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# Brain metabolic response to repetitive transcranial magnetic stimulation to lesion network in cervical dystonia☆

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ABSTRACT

*Background:* A previous study identified a brain network underlying cervical dystonia (CD) based on causal brain lesions. This network was shown to be abnormal in idiopathic CD and aligned with connections mediating treatment response to deep brain stimulation, suggesting generalizability across etiologies and relevance for treatment. The main nodes of this network were located in the deep cerebellar structures and somatosensory cortex (S1), the latter of which can be easily reached via non-invasive brain stimulation. To date, there are no studies testing brain stimulation to networks identified using lesion network mapping.
*Objectives:* To assess target engagement by stimulating the S1 and testing the brain's acute metabolic response to repetitive transcranial magnetic stimulation in CD patients and healthy controls.
*Methods:* Thirteen CD patients and 14 controls received a single session of continuous theta burst (cTBS) and sham to the right S1. Changes in regional brain glucose metabolism were measured using [$^{18}$F]FDG-PET.
*Results:* cTBS increased metabolism at the stimulation site in CD ($P = 0.03$) but not in controls ($P = 0.15$; group difference $P = 0.01$). In subcortical regions, cTBS increased metabolism in the brainstem in CD only ($P_{FDR} = 0.04$). The remote activation was positively associated with dystonia severity and efficacy of sensory trick phenomenon in CD patients.
*Conclusions:* Our results provide further evidence of abnormal sensory system function in CD and show that a single session of S1 cTBS is sufficient to induce measurable changes in brain glucose metabolism. These findings support target engagement, motivating therapeutic trials of cTBS to the S1 in CD.

## 1. Introduction

Cervical dystonia (CD) is the most common type of adult dystonia, characterized by abnormal muscle activity, postures, and pain in the head and neck area [1,2]. Current treatment options for CD include oral pharmacotherapy, such as benzodiazepines, anticholinergics and baclofen, botulinum toxin injections, and deep brain stimulation of the globus pallidus interna (GPi-DBS) [3]. GPi-DBS can be highly efficacious but requires an invasive neurosurgical procedure, which limits the use to most severe cases of CD where sufficient treatment response is not achieved with oral medications or botulinum toxin injections [4,5]. Non-invasive brain stimulation (NIBS) methods have been suggested to fill in this gap as a potential intermediate-level treatment between pharmacological interventions and neurosurgery [6,7].

☆ The study was approved by the ethics committee of the Hospital District of Southwest Finland in May 2019 (ETMK 54/1801/2019). All subjects provided written informed consent, and the study was conducted according to the principles of the Declaration of Helsinki.

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The most widely used NIBS method is repetitive transcranial magnetic stimulation (rTMS), which is already a widely used treatment option for neurological and psychiatric disorders, including 10Hz rTMS or intermittent theta burst stimulation (iTBS) to the left dorsolateral prefrontal cortex (DLPFC) in depression, and 10Hz rTMS to the primary motor cortex in neuropathic pain [8–10]. In CD, a recent meta-analysis demonstrated that numerous rTMS targets have been probed, yet the results have so far been variable, with considerable heterogeneity in study methods [11]. One of the major barriers to the discovery of an effective NIBS protocol in CD is that we do not yet know what the optimal treatment target is: although CD has traditionally been viewed as a disorder of the basal ganglia, neuroimaging studies have implicated numerous other brain regions, suggesting that CD may actually be a brain network disorder [12–15]. However, given that case-control neuroimaging studies can indicate correlative changes in brain activity that may not drive symptoms, it is uncertain whether these regions would be effective therapeutic targets.

A recent study addressed this issue by using lesion network mapping to identify a brain network causally linked with CD symptoms [16]. This network covered several subcortical regions, including the brainstem and midline cerebellum, but crucially, demonstrated that all of the 25 lesions causing CD were connected to the somatosensory cortex (S1), which can be easily reached with NIBS (Fig. 1). The study also demonstrated that connectivity from the S1 was also abnormal in idiopathic CD and associated with treatment response in patients with GPi-DBS, suggesting relevance for treatment. While this is a promising candidate for NIBS in CD, the neurobiological effects of NIBS to the S1 has not yet been investigated in detail [11]. In addition, more broadly, although there is great hope for lesion network mapping as a method to localize treatment targets for brain stimulation [17–20], to date, there are no published studies investigating the effect of neuromodulation to a target selected based on lesion network mapping findings, in any clinical condition [11, 21].

The aim of this study was to investigate the neurobiological effect of continuous theta burst stimulation (cTBS) to the specific S1 site connected to causal CD lesions (Fig. 1) [16]. cTBS was selected because lesions causing CD were negatively connected to this brain region, which is hypothesized to reflect disrupted inhibitory connections to the S1 [16,22], and because it is a shorter stimulation protocol that is less burden to the patients.

## 2. Methods

### 2.1. Subjects

Altogether, 15 patients with CD and 21 healthy controls were invited to the screening visit. The inclusion criteria were: 1) age over 18 years; 2) cooperative and willing to participate in the study; 3) adult-onset isolated idiopathic focal cervical dystonia (CD group) or no chronic neurological disorders (control group). The exclusion criteria were: 1) any contraindications for MRI, TMS or PET; 2) weight over 180 kg (scanner limit); 3) other major psychiatric or neurological disorders; 4) currently use or have past long-term use of psychoactive medications except medications used to treat CD; or 5) any medical condition that could be considered to cause additional risks for the subject, or compromise data quality or interpretation of the results (e.g. diabetes with insulin treatment, unstable cardiac disorders, etc.).

Of the subjects initially recruited, one patient discontinued the study for personal reasons, and one patient was excluded because of failure to fast before the PET scan. Two healthy subjects were excluded due to structural brain abnormalities in the brain MRI, and one for suspected neurological disorder (rest tremor in clinical evaluation). Three healthy subjects were excluded because of a failure to determine the TMS motor threshold (exceeded the TMS device power output), and one for

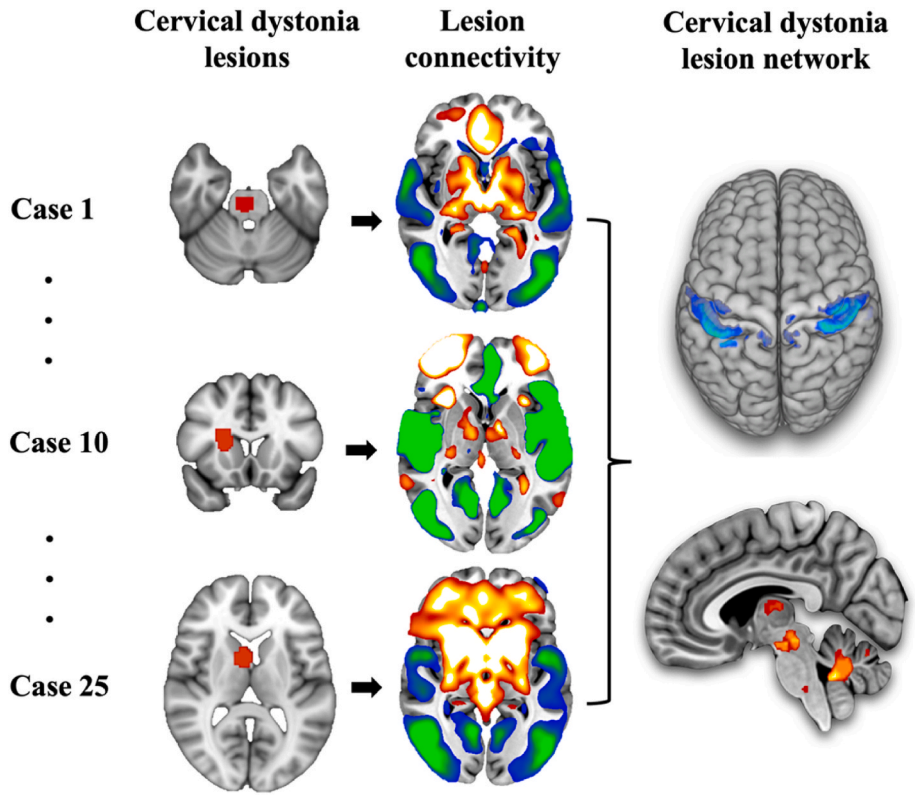


**Fig. 1. Cervical dystonia lesion network.**
A recent study by Corp. et al. [16] used lesion network mapping to identify a brain network causally linked with cervical dystonia (CD). This network covered several subcortical regions, including the brainstem and midline cerebellum, but crucially, also showed that all of the 25 lesions causing CD were connected to the somatosensory cortex (S1), which can be easily reached with non-invasive brain stimulation.

technical error in identifying the correct stimulation target. Therefore, the final sample included in the analyses was 13 CD patients and 14 healthy controls who completed all aspects of the study protocol.

The subjects were clinically evaluated using Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Twelve out of 13 subjects in the CD group were receiving botulinum toxin injection treatment with 2.5–3 month intervals. Patients were tested at their most severe stage in their injection treatment cycle as reasonably possible, without interfering with their treatment schedule. This was done to minimize the effects of the botulinum toxin on symptoms and neuroimaging outcomes, and to avoid any adverse effects caused by treatment delays. Two out of the 13 subjects in the CD group were also using clonazepam somewhat regularly. They were instructed to pause the medication for at least three days before the study visits. None of the other subjects in either group used any other medications affecting the central nervous system.

### 2.2. Study design

The study design is illustrated in Fig. 2. All subjects underwent a brain MRI to exclude structural brain abnormalities and for neuronavigation. A crossover design was used, and each subject received on separate days a single session of cTBS or sham stimulation followed by brain [$^{18}$F]FDG-PET imaging with tracer injection immediately after the end of the stimulation. To limit the radiation dose to the subjects, PET scans were limited to two scans per subject. As the objective of the study was to investigate the brain metabolic effects of cTBS, we chose a crossover design, where participants were scanned after cTBS stimulation and after sham without imaging of baseline brain metabolism at rest. The order of cTBS and sham stimulation sessions was counterbalanced between the subjects. The subjects were blinded to the type of stimulation they received. Before all study visits, the subjects were instructed to avoid alcohol for at least 48 h, caffeine for at least 12 h and sleep normally.

All stimulation sessions and imaging were performed by one clinical investigator (A.K.) under the supervision of the principal investigator (J. J.).

### 2.3. Transcranial magnetic stimulation

A 70 mm figure of eight TMS coil (70BF-Cool) with DuoMAG™ XT-100 biphasic stimulator (DEYMED Diagnostic s.r.o., Hronov, Czech Republic) was used to deliver stimulation. Sham stimulation was delivered using a corresponding sham coil (70BFP-Cool-sham) with identical design and protocol providing similar acoustic stimulus. The motor hotspot for the contralateral abductor pollicis brevis (APB) muscle was determined as per the most recent guidelines [23]. Briefly, the coil was placed perpendicular to subjects' head at approximately 45° to the medial-sagittal plane, to induce a posterior to anterior (P-A) current in the brain [24]. The coil was then systematically varied within the motor cortex to find the site at which the highest amplitude MEP was elicited in the contralateral APB muscle (defined as the motor hotspot). Resting motor threshold (RMT) was determined as the minimum single pulse intensity to produce MEPs greater than 50 μV peak-to-peak amplitude in at least five out of ten consecutive trials from the contralateral APB muscle [25]. Active motor threshold (AMT) was determined as the minimum single pulse intensity to produce MEPs greater than 200 μV peak-to-peak amplitude on at least five out of ten consecutive trials from the contralateral APB muscle [26] while the subject was maintaining slight voluntary contraction, gently holding a coin between their thumb and little finger, respectively. The S1 cTBS protocol consisted of 3 pulses of stimulation given at 50Hz repeated every 200 ms for 40 s, totaling to 600 pulses with 80% AMT, as described previously [27]. With cTBS, the same coil orientation and direction parameters were used as in the threshold measurements (approximately 45° to medial-sagittal plane), but the coil was placed over the stimulation site within the S1.

### 2.4. MRI and neuronavigation

All subjects underwent a brain MRI at the first study visit. MRI sequences included T1-and T2-weighted, fluid-attenuated inverse recovery (FLAIR), and diffusion weighted imaging (DWI). All structural MRIs were reviewed by a consultant neuroradiologist (J.H.) to exclude structural abnormalities that are clinically relevant or could bias the analyses.

First, a brain extraction was performed for the anatomical T1-weighted MRI, and the resulting images were normalized to MNI space using rigid, affine, and diffeomorphic (SyN) registration methods implemented in the Advanced Normalization Tools -package (ANTs) [28]. Next, the target for cTBS stimulation was located within the right S1. This target was selected based on the lesion network mapping study of Corp et al. [16], showing that that 25/25 lesions causing CD were connected to a cluster (32 voxels) in the right S1, with the centre of gravity of this cluster at MNI x,y,z = 45,-30,58. The MNI space target was transferred to the subject native space using the inverse of the transformation matrix obtained in the first step. The cTBS stimulation was targeted in subjects' native space, holding the coil tangential to the scalp surface at 45° angle compared to the antero-posterior line. The neuronavigation was performed using Brainsight® (Version 2.3.12).

### 2.5. Positron emission tomography

PET imaging was performed as described earlier [29]. Briefly, subjects were requested to fast for 4 h before stimulation and PET scans to ensure normoglycemia. Immediately after the stimulation, the subjects received an intravenous bolus of [$^{18}$F]FDG (mean dose 198 MBq, SD 5.4,

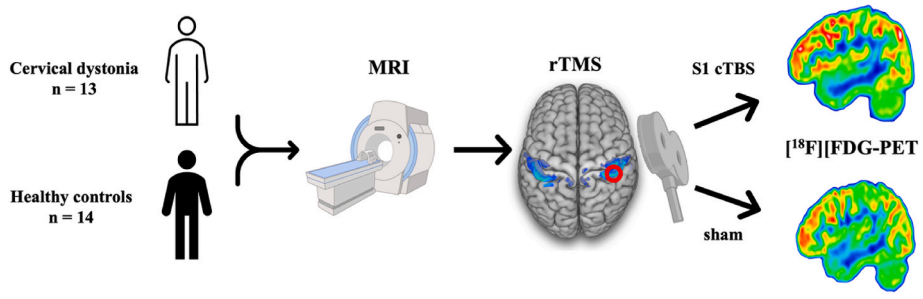


**Fig. 2. Study design.**
Thirteen patients with cervical dystonia (CD) and 14 healthy volunteers completed the study. The subjects were first scanned using MRI to identify the personalized stimulation target (red circle) in the right somatosensory cortex (S1). At separate study visits with a crossover design, the subjects received neuronavigated continuous theta burst stimulation (S1 cTBS) or sham stimulation using the same target and protocol (sham) in counterbalanced order, and were scanned with [$^{18}$F]FDG-PET to measure brain regional glucose metabolism immediately after the stimulation. BioRender software (BioRender.com) was used to create this figure.

range 187–216). After the injection, the subjects remained sitting on the TMS chair in a dimly lit, quiet room with their eyes open to prevent the subjects from falling asleep. The 20 min PET emission scan was started 35 min after the tracer injection. In one of the healthy volunteers, the scan was started 43 min after the injection due to a temporary scanner malfunction. The scanning was performed using GE Discovery MI PET/TT scanner (Milwaukee, Wisconsin, USA) at the Turku PET Centre, Turku, Finland.

PET time series were motion corrected with MCFLIRT-function implemented in FSL (FMRIB Software Library, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [30,31]. The average of the motion-corrected frames was linearly registered to the individual brain-extracted T1-weighted MRI with ANTs rigid registration and then normalized to the MNI space using the transformation matrix obtained in the first step of the MRI preprocessing and applied to each motion-corrected frame.

Standardized uptake value ratio (SUVR) images were computed voxel-wise by calculating a sum of all frames for each voxel and dividing these values with whole brain average [$^{18}$F]FDG uptake, as previously [29]. The change in glucose metabolism following stimulation was computed by subtracting sham from the cTBS scan. The images were smoothed using an 8 mm full-width at half-maximum Gaussian kernel to improve the signal-to-noise ratio. All preprocessing steps were carefully inspected visually by the investigators. After visual inspection, one CD patient was excluded from the voxel-wise analyses because of a slight misalignment between cTBS and sham scan. However, this misalignment did not affect the evaluation of the local metabolism at the stimulation site. Local glucose metabolism at the stimulation target was computed as an average voxel SUVR within a 5-mm radius circular region-of-interest (ROI) centered on the stimulation target.

### 2.6. Statistical analyses

All statistical analyses apart from imaging data analyses were conducted using IBM SPSS Statistics (Version 29.0.0.0). Group differences in demographic and clinical data, as well as local glucose metabolism at the stimulation target (ROI data) were investigated using Independent Sample *t*-test, Welch's *t*-test and Fishers exact test, as appropriate. Correlations between demographic/clinical variables and glucose metabolism were investigated using Spearman's Rank Order Correlation coefficient due to the small sample size for correlation analyses. P-values below 0.05 were considered significant.

The neurobiological effects of the cTBS stimulation were investigated by comparing cTBS vs. sham at the site of the stimulation (ROI data), and voxel-wise using Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB (MathWorks, Inc., Natick, MA, USA), 2022. version 9.12.0 (R2022a). As the study set out to investigate the local effects of cTBS in S1 and propagation of these effects to the subcortical regions, voxel-wise analyses of the remote effects of the stimulation were performed with a subcortical mask, including the subcortical grey matter regions and cerebellum. The mask was created using Harvard-Oxford subcortical structural atlas (FSL: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). False discovery rate (FDR) corrected clusters with $P < 0.05$ at height-threshold of uncorrected $P < 0.01$ were considered significant, as previously [29]. SUVR changes in the significant clusters were calculated by averaging the voxel-wise changes (cTBS minus sham) within the cluster for post-hoc analyses. In these analyses, the association between cluster SUVR changes and local response at the stimulation site, and demographic (sex, age) and clinical data (age of onset, disease duration, sensory trick, TWSTRS scores and subscales) were investigated using Independent Sample *t*-test and Spearman's Rank Order Correlation coefficient, as appropriate.

## 3. Results

The demographical and clinical data of the groups are shown in Table 1. There were no significant differences in age, sex, or cognition (MMSE) between the CD and control group (Table 1). In CD patients with botulinum toxin treatment, the time interval between the last injection and study visits was at least 56 days (CD mean ± SD = 78 ± 15 days). There were no significant differences in the time interval from the most recent injection to the study visit between the conditions (cTBS 77.8 ± 18.4 vs. sham 78.8 ± 12.3, P = 0.84). There were no differences in the RMT (CD 64.2 ± 10.6 vs. HC 66.1 ± 14.0, P = 0.71) or AMT between the groups (CD 52.1 ± 7.5 vs. HC 53.1 ± 7.5, P = 0.72). Only mild, transient adverse effects (mild headaches, mild discomfort in the skin regarding TMS) were reported by the subjects, and there were no severe adverse events.

**Table 1**
Demographic and clinical data.

| | CD (n = 13) | HC (n = 14) | P-value |
|---|---|---|---|
| Age | 56.4 (11.3) | 54.4 (18.7) | 0.73 |
| Sex (m/f) | 5/8 | 6/8 | 1.0 |
| MMSE | 29 (1.1) | 29 (1.3) | 0.88 |
| Age of onset | 47.4 (10.9) | – | |
| Disease duration | 9.0 (6.7) | – | |
| RMT | 64.2 (10.6) | 66.1 (14.0) | 0.71 |
| AMT | 52.1 (7.5) | 53.1 (7.5) | 0.72 |
| **TWSTRS** | | | |
| Total score | 27.1 (10.0) | – | |
| Severity score, sTWSTRS | 12.4 (3.7) | – | |
| Disability score, dTWSTRS | 7.3 (4.1) | – | |
| Pain score, pTWSTRS | 7.4 (4.4) | – | |

Mean (SD) are presented unless otherwise specified.
TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.
RMT, resting motor threshold.
AMT, active motor threshold.

There was a significant difference in change of the local glucose metabolism at the stimulation site between the CD and control group (P = 0.01) (Fig. 3). CD patients showed a significant increase in glucose metabolism after cTBS compared to sham (0.031 ± 0.044, P = 0.03), while there was a non-significant decrease in glucose metabolism in controls (−0.015 ± 0.035, P = 0.15) (Fig. 3). The change in local glucose metabolism in CD patients did not correlate with the time interval from the latest botulinum toxin injection to cTBS (rho = −0.20, P = 0.54) or with difference in time intervals from the injection to study visits between cTBS and sham (rho = 0.20, P = 0.54). There was no significant difference in the local metabolism at the stimulation site between the groups in the sham scans (P = 0.32). To ensure that the results at the stimulation site were not driven by the selected ROI size (5 mm), the findings were confirmed using other commonly used ROI sizes (4 mm, 6 mm and 8 mm radius), and the significance of the results did not change.

In the voxel-wise analysis of distal effects, cTBS significantly increased regional glucose metabolism remotely in the brainstem in the CD patients compared to sham ($P_{FDR} = 0.04$) (Fig. 4), but not in controls. There were no significant group differences in glucose metabolism in the voxel-wise comparison of the sham scans. The increased brainstem glucose metabolism also was positively associated with the severity of dystonia (sTWSTRS, rho = 0.63, P = 0.03), but not with local metabolic response at the stimulation site, sex, age, duration of dystonia, or other subscales of TWSTRS, time interval from the last botulinum toxin injection to cTBS, or difference in the time intervals from the injection to the study visits between the cTBS and sham ($P > 0.05$). CD subjects with complete relief of symptoms by sensory trick (n = 7) showed a significantly higher increase in brainstem glucose metabolism after cTBS (cTBS vs. sham) compared to subjects with only limited relief or no relief at all (n = 5) (0.023 ± 0.007 vs. 0.007 ± 0.012, P = 0.02). With the whole brain mask, the analyses did not reach our threshold for statistical significance, indicating that there were no remote cortical regions showing significant change in metabolism following cTBS compared to sham.

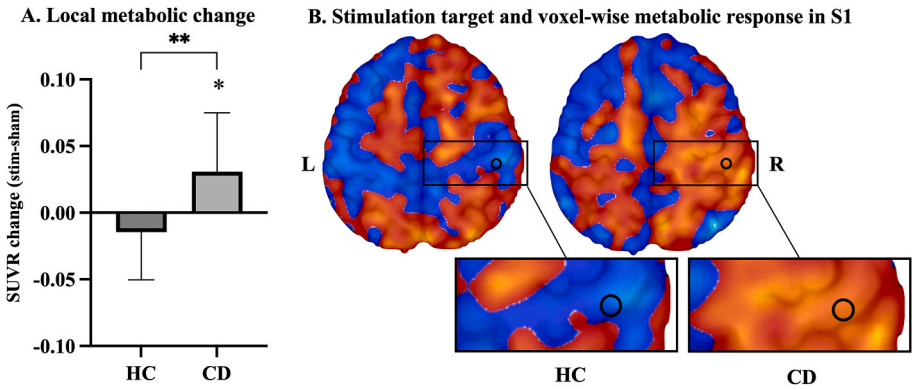


**Fig. 3. Local increase in the glucose metabolism at the stimulation site.**
A) There was a significant difference between the groups in the glucose metabolism response to the continuous theta burst stimulation (cTBS) compared to sham (P = 0.01). Subjects with cervical dystonia (CD) showed a significant (P = 0.03) increase in glucose metabolism locally at the S1 stimulation site (x,y,z = 45,-30,58) derived from connectivity to causal CD lesions (Fig. 1). With healthy controls (HC), an opposite non-significant metabolic response was seen (P = 0.15). B) Visualization of the stimulation site (S1) showing the opposite metabolic responses in the S1 after the cTBS compared to sham between CD and HC, demonstrating abnormal reactivity of the network in CD. The black circles mark the stimulation site, overlaid on the unthresholded group t maps (cTBS compared to sham, scaled from 0 to 4) with hot colors indicating increase and cool colors decrease in glucose metabolism.

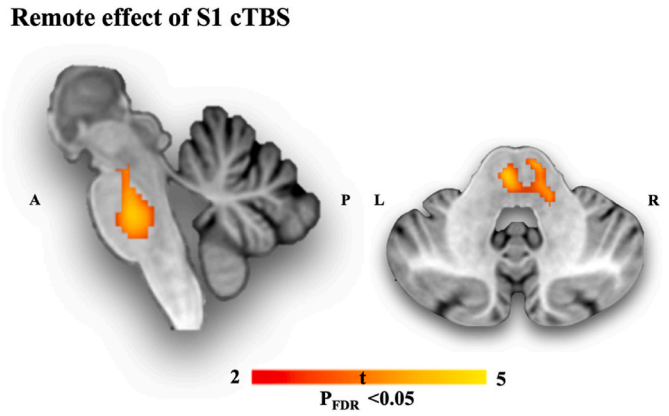


**Fig. 4. Increase in brainstem glucose metabolism in CD patients.**
Continuous theta burst stimulation (cTBS) to the somatosensory cortex (S1) significantly increased regional glucose metabolism remotely in the brainstem in cervical dystonia (CD) patients ($P_{FDR}$ = 0.04) but not in controls. This cluster is located close to the brainstem cluster in the cervical dystonia lesion network shown in Fig. 1.

## 4. Discussion

This study was the first to prospectively investigate the effects of non-invasive brain stimulation targeted based on a brain network identified using lesion network mapping. There are several important findings. First, our findings demonstrated an abnormal response to stimulation in CD, providing further evidence of abnormal S1 function in this disorder. Second, our results showed that a single session of S1 cTBS is sufficient to induce local brain metabolic changes at the stimulation site. Third, the effects of the S1 stimulation in CD extended to the brainstem, remote from the stimulation target, demonstrating network effects of the stimulation.

Advances in lesion-based symptom localization have enabled the identification of brain networks causally linked with neurological symptoms [18,32]. Several studies have provided evidence that these networks may also be abnormal in idiopathic conditions causing similar symptoms, indicating that the findings are symptom-specific and generalize across etiologies [16,33–36]. Lesion networks also seem to align with the known efficacious brain stimulation treatments, suggesting that targeting the causal network could be beneficial [16,33,34]. The networks in movement disorders mostly centralize to the basal ganglia, making them difficult to reach via non-invasive brain stimulation. However, the CD network included a hub in the cerebral cortex [16], and authors suggested that this site could form a therapeutic target for NIBS. Given the relatively poor success rate of previous non-invasive brain stimulation targets in dystonia [11,37], we sought to test the neurobiological effects of modulation of this site.

In addition to lesion network mapping, multiple other lines of evidence have suggested dysfunction of the somatosensory system in CD. Neuroimaging studies have repeatedly highlighted abnormalities in the sensory cortical areas [13,38,39]. Clinically, many patients benefit from the sensory trick (geste antagoniste), which acutely improves symptoms in CD, and this phenomenon seems to be quite specific for CD [15]. The sensory trick may lead to normalization of the activity in the premotor and primary motor cortex [40], which also have been reported to mediate symptom relief with GPi-DBS [29]. The results of the current study provide further evidence of the involvement of the sensory system in CD by demonstrating a significant difference in the brain's metabolic response of this region to cTBS, compared to healthy controls.

The direction of the local metabolic response at the S1 stimulation site in CD (significant increase relative to sham) was opposite to that of controls (non-significant decrease), and could be considered counter-intuitive considering that cTBS is generally considered inhibitory. Further, the S1 is generally considered to be hyperactive in CD [16,41,42], and so one might expect normalization to be evidenced by a reduction in S1 activity after cTBS. Therefore, increased metabolism at the stimulation site in CD could indicate that our assumption is incorrect, and the S1 may actually be underactive in CD patients. However, this is not well supported by prior literature. We suggest that it is more likely that this reflects an acute response to the cTBS that further demonstrates the abnormality of the S1 in CD, and that the chronic changes in brain activity after stimulation may not necessarily correlate with this acute response. One mechanism that could explain this effect is metaplasticity, which may not be expressed by a typical acute neural response to stimulation, but is instead manifested through a modification in the ability of neural circuits to undergo subsequent synaptic plasticity [43,44]. This has been demonstrated in rTMS in depression, where efficacy of the stimulation may be increased through a priming of the prefrontal cortex through stimulation of a different type of rTMS [45–47]. However, this suggestion is speculative given that we only measured the brain's response at the acute timepoint. Future studies of S1 stimulation in CD should correlate the brain's chronic response to cTBS with changes in CD symptoms to resolve this issue.

S1 cTBS was also associated with increased metabolic activation in

the brainstem, demonstrating that the effects of the stimulation propagate beyond the stimulation target. This finding corroborates observations in previous molecular imaging studies in which primary motor cortex stimulation has been shown to elicit remote effects in the motor circuitry in addition to the local effects at the stimulation target [21]. The location of the remote activation observed in the present study, however, was clearly distinct from the remote activations associated with the primary motor cortex (M1) activation studies, supporting that the effect could be attributed to the S1 and not spill-over of the electric field to the adjacent M1. The brainstem activation was also correlated with symptom severity and the presence of sensory trick, indicating that the sensory system abnormality in CD may be critical for propagating of the stimulation effects.

Multiple different rTMS targets have previously been probed to treat dystonia, including M1, S1, ACC, dorsal premotor cortex, and cerebellum [11], yet there is no consensus as to the optimal target(s), and the overall efficacy of rTMS in dystonia has remained weak [11,37]. Only two studies have previously targeted S1, both applying conventional low-frequency rTMS, in specific types of dystonia. In these studies, 1Hz S1 rTMS slightly improved hand writing in the writer's cramp [48], but there was no effect on hand dystonia in Wilson's disease [49]. However, these previous studies did not use precise predefined coordinates and neuronavigation to target the stimulation and therefore the stimulation target was not identical to the target in the present study. In addition, as different types of dystonia are also neurobiologically different, the observations from the previous S1 studies cannot be generalized to CD or across all dystonias [15].

There are some limitations in the present study that should be taken into consideration when interpreting the results. First, as the study was designed to investigate the brain metabolic effects of S1 cTBS in CD, and not to test clinical efficacy, we did not measure clinical dystonia symptom changes following the single stimulation session. Here, we reasoned that as with almost all therapeutic approaches with rTMS, treatment of dystonia likely requires multiple stimulation sessions to potentiate and prolong the clinical effects [50,51]. Thus, further studies are needed to determine the clinical efficacy of S1 stimulation. Second, although our sample size is one of the largest to date investigating the effects of a single rTMS session using PET, it is still relatively small, which may have limited the power to detect more subtle effects on brain metabolism [21]. Third, we were only able to include two PET scans per subjects to keep the radiation dose within the local ethics board limits for research. Therefore, we were not able to collect baseline PET data without any intervention to investigate possible differences in baseline metabolism that could contribute to the different cTBS effects between the groups. However, there were no significant differences between the CD and healthy control groups in regional brain metabolism measured after the sham stimulation. Finally, there was some variation in the timing of the study visits from the latest botulinum toxin injections in the CD patients. However, the time intervals from the latest injection to the study visit did not differ significantly between cTBS and sham conditions or correlate with metabolic responses to the stimulation.

## 5. Conclusions

In summary, our study shows that cTBS to the S1 lesion network hub in CD patients demonstrates target engagement both locally at the stimulation site, and distally outside the stimulated brain region. Our findings provide further evidence of abnormal sensory system function in CD, and show that S1 stimulation can facilitate metabolic changes in the CD network.

## CRediT authorship contribution statement

**Aleksi Kokkonen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Daniel T. Corp:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Juho Aaltonen:** Software, Formal analysis. **Jussi Hirvonen:** Writing – review & editing, Validation. **Anna K. Kirjavainen:** Resources. **Johan Rajander:** Resources. **Juho Joutsa:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

## Data availability

The data is available from the corresponding author upon reasonable request.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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