Clinical Neuroimaging of Photophobia in Individuals With Chronic Ocular Surface Pain

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• PURPOSE: To examine neural mechanisms underlying photophobia in individuals with chronic ocular surface pain by using functional magnetic resonance imaging (fMRI).

• DESIGN: Cross-sectional case/control analysis.

• METHODS: A total of 16 individuals from the Miami Veterans Affairs eye clinic underwent comprehensive ocular surface evaluations and were surveyed for ocular surface symptoms. Case patients included patients who reported chronic ocular surface pain symptoms and light sensitivity at least most of the time over 1 week. Controls included persons without chronic ocular surface pain who reported no or minimal light sensitivity. All patients viewed light stimuli during 2 fMRI scans, one before and one after topical anesthetic instillation, and rated their level of pain intensity to the stimulus at the end of each scan. Areas of brain activation in response to light stimuli presentation were correlated with pain responses and examined post- vs pre-anesthesia.

• RESULTS: Case patients (n = 8) reported higher pain intensity ratings than controls (n = 8) in response to light stimuli during fMRI. Case patient ratings correlated more with light-evoked activation in pain-related areas within the trigeminal brainstem, primary somatosensory cortex (S1), anterior mid-cingulate cortex (aMCC), and insula than in controls. Topical anesthesia led to varying responses in pain ratings among case patients as well as decreased light-evoked activation in S1 and aMCC.

• CONCLUSIONS: The trigeminal nociceptive system may contribute to photophobia in individuals with chronic ocular surface pain. We demonstrate modulation of cortical structures in this pathway with topically applied anesthetic to the eyes. Further understanding of modulatory interactions that govern ocular surface pain and photophobia is critical for developing effective, precision-based therapies. (Am J Ophthalmol 2023;246: 20–30. Published by Elsevier Inc.)

Ocular surface complaints are common in the general population, with an estimated prevalence of 5% to 30% worldwide.[1,2] Traditionally, reports of ocular surface pain have been incorporated under the umbrella term of dry eye (DE), which is defined as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[3] Although ocular surface pain has long been attributed to tear abnormalities, nerve dysfunction is now acknowledged as another important contributor.[4] Thus, a better understanding of peripheral and central contributors to ocular surface pain is needed to provide precision-based treatment algorithms to an individual patient.

When managing chronic ocular surface pain, one must consider the potential origins of pain, such as primary afferent nerves in the cornea correctly signaling information from their environment (ie, nociceptive pain) and/or dysfunctional pathways within trigeminal regions (peripheral and/or central) sending inappropriate signals to evoke pain (ie, neuropathic pain).[4] Common sources of nociceptive pain in the eye include low tear volume, fast tear film breakup, and epithelial irregularities that can be evaluated at the slitlamp examination. The diagnosis of neuropathic pain remains a clinical one, with clues that include symptoms out of proportion to ocular surface signs[5,6] and sensory hypersensitivity, such as evoked pain to wind and light.[7] In fact, we have found that self-reported light sensitivity (ie, photophobia) can be used as a screening tool for central abnormalities in the form of persistent aftersensations to a thermal stimulus applied to the forearm.[8] The "anesthetic challenge" is another clinical test used to identify a potential neuropathic contribution to pain, with persistent pain after placement of an anesthetic suggestive of a central or non–ocular surface source of pain.[9]

Studies that directly image central pathways in individuals with chronic ocular surface pain are lacking in the litera-

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ture. However, imaging techniques, such as functional magnetic resonance imaging (fMRI), have been useful in studying other head and facial pain conditions, including trigeminal neuralgia.[10] In an event-related fMRI study on trigeminal neuralgia, tactile stimulation of trigger zones activated brain regions traditionally associated with pain, including the somatosensory cortices, cingulate cortex (CC), and anterior insula (AI) as well as the spinal trigeminal nucleus (spV) in the brainstem.[10] After curative treatment by radiofrequency thermocoagulation of the Gasserian ganglion, significantly reduced activation in these central areas was noted on fMRI. Patients also reported that although they still felt light touch over the trigger zones, the tactile stimulation no longer caused pain. These results highlight the potential of applying fMRI to the study of chronic ocular surface pain. As such, we developed a protocol to evaluate central nervous system pathways in individuals with chronic ocular surface pain with neuropathic features (ie, photophobia, symptoms out of proportion to ocular surface signs).

METHODS

• **STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS:** The study was approved by the Miami Veterans Affairs (VA) and the University of Miami Institution Review Boards (IRB approvals #3011.08 and 20190340, respectively). The study was conducted in accordance with the principles of the Declaration of Helsinki and complied with the requirements of the United States Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants prior to any study activities.

• **STUDY POPULATION:** We recruited 16 patients who presented to the Miami VA eye clinic for yearly screening and divided them into 2 equal groups: patients with ocular surface pain (≥6 months), and patients without pain (controls). This classification followed guidelines by the International Association for the Study of Pain (IASP), which defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" and acknowledges various forms of expression of pain, including verbal descriptors.[11] Given our previous data demonstrating a relationship between self-reported light sensitivity and central abnormalities,[8] we also examined responses to question 1 of the Ocular Surface Disease Index (OSDI),[12] which assesses for eyes that are sensitive to light over the past week on a scale of 0 to 4 (0 = none; 1 = some; 2 = half; 3 = most; 4 = all of the time). All individuals with chronic ocular pain had scores ≥3, whereas individuals without pain reported no light sensitivity (score 0, n = 2) or light sensitivity some (score 1, n = 5) or half (score 2, n = 1) of the time. Exclusion criteria for both groups included ocular diseases that could confound photophobia, such as glaucoma; use of glaucoma medications; uveitis; iris transillumination defects; retinal degeneration; and anatomic abnormalities of the cornea, conjunctiva, or eyelids. We also excluded individuals with contraindications to fMRI scanning (eg, pregnancy, pacemaker, implanted metal device).

• **QUESTIONNAIRES:** Participants were administered questionnaires to collect demographic and supporting health information, including age, sex, race, ethnicity, and medical history. The 15-item short form McGill Pain Questionnaire[13] and a 9-item list of common descriptors for ocular surface pain symptoms were presented to each participant (Supplemental Tables 1 and 2). Standardized DE questionnaires included the Dry Eye Questionnaire—5 (DEQ-5)[14] and OSDI. The Neuropathic Pain Symptom Inventory—Eye (NPSI-Eye), a validated eye-centric variation of the NPSI,[15] was obtained to quantify neuropathic-like eye symptoms.

• **OCULAR SURFACE EVALUATION:** Each patient underwent a clinical examination that included (in the order performed) tear breakup time (TBUT, measured in seconds; lower values indicate less tear stability), corneal staining (graded to the National Eye Institute scale[16]; higher values indicate more epithelial irregularity), and anesthetized tear production using Schirmer strips (measured by millimeters of wetting at 5 minutes; lower values indicate lower tear production).

• **FMRI PROTOCOL:** The fMRI protocol was adopted and modified from a prior study on photophobia using visual stimuli to evoke pain and to identify trigeminal nociceptive and other pain-related pathways.[17] In a single session, all individuals underwent 2 fMRI scans: one before and one after anesthetic instillation. During each scan, individuals were presented with 2 screen conditions: a resting black screen condition, which featured a white fixation cross on a black background (~0.5 lux), and a light stimulus white screen condition, which featured a black fixation cross on a white background (~65 lux). Subjects were presented with 16 episodes of the white screen, each lasting 6 seconds. To avoid anticipatory processes, the interstimulus interval varied between 26 and 34 seconds in 2-second increments. The scanner environment was kept dark during the entire experiment, with only a projector providing intermittent brief illumination. The first fMRI scan was performed immediately following placement of a single eye drop of artificial tears (Refresh Plus Lubricant Eye Drops, Allergan) in each eye, and the second fMRI scan was performed immediately following placement of a single eye drop of 0.5% proparacaine (Bausch & Lomb Inc) topical anesthetic in each eye. Participants were instructed to keep eyes open and to blink normally throughout the duration of each scan.

TABLE 1. Demographic and Clinical Characteristics of Case Patients and Controls.

	Case Patients (n = 8)	Controls (n = 8)	*P* Value
Demographics			
Age, y, mean ± SD	49.9 ± 9.6	59.6 ± 7.7	<.05[a]
Sex, male, % (n)	38% (3)	88% (7)	<.05[b]
Race, white, % (n)	88% (7)	38% (3)	<.05[b]
Ethnicity, Hispanic % (n)	50% (4)	38% (3)	.61
Co-morbidities			
Diabetes mellitus, % (n)	0% (0)	0% (0)	1.00
PTSD, % (n)	38% (3)	13% (1)	.25
Depression, % (n)	63% (5)	75% (6)	.59
Arthritis, % (n)	13% (1)	0% (0)	.05
Sleep apnea/CPAP % (n)	25% (2)	25% (2)	1.00
Migraine, % (n)	38% (3)	0% (0)	.05
Traumatic brain injury, % (n)	13% (1)	13% (1)	1.00
Past or current smoker, % (n)	25% (2)	88% (7)	<.05[b]
Questionnaires			
DEQ5, mean ± SD	13.6 ± 1.8	10.3 ± 5.9	.16
OSDI-1, mean ± SD	3.6 ± 0.5	0.9 ± 0.6	<.05[a]
OSDI total, mean ± SD	60.8 ± 15.1	30.7 ± 23.6	<.05[a]
NPSI-Eye total, mean ± SD	28.0 ± 16.1	10.6 ± 11.3	<.05[a]
Tear parameters[c]			
TBUT (sec), mean ± SD	7.1 ± 3.8	7.2 ± 3.4	.98
Corneal staining, mean ± SD	0.8 ± 1.4	0.9 ± 1.7	.88
Schirmer, mm, mean ± SD	8.0 ± 3.8	15.3 ± 8.1	<.05[a]

CPAP = continuous positive airway pressure; DEQ5 = Dry Eye Questionnaire−5; NPSI-Eye = Neuropathic Pain Symptom Inventory−Eye; OSDI-1 = Ocular Surface Disease Index question 1 regarding light sensitivity; PTSD = post-traumatic stress disorder; TBUT = tear breakup time.

[a] Independent *t* test, $P < .05$.

[b] χ^2 Test, $P < .05$.

[c] Tear parameter means calculated based on the more abnormal value in either eye. A higher corneal staining score represents more epithelial irregularity. A lower TBUT and Schirmer score represent faster tear breakup and lower tear production, respectively.

• **FMRI SCREEN CONDITION RATINGS:** At the end of each scan, subjects rated the pain intensity experienced in their eyes when viewing either the black screen (rating at rest) or the white screen (rating to light stimulus). Pain intensity was rated via a verbal, numerical rating scale ranging from 0 ("no pain") to 100 ("most intense pain imaginable").

• **FMRI ACQUISITION AND PROCESSING:** Supplemental Text 1 provides methodological detail regarding neuroimaging parameters and processing.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using the SPSS V.28.0 statistical package (SPSS Inc). Demographic and clinical variables between groups were compared using an independent *t* test or χ^2 test, as appropriate. Significant differences in pain intensity ratings to each screen condition were analyzed between groups using an independent *t* test.

Measures of "evoked pain" were determined for each participant by calculating the difference in pain intensity ratings between the light stimulus and the resting condition. Pre- and post-anesthetic evoked pain scores were compared between groups using an independent *t* test and within groups using a paired *t* test.

The statistical significance for both brainstem and whole-brain group-level contrast analyses was set at a cluster-level threshold of $P < .05$. Significant clusters were identified by region, and parameter estimate (PE) values of activation from each subject were extracted from significant voxels within each region. The PEs across all significant cluster-based voxels of a given region were averaged for each subject. Using Pearson correlation coefficients, averaged PE values were compared against pre-anesthetic evoked pain scores.

RESULTS

• **PARTICIPANTS:** A total of 16 participants, 8 case patients with chronic ocular surface pain and photophobia and 8 controls, were enrolled into the study. Demographics,

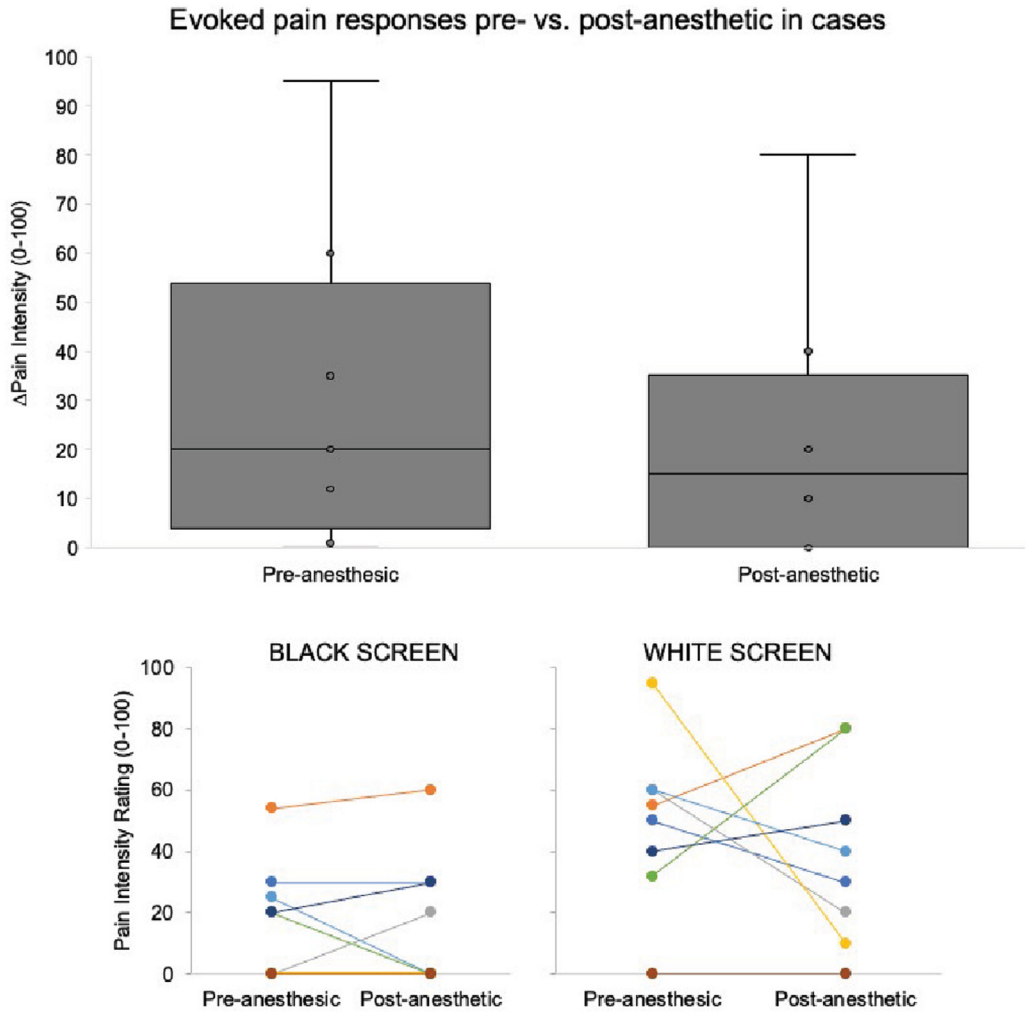

FIGURE 1. Light-induced pain intensity ratings relative to rest in case patients, pre- and post-anesthesia. Case patients had greater evoked pain to the light stimulus pre-anesthetic compared to post-anesthetic conditions. Case patients reported variable effects in response to anesthetic on pain intensity ratings. Overall, 3 case patients reported decreased, 3 increased, and 2 no change in evoked pain post- vs pre-anesthetic.

questionnaire scores, and clinical parameters for all subjects are summarized in Table 1. Of all participants, 8 reported chronic (≥6 months) ocular surface pain symptoms, which the majority characterized as "itchiness," "irritating," "dryness," and "soreness" from the 9-item list of ocular surface pain descriptors (Supplemental Table 1). Pain in case patients was also described as "stabbing" and "aching" based on the short form McGill Pain Questionnaire (Supplemental Table 2).

• **SUBJECTIVE RATINGS DURING FMRI SCANNING:** In case patients, pre-anesthetic pain intensity ratings were significantly greater when viewing the light stimulus (white screen) vs rest (black screen) [mean ± SD: 49.0 ± 27.2 vs 18.6 ± 18.8, paired *t* test t(7) = 2.64, *P* = .03]. Post-anesthetic pain ratings in case patients for the light stimulus increased vs rest, but the change was not statistically significant [38.6 ± 30.0 vs 17.5 ± 21.9, paired *t* test t(7) = −2.12, *P* = .07] (Figure 1). Furthermore, evoked pain scores in case patients showed a decreased trend post-anesthesia vs pre-anesthesia [post- vs pre-anesthesia difference in evoked pain mean ± SD: −9.1 ± 47.2, paired *t* test t(7) = −0.55, *P* = .60]. Specifically, within the case patient group, 3 individuals reported decreased evoked pain to light stimulus after anesthesia, 3 reported increased pain, and 2 no change in pain.

In controls, pre-anesthetic pain intensity ratings were not significantly different during the light stimulus vs rest [0.4 ± 1.1 vs 0.63 ± 1.8, paired *t* test t(7) = 0.18, *P* = .35].

Post-anesthetic pain ratings in controls for the light stimulus were also not statistically different [0.5 ± 0.8 vs 0.1 ± 0.4, paired *t* test t(7) = −1.43, *P* = .20]. Near-zero pain scores in controls prior to anesthesia left no practical room for improvement as seen in evoked pain scores [post- vs pre-anesthesia difference in evoked pain mean ± SD: 0.1 ± 1.1,

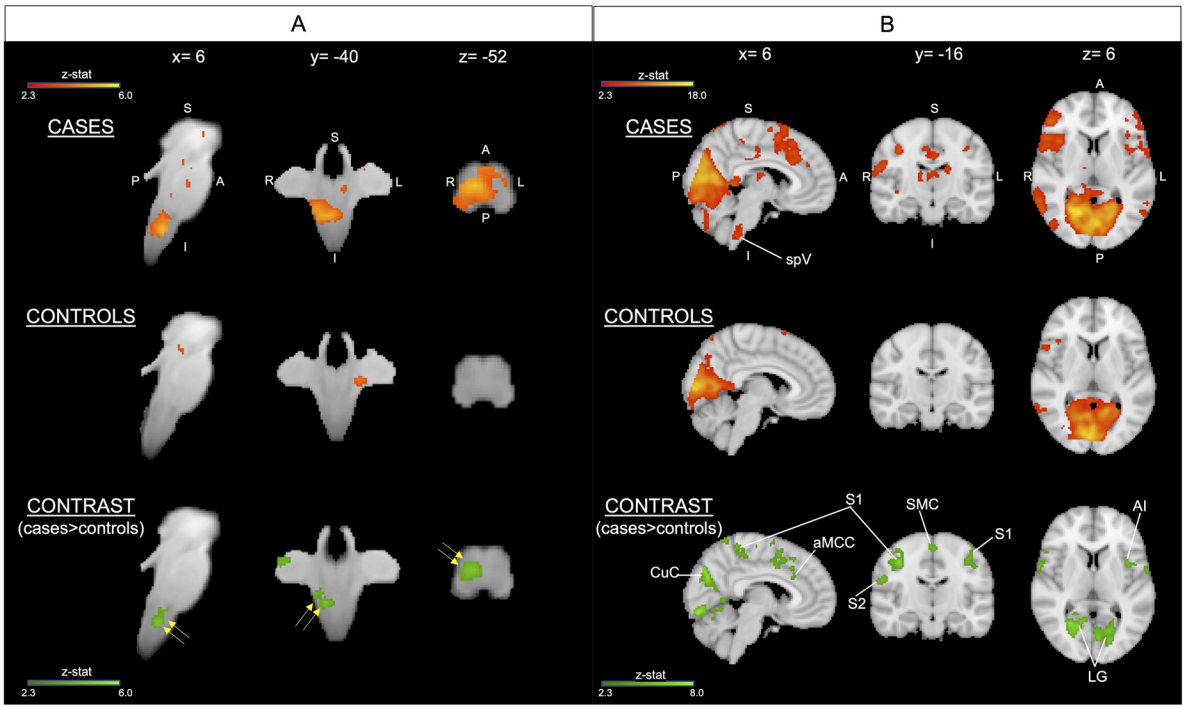

FIGURE 2. A. Case patients had greater light-induced activation in the brainstem compared with controls before anesthetic placement. Spinal trigeminal nucleus (spV) (yellow arrows) shows greater activation in case patients than in controls. Brainstem activation findings are overlaid onto the spatially unbiased infratentorial and cerebellar template (SUIT) atlas with corresponding Montreal Neurological Institute (MNI) coordinates. Group average activation for case patients and controls (red-to-yellow) and group contrast for case patients > controls (dark-to–light green) are displayed. No areas were significantly decreased in case patients relative to controls. Both activation and contrast maps had an individual voxel threshold of $z > 2.3$ and a cluster threshold of $P < .05$. B. Case patients had greater light-induced activation in the whole brain compared with controls before anesthetic placement. Group average activation for case patients and controls (red-to-yellow) and group contrast for case patients > controls (dark-to–light green) are displayed with Montreal Neurological Institute (MNI) atlas underlay. Both activation and contrast maps had an individual voxel threshold of $z > 2.3$ and a cluster threshold of $P < .05$. AI = anterior insula; aMCC = anterior mid-cingulate cortex; CuC = cuneal cortex; LG = lingual gyrus; S1= primary somatosensory cortex; S2 = secondary somatosensory cortex; SMC = supplementary motor cortex; spV = spinal trigeminal nucleus.

paired *t* test $t(7) = -0.31$, $P = .72$]. Overall, this highlights a "floor effect" and further support the participants' placement as controls.

• LIGHT-INDUCED FMRI RESPONSES IN CASE PATIENTS VS CONTROLS:

Brainstem analyses

Several brainstem structures showed greater blood oxygen level–dependent (BOLD) responses to light in case patients vs controls prior to anesthetic placement. Specifically, case patients demonstrated significantly greater activation of right spV during the light stimulus condition compared with controls (Figure 2a, Supplemental Table 3). Post- vs pre-anesthetic contrast analyses revealed no significant changes in brainstem activity for either group.

Whole-brain analyses

Several cortical structures showed significantly greater BOLD responses to light in case patients vs controls prior to anesthetic placement (Figure 2b, Supplemental Table 3). Specifically, case patients displayed greater activity of the visual, primary somatosensory (S1), insular, and anterior mid-cingulate (aMCC) cortices. The magnitude of BOLD activation, as reflected by PEs, was correlated with pain intensity ratings in several brain regions (Figure 3).

Decreased light-induced fMRI activity with proparacaine in case patients

In case patients, topical anesthesia decreased activation within regions of S1 and aMCC but not in visual cortex or insula (Figure 4, Supplemental Table 4). In controls, decreased activation following anesthesia was detected only within visual cortex (Supplemental Table 4). Between groups, case patients demonstrated increased activation relative to controls in bilateral S1 and visual cortex after anesthesia (Supplemental Table 5).

Although decreased cortical activity was observed at the group level, changes in BOLD responses to light follow-

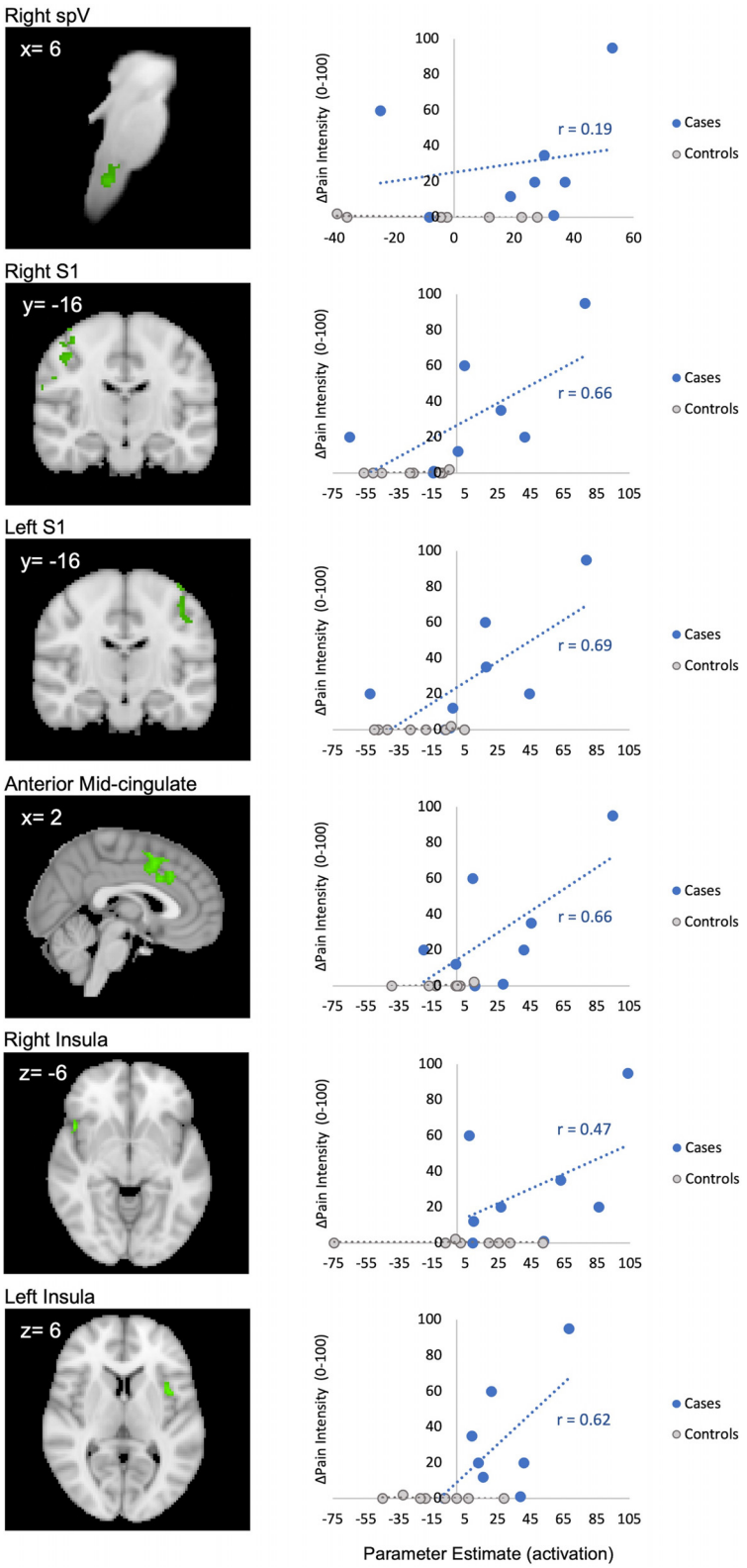

FIGURE 3. Correlations between parameter estimates of functional magnetic resonance imaging (fMRI) activation and light-induced pain intensity ratings in case patients vs controls before anesthetic placement. Case patients had positive correlations between light-induced pain ratings and activity in cortical areas related to pain processing. The WIKIBrainstem and Harvard–Oxford Subcortical and Cortical atlases were used to create anatomical masks of each region. Functional masks were created from group-level contrast maps to pull parameter estimates using fMRI Expert Analysis Tool (FEAT). S1 = primary somatosensory cortex; spV = spinal trigeminal nucleus.

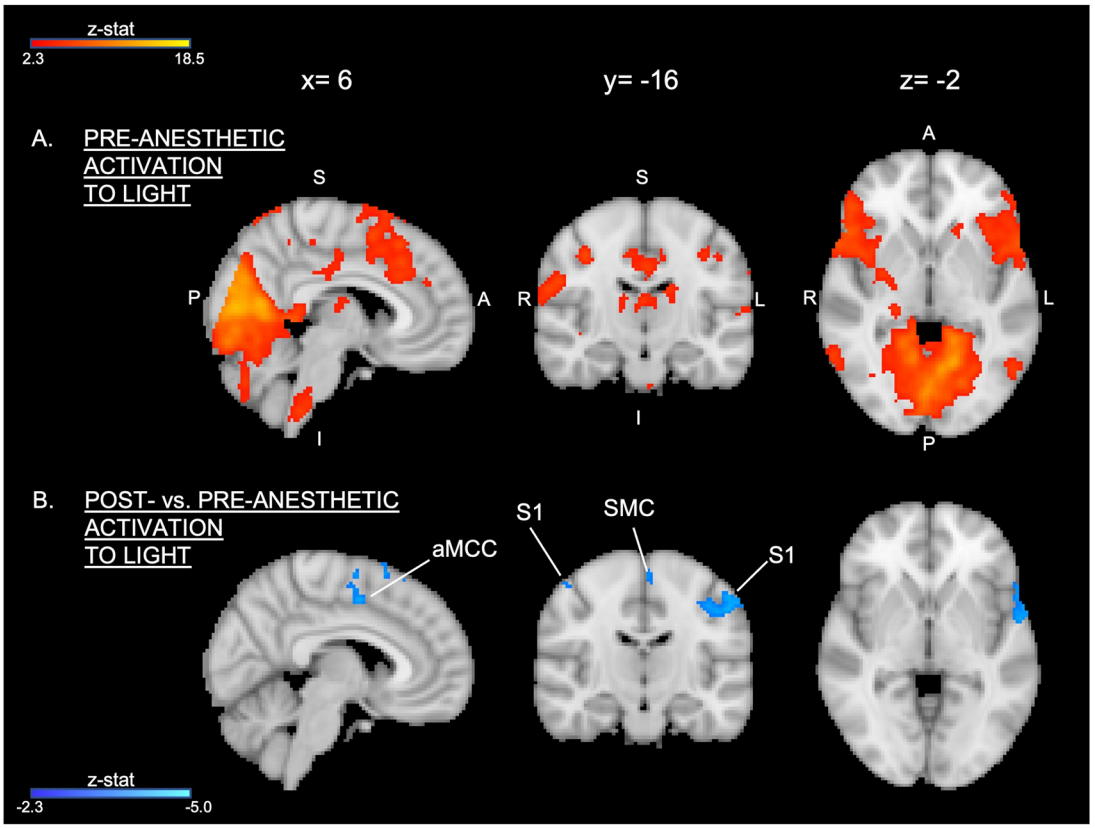

FIGURE 4. Light-induced activation in case patients before vs after anesthesia. A. Pre-anesthetic activation and (B) areas of significantly decreased activation in response to light following anesthesia at the whole-brain level. Group average activation for case patients (red-to-yellow) and contrast post- vs pre-anesthetic within case patients (dark-to—light blue) are displayed with Montreal Neurological Institute (MNI) atlas underlay. Both activation and contrast maps had an individual voxel threshold of $z > 2.3$ and a cluster threshold of $P < .05$. aMCC = anterior mid-cingulate cortex; S1 = primary somatosensory cortex; SMC = supplementary motor cortex.

ing anesthesia were not uniform at the individual subject level. In addition, this nonuniformity did not correspond with the variable impact of proparacaine on light-evoked pain intensity. Table 2 shows the difference in post- vs pre-anesthetic BOLD signal responses to light (reflected by PEs) for each case patient, as well as their corresponding change in evoked pain scores.

DISCUSSION

In this preliminary study, we found that individuals with vs without chronic ocular surface pain and photophobia had greater activation within brain regions associated with pain processing, including structures within and beyond the trigeminal nociceptive pathway, in response to a light stimulus. Light-induced brain activation directly correlated with increases in pain intensity ratings. Although subjective pain responses after anesthetic placement varied between case patients, reduced cortical activation was observed when they were examined as a group. These findings support the hypothesis that pathologic central sensitization within the trigemino-cortical nociceptive pathway contributes to photophobia in individuals with chronic ocular surface pain.

• **NOCICEPTIVE SOURCES OF PAIN LEAD TO CENTRAL PATHWAY CHANGES:** Both nociceptive and neuropathic sources can contribute to the phenotype of chronic ocular surface pain. Apart from Schirmer scores (in which tear production was lower in the chronic ocular surface pain group), our cohort showed very few differences in the ocular surface parameters between chronic ocular surface pain case patients and pain-free controls. Despite this, we found significantly poorer baseline measures of subjective pain at rest, as well as in response to light, among our case patient group. These findings are corroborated by previous reports that demonstrate how individuals with chronic ocular surface pain often perceive symptoms that are out of proportion to observed ocular surface abnormalities.[18,19] When encountered in clinic, this presentation may suggest the presence of

TABLE 2. Subject-Level Change in Post- vs Pre-anesthetic Light-Induced Activation and Evoked Pain Scores Among Case Patients.

Case Patient No.	ΔS1	ΔaMCC	ΔEvoked Pain
1	−150.8	−107.2	↑
2	−145.8	−80.4	↓
3	−63.4	−37.4	↓
4	−62.0	−28.7	No change
5	−40.2	−28.9	No change
6	−38.2	−26.3	↑
7	−37.7	−26.4	↑
8	52.2	12.4	↓

aMCC = anterior mid-cingulate cortex; S1=primary somatosensory cortex.

Note: As a group, case patients demonstrated significant decreases in S1 and aMCC activity in response to light following anesthesia. However, individual blood oxygen level−dependent (BOLD) response signals (as reflected by parameter estimates) from these regions were nonuniform and showed no appreciable trend when compared to change in evoked pain scores.

underlying nerve dysfunction.[20] This is explained by "sensitization," in which an exposure to an acute or chronic adverse condition (eg, nerve injury in the setting of surgery, environmental) induces nerve alterations that remain even after removing the triggering source.[20]

Our findings demonstrate increased activity of central nervous structures in individuals with chronic ocular surface pain compared to controls, and are similar to a prior case report of an individual with acute ocular surface pain who underwent fMRI imaging.[17] Specifically, a male patient with a corneal abrasion secondary to contact lens overuse underwent 2 fMRI sessions: one while he was acutely suffering from pain and photophobia and one after recovery. In response to intermittent bright light during the first session, activation was noted within the trigeminal nociceptive pathway, including spV and S1, as well as within other cortical regions, including the CC. Activation in these regions was no longer present on repeat scan after symptom resolution. Our study also identified light-induced activation of the same trigeminal pathway and cortical structures in patients with chronic ocular surface pain. These data suggest 2 main points. First, in acute pain, central activation represents a noxious response, which resolves as tissue heals. Second, in chronic cases, persistent activity may indicate sensitization of pathways such that central plasticity may prime photophobia expression. Thus, as seen in our study and as supported by our prior work,[8] photophobia in individuals with chronic ocular surface pain may serve as a phenotypic marker of central neuroplasticity.

• **TRIGEMINAL NERVE INVOLVEMENT IN PHOTOPHOBIA-ASSOCIATED OCULAR SURFACE PAIN:** Innervation of the eye is primarily supplied by sensory, sympathetic, and parasympathetic afferents of the trigeminal nerve, but the effect of light exposure on pain signaling by this pathway is unclear. Further research is warranted to determine the exact details of the dysfunction, as most evidence for light-mediated activation of the trigeminal system comes from animals and experimental models of chronic ocular surface pain.[21,22]

One comorbid condition with chronic ocular surface pain that has been found to overlap in pathophysiology is migraine.[23] Several neuroimaging studies have demonstrated functional alterations in patients with migraine.[24,25] Migraine pain is thought to originate from irritation of the meninges, which leads to transmission of nociceptive signals from the dura mater to the brain via the trigeminovascular pathway (shown in yellow and purple in Figure 5).[26] Photophobia, a common presenting symptom in patients with migraine, has also been studied as a mechanism of pain in these individuals.[26-30] One study examined the link between the visual and pain processing systems in chronic migraine using fMRI.[30] Compared to healthy controls, migraine patients with and without headache during the scan showed greater activation within the spinal trigeminal nucleus upon presentation of noxious visual stimuli. This needs to be taken under consideration when interpreting our results, as 3 case patients in our study had a migraine history without an active episode during the scanning session. Taken together, these observations suggest direct co-activation of intraocular trigeminonociceptive fibers within spinal trigeminal nuclei, thereby representing crosslinks between the visual and trigeminal pain processing systems.

• **PAIN PROCESSING AND MODULATION BEYOND THE TRIGEMINAL PAIN PATHWAY:** Although the trigeminal pathway is an important modulator of oculofacial pain sensation, it is important to consider other drivers of symptoms that exist outside this circuit, as illustrated by the heterogeneity of our case group's subjective pain scores after applying topical anesthesia to the ocular surface. Pain processing is a multidimensional state that activates brain networks related to sensory−discriminative, affectional−motivational, cognitive−evaluative, and pain modulatory systems.[31] In our study, the aMCC and insula displayed greater activation in case patients vs controls. Experimental pain models in humans attribute functional activity observed within the cingulate and insula to the influence of pain regulation by negative affect and cognitive control.[32] Such studies highlight how negative emotions may enhance pain sensitivity by functional amplification of cingulate and insular cortices. Our current findings are suggestive of a functional explanation of the clinical findings of extreme depression and anxiety that often accompany chronic ocular pain and photophobia, in which some cases of suicide have been reported.[18]

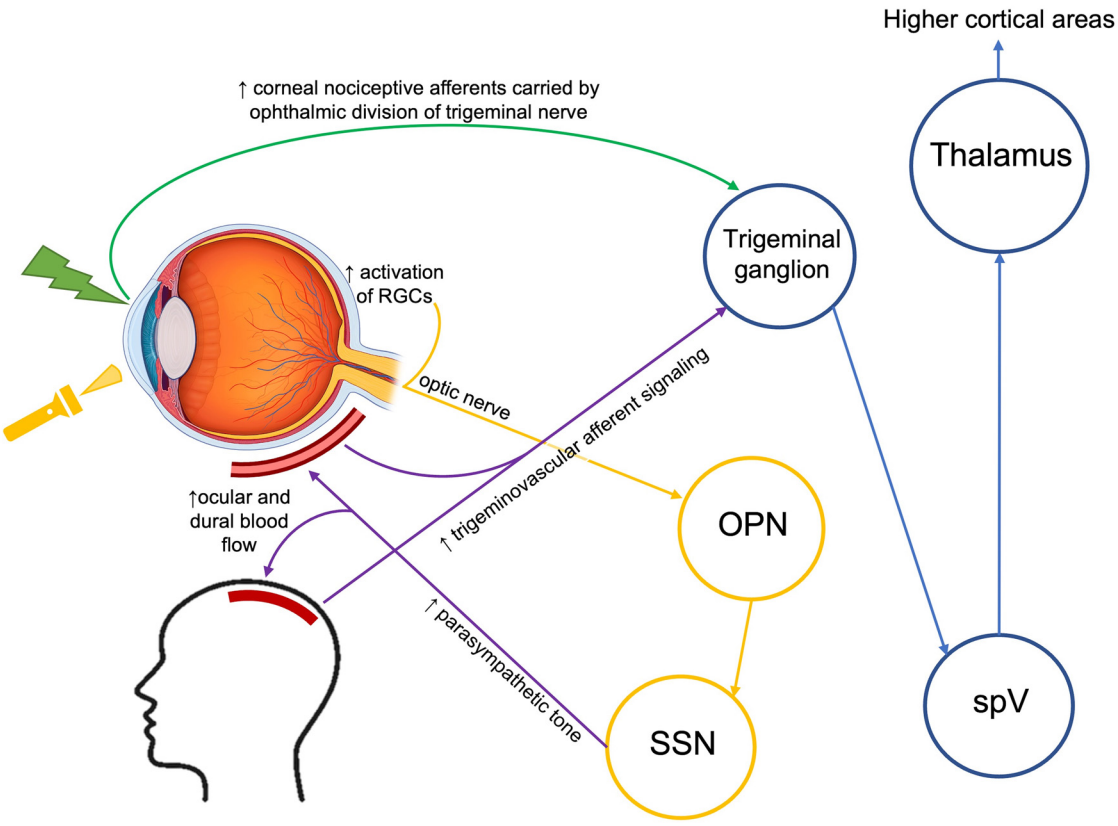

FIGURE 5. Schematic representation of shared trigeminal-related mechanisms in ocular pain, migraine, and photophobia. OPN = olivary pretectal nucleus; RGC = retinal ganglion cells; spV = spinal trigeminal nucleus; SSN = superior salivatory nucleus. Figure adapted with permission from Cheng et al.[41]

• **STUDY LIMITATIONS:** Our findings are based on a small population with differences in multiple parameters, including demographics, comorbidities, and clinical tear characteristics. The influence on pain networks by various demographic features may exist as confounders to our findings, as there has been support for sex-specific and age differences in pain-related brain activity detected by neuroimaging, but not for race or ethnicity.[33-39] Overall, the impact on demographics on fMRI findings are not well understood in the field of neuropathic pain and warrant further investigation. Unmeasured factors may also confound differences in functional brain activation and pain reports (eg, ocular medications, systemic pain medications or mood modulators, genetic differences).

Similarly, the heterogenous response to anesthetic suggests heterogeneity within the case group, with potentially different neural mechanisms that need to be further examined in larger studies. Also, as we observed no differences in brainstem activity following the use of anesthetic, either between or within groups, our contrast analysis with these participant numbers may not be sensitive enough to identify smaller brainstem structures.

• **CONCLUSION:** Despite these limitations, our study is the first to examine neural mechanisms in individuals with chronic ocular surface pain and photophobia, providing support for involvement of the trigemino-cortical pain pathway in driving photophobia in persons with chronic ocular surface pain. We also demonstrated partial benefit in subjective pain report and fMRI metrics after topical anesthesia was applied to the eye, providing the foundation for developing therapies that can be administered topically to modulate central pain pathways.

In addition, painful ocular surface symptoms can exist as an isolated condition or can be co-morbid with other chronic pain syndromes,[40] and our paper highlights potential shared mechanistic pathways that can be addressed with similar treatments. In fact, a few reports have described how oral medications, such as gabapentin, naltrexone, and tricyclic antidepressants, can improve chronic ocular surface pain in some individuals.[40] Our findings give biological relevance to this clinical observation that need to be tested more robustly in future studies.

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