# Network localization of cervical dystonia based on causal brain lesions

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## Abstract

Cervical dystonia is a neurological disorder characterized by sustained, involuntary movements of the head and neck. Most cases of cervical dystonia are primary, with no obvious cause, but other cases are secondary to focal brain lesions. These latter cases are valuable as they link symptoms to neuroanatomy in a causal way. However, lesions causing cervical dystonia have been reported in different brain locations, leaving localization unclear. Further, symptoms can come from remote regions connected to the lesion location rather than the lesion site itself. Here, we employ a recently validated technique termed 'lesion network mapping', to overcome these obstacles. First, we performed a systematic search for lesions causing cervical dystonia, identifying 25 lesions located throughout the cerebellum, brainstem, and basal ganglia. Second, voxels functionally connected to each lesion location were identified using a normative dataset of resting-state fMRI scans from 1000 healthy individuals. Individual lesion network maps were thresholded and overlaid to identify brain regions connected to all or most lesion locations. Third, we assessed specificity by comparing our results to lesions causing other neurological symptoms. Finally, we assessed the relevance of our lesion-based findings for patients with *primary* cervical dystonia by utilizing a resting state functional connectivity dataset from patients (N = 23) versus controls (N = 22). Our results demonstrated that lesion locations causing cervical dystonia were part of a common brain network that had positive functional connectivity to the cerebellum and negative connectivity to sensorimotor cortex. This pattern of connectivity was highly specific to cervical dystonia lesions compared to lesions causing other neurological symptoms. Finally, our regions in the cerebellum and sensorimotor cortex, identified based on secondary dystonia cases, were highly abnormal in patients with primary cervical dystonia, with the magnitude of this abnormality correlating with the magnitude of patient's symptoms. These results suggest that the cerebellum and sensorimotor cortex are critical nodes in a distributed brain network underlying both primary and secondary cervical dystonia. These brain regions are testable therapeutic targets for further research.

## Keywords

Cervical dystonia, lesions, functional connectivity, cerebellum, sensorimotor cortex

## Introduction

Cervical dystonia (CD) is a chronic neurological disorder characterized by sustained and involuntary contractions of the neck muscles, and is the most common form of focal dystonia (Xiao et al., 2012). CD has traditionally been ascribed to dysfunction of the basal ganglia (Galardi et al., 1996; Naumann et al., 1998), but abnormalities have been observed in many other brain regions including the cerebellum (Batla et al., 2015), prefrontal cortex (Li et al., 2017), midbrain (Holmes et al., 2012), motor cortex (Richardson, 2015), and sensory cortex (Prudente et al., 2016). This has led to the suggestion that CD is a 'network disorder' resulting from dysfunction in multiple different brain regions (Jinnah & Hess, 2006). However, the key nodes of this network have yet to be identified. Further, it remains unclear which brain regions are causing CD symptoms, as observed abnormalities could be compensating for symptoms or incidental correlates.

Occasionally, a focal brain lesion can cause symptoms that are nearly identical to those seen in primary CD (LeDoux & Brady, 2003). Although these cases of secondary CD are less common than cases of primary CD, they are uniquely valuable because lesions allow for causal links between the lesioned brain region and resulting symptoms (Rorden et al., 2007). However, lesions causing CD can occur in numerous locations, spanning the cerebellum, pons, medulla, and basal ganglia (LeDoux & Brady, 2003). Further, symptoms can emerge not only from the lesion itself, but also from the effect of the lesion on remote but connected brain regions, a phenomenon referred to as diaschisis (von Monakow, 1914). These factors complicate the localization of brain regions causing CD symptoms based on focal brain lesions alone.

Recently, we validated a novel technique termed 'lesion network mapping', which can link lesions in different locations to a common brain network, and identify connections common to lesions causing similar symptoms (Boes et al., 2015). Rather than focus on lesion location alone, this technique uses a database of normative resting state functional connectivity MRI scans to map the connectivity of lesions, and turn each lesion location into a network. This technique has already lent insight into localization of several neuropsychiatric symptoms, including hemichorea-hemiballismus (Laganiere et al., 2016), freezing of gait (Fasano et al., 2016),

delusional misidentifications (Darby, Laganiere, et al., 2017), and criminal behavior (Darby, Horn, et al., 2017). Here, we apply this technique towards lesions causing CD.

## Materials and methods

### Case selection

Cases of lesions causing CD were identified from a systematic search of Pubmed in March 2017, using the combination of synonyms of the following terms: CD, lesion, magnetic resonance imaging, and computerized tomography. In addition, reference lists from each selected article were searched for cases missed in the initial search. Inclusion criteria were as follows: 1) neurological examination documenting CD that was assumed to be secondary to the intraparenchymal lesion(s) of the brain; 2) the lesion was displayed in enough clarity for it to be reliably traced onto a standard brain atlas. Exclusion criteria were: 1) lesions in children where the brain was not sufficiently developed to resemble the standard adult brain; 2) lesions of the central nervous system outside of the brain. As the emergence of dystonia may be delayed by months or even years following a brain insult (LeDoux & Brady, 2003; Scott & Jankovic, 1996), we did not apply a strict time limit for the onset of symptoms post-lesion.

### Lesion network mapping

Our group recently developed a technique termed ‘lesion network mapping’ that identifies brain regions functionally connected to lesion locations causing a given neurological symptom (Boes et al., 2015). Lesion network mapping can link heterogeneous lesion locations to specific sites known to be involved in symptom expression. Briefly, the technique proceeded in three steps: 1) the volume of each of the lesions was transferred to a standard brain; 2) voxels functionally connected to each lesion were computed using rs-fcMRI data derived from a normative dataset of 1000 healthy, young adults (Yeo et al., 2011); 3) the resulting lesion network maps were thresholded and overlaid to identify common network sites across the lesions (Figure 1). The methodology has been presented in detail previously (Boes et al., 2015). As some patients also had dystonia in other body regions, the analysis was verified with lesions from patients with only *cervical* dystonia (n=19).

For step one, lesions were traced by hand onto a standardized brain atlas (2x2x2mm MNI 152 brain) using FSL software (version 5.0.9) (Jenkinson et al., 2012). For step two, resting state functional connectivity MRI (rs-fcMRI) maps were created for each lesion using a standard seed-based approach. The time course of the average blood oxygen level–dependent signal within the lesion volume was extracted for each participant in the normative cohort and correlated with all brain voxels to create a connectivity map for each lesion. For step three, each of the lesion network maps was thresholded at a t-value of $\geq 7$ (both positive and negative correlations with the time course of the lesion location were included), in order to create a binarized map to calculate the lesion network overlap in each brain voxel. The image processing and analyses are described in detail previously (Darby, Horn, et al., 2017).

< Figure 1 here (three step method) >

## Specificity

To test if our results were specific to CD, we compared our lesion network to two other 'control' datasets. Firstly, we used a 'non-specific' dataset of lesions that were distributed throughout the brain without a common neuropsychiatric phenotype (n=135) (Corbetta et al., 2015). Second, we used a 'movement disorders' dataset of 73 lesions causing movement disorders other than dystonia: asterixis (n=30) (Kim, 2001; Laganiere et al., 2016); hemichorea-hemiballismus (n=29) (Laganiere et al., 2016), and freezing of gait (n=14) (Fasano et al., 2016).

We compared our results to these two control lesion datasets using two methods: 1) a Liebermeister test, using voxel-based lesion-symptom mapping (VLSM) (Rorden et al., 2007), and 2) a two-sample t-test, using Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) (Ashburner, 2012). Both statistical approaches identify voxels that are significantly more or less connected to CD lesion locations than control lesion locations. The difference between these approaches is that the Liebermeister test is used to analyze voxels in a binary fashion (functionally connected or not), and is more commonly used in lesion analyses, while the t-test takes into account the strength of the connection, and is more commonly used in

functional neuroimaging (Fasano et al., 2016). Because the Liebermeister test is used for binary image analyses, the group comparisons were conducted separately for positive and negative connectivity maps.

Correction for multiple comparisons was conducted using voxel-level family-wise error (FWE) for t-tests and false discovery rate (FDR) for Liebermeister tests across the whole brain. Corrected p-values less than 0.05 were considered significant. However, because the goal of these analyses was to assess specificity of our findings, this investigation was restricted to regions within the CD lesion network map (i.e. regions that were functionally connected to at least 23/25 lesions, as shown in Figure 2).

## Relevance to primary cervical dystonia

We then investigated whether regions identified through secondary CD cases were also abnormal in patients with *primary* CD. To define these ROIs, we performed a conjunction analysis to find brain regions that were both sensitive (functionally connected to >90% of cases) and specific (specific to CD lesion locations across all 4 'specificity' analyses) to CD lesion locations. We then ran these ROIs as seed regions in an existing rs-fcMRI dataset from patients with primary CD (23 primary CD patients, and 22 controls) (Delnooz et al., 2013).
– image processing using Hesheng's new script -- .

Voxelwise correlation coefficient maps from each seed ROI were z-transformed and smoothed using 8mm full-width-at-half-maximum (FWHM) Gaussian kernel to improve the signal-to-noise ratio. Finally, patients and controls were compared using two-sample t-test implemented in SPM12. Family-wise error corrected p-values less than 0.05 at cluster-level (height-threshold $p<0.005$, whole brain search volume) were considered significant. The z-transformed values were extracted from the clusters shown in Figure 4 to illustrate the direction of connectivity (positive or negative) and for correlation analyses with the symptom severity as measured with Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) in CD patients. As the TWSTRS score distribution was not normal, the correlation analyses were conducted using

Spearman's rank order correlation coefficient, with p-values <0.05 considered significant.

## Results

### Lesions causing cervical dystonia

We identified 25 cases of lesion-induced CD (Table 1, Figure 2). Lesions occurred in a number of different brain locations including the cerebellum (11 lesions), brain stem (9), basal ganglia (8), thalamus (1), and occipital lobe (1). Note that the number of lesions is greater than 25 because some patients had multiple lesions.

< Figure 2 here (drawn lesions) >

< Table 1 here (cases) >

### Lesion network map

Clusters of voxels positively functionally connected to at least > 90% causing CD were found within the thalamus, midbrain, and cerebellum (Figure 3A). Clusters within the cerebellum involved the bilateral cerebellar cortex, the dentate nucleus, and the vermis. Negatively functionally connected clusters were found within the sensory cortex extending into the primary motor cortex (termed sensorimotor cortex henceforth) (Figure 3A). Medial and lateral clusters were found within the sensorimotor cortex, agreeing with previous reports of both a medial and lateral representation for the neck within motor and sensory homunculi (Prudente et al., 2015; Prudente et al., 2016). Brain regions with smaller clusters of (positive and negative) functionally connected voxels can be found in Supplementary Figures 1&2. Voxels with functional connectivity to all 25 lesion locations were found within the cerebellum, midbrain, sensory cortex, and lateral geniculate nucleus (Table 2).

### Specificity

Multiple voxels showed significantly greater functional connectivity to lesion locations causing CD compared to control lesions, independent of the statistical approach and control dataset (Figure 3B, Supplementary Figure 4). Regions that survived all specificity tests (4/4) were located within the cerebellum (center of

gravity in the largest cluster of 505 voxels at xyz MNI-coordinate 1 -54 -34 mm) and sensorimotor cortex (14 voxels at -8 -43 75 mm).

Because this sensorimotor cluster was quite small (Supplementary Figure 4D), negatively connected voxels surviving 3 out 4 analyses were used to define an ROI for the subsequent analysis in primary CD patients (as opposed to 4/4 in the positively correlated seed) (largest cluster of 548 voxels with center of mass at 45 -24 60 mm in the left and 478 voxels at -45 -28 59 mm in the right hemisphere).

To test whether positive connectivity to cerebellum and negative connectivity to sensorimotor cortex were independent or redundant predictors of lesion-induced CD, we included both factors in a linear model versus all control lesions. Cerebellum connectivity was a strong independent predictor of CD ($p = 0.002$), while sensorimotor connectivity fell just short of our threshold for significance ($p = 0.051$).

< Figure 3 here (lesion network map) >

## Relevance to primary cervical dystonia

CD patients (n=23) showed abnormal functional connectivity, compared to healthy volunteers (n=22), from our seed ROI in the cerebellum to a cluster of voxels within the sensorimotor cortex (peak MNI-coordinate 44 -6 3 mm; $T_{max}$=5.70; cluster size 1690 voxels; $P_{FWE}$=0.001) (Figure 4A). Specifically, healthy volunteers had negative connectivity, which was inverted in patients (Figure 4A). From our seed ROI within the sensorimotor cortex, patients showed lower positive connectivity to a slightly anterior cluster, mainly within the primary motor cortex, and also lower negative connectivity to a cluster including the basal ganglia, thalamus, and anterior cingulate cortex. In both cases, loss of connectivity correlated with the patient symptom severity as measured using TWSTRS scores (Figure 4B).

There was no significant difference in average frame-to-frame motion between patients and controls ($p=0.08$), and the motion did not correlate with any of the

extracted cluster values in Figure 4: r= 0.24 p=0.28 (top panel, Figure 4), r= -0.01 p=0.98 (middle panel) and r= 0.10 p=0.66 (bottom panel).

< Figure 4 here – our seeds showing different connectivity between Delnooz patients and controls >

## Discussion

There are several noteworthy findings. First, consistent with prior findings (LeDoux & Brady, 2003), we found that lesions in multiple different brain locations can cause CD. However, our findings also demonstrated that all lesion locations causing CD were part of a common brain network, with positive connectivity to the cerebellum and negative connectivity to sensorimotor cortex. This pattern of connectivity was highly specific to lesions causing CD compared to control lesions. Finally, we showed that these lesion-derived findings are also relevant in *primary* CD, with abnormal functionally connectivity in patients that correlated with symptom severity.

### Lesion network mapping in cervical dystonia

Because lesions causing CD are rare and have occurred in a number of different areas of the brain, previous lesion mapping approaches have had trouble isolating specific brain regions causing CD symptoms (LeDoux & Brady, 2003). Due to this heterogeneity, it has been hypothesized that brain connectivity may play an important role (LeDoux & Brady, 2003; Prudente et al., 2014). Our recently validated technique, lesion network mapping, integrates brain connectivity into lesion analysis (Boes et al., 2015). Previous studies have applied lesion network mapping to a variety of different neuropsychiatric symptoms, including other movement disorders (Fasano et al., 2016; Laganiere et al., 2016). For example, Laganiere et al. (2016) found that lesions causing hemichorea-hemiballismus were connected to the posterolateral putamen, and Fasano et al. (2016) found that lesions causing freezing of gait were connected to the cerebellar locomotor region. Using lesion network mapping in the present paper, we have identified the cerebellum and the sensorimotor cortex as being causally linked to CD.

Our paper goes beyond prior lesion network mapping studies, as it is the first to confirm lesion-based findings in a dataset from patients with similar symptoms but without brain lesions. Specifically, we show that regions identified by lesion network mapping are also abnormal in patients with primary CD, suggesting a shared neuroanatomic substrate independent of symptom etiology.

## The cerebellum in cervical dystonia

It has previously been suggested that CD may arise from dysfunction of the cerebellum or its functional connections (Jinnah & Hess, 2006; LeDoux & Brady, 2003). The present study strengthens this hypothesis by showing that lesions causing CD, although occurring in many different locations, are specifically connected to the cerebellum, and in particular, the cerebellar cortex, the vermis, and the dentate nucleus. These findings are supported by fMRI studies showing abnormalities of the vermis and cerebellar cortex of CD patients (Li et al., 2017; Prudente et al., 2016), and post-mortem Purkinje cell loss from the cerebellar cortex in human primary CD patients (Prudente et al., 2013). In addition, pharmacological manipulation of the vermis (Pizoli et al., 2002) and cerebellar cortex (Calderon et al., 2011) of mice has been shown to cause dystonia.

An important role of the cerebellum is to process and integrate descending and ascending inputs to coordinate and adjust bodily movement (Coffman et al., 2011; Huang et al., 2013). The cerebellum is thought to act as a 'comparator' of these inputs to provide rapid, involuntary adjustments in muscle activity without delays inherent to cortical processing (Ramnani, 2006). As proposed by LeDoux and Brady (2003), our findings suggest that disruption of these inputs may underlie CD. Specifically, in light of the three particular cerebellar regions included in our lesion network map, dysfunction of the vermis and the cerebellar cortex may result in misprocessing of proprioceptive information, and lead to inappropriate involuntary adjustments of head/neck muscles by the dentate nucleus.

## The sensorimotor cortex in cervical dystonia

Our lesion network map also implicates the sensorimotor cortex in the pathophysiology of CD. These findings are backed up by fMRI and electrophysiological studies in patients with primary CD, which have shown increased activity in the sensorimotor cortex during isometric head rotation (Prudente et al., 2016), and increased sensorimotor plasticity, respectively (Koch et al., 2014; Kojovic et al., 2013). In addition, Inoue et al. (2004) demonstrated decreased amplitudes of high-frequency oscillations in the sensory cortex in CD patients, reflecting decreased inhibition. Such observations had led researchers to suggest that dystonia patients may have a net increase in proprioceptive input to the sensory cortex, leading to 'motor overflow', or co-contraction of muscles (Hallett, 2011; Kaňovský & Rosales, 2011). Interestingly, lesion locations were negatively correlated to the sensorimotor cortex, which could result in hyperactivity to this region in patients (Boes et al., 2015; Darby, Laganiere, et al., 2017). Therefore, lesions could result in a loss of the normal suppressive input from these brain locations in secondary CD patients, leading to a net increase in sensorimotor cortex activity.

The functional interpretation of negative correlations seen in rs-fcMRI remains a matter of debate (Fox et al., 2005; Murphy & Fox, 2016), however negative correlations appear to be critical for linking lesion locations to the brain regions generating the symptoms, with Boes et al. (2015) demonstrating that lesions resulting in visual or auditory hallucinations were negatively correlated to visual and auditory cortices respectively. The fact that lesions causing CD are negatively correlated to the sensory cortex raises the question as to whether CD may share similarities with sensory or proprioceptive hallucinations. Indeed, visual and auditory hallucinations can improve with visual and auditory input (Corlett et al., 2009; Teunisse et al., 1996), possibly reminiscent of sensory tricks in CD. Sensory tricks may relieve symptoms by providing additional proprioceptive input, and have been shown to reduce sensorimotor cortex, and EMG, activity in CD patients (Naumann et al., 2000; Schramm et al., 2004).

## A two-hit model of cervical dystonia

The involvement of two distinct brain regions differs from previous 'lesion network mapping' studies of movement disorders where lesion locations shared connectivity

to just a single location (Fasano et al., 2016; Laganiere et al., 2016). However, results in CD are similar to lesion network mapping of complex hallucinations (Boes et al., 2015), delusions (Darby, Laganiere, et al., 2017), and criminality (Darby, Horn, et al., 2017), in which lesion locations were positively connected to one brain region and negatively connected to another. Connectivity of lesion locations to two different brain regions is consistent with two-hit models of symptom generation. For example, delusions are thought to require both a disruption in sensory processing and reality monitoring (Coltheart, 2010). A two-hit model has previously been proposed for dystonia, but these models usually suggest a network involving the cerebellum and basal ganglia (Jinnah & Hess, 2006; Neychev et al., 2008). Our results instead implicate the cerebellum and sensorimotor cortex, and suggest that CD symptoms may be caused by combined dysfunction of these two brain regions responsible for sensorimotor integration of head/neck position.

## Relevance to primary cervical dystonia

Primary and secondary CD can be indistinguishable clinically; both primary and secondary CD patients use sensory tricks, and seem to have similar responsiveness to treatment (LeDoux and Brady (2003). Here, we have demonstrated that the cerebellum and sensorimotor cortex, which were functionally connected to lesions causing secondary CD, are also abnormal in patients with *primary* CD. This suggests that primary and secondary CD patients may share dysfunction of a common brain network. This increases the clinical relevance of our findings given that primary CD is far more prevalent than secondary CD (Nutt et al., 1988).

Our results generate testable hypotheses for identifying and refining therapeutic targets in CD. For example, deep brain stimulation (DBS) to the globus pallidus interna is effective for many but not all patients with CD (Kiss et al., 2007). Given the present results, we hypothesize that patients whose DBS electrode locations are connected to the cerebellum and sensorimotor cortex will respond best, similar to recent work in Parkinson's Disease (Horn et al., 2017). Similarly, transcranial magnetic stimulation to the lateral cerebellum has shown some promise in patients with CD (Koch et al., 2014), and this target could possibly be refined based on the current results. Finally, the present results highlight the sensory cortex as a potential

therapeutic target easily amenable to noninvasive brain stimulation. Though this target has yet to be tried in CD, there is evidence that this target may provide benefit to patients with hand dystonia (Havrankova et al., 2010).

### Limitations

A number of limitations should be acknowledged. First, although we conducted a systematic search to collect a representative sample of brain lesions causing CD, we cannot exclude a publication bias, as lesions in locations previously linked to CD may be more likely to be reported. Second, some lesions causing CD were located in the spinal cord (LeDoux & Brady, 2003), and thus, the functional connectivity from these lesion locations could not be evaluated. However, the spinal cord contains afferent and efferent connections with the sensorimotor cortex, and the cerebellum (LeDoux & Brady, 2003). Third, there are potential limitations regarding the lesion network mapping, such as using 2D instead of real 3D lesions and use of a normative connectome dataset, which have been addressed in detail previously (Boes et al., 2015; Darby, Horn, et al., 2017).

### Conclusions

Lesion locations causing CD share a unique pattern of brain connectivity to the cerebellum and the sensorimotor cortex. These regions, identified based on brain lesions, are also abnormal in patients with primary CD, and correlate with symptom severity. We suggest a shared substrate for primary and secondary CD, propose a two-hit model of CD symptoms, and provide therapeutic targets and testable hypotheses for improving treatment.

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