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Tremor and Other Hyperkinetic Movements

Case Reports

Sensorimotor Integration and GABA-ergic Activity in Embouchure Dystonia: An Assessment with Magnetoencephalography

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Abstract

Background: Embouchure dystonia (ED) is a task-specific dystonia affecting musicians thought to be related to alteration in sensorimotor processing and loss of cortical inhibition.

Case Report: Magnetoencephalography-coherence source imaging (MEG-CSI) was used to map connectivity between brain regions by imaging neuronal oscillations that are coherent across the brain in patient with ED at rest and while using the index finger to evoke dystonia normally triggered by playing the flute.

Discussion: During rest, there was increased coherence in the bilateral frontal and parietal regions that became more focal during dystonia. Diffuse hyperexcitability and increased coherence persisted in bilateral parietal regions as well as the bilateral frontal regions.

Keywords: Embouchure dystonia, MEG, sensorimotor integration, magnetoencephalography, coherence source imaging, MEG-CSI

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Introduction

Embouchure dystonia (ED) is a focal task-specific dystonia affecting musicians who use brass and woodwind instruments. Symptoms include incoordination of the lower face, jaw, and tongue as well as task-specific embouchure lip tremor and lip-pulling and may vary based on the type of instrument.[1]

There are four main embouchure types: brass, single reed, double reed, and flute. Flutists rely mainly on the upper lip to control speed and direction of airflow and use their mandible to keep the instrument steady. The tongue also plays a critical role in flutists, with techniques such as "double tonguing" and "triple tonguing" mentioned in the flute literature.[2] Phenotypically, jaw or tongue dystonia is more commonly present in woodwind players, with occasional involvement of the most active digits of the most active hands.[3] In musician's focal hand dystonia, there is distortion of the corticospinal somatosensory map with loss of spatial separation between individual digits. Patients with focal hand dystonia show fusion of the primary somatosensory cortex representations analogous to non-musicians with focal hand dystonia.[4] A functional magnetic resonance imaging (fMRI) study of 15 professional brass players revealed that affected musicians have increased stimulation-induced activity in the contralateral primary and bilateral secondary somatosensory representation of dystonic and non-dystonic body regions, as well as in the cerebellum ipsilateral to the to the left dystonic upper lip. Alterations in intracortical distances and between-group differences of the centers of representations were found in the right primary and bilateral secondary somatosensory cortex and left cerebellum.[5] The involvement of non-dystonic areas was attributed to underlying compensatory mechanisms. Another fMRI study of 10 brass players with ED revealed that compared to controls, they had

increased activation of somatotopic face representations within bilateral primary somatosensory cortices and bilateral premotor cortices.[6]

Limited understanding of the underlying pathophysiology of ED contributes to limited treatment options, making this order disabling for the affected patient. Various modalities including transcranial magnetic stimulation (TMS), fMRI and magnetoencephalography (MEG) have been used to investigate the possible underlying pathophysiology of this rare disorder. Alteration in sensory processing and sensorimotor integration, abnormal cortical plasticity and loss of cortical inhibition have all been implicated as proposed mechanisms.[3]

Magnetoencephalography-coherence source imaging (MEG-CSI) is a technique to non-invasively image the connectivity between brain regions by detecting and imaging the neuronal oscillations that are coherent across the brain. MEG-CSI has been studied for pre-surgical mapping in patients with focal epilepsy where its use is associated with improved surgical outcomes.[7,8] MEG-CSI has also been used in subjects with autism to understand the networks that are activated in a gaze-cued paradigm.[9] Our lab has also previously published work on cervical dystonia using MEG-CSI.[10,11] In the present study, we characterized the functional connectivity in a patient with ED where touch is used to evoke dystonic movements.

Methods

MEG data were collected on a 29-year-old left-handed professional female flutist with a history of ED since August 2017 manifesting as a task-specific, technique-specific, dystonic tremor of the upper lip when the flute touched her bottom lip. No other oral tasks triggered dystonia in this patient. No other non-dystonic disorders of the embouchure, such as muscle tearing, anterior superior alveolar nerve compressive neuropathy, or intraoral pathology, were present. Furthermore, the patient did not report any previous history of trauma or dental work. Data were then compared with previously collected resting state MEG data from age- and sex-matched normal controls. The controls used in our case study were not musicians.

A detailed description of the following MEG-based MEG-CSI methodology and data processing used in this study has been previously published by our lab.[10,11]

A 10-minute resting state MEG scan was performed while the patient laid still with eyes open. MEG data were acquired using a 148-channel whole-head magnetometer system (4D, Neuroimaging, San Diego, CA) inside a magnetically shielded room. After the resting state scan was performed, a second scan was performed where 2 minutes of baseline was recorded, then the patient placed her right index finger on her bottom lip to simulate the sensation of the flute touching lip for an additional 2 minutes. The patient's finger, which is non-metallic and does not cause magnetic artifact in the MEG, induced the same, exact dystonic tremor as if she had actually used her flute. Then she removed her hand and a post-simulation recording was obtained for 2 minutes. The dystonic movement stopped as soon as the patient stopped touching her lip. Since no dystonic movement is present in the post-touch state, it is assumed that only the coherent connectivity is still persistent. MEG signals before touch and after touch were recorded, assuming the connections are still active even after tactile stimulation is removed. In order to determine where the connection took place anatomically, pre-touch and post-touch subtraction was completed.

Results

Compared to normal controls, this patient displayed hyperexcitability and increased coherence diffusely in the bilateral parietal cortices (right > left) as well as in the bilateral inferior frontal regions (right > left) during rest, whereas a control subject primarily activates visual cortex and visual association cortex due to all subjects looking at a colorful picture displayed on the ceiling of the MEG scanner.

Frequency bands

Pre-dystonia (baseline), before touching the lip and inducing dystonia, areas of high coherence were seen the highest in the alpha band (0.46) peaking in at 10 Hz (see Figure 1). Beta coherence level was 0.42 and gamma level was 0.43 prior to dystonic activity. During the dystonic activity, touching under the lower lip, alpha activity (0.49) and beta activity (0.46) at 26 Hz and gamma activity (0.46) at 42 Hz all increased. Specific peaks can be seen in the graphs (Figure 1). Following the dystonic activity, alpha (0.435) and beta (0.435) activity decreased and gamma (0.47) activity increased. Dashed line in the graph indicates similar coherent levels across graphs at 0.45 (Figure 1).

MEG imaging of activated coherent networks

Highly coherent networks became more focal/localized within bilateral sensorimotor cortices when the patient touched her bottom lip, inducing the dystonic tremor (Figure 1). After the finger was removed, hyperexcitability and increased coherence persisted in the bilateral parietal regions as well as the bilateral frontal regions (Figure 2). Throughout the duration of the study, there was increased coherence in the auditory cortices as well.

MEG imaging of connectivity within the activated networks

Connectivity maps (Figure 3) provide information on individual locations in the brain that transmit or receive information during the scan. Prior to the induction of dystonic activity, the cingulate and insular regions were seen to be receiving information (green), while the right inferior frontal region was transmitting information (red). During the dystonic activity, the right inferior frontal region was not significantly activated, while the cingulate and insular regions, initially seen to be receiving information, were seen to be transmitting information. This transmission of information from the cingulate and insular regions persisted in the post-dystonic phase.

Discussion

To our knowledge, this is the first study using MEG to explore functional networks evoked by touch in patients with ED. Our exploratory study revealed increased overall coherence in bilateral parietal and inferior frontal lobes with increased gamma frequencies during the dystonic activity.

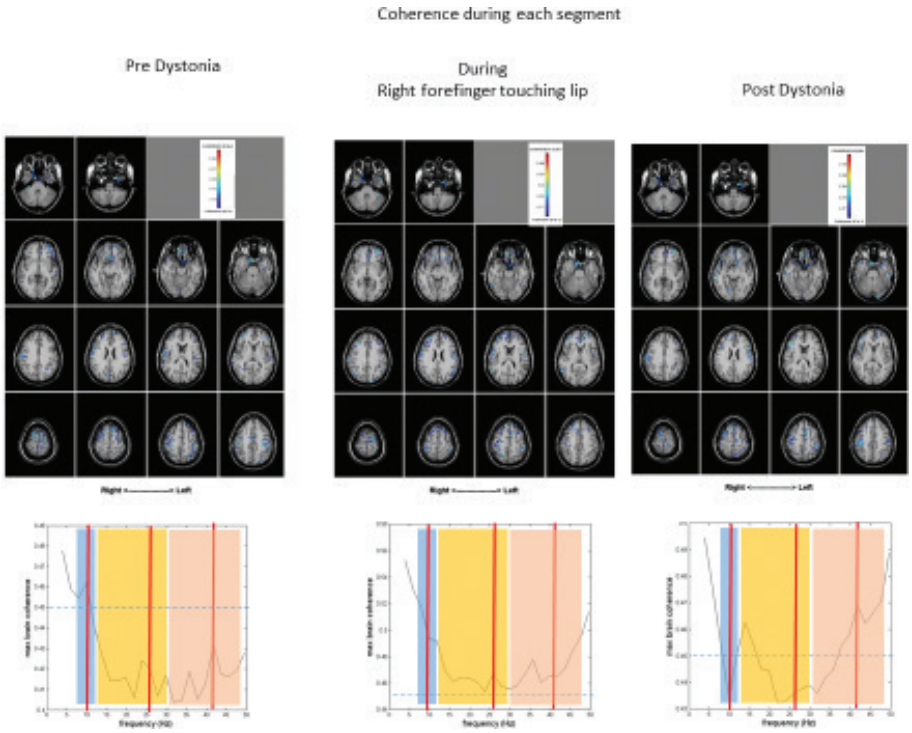

Figure 1. **Coherence at Baseline, during Dystonia, and Post-Dystonia.** Coherence at baseline measured for 2 minutes prior to the elicitation of dystonic tremor by touching the right index finger to bottom lip, during the dystonic activity and 2 minutes following the dystonic activity. Highly coherent networks within the somatosensory cortices become more focal when the patient touched her bottom lip (middle image, bottom row, third slice).

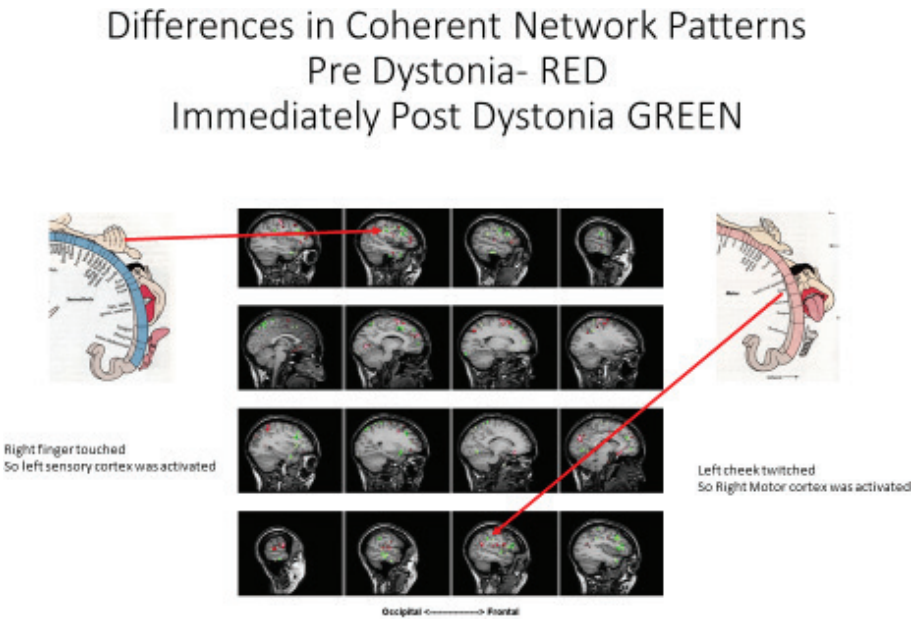

Figure 2. **Differences in Coherent Networks Pre-Dystonia and Post-Dystonia.** Subtraction of the coherence images pre-dystonia (red) versus post-dystonia (green) depicts homunculus with arrow pointing to right finger (top) sensory cortex in the left post-central gyrus and left facial region with an arrow pointing to facial (bottom) motor cortex in the right pre-central gyrus.

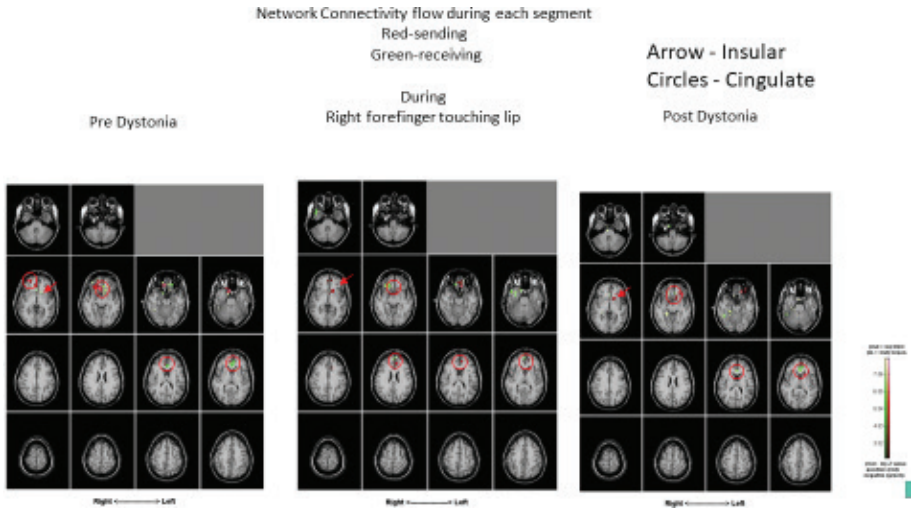

Figure 3. **Connectivity Maps Pre-Dystonia, during Dystonia and Post-Dystonia.** Pre-dystonia, the cingulate gyrus (circle) and insular gyrus (arrow) are seen receiving information (green), while the right inferior frontal region is transmitting information (red). During dystonia, the right frontal region is not particularly active, while the cingulate and insular regions are seen to be transmitting information, something which persisted post-dystonia.

Increased coherence in these regions at baseline as well as during dystonic activity reflects decreased intracortical inhibition and abnormal sensorimotor processing in ED. Previously, the functional activity of cerebellum and sensorimotor cortex has been described to reflect symptomatology in cervical dystonia.[12] A recently published study using MEG-CSI in cervical dystonia reported increased coherence in the left putamen and right superior parietal gyrus, with the administration of botulinum toxin suggestive of the role of sensorimotor integration.[11] The first and, to our knowledge, the only other MEG study in ED also implicated disorganization of the somatosensory homunculus.[13] Our study further demonstrates the importance of sensorimotor integration in the pathophysiology of dystonia and, specifically, ED.

The role of cerebellum in dystonia is increasingly being recognized, with some suggesting that the cerebellum might be the pathological node in dystonia.[14,15] Our study shows increased coherence in the contralateral cerebellum during and post-dystonic tremor, thereby adding to the literature on the topic.

In primary dystonia, three distinct cortico-pallidal oscillatory networks have been described using MEG: pallido-temporal (theta frequencies of 4–8 Hz) coherence, pallido-cerebellar (alpha frequencies of 7–13 Hz) coherence, and cortico-pallidal (beta frequencies of 13–30 Hz) coherence.[16] The increased alpha-, beta-, and gamma-band frequencies during dystonic activity implicate abnormal pallido-cerebellar and cortico-pallidal pathways. In another MEG study where sensory touch was used to stop dystonic activity, post-dystonic activity alpha and beta activities decreased, while gamma activity increased.[10] We found that the alpha, beta, and gamma frequencies all increased with actions provoking dystonia, while immediately after dystonic activity both beta and gamma frequencies remained high. This increase in gamma activity post-dystonia is likely due to the increased GABA-ergic levels remaining high, as shown previously.[17] During the post-dystonic activity, our patient had a reduction in alpha and beta activities similar to the previous MEG study that used sensory activity to stop the dystonic movements. In both of these cases, sensory activity by fingers was used to disrupt the dystonic moment that was arising from abnormal motor network activity.

Throughout the duration of the study, there was increased coherence in the auditory cortices as well. The likely explanation of this could be attributed to the auditory cortices being activated by the rhythmic sound of the Helium recycler, just outside of the magnetically shielded room. Individual controls subjects were also found to have activation in the auditory cortex when the Helium recycler was on.

Our case report has several limitations. Given its nature, the findings cannot be readily extrapolated to other musicians with ED but rather could add to the literature on this rare condition. Furthermore, using non-musician controls does not account for baseline differences between healthy musician and non-musician controls. Our patient was used as her own control pre-touch and post-touch in this case. A strength of our study is the use of MEG. By measuring direct neuronal activity, MEG offers unique advantages in the assessment of functional cortical networks, specifically excellent spatial resolution with respect to deeper cortical structures. While other functional neuroimaging techniques such as positron emission tomography (PET) and fMRI may offer high spatial resolution by indirectly measuring brain activity, their temporal resolution is inherently less precise. Our report provides exploratory insights into the pathophysiology of ED in a patient with an activity-associated dystonia. In future studies, with larger samples of both patients with ED and healthy controls, similar control conditions would be maintained. The future use of tailored effective clinical treatments could be measured by a decrease or increase in hyperexcited cortical activity detected by MEG.

References

1. Frucht S. Embouchure dystonia-portrait of a task-specific cranial dystonia. *Mov Disord* 2009;24:1752–1762. doi: 10.1002/mds.22550

2. Termsarasab P, Frucht S. Evaluation of embouchure dysfunction: experience of 139 patients at a single center. *Laryngoscope* 2016;126:1327–1333. doi: 10.1002/lary.25723

3. Sussman J. Musician's dystonia. *J Pract Neurol* 2015;15:317–322. doi: 10.1136/practneurol-2015-001148

4. Elbert T, Candia E, Altermuller E, Rau H, Sterr A, Rockstroh B, et al. Alteration of digital representations in somatosensory cortex in focal hand dystonia. *Neuroreport* 1998;16:3571–3575. doi:10.1097/00001756-199811160-00006

5. Mantel T, Dresel C, Altenmuller E, Zimmer C, Noe J, Haslinger B. Activity and topographic changes in somatosensory system in embouchure dystonia. *Mov Disord* 2016;31:1640–1648. doi: 10.1002/mds.26664

6. Haslinger B, Altenmuller E, Castrop F, Zimmer C, Dresel C. Sensorimotor overactivity as a pathophysiologic trait of embouchure dystonia. *Neurology* 2017;74:1790–1797. doi: 10.1212/WNL.0b013e3181e0f784

7. Elisevich K, Shukla N, Moran JE, Smith B, Schulz L, Mason K, et al. An assessment of MEG coherence imaging in the study of temporal lobe epilepsy. *Epilepsia* 2011;52:1110–1119. doi: 10.1111/j.1528-1167.2011.02990.x

8. Nazem-Zadeh MR, Bowyer SM, Moran JE, Davoodi-Bojd E, Zillgitt A, Weiland BJ, et al. MEG coherence and DTI connectivity in mTLE. *Brian Topogr* 2016;29:598–622. doi: 10.1007/s10548-016-0488-0

9. Lajiness-O'Neill R, Richard AE, Moran JE, Olszewaki A, Pawluk L, Jacobson D, et al. Neural synchrony examined with magnetoencephalography (MEG) during eye gaze processing in autism spectrum disorders: preliminary findings. *J Neurodev Disord* 2014;6:15. doi: 10.1186/1866-1955-6-15

10. Mahajan A, Zillgitt A, Bowyer SM, Sidiropoulos C. Sensory trick in a patient with cervical dystonia: insights from magnetoencephalography. *Brain Sci* 2018;8:51. doi: 10.3390/brainsci8040051

11. Mahajan A, Alshammaa A, Zillgitt A, Bowyer SM, LeWitt P, Kaminski P, et al. The effect of botulinum toxin on network connectivity in cervical dystonia: lessons from magnetoencephalography. *Tremor Other Hyperkinet Mov* 2017;7:1–7. doi: 10/7916/D84M9H4W

12. Burciu RG, Hess CW, Coombes SA, Ofori E, Shukla P, Chung JW, et al. Functional activity of the sensorimotor cortex and cerebellum relates to cervical dystonia symptoms. *Hum Brain Mapp* 2017;38:4563–4573. doi: 10.1002/hbm.23684

13. Hirata Y, Schulz M, Altenmuller E, Elbert T, Pantev C. Sensory mapping of the lip representation in brass musicians with embouchure dystonia. *Neuroreport* 2004;15:815–818. doi: 10.1097/00001756-200404090-00015

14. Bologna M, Berardelli A. Cerebellum: an explanation for dystonia? *Cerebellum Ataxias* 2017;4:6. doi: 10.1186/s40673-017-0064-8

15. Shakkottai V, Batla A, Bhatia K, Dauer WT, Dresel C, Niethammer M, et al. Current opinions and areas of consensus on the role of the cerebellum in dystonia. *Cerebellum* 2017;16:577–594. doi: 10.1007/s12311-016-0825-6

16. Neumann WJ, Jha A, Bock A, Huebl J, Horn A, Schneider GH, et al. Cortico-pallidal oscillatory connectivity in patients with dystonia. *Brain* 2015;138:1894–1906. doi: 10.1093/brain/awv109

17. Muthukumaraswamy SD, Edden RA, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proc Natl Acad Sci U S A* 2009;106:8356–8361. doi: 10.1073/pnas.0900728106