbid profile and ongoing treatment. For this reason, we opted to correlate functional connectivity measures with state measures of depression and anxiety rather than with psychiatric diagnoses based on clinical criteria. Our patient population showed, overall, a low burden of depressive and anxiety symptoms, which may have skewed our observation towards a milder sample of CD patients with respect to mood symptoms. New studies recruiting larger clinical samples, and with greater representation of depressive and anxiety symptoms, should address the group effect of psychiatric diagnoses on resting state functional connectivity in this patient population. An important limitation is that our control group did not undergo psychiatric and social cognition assessments. Previous research has consistently demonstrated a higher burden of depression and anxiety symptoms in CD patients compared to healthy volunteers, as well as changes in specific social cognition domains [51]. However, this limitation does not allow us to evaluate whether the observed correlation between connectivity of the insula and HADS Anxiety score and Affect Naming score is specific for CD or detectable also in healthy individuals. Finally, our study focus was exclusively on ROI and networks involved in emotional processing. For this reason, and due to sample size limitations, we did not test the effect of other motor (e.g., tremor) or nonmotor (e.g., pain, sleep disruption, cognitive changes) features of dystonia on functional connectivity.

In conclusion, our study demonstrates relevant changes in functional connectivity within and between ROIs and networks associated with the processing of emotional and socially salient stimuli in patients with CD, highlighting the right insula as the region linked to greatest connectivity dysfunction. The observed changes direct towards both defective and compensatory mechanisms that regulate social cognition domains and cognitive processing of socially salient stimuli, and in part yield a correlation with the severity of anxiety in CD. These findings add to a growing body of evidence supporting a substantial involvement of abnormalities in the cognitive processing of socially salient and emotionally relevant stimuli in the most common form of isolated dystonia. From a clinical perspective, our results highlight the importance of evaluating psychiatric features in this population jointly with motor and other non-motor features, as well as directly assessing their impact on social functioning.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Conjoint Health Research Ethics Board, University of Calgary. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

VG: Conceptualization, Methodology, Data curation, Writing. FB: Conceptualization, Methodology, Data curation, Visualization, Writing. BC: Methodology, Reviewing and Editing. GI: Conceptualization, Supervision, Reviewing and Editing. DM: Conceptualization, Data curation, Supervision, Writing- Reviewing and Editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

Author VG was employed by Cerebra Medical LTD.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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