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# Shortened cortical silent period in adductor spasmodic dysphonia: Evidence for widespread cortical excitability

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## HIGHLIGHTS

- Cortical inhibition is significantly reduced in FHD and AdSD compared to healthy.
- Abnormalities exist in hand region of motor cortex in AdSD without hand symptoms.
- Abnormality in $GABA_B$-ergic mechanism may be a feature of AdSD and FHD.
- TMS response could potentially play a role in assisting in differential diagnosis.

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## ABSTRACT

The purpose of this study was to compare cortical inhibition in the hand region of the primary motor cortex between subjects with focal hand dystonia (FHD), adductor spasmodic dysphonia (AdSD), and healthy controls. Data from 28 subjects were analyzed (FHD $n = 11$, $53.25 \pm 8.74$ y; AdSD: $n = 8$, $56.38 \pm 7.5$ y; and healthy controls: $n = 941.67 \pm 10.85$ y). All subjects received single pulse TMS to the left motor cortex to measure cortical silent period (CSP) in the right first dorsal interosseus (FDI) muscle. Duration of the CSP was measured and compared across groups. A one-way ANCOVA with age as a covariate revealed a significant group effect ($p < 0.001$). Post hoc analysis revealed significantly longer CSP duration in the healthy group vs. AdSD group ($p < 0.001$) and FHD group ($p < 0.001$). These results suggest impaired intracortical inhibition is a neurophysiologic characteristic of FHD and AdSD. In addition, the shortened CSP in AdSD provides evidence to support a widespread decrease in cortical inhibition in areas of the motor cortex that represent an asymptomatic region of the body. These findings may inform future investigations of differential diagnosis as well as alternative treatments for focal dystonias.



## 1. Introduction

Dystonia is a "movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation" [1]. Dystonia is considered focal if it primarily affects a specific group of muscles such as in the hand, referred to as focal hand dystonia (FHD). The term adductor spasmodic dysphonia (AdSD) refers to focal dystonia affecting the intrinsic muscles of the larynx responsible for adducting the true vocal folds. AdSD is characterized by a strained/strangled vocal quality with vocal breaks during speech tasks. The accurate diagnosis of FHD and AdSD is particularly difficult due to similar clinical presentation as other disorders. In addition, there are no available diagnostic tests that are considered gold standard for differential diagnosis. In AdSD, differential diagnosis is particularly challenging as the perceptual voice characteristics are often misdiagnosed as a functional voice disorder, muscle tension dysphonia (MTD) [2,25,26]. Due to the differences in etiology, effective treatment options for MTD and AdSD are vastly different; people with MTD typically respond favorably to traditional behavioral voice therapy and people with AdSD can achieve temporary symptom relief through injections of botulinum toxin into the thyroarytenoid muscle (true vocal fold), dennervation of the recurrent laryngeal branch of the vagus nerve and, in some cases, laryngeal framework surgery [19]. However, AdSD does not respond to behavioral voice therapy. Thus, a misdiagnosis can lead to ineffective, time consuming and expensive treatment that may not be beneficial. Similarly, FHD is

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commonly misdiagnosed as essential tremor, carpel tunnel syndrome, overuse syndrome or psychogenic dystonia [18].

Transcranial magnetic stimulation (TMS) is a non-invasive method to measure cortical excitability and has been used to investigate neurophysiological differences in those with focal dystonia compared to healthy populations. The cortical silent period (CSP) is one measure of cortical excitability that can be elicited using TMS. CSP is an interruption of electromyographic (EMG) activity in the targeted muscle under slight contraction [7]. The initial phase of CSP is thought to reflect spinal inhibitory mechanisms such as suppression of H-reflexes due to Renshaw inhibition [8,9], while the later phase due to suppression of voluntary motor drive by gamma-amino-butyric acid ($GABA_B$) receptor-mediated inhibition within the cortex [16,27,30,31]. Significantly shortened CSPs have been reported in those with task-specific focal dystonia compared to those with segmental, generalized dystonia or healthy subjects [23].

A shortened cortical silent period (CSP) measured by TMS has been reported in those with FHD supporting the idea that reduced cortical inhibition is a neurophysiological feature in this population [4,22,23]. Cakmur et al. [5] compared CSP in orbicularis oculi, orbicularis oris, sternocleidomastoid (SCM) and abductor pollicis brevis (APB) in three groups: healthy controls, blepharospasm and cervical dystonia. When compared to controls, people with either dystonia had a shorter mean CSP in both orbicularis oris and orbicularis oculi, but not in APB [6]. These findings suggest the reduction of cortical inhibition is not isolated solely to the affected musculature, but not pervasive throughout the entire representation in patients with blepharospasm or cervical dystonia. Cortical excitability has not yet been reported in AdSD. Considering shortened CSP has been reported in other forms of focal dystonia, it was chosen as the outcome variable for this study to provide an improved understanding of the neuropathophysiology of AdSD.

Thus, the purpose of this investigation was to compare CSP in first dorsal interosseus (FDI) in healthy controls, subjects with FHD and subjects with AdSD to determine if a shortened CSP in FDI is a feature of both forms of focal dystonia which would not only provide additional evidence of widespread decreased cortical inhibition in dystonia, it may also serve as a contributing factor in differential diagnosis.

## 2. Methods

### 2.1. Subjects

All 28 subjects were right-handed and between the ages of 26–68 years of age (mean: $50.21 \pm 11.18$ y; FHD $n = 11$, $53.25 \pm 8.74$ y; AdSD: $n = 8$, $56.38 \pm 7.54$ y; and healthy controls: $n = 9$, $41.67 \pm 10.85$ y) (Table 1). All subjects with FHD were symptomatic in the right hand. Data for the FHD group were obtained from a previously conducted study using the same protocol, equipment, and location [4]. In addition to having a diagnosis of AdSD from a laryngologist and/or speech language pathologist specializing in voice, subjects in the AdSD group had voice symptoms that were task specific, received little to no reported benefit from traditional voice therapy and reported benefit from low dose botulinum toxin injections into the vocal folds. Subjects in all groups were screened for TMS safety including no history of seizures, neurologic conditions such as stroke or degenerative disease, metal implanted devices (excluding dental fillings) and pregnancy. Potential subjects were also excluded if there had been recent use of dystonia medication including botulinum toxin injection within three months. This study was approved by the University of Minnesota Institutional Review Board and written informed consent was received according to the Declaration of Helsinki prior to participation. Data collection was carried out at University of Minnesota Clinical Translational Science Institute.

### 2.2. Cortical silent period

All cortical excitability testing was conducted by the primary researchers to ensure consistency. Each subject was seated comfortably in a reclining chair and fit with a swim cap to allow cranial landmarks to be first approximated and later confirmed using TMS. Electromyographic (EMG) traces from target muscle was acquired at a sampling rate of 2560 Hz with a bandpass filter width of 20–2000 Hz using a Cadwell Sierra EMG amplifier (Cadwell Laboratory, Washington). Considering the evidence to support widespread reduced cortical inhibition and accessing the laryngeal musculature can be invasive and difficult, the FDI was chosen as the target muscle. Surface electrodes were placed on the right hand over the FDI muscle using a tendon-belly montage with a ground electrode placed over the dorsum of the hand. TMS was applied using a 70-mm figure of eight coil connected to a Magstim 200 Rapid magnetic stimulator (Magstim So., Whitland Dyfed, UK). Single pulse TMS was delivered over the left primary motor cortex associated with the hand region and was systematically moved in 1 cm increments until "hotspot" was found. This location was marked and used throughout the remainder of the study. Each subject's resting motor threshold (RMT) was determined as the minimum intensity required to produce a motor evoked potential (MEP) of ~50 μV in at least 3 of 5 trials while the patient was at rest [24]. The test pulse intensity used for measurement was 120% of RMT, which was approximately equal to a 1 mV response at rest. CSP was measured by having the subjects perform an isometric contraction by abducting their index finger against a ring coupled to a 5-Beam load cell (Interface Inc., Scottsdale, AZ, USA) at 25% of maximum voluntary contraction (best of 3 maximal attempts), while

**Table 1**
Subject demographics.

| Healthy | | Focal hand dystonia | | | Adductor spasmodic dysphonia | | |
|---|---|---|---|---|---|---|---|
| Age | Sex | Age | Sex | Symptom duration (months) | Age | Sex | Symptom duration (months) |
| 26 | M | 64 | F | 252 | 44 | M | 18 |
| 28 | F | 42 | M | 168 | 62 | F | 216 |
| 51 | F | 55 | M | 108 | 53 | M | 120 |
| 39 | F | 49 | F | 60 | 50 | M | 408 |
| 37 | F | 63 | M | 84 | 67 | M | 324 |
| 40 | F | 41 | M | 36 | 55 | F | 96 |
| 43 | M | 68 | M | 60 | 54 | M | 96 |
| 48 | F | 46 | M | 72 | 66 | M | 228 |
| 63 | F | 50 | M | 30 | | | |
| | | 59 | M | 444 | | | |
| | | 50 | M | Unknown | | | |

M = male; F = female.