

Voice Tremor

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INTRODUCTION

Voice tremor is characterized by involuntary oscillatory movements of muscles of the vocal tract, causing rhythmic modulations of the voice in pitch and loudness. Voice tremor may present as an isolated disorder; as a feature of other neurological disorders, including essential tremor, laryngeal dystonia, or Parkinson disease; or as a result of a physiological process.

Under various physiological conditions, a tremulous voice may manifest as a pattern of affective vocalization commonly associated with fear, sadness, wrath, or even joy. Remarkably, in its earliest referrals in the English literature, tremor was used to denote terror and was described as a shaking that happens “involuntarily as with fear or other emotion, cold, or weakness.”¹ Those affected by pathological voice tremor not only suffered from difficulty speaking but were frequently mistaken to be emotional or weak. Unfortunately, these misperceptions about voice qualities tied to personality traits continue to persist to date, causing social embarrassment and anxiety for those with voice tremor, further exacerbating the condition and driving affected individuals into a vicious loop of social isolation and depression. Similarly, disorders that cause voice tremor have been misinterpreted as psychosomatic, a misconception that only increased the stigma surrounding affected individuals, while delaying investigations into the neurological underpinnings of voice tremor symptoms.

Although notable advances have been recently made in the medical and scientific understanding of voice tremor, ongoing challenges include diagnostic inconsistencies across clinical specialties and limited availability of therapeutic options. Pharmacological and neurosurgical treatments that are effective for alleviation of tremor affecting extremities often show worse results when used to treat voice tremor. The existing limitations to better treat voice tremor are due, in part, to the fact that the underlying etiopathophysiological mechanisms that generate tremor are not well understood.

This chapter aims to describe the most frequent presentations of voice tremor, their clinical features, and therapeutic options. Given the current lack of consensus between clinicians on the nomenclature or taxonomy of voice changes associated with tremor, we use “voice tremor” as an umbrella term for tremor-related terms used in the literature, including “vocal tremor,”² “tremulous voice,” “laryngeal tremor,” and “phonatory instability.”^{3,4} While different presentations of voice tremor can be clinically identified, recent brain imaging studies suggest that they are likely distinct manifestations of the spectrum of this disorder. Since the understanding of the voice tremor spectrum is still being developed, we also discuss the ongoing efforts and challenges in the classification of this disorder and the future diagnostic and therapeutic directions.

VOICE TREMOR AS A SYMPTOM OF ESSENTIAL TREMOR

Essential tremor (ET) is a movement disorder, whose clinical hallmark is a 4–12-Hz action tremor of the upper extremities (arms and hands). In 25–62% of patients, ET can spread to involve cranial structures, such as the larynx, soft palate, tongue, jaw, and neck, causing ET of voice (ETv) and/or head. In some, ETv may present as an isolated symptom without co-occurring tremor of extremities (Figure 10.1). The marked variability in ETv prevalence and presentations is likely due to the differences in patient cohorts studied, diagnostic methodologies applied, and the clinical expertise present across study centers.

It is worth noting that, although isolated voice tremor appears to be a focal presentation of ET based on its onset, progression, and clinical characteristics, there is still little consensus between clinicians regarding its classification.^{5–7} On the one hand, the recent consensus paper of the Task Force on Tremor by the International Parkinson and Movement Disorder Society (IPMDS) excluded isolated voice and head tremors from ET classification,

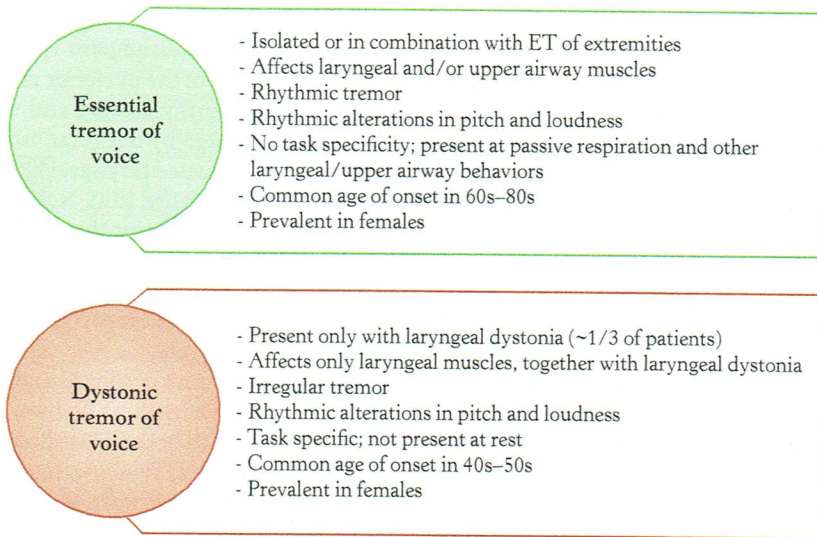


FIGURE 10.1: Essential and Dystonic Voice Tremor Classification Based on Clinical Features Obtained through Medical History, Acoustic Perceptual Voice Evaluation, and Neurological and Laryngological Examinations.

restricting the latter diagnosis to at least tremor of upper extremities.⁷ On the other hand, a report by the Neurolaryngology Committee of the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) defined isolated voice tremor as ET affecting the intrinsic muscles of the larynx and, variably, other muscles of the phonatory apparatus.⁸ To reach common ground, a recent review paper strongly recommended to reconsider the inclusion of isolated voice tremor as a clinical variant of ET, highlighting that both isolated and ET-associated forms of voice tremor demonstrate the similar spread of disease through structures in the speech apparatus and share similar familial prevalence and female preponderance.⁹ Supporting this recommendation, a recent brain imaging study in patients with voice tremor, both isolated and with ET affecting extremities, has identified only subtle differences in cortical thickness within parietal and temporal cortices, without any other differences in functional, white matter, or volumetric gray matter organization between the two cohorts.¹⁰ Based on similarities of brain alterations in isolated voice tremor and ET, this study provided a pathophysiological justification for a re-classification of isolated voice tremor as a focal phenotype of ET.

Similar to ET affecting other body regions, the diagnosis of ETv, both isolated to the vocal tract and combined with tremor in the extremities, depends on a careful analysis of case history and neurological and otolaryngologic evaluations to rule out other

tremor etiologies. The onset of ETv is more prevalent in females in their 60–80s,^{2,6,11,12} with patients most often presenting with the intensity fluctuations associated with a perception of increased phonatory effort (Figure 10.1). Additionally, muscular discomfort and fatigue may also result from compensatory efforts to stabilize the vocal tract.

On clinical examination, voice tremor is best appreciated during phonation of prolonged vowels, such as /i/or/a/ at a normal pitch, and usually decreases at the high pitches.¹³ ETv, both isolated and combined with ET affecting extremities, may become so severe that a stoppage of voice occurs, making it easily misdiagnosed as dystonic tremor of voice (DTv) present in laryngeal dystonia (LD). Differentiation between essential and dystonic tremor is reliant on the task specificity of laryngeal behavior to volitional speech tasks in DTv compared to non-volitional respiration (i.e., tidal breathing) in ETv. Therefore, voice tremor that does *not* have task specificity, occurring during both respiration and speech tasks, is characterized as ETv (Figure 10.1). This differentiation is best notable with stroboscopic examination of oscillation of the laryngeal musculature and oral articulators (e.g., pharyngeal constrictors, tongue, soft palate, jaw, and lips) during both speech tasks and passive respiration. Electromyography (EMG) may also help determine the anatomical source of tremor within the laryngeal and upper airway structures. The EMG recordings performed in experimental settings

have shown that the intrinsic laryngeal muscles, specifically thyroarytenoid muscles, are the most frequently involved, with the frequency of about 5 to 7 Hz.¹⁴ Other distinguishing factors in ETv compared to voice tremors in other neurological disorders include higher rates of a family history of tremor and alleviation of symptoms with alcohol intake, i.e., alcohol responsiveness.^{2,15}

The current standard of care of voice tremor is the management of symptoms with onabotulinum toxin A injection (BoNT) into the overactive laryngeal or upper airway musculature.¹⁶ Response to BoNT injections may vary significantly, depending on the affected structures by voice tremor. The isolated lateral variant, which involves intrinsic laryngeal (thyroarytenoid) muscles, receives greater benefits from BoNT treatment into adductor muscles compared to tremors originating from extralaryngeal sources. On average, a lower BoNT dose requirement and less pronounced effects are observed in ETv compared to DTv and LD.

Regarding the pharmaceutical treatment, there is some evidence that patients with ETv may exhibit similar improvement in voice symptomatology as those with ET of extremities.¹⁷⁻²¹ Medications used to manage ETv typically include propranolol and primidone, although their effects are not as beneficial in voice tremor as in action tremors of extremities in ET or Parkinson disease.²² Similarly, ETv has shown variable responsiveness to deep brain stimulation (DBS) of the ventral intermediate nucleus and caudal zona incerta of the thalamus, with better outcomes at bilateral stimulation.²³⁻²⁵ Currently, DBS is reserved for ET patients with a treatment-refractory severe tremor of upper extremities who may or may not have associated ETv. Whether severe voice tremor can become itself an indication for DBS depends on future research studies to identify different tremorgenic brain networks and link these to specific anatomical end-target(s). Additionally, speech and language therapy (SLP) can equip patients with complementary strategies to improve voice loudness and speech intelligibility, although widely variable outcomes across patients should be considered.

VOICE TREMOR AS A SYMPTOM OF DYSTONIA

DTv is observed in about one-third of patients with LD. It is most commonly present in patients with adductor type of LD, where irregular contractions of the thyroarytenoid and lateral cricoarytenoid muscles produce strained and effortful

voicing and voice breaks. Less commonly, it can be associated with the abductor type, where dystonic contractions of the posterior cricoarytenoid muscle lead to breathy voicing and voice breaks. DTv is characterized by irregular, isometric contractions of the affected laryngeal muscles during dystonic activity (Figure 10.1). Notably, it is characterized by task specificity, that is, DTv is present only with LD and selectively affects speech production, while being absent during respiration and other laryngeal or upper airway behaviors. Similar to LD, DTv may be responsive to sensory tricks, e.g., application of topical anesthesia.^{9,26-28} Clinically, patients with DTv have similarities and differences with both LD without tremor and ETv. Patients with DTv show intermediate age and sex distributions between those with ETv and LD without tremor.²⁸⁻³¹ A family history of dystonia is rare in patients with and without a tremor, but higher than in the general population, with the variability from 1% to 16%.^{31,32} A family history of tremor is, however, more common in LD patients with DTv compared to LD patients without tremor.^{15,31} This difference is consistent with the fact that tremor conditions, both dystonic and essential, have a stronger underlying genetic predisposition, while purely dystonic disorders are more commonly sporadic than familial.

The pathophysiology of DTv is thought to broadly overlap with LD, while also sharing some similarities with ETv (Figure 10.2). Recent studies investigating alterations in brain structure and function in LD vs. DTv and ETv vs. DTv have proposed that these disorders may be characterized within the same pathophysiological spectrum, presenting both common and distinct patterns of neural alterations. Compared to healthy individuals, all patients have been shown to share the involvement of cortical brain regions controlling sensory and motor aspects of speech production. In addition, DTv and LD patients share functional and structural abnormalities in the sensorimotor cortex, basal ganglia, and thalamus, while being distinguished by greater cerebellar and middle frontal cortical changes in DTv. On the other hand, ETv and DTv show common changes in the primary sensorimotor cortex, superior and inferior parietal lobules, and inferior temporal gyrus, with distinct greater alterations of cortical vs. cerebellar changes in DTv vs. ETv.^{10,33,34} It has been further determined that hyperexcitable parietal→ putaminal and right→ left interhemispheric premotor cortical information flow underlies the pathophysiological network alterations in both LD and DTv,

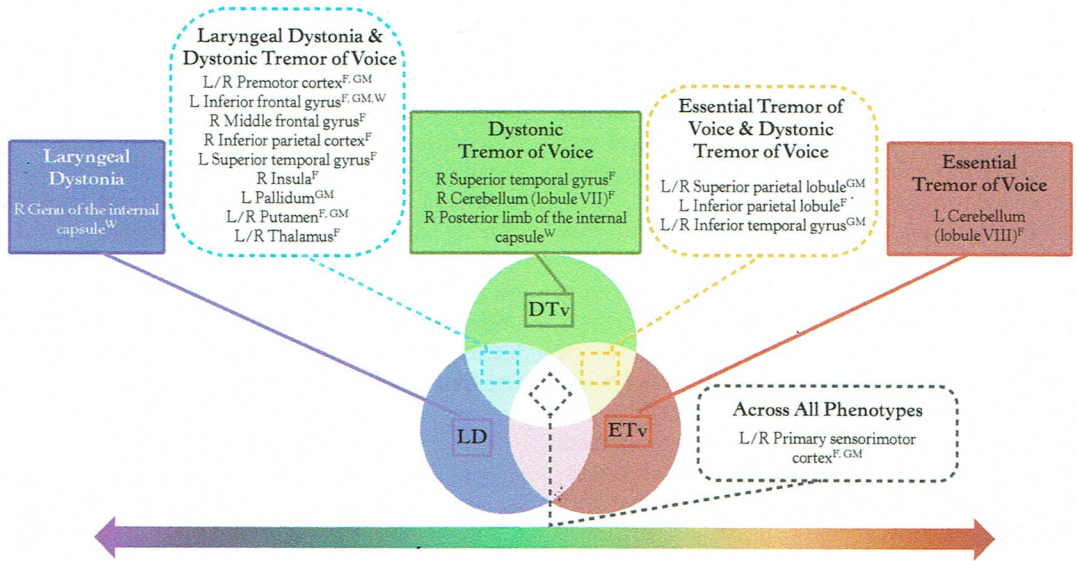


FIGURE 10.2: A Schematic Diagram Summarizing the Main Findings Retrieved from Neuroimaging Studies on Functional and Structural Abnormalities in Neurologic Disorders that Present with Voice Tremor.^{10,33,34} Solid panels list abnormalities that are characteristic to laryngeal dystonia, dystonic tremor of voice, and essential tremor of voice tremor; panels with dashed lines and white background list regions where the alterations of brain function and structure are present across the spectrum of these disorders. Abbreviations: L = left; R = right; LD = laryngeal dystonia; DTv = dystonic tremor of voice; ETv = essential tremor of voice; F = functional alterations; GM = gray matter alterations; W = white matter alterations.

whereas decreased self-inhibitory influences of these brain regions contribute to differences between LD with and without DTv.³⁴

Despite differences in the pathophysiology, the primary treatment of DTv is the same as for LD and ETv and consists of BoNT injections into the affected laryngeal muscles. BoNT injections yield an intermediate response in DTv, with better outcomes in LD without tremor, and worse in ETv.^{15,35,36} In contrast, alcohol responsiveness is more common in ETv, followed by DTv and LD without tremor, which has been proposed to be associated with the varying degree of cerebellar involvement across these disorders.^{17,37}

In alcohol-responsive patients with LD and DTv, sodium oxybate (Xyrem®) has recently shown efficacy in treating symptoms of both dystonia and tremor in an open-label study.^{38,39} As a potentially novel oral therapeutic agent, sodium oxybate mimics the effects of alcohol and acts on the GABAergic neurotransmission, which is deficient in these patients. A brain imaging study in these patients has demonstrated that sodium oxybate significantly reduces hyperfunctional activity of cerebellar, thalamic, and primary/secondary sensorimotor cortical regions, with Xyrem-induced LD and DTv symptom improvement being

correlated with decreased to normal levels of cerebellar activity.⁴⁰ These studies outlined the first use of a pathophysiologically relevant, centrally acting medication; results are being confirmed in a double-blind, placebo-controlled clinical trial of LD and DTv, as well as ETv (NCT03292458). Clinical observations of the use of sodium oxybate in other forms of dystonia and ETv,^{6,41,42} point to a broader indication of this drug in these disorders, further tying in the pathophysiology of their different clinical phenotypes.

Other therapies available for LD with and without DTv include recurrent laryngeal nerve (RLN) section,⁴³ selective laryngeal adductor branch denervation and reinnervation,⁴⁴ and laryngoplasty.⁴⁵ However, these invasive and irreversible operations do not address disorder pathophysiology, offer only compensatory management of symptoms, and carry a higher risk of inconsistent outcomes.

VOICE TREMOR IN OTHER NEUROLOGICAL DISORDERS

Voice tremor can also be associated with other neurological disorders, such as Parkinson disease, multisystem atrophy, progressive supranuclear

palsy, multiple sclerosis, or cerebellar diseases. As a comorbidity in these disorders, voice tremor is usually accompanied by other cranial nerve abnormalities, arises from sources other than the laryngeal musculature, cannot be managed well by BoNT injections, and often responds poorly to other treatment modalities.

In Parkinson disease (PD), voice dysfunction is one of the earliest signs of speech motor impairment. These symptoms affect as many as 89% of patients and may include hypokinetic dysarthria, stuttering, breathy or strained voice, and spastic dysarthria, along with voice tremor. It is unclear how many people with PD have clinically identified voice tremor; studies have shown a range from 13% to 68%.^{46–48} Although voice tremor represents a functionally significant factor for patients with PD, little is known about the underlying anatomical sources and pathophysiological mechanisms. Voice tremor in PD can involve many structures of the voice apparatus, including the palate, but less often the vocal folds.⁴⁹ Available treatments of PD have also shown variable outcomes related to voice symptoms. For example, levodopa and DBS of the subthalamic nucleus (STN) can mildly improve or significantly impair speech production.^{50–55} The effects of DBS specifically on voice tremor are even less well understood. In one study, STN-DBS ameliorated voice tremor and speech intensity but deteriorated overall speech intelligibility in most patients.⁵⁶

Cerebellar lesions and disorders frequently affect voice and speech production and give rise to distinct articulatory and phonatory deficits, generally categorized as ataxic dysarthria.⁵⁷ Among these deficits, amplitude, and frequency of voice fluctuations during sustained vowel productions underlie voice tremor. The tremor rate in ataxic speakers is distinctively slower than in normal speakers and other voice tremor phenotypes, at a frequency of about 3 Hz.^{3,58,59} As with DTv, it seems to preferentially affect volitional phonation.⁶⁰ While the cerebellum is known to be involved in speech motor control, the specific range of alterations affecting voice and speech production are less known. The cerebellum is functionally connected to various cortical and subcortical brain regions engaged in speech motor control, including movement preparation and motor execution processes.⁵⁷ Speech motor deficits have been described as predominantly bound to left-sided paravermal lesions (lobules VI and VII).⁶¹ Why voice tremor affects only a subset of dysarthric ataxic patients and what therapies can be used to treat it warrant further research.

CONCLUSIONS

In summary, the most frequent clinical presentations of voice tremor fall within the broad pathophysiological spectrum of ET and LD. Current differential diagnosis of voice tremor is largely based on a syndromic approach, and its targeted treatment is lacking. Identification of specific clinical features and pathophysiological mechanisms underlying different clinical representations of voice tremor would not only explain its underpinning causes but also open new avenues for the objective differential diagnosis and selective treatment of affected individuals.

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