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| 14. ABSTRACT The overall goal of the project was to develop an animal model of the focal dystonia benign essential blepharospasm. Consistent with the widely held view that dystonia results from an interaction between a predisposing condition and an environmental trigger, we proposed to use 7 Hz deep brain stimulation of the basal ganglia as the predisposing condition and dry eye as an environmental trigger. Based on experiments during the 1 st year of the grant, our publication, Evinger, J. Neuro-Ophthalmol. 35:374-379, 2015 demonstrated the feasibility of this approach. In addition, we began important control experiments and preliminary recordings from the superior colliculus. | | | | | |
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1. Introduction

The focal dystonia benign essential blepharospasm (BEB), arises from the convergence of a predisposing condition and an environmental trigger (Hallett et al., 2008). The overall goal of our project was to develop an animal model of BEB based on the hypothesis that hypersynchronized, 7 Hz neuronal oscillations of the basal ganglia created the predisposing condition and that eye irritation from dry eye was the environmental trigger. The basis for our hypothesis that hypersynchronized basal ganglia activity creates a predisposing condition is our demonstration that hypersynchronized oscillations in the basal ganglia produced by 7 Hz deep brain stimulation of the subthalamic nucleus (**STN DBS**) exaggerated neural plasticity in normal rats (Kaminer et al., 2014). Knowing that neural plasticity enables the brain to modify blinking to compensate for dry eye (Evinger et al., 2002; Schicatano et al., 2002), we predicted that combining 7 Hz DBS and dry eye would exaggerate neural plasticity and force the normally compensatory adaptive processes in response to dry eye to transform into the characteristics of BEB, spasms of lid closure, excessive blinking, and trigeminal hyperexcitability. We proposed two Specific Aims to test our hypothesis. The first Specific Aim was to demonstrate that synchronized theta oscillations in the basal ganglia exaggerate plasticity in the cerebellum and the excitability of trigeminal blink circuits as occurs in BEB patients. The Major Tasks to accomplish Specific Aim 1 were: 1) to investigate effects of synchronized basal ganglia oscillations on activity of the deep cerebellar nucleus neurons; and 2) to investigate the effects of synchronized basal ganglia oscillations on activity of the superior colliculus neurons. The second Specific Aim was to demonstrate that synchronized theta (7 Hz) oscillations established in the basal ganglia are sufficient to predispose mammals to develop BEB. The Major tasks to accomplish Specific Aim 2 were: 1) to determine whether combining synchronized basal ganglia theta oscillations with corneal irritation is sufficient to develop spasms of lid closure and other characteristics of the focal dystonia BEB; and 2) to perform control experiments to determine that theta frequency is critical in enabling the development of spasms of lid closure. We completed Major Task 1 of Specific Aim 2 and acquired significant preliminary data for Major Task 2 of Specific Aim 2 in the first year of the award.

2. Keywords

Dystonia, benign essential blepharospasm, dry eye, motor plasticity, basal ganglia, deep brain stimulation

3. Accomplishments

Major goals of the project

The overarching goal of the investigations proposed in this grant was to test our hypothesis that in response to dry eye, the hypersynchronized theta oscillations in the basal ganglia exaggerated neural plasticity of predisposed individuals to develop the focal dystonia benign essential blepharospasm (BEB). We proposed that in the presence of the predisposing condition the normally compensatory adaptive processes engendered by dry eye transformed into the characteristic spasms of lid closure, excessive blinking, and trigeminal hyperexcitability characteristic of BEB. To test this hypothesis, the 1st Specific Aim of the project was to demonstrate that synchronized theta oscillations in the basal ganglia exaggerate plasticity in the cerebellum and excitability of trigeminal blink circuits. Major Task 1 of Specific Aim 1 was to investigate effects of synchronized basal ganglia oscillations on activity of the deep cerebellar nucleus neurons. Major Task 2 of Specific Aim 1 was to investigate the effects of synchronized basal ganglia oscillations on the activity of the superior colliculus neurons. The 2nd Specific Aim of the project was to demonstrate that synchronized theta oscillations established in the basal ganglia are sufficient to predispose mammals to develop blepharospasm. Major Task 1 of Specific Aim 2 was to determine whether combining synchronized basal ganglia theta oscillations with corneal irritation is sufficient to

develop spasms of lid closure and other characteristics of the focal dystonia BEB. Major Task 2 of Specific Aim 2 was to perform control experiments to determine that theta frequency is critical in enabling the development of spasms of lid closure.

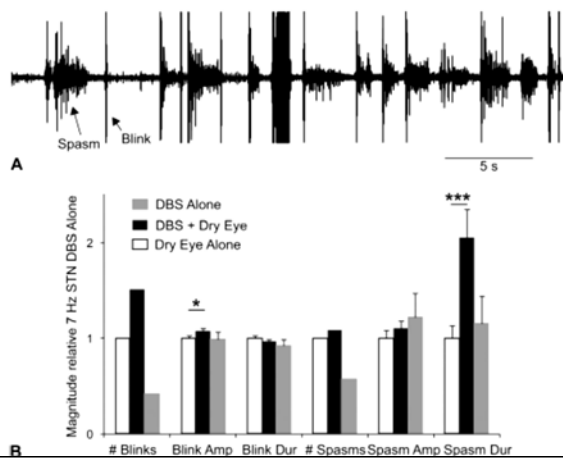


Fig. 1. An animal model of benign essential blepharospasm using 7 Hz deep brain stimulation (DBS) as the predisposing condition. A. A recording of spasms of lid closure and excessive blinking by a rat with dry eye receiving 7 Hz subthalamic nucleus (STN) DBS. B. Average number of blinks (# Blinks), blink amplitude (Blink amp), blink duration (Blink Dur), number of spasms (# Spasms), amplitude of spasms (Spasm Amp), and duration of spasms (Spasm Dur) relative to 7 Hz STN DBS alone condition. Spasms were lid closures lasting >100 milliseconds. Error bars are SEM. *P < 0.05; ***P < 0.001. from: Evinger *J. Neuro-Ophthalmology*, 2015;35:374–379

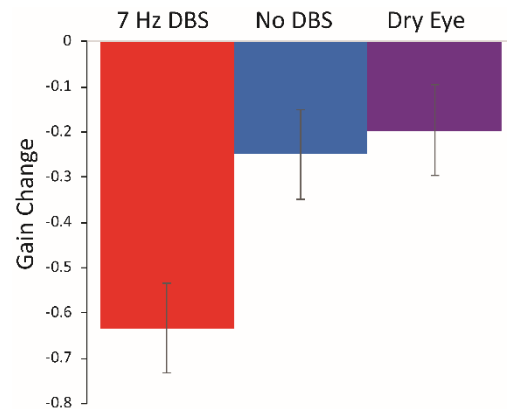


Fig 2. Comparison of blink plasticity among normal rats with 7 Hz DBS and no DBS and rats with dry eye receiving 130 Hz DBS. Error bars are SEM.

What was accomplished under these goals?

In the first year, we completed Major Task 1 and collected preliminary data on Major Task 2 of Specific Aim 2.

Specific Aim 2, Major Task 1: We combined dry eye with theta, 7 Hz, deep brain stimulation (STN DBS) of the subthalamic nucleus of the basal

ganglia. Rats in this paradigm developed spasms of lid closure and excessive blinking (Fig. 1 taken from Appendix). These data demonstrated that the theta frequency basal ganglia hypersynchronization created by STN DBS interacted with the plastic compensatory processes initiated by dry eye to create spasms of lid closure typical of BEB. This result supported our hypothesis that theta frequency STN DBS exaggerates the plasticity initiated by dry eye to create spasms of lid closure typical of BEB.

Specific Aim 2, Major Task 2: As described in the project narrative of the grant proposal (page 11), an important control experiment was to demonstrate that the 7 Hz STN DBS is the critical frequency to exaggerate blink plasticity in dry eye into spasms of lid closure. 130 Hz STN DBS does not affect blink plasticity in normal rats (Kaminer et al., 2014), but the appropriate comparison is the dry eye combined with 130 Hz STN DBS because dry eye initiates blink plasticity to compensate for the eye irritation of dry eye. With dry eye initiated plasticity, any frequency of STN DBS might affect blink plasticity. Our hypothesis predicted that the combination of dry eye and 130 Hz STN DBS should not exaggerate blink plasticity. As described on page 8 of the grant proposal project narrative (Trigeminal Reflex Blink Gain Paradigm), we employed our previously published paradigm that decreased trigeminal reflex blink gain in rodents as well as humans (Mao and Evinger, 2001; Ryan et al., 2014) to investigate blink plasticity. In this paradigm, high frequency stimulation of the supraorbital branch of the trigeminal nerve reduced the amplitude of subsequent reflex blinks, a decrease in blink gain. Our data demonstrated that 7 Hz STN DBS (Fig. 2, red) significantly exaggerated the reduction in blink gain relative to normal rats with No STN DBS (Fig. 2, blue) and rats with dry eye receiving 130 Hz STN DBS (Fig. 2, purple). Importantly, there was no

significant difference in the plasticity exhibited by normal rats without STN DBS and rats with dry eye receiving 130 Hz STN DBS. Moreover, the rats with dry eye and 130 Hz STN DBS did not develop spasms of lid closure as occurs with 7 Hz STN DBS. Thus consistent with our hypothesis, the data demonstrated that combining dry eye with high frequency STN DBS did not exaggerate blink plasticity. The second control experiment of Major Task 2, combining dry eye with 16 Hz STN DBS is ongoing.

Changes to SOW Order

The decision to begin our investigations with Specific Aim 2 instead of Specific Aim 1 resulted from the lack of personnel available to work on the experiments in Specific Aim 1. The microelectrode recording experiments of Specific Aim 1 require assistance from an individual with some experience in single neuron recording. I was unable to hire a postdoctoral fellow in the first year and have been unable to attract a graduate student to replace the one who just graduated. In contrast, the experiments of Specific Aim 2 could be performed by closely supervised undergraduate students currently in my laboratory. To enable me to start the experiments of Specific Aim 1, I hired a technician who can assist me with the microelectrode recording experiments. We have implanted microelectrode arrays and DBS electrodes in rats and will begin the experiments of Specific Aim 1 in January 2017. We expect to complete the experiments in Major Task 2 of Specific Aim 1 and begin the experiments of Major Task 1 of Specific Aim 1 by the time for the 2017 renewal. The choice of beginning with Major Task 2 rather than Major Task 1 of Specific Aim 1 was that the relative ease of recording from superior colliculus compared to the cerebellar interpositus nucleus enables me to bring the research technician up to speed more quickly.

What opportunities for training and professional development has the project provided?

The graduate student had the opportunity to acquire technical skills in animal behavior, surgical procedures, and alert rodent brain recording.

How were the results disseminated to communities of interest?

We published one manuscript.

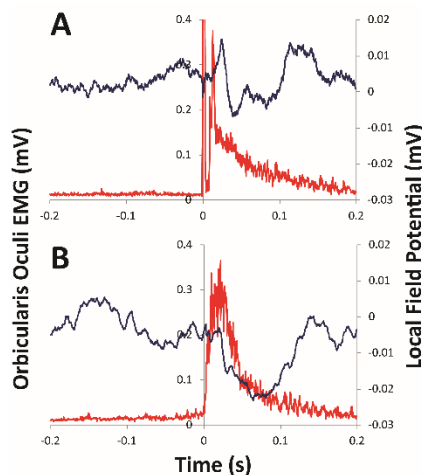


Fig. 3. Superior colliculus LFP associated with blinks. A) Averaged LFP (blue) and rectified reflex blink EMG (red). B) Averaged LFP and blink EMG synchronized to occurrence of a spontaneous blink.

What are the plans for the next reporting period to accomplish the goals?

The work during the next reporting period will focus on completing the control experiments of Major Task 2 of Specific Aim 2 as well as the experiments of Major Task 2 of Specific Aim 1. We also hope to begin the experiments of Major Task 1 of Specific Aim 1.

Major Task 2 of Specific Aim 1 (Project Narrative page 9): The goal of these experiments is to determine how different frequencies of basal ganglia oscillations modify superior colliculus activity and to correlate these changes with alterations in trigeminal reflex excitability, a primary characteristic of BEB. We will record from the intermediate and deep layers of the superior colliculus receiving spinal trigeminal inputs. Our data demonstrate that both 7 and 16 Hz STN DBS increase reflex blink excitability and that 130 Hz STN DBS has no effect (Kaminer et al., 2014). We will compare the activity of superior colliculus neurons and local field potentials (LFP) with all three frequencies to the No DBS condition. Each day, rats will receive 7 Hz STN DBS, 16 Hz STN DBS, 130 Hz STN DBS, and No DBS blocks of thirty trials of pairs of 2T SO stimuli with a 100 ms interstimulus interval

every 20 ± 5 s. These experiments are already in progress (Fig. 3).

Major Task 1 of Specific Aim 1 (Project Narrative page 9):

The goal of these experiments is to determine how different frequencies of basal ganglia oscillations modify cerebellar interpositus (IP) activity and to correlate these changes with shifts in blink plasticity. As our data demonstrate that 7 Hz STN DBS exaggerates blink plasticity, 16 Hz STN DBS impairs blink plasticity, and 130 Hz STN DBS has no effect on the blink plasticity of normal rats (Kaminer et al., 2014), we will compare IP neural activity across all three frequencies. We will simultaneously record unitary activity and local field potentials (LFP) from blink related IP regions during SO stimulation before, during, and after our trigeminal reflex blink gain paradigm (page 8, project narrative). We will compare the activity of individual IP neurons and LFP before the trigeminal reflex blink gain paradigm to their activity after the trigeminal reflex blink gain paradigm.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

The preliminary data had an impact on the interpretation of the Neuro-Ophthalmology community as can be seen in the editorial on our manuscript in the Appendix (KB Digre, "Benign Essential Blepharospasm—There Is More to It Than Just Blinking, J. Neuro-Ophthalmol. 35(4):379-381, 2015).

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. Changes/Problems

Changes in approach and reasons for change

There were no changes in approach.

Actual or anticipated problems or delays and actions or plans to resolve them

The one delay in the work has been the difficulty of finding a postdoctoral fellow to participate in the project. I made offers to two individuals. For personal reasons, these two decided not to come to Stony Brook University. My search for a postdoctoral fellow continues. I have also been unable to attract a new graduate student to replace the one who graduated. To speed up the research, I have hired a new research technician to assist with the microelectrode studies of Specific Aim 1.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

6. Products

Journal publications

“Benign Essential Blepharospasm is a Disorder of Neuroplasticity: Lessons from Animal Models.” J. Neuro-ophthalmol. 35:374-379, 2015

Books or other non-periodical, one time publications

None to Report

Other publications, conference papers, and presentations

International:

“Trying to Raise the Window Shades: The Functional Blindness of Benign Essential Blepharospasm”

Invited lecture at Cardiff University, October 28, 2015

Website(s) or other internet site(s)

None to Report

Technologies or techniques

None to Report

Inventions, patent applications, and/or licenses

None to Report

Other Products

None to Report

7. Participants & other collaborating organizations

What individuals have worked on the project?

| | | | | |
|------------------------------|---|------------------------|------------------------|------------------------|
| Name: | Leslie Craig Evinger | Patricia Enmore | Ashley Culoso | Donna Schmidt |
| Project Role: | PI | Graduate Student | Technician | Technician |
| Research Identifier: | 0000-0002-0039-3348 | | | |
| Nearest Person Month Worked: | 12 | 12 | 3 | 6 |
| Contribution: | Experimental design, manuscript preparation, performing experiments | Performing experiments | Performing experiments | Lab manager, histology |
| Funding Support: | | | | |

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

None to Report

What other organizations were involved as partners?

None to Report

8. Special reporting requirements

Not Applicable

9. Appendices

"Benign Essential Blepharospasm is a Disorder of Neuroplasticity: Lessons from Animal Models" J. Neuro-ophthalmol. 35:374-379, 2015

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Benign Essential Blepharospasm is a Disorder of Neuroplasticity: Lessons From Animal Models

Craig Evinger, PhD

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Effectively modeling benign essential blepharospasm (BEB) requires mimicking its root causes. Current evidence points to BEB arising from the confluence of a genetic predisposing condition and an environmental trigger (1). In this “2 hit” hypothesis, the appropriate environmental trigger engenders dystonic behavior because the predisposing condition creates inappropriate brain functioning. Epidemiological studies demonstrate that eye irritation from dry eye, blepharitis, or keratoconjunctivitis is the environmental trigger (1–6). The strength of the association between dry eye and BEB increases in the fifth and sixth decades of life (6) when BEB typically arises (7). Available data strongly support that the predisposing condition is genetic (1,8–12). There is evidence for an autosomal-dominant gene with reduced penetrance contributing to BEB (9,13), but current studies fail to identify any specific genes (8,14). Thus, creating a useful animal model of BEB must involve combining an environmental trigger with a predisposing condition.

Another goal of an animal model is to reproduce the typical symptoms of BEB. The hallmark of BEB is excessive involuntary bilateral lid closure primarily involving the orbicularis oculi muscles (1,15–18). In addition to lid spasms, patients with BEB exhibit trigeminal hyperexcitability (1,15,19–22), an elevated spontaneous blink rate (23), and photophobia (1,24–26). These characteristics are consistent with eye irritation serving as the environmental trigger for BEB because they all appear in patients with dry eye (21,27,28). This relationship between eye irritation and BEB

characteristics indicates that eye irritation should be 1 component of an animal model and that the predisposing condition should cause the adaptive changes in eyelid control in response to dry eye to develop into BEB-like characteristics.

Current evidence demonstrates that trigeminal blink circuits undergo plastic, adaptive modifications to compensate for the rapid breakup of the corneal tear film in dry eye (29–32). Dry eye or eye irritation elevates trigeminal blink amplitude and duration to increase meibomian gland secretion and enhance restoration of the tear film (20,32–37). Blink frequency increases to reform the tear film more regularly (20,36–40). The trigeminal reflex blink circuit becomes hyperexcitable to allow tear film breakup to evoke a reflex blink more readily (20,21,32). Finally, the trigeminal reflex blink circuit responds to a single reflex evoking stimulus with multiple blinks to help restore the tear film (20,21,32).

A simple experiment demonstrates that these modifications are part of a compensatory plastic change occurring in the trigeminal complex (32). Within 30 minutes of restraining 1 eyelid to make blinking more difficult, stimulating the supraorbital nerve ipsilateral to the restrained eyelid evokes hyperexcitable reflex blinks and additional blinks in both eyelids. Stimulating the supraorbital nerve contralateral to the restrained eyelid, however, elicits normal blinks in both eyelids. This pattern would occur only if the trigeminal complex receiving signals of corneal irritation from eyelid restraint expressed the plastic changes. Thus, eye irritation initiates plastic compensatory changes in blinking that could be exaggerated in BEB to produce the eyelid abnormalities of this focal dystonia.

We hypothesize that the predisposing condition exaggerates neuroplasticity so that modifications in response to eye irritation become maladaptive and amplify into the characteristics of BEB. There is significant evidence for exaggerated plasticity in dystonia (41,42). With generalized dystonia, homeostatic synaptic plasticity in the striatum is abnormal (43,44). Exaggerated associative plasticity accompanies focal hand dystonia (45–48). Important for our hypothesis, exaggerated plasticity of the trigeminal blink reflex accompanies BEB (49).

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The author reports no conflicts of interest.

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Our initial rodent model of BEB (50) used a small reduction of substantia nigra dopamine neurons to create the predisposing condition and crushing 1 branch of the facial nerve innervating the orbicularis oculi to generate the environmental trigger. The choice of dopamine depletion as a predisposing condition came from observations showing that baboons undergoing poisoning with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) of dopamine neurons exhibited dystonia before developing Parkinsonian movement abnormalities (51) and that there was a disruption of D₂ receptors in patients with BEB (52,53). Thus, changes in dopamine levels or the functioning of specific dopamine receptor subtypes could create the “predisposing condition” for BEB. For an environmental trigger, we created a transient eye irritation by crushing a branch of the facial nerve that provides approximately 30% of the orbicularis oculi innervation. This procedure produced a transient dry eye condition because the weakened eyelid became less effective at restoring the tear film with each blink. The condition was only temporary, however, because regeneration of the crushed nerve branch restored complete lid function within 3 weeks.

In the Schicatan model (50), the BEB-like spasms of lid closure only occurred with the combination of the environmental trigger and the dopaminergic predisposing condition. In the absence of the predisposing condition, the environmental trigger of transient eye irritation slightly increased trigeminal reflex blink excitability and resulted in the development of additional blinks similar to those seen in human dry eye (20,21). Without the environmental trigger, the predisposing condition of a small dopamine neuron loss slightly increased trigeminal reflex blink excitability but did not generate spasms of lid closure. Combining the predisposing condition and the environmental trigger, however, caused long-lasting spasms of lid closure, dramatically elevated trigeminal reflex blink excitability, and increased spontaneous blinking similar to the pattern of blink abnormalities of patients with BEB. These BEB-like characteristics continued after the facial nerve regained full function and eliminated the dry eye. Thus, the BEB-like characteristics of this animal model seemed to result from an exaggeration of the normally compensatory process evoked by eye irritation.

The Schicatan BEB model also was consistent with the important interactions between the cerebellum and basal ganglia that underlie dystonia (54–63). Previous studies demonstrated that the cerebellum was essential for adaptive responses to the eye irritation created by eyelid restraint. Lesions of the cerebellum (30,31) blocked the increases in blink amplitude and duration initiated by eye irritation (20,32–37). Recordings from blink-related neurons in the cerebellar interpositus nucleus revealed the changes in cerebellar activity that accounted for the changes in blink amplitude and duration associated with lid restraint (29). Although the Schicatan model supported the 2 hit hypothesis as the basis of BEB and identified the basal ganglia and cerebellum as key players in this focal dystonia, the model did not explain how the predisposing condition created the

exaggerated plasticity that allowed normally adaptive modification to eye irritation to swell into spasms of lid closure.

We hypothesize that the key to the exaggerated plasticity of dystonia is hypersynchronized low-frequency oscillations of basal ganglia activity. Basal ganglia neurons in patients with Parkinson disease and animal models of Parkinson disease exhibit hypersynchronized oscillations in the broad beta band, 10–30 Hz (64–71). In contrast, basal ganglia neurons in dystonic patients exhibit hypersynchronized oscillations in the theta band, 3–10 Hz (71–74). Although the role of these oscillations in modifying voluntary movement is unclear (66,73,75–81), our study in rodents demonstrate that these basal ganglia oscillations modify trigeminal reflex blink plasticity (82).

We directly tested the role of basal ganglia oscillations in blink plasticity by delivering deep brain stimulation to the basal ganglia subthalamic nucleus of normal rats undergoing a blink plasticity paradigm (82). The procedure was a cerebellar-dependent plasticity paradigm that we developed for humans (83) and modified for rodents (84). Other investigators used this paradigm to demonstrate impaired blink plasticity with Parkinson disease (85), but exaggerated blink plasticity with BEB (49). If the frequency of basal ganglia oscillations modulates brainstem plasticity, then beta frequency deep brain stimulation in normal rats should impair trigeminal reflex blink plasticity, whereas theta frequency deep brain stimulation should exaggerate blink plasticity. The Kaminer et al study (82) demonstrated the validity of this postulation. Beta frequency, 16 Hz, deep brain stimulation impaired blink plasticity, whereas theta frequency, 7 Hz, deep brain stimulation exaggerated trigeminal reflex blink plasticity in normal rats. Deep brain stimulation at 130 Hz, a therapeutic frequency for deep brain stimulation in humans (86), however, did not affect blink plasticity in normal rats. Thus, hypersynchronized theta frequency basal ganglia oscillations could create a predisposing condition in which adaptive plasticity initiated by eye irritation exaggerated into spasms of lid closure typical of BEB.

In a preliminary study on 1 rat, we monitored blinking and spasms of lid closure in a normal rat receiving 7 Hz deep brain stimulation of the subthalamic nucleus 4 hours a day combined with mild dry eye produced by exorbital lacrimal gland removal (36). We tested 3 conditions: 1) 7 Hz subthalamic nucleus deep brain stimulation alone (Fig. 1B, gray bars); 2) 7 Hz subthalamic nucleus deep brain stimulation combined with dry eye (Fig. 1B, black bars); and 3) dry eye alone (Fig. 1B, white bars). In Condition 1, the rat received 5 days of 7 Hz subthalamic nucleus deep brain stimulation alone. In Condition 2, combining the predisposing condition and the environmental trigger, we removed the exorbital gland and the rat received 5 days of 7 Hz subthalamic nucleus deep brain stimulation for 4 hours each day. In Condition 3, we discontinued the 7 Hz subthalamic nucleus deep brain stimulation. For all conditions, we monitored blinking (lid closures <100 milliseconds) and lid spasms (lid closures >100 milliseconds) continuously over a 30-minute period on the last 2 days of each

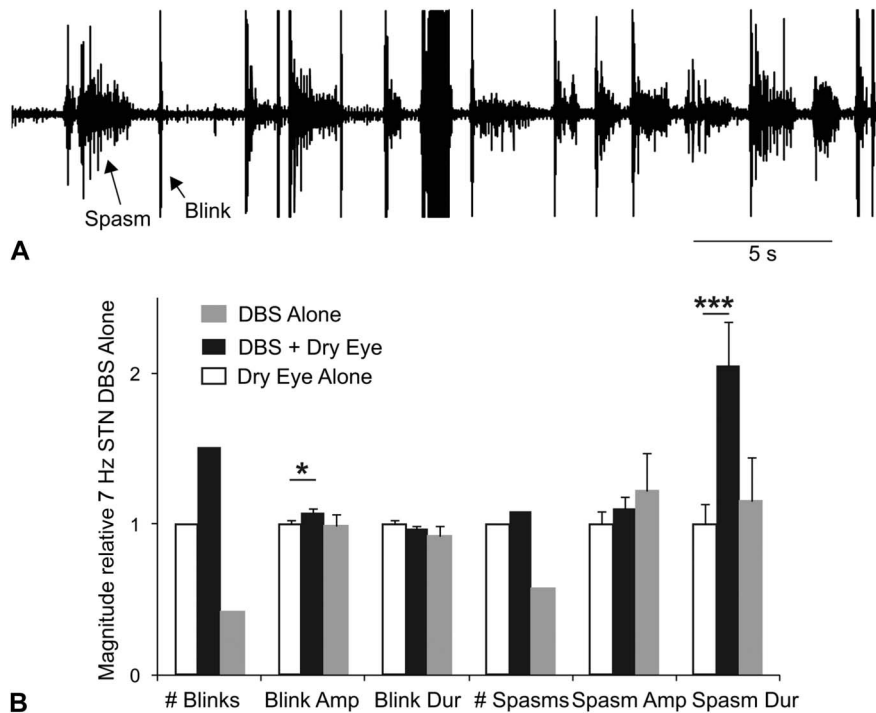


FIG. 1. An animal model of benign essential blepharospasm using 7 Hz deep brain stimulation (DBS) as the predisposing condition. **A.** A recording of spasms of lid closure and excessive blinking by a rat with dry eye receiving 7 Hz subthalamic nucleus (STN) DBS. **B.** Average number of blinks (# Blinks), blink amplitude (Blink amp), blink duration (Blink Dur), number of spasms (# Spasms), amplitude of spasms (Spasm Amp), and duration of spasms (Spasm Dur) relative to 7 Hz STN DBS alone condition. Spasms were lid closures lasting >100 milliseconds. Error bars are SEM. * $P < 0.05$; *** $P < 0.001$.

condition and normalized all data to the 7 Hz subthalamic nucleus deep brain stimulation alone condition. In the combined 7 Hz subthalamic nucleus deep brain stimulation and dry eye condition, the rat made more blinks than either the 7 Hz subthalamic nucleus deep brain stimulation alone or dry eye alone conditions (Fig. 1B, # Blinks). In the combined 7 Hz subthalamic nucleus deep brain stimulation and dry eye condition, the rat also exhibited more spasms of lid closure than in the other conditions (Fig. 1B, # Spasms). Moreover, the spasm duration was longer in the combined 7 Hz subthalamic nucleus deep brain stimulation and dry eye condition than in the 7 Hz subthalamic nucleus deep brain stimulation alone or dry eye alone condition (Fig. 1A, B, Spasm Dur). Finally, the rat made significantly larger blinks in the combined 7 Hz subthalamic nucleus deep brain stimulation and dry eye condition than in 7 Hz subthalamic nucleus deep brain stimulation alone condition ($P < 0.05$; Fig. 1B, Blink Amp). Although preliminary, these data indicate that the next rodent model of BEB should be developed by combining theta frequency deep brain stimulation of the subthalamic nucleus and dry eye.

Thus far, animal models of BEB have not been tested for the abnormal sensitivity to light associated with BEB (1,24,87). The neural bases of photophobia in patients with BEB are unknown. Physiological and behavioral studies of photophobia implicate changes in blood flow (88), melanopsin ganglion cell inputs to somatosensory thalamic regions (89), intraocular no-

ciceptors (90), and calcitonin gene-related peptide trigeminal sensitization (91,92). Because all of these mechanisms involve elevated trigeminal excitability, we anticipate that rodent models of BEB will also exhibit exaggerated light sensitivity.

The evidence from animal models indicates that spasms of lid closure and trigeminal hyperexcitability of BEB result from exaggerated neuroplasticity, an amplification of the normally adaptive modifications of blinking initiated by eye irritation. The adaptive plasticity initiated by eye irritation seems to involve the cerebellum (29–31), and the exaggeration of plasticity ensues from abnormal basal ganglia modulation of cerebellar activity (82). These results are consistent with the available data pointing to abnormal cerebellar basal ganglia interactions as a major component of dystonia (62,93–96). Although animal models are not identical to human BEB, they are invaluable for identifying the neural mechanisms and circuits causing BEB.

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Benign Essential Blepharospasm—There Is More to It Than Just Blinking

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Benign essential blepharospasm (BEB) is recognized today as a primary dystonia causing excessive blinking, squeezing, and involuntary contractions of the orbicularis oculi muscles. This involuntary lid closure leads to functional blindness and decreased quality of life. Besides the blinking and squeezing, patients with BEB are known to have trigeminal hyperexcitability as demonstrated by blink reflex testing and photophobia. Patients with BEB frequently use sensory tricks, like touching the side of the eye, humming, or singing that will temporarily improve the spasms. For decades, this led clinicians to consider blepharospasm to be a nonphysiological disorder. However, many studies in the last 60 years have dispelled that belief.

The condition occurs more frequently in women by a ratio of almost 3 to 1. Most are white. Although the median age is approximately 53 years, blepharospasm occasionally has been reported in children. Many individ-

uals go years before they are appropriately diagnosed. The most valid findings to make the diagnosis are involuntary eyelid narrowing or closure due to spasms of the orbicularis oculi muscle, bilateral spasms that are synchronous and stereotyped, a sensory trick, and inability to suppress the spasms and blink count voluntarily (1). Many individuals report that there is a family history of dystonia or benign tremor or Parkinson disease. Some predisposing factors are believed to be recent stressful events, a history of dry eye or keratitis, and head trauma (2). BEB has profound effects on visual quality of life and overall quality of life, and there is a tendency to more depression (3). For such a disabling condition, we have limited treatment options. There is a real need for greater understanding of this disorder and better treatments to help our patients.

In the accompanying article, Evinger (4) reviews what animal models teach us about this vexing condition. These models provide hope that if we can model a condition in an animal, we are more likely to be able to understand factors that cause it and create more effective treatments for our patients.

Initially, Evinger reminds us that the etiology of BEB may occur due to a predisposition (e.g., genetic) and an environmental trigger—the so called “2 hit” hypothesis. Although there is no known gene for the condition, frequency of a positive family history suggests that there is a genetic component. But there must also be an environmental trigger. Epidemiological data strongly point to the association of dry eyes and blepharitis as potential environmental triggers.

What dry eye and dry eye symptoms do in predisposed individuals is to exaggerate neuroplasticity by increasing blink frequency and amplitude in an attempt to restore tears. Modifying the trigeminal blink reflex becomes

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K. B. Digre is listed as an inventor on a patent pending for thin-film coatings designed for the treatment of photophobia; she could receive royalties on any commercial sales of these coatings.

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