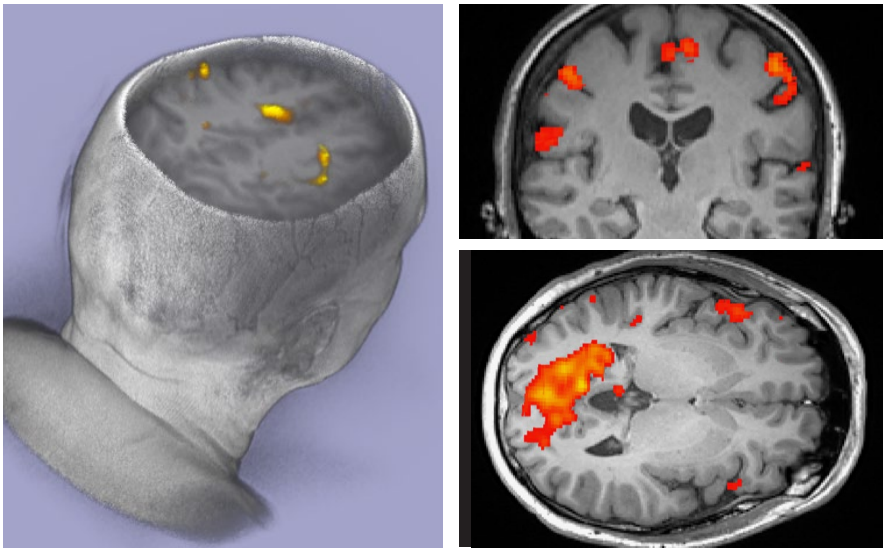


BENEATH THE SURFACE. *Light-induced activation of the somatosensory cortices and supplementary motor area in a patient with chronic ocular surface pain.*

Eric A. Moulton, OD, PhD

CORNEA

MRI Sheds Light on Chronic Ocular Surface Pain

WHILE OCULAR SURFACE PAIN HAS long been attributed to tear abnormalities, recent research indicates that nerve dysfunction also plays a role. Now researchers report that in patients with ocular surface pain and photophobia, the brain systems related to sensations of physical pain can be provoked by viewing light.[1]

Their preliminary investigation, the first to examine neural mechanisms in individuals with chronic ocular surface pain and photophobia, suggests that the trigeminal pain pathway may contribute to photophobia. The study's results also demonstrated a partial benefit of topical anesthetic for the pain.

"The findings may explain why light can result in pain for these patients," said Eric A. Moulton, OD, PhD, at Boston Children's Hospital. Moreover, he said, the results "suggest that when a patient presents with photophobia and chronic ocular surface pain, clinicians should consider that neural changes are also likely occurring in pain processing areas within the central nervous system."

A role for fMRI. For this study, the researchers recruited 16 patients from the Miami Veterans Affairs eye clinic. Half reported experiencing chronic ocular surface pain for six months or longer; the remaining eight served as controls. Those with chronic ocular surface pain also reported experiencing light sensitivity at least most of the time over one week.

Using functional magnetic resonance imaging (fMRI), the researchers measured brain activity triggered by light. In a single session, subjects viewed light stimuli during two fMRI scans—one before and one after application of a single drop of .5% proparacaine topical anesthetic in each eye. Each scan presented two screen conditions: 1) a resting black screen, which featured a white fixation cross on a black background, and 2) a light stimulus white screen, which had a black fixation cross on white background. Following each scan, patients rated their level of pain to the stimulus.

Light-induced outcomes. In all participants, light-induced activity occurred in brain areas related to visual processing. However, those with chronic pain and photophobia reported evoked pain, while those serving as controls did not.

Before receiving proparacaine, the case patients reported that viewing the white light stimulus screen evoked pain. This decreased following treatment. Furthermore, significantly decreased light-evoked fMRI activity was detected in pain-related areas following proparacaine application.

Potential pain relief? The proparacaine findings indicate that topical treatments may be able to mitigate symptoms of light sensitivity in a subset of patients, the researchers wrote.

For refractory cases of ocular surface pain, Dr. Moulton advised considering use of centrally acting pain medications as well as referral to chronic pain specialists. And while sunglasses and specialized tints may offer some relief, he noted that the underlying pathology remains. Finally, he said, doctors should be aware of comorbidities that often occur with other chronic pain conditions, such as mood disorders.

—Miriam Karmel

1 Choudhury A et al. *Am J Ophthalmol.* 2023;246: 20-30.

Relevant financial disclosures: Dr. Moulton—NEI: S; U.S. Department of Veterans Affairs: S.

COMPREHENSIVE

Defining Risk Factors for Fungal Endophthalmitis

DIAGNOSIS OF FUNGAL ENDOPHTHALMITIS remains a clinical challenge, but researchers at the Wilmer Eye Institute in Baltimore have identified specific factors that should raise a clinician's index of suspicion.[1]

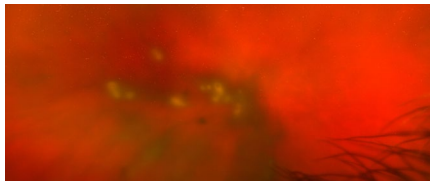
Study goals. The researchers' primary objective was "to determine risk factors [for fungal endophthalmitis] at presentation that might help clinicians with diagnosis and prognosis," said Mark P. Breazzano, MD, now at Retina-Vitreous Surgeons of Central New York in Syracuse.

Study design. For this retrospective study, the researchers assessed patients (age, 58.1 ± 16.9 years) who received antifungal injections at Johns Hopkins from 2014 to 2021. All told, 75 patients (81 eyes) were included. The patients' clinical courses, visual outcomes, and final diagnoses were reviewed, and case features were compared between fungal endophthalmitis and clinically similar diseases.

Outcomes. Eleven patients (12 eyes) had confirmed fungal endophthalmitis, 13 (16 eyes) had presumed fungal endophthalmitis, and 38 (40 eyes) were diagnosed with another condition. The following factors were more likely to occur in cases of fungal endophthalmitis than in masquerade syndromes:

Systemic: Diagnosis of hepatitis C; diagnosis of complicated diabetes; cancer under active treatment; diagnosis of sepsis within the previous six months; or any other immunocompromising condition, including HIV and chronic kidney disease.

Drugs and devices: Intravitreal administration of an antifungal agent in the emergency department or in



UNCLEAR CAUSE. *Vitreous cells, haze, and debris in a patient with a history of IV drug use. Treatment involved broad-spectrum antimicrobial treatment and systemic steroids. No ocular tissue sample confirmed a fungal cause for this inflammation.*

RESEARCH

Training the Mind to Avoid Visual Distractors

OBJECTS THAT STAND OUT FROM THEIR SURROUNDINGS and grab our attention can easily distract us. Now researchers report that with training, the brain can rapidly suppress distractions and allow us to efficiently reach our goals.[1] Their findings bolster one side of a debate in cognitive psychology about what type of visual information captures attention, what we ignore, and how these processes happen.

Some researchers believe that to suppress and ignore "distractors," the brain needs to know about them in advance. However, this study, based on recordings of neuronal activity in the visual cortex of monkeys, demonstrates that the brain can detect a distraction in real time and then rapidly suppress it so that it won't interfere with goal-directed behavior.

"The findings were predicted by previous behavior and theoretical work, but given the large debate surrounding the topic, it was nice to see it so clearly in the neuronal responses," said P. Christiaan Klink, PhD, at the Netherlands Institute for Neuroscience in Amsterdam.

The monkey mind observed. The researchers trained two monkeys to play a video game in which they had to select a unique shape (the target) from an array of distracting shapes. For example, they had to choose the single circle among five squares, or vice versa. One of the five nontargets had a distinct color, making it "pop out," and the monkeys were trained to avoid this distractor and focus instead on the target.

Staying on task. Arrays of microelectrodes were implanted in the monkeys' brains to track visual processing. As the monkeys searched for the target shape, the researchers observed a corresponding pattern in the activity of neurons in area V4 of the visual cortex, a brain region that processes visual information relatively early after it is captured by the eye.

The investigators found that the unpredictable "pop-out" distractor captured the monkeys' attention, eliciting a brief enhancement of V4 activity that was then rapidly suppressed. During repeat sessions, the monkeys learned to avoid distraction and stay on task, choosing the distractor stimulus only 2% of the time.

Implications for humans? Humans probably can be trained to reach similar performance on this specific video game, Dr. Klink said. However, this does not mean that such training would necessarily help them with very different types of distractions. Long-term, however, the research may inform neurotechnological developments involved in creating visual prosthetic devices for blind patients, which is a focus of the lab. "For such neurotechnology, it might be useful to understand how the brains selects visual information for further processing," Dr. Klink said. "With prosthetic vision, we can transfer far less visual information than with natural vision. By using selection mechanisms that are similar to those of the brain itself, we hope to make it easier for future patients to use such technology." *—Miriam Karmel*

1 Klink PC et al. *PNAS*. 2023;120(9):e2210839120.

Relevant financial disclosures: Dr. Klink—Dutch Research Council: S; European Union: S: Friends Foundation of the Netherlands Institute for Neuroscience: S; Human Brain Project: S.

Mark P. Breazzano, MD

an inpatient setting; presence of an artificial indwelling line; total parenteral nutrition within the previous week; or an immunosuppressant medication within the last year.

Ophthalmic: Relatively greater preserved VA; longer duration of vision loss prior to presentation; or longer duration of ocular pain prior to presentation. Of note, presenting VA correlated with final vision.

Common masquerades. Other observed conditions included bacterial endophthalmitis (n = 16), nonfungal infectious endophthalmitis (n = 13), presumed syphilis (two eyes of one patient), and undifferentiated intermediate uveitis (two eyes of one patient).

Putting it all together. "Interestingly, the clinical presentations overall were nonspecific across other causes of infection and inflammation, including bacterial and viral," Dr. Breazzano said. Moreover, he said, "None of the patients were captured by routine ocular screening for a fungal bloodstream infection over all seven years of the study."

A note on screening guidelines. The findings add "to the body of knowledge that systemic medical management for fungal infection should not change based on a routine ocular screening examination," Dr. Breazzano said.

The issue of screening has been somewhat controversial recently, he added. For instance, the Infectious Diseases Society of America (IDSA) published guidelines recommending a dilated retinal exam, preferably by an ophthalmologist, within a week after a diagnosis of candidemia, regardless of eye symptoms.[2] However, according to guidelines issued by the Academy, routine eye exams in candidemia are a "low-value practice."[3] Other international societies also disagree with the IDSA position.[4]

What's next? More research needs to be done to elucidate presumed fungal endophthalmitis, Dr. Breazzano said. "Endophthalmitis can be a devastating disease and is, fortunately, rare. It is important that we continue to consider not only fungus as a cause but also other etiologies, even if we are confident or potentially biased [in favor of] a particular diagnosis."

—Patricia Weiser, PharmD

1 Priluck AZ et al. *Am J Ophthalmol.* Published online Feb. 21, 2023.

2 Pappas PG et al. *Clin Infect Dis.* 2016;62(4):e1-e50.

3 Breazzano MP et al. *Ophthalmology.* 2022;129(1):73-76.

4 www.rcophth.ac.uk/wp-content/uploads/2021/01/Intensive-Care-Unit.pdf. Accessed March 17, 2023.

Relevant financial disclosures: Dr. Breazzano—None.

RETINA

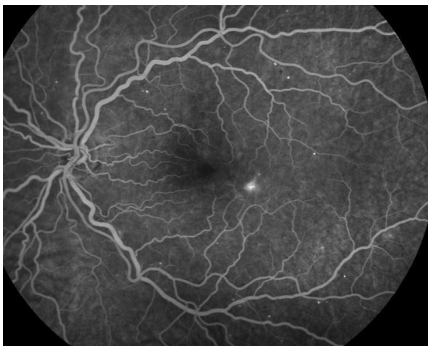
Early Anti-VEGF Fails to Improve VA in NPDR

WHEN IS IT APPROPRIATE TO USE aflibercept for patients with nonproliferative diabetic retinopathy (NPDR) but no center-involved diabetic macular edema (CI-DME)? Results from the DRCR.net Protocol W indicate that the best strategy is to regularly monitor patients and initiate treatment with aflibercept (Eylea) only when vision-threatening complications develop.[1]

The researchers investigated the effects of early aflibercept on VA and the rate of vision-threatening complications in patients with moderate to severe NPDR. Although anti-VEGF treatment reduced the risk of progression to proliferative DR and CI-DME with vision loss, the preventive injections failed to produce better VA outcomes than sham treatment.

Study rationale. Although anti-VEGF agents are used in patients with proliferative diabetic retinopathy and CI-DME with vision loss, some physicians use them for prophylaxis in patients with NPDR, said Raj Maturi, MD, at Indiana University School of Medicine and Retina Partners Midwest in Indianapolis. Dr. Maturi also served as protocol chair for the study.

Study specifics. This multicenter study involved 328 adults (399 eyes) with moderate to severe NPDR without CI-DME. Half of the eyes were injected with aflibercept, the other half with sham. All eyes received injections at one, two, and four months after enrollment, and then every four months for the rest of the first two years. Preventive treatment with aflibercept was given every four months until the four-year mark except in those whose NPDR improved to mild disease. This allowed the researchers to assess the rate of disease progression and the difference in VA between the two groups.



TOO EARLY TO TREAT. *Based on the study's findings, this patient with mild NPDR should not be treated prophylactically with aflibercept.*

Risk of progression. The researchers found that the four-year cumulative risk of developing proliferative DR or CI-DME with vision loss was lower in the anti-VEGF group than in the sham group (33.9% vs. 56.9%; $p < .001$).

Anatomic benefit and VA. The anti-VEGF therapy slowed disease progression, as measured by the diabetic retinopathy severity scale. However, no differences in VA emerged between the two groups after four years.

Monitoring is essential. Given these findings, ophthalmologists are advised to regularly monitor patients and promptly treat those who progress to proliferative disease or develop DME, Dr. Maturi said. At this time, however, prophylactic treatment is "not generally warranted" for patients who have NPDR without CI-DME, the investigators wrote. *—Christos Evangelou, PhD*

1 Maturi RK et al. *JAMA.* 2023;329(5):376-385.

Relevant financial disclosures: Dr. Maturi—None.

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.