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REVIEW ARTICLE

Does the network model fits neurophysiological abnormalities in blepharospasm?

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Abstract
Several neurophysiological abnormalities have been described in blepharospasm, including loss of inhibition in sensorimotor pathways at cortical and brainstem level and abnormalities of sensory processing. These changes have traditionally been linked to a basal ganglia dysfunction. However, this interpretation has recently been questioned and alternative pathophysiological model positing that dystonia is a network disorder has been proposed. On the basis of available information, we can speculate that loss of inhibition at cortical and brainstem level and abnormalities of sensory processing in blepharospasm probably reflect the functional derangement of a network involving frontal and parietal cortical areas, basal ganglia, thalamus, and, possibly, the cerebellum.

Keywords Blepharospasm · Neurophysiology · Neuroimaging · Physiopathology

Introduction

Idiopathic blepharospasm (BSP) is an adult-onset focal dystonia that manifests more frequently in women and has a peak age at onset in the fifth to sixth decade [1]. BSP is typically characterized by orbicularis oculi muscle spasms that are usually bilateral, synchronous, and symmetric [2, 3]. Dystonic spasms may be phenomenologically heterogeneous, with either brief or prolonged spasms and narrowing or closure of the eyelids [4]. In addition to spasms, BSP patients may manifest a spectrum of additional signs/symptoms, including sensory symptoms in the eyes [5], increased spontaneous blink rate [6], sensory tricks (stretching, massaging, or touching the eyebrow, the eyelid, or the forehead) transiently improving eyelid spasm [7], apraxia of eyelid opening [8], and dystonia and tremor in other body parts [9]. BSP patients may also have psychiatric disturbances, most frequently depression and obsessive compulsive disorder, and mild cognitive disturbances affecting executive function, with impairment in working memory, processing speed, visual motor ability, and short-term memory [10, 11].

Conventional imaging studies and autopsy findings failed to identify structural brain lesions in idiopathic BSP. Nevertheless, a pattern of functional abnormalities has been established by neurophysiological investigations, including loss of inhibition at different levels of the central nervous system, maladaptive plasticity, and abnormal sensory processing. These abnormalities were traditionally interpreted as the consequence of a primary basal ganglia disturbance. Recent evidence, however, points to anatomical and functional involvement of several brain regions besides the basal ganglia. A summary of individual case reports addressing secondary cranial dystonia and new neuroimaging tools allowing measurement and examination of functional interactions and connectivity among brain regions provided support to the emerging hypothesis of BSP as a network disorder.

The aim of this paper was to review available evidence supporting BSP as a network disorder and to understand whether the proposed network model fits the well-known neurophysiological abnormalities described in BSP.

The network model

Evidence from acquired BSP

Acquired BSP has been associated with structural lesions in several brain regions including not only the basal ganglia but

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also the thalamus, the brainstem, the cerebellum, and the cortex [12–52] (Table 1). Brain lesions can be focal or more widespread and include ischemia or stroke, tumors, demyelinating lesions, and other pathologies. The onset of BSP can be temporally related to the occurrence of the presumed causative lesion or be delayed by months or even years [29–31]. Symptoms can be persistent needing chronic treatment with botulinum toxin or remit spontaneously over a variable period of time or after the treatment of the underlying disease process [15, 16, 25, 27]. Acquired BSP may present as isolated focal dystonia, be part of a segmental or multifocal dystonia, or be associated with other neurological symptoms [12–52].

Evidence from non-conventional magnetic resonance imaging studies

Non-conventional imaging investigations performed in BSP patients include voxel-based morphometry (VBM) studies, diffusion tensor imaging (DTI) studies, and functional magnetic resonance imaging (fMRI) studies.

VBM studies performed in patients with idiopathic BSP showed gray matter changes in the caudate/putamen, thalamus, cerebellum, and cortical/subcortical regions highly relevant to sensory processing and cognitive modulation of motor behavior like the primary sensorimotor cortex and the cingulate gyrus [53–58]. Although not tested in all studies, the abnormal changes found in some areas did not correlate with clinical variables such as disease duration or severity (Table 2).

DTI is a technique that assesses microstructural changes of the nervous tissue through the analysis of water diffusion. Among DTI indices, fractional anisotropy (FA) quantifies directionality of water diffusivity, thus providing a measure of axonal integrity, while mean diffusivity is a measure of cellular and membrane density [59, 60]. No DTI change was observed in three studies comparing 5 to 16 patients with healthy controls [58, 61, 62]. However, a more recent study on 31 BSP patients showed decrease of FA in the white matter of the left anterior lobe of the cerebellum and in the right precuneus of the parietal lobe, and increased diffusivity in the right lentiform nucleus, thalamus, and insula. FA abnormalities significantly correlated with BSP severity and duration. By contrast, increased diffusivity changes lacked any correlation with severity/duration of BSP [63].

Functional magnetic resonance imaging (fMRI) is a tool that studies brain function by exploiting the blood oxygen level-dependent (BOLD) signal changes, i.e., the signal changes due to the increased levels of deoxy-hemoglobin following the activation of brain areas. Signal can be measured while performing specific tasks (task-dependent fMRI) or in the absence of a task or stimulus (resting state-fMRI (rs-fMRI)) [64, 65].

In BSP, task-dependent fMRI studies investigated patients during spontaneous or voluntary blinking [66] and spontaneous spasm [67] with evidence of abnormal activation in subcortical regions and in various cortical areas, including visual and motor cortex. When a task not related to dystonia was applied, abnormalities were found in the basal ganglia and thalamus [68] (Table 3).

In rs-fMRI, different analytic methodologies can be applied, including the amplitude of low frequency fluctuations (ALFF), the regional homogeneity analysis (ReHo), model-free methods like the seed-based analysis and the independent component analysis (ICA), the graph theoretical analysis, and the voxel-mirrored homotopic connectivity [65, 69, 70] (Table 4).

ALFF and ReHo methodologies explore the function of and connectivity within specific pre-established brain regions. In BSP, abnormal values of ALFF and ReHo were found in various cortical and subcortical regions consistent with dysfunctions in multiple neural networks [71, 72, 76, 77]. In the studies by Yang [72] and Ni [76], some of these changes correlated with BSP severity, a finding not confirmed in the later investigation of Jiang [77].

Seed-based analysis and ICA assess functional connectivity (FC) of spatially distinct brain areas through the identification of their synchronous BOLD fluctuations at rest. The analysis of FC identified different resting-state networks in the normal brain, including the default mode network (posterior cingulate cortex, medial prefrontal cortex, and lateral parietal cortex), the salience network (dorsal anterior cingulate cortex, bilateral insula, and pre-supplementary motor area), the basal ganglia network, sensorimotor network (within and between left and right sensory and motor cortices), the dorsal attentional network, and the frontoparietal network (lateral prefrontal cortex and inferior parietal lobule) [65, 69]. In BSP patients, seed-based analysis and ICA showed dysfunctions within the sensory motor network, the salience network, the default mode network, and the right frontoparietal network [71, 73–75].

The graph theoretical analysis is an analytic methodology that measures brain functional organization on a large-scale level and allows examination of the whole brain connectivity patterns. [65]. By this approach, abnormal network architecture at large-scale level was found in BSP patients along with the detection of sensorimotor and frontoparietal networks' FC alteration [73].

Finally, the voxel-mirrored homotopic connectivity, a method of rs-fMRI designed to compare the interhemispheric rs-fMRI FC revealed enhanced homotopic coordination in the brain regions associated with sensory integration networks and default-mode network [70].

Overview of neuroimaging studies

Reports on acquired BSP have limitations. First, the structural abnormalities associated with BSP lack specificity because it

Table 1 Reports on acquired blepharospasm

study	No. of patients	Lesion site	Lesion type	Dystonia distribution
Cavalheiro et al. [12]	1	Left thalamus	Angiocentric glioma	BSP
Singer et al. [13]	1	Right midbrain	Cyst	Right BSP
Persing et al. [14]	1	Cerebellopontine angle	Meningioma	BSP and OMD
Yin Foo Lee et al. [15]	1	Left lateral ventricle	Ganglioglioma	Left BSP
Lambrecq et al. [16]	1	Right lateral ventricle + HCN	Ependymoma	BSP and CD
Leenders et al. [17]	1	Left Rostral brainstem--thalamus	Calcified mass	Left BSP and right HD
Aramideh et al. [18]	1	Left dorsomedial lower pons	Metastatic lesion	BSP
Jancovick and Patel [19]	2	Brainstem	SM	BSP
	4	Rostral brainstem	Vascular (infarction)	BSP and OMD (2)
Awada [20]	1	Bilat thalamus	Vascular (infarction)	BSP
Powers [21]	1	Left thalamus	Vascular (infarction)	BSP
Keane and Young [22]	1	Bilat putamen and caudate nucleus	Hypoxic encephalopathy	BSP and limb dystonia
Palakurthy and Iyer [23]	1	Bilat basal ganglia right perysilvian area	Hypoxic encephalopathy	BSP
Kirton and Riopelle [24]	1	Bilat basal ganglia	Hypoxic encephalopathy	BSP,OMD and CD
Velnar et al. [25]	1	Right subdural space	Hematoma	BSP
Gilbert et al. [26]	1	Left pons	Capillary telangiectasia	BSP
Grandas et al. [27]	1	Left striatum	Vascular (infarction)	Reflex BSP
Larumbe et al. [28]	1	Bilateral basal ganglia	Hypoxic encephalopathy	Reflex BSP and LD
Kulisevsky et al. [29]	1	Left Thalamus-midbra-in	Vascular (infarction)	Left BSP
Miranda and Millar [30]	1	Bilat paramedian thalamic nuclei	Vascular infarction	BSP
Lal et al. [31]	1	Thalamus	Vascular (hemorrhage)	BSP
Algoed et al. [32]	1	Right frontal cortex	Vascular (infarction)	AEO
Johnston et al. [33]	2	Right middle cerebral artery	Vascular (infarction)	AEO
O'Rourke et al. [34]	1	Bilat cerebellar hemispheres and right occipital cortex	Vascular (infarction)	BSP and OMD
Gibb et al. [35]	1	Dorsal pons	Angioma	BSP
Lang and Sharpe [36]	1		CH	BSP
Wali GM [37]	1	Left frontal cortex	Vascular (VT and infarction)	BSP
Lee and Lee [38]	1	Right subcortical frontal	Vascular (infarction)	AEO
Kim et al. [39]	1	Bilat frontal and right temporal cortex	Traumatic injury	AEO
Jacob and Chand [40]	1	Bilateral parietal cortex	Vascular (infarction)	BSP and OMD
Jankovic [41]	1	Bilateral thalamus (VIM)	Surgery	BSP
Sandyk and Gillman [42]	1		CH	BSP
Day et al. [43]	1	Pons	Vascular (infarction)	BSP
Herraiz et al. [44]	1	Bilat pallidum	Calcifications	BSP and OMD
Blin et al. [45]	1	Bilat basal ganglia	Calcifications	BSP

Table 1 (continued)

study	No. of patients	Lesion site	Lesion type	Dystonia distribution
Verghese et al. [46]	1	Putamen	Hemorrhage	BSP
Jimenez-Jimenez et al. [47]	1	Left thalamus and others	Neurocysticercosis	BSP
Choe and Gausas [48]	1	Not identified	Paraneoplastic encephalitis	BSP
Armangue et al. [49]	1	Right frontobasal cortex	Autoimmune encephalitis	BSP
Nociti et al. [50]	1	Left parietal cortex and periventricular	Multiple sclerosis	BSP
	1	Left parietal cortex		
Kostić et al. [51]	1	Left thalamus, frontoparietal cortex	Tumor	BSP
	1	Left thalamus and upper brainstem	Trauma	
Khooshnoodi et al. [52]	18	5 thalamus, 4 cerebellum, 5 brainstem, 3 basal ganglia, 1 parietal cortex	15 vascular (infarction), 2 vascular malformation, 1 cyst	BSP and OMD (2) or CD (2) or truncal dystonia (1)

BSP, blepharospasm; *OMD*, oromandibular dystonia; *AEO*, apraxia of eyelid opening; *CD*, cervical dystonia; *HD*, hemidystonia; *LD*, limb dystonia; *CH*, communicating hydrocephalus; *HCN*, head of caudate nucleus

may also be found in non-dystonic people; second, we cannot exclude a physiopathological role of microstructural defects or functional disturbances arising from apparently normal brain regions; finally, a temporal relationship between lesion development and emergence of symptoms is not always evident. Therefore, it is sometimes difficult to rule out the possibility of an idiopathic BSP with coincidental lesions [52].

Nevertheless, it is of interest that the microstructural alterations found in idiopathic BSP on DTI and VBM investigations largely affect brain regions associated with acquired BSP. The possibility that a structural lesion within a neural network induces functional changes leading to the appearance of dystonic symptoms still remains a plausible physiopathological mechanism. The consistency of the findings between idiopathic and acquired BSP strongly supports the hypothesis that many brain regions are involved in the physiopathology of BSP. Supporting this view, information from functional imaging studies indicated that BSP patients may have both abnormal intraregional brain activities and interregional dysfunctional connectivities and supported derangements in communication among frontal and parietal cortical areas, the basal ganglia, the thalamus, and the cerebellum.

Another issue to be considered is the lack of correlation between severity/duration of BSP and the abnormalities found in some regions of the brain. Although the correlation between clinical variables and imaging findings was not tested systematically, this observation would suggest that the abnormalities found in multiple brain regions not limited to the basal ganglia may be trait alterations in BSP patients.

In conclusion, information provided by imaging studies supports the hypothesis that BSP may arise from a disordered brain network [78].

Neurophysiological abnormalities

Several neurophysiological abnormalities affecting sensorimotor pathways at different levels of the central nervous system have been described in BSP (Table 5).

The earliest detected abnormality was the decreased inhibition of the R2 response of the blink reflex by paired electrical stimulation of the supraorbital nerve [79–81, 84, 85] that relies on brainstem oligosynaptic circuits [87]. As botulinum toxin treatment leaves the blink reflex recovery cycle unchanged but significantly improves OO muscle spasms, [82, 83] the blink reflex abnormalities in BSP are likely to reflect a pathophysiological mechanism rather than dystonic activity in the OO muscle. The enhanced excitability of interneurons in the brainstem extends outside the blink reflex to include an enhanced recovery curve of the silent period 2 of the masseter inhibitory reflex [85, 92], and the trigemino-facial circuits to include an abnormal auditory startle reaction [88], an abnormal trigemino-sternocleidomastoid reflex, [84] and an abnormal somatosensory pre-pulse modulation of the blink reflex

Table 2 Morphometric studies on blepharospasm

Study	No. of patients/controls	Analytic method	Brain regions with abnormalities	Correlation with clinical variables
Black et al. [54]	5/13	Stereologic method Manual tracing	Enlarged putaminal volume bilaterally	Not tested
Etgen et al. [55]	16/16	VBM	GMI in the putamen bilaterally GMD in left inferior parietal lobe	BoT treatment duration with GMD
Obermann et al. [56]	11/14	VBM	GMI in the caudate head and cerebellum GMD in putamen and thalamus bilaterally	Not tested
Martino et al. [57]	25/24	VBM	GMI in the right middle frontal gyrus GMD in left postcentral and superior temporal gyrus	No correlation
Suzuki et al. [58]	32/48	VBM	GMI density in primary sensory-motor cortex bilaterally and left cingulate gyrus	Disease duration and severity
Horovitz et al. [59]	14/14	VBM	GMI in left lateral middle temporal gyrus, right postcentral gyrus, and bilateral precuneus GMD in right orbitofrontal cortex, left facial portion of the precentral cortex, left lateral inferior frontal gyrus, right occipital cortex, and right anterior cingulate gyrus Decreased left CBT volume and connectivity	Disease duration with right occipital cortex GMD

VBM, voxel-based morphometry; *GMI*, gray matter increase; *GMD*, gray matter decrease; *BoT*, botulinum toxin; *CBT*, corticobulbar tract

by peripheral stimuli [81, 86]. Brainstem interneuron hyperexcitability secondary to a suprasegmental dysfunction may explain the enhancement of the recovery curves of the R2 response of the blink reflex as well as the abnormal changes observed in other brainstem reflex responses [87, 88, 92]. The basal ganglia would influence the blink reflex circuit through two main routes. First, basal ganglia projections via thalamus to cortex might change the activity in descending corticobrainstem pathways controlling blink reflex excitability. Alternatively, there could be a route via projections to either pedunculopontine nucleus (PPN), or most likely the superior colliculus (SC); in turn, outputs from the SC could project to the raphe magnus and hence to interneurons in the trigeminal sensory nucleus [93–95].

Transcranial magnetic stimulation (TMS) showed abnormal excitability of the primary motor cortex (M1) in BSP, as demonstrated by reduced short-interval intracortical inhibition (SICI) in the hand muscles and by reduced duration of the cortical silent period in the cranial muscles of such patients [89, 90]. Using paired associative stimulation, a technique that investigates cortical plasticity, Quartarone and colleagues [91] observed that the plasticity of cortical motor areas is increased in the hand muscles of patients with BSP. Although the aforementioned TMS were traditionally attributed to a basal ganglia dysfunction, deep brain stimulation (DBS) studies performed in patients with a variety of movement disorders have shown that stimulation of the subthalamic nucleus (STN) restores SICI in patients with Parkinson's disease (PD) [96]; stimulation of the ventralis intermedius nucleus of thalamus (VIM) may enhance M1 excitability to TMS in patients with essential tremor [97]; stimulation of the STN may improve silent period changes in patients with PD [98]; and GPI stimulation may modulate M1 excitability in patients with dystonia [99]. Finally, electrical or magnetic stimulation of the cerebellum can modulate excitatory and inhibitory M1 circuits [100–103].

Earlier studies tested the sensory system in dystonic patients by assessing somatosensory-evoked potentials (SEPs) that is electrical potentials generated in sensory pathways at peripheral, spinal, subcortical, and cortical levels of the nervous system [104]. SEPs may be used to assess sensory integration in the time domain by applying the paired-pulse

Table 3 Task-dependent fMRI studies on blepharospasm

Study	No. of patients/ controls	Task explored	Statistical analysis	Brain regions with abnormalities
Baker et al. [66]	5/5	Spontaneous blinking and voluntary blinking	Spontaneous blinking versus eye closed	Abnormal increased activation in primary visual cortex, area prostriata, and occipital visual association areas
			Voluntary blinking versus eye closed	Abnormal increased activation in primary visual cortex, central thalamus, posterior putamen, and supplementary and primary motor cortex
			Spontaneous blinking versus voluntary blinking	Abnormal increased activation in primary visual cortex, primary motor cortex, cerebellar paravermian area, central thalamus, and anterior cingulate gyrus
Schmidt et al. [67]	6/4	Eyelid spasm in patients	Eyelid spasm intervals versus no spasm intervals	Unilateral or bilateral activation in the putamen not present during voluntary blinking in controls
		Voluntary blinking in controls	Voluntary blinking versus spontaneous blinking	
Obermann et al. [68]	11/14	Grip force forearm contraction	Grip force forearm contraction versus rest condition	Increased activation in the thalamus, caudate nucleus, putamen and lateral globus pallidus

paradigm; in normal subjects, a preceding (conditioning) stimulus induces suppression of SEP amplitude evoked by the following (test) stimulus [105]. In patients with dystonia, this inhibitory effect is impaired [106–108]. Supporting this view, several studies on patients with various forms of focal dystonia including BSP have reported increased somatosensory temporal discrimination thresholds (STDT), the shortest time interval needed to discriminate two consecutively applied tactile stimuli [109–112]. Increased STDT values are present in body parts that may be affected or unaffected by dystonia and do not improve after botulinum toxin [112, 113]. Because altered STDT has been observed in BSP and in other focal dystonias, does not correlate with clinical severity, and has been also observed in unaffected first-degree relatives of patients, the abnormal temporal processing of sensory information is likely to enhance the permissive environment that predisposes patients to the development of dystonia [106, 114–118]. Supporting this view, STDT abnormalities have been reported in patients with increased blinking as prodromal phase of BSP [119, 120].GABA-mediated mechanisms of inhibition in the somatosensory cortex S1 as well as a dopamine-mediated subcortical network, involving the basal ganglia, thalamus, and superior colliculus, probably contribute to the mechanisms underlying STDT [111, 121, 122].

Overview of neurophysiological studies

Neurophysiological investigations in idiopathic BSP found abnormal functional changes that were consistent with loss of inhibition at different levels of the nervous system. Some of these studies may have been limited by the small size of the study sample and the lack of attention to the possible correlations between neurophysiological changes and clinical variables. Furthermore, several neurophysiological abnormalities could also be found in movement disorders other than dystonia [123–126]. Nevertheless, loss of inhibition is a well-defined functional trait of dystonia [127] that could also be detected in unaffected body regions of dystonic patients or in non-manifesting DYT1 mutation carriers, thus raising the possibility that these changes are an endophenotype of dystonia [128–130].

Discussion

Although BSP is traditionally considered a basal ganglia disorder, accumulating evidence from structural and functional investigations points to the anatomical and functional involvement of several brain regions. This has led to the hypothesis that BSP may arise from a disordered brain network [78]. Considering the remarkable clinical heterogeneity of motor and non-motor manifestations characterizing BSP, a related heterogeneity of the underlying anatomical substrates would not be surprising.

Available information makes it highly likely that the primary defect in BSP lies somewhere in a network connecting the basal ganglia, thalamus, frontal and parietal cortices, cerebellum, and brainstem [78]. Likewise, similar findings from clinical reports and non-conventional imaging studies also support a derangement of brain networks in other focal

Table 4 Resting-state fMRI studies on blepharospasm

Study	No. of patients/ controls	Analytic method	Brain regions with abnormalities	Correlation with clinical variables
Zhou et al. [71]	9/9	ALFF analysis	Increased ALFF: insula lobe, left putamen, pallidum, medial prefrontal cortex. Decreased ALFF: cerebellum, thalami, bilateral somatosensory regions, medial and posterior cingulate cortex	Not tested
Yang et al. [72]	18/18	ALFF analysis	Increased ALFF: left orbitofrontal areas Decreased ALFF: left thalamus	Negative correlation between decreased left thalamus ALFF and JRS score and positive correlation between increased left orbital areas ALFF and disease duration
Battistella et al. [73]	9/15	ICA	Decreased FC: bilateral primary sensorimotor cortex, supplementary motor area, left superior temporal gyrus, left prefrontal cortex, bilateral middle temporal gyrus Increased FC: left insular cortex	No correlation with disease duration and severity (BFMDRS)
		Graft theoretical analysis	Abnormal large-scale neural network	
Jochim et al. [74]	13/13	Seed analysis	Reduced FC between: caudate and primary sensorimotor, somatosensory association and visual cortices; putamen and parietal association cortex; cerebellum and somatosensory and visual associative areas; cingulate cortex and the primary sensorimotor/premotor and parietal association cortex; premotor areas and the primary somatosensory cortices; postcentral gyrus and temporoparietal, secondary somatosensory, cingular, and cerebellar regions.	Negative correlation between FC reduction cerebellum-visual cortex and BDS score
Huang et al. [75]	25/25	ICA	Decreased FC in bilat sensorimotor cortex, SMA, right premotor cortex, bilat precuneus, left superior parietal cortex, right middle and inferior frontal gyrus and right dorsolateral prefrontal cortex. Increased FC; left superior frontal gyrus, middle frontal gyrus.	Negative correlation between reduced FC in right superior frontal gyrus and disease duration; higher FC in the premotor area in sensory trick + patients
Ni et al. [76]	26/26	fALFF analysis ReHo analysis FC analysis	Increased fALFF and ReHo in the right caudate head Increased FC between right caudate head and left striatum and right supplementary motor area	Positive correlation of fALFF and ReHo values in right caudate head and FC right caudate head -left striatum with JRS sum score
Wei et al. [70]	26/24	VMHC	Enhanced homotopic coordination in inferior temporal gyrus, inferior frontal gyrus, posterior cingulated cortex, postcentral gyrus	No correlation with symptom severity (JRS), disease duration, SAS and SDS scores
Jiang et al. [77]	24/24	ReHo analysis	Decreased ReHo: left superior temporal pole/left insula, left calcarine cortex, bilateral superior medial frontal gyrus. Increased ReHo: bilateral supplementary motor area	No correlation with symptom severity (JRS), disease duration, SAS and SDS scores

ALFF, amplitude of low-frequency fluctuations; *fALFF*, fractional ALFF; *ReHo*, regional homogeneity analysis; *ICA*, independent component analysis; *FC*, functional connectivity; *VMHC*, voxel-mirrored homotopic connectivity; *JRS*, Jankovic Rating Scale; *SAS*, self-rating anxiety scale; *SDS*, self-rating depression scale; *BDS*, blepharospasm disability scale; *BFMDRS*, Burke–Fahn–Marsden Dystonia Rating Scale

dystonias like cervical dystonia and upper limb dystonia [78, 131]. If the network model can also explain the well-established neurophysiological abnormalities that are present in BSP and were previously attributed to a basal ganglia disturbance, then this would enhance the likelihood of the network model itself.

Table 5 Neurophysiological studies on blepharospasm

Neurophysiological protocol	Study	No. of patients/controls	Abnormality
Blink reflex recovery cycle	Berardelli et al. [79]	16/10	Enhanced R2 recovery
	Tolosa et al. [80]	14/15	Enhanced R2 recovery
	Baione V et al. [81]	24/24	Enhanced R2 recovery
	Conte et al. [82]	23	Unchanged R2 recovery after BoT-T
	Valls-Sole et al. [83]	14/17	Enhanced R2 recovery, unchanged after BoT-T
	Carella et al. [84]	13/10	Enhanced R2 recovery
	Pauletti et al. [85]	21/13	Enhanced R2 recovery
Pre-pulse inhibition of the blink reflex	Gomez-Wong et al. [86]	17/11	Reduced inhibition of R2
	Baione et al. [81]	24/24	Reduced inhibition of R2
Masseter inhibitory reflex recovery cycle	Cruccu et al. [87]	5/50	Enhanced SP2 recovery cycle
	Pauletti et al. [85]	21/13	Enhanced SP2 recovery cycle
Trigemino-sternocleidomastoid reflex	Carella et al. [84]	13/10	Reduced suppression of EMG activity
Auditory startle reaction	Muller et al. [88]	13/13	Enhanced reflex EMG activity
Paired-pulse TMS paradigm	Sommer et al. [89]	16/23	Reduced intracortical inhibition
Cortical silent period	Currà et al. [90]	23/10	Facial muscles silent period shortening
Paired associative stimulation	Quartarone et al. [91]	8/10	Excessive motor cortex plasticity

BoT-T, botulinum toxin treatment

In patients with BSP, neurophysiological studies highlighted loss of inhibition at cortical and sublevels (cortical and subcortical) of the central nervous system. Theoretically, changes of excitability in restricted brain areas like cortical M1, brainstem, and cortical S1 may depend on intrinsic disorders in these areas and/or may reflect abnormal influences from distant brain structures. The latter hypothesis is supported by several evidences: DBS studies have shown that stimulation of the STN, GPi, or VIM modulates M1 excitability [96–99]; excitatory and inhibitory M1 circuits are also affected by electrical or magnetic stimulation of the cerebellum [100–103]; and GPi stimulation increases R2 inhibition of the blink reflex recovery curve in dystonic patients [132]. Therefore, changes in cortical/brainstem excitability may reflect dysfunctions possibly involving the basal ganglia-thalamo-cortical projections and the cerebello-thalamo-cortical projections. Likewise, cortical S1 abnormalities underlying STDT disturbances may develop secondarily to abnormal connectivity from subcortical projections from the basal ganglia, thalamus, and superior colliculus rather than occurring independently.

If impaired inhibition at cortical/brainstem levels and tactile information processing abnormalities can be interpreted as dysfunctional connectivity between subcortical networks and M1/S1 cortices, then neurophysiological abnormalities carried by BSP patients would be coherent with the pathophysiological model positing that BSP arise from a disordered network connecting the basal ganglia, thalamus, frontal and parietal cortical areas, cerebellum, and brainstem. In this network organization, the thalamus would be a central dysfunctional hub because it not only gates bottom-up and top-down streams of sensory information directed to and from the cortex but also integrates sensory inputs of different modalities with output from the basal ganglia and cerebellum [133]. The cerebellum might be considered an additional dysfunctional hub in the network model of dystonia, as suggested for cervical dystonia and focal hand dystonia by dysfunction of cerebello-thalamo-cortical circuits [134–136] and impaired cerebellum-dependent associative learning explored by the classical eyeblink conditioning paradigm (EBCC), a Pavlovian learning protocol integrated at the level of Purkinje cells and deep cerebellar nuclei [137–139]. However, there is no neurophysiological evidence as yet of cerebellar involvement in idiopathic BSP. Future studies designed to assess the EBCC and the functional interactions between cerebellum and M1 in BSP patients may clarify whether different forms of focal dystonia share the same dysfunctional circuits.

In conclusion, evidence from structural and functional investigations supports the hypothesis that BSP could arise from a disordered brain network. This model seems also to fit the neurophysiological abnormalities so far reported in idiopathic BSP. However, several questions still remain open. Further studies are needed to better understand which is the core of the dysfunctional network and which are sites that can be permissive; which abnormalities play a causative role and which are compensatory phenomena; which factors may cause BSP to fully clinically express; how structural and functional abnormalities correlate with clinical symptoms and disease evolution; and whether the spectrum of non-motor symptoms characterizing BSP is in some way related to the abnormal network of brain structures thought to contribute to the condition.

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All the authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval None

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