Central Mechanisms and Pathophysiology of Laryngeal Dystonia: An Up-to-Date Review

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Summary: Objective. Laryngeal dystonia (LD), previously termed spasmodic dysphonia, is an isolated focal dystonia that involves involuntary, uncontrolled contractions of the laryngeal muscles during speech. It is a severely disabling condition affecting patients' work and social lives through prevention of normal speech production. Our understanding of the pathophysiology of LD and available therapeutic options are currently limited. The aim of this short review is to provide an up-to-date summary of what is known about the central mechanisms and the pathophysiology of LD.

Methods. A systematic review of the literature was performed searching Embase, CINHAL, Medline, and Cochrane with the cover period January 1990–October 2023 with a search strategy ((“Laryngeal dystonia” OR “Spasmodic dysphonia”) AND (“Central Mechanism” OR “Pathophysiology”)). Original studies involving LD patients that discussed central mechanisms and/or pathophysiology of LD were chosen.

Results. Two hundred twenty-six articles were identified of which 27 articles were included to formulate this systematic review following the screening inclusion and exclusion criteria. LD is a central neurological disorder involving a multiregional altered neural network. Affected neural circuits not only involve the motor control circuit, but also the feedforward, and the feedback circuits of the normal speech production neural network, involving higher-order planning, somatosensory perception and integration regions of the brain.

Conclusion. Speech production is a complex process, and LD is a central neurological disorder involving multiregional neural network connectivity alteration reflecting this. Neuromodulation targeting the central nervous system could therefore be considered and explored as a new potential therapeutic option for LD in the future, and should assist in elucidating the underlying central mechanisms responsible for causing the condition.

Key Words: Laryngology–Neurolaryngology–Laryngeal dystonia–Voice.

INTRODUCTION

Laryngeal dystonia (LD), previously termed spasmodic dysphonia,[1] is an isolated focal dystonia that involves involuntary, uncontrolled contractions of the laryngeal muscles during speech. It is task specific, where whispering, singing, and innate vocalizations such as laughing are not typically affected. LD is primarily categorized into three types depending on the group of laryngeal muscles affected. Adductor laryngeal dystonia (ADLD), the most common type of LD, is characterized by intermittent hyperadduction of the vocal folds. Hyperadduction of the vocal folds leads to voice breaks on vowels and a strained voice quality. Abductor laryngeal dystonia (ABLD) is rarer, and is characterized by a breathy voice and voice breaks on voiceless consonants from the overabduction of the vocal folds. Lastly, mixed LD, the rarest type, combines the features of both ADLD and ABLD.

LD is a severely disabling condition significantly impairing patients' ability to communicate both occupationally and socially. During speech, the involuntary, uncontrolled contractions of the laryngeal muscles prevent affected individuals from producing normal speech. There is no cure currently, and the current gold standard treatment for LD is Botulinum Toxin A (BoNT-A) injection into the laryngeal muscles.[2] It aims to reduce the effect of uncontrolled laryngeal muscle contraction during speech production through (partial) muscle paralysis. However, there are many limitations with BoNT-A. First and foremost, BoNT-A targets the end organ responsible (muscle) providing symptomatic relief, but does not target the underlying cause of the condition and, therefore, does not offer a permanent cure for the condition. In addition, failed injections can occur, and there is an initial period of trial-and-error dosing. It can be ineffective in some patients, and for the patients who respond, therapeutic effects are temporary, requiring repeated injections every 3–4 months. Furthermore, patients can develop antibodies against BoNT-A over time, resulting in treatment resistance. Delivering BoNT-A injection also requires a highly specialized clinic with laryngeal electromyography, or injection via channeled endoscopes or directly under a general anesthesia. Surgical intervention in the form of selective laryngeal denervation and reinnervation, laryngeal muscle myectomy and myoneurectomy, and type II thyroplasty

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have been reported.[3–7] However, outcomes have been variable with a lack of reproducibility across different units.[1]

An improved understanding of the mechanisms involved in the pathophysiology of LD should help clinicians improve the current standard of care for LD patients. Previous landmark review papers by Hintze et al,[8,9] and Simonyan et al[1] provided a great insight into the LD pathophysiology involving multilevel widespread alterations of neural network function and structure. There remains much unknown or not fully understood with regard to the exact mechanisms and the pathophysiology of LD, and both reviews have identified gaps and research priorities in this area for future directions.[1,8,9] The aim of this current review is, therefore, to provide an up-to-date summary of what is known about the central mechanisms and the pathophysiology of LD though a systematic review of the literature.

METHODS

Embase, CINHAL, Medline, and Cochrane were searched covering the period January 1990–October 2023 on October 20, 2023. The search strategy used was ((“Laryngeal dystonia” OR “Spasmodic dysphonia”) AND (“Central Mechanism” OR “Pathophysiology”)).

The initial search yielded 226 articles. From these articles, duplicates were first identified and removed. Following this, literature search began with screening titles and abstracts. Original studies evaluating central mechanisms and/or pathophysiology of LD were included. Full-text review was performed if the content of the abstract was unclear. Following the title and abstract screening, a full-text review was conducted assessing for the following inclusion criteria: (1) original studies involving LD patients; (2) aimed at elucidating central mechanisms and/or pathophysiology of LD; (3) English language. The exclusion criteria were case reports/series, review articles, conference abstracts, full text unavailable, not written in English, original studies evaluating the efficacy of LD treatment, original studies evaluating the mechanisms of LD treatment, and original studies aimed at evaluating central mechanisms and/or pathophysiology of focal dystonia. Figure 1 shows the PRISMA flow chart used for this systematic review.

Findings from each included study were summarized descriptively, and were brought together to create a small synthesis summarizing our current understanding of the central mechanisms and the pathophysiology of LD.

RESULTS

The search yielded 226 articles. Twenty-seven articles were included and utilized to formulate the review after screening (Figure 1).[10–36]

The 27 included studies evaluated 1553 adult (≥18 years) LD patients. The majority of the patients were female (n = 1159). Nine hundred fifty-three ADLD patients, 449 ABLD patients, and 82 mixed-type patients were studied; four studies did not explicitly categorize their LD patients.[18,25,26,32] LD diagnosis was largely confirmed by Otolaryngologists; seven studies did not explicitly state how the LD diagnosis was confirmed[10,13,17,20,21,25,30]; in one study, the diagnosis of LD was confirmed by Neurologists although a flexible nasendoscopy was performed.[26] The majority of studies excluded patients with coexisting neurological, psychiatric, and/or laryngological disorders with the exception of a vocal tremor with only one study explicitly excluding LD patients with coexisting vocal tremor.[14] Five studies did not explicitly mention their included LD patients’ neurological, psychiatric, laryngological comorbidities.[14,17,25,30,32] One study allowed the inclusion of LD patients with coexisting neurological, psychiatric, and/or laryngological comorbidities.[36] In all papers, patients were fully symptomatic at the time of the study except for the postmortem study[30] and the questionnaire study.[36] If the patients were previously treated with BoNT-A injection prior to the study, patients were recruited at > 3/4 months after the patient’s injection or at the end of their cycle.[10,11,14,16–22,24–31,33–35] Twelve studies evaluated English native speakers,[10,16,18–22,24,27–29,33] two studies evaluated Japanese native speakers,[15,23] and one study evaluated Serbian native speakers.[26] There was no explicit mention of the native language spoken by the LD patients in other studies although presumably they were English based on authors’ affiliations. Eighteen studies explicitly stated the handedness of the studied LD patients, and they were all exclusively right-handed.[10,15,16,18–29,33–35] The date of LD onset and the duration of LD for the studied patients were not always available.

There were 14 functional neuroimaging studies,[11,14,15,18,21–27,29,33,34] three histological studies,[30–32] two genetic studies with functional neuroimaging,[19,35] two radioligand studies,[20,28] two electroencephalography studies,[10,17] two sensory testing,[12,13] and two case-control/questionnaire studies with or without functional neuroimaging[16,36] aimed at elucidating central mechanisms and/or pathophysiology of LD (Table 1). All studies apart from two had controls to compare the study results (Table 1).

DISCUSSION

The normal speech production neural network will be discussed first. A summary of how this neural network is altered in patients with LD will subsequently be discussed based on the current literature.

The central voicing mechanism and the speech production neural network

Voice, speech, and language are different concepts. Voice is a sound produced by the larynx. Speech is how the words are said using voice. Language refers to the expression of a message through formulation of meaningful phrases using the words in a grammatically accurate way through speech.

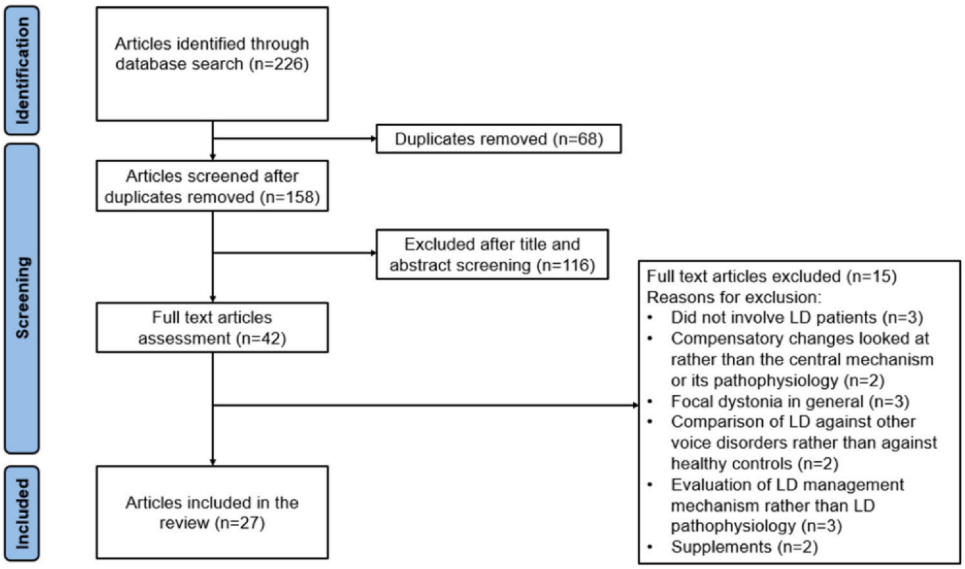

FIGURE 1. Systematic review protocol. LD, laryngeal dystonia.

TABLE 1.
Included Reviewed Studies

Author	Year	Number of patients	Number of controls	Investigation	Ref
Ehrlich	2023	24	22	EEG	10
Kothare	2022	22	18	MEG	11
Young	2022	13	33	Tactile aesthesiometer	12
Frankford	2023	100	44	Puretones and Sniffin' stick smell test	13
Chen	2020	12	14	TMS and fMRI	14
Kanazawa	2020	11	11	fMRI	15
de Lima Xavier and Simonyan	2019	186* and 62**	85* and 35**	Case-control* and fMRI**	16
Khosravani	2019	10	10	EEG	17
Battistella and Simonyan	2019	40	35	fMRI	18
Putzel	2018	57	30	Whole-exome sequencing and fMRI	19
Simonyan	2017	12	12	High-resolution research tomograph with radioligand	20
Fuertinger and Simonyan	2017	90	32	fMRI	21
Bianchi	2017	89	-	MRI	22
Kiyuna	2016	12	16	fMRI	23
Battistella	2016	83	30	fMRI	24
Waugh	2016	7	7	MRI	25
Kostic	2016	13	13	MRI	26
Termsarasab	2015	84	30	TDT and SDT measures and MRI and fMRI	27
Simonyan	2013	18	18	PET with radioligand	28
Simonyan and Ludlow	2010	22	11	fMRI	29
Simonyan	2010	2	4	Postmortem histology	30
Simonyan	2008	20# and 1+	20# and 3+	MRI# and Postmortem histology+	31
Chhetri	2008	9	5	Histology	32
Daliri	2020	12	12	fMRI	33
Mantel	2020	14	15	fMRI	34
Putzel	2016	57	27	Sanger sequencing and fMRI	35
Kirke	2015	531	-	Questionnaire survey	36

Abbreviations: EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomograph; SDT, spatial discrimination thresholds; TDT, temporal discrimination thresholds; TMS, transcranial magnetic stimulation.

*Number of patients for the Case-control part of the study.[16] **Number of patients for the fMRI part of the study.[16] #Number of patients for the MRI part of the study.[31] +Number of patients for the postmortem histology part of the study.[31]

From studying squirrel monkey with their phonatory species-specific calls, Jürgens and colleagues have found that the central vocal control neural pathways are organized hierarchically.[37–39] They found that the innate voice production is generated in the pontine and the medullary reticular formation with the lower-level neural pathway running from the cingulate cortex via the peri-aqueductal gray into the reticular formation of pons and medulla oblongata, and from there to the phonatory motorneurons, responsible for controlling the readiness to vocalize.[37–39] Lesional studies have shown that the destruction of the peri-aqueductal gray results in mutism suggesting its role in vocal gating.[39] The destruction of the cingulate cortex, on the other hand, did not cause mutism, but caused a loss of the voluntary control over vocalization initiation.[39] In humans, some aspects of the innate emotive voicing appear to exploit this rudimentary pathway.[40] However, for linguistic and paralinguistic speech, the process is more complex with the language production requiring three broad stages.[41] First, the conceptualization of the message to express; second, the formulation of the message into linguistic representations; and finally, articulation through appropriate speech production.[41]

Wernicke's and Broca's areas have been found to be strongly linked to speech. Wernicke's area located in the posterior section of the superior temporal gyrus in the left, or dominant, cerebral hemisphere and encircling the auditory cortex, has been the site most consistently implicated in understanding of written and spoken language on functional MRI studies.[42] Broca's area located in the frontal lobe of the left hemisphere, abuts on the motor cortex. Therefore, it has been traditionally believed that information passed from Wernicke's to Broca's area through the arcuate fasciculus, with the Broca's area initiating a motor plan that is transmitted to the primary motor cortex to pronounce the words. The motor cortex, in coordination with the supplementary motor area, basal ganglia and cerebellum, sends corticobulbar fibers to implement speech sounds.[43] With further functional imaging studies, it is now supported that a larger range of processing areas are involved, and forms, the speech production neural network.[40]

Tourville and Guenther in 2011 proposed the Directions Into Velocities of Articulators (DIVA) model to describe the normal speech production neural network (Figure 2).[44] DIVA model proposes that speech production begins with the activation of a speech sound map cell in the left premotor and the adjacent inferior frontal cortex. This information then directly feeds forward to the primary motor cortex and the cerebellum to produce speech via muscles of the vocal tract. The quality of the produced speech is then fed back to the primary motor cortex and the speech sound map via the auditory and somatosensory feedback, which the brain then uses to fine-tune and/or relearn the speech production. Thus, the model consists of integrated feedforward and feedback control subsystems involving multiple brain regions.[44]

The central neural network in LD

Structural alteration

Findings from neuroimaging and neuropathological (postmortem) studies suggest that there appear to be no gross neuropathological abnormalities in the majority of cases of LD.[25,26,30,31] However, studies suggest that regions of the brain involved in the DIVA model have different cortical surface area[26] and their structural connectivity altered[25,31] in LD patients.

Neuroimaging studies have shown LD patients to have an increased cortical surface area of the following areas compared to healthy controls: the primary somatosensory cortex bilaterally, right primary motor cortex, left superior temporal gyrus, left supramarginal gyrus, and the left superior frontal gyrus.[26] Conversely the following areas had a decreased cortical surface area compared to healthy controls: Rolandic operculum bilaterally, right angular gyrus, left superior and inferior parietal gyri, and left superior and inferior lingual gyri.[26] LD patients exhibited focal reduction of axonal density and myelin content along the corticobulbar/corticospinal tracts.[31] Waugh et al found a regionally-specific reduction in gross thalamic volume in LD patients compared to healthy controls using volumetric segmentation technique.[25] However, this finding was not replicated using Voxel-based morphometry.[25] Although the number was small (n = 2), postmortem tissue analysis of the brainstem did not show any gross neuropathological difference between LD patients and healthy controls.[30]

Connectivity (network) alteration

Neuroimaging, electroencephalography, magnetoencephalography, and transcranial magnetic stimulation studies revealed that the functional connectivity between the brain regions was significantly altered in LD patients compared to healthy controls.[10,11,14–18,20,21,23,24,27,29,34]

Movement control network. Abnormal basal ganglia connectivity and reduced level of motor cortical network activity have been reported in LD.[14,17,20,21,23,29] The thalamo-motor-cortical circuit was found to be hyper-excitable with a hyperfunctional excitatory direct basal ganglia pathway and a hypofunctional inhibitory indirect basal ganglia pathway.[20] An abnormal functional integration and over-representation of basal ganglia, cerebellum, and thalamus were found.[21,23] A reduced level of intracortical inhibition was seen in the laryngeal motor cortex,[14] as well as a reduced task-specific desynchronization of motor cortical networks.[17] This is not a surprising finding, considering that LD is a form of focal dystonia.

Feedforward movement planning network. In addition to the abnormal movement control network, the feedforward circuit of the DIVA model was found to be hyperfunctional, with abnormal activity and connectivity seen in the brain regions involved in higher-order processing for movement planning and execution in LD.[10,11,15–18,24,29] An

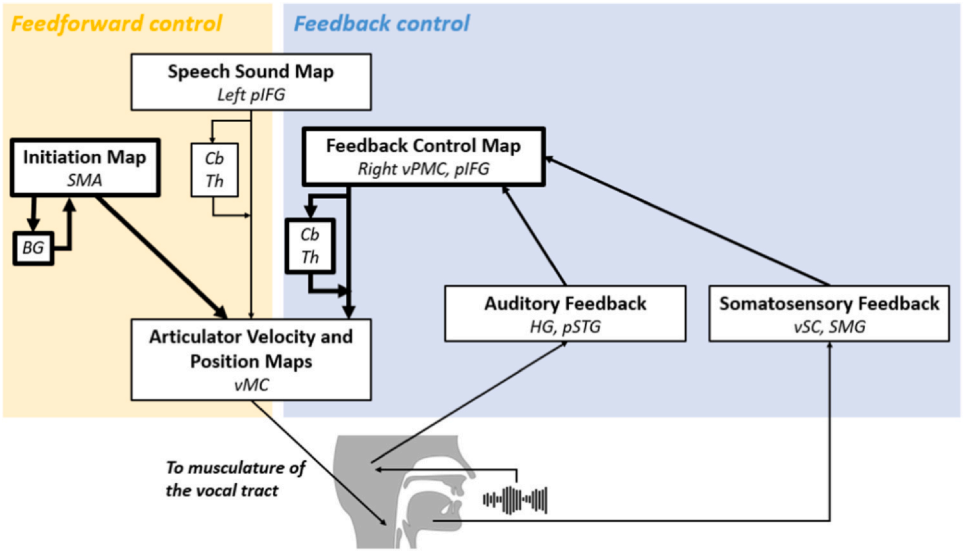

FIGURE 2. The simplified Directions Into Velocities of Articulators (DIVA) model for speech production (simplified form of Figure 1 from Tourville and Guenther[44]). BG, basal ganglia; Cb, cerebellum; HG, Hesch's gyrus; pIFG, posterior inferior frontal gyrus; pSTG, posterior superior temporal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; Th, thalamus; vMC, ventral motor cortex; vPMC, ventral premotor cortex; vSC, ventral somatosensory cortex.

increased excitatory activity and a hyperfunctional connectivity of the premotor-parietal-putaminal circuits have been repeatedly reported in LD.[10,11,17,18]

Feedback sensory network. Equally, in LD, the feedback circuit of the DIVA model has been found to be hyperfunctional with an abnormal primary somatosensory network, and an abnormal integration of sensory information.[11,15,21,23,24,27,34] Increased functional connectivity between the somatosensory cortex and the frontal lobe was found in LD.[23,24] An overactivity in the sensorimotor network was seen during voice perception[15] and at rest.[34] Kanazawa et al have shown that the left sensorimotor cortex was activated more in LD than for healthy controls for a modal voice (ie, symptomatic).[15] Yet, for a falsetto voice (ie, asymptomatic), there was no difference in its activation between LD and healthy controls.[15] Impaired sensitivity to somatosensory feedback before and during phonation has been observed.[11] Interestingly, a functional deficiency of parietal and primary somatosensory cortices has been reported for LD.[21] Put together, the hyperexcitability and the hyperfunctional connectivity may, in fact, represent a compensatory response to an actually decreased functional connectivity, or an inefficient connection between these brain regions. Temporal discrimination thresholds were found to be significantly altered in LD patients, with neural correlates of abnormal temporal discrimination being found with structural and functional changes in the middle frontal and primary somatosensory cortices.[27]

In addition, decreased functional connectivities in sensorimotor networks,[24] a reduced functional connectivity between the left putamen and the sensorimotor network,[24] and a decreased functional connectivity between the thalamus and the sensorimotor network[15] have been reported. Abnormal hypoactivity of the inferior parietal cortex, a region known to be involved with sensorimotor processing and integration prior to execution of voluntary movements, has been observed.[16] Inter-hemispheric circuit alteration involving right-to-left hyperexcitable premotor coupling has also been found.[18] An increased functional activity in the primary somatosensory cortex was seen during asymptomatic tasks in LD, for example, tactile stimulation.[34]

Auditory pathway. Hearing, and hence an auditory neural network, forms an important aspect of the speech feedback pathway as it provides direct information on the quality of the speech produced (Figure 2). Some studies have reported an increased resting-state functional connectivity of the auditory network,[34] and an increased functional connectivity between the motor cortex and the auditory network,[23] with an abnormal auditory feedback processing in LD.[11] However, Frankford et al demonstrated that the sensory processing within the auditory domain is normal in LD,[13] and Daliri et al demonstrated LD patients still produced symptomatic speech even when their auditory feedback was eliminated through masking.[33] Thus, the auditory feedback pathway may not be directly implicated in LD pathophysiology. Its hyperfunctionality may reflect a state of chronic hyperactivation simultaneously happening during speech, or a result of an increased influence from hyperactive motor/premotor areas.

Summary. Put together, current literature shows that in LD, the movement control network is hyperexcitable with hypofunctional inhibitory pathway, the higher-order movement planning neural network is hyperfunctional, the somatosensory feedback neural network is hyperfunctional,

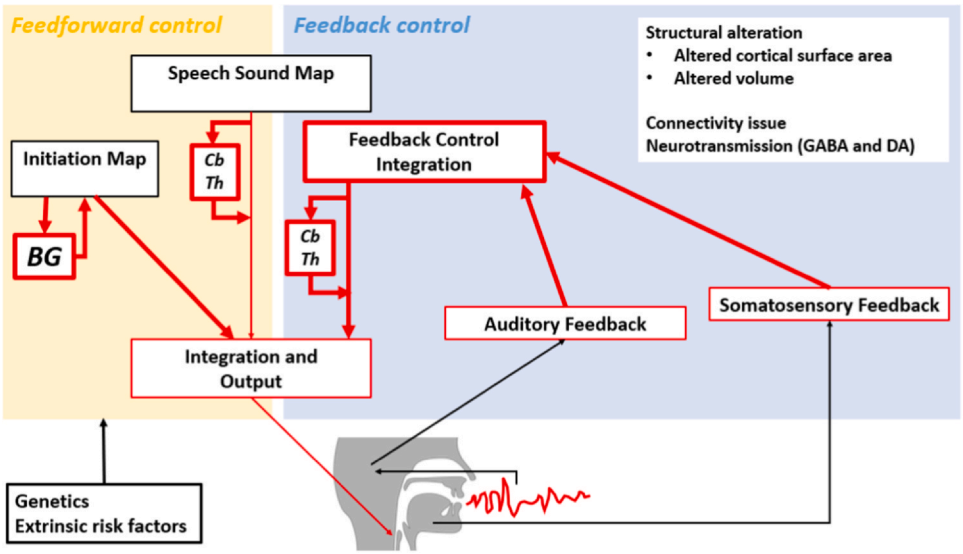

FIGURE 3. Schematic diagram of laryngeal dystonia central mechanisms. In red shows an affected neural circuit. DA, dopamine; GABA, gamma-aminobutyric acid. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and the functional connectivity within the sensorimotor networks is reduced compared to healthy controls (Figure 3).

The main limitation in interpreting all the above study findings is whether the observed brain changes reflect the primary pathophysiology of the disorder or compensatory changes developed due to the presence of LD symptoms.

Neurochemical alteration

Alteration in gamma-aminobutyric acid (GABA) and dopamine signaling have been implicated in LD. Abnormally decreased GABAergic function has been found in the inferior parietal cortex of LD. Some LD patients notice symptomatic improvement with alcohol ingestion, and although its exact mechanism is unclear, it is currently thought that GABAergic transmission is implicated.[34] Global abnormal striatal dopaminergic neurotransmission has been found during the resting state as well as symptomatic, and asymptomatic tasks.[28] This was found especially to be the case in the bilateral putamen and bilateral caudate nuclei. Abnormally increased putaminal dopamine release is observed during symptomatic speech,[45] and upregulated dopamine D1 receptors, and downregulated dopamine D2 receptors have been observed in the direct and the indirect basal ganglia pathway, respectively, in LD.[20] It is thought that this abnormal dopaminergic neurotransmission underlies the hyperexcitable thalamo-motor-cortical circuit in LD.[20]

The peripheral system – the larynx in LD

Chhetri et al examined the histology of the adductor branch of the recurrent laryngeal nerve and the lateral cricoarytenoid muscles in patients with LD.[32] They found no major differences between LD and the controls for the histology of the peripheral laryngeal nerve. Similarly, no major differences in the histology of the laryngeal muscle were found apart from the type 2 muscle dominance seen in the majority of LD patients. This most likely reflects changes in the neuromuscular activation pattern. Laryngeal hypersensitivity has been demonstrated in LD.[12] It is unclear whether this represents a potential cause for LD, or simply a reflection of an abnormal somatosensory feedback.

Etiology

It is unclear what causes LD. The current hypothesis is that LD is multifactorial in its etiology, and that repeated peripheral somatosensory stressors (ie, extrinsic risk factors) influence the internal neural representations and the sensorimotor integration of speech-related movements.[16] This is thought to subsequently trigger the widespread alteration in the individuals' neural circuit in a susceptible individual.[16] The polygenic risk analysis showed many genetic variants close to genes related to synaptic transmission and neural development.[19] LD genotypes (ie, familial vs sporadic) were associated with structural changes in higher-order extra-Sylvian regions and their connecting pathways.[22] Recurrent upper respiratory tract infections, gastroesophageal reflux disease, and neck injury have been identified as extrinsic risk factors for LD.[16]

A positive familial history of dystonia is reported in about 12% of LD patients, suggesting an element of genetic risk factors.[35] Furthermore, laryngeal involvement has been observed in patients with generalized or segmental dystonias.[35] More specifically, mutations in the DYT6 gene *THAP1* have been found to be causal for up to 25% of familial cases of generalized dystonia with prominent laryngeal involvement exhibiting LD symptoms.[46] However, on screening LD patients without other movement disorders, the prevalence of *THAP1* mutations was found to be very infrequent, with < 1%.[47–50] Only one case of mutation in one of the known

dystonia genes, *GNAL* (DYT25), has been found to cause an isolated ADLD in the absence of familial history of dystonia or other movement disorders.[35] At least 13 genes or chromosomal loci have been implicated in association with certain forms of dystonias, but in general this has yet to be proven in most cases of LD.[46,48]

CONCLUSION

Studies to date suggest that LD is a central neurological disorder that primarily involves multiregional neural network connectivity alterations. This is somewhat unsurprising considering that the speech production is a complex process requiring conceptualization, formulation, and articulation of the message one wishes to convey into grammatically correct linguistic representations, thereby requiring a complex involvement of multiple brain regions. Affected neural circuits in LD not only involve the motor control circuit, but also the feedforward, and the feedback circuits of the normal speech production neural network, involving higher-order planning, somatosensory perception and integration regions of the brain (Figure 3). There is a separate simpler neural network for the innate voice production representing emotive voicing such as a cry or a laughter involving the cingulate cortex and the peri-aqueductal gray. This network appears to be spared in patients with LD which would explain the task-specific nature of LD symptoms with innate vocalizations such as laughing not being typically affected.

Potential future direction

LD is a severely disabling and debilitating condition. There is no cure currently, and all the currently available management options have limitations. Part of their limitation comes from the fact that all of them target the peripheral system when the problem ultimately lies centrally.

Despite much still remaining unknown with regard to the exact mechanisms and the underlying pathophysiology of LD, our current understanding suggests that neuromodulation could be considered to target the affected neural circuit to restore the normal speech production. Deep brain stimulation (DBS) offers a form of neuromodulation, and it has shown success in treating movement disorders and other forms of dystonia.

Case reports exist in the literature reporting unexpected benefits in patients' voice symptoms in patients who received DBS primarily for their treatment-refractory essential tremor who also happened to have LD.[51–54] Recently, a phase I prospective randomized double-blind crossover trial was conducted primarily assessing the safety of DBS in LD patients.[55] The trial, whilst confirming that DBS can be performed safely, showed good clinical effect on LD with unilateral left thalamic stimulation in six right-handed patients with ADLD.[55]

The preliminary data of trialing DBS for LD appears promising, with the target for the DBS for LD appearing to be the ventralis intermedius nucleus (Vim) of the thalamus.[51–57] However, with fewer than 15 patients in the published literature,[51–57] reproducibility needs to be checked, and many questions remain. Furthermore, the mechanism of how DBS has improved symptoms in LD patients are currently unknown. Therefore, studying the effect of DBS on LD neural circuits should help elucidate the central mechanisms and the pathophysiology of LD further as well. We propose that it would be worth exploring and evaluating neuromodulation as a potential therapeutic option for LD moving forward.

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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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None used.

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