Article

Detectability and Bias Indices of Pneumatic Corneal Stimuli Using Signal Detection Theory

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Purpose: To evaluate the feasibility of using signal detection theory (SDT) in estimating criterion and detectability indices for corneal pneumatic stimuli and test corneal psychophysical data against linking hypotheses from nonprimate physiology using Bayesian analysis.

Methods: Corneal pneumatic stimuli were delivered using the Waterloo Belmonte esthesiometer. Corneal thresholds were estimated in 30 asymptomatic participants and $1.5\times$ threshold stimuli were used as signals (with 0.4 probability). There were 100-trial mechanical and cold stimulus experiments and 50-trial chemical experiments. Trials were demarcated auditorily and "yes" or "no" recorded after each trial. Cold stimulus experiments were conducted with 0.6 signal probability. Criterion (c), likelihood ratio ($\ln\beta$), and d' were calculated from the yes-no responses.

Results: Average d' was 0.59 ± 0.1, 1.65 ± 0.37, and 1.14 ± 0.3 units for cold, mechanical, and chemical stimuli, respectively. Bayes factors obtained using Bayesian analysis of variance mildly favored ($BF_{10} = 1.55$) differences between d's of the stimulus types, with no support for differences in criteria between stimulus types. Multiple comparisons of d' supported linking hypotheses based on nociception and nerve conductance theories.

Conclusions: Our experiments are the first to demonstrate the feasibility of estimating SDT indices and test different hypotheses. The conservative strategy (reporting "no" more often) chosen by participants was anticipated due to relatively large proportion of catch trials.

Translational Relevance: SDT when using pneumatic esthesiometry is vital to evaluate bias in responses of participants. Considering the varied forms of inherent noise in the corneal sensory system, SDT is critical to understand the sensory and decisional characteristics.

Introduction

The corneal neural network has been assumed to be similar to the somatic pain network, consisting of a complex network of neurons with the nerve terminals on the corneal surface detecting potentially noxious stimuli and other ocular surface changes.[1–4] The human cornea is considered one of the most sensitive and most densely innervated structures of the human body, but its underlying sensory processes are still unclear perhaps partly due to the lack of electrophysiologic studies.[3,5–8] Traditionally, corneal thresholds have been used as estimates of human corneal sensory processing, whereas the underlying neuro-physiologic concepts are adapted from the electrophysiologic studies on cat, rabbit, and guinea pig corneas.[3,4,9–17] However, these thresholds are susceptible to bias (something unable to have been determined during or after these experiments),[18,19] and therefore in this study, we would like to use signal detection theory (SDT) to estimate both sensory (detection) and non-sensory (decision or bias) components of the processing of pneumatic corneal stimulation and test the support provided by these detection and decision estimates using evidence based on nonprimate electrophysiology.[20–23]

Among many others, there are two theories about sensory processing of corneal stimuli we will directly test, based on nociception and nerve conductance.

Histochemical and microscopy studies of human cornea and electrophysiologic studies of nonprimate corneas have identified two types of corneal nerve fibers based on conduction velocities, diameter, tortuosity, and thickness of myelin sheath surrounding the axons: these are thinly myelinated fast-conducting Aδ fibers and unmyelinated slow-conducting C fibers.[4,10–12,24,25] In addition, most nonprimate corneal electrophysiologic studies have identified three functional types of sensory receptors (mechano-nociceptors, polymodal nociceptors, and cold thermoreceptors) that conduct nerve impulses either through Aδ or C fibers.[3,13,14,26,27] The cold thermoreceptors and polymodal nociceptors have been shown to conduct impulses through the C fibers, whereas rapidly adapting low-threshold mechano-sensitive nociceptors use Aδ fibers for an instantaneous response to the nociceptive stimuli.[25,27,28] Since there is no systematic neurophysiologic examination on the effects of human corneal stimulations, the presence of receptors/channels in the human cornea has been evaluated psychophysically.[29] Feng and Simpson[29] have hypothesized multiple corneal psychophysical channels in the human cornea, and the detection of the human corneal and conjunctival stimuli has been shown to be complex due to the interdependence of these components of the ocular surface sensory processing system (both within and between the cornea and conjunctiva).

The sensitivity of the ocular surface is usually measured with an esthesiometer such as the Cochet-Bonnet esthesiometer[30] and the Belmonte esthesiometer.[3,28,31–33] Traditionally, corneal sensitivity has been estimated using a classical psychophysical technique such as the method of limits, method of constant stimuli, or (more recently) staircases.[3,24,31,32,34–37] The detection threshold (generally, the statistically lowest stimulus intensity reliably detected by the participants[18]) has frequently been used to measure ocular surface sensation.[32,34,36,38–40] However, these thresholds have been found to vary and often produced conflicting results when compared between groups[2,33,40] and with or without dry eye disease (among others).[4,33,41,42] Generally, participants were also able to correctly identify suprathreshold stimulus type above chance when presented in random order (except the mechanical one, identified as mechanical about half the time and reported as a chemical, hot, or cold stimulus approximately equally for the rest of the time).[43] Other aspects of ocular surface sensory processing that also have been examined using pneumatic esthesiometry include adaptation to the stimuli,[44–46] difference thresholds,[47] and hypersensitivity.[42,48,49]

In classical psychophysics, the decision criterion is assumed to be fixed (and therefore cannot be assessed; only the threshold is estimated). The observer's criterion, both if it is constant or if it varies during the psychophysical test, may lead to bias in response to a stimulus.[18,19] Each observer chooses their own decision criteria based on multiple factors that are available to them at the time of the experiment, including the previous experience, characteristics of the instruction, frequency of the signal perceived, and the intensity of the stimulus.[50,51] When the stimulus is presented, if the result of the sensory process exceeds the decision criteria, a "yes" response would be provided by the participant or else a "no" would be provided. However, in an experiment, the participants might choose a liberal or a conservative criterion (being more likely to say "yes" or less likely to say "yes," respectively) or also might change within an experiment. Therefore, because the criterion in a classical method cannot be controlled (or evaluated), the threshold obtained is not independent of bias. The criterion may change depending on the participant's level of habituation, anticipation, or both.[18,19] Non-sensory factors such as anxiety, personality, or previous experiences have been reported to influence the criterion while detecting the painful stimuli.[52–55]

Unlike classical methods, SDT has been used in examining both sensory and decisional aspects of responses to the painful stimuli since pain is subjective and the perception of pain could vary.[20–22,56,57] There are also reports that have questioned the use of SDT in pain literature.[58,59] However, the utility of the SDT in somatic, dental, and other areas of pain perception has been demonstrated in several studies.[53,56,58,60–71] The sensory component of the pain perception is given by the detectability (d') and the decisional aspects are given by the criterion (c) and likelihood ratios (lnβ). The d' provides the participant's ability to detect a stimulus from the background noise, and the location of the c on the decision axis defines the general tendency of the participants to respond yes-no to the trials.[72]

Since electrophysiologic studies are not available on human cornea, linking propositions (as explained by Teller[73]) are used in this study to understand the relationship between the psychophysical data of human ocular surface sensitivity and the electrophysiologic studies on cat and rabbit corneas. In making these links in this article, we acknowledge the scientific tenuousness of relating primate human and conscious data to primarily extracellular neural events measured in unconscious nonprimates. Since, currently, these are the only corneal electrophysiologic data, all we are able to do is test specific linking hypotheses, attempting to

account for our data based on these extant results. The linking hypotheses are tested using Bayesian analyses, which provide a measure of support provided by the data pertaining to the hypothesis tested. Several studies have shown the effectiveness of using Bayesian data analysis in place of the traditional frequentist model of null hypothesis significance testing (NHST) because it allows the researchers to consider both null and alternate hypotheses while interpreting the results in terms of the probability (in this instance) using the Bayes factor (BF) and 95% high-density intervals (HDIs).[74–76]

The main aim of this study is to test the utility of an SDT approach to obtain d', c, and $\ln\beta$ of the suprathreshold corneal pneumatic stimuli in "normals." Another aim is to test these psychophysical data against different theories that are proposed, using animal models as direct representations of the human corneal sensory system.

Hypothesis

- The detection theory indices of suprathreshold stimuli are different between the stimulus types.

Restrictive Hypothesis for Bayesian Testing

1. Detection theory indices of the nociceptive stimuli (mechanical and chemical) are different from the non-nociceptive (cool) stimuli.

$$((Chemical = Mechanical) \neq Cold)$$

Hypothesis 1 examines the linking hypothesis that nociceptive corneal receptors detect mechanical and chemical stimuli, whereas cold stimuli are sensed by non-nociceptive cold receptors.

2. Detection theory indices of the mechanical stimuli (myelinated Aδ fibers) are different from the rest (unmyelinated C fibers).

$$((Chemical = Cold) \neq Mechanical)$$

Hypothesis 2 examines a nerve conductance linking hypothesis that mechanical processing is primarily by faster conducting Aδ fibers, producing sharp pain, whereas the other (cool and chemical) stimuli are processed using slower conducting C fibers.

3. Detection theory indices of chemical processing differ from mechanical and cool indices.

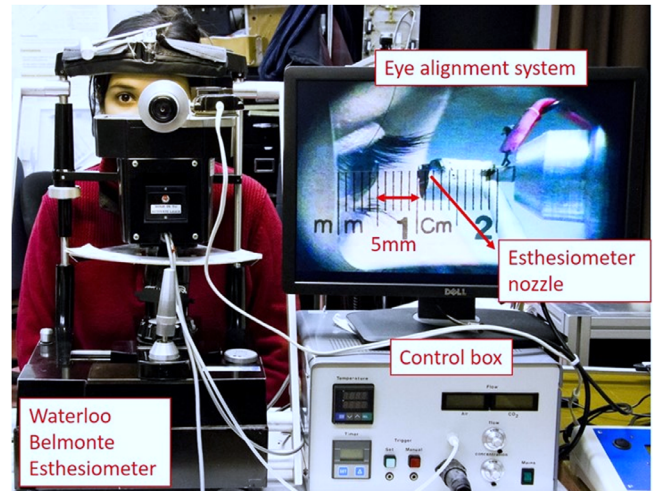$$((Cold \text{ (mL/min)} = Mechanical \text{ (mL/min)}) \neq Chemical \text{ (\%CO}_2\text{))}$$

Figure 1. The control box and alignment video camera setup of the Waterloo Belmonte pneumatic esthesiometer.

Hypothesis 3 examines the theory that the cool and mechanical stimuli are a distinct group and are different from chemical stimuli.

Methods

Ethics Statement

This project was reviewed and approved by the University of Waterloo Office of Research Ethics (ORE #19252) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the participants.

Subjects and Study Protocol

Experiments were conducted to measure the d', c, and $\ln\beta$ of suprathreshold pneumatic corneal stimuli, and the experiments were divided based on the type of the stimulus used. Participants were recruited separately for each stimulus type using convenience sampling from the graduate student community of the School of Optometry and Vision Science, University of Waterloo. Participants had no history of any ocular surface abnormalities, had no systemic conditions that might affect the ocular surface, and were asymptomatic at the time of study visit. Contact lens wearers were advised not to wear their lenses on the day of the study visit. The ocular surface was screened using slit-lamp biomicroscopy. The Waterloo Belmonte esthesiometer[32] was used to deliver pneumatic stimuli to the center of the corneal surface (Fig. 1). After the end of each visit, the ocular surface was evaluated using slit-lamp biomicroscopy and fluorescein staining.

Esthesiometry

The stimuli were presented using the Waterloo Belmonte esthesiometer, and the stimulus types used were mechanical, chemical, and cold.[31,46,47] The mechanical stimulus was medical air heated to 50°C (which translates to approximately 33°C at the ocular surface[47,77]). The "cold" or "cool" (non-noxious) stimulus was room-temperature medical air that was estimated to reduce the corneal surface temperature by 1.4°C.[77] The flow rate of the stimulus through the nozzle was either increased or decreased to change the mechanical and cold stimulus intensity. The mechanical threshold was always obtained before the chemical threshold estimate, as flow rate for the chemical stimulus was set to half of the mechanical threshold to avoid any mechanical effect contaminating the participants' indices with the chemical stimulus. The carbon dioxide (CO_2) proportion in the medical air (%CO_2) was systematically varied at a constant flow rate (half mechanical threshold) to change the intensity of the chemical stimulation. The stimulus duration of mechanical and cold stimuli was 3 s, and the chemical stimuli were presented for 2 s. The esthesiometer nozzle was positioned 5 mm in front of the corneal surface. Participants received instructions read from a script before each experiment. Additional computer-controlled tones demarcated the stimulus intervals indicating times before and after, during which participants could blink and during which it was requested that they not blink. An additional audio prompt was used during the chemical trials because the previous stimulus air column had to be removed after each trial before the next chemical stimulus was presented. During this interval, participants were explicitly instructed to keep their eyes closed or to look down so that their eyelids completely prevented the purged air from stimulating their ocular surface. Each trial consisted of either a signal (stimulus) or a catch trial (no stimulus). After each trial, participants responded either "Yes, the signal was present" or "No, there was no stimulus" using a button box. Participants were also instructed at the start of each experiment to respond based on the irritation (in the case of the mechanical stimulus), stinging/burning (chemical), or cooling "breezy" sensation (for the cold stimulus). The instructions to participants were identical for mechanical, chemical, and cold stimuli except for detailing the stimulus type itself. Participants could blink freely between trials, and the intertrial intervals were approximately 10 s for mechanical and cold stimuli and at least 30 s for chemical stimuli. The experiment (audio prompts, stimuli intensities, and presentation sequences) and the participant's response recordings were automated using the custom software. Breaks were provided at the halfway mark of the experiment and when requested by the participants in an attempt to minimize the fatigue.

Experiment 1: Detectability and Bias of Non-nociceptive Suprathreshold Pneumatic Corneal Cold Stimuli

This experiment with cold stimuli included two study visits, and 9 of 10 participants recruited were able to complete both study visits. In each visit, thresholds were measured twice using the ascending method of limits (AMOL) and averaged. The SDT trials were conducted following the threshold experiment. There were 100 trials in each visit, but the stimulus probability was 0.4 or 40% (40% signal trials and 60% catch trials) in the first visit and 0.6 or 60% in the second visit. The initial protocol used 0.4 stimulus probability; it was subsequently decided to add 0.6 stimulus probability to the protocol, and these data were collected after all of the 0.4 stimulus probability experiments were completed. It was anticipated that participants would adopt different criteria at each visit (stricter criteria on the first visit and more liberal on the second visit). A suprathreshold stimulus of the 1.5× threshold was used in the signal trials. Catch trials were randomly presented during the experiment and the audio prompts/instructions for the catch trials were the same as the signal trials, but no stimulus was presented during the trial. The pre-SDT instructions to the participants were the same for both visits. Based on the results of this dual-criteria experiment, the stimulus probability for nociceptive stimuli experiment (Experiment 2) was chosen.

Experiment 2: Detectability of the Nociceptive Suprathreshold Pneumatic Corneal Stimuli

Twenty participants (10 for each type of stimulus) were recruited. The nociceptive stimuli used were mechanical and chemical 1.5× threshold stimuli, and the experiments were conducted on two separate study visits. For the mechanical stimuli, the threshold was derived initially by averaging two AMOL estimates, followed by SDT experiments. For the chemical stimuli, the mechanical thresholds (to determine the flow rate of chemical stimuli) were measured first, followed by the chemical thresholds (by increasing the %CO_2 in the stimulus column with the flow rate at 50% of the mechanical threshold) and chemical SDT experiments. Similar to the cold SDT experiment, the mechanical

SDT experiment was conducted using a $1.5\times$ threshold intensity stimulus. The chemical SDT experiment was conducted using a $1.5\times$ CO_2 threshold intensity stimulus. A stimulus probability of 40% was used in both the mechanical and chemical SDT experiments since the variances of SDT parameters were lower in Experiment 1 with 40% probability (see Results). There were 100 trials in the mechanical experiment and 50 trials in the chemical experiment. The reduction in the number of trials for the chemical experiment was necessary because of the longer interstimulus intervals needed to purge previous stimulus air columns and prepare and deliver the next stimulus.

Analysis

Signal Detection Theory Analysis

Theoretically, participants were required to separately identify the distribution of the neurosensory effect when the stimulus was present (the "signal") from the distribution of the neurosensory effect when the stimulus was absent (the "noise"). The *yes-no* responses were compiled for each participant separately for each stimulus type, and the hit rates (HRs) (the proportion of signal trials correctly identified as a signal) and false alarm rates (FARs) (proportion of catch trial incorrectly identified as a signal) were calculated. Using the HR and FAR, the detection theory indices were calculated using the formula in the Excel spreadsheet.[72]

The d' is the separation between the means of signal ($z\,(HR)$) and noise distribution ($z\,(FAR)$) in standard deviation units (Equation (1)). The d' is a parametric estimate based on the assumption of both signal and noise being Gaussian normal distributions, and A_z provides the nonparametric estimation of detectability. Bias is determined (among others) using the criterion (c) and likelihood ratio (β).[18,51,72] The location of the criterion on the decision axis defines the general tendency of the participants to respond yes-no to the trials. The criterion is effectively the distance between the neutral point (where there is no bias) and the location of the criterion in standard deviation units (Equation (2)). The other form of bias determination, β, is the estimation of how likely the participant would respond "yes" to each trial (Equation (3)).

$$d' = z\,(HR) - z\,(FAR) \tag{1}$$

$$c = -0.5\,(z\,(HR) + z\,(FAR)) \tag{2}$$

$$\beta = \exp\left(0.5\left(z\,(FAR)^2 - z\,(HR)^2\right)\right) \tag{3}$$

Table 1. Jeffreys Interpretation of Bayes Factor (BF_{10})[82,83]

Bayes Factor (BF_{10})	Support for Alternate Hypothesis (Jeffreys)
1–3	Anecdotal
3–10	Substantial
10–20	Strong
20–30	Strong
30–100	Very strong
100–150	Decisive
>150	Decisive

Statistical Data Analysis

The detection theory indices for the cold stimuli from two different stimulus probabilities were compared using the Bayesian paired *t*-test, and the detection theory indices between three stimulus types were compared using the Bayesian analysis of variance. Also, Bayesian correlations were used to find the relationship between the thresholds using AMOL and the indices of detection theory. Alongside Bayesian analysis, appropriate NHST analyses were also conducted for comparison. R software[78,79] was used in the analysis: the BayesianFirstAid[80] R package was used to obtain Bayesian probabilities and HDI estimates for paired *t*-test and correlations. The prior used by the "BayesianFirstAid" package for Bayesian posterior estimation was an exponential distribution.[74,80] The 95% HDIs provide estimates of the ranges of values between which the highest probability densities of the data are located.[74] If the 95% HDI of the paired *t*-test involved 0, then there is enough evidence that zero mean difference is a possibility. Similarly, if the 95% HDI in Bayesian correlation analysis included 0, it indicates there is enough evidence in the data to demonstrate no association between the variables compared.

In addition to 95% HDIs, Bayes factors were estimated for both paired *t*-tests and analyses of variance (ANOVAs) using the BayesFactor[81] R package. The prior distribution to calculate Bayes factor was a noninformative Jeffreys prior on means of the distribution and a Cauchy prior with r scale $= \sqrt{2}/2$ (or 0.707) on standardized effect size.[81] The BFs obtained from the analysis were interpreted with Jeffreys scaling for Bayes factors[82,83] (Table 1), which provides a ratio of the probability of the data favoring one hypothesis relative to another.[75] The BF is typically denoted by BF_{10} (data in favor of the alternate hypothesis) or BF_{01} (data in favor of the null hypothesis). Multiple comparisons (restrictive hypotheses 1, 2, and 3) between the stimulus types were tested by

taking advantage of the BF analysis as explained by Morey.[84–86]

The variance of the paired samples was tested using the Bonett-Seier test of scales for paired samples using the PairedData R package.[87] The violin plots (vioplot R package) were used in place of regular boxplots as they provide a distribution of the data along with the boxplot.[88]

Results

Thresholds

Even though the main aim of the study was to evaluate the detection theory indices, to scale the stimulus relatively across the participants, the threshold from the AMOL was used as a baseline for the detection theory experiment. The average cold thresholds ($\pm$ SE) for visits 1 and 2 were 27.43 $\pm$ 3.79 and 31.14 $\pm$ 9.18 mL/min, respectively. The Bayesian analysis of the paired differences of the thresholds obtained between visits suggested a paired difference of zero as a credible outcome (95% HDI: –21.1 to 15.4), and a BF_{01} of 2.5 suggested the data were also in favor of the null hypothesis (Fig. 2A). The variance of the paired differences between the visits was in the range of 9.04 to 1540 $(mL/min)^2$ (Fig. 2B). The NHST equivalent Student's paired t-test of the thresholds was not significantly different between the visits ($p = 0.62$). The average thresholds ($\pm$ SE) for the mechanical and chemical stimuli were 34.8 $\pm$ 4.6 mL/min at 50°C and 20.8% $\pm$ 3.7% CO_2, respectively. The threshold between the stimulus types could not be compared due to the difference in the unit of measurement.

Detectability

Experiment 1

The average ($\pm$ SE) d' for the suprathreshold cold stimulus for the experiment with 40% and 60% stimulus probabilities was 0.60 $\pm$ 0.13 and 1.05 $\pm$ 0.30, respectively. The Bayesian paired comparison of the d' suggested the data were in favor of the null hypothesis by a factor (BF_{01}) of 1.70, indicating a higher probability of obtaining zero difference in the d' between stimulus probabilities. The 95% HDI obtained from the posterior distribution of the paired d' differences ranged from –1.53 to 0.675 and included zero paired difference as a credible outcome (Fig. 3). The NHST paired Student's t-test also did not show any significant difference ($p = 0.29$) between the d' obtained in each study visit.

The variance of the d' was also compared between study visits. The Bonett-Seier test of the paired sample showed a significant difference ($p = 0.032$) in the variance of the d' between stimulus probabilities. The variability of the data was higher during the visit with 60% stimulus probability, which was apparent from the violin plot (Fig. 3B). Similar to the NHST variance analysis, the variance of the paired differences obtained using Bayesian analysis also showed a larger variability in the posterior distribution with 95% HDI ranging from 0.198 to 5.52 square units (Fig. 3B).

Experiment 2

The average d' of the noxious suprathreshold mechanical and chemical stimuli with 0.4 stimulus probability was 1.65 $\pm$ 0.37 and 1.14 $\pm$ 0.4, respectively (Fig. 4 and Table 2). The d' of all three stimulus types was compared using a Bayesian one-way ANOVA. A
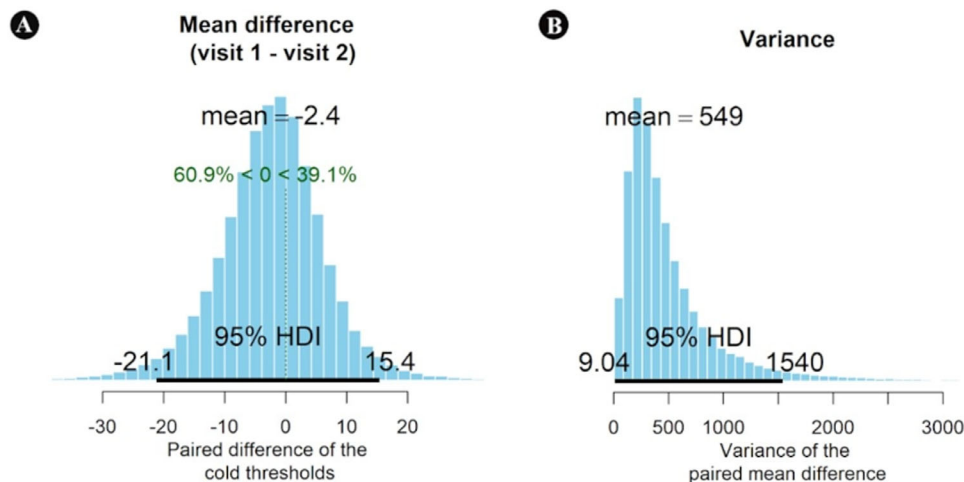

Figure 2. The Bayesian posterior distribution of paired differences of the thresholds between visits (A) and variance of the paired threshold differences (B).
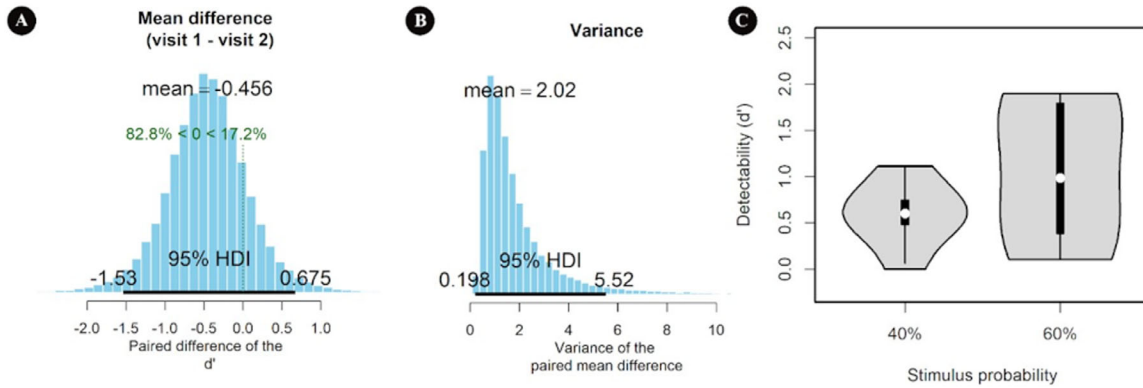
Figure 3. (A) Histogram of the predicted posteriors using the default prior distribution for the paired mean differences of detectability along with the HDI. (B) The variance of the paired differences of the d' of cold stimuli between two stimulus probabilities. (C) The boxplot (*center*) and density distribution (*gray shaded area*) of the original data represented using violin plots.

Table 2. Average ($\pm$ SE) Detection Theory Parameters for Cold, Mechanical, and Chemical Suprathreshold Stimuli

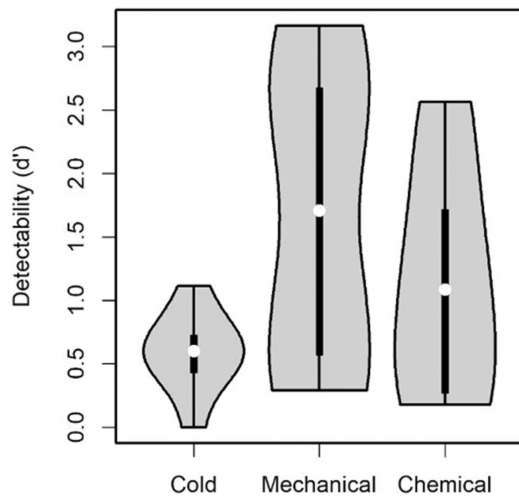| Variable	Stimulus Strength	Stimulus Probability, %	d' (Mean $\pm$ SE)	c (Mean $\pm$ SE)	$\ln\beta$ (Mean $\pm$ SE)
Cold	1.5× threshold	40	0.60 $\pm$ 0.13	0.33 $\pm$ 0.09	0.08 $\pm$ 0.03
Cold	1.5× threshold	60	1.05 $\pm$ 0.30	0.54 $\pm$ 0.13	0.27 $\pm$ 0.11
Mechanical	1.5× threshold	40	1.65 $\pm$ 0.37	0.58 $\pm$ 0.10	0.48 $\pm$ 0.14
Chemical	1.5× threshold	40	1.14 $\pm$ 0.40	0.37 $\pm$ 0.13	0.21 $\pm$ 0.12

Figure 4. The d' of the suprathreshold stimuli at 40% stimulus probability for three stimulus types are presented as boxplots in the middle of the violin plot. The *white dot* in the middle of the boxplot represents the median, with the edges of the box representing the quartiles. The outlines of the violin plot represent the kernel density curves (i.e., the width of the *shaded area* represents the proportion of data located there).

factor (BF_{10}) of 1.55 indicated an anecdotal/mild favoring of the data toward the alternate hypothesis. The restrictive hypotheses listed above were tested against both the null hypothesis and alternative hypothesis

(even though we observed slight favoring of alternate hypothesis). The NHST analysis using one-way ANOVA showed no significant difference, $F(2, 26) = 3.25, p = 0.06$, between the d' of stimulus types.

While testing restrictive hypothesis 1 against the null hypothesis, the data favored the restrictive hypothesis based on nociception with a BF_{10} of 1.98. When compared to the default alternate hypothesis, the restrictive nociception hypothesis was mildly favored by a $BF_{10} = 1.27$. Restrictive hypothesis 2 tested the difference in the d' based on the type of nerve fibers (α versus C) used by the receptors. Similar to the results of hypothesis 1, the data favored the difference in nerve fiber hypothesis compared to the null hypothesis ($BF_{10} = 1.87$) or the default alternate hypothesis ($BF_{10} = 1.21$), whereas the data substantially favored the null hypothesis and alternate hypothesis when compared against restrictive hypothesis 3 based on the chemical combination of the stimulus with BF_{01}s of 2.76 and 4.29, respectively.

Bias Indices

Experiment 1

The average c ($\pm$ SE) for the cold suprathreshold stimulus with an experiment stimulus probability of 40% and 60% was 0.33 $\pm$ 0.09 and 0.54 $\pm$
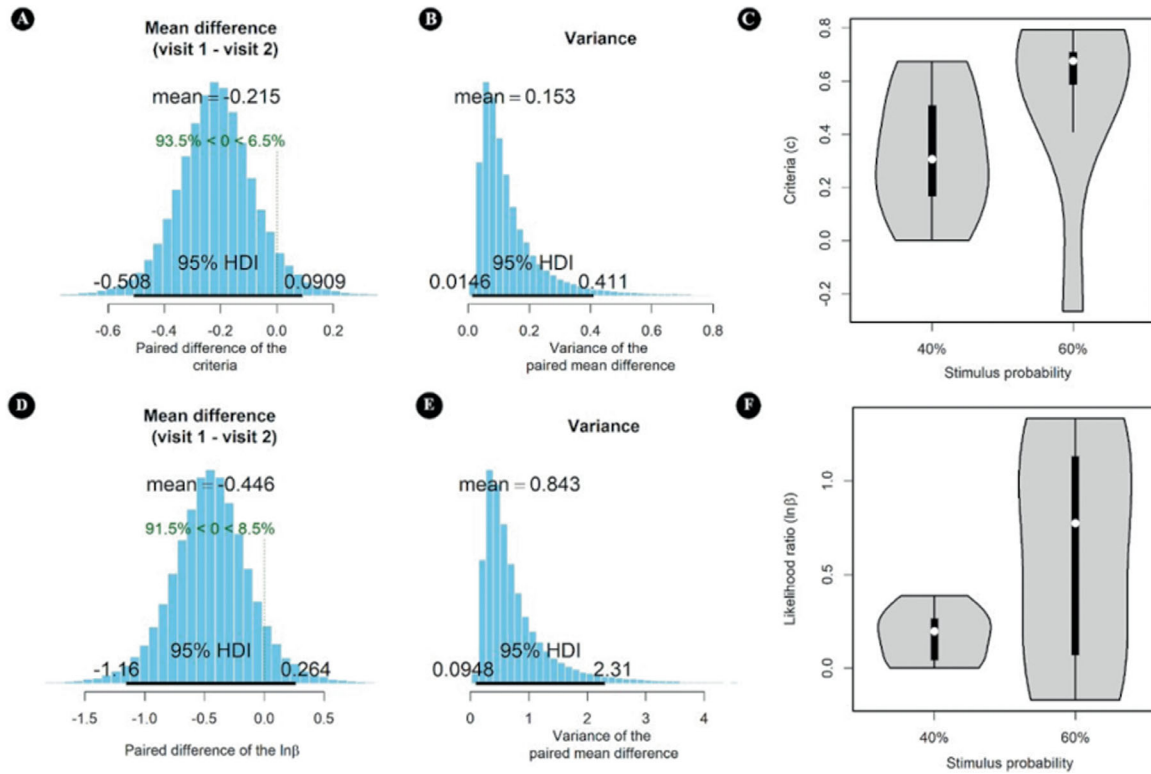
Figure 5. The posterior Bayesian probabilities and HDI for paired mean criteria (A) and lnβ (D) differences; the posterior distribution of the variance of paired difference (B and E). The violin plots for original data of criteria (c) and lnβ (F). Each plot compares the values obtained using the 40% and 60% stimulus probabilities.

0.13, respectively. The average lnβ ($\pm$ SE) for the cold suprathreshold stimulus was 0.08 ± 0.03 (40% stimulus probability) and 0.27 ± 0.11 (60%). The BF_{10} for c (1.23) and lnβ (1.04) between stimulus probabilities anecdotally favored the alternate hypothesis of the bias being marginally different between the probabilities. Although the BF_{10} for bias provided evidence of anecdotal favoring of the alternate hypothesis, the Bayesian estimation for c (HDI: –0.51 to 0.09) and lnβ (–1.16 to 0.27) suggested zero paired difference between the probabilities as a credible parameter (Fig. 5). An NHST paired t-test of bias showed no significant difference in the bias (c, $p = 0.09$; lnβ, $p = 0.13$).

The variance of the paired sample using Bayesian (95% HDI) ranged from 0.015 to 0.41 for c and 0.095 to 2.31 for lnβ. The difference in the variance of the bias compared using the Bonnet-Seier test showed no significant difference for the c ($p = 0.95$), whereas a significant difference ($p < 0.001$) was observed for the lnβ between stimulus probabilities.

Experiment 2

The average ($\pm$ SE) criterion with 40% stimulus probability for the mechanical, chemical, and cold

stimuli was 0.58 ± 0.097, 0.37 ± 0.13, and 0.33 ± 0.09, respectively (Table 2). The comparison of c between the stimulus types produced a BF_{10} of 1.08, suggesting the data favored neither the null nor the alternate hypothesis. The NHST one-way ANOVA of criterion showed no significant difference ($p = 0.09$) between stimulus types (Fig. 6). A Kruskal-Wallis rank-sum test was performed on lnβ values due to the chemical and mechanical distribution being non-normal. The lnβ was significantly different between the stimulus types ($p = 0.03$).

Similar to d', the restrictive hypotheses were tested against the null and alternative hypothesis for the bias indices as well. The c was anecdotally in favor of nociception (hypothesis 1) and nerve fiber type (hypothesis 2) restrictive hypothesis by a BF_{10} of 1.19 and 1.7, respectively, against the null hypothesis and 1.09 and 1.57, respectively, against the default alternate hypothesis. The c did not support the hypothesis based on the chemical composition (hypothesis 3) by a BF_{01} of 2.7 and 2.9 against null and alternate hypothesis, respectively. The lnβ also anecdotally favored the default alternate hypothesis ($BF_{10} = 1.278$) against the null hypothesis. The lnβ favored the nerve conductance
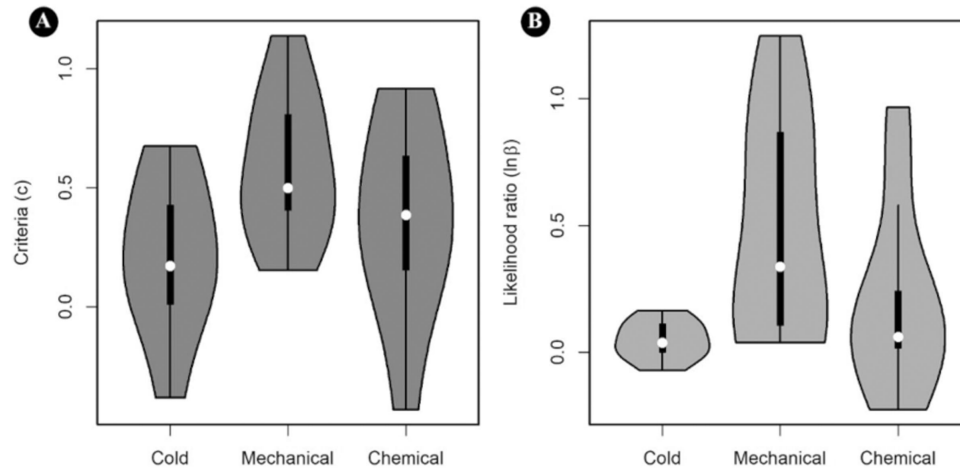
Figure 6. Violin plot with boxplot in the middle of the violin plot. The violin plot representing the distribution, median, and quartiles of the *c* (A) and lnβ (B) for suprathreshold stimulus types. The frequency distribution of the data is given by the kernel density curve on either boxplot.

(hypothesis 2) against the null hypothesis with the BF_{10} of 2.32. The lnβ favored the default alternate hypothesis or the null hypothesis more than the first (BF_{10} = 1.08) or third (BF_{01} = 2.5) restrictive hypothesis.

Correlations

A Bayesian Pearson correlation analysis was performed to obtain the relationship between thresholds, *d'*, *c*, and lnβ for each stimulus type. Mild to strong positive relationships were observed between the parameters. However, the Bayesian analysis found only a few relationships that were supported by the data (Fig. 7). Strong evidence (BF_{10} = 44.02) was found in favor of a positive association between the mechanical thresholds and *d'* of the mechanical stimuli with a 95% HDI between 0.67 and 0.99. Strong evidence (BF_{10} = 12.13) was found in favor of a positive association between the mechanical *d'* and lnβ with a 95% HDI between 0.47 and 0.98. Substantial evidence (BF_{10} = 7.07) was observed in favor of a positive relationship between the mechanical threshold and lnβ with a 95% HDI between 0.33 and 0.97. Substantial evidence (BF_{10} = 3.51) was observed in favor of a positive relationship between the cold threshold and lnβ with a 95% HDI between 0.17 and 0.96.

The NHST Pearson correlation analysis (Fig. 8) revealed that the mechanical threshold was positively correlated with *d'* (r = 0.93, p < 0.001) and lnβ (r = 0.81, p = 0.005). The *d'* for the mechanical stimuli was positively correlated with lnβ (r = 0.86, p = 0.002). Similarly, the cold stimulus threshold was positively correlated with the lnβ (r = 0.76, p = 0.017).

Discussion

In the present study, we showed that sensory and non-sensory (bias) signal detection parameters could be assessed for all three types of corneal pneumatic stimuli, and this is the first study to obtain SDT parameters for such potentially problematic stimuli. We also showed using Bayesian analysis that the detection theory indices from human participants were in favor of theories based on nonprimate corneal neurophysiology (hypotheses 1 and 2). We also showed that the detection theory indices favored responses to different types of stimuli being independent of each other, based on chemical composition and temperature (hypothesis 3).

The literature on using SDT to study pain has indicated a need for careful selection of the stimulus to obtain *d'* and bias.[58,89] Since no detection theory experiments have been conducted before for corneal pneumatic stimuli, we used the somatic pain literature to choose an appropriate stimulus for our feasibility study. The experimenters in pain SDT studies have used stimuli scaled to detection thresholds[90–94] or stimuli of predefined intensities.[89,95] The advantages and disadvantages of both methods were discussed in the thesis by Tan.[89] An experiment with a predefined stimulus intensity for ocular pneumatic stimuli will not be plausible due to the unavailability of any normative data and the possibility of damaging the corneal surface with a high intense stimulus. So, it is advisable to use a stimulus that is scaled to detection thresholds. To determine whether a detection theory approach was feasible with pneumatic esthe-
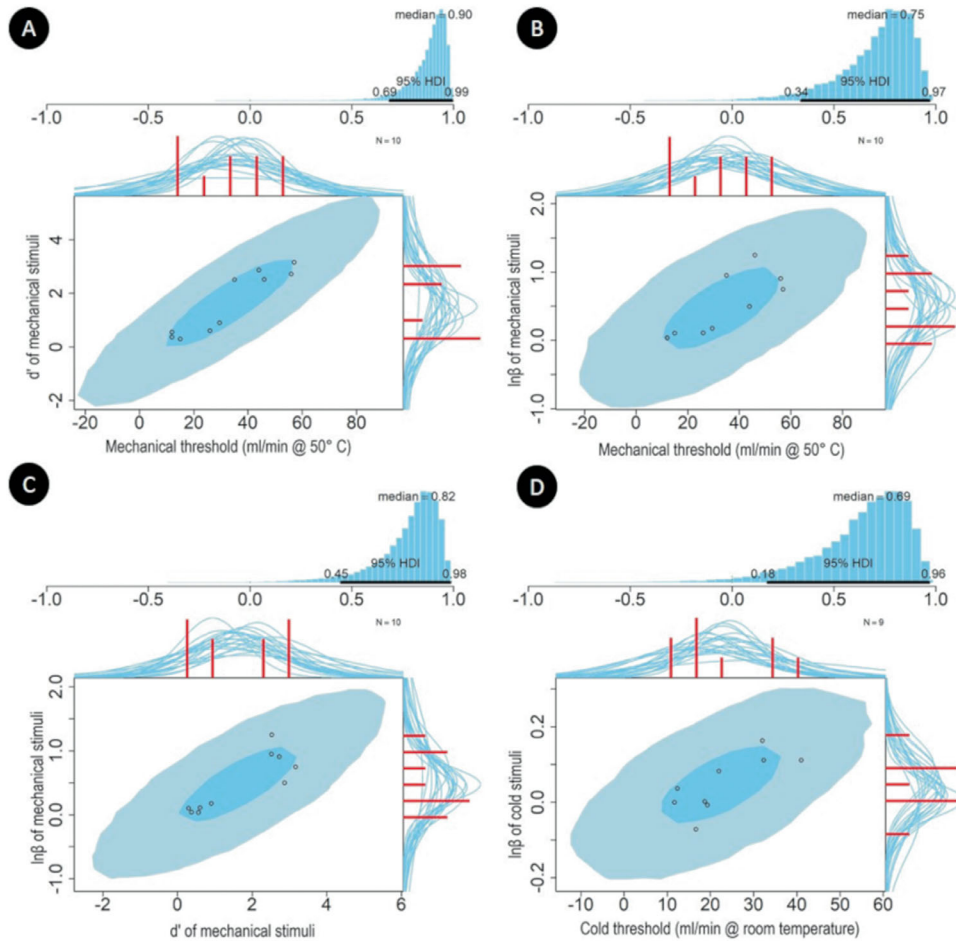
Figure 7. Bayesian estimation of Pearson correlation to obtain the relationship between the thresholds, d', c, and $\ln\beta$ for each stimulus type. Data that favored the relationship are shown in graphs between (A) threshold and d' of mechanical stimuli, (B) threshold and $\ln\beta$ of mechanical stimuli, (C) d' and $\ln\beta$ of mechanical stimuli, and (D) threshold and $\ln\beta$ of cold stimuli. The *red lines* on the upper x- and right-hand y-axes of each panel show the histograms of the x and y data, respectively. The 95% HDIs show the range over which 95% of the posterior estimates lie.

siometry, we needed a "Goldilocks stimulus" that was neither too strong nor too weak. Studies that have previously examined the intensity of the stimuli for SDT experiments have commonly used the threshold-level stimuli, but there are suggestions from pain literature to rather use more intense (suprathreshold) stimuli to examine pain.[22,96] A very strong stimulus might be easily detectable, but it would have produced a perfect HR and no FAR, resulting in an error/difficulty in calculating SDT parameters. Participants could also adapt to the strong stimulus if multiple presentations were presented, altering the perceived intensity as the experiment progressed.[46,48] On the other hand, a weak stimulus may not be readily detected, resulting in a higher FAR and lower HR.[97] Also, in the previous corneal sensitivity experiment in our lab, with the same instrument and stimulus, participants categorized the 1.5× detection threshold stimuli as mild to moderately intense.[45,46] Therefore, pilot experimentation and

theoretical considerations led us to use the stimulus intensity of 1.5× detection threshold.

The feasibility of this type of experimental assessment of corneal sensory processing was determined in terms of the variability of the detection theory indices, the number of participant discontinuations, and frequency of the symptoms of severe discomfort during/end of the experiment or severe staining at the end of the experiment. All participants completed the 40% stimulus probability experiments, but one participant discontinued the study before the 60% stimulus probability experiment of the cold stimuli for personal reasons not related to the stimulation or the psychophysical task. Five participants took extra breaks during the experiment, which were mostly due to non-experiment-related factors. Mild corneal staining was observed for three participants at the end of the experiment with the mechanical suprathreshold stimulus, but no discomfort, irritation, or pain sensa-
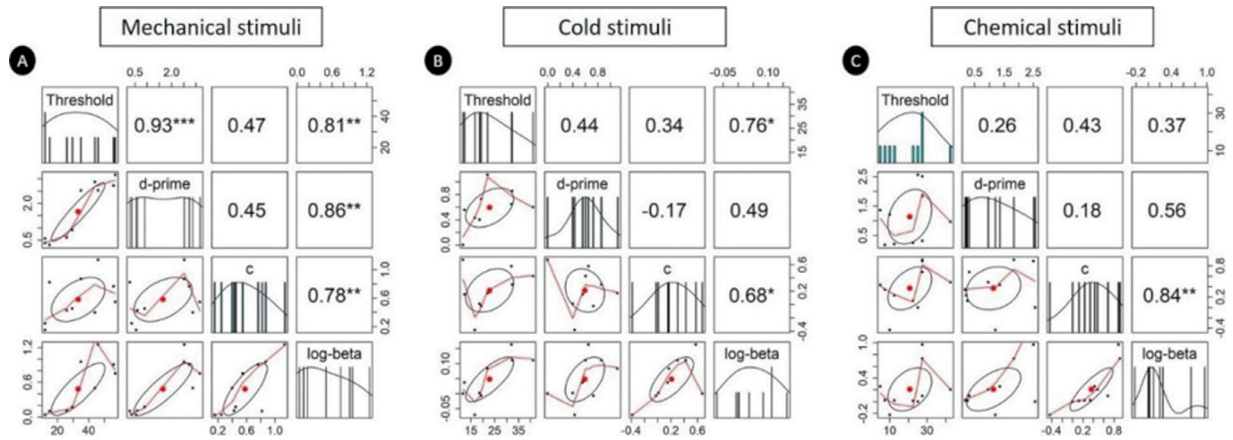
Figure 8. Correlation matrix with Pearson correlations to analyze the relationship between the thresholds, d', c, and $\ln\beta$ for (A) mechanical, (B) cold, and (C) chemical stimuli. The scatterplot with loess line fit and correlation ellipses provide the relationship between the variables analyzed. The numbers represent the correlation coefficient for each comparison, with *stars* indicating the correlation probability (*$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$).

tions were reported by the participants. The next day, no symptoms were present, and there was no corneal staining.

In terms of study outcomes, we were able to obtain d' and bias for all participants who completed the experiment. In addition to being able to derive detection and criteria metrics, we were able to use Bayesian analysis to evaluate different hypotheses based on hypothetical extensions of nonprimate corneal neurophysiology and somatic nociception. Higher variability in d' was observed for the experiment with the cold stimulus and 60% stimulus probability compared to the experiment with 40% stimulus probability. A similar observation was observed for the bias indices as well. The variability of d' of the mechanical and chemical stimuli was also larger than cold stimuli at 40% stimulus probability, but the variability of the criteria was lower and similar for all the experiments, with 40% stimulus probabilities similar across stimulus types. The criterion has been considered an unbiased estimate of bias by SDT literature, and considering the criterion was not highly variable between the stimulus types, the variability in the d' between stimulus types was analyzed further. These observations collectively suggest that this suprathreshold protocol is feasible and safe when measuring SDT attributes of ocular surface sensing.

With the limitation of not being able to measure a neurophysiologic effect of human corneal stimulation, it was also evident from the studies that the corneal sensory information such as thresholds could not be compared between the stimulus types due to the difference in the stimulus characteristics/measurement units. However, with SDT, d' becomes a common measure

of sensitivity across the stimulus types provided the intensity was relatively same across stimulus types. We did scale the stimulus based on the detection thresholds ($1.5\times$ threshold) to keep the perceived sensation similar across participants and stimulus types psychophysically.[89] There were no negative d-primes obtained for the mechanical and chemical stimuli, but two participants (one for each stimulus probability) had a small negative d' in the cold stimulus category. The average d' of the cold stimuli was also low, indicating a general difficulty in detecting cold stimuli. The bias (both c and $\ln\beta$) for all three stimulus types were generally toward the conservative side, indicating a cautious approach by the participants in their responses to the suprathreshold stimuli. There is only one previous report of ocular surface sensing based on SDT (in contact lens wearers) by Beuerman and Rozsa,[94] but the study reported detection theory parameters for corneal thermal stimuli (warm waterjet), delivered when the ocular surface was immersed in a water bath. Since the water bath produces a raised background stimulation compared to normal conditions, this experiment is more similar to the discrimination experiment for the thermal stimuli than a detection experiment. This difference in their sampling, stimulation and psychophysical task, making it rather difficult to perform comparisons between the results of their and our experiments.

As mentioned earlier, the average d' of the cold stimuli was lower than the mechanical and chemical stimuli. We could only speculate on the reason for the smaller d' for cold stimuli because there are electrophysiologic studies on nonprimate corneas, but no similar studies on the human cornea and a general assump-

tion are that the neural behavior is similar. One possibility for the lower detectability is higher background activity of the cold receptor, and another is the non-noxious nature of the cold stimuli compared to other stimuli affecting mechano- and polymodal nociceptors (which also have been reported to have little background activity).[3,4,17,28,98,99] This sort of distinction between painful and nonpainful stimuli has been proposed before.[100]

Our linking hypothesis explicitly assumes similar functioning in primate as in nonprimate corneas.[43] In reports about corneal sensitivity, the authors appear to assume similar animal-human linking hypotheses in reaching conclusions about the human cornea.[3,24,28] Many factors in this assumption are unknown, and making these links becomes problematic when attempting to apply SDT to a human cornea. For example, the amount of noise (frequency and amplitude of background activity) and the factors controlling the background activity are unknown and could not be controlled. After deliberation, assuming all the factors mentioned above were constant during the experiment, we analyzed the psychophysical data using Bayesian ANOVA.

The Bayes factor and Bayesian estimates find the data were in favor of this nociception theory (hypothesis 1), and this is the first time the theory has been psychophysically tested directly in human participants. Similar to the nociception theory (hypothesis 1), the psychophysical data also supported the nerve conductance theory (hypothesis 2). Since histochemical[6] and nerve conductance analyses[3] are currently impossible in living human cornea, the identification and classification of the type of nerve fibers in the human cornea have not been achieved. Even though there is still little evidence of the presence these fibers,[6] the Aδ and C fibers have been assumed to be present in the human cornea similar to the nonprimate cornea.

As described in the Methods, the mechanical and cold stimuli use medical air at different temperatures, whereas the chemical stimulus contains a mixture of CO_2 and medical air. Cold stimuli have been frequently used to evaluate corneal sensitivity in place of mechanical sensitivity, but in theory, the cool stimuli should not have any mechanical/thermal component.[33,40,101–103] According to a study by Nosch et al.,[101] room-temperature stimuli plus 10°C or 15°C (similar to the temperature of the mechanical stimuli of our study) produced the least amount of change in the ocular surface temperature (i.e., it produced only the intended mechanical effect) and suggested that if the stimulus was outside of this range (room + 10°C to 15°C), there would be a thermal component in a pneumatic mechanical stimulus. We tested hypothesis 3 with the assumption that if the mechanical stimulus had a cold component, then the mechanical and cold stimuli would be detected similarly by the participants. However, our psychophysical data did not favor hypothesis 3.

We observed a higher variability in the d' of the mechanical and chemical stimuli. Also, we observed a significant correlation between the mechanical threshold and d' and also a significant correlation between the mechanical threshold and $\ln\beta$ (Fig. 7). Even though there was no obvious grouping of the data in the mechanical threshold, we observed two groups of participants in the d' of mechanical stimuli. Participants had a low d' or high d', and the participants who had lower d' had a low threshold and lower bias using $\ln\beta$ or vice versa. A similar decrease in d' and bias has been seen in SDT literature that analyzed the effect of anxiety,[52,58,96,104–109] although most of the articles reported changes in the β and no change in the detectability. It is also not clear whether the conservative approach by the participants resulted in a higher threshold, which in turn increased the detectability in SDT (since we used threshold from the AMOL to obtain suprathreshold stimulus), or participants really had high thresholds. In addition, we obtained a binary (yes-no) response from the participants and used a conservative stimulus probability (40%), which may have constrained the participants to choose a more conservative strategy (less false alarms).

We were also unable to statistically detect criterion changes during the experiment that might partly be due to the binary response that participants used: uncertainty was not allowed, and perhaps, this too was a drawback of a yes-no experimental design. We would need a multiple criterion experiment such as the rating SDT to analyze the changes in the criterion and evaluate the role of other psychological factors such as anxiety that, as we stated earlier, can affect the signal detection metrics.

In summary, for the first time, the feasibility of using basic yes-no SDT was demonstrated, despite the ocular surface being a relatively noisy sensory system. In addition, the experiments provided some support for corneal sensory linking hypotheses based on animal models.

Acknowledgments

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