Original Investigation | CLINICAL SCIENCES

Relationship Between Dry Eye Symptoms and Pain Sensitivity

Jelle Vehof, PhD; Diana Kozareva; Pirro G. Hysi, PhD; Juliette Harris, PhD; Ayrun Nessa; Frances K. Williams, PhD;
David L. H. Bennett, PhD; Steve B. McMahon, PhD; Samantha J. Fahy, PhD; Kenan Direk, MSc;
Tim D. Spector, PhD; Christopher J. Hammond, PhD

IMPORTANCE Dry eye disease (DED) is common, but little is known about factors contributing to symptoms of dry eye, given the poor correlation between these symptoms and objective signs at the ocular surface.

OBJECTIVE To explore whether pain sensitivity plays a role in patients' experience of DED symptoms.

DESIGN, SETTING, AND PARTICIPANTS A population-based cross-sectional study of 1635 female twin volunteers, aged 20 to 83 years, from the TwinsUK adult registry.

MAIN OUTCOMES AND MEASURES Dry eye disease was diagnosed if participants had at least 1 of the following: (1) a diagnosis of DED by a clinician, (2) the prescription of artificial tears, and/or (3) symptoms of dry eyes for at least 3 months. A subset of 689 women completed the Ocular Surface Disease Index (OSDI) questionnaire. Quantitative sensory testing using heat stimulus on the forearm was used to assess pain sensitivity (heat pain threshold [HPT]) and pain tolerance (heat pain suprathreshold [HPST]).

RESULTS Of the 1622 participants included, 438 (27.0%) were categorized as having DED. Women with DED showed a significantly lower HPT (P = .03) and HPST (P = .003)—and hence had higher pain sensitivity—than those without DED. A strong significant association between the presence of pain symptoms on the OSDI and the HPT and HPST was found (P = .008 for the HPT and P = .003 for the HPST). In addition, participants with an HPT below the median had DED pain symptoms almost twice as often as those with an HPT above the median (31.2% vs 20.5%; odds ratio, 1.76; 95% CI, 1.15-2.71; P = .01).

CONCLUSIONS AND RELEVANCE High pain sensitivity and low pain tolerance are associated with symptoms of DED, adding to previous associations of the severity of tear insufficiency, cell damage, and psychological factors. Management of DED symptoms is complex, and physicians need to consider the holistic picture, rather than simply treating ocular signs.

Author Affiliations: Department of Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital, Waterloo, London, England (Vehof, Kozareva, Hysi, Harris, Nessa, Williams, Fahy, Direk, Spector, Hammond); Department of Ophthalmology & Epidemiology, University Medical Center Groningen, Groningen, the Netherlands (Vehof); Wolfson Centre for Age-Related Diseases, King's College London, London, England (Bennett, McMahon); Division of Primary Care, University of Nottingham, University Park, Nottingham, England (Fahy); Department of Ophthalmology, King's College London, St Thomas' Hospital, London, England (Hammond).

Corresponding Author: Jelle Vehof, PhD, Department of Ophthalmology & Epidemiology, University Medical Center Groningen, Hanzeplein 1, Postbus 30.001, Groningen, the Netherlands (j.vehof@umcg.nl).

D ry eye disease (DED) is a multifactorial disease of the tears that can potentially damage the ocular surface.[1] It causes considerable morbidity, with symptoms of pain, irritation, and interference with normal visual tasks.[2] Dry eye disease is a common problem, affecting 5% to 35% of middle-aged and elderly individuals, depending on the definition used.[3-7] Women are at increased risk compared with men.[5,6,8,9]

Studies of DED and the management of patients with DED in practice are complicated by the lack of an association with objective diagnostic signs of the ocular surface.[10,11] For example, patients without any signs of DED may have symp-toms, while others with extensive signs of DED may have few symptoms. So, besides the integrity of the optical tear layer, the corneal pain system has been proposed as a central pathogenic feature of dry eye.[12,13] Moreover, the cornea is one of the most sensitive parts of the human body, since it is more densely innervated with sensory nerve fibers than any other organ.[14-16]

We hypothesized that (generalized) pain sensitivity might play an important role in the experience of DED symptoms. Therefore, we investigated the association between DED symptoms and pain sensitivity (the heat pain threshold [HPT]) and pain tolerance (the heat pain suprathreshold [HPST]) in a large group of healthy volunteers.

Methods

Participants

The local Research Ethics Committee at St Thomas' Hospital approved all procedures, and all participants provided informed consent. The experiment was conducted on 1635 white female volunteers from 1025 families (610 complete twin pairs and 415 unrelated twin participants), aged 20 to 83 years, from the TwinsUK adult registry of identical and nonidentical twins at St Thomas' Hospital, London. This cohort of mostly female twins has been recruited from the general population via successive local and national media campaigns.[17] The TwinsUK cohort is, we believe, representative of the general population and has been comparable to a UK singleton female cohort for a wide range of diseases and traits.[18] It has been used in many epidemiologic studies of healthy aging.[19] Although all participants were part of a twin pair, we did not make use of the twin relationship in this study. All participants completed extensive questionnaires gathering demographic information, clinical history, and current medications. Participants were asked not to take analgesic medication within 12 hours of the study visit, if possible, and were excluded if they did. Individuals with impaired arm function such as that caused by repetitive strain injury, neuropathy, or chemotherapy were also excluded.

DED Questionnaires

All 1635 participants were asked the following 3 questions as a proxy for having DED, which have been used separately in other population-based epidemiologic studies[5,20]: (1) "Have you ever been diagnosed (by a clinician) as having dry eye syndrome?" (2) "Do you currently use artificial tear eyedrops or gel?" and (3) "For the past three months or longer, have you had dry eyes? (This is described as a foreign body sensation with itching and burning, sandy feeling, not related to allergy)." If a participant answered yes to any of these questions, she was assigned as having DED.

In addition, to investigate pain symptoms in further detail, we asked a consecutive subset of 689 participants (from 394 families) attending for quantitative sensory testing to complete the Ocular Surface Disease Index (OSDI). The OSDI, developed by the Outcomes Research Group at Allergan, Inc, is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with DED and their effect on vision-related functioning.[21] The presence of symptoms during the past week was rated on a 5-point scale from *none of the time* to *all of the time*. The OSDI score (range, 0-100) can be calculated with a formula using the sum score of all questions. An OSDI score of 15 or higher was used to define those with DED.[21,22] Since this study is about pain sensitivity, we were particularly interested in the presence of pain symptoms. The first 3 questions of the OSDI investigate pain and discomfort symptoms by asking whether participants have experienced (1) eyes that are sensitive to light, (2) eyes that feel gritty, and (3) painful or sore eyes. Other questions relate to problems with vision and limitation of performance and/or discomfort in certain situations such as watching television and windy conditions. Pain symptoms of DED were evaluated by scoring these first 3 questions of the OSDI. An individual with a sum score of 3 or higher on those questions was regarded as having DED pain symptoms. Those who scored 0 on all these questions were regarded as having no DED pain symptoms. In addition, this subset of participants also was asked whether they had been through menopause and, if yes, if they had used hormone therapy.

HPT and HPST

Quantitative sensory testing using heat as the stimulus was used to capture the variation in participants' perception of pain (thus, endogenous pain sensitivity) by measuring pain threshold and tolerance.[23] The volar surface of the forearm was inspected for possible confounding factors (eg, cuts, bruises, burns, or skin irritation). The participant, while seated, placed her arm on the table in front of her. A 25 × 50-mm probe connected to a Modular Sensory Analyzer (Somedic) was placed on the volar surface of the upper central forearm and secured gently with a fabric-covered band. The starting arm for quantitative sensory testing was alternated, depending on the day of the week, and recorded. The HPT, a measure of pain sensitivity, was measured by slowly heating the probe from an adaptation temperature of 32°C at a rate of 0.5°C per second until the participant perceived the stimulus as changing from hot to painful and stopped the experiment by pressing a button, at which point the temperature (the HPT) was logged, with the probe temperature then quickly returning to 32°C. If the probe reached 50°C, the machine automatically returned to the adaptation temperature to prevent thermal burning. All participants were given standardized instructions before having a practice run at measuring the HPT. Following the HPT assessment, the probe was removed and replaced at the same position on the opposite arm. The HPST, a measure of pain tolerance, was ascertained by heating the probe from an adaptation temperature of 32°C at a rate of 1°C per second until the participant perceived the stimulus as changing from painful to unbearable and stopped the experiment by pressing a button. At this point, the temperature (the HPST) was logged, and the probe temperature quickly returned to 32°C. If the probe reached 50°C, the machine automatically returned to the adaptation temperature to prevent thermal burning. All participants were given standardized instructions. The HPST was assessed without a practice run.

Statistical Analysis

Data were analyzed with the SPSS statistical package (version 17.0; SPSS, Inc). The Kolmogorov-Smirnov test was used to analyze the distribution normality of the variables ($P > .05$). First, the demographics of the study population and the prevalence of the different DED criteria were calculated. Participants were divided into having high (below median value HPT) or low (above median value HPT) pain sensitivity. We analyzed the relationship of potential confounders—age and menopausal status with DED and high pain sensitivity—by using logistic regression. Next, mean HPT and HPST values were calculated per group using several DED criteria. To compare differences in the HPT and HPST between participants with and

Table. Mean HPT and HPST in Participants With and Without DED, Using Several Criteria

	No. (%)		Mean HPT, °C			Mean HPST, °C		
DED Case Definition	Case	No Case	Case	No Case	P Value[a]	Case	No Case	P Value[a]
All (N = 1635)								
DED diagnosis by physician	218 (13.4)	1408 (86.6)	45.59	45.41	.76	47.07	47.13	.46
Use of artificial tears	260 (16.2)	1348 (83.8)	45.42	45.45	.58	47.01	47.14	.27
DED symptoms past 3 mo	354 (21.7)	1281 (78.3)	45.25	45.5	.15	46.91	47.18	.01[b]
Any of above	438 (27.0)	1184 (73.0)	45.22	45.51	.03[b]	46.89	47.2	.003[b]
Subset (n = 689)								
OSDI sum score 15 or more	217 (31.5)	472 (68.5)	44.69	44.84	.12	46.6	46.8	.15
DED pain symptoms	118 (17.1)	336 (48.8)	44.27	45.1	.008[b]	46.28	46.9	.003[b]

Abbreviations: DED, dry eye disease; HPST, heat pain suprathreshold; HPT, heat pain threshold; OSDI, Ocular Surface Disease Index.

[a] P value for a difference between groups calculated by the Mann-Whitney test.

[b] Statistically significant (P < .05).

without DED, we used the Mann-Whitney test. Finally, logistic regression was used to analyze whether women with high pain sensitivity had more DED pain symptoms than those with low pain sensitivity. These results were corrected for potential confounders. *P* < .05 was considered statistically significant in all analyses.

Results

Demographics and Prevalence of DED

The median age of the 1635 participants was 60 years (first and third quartiles, 54 and 66 years, respectively). All participants were female. Depending on the question, up to 1.6% of participants answered "not sure" and were excluded from the analysis of that item from the questionnaire. Of the included participants, 438 (27.0%) were categorized as having DED from questionnaire answers, with 354 (21.6%) having dry eye symptoms in the past 3 months, 260 (16.2%) using artificial tears, and 218 (13.2%) being diagnosed with DED by a physician.

Of the consecutive subset of 689 participants (median age, 60 years; first and third quartiles, 52 and 65 years, respectively) who completed the OSDI questionnaire, 217 (31.6%) were diagnosed with DED by having an OSDI score higher than 15. In total, 13.7% were diagnosed by both the OSDI and the 3 questions, 17.8% by the OSDI but not by any of the 3 DED questions, and 14.1% by any of the 3 DED questions but not by the OSDI. Of the participants, 118 (17.1%) had an OSDI pain sum score of 3 or higher, while 338 (48.8%) had no DED pain symptoms. Although age was associated with having DED symptoms in the past 3 months (odds ratio [OR], 1.014 per year; *P* = .03, whole sample), it was not associated with having DED pain symptoms on the OSDI (OR, 1.001 per year; *P* = .94, random subset). Menopausal status or hormone therapy showed no statistically significant association with DED pain symptoms in the subset.

Pain Sensitivity

The mean (SD) HPT and HPST of all participants were 45.4°C (2.5°C) and 47.1°C (1.8°C), respectively. The median HPT was 46.0°C, so those with a lower value were regarded as having high pain sensitivity. Age showed a strong association with high pain sensitivity (OR, 1.03 per year; *P* < .001). Menopausal status showed a statistically significant association with high pain sensitivity as well (OR, 1.55 if postmenopausal; *P* = .02), which was independent of age (OR, 1.72; *P* = .04, when corrected for age). The use of hormone therapy did not alter the association between menopause and pain sensitivity. The mean HPTs among those with and without DED, using several criteria, are presented in the **Table**. No significant differences in the HPT or HPST were found between participants with and without a diagnosis of DED by a physician or those who did and did not use artificial tears. However, a significantly lower HPST was observed in women who had dry eye symptoms in the past 3 months compared with those who had not (*P* = .01). Combining all 3 DED questions, persons with DED showed a significantly lower HPT (*P* = .03) and HPST (*P* = .003) than those without DED.

In the random subset that completed the OSDI questionnaire, the HPT and HPST were lower in women who reached the cutoff OSDI score of 15 for DED than in those who did not, although this difference was not significant in this smaller sample size (*P* = .12 and *P* = .15, respectively; Table). A strong significant association between the presence of pain symptoms and high pain sensitivity was found (*P* = .008 for the HPT and *P* = .003 for the HPST). In addition, participants with a high pain sensitivity had DED pain symptoms approximately 75% more often than those with a low pain sensitivity (31.2% vs 20.5%; OR, 1.76; 95% CI, 1.15-2.71; *P* = .01). The strength of the association increased after correction for age as a possible confounder (OR, 1.95; 95% CI, 1.24-3.06; *P* = .004). Including menopausal status as well in this regression model did not alter the association (OR, 1.89; 95% CI, 1.20-2.98; *P* = .006).

Discussion

The current data provide the first empirical evidence that individuals with DED diagnosed by population-based questionnaires show altered pain sensitivity. Specifically, this study demonstrates that those with DED pain and discomfort symptoms have a lower pain threshold and pain tolerance of a heat-based stimulus than those without DED. Similarly, participants with HPTs below the median were almost twice as likely to report DED pain symptoms as those above the median. These findings support the hypothesis that a subset of persons with DED is more sensitive to pain.

In future studies, it would be interesting to investigate whether patients without signs but with symptoms of DED particularly show higher pain sensitivity compared with those with both signs and symptoms, or whether minor signs of DED provoke pain in patients with low pain thresholds. Similarly, given the generally poor relationship between symptoms and signs in DED, it would be useful to examine whether any particular clinical findings in DED populations (such as corneal staining, reduced tear breakup time, or reduced Schirmer values) relate to pain sensitivity and pain symptoms.

Pain is a complex, multidimensional sensory experience that is difficult to represent as a single parameter. Quantitative sensory testing has been applied to assess pain, since it is a sensitive and quantitative tool, but the stimulus modalities applied and perceptual responses vary widely.[24] Our group elected to use the HPT tests because we previously have shown them to be reliable and heritable.[25] More recently, we have found that the HPST is more reliable and reproducible than the HPT in our cohort (J.H., A.N., F.K.W., D.H.L.B., and S.B.M., unpublished data, 2007), and indeed the present study has discovered stronger associations using this measure than the HPT (Table). Results vary with HPT tests in other chronic pain conditions: some studies on chronic back pain report higher and others report lower pain thresholds, which may reflect differing testing protocols, definitions, and patient populations.[26] Decreased heat pain detection threshold (ie, increased pain sensitivity) has been reported in burning mouth syndrome, another chronic pain condition that may reflect subclinical neuropathic pain or central pain.[27]

Consistent evidence demonstrates that psychological factors influence the perception of pain and pain sensitivity, exerting a significant influence on the development and maintenance of chronic pain conditions.[28,29] Similarly, anxiety and depression are more common among patients with DED,[30] and while this may be secondary to reduced quality of life caused by the symptoms of disease, psychological distress may be associated with increased sensitivity and more symptoms. Moreover, Kim et al[31] recently have shown that depression is associated with DED only in patients who have a normal to mildly reduced tear production. This association between depression and DED was not found in patients with a Schirmer score of 5 mm or lower. Patients with a chronic pain condition also appear to have morpho-

metric changes on brain magnetic resonance imaging, particularly in the cingulate cortex, insula, and temporal lobe, which all deal with supraspinal nociceptive processing.[32] It remains to be proven whether this is a cause or a consequence of the pain, but hope remains that some way of modulating brain processing may break the cycle of chronic pain.

It has been shown in human experiments that selective stimulation of corneal cold receptors by small decreases in temperature leads to awareness of cooling sensations that become increasingly unpleasant with lower temperature.[33,34] If the same pain pathways are involved in the skin nerves, increased sensitivity of the skin could be associated with increased sensitivity of the corneal nerves, which provides a direct explanation for our results. However, we used increasing instead of decreasing temperature, but similar mechanisms might be involved. Belmonte[35] first proposed that altered expression of membrane ion channels in the cornea could give rise to abnormal spontaneous and stimulus-evoked nerve firing in damaged nerves after photorefractive surgery. This study also speculated that these abnormal sensory discharges are read by the brain as ocular surface dryness. It may be that healthy variation in expression of these ion channels may cause variable pain sensitivity and symptoms of dry eye.

With regard to pain sensitivity, some authors have found corneal *hyper*sensitivity in DED,[36,37] whereas others have found *hypo*sensitivity of the cornea.[38-41] It has been suggested that tear hyperosmolarity and its inflammatory consequences lead to epithelial injury in the cornea, which subsequently stimulates corneal nerve endings, leading to an increased sensory drive from the ocular surface.[42] The reasons for these paradoxical results of hypersensitivity and hyposensitivity of the cornea in DED remain to be fully explained. Longitudinal studies may help in the future.[42] For reasons of clarity, the present study is different from those studies, since we measured a "generalized" pain sensitivity via arm HPT and not (changes in) sensitivity in the affected organ (ie, the cornea), as done in the DED studies cited.

The TwinsUK cohort was chosen to study DED because it is an extensively phenotyped and genotyped large national volunteer cohort of perimenopausal women with an expected high prevalence of DED. While the results of this study are based on a twin cohort, random selection of 1 individual within each twin pair did not alter the effect size of the results (not shown). The age-related rise in the prevalence of DED in our cohort using questionnaire-based diagnostic criteria is similar to that found in epidemiologic studies of women of a similar age.[9] As shown in our results, DED prevalence is highly variable when different criteria and questions are used. Finally, the results may not necessarily be generalizable to men.

This study has demonstrated that high pain sensitivity and low pain tolerance are associated with pain symptoms in DED, adding to previous associations among the severity of tear insufficiency, cell damage, and psychological factors. Management of DED symptoms is complex, and physicians need to consider the holistic picture, rather than simply treating ocular signs.

REFERENCES

1. Dry Eye WorkShop. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):108-152.

2. Tutt R, Bradley A, Begley C, Thibos LN. Optical and visual impact of tear break-up in human eyes. *Invest Ophthalmol Vis Sci*. 2000;41(13):4117-4123.

3. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology*. 1998;105(6):1114-1119.

4. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology*. 2003;110(6):1096-1101.

5. Moss SE, Klein R, Klein BE. Long-term incidence of dry eye in an older population. *Optom Vis Sci*. 2008;85(8):668-674.

6. Uchino M, Nishiwaki Y, Michikawa T, et al. Prevalence and risk factors of dry eye disease in Japan: Koumi study. *Ophthalmology*. 2011;118(112):2361-2367.

7. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):93-107.

8. Yao W, Davidson RS, Durairaj VD, Gelston CD. Dry eye syndrome: an update in office management. *Am J Med*. 2011;124(11):1016-1018.

9. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol*. 2009;3:405-412.

10. Lemp MA. Advances in understanding and managing dry eye disease. *Am J Ophthalmol*. 2008;146(3):350-356.

11. Lemp MA. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. *CLAO J*. 1995;21(4):221-232.

12. Belmonte C, Gallar J. Cold thermoreceptors, unexpected players in tear production and ocular dryness sensations. *Invest Ophthalmol Vis Sci*. 2011;52(6):3888-3892.

13. Rosenthal P, Borsook D. The corneal pain system, part I: the missing piece of the dry eye puzzle. *Ocul Surf*. 2012;10(1):2-14.

14. Schimmelpfennig B. Nerve structures in human central corneal epithelium. *Graefes Arch Clin Exp Ophthalmol*. 1982;218(1):14-20.

15. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res*. 2003;76(5):521-542.

16. Rózsa AJ, Beuerman RW. Density and organization of free nerve endings in the corneal epithelium of the rabbit. *Pain*. 1982;14(2):105-120.

17. Moayyeri A, Hammond CJ, Hart DJ, Spector TD. The UK Adult Twin Registry (TwinsUK Resource). *Twin Res Hum Genet*. 2013;16(1):144-149.

18. Andrew T, Hart DJ, Snieder H, de Lange M, Spector TD, MacGregor AJ. Are twins and singletons comparable? a study of disease-related and lifestyle characteristics in adult women. *Twin Res*. 2001;4(6):464-477.

19. Moayyeri A, Hammond CJ, Valdes AM, Spector TD. Cohort profile: TwinsUK and healthy ageing twin study. *Int J Epidemiol*. 2013;42(1):76-85.

20. Gulati A, Sullivan R, Buring JE, Sullivan DA, Dana R, Schaumberg DA. Validation and repeatability of a short questionnaire for dry eye syndrome. *Am J Ophthalmol*. 2006;142(1):125-131.

21. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol*. 2000;118(5):615-621.

22. Pult H, Riede-Pult BH. A new modified fluorescein strip: its repeatability and usefulness in tear film break-up time analysis. *Cont Lens Anterior Eye*. 2012;35(1):35-38.

23. Heldestad V, Linder J, Sellersjö L, Nordh E. Reproducibility and influence of test modality order on thermal perception and thermal pain thresholds in quantitative sensory testing. *Clin Neurophysiol*. 2010;121(11):1878-1885.

24. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain*. 2009;10(6):556-572.

25. Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. *Brain*. 2007;130(pt 11):3041-3049.

26. Lautenbacher S, Fillingim R. *Pathophysiology of Pain Perception*. New York, NY: Kluwer Academic/Plenum; 2004:67.

27. Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, Ughetto S, Woda A. Effect of lingual nerve block on burning mouth syndrome (stomatodynia): a randomized crossover trial. *Pain*. 2010;149(1):27-32.

28. MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. *Arthritis Rheum*. 2004;51(2):160-167.

29. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85(3):317-332.

30. Li M, Gong L, Sun X, Chapin WJ. Anxiety and depression in patients with dry eye syndrome. *Curr Eye Res*. 2011;36(1):1-7.

31. Kim KW, Han SB, Han ER, et al. Association between depression and dry eye disease in an elderly population. *Invest Ophthalmol Vis Sci*. 2011;52(11):7954-7958.

32. May A. Structural brain imaging: a window into chronic pain. *Neuroscientist*. 2011;17(2):209-220.

33. Acosta MC, Belmonte C, Gallar J. Sensory experiences in humans and single-unit activity in cats evoked by polymodal stimulation of the cornea. *J Physiol*. 2001;534(pt 2):511-525.

34. Acosta MC, Tan ME, Belmonte C, Gallar J. Sensations evoked by selective mechanical, chemical, and thermal stimulation of the conjunctiva and cornea. *Invest Ophthalmol Vis Sci*. 2001;42(9):2063-2067.

35. Belmonte C. Eye dryness sensations after refractive surgery: impaired tear secretion or "phantom" cornea? *J Refract Surg*. 2007;23(6):598-602.

36. De Paiva CS, Pflugfelder SC. Corneal epitheliopathy of dry eye induces hyperesthesia to mechanical air jet stimulation. *Am J Ophthalmol*. 2004;137(1):109-115.

37. Tuisku IS, Konttinen YT, Konttinen LM, Tervo TM. Alterations in corneal sensitivity and nerve morphology in patients with primary Sjögren's syndrome. *Exp Eye Res*. 2008;86(6):879-885.

38. Xu KP, Yagi Y, Tsubota K. Decrease in corneal sensitivity and change in tear function in dry eye. *Cornea*. 1996;15(3):235-239.

39. Bourcier T, Acosta MC, Borderie V, et al. Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci*. 2005;46(7):2341-2345.

40. Benítez-Del-Castillo JM, Acosta MC, Wassfi MA, et al. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. *Invest Ophthalmol Vis Sci*. 2007;48(1):173-181.

41. Villani E, Galimberti D, Viola F, Mapelli C, Ratiglia R. The cornea in Sjogren's syndrome: an in vivo confocal study. *Invest Ophthalmol Vis Sci*. 2007;48(5):2017-2022.

42. Bron AJ, Yokoi N, Gafney E, Tiffany JM. Predicted phenotypes of dry eye: proposed consequences of its natural history. *Ocul Surf*. 2009;7(2):78-92.