Ocular Surface Sensory Processing and Signal Detection Theory

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Purpose: The main aim of the experiments in this thesis is to evaluate the feasibility of using signal detection theory (SDT) to determine the detectability and bias of various ocular surface pneumatic stimuli.

Chapter specific purpose:

Chapter 2: To determine the feasibility of using a portable carbon dioxide sensor to calibrate a pneumatic esthesiometer and then to calibrate the chemical stimuli.

Chapter 3: i) To evaluate the feasibility of using signal detection theory (SDT) to measure the detectability and bias for nociceptive and non-nociceptive corneal pneumatic stimuli. ii) To compare the detection theory estimates between stimulus types. iii) To test the human corneal psychophysical data from this study against the linking hypotheses based on the non-primate physiology using the Bayesian analysis.

Chapter 4: To evaluate the detectability of pneumatic corneal stimuli and response bias using multi-stimuli multi-criterion signal detection theory (MSDT) and analyze the effect of different factors on each detection theory parameter. Also, to evaluate the non-sensory/psychological participant attributes of anxiety and general decision making and determine the relationship between psychological and psychophysical parameters.

Methods:

Chapter 2: The chemical stimuli in ocular surface experiments, are combinations of medical air and added carbon dioxide (%CO_2). These stimuli were calibrated using a portable CO_2 sensor (COZIR CM-0041) and data logger, delivered for 90 seconds using the Waterloo Belmonte esthesiometer. The distances between sensor and esthesiometer tip were 0mm (to measure feasibility), 3, 5, and 10mm. In Experiment I, 100% CO_2 was tested using 4 different flow rates (50,100,150 and 200 mL/min) at 3 working distances. In Experiment II, flow rates

of 20-100 mL/min and concentrations of 20-100%CO_2 were tested in 20 steps at 3 working distances.

Chapter 3: 30 asymptomatic participants (10 in each experiment) were recruited after screening for ocular surface abnormalities using slit-lamp biomicroscopy. The pneumatic stimuli were delivered from a 5mm working distance to the center of the corneal surface using the Waterloo Belmonte esthesiometer. Initially, corneal thresholds were estimated as a baseline for the SDT experiments using the ascending method of limits, followed by the SDT experiment to estimate detectability (*d'*) and bias. The signal for the SDT experiment, a supra-threshold stimulus of intensity 1.5x the estimated threshold, was presented with a probability of 0.4 (i.e., 40% signal and 60% catch trials). *d'* and bias were estimated for mechanical, chemical, and cold supra-threshold pneumatic stimuli in separate experiments. 100 trials were presented for participants in the mechanical and cold stimuli groups; 50 trials were presented for the chemical stimuli group. The trials were demarcated using automated auditory prompts and participants responded whether they detected the stimulus or not using a button box after each trial. An additional experiment was conducted using the cold stimulus with 60% stimulus probability on a separate study visit. The *d'*, criterion (*c*) and likelihood ratio ($ln\beta$) were calculated for each participant from the yes/no responses.

Chapter 4: Thirty-six participants were recruited using convenience sampling and grouped based on the symptoms score from the DEQ-5 questionnaire and contact lens usage. Psychological and psychophysical assessments were done sequentially. At the start of the first visit, general decision-making (DM) and trait anxiety were evaluated. DM was assessed using the Melbourne decision-making questionnaire II (MDMQ II) and trait anxiety was assessed using the trait version of the State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA) questionnaire. A Waterloo Belmonte esthesiometer was used to deliver cold, mechanical, and chemical stimuli to the center of the cornea at three separate study visits. The stimulus type was assigned randomly to each visit at the start of the study. The threshold (baseline for detection theory experiment) for the assigned stimulus type was obtained using

the ascending method of limits. State anxiety was assessed using the state STICSA questionnaires, which were administered before (pre-) and after (post-) corneal threshold measurements. In the cold and mechanical MSDT experiments, 100 trials (80 signal (20 each for 4 intensities) and 20 catch trials) were presented in randomized order, and participants responded with a 5-point confidence rating to each stimulus. In the chemical MSDT experiments, 50 trials (20 signal trials each for two intensities and 10 catch trials) were presented, and responses were provided using 4-point confidence ratings. Detection theory indices were obtained individually and as groups, which were then analyzed using mixed models and paired t-tests. The relationships between psychological (DM, anxiety) and psychophysical (threshold, detectability, and bias) indices were analyzed using Spearman correlations.

Results:

Chapter 2: The CO_2 sensor correctly reported the esthesiometer extremes of 0% and 100% CO_2 when placed at the esthesiometer tip. There were progressive, systematic increases in concentrations reaching/reported by the sensor with increasing flow rates and nominal concentrations, and progressive decreases in measurements with increases in working distance.

Chapter 3: The average (±SE) *d'* of the supra-threshold cold stimuli was 0.59 ± 0.1 units, while the average *d'* of the mechanical and chemical stimuli were 1.65 ± 0.37 and 1.14 ± 0.3 units. The average (±SE) criterion for the mechanical, chemical and cold stimuli were 0.58 ± 0.097, 0.37 ± 0.13 and 0.23 ± 0.1 respectively. The Bayes factor (BF) obtained using the Bayesian ANOVA mildly favored (BF_{10} = 1.55) a difference between the *d'* of the stimulus types, with no support for a difference in the criterion between stimulus types. Further analysis of *d'* using multiple comparisons supported the linking hypotheses based on the nociception and nerve conductance.

Chapter 4: *SDT:* d_a and the area under the curve (A_z) were significantly different between stimulus intensities within each stimulus type (all $p < 0.001$) but were not different between

the stimulus types. Receiver operating characteristics (ROC) curves were separable between the scaled intensities for all stimulus types, and no overlaps were observed in the z-ROC space. Bias calculated using the location of criterion (*c*), as expected, was significantly different between each psychophysical criterion level and between the intensities within a stimulus type (all $p < 0.001$). For the chemical stimulus, *c* varied with stimulus intensity and was affected by factors (asymptomatic/symptomatic, non-contact/contact lens wearers, and both, all interaction $p < 0.01$). In addition, another bias metric, $ln\beta$, depended on stimulus intensity and psychophysical criterion for all stimulus types. *Decision-making:* The scores for DM components were significantly different from each other ($F(3,105) = 121$, $p < 0.001$), and the contrast analysis showed that the DM-vigilance scores were significantly different from other DM-types. Significant positive correlations were observed between procrastination, hypervigilance, and buck-passing scores ($p < 0.01$). The chemical detection thresholds were negatively correlated with the vigilance scores ($p = 0.04$), and the buck-passing scores were positively correlated with the d_a of mechanical threshold stimuli ($p = 0.049$). There were significant correlations observed between the bias and DM scores, but most of the correlations were observed only for either $c1$ or $c4$. The $c4$ obtained for cold threshold, 1.5x, and 2x threshold stimuli were positively correlated with the buck-passing and procrastination scores (all $p < 0.05$). *Trait anxiety:* Cognitive and somatic trait anxiety were significantly different from each other ($p < 0.001$) and were positively correlated ($p < 0.001$). A significant interaction of gender was observed in the relationship between cognitive trait anxiety and mechanical detection thresholds ($p < 0.05$). The d-primes were not correlated with either trait anxiety scores. The bias (c and lnβ), mostly criterion 1 or 4, were significantly correlated with the trait anxiety scores ($p < 0.05$). The cognitive trait anxiety scores were significantly correlated with their buck-passing, procrastination, and hypervigilance DM scores (all $p < 0.05$). *State anxiety:* The somatic component of the state anxiety significantly reduced as the study progressed ($p < 0.05$), but no significant change was observed in the cognitive component. The state anxiety scores from pre- and post- threshold measurements were not

significantly different from each other, There were significant correlations observed between the bias (mostly criterion 1 or 4) and state anxiety scores (all $p < 0.05$).

Conclusion:

Chapter 2: CO_2 concentrations in pneumatic esthesiometers can be calibrated and as expected, vary with flow rate and distance, highlighting the importance of calibration and standardization of CO_2 stimuli in these instruments.

Chapter 3: Our experiments were the first to show that it is feasible to use a detection theory approach to examine ocular surface sensory processing. The detectability of the cold stimuli was low compared to the noxious mechanical or chemical stimuli. The participants in this experiment chose a conservative strategy (reporting 'no' to trials more commonly), but this strategy might be anticipated considering that the experiment was designed with a relatively large proportion of catch trials. Based on the outcomes, there is a need for a multi-criterion multi-stimulus repeated measures experiment to analyze the *d'* and bias characteristic.

Chapter 4: It is feasible to use MSDT for analyzing ocular surface sensory processing and the theory provides insight into the possible bias associated with the use of pneumatic stimuli. With noxious and non-noxious pneumatic stimulation, detectability and criteria vary systematically with stimulus intensity, a result that cannot be derived using classical psychophysics.

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°C	Degree Celsius
Aδ	A-Delta fibers
CO_2	Carbon dioxide
$\%CO_2$	Carbon dioxide concentration
ppm	Parts per million
C-B	Cochet Bonnet
NDIR	Non-dispersive infrared
BF/ BF_{10}	Bayes factor
HDI	High-density interval
NHST	Null hypothesis significance testing
AMOL	Ascending method of limits
SDT	Signal detection theory
MSDT	Multiple criteria multiple stimulus signal detection theory
HR	Hit rate
FAR	False alarm rate
d' or d_a	Detectability
C	Criterion or in some places it refers to C- fibers as indicated

β	Beta
lnβ	Log beta
ROC	Receiver operating characteristics
DM	Decision-making
STICSA	State-Trait inventory for cognitive and somatic anxiety
MDMQ	Melbourne decision-making questionnaire
Signal	Signal + noise

Chapter 1
Introduction

1.1 Cornea:

The cornea is a multifaceted part of the eye that is responsible for maintaining both the structural and functional integrity of the anterior surface and also the entire eye.[1–6] It is the anterior-most part of the human eye which is transparent, highly sensitive, and predominantly avascular[1–6], and although quite well described, some anatomical, physiological and neural mechanisms remain unclear.[7–10]

The cornea is a five-layered structure consisting of epithelium, Bowman's, stroma, Descemet's, and endothelial layers (anterior to posterior).[11] Recent studies have also reported a sixth layer in the form of pre-Descemet's or Dua's layer but the existence of this layer is still debated.[12,13] The epithelial layer is the anterior-most or the outermost layer of the human cornea which has multiple layers of tightly packed squamous cells. This layer acts as a barrier against the disease-causing micro-organisms from entering the eye and regulates the fluid and nutrient exchange between the corneal layers and tear film.[14] This is also the layer where the majority of nerve endings/receptors are located.[1,6] The second layer is Bowman's layer consisting of randomly arranged collagen fibrils which act as an anchor for the epithelial cells to adhere to the corneal stroma. This membrane also helps in maintaining corneal integrity and shape. The thickest layer of the cornea is the stromal layer which is 80-90% of the total corneal volume consists of collagen fibrils and keratocytes providing structural integrity and transparency to the cornea.[14] The optimal functioning of this layer is dependent on the fluid regulation by the epithelial and endothelial layers of the cornea. In addition to the structural integrity, the stroma also acts as the entry point for the sensory nerve bundles into the cornea and since these are nerve bundles the diameter of nerve fibers is usually thicker than the nerves in the sub-epithelial layer. The nerve bundles travel in a straight path parallel to the stromal collagen fibrils. Descemet's layer is a basement membrane that helps in the adherence of endothelial cells to the stroma. The posterior-most layer is the endothelial layer made of tightly packed hexagonal cells, which helps in regulating the fluid and nutrient transfer between the

posterior stroma and aqueous humor.[14] Damage to these layers would affect both the structural and functional integrity of the cornea.

1.2 Corneal innervation:

The corneal innervation is mainly sensory with a few sympathetic nerve fibers to monitor and manage surface dryness.[8] The dense sensory innervation of the cornea comes mainly from the ophthalmic branch of the trigeminal nerve and a smaller proportion of nerves from the maxillary branch of the trigeminal nerve which is predominantly found to innervate the inferior region of the cornea. The nasociliary nerves, which is also the ophthalmic branch of the trigeminal nerve, enter the eye's orbit alongside the optic nerve and then branches to form the long ciliary nerves to innervate the cornea and other ocular structures. These ciliary nerve bundles, through the limbal region, enter the cornea at the level of mid-stroma and ascend anteriorly towards the epithelium, leaving the posterior half of the cornea devoid of nerve fibers. After entering the cornea, at around 1mm from the limbal area, these stromal nerve bundles lose their myelin sheath to become transparent and are protected by the transparent Schwann cell sheaths instead. The stromal fibers then ascend anteriorly to penetrate Bowman's membrane and then bifurcate into smaller fibers in the basal cell layer of the epithelium.[1,6,15–17]

The branched sub-basal fibers are either thick and straight (forming bundles) or tortuous and beaded (single nerve fibers). These nerve bundles at the sub-basal level run parallel to the surface and bifurcate several times to form the sub-epithelial nerve plexus which are visible as a vortex pattern.[1,5,17–19] Some of these nerves have been observed to end as free nerve endings parallel to the surface of the epithelium at the sub-basal layer. [1,5,17–19] Similar to the thick and straight nerve bundles, the tortuous and beaded branch of sub-basal nerve fibers run parallel to the surface but diagonal to the straight nerve bundles and then turn perpendicular to form multiple bulbar nerve endings closer to the anterior surface. Some of these neurons bifurcate further before forming nerve endings.[9] The functional differentiation between these fibers is unknown but the nerve endings were found to have different types of receptors to detect

stimuli.[4] The bead-like enlargements in the tortuous sub-basal nerve fibers were found to contain mitochondria and glycogen particles. A few nerve endings do not appear to have any receptors and the functionality of those nerve endings is still unknown. [1,6,15–17] Though there are various advancements in corneal imaging, the structural details of the receptors and smaller nerve fibers remain unclear.[1,6,15–17]

1.3 Sensory pathway of ocular surface stimuli:

As mentioned earlier, the corneal sensory trigeminal neurons detect the stimuli from the ocular surface and transmit the sensory impulses to the spinal cord, brainstem, and somatosensory cortex, where different types of pain are processed and to elicit an appropriate response like evasive action, blinking or tearing to counter the stimuli (Figure 1.1). The first and second-order pathways for the processing of information from the ocular surface have been identified, but the higher-order processing of individual components of ocular surface nociception, such as irritation, itching, burning, discomfort, etc., are still unclear. The ascending pathway of the trigeminal system carries the signal to the spinal cord (C1 & C2) and brain stem. The ocular surface is represented mainly in the trigeminal nucleus interpolaris-caudalis (Vi/Vc) transition and subnucleus caudalis-upper cervical spinal cord (Vc/C1) junction regions. The second-order neurons responsive to noxious mechanical, chemical, or thermal stimuli have been found in both Vi/Vc and Vc/C1 regions. Vi/Vc corneal neurons may play a role in specialized ocular functions such as blink and tear reflexes and represent an endogenous antinociceptive control pathway, while Vc/C1 neurons may mediate sensory-discriminative aspects of pain sensation.[8,9,20]

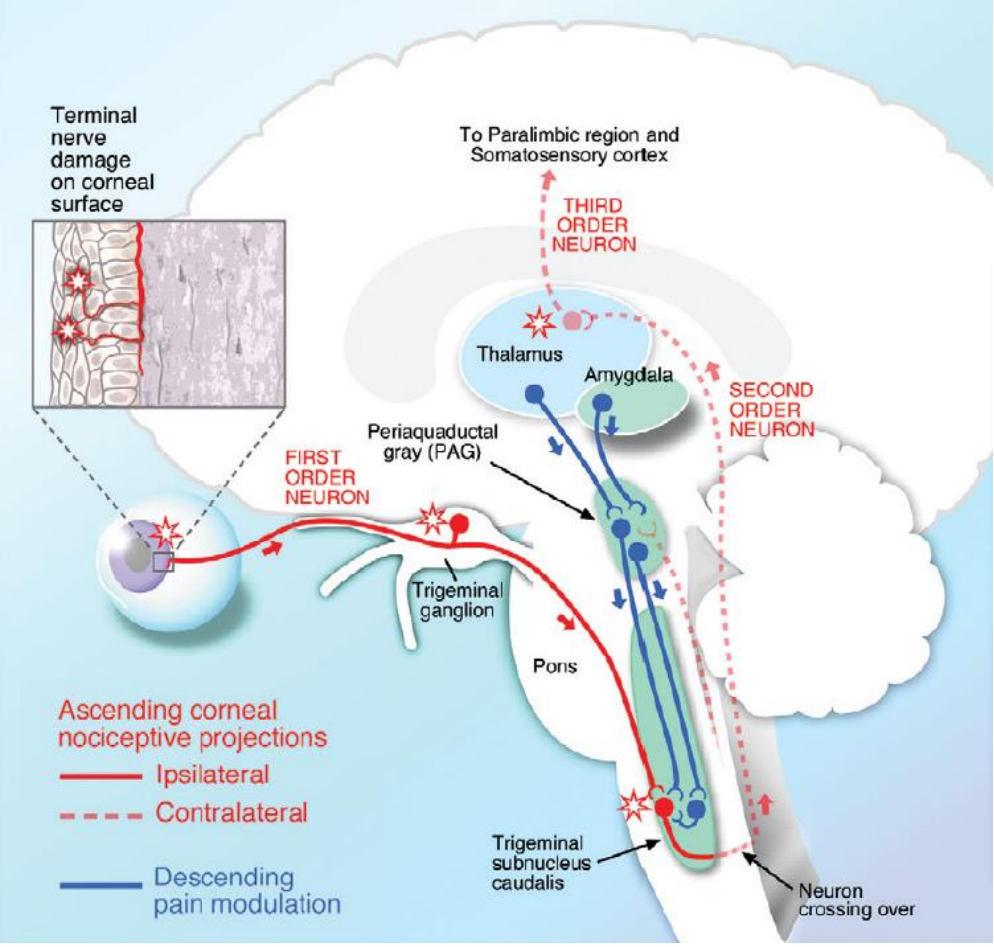

Figure 1.1: Physiologic corneal pain pathway (Reprinted with permission from Rosenthal P, et al.[181]).

1.4 Ocular surface sensory system:

The corneal nerves assist in protecting the corneal surface by detecting the factors that can harm the corneal integrity and the nerves are bombarded continuously with multiple types of stimuli.[8] The corneal neural network, similar to the somatic pain network, consists of a complex system of neurons with nerve endings at the corneal surface to detect potentially noxious stimuli.[8,9,21,22] Since there are no electrophysiological studies conducted to evaluate human/primate corneal neuro-physiology, the concepts are adapted from the cat, rabbit, and

guinea-pig corneal neurophysiological studies.[6,8,22–30] The corneal neurons are classified into two types based on their conduction velocities and presence of myelin sheath surrounding the neurons: thinly myelinated, fast conducting Aδ-fibers and unmyelinated slow conducting C-fibers.[22,25–27,31,32] The electrophysiological studies on cat and rabbit corneas identified three functional types of corneal sensory nerve fibers which conduct nerve impulses either through Aδ or C-fibers.[6,8,28,33,34]The proportion of nerve fibers in the cornea vary significantly between the different species and it was found to be approximately 70% polymodal nociceptors, 20% mechano-nociceptors, and 10% cold receptors in cat and rabbit corneas.[7–9,35] The sympathetic and parasympathetic fibers are also present in the rabbit and cat corneas, but only few fibers are identified in nonprimate corneas.[6] The signal detected by the cold thermo-receptors and polymodal nociceptors is conducted through the C-fibers, and the low threshold mechano-nociceptors transmit impulses through the fast-conducting Aδ-fibers for a rapid response to the painful mechanical stimuli.[2,32,34] Since there is no systematic neurophysiological examination on the effects of human corneal stimulations, the presence of receptors/channels in the human cornea has been evaluated psychophysically.[36] Multiple corneal psychophysical channels in the human cornea have been identified by Feng and Simpson[36] and the detection of the human ocular surface stimuli are complex due to the interdependence of the components of the ocular surface sensory processing system (both within and between the cornea and conjunctiva).

Cold receptors are the non-noxious thermoreceptors that detect a drop in the temperature of the anterior ocular surface. The cold receptors' impulse frequencies increase when the surface temperature drops.[8,22,37]The evaporation of the tear film has been found to be a probable physiological basis for the reduction in the surface temperature and as little as 0.1°C downward change has been reported to alter the impulses from the cold receptors.[7,22,37] The polymodal nociceptors detect a wide range of noxious mechanical, chemical and thermal stimuli, whereas the low threshold mechano-nociceptors detect only the noxious mechanical forces.[8,38] The polymodal nociceptors have a higher mechanical threshold compared to the mechano-nociceptors.[2] In humans, polymodal nociceptors are hypothesized to produce the

stinging/burning sensation, whereas mechano-nociceptors produce a sharp discomfort/irritation.[2] In addition to the physiological differences, four modality-specific nerve fiber population have been identified based on the nerve conduction velocities and stimulus energy (from slowest to fastest): 1) cold receptors (C-fibers) with velocities between 0.25- 1.6 m/sec, 2) Chemosensitive receptors (C fibers) with velocities between 1.1- 1.8 m/sec, 3) mechanosensitive Aδ fibers with velocities between 1.5- 2.8 m/sec, and 4) high-threshold mechano and thermo- sensitive Aδ fibers with velocities between 3.5– 4.4 m/sec.[28,32,34]

1.5 Esthesiometers:

Contact and non-contact corneal esthesiometers have been used in measuring ocular surface sensation. The contact esthesiometer can only deliver a focal mechanical stimulus and the first contact esthesiometer was built by von Frey[39] with calibrated horse hairs of different lengths attached to the glass rods. Based on von Frey's concept that the force produced by a long hair axially on the corneal surface is proportional to the diameter and the length of the hair, Boberg-Ans[40] invented a device using a single nylon thread of constant diameter but of varying length to measure sensitivity; this was further improved by Cochet and Bonnet[41].

Cochet-Bonnet esthesiometers (C-B) consist of hair or nylon filaments of variable diameter and length to deliver tactile stimuli to the ocular surface and it is widely used in both clinical and research settings due to the convenience and relative ease of use.[42–47] The nylon monofilament that is commonly used[42–47] is 60 mm in length and 0.12 mm in diameter, and this produces pressures ranging from 11 to 200 mg per 0.0113 mm^2. Though it is widely utilized, the C-B esthesiometer has major drawbacks such as focal measurements, filament bending resulting in stimulus intensity variation, narrower stimulus intensity range compared to a pneumatic esthesiometer, and the ability to measure only mechanical sensitivity.[48,49] Also, the filament is also a visual stimulus that can produce bias in the responses provided due to anxiety about the filament coming close or touching the eye.[48,49]

To overcome the weaknesses of the Cochet-Bonnet esthesiometers, more sophisticated devices have been developed, which presumably provided greater precision. These devices either have different types of probes directly placed on the corneal surface[50,51] or use different types of pneumatic stimuli[33] to determine the threshold for a localized mechanical force. However, these devices are limited to measuring mechanical sensitivity. Although a temperature-controlled saline jet esthesiometer[50,†] and a CO_2 laser esthesiometer[52] have been developed to measure thermal sensitivity, they have not been widely applied.

The Belmonte esthesiometer delivers air pulses of controlled flow rate, temperature, and air-CO_2 mixture to the ocular surface, allowing measurement of sensitivity over a range of mechanical, thermal, and chemical stimuli.[33] These esthesiometers consist of two gas cylinders, one containing medical-grade compressed air (78% nitrogen, 21% oxygen,0.9% argon, 0.03% CO_2 and other trace elements) and one of 98.5% CO_2, connected through two pressure regulators and two unidirectional regulators to an electronic proportional directional control valve (PCV). The PCV adjusts the flow of air and CO_2 separately, producing gas mixtures with a controlled proportion of CO_2 and air. The final flow of the gas mixture is adjusted with a flowmeter and supplied to a probe with an internal diameter of 0.8 mm on a mount with fine position control. The probe contains a temperature controlling device comprising a thermode, a servo-regulator, a Peltier cell that warms the gas, and a solenoid valve to control the output of gas. During stimulation, the gas is transiently directed to the tip of the probe by changing the direction of flow from the PCV. A pulse with a defined CO_2 concentration, temperature, and flow rate from the tip of the probe flows towards the ocular surface for specific intervals (ranging typically from 1 to 10 seconds).[33]

[†]There is a newer but abandoned US patent application for a liquid jet esthesiometer by Ehrmann et al, 2018, US patent application 21090099071)

A modified Belmonte esthesiometer was manufactured at CRCERT at the University of New South Wales.[53] The design is similar to the original device but with different electronic flowmeters and temperature controllers, a heating coil at the tip of the probe to keep the stimulus delivered approximately at corneal temperature, and a smaller inner diameter (0.5 mm) of the probe. The temperature sensor provides feedback to maintain a steady temperature independent of airflow and ambient temperature. The modified Belmonte esthesiometer is mounted in an American Optical non-contact tonometer housing with an optical range finder to allow a "precise" stimulus distance control from the corneal apex.[53]

Using the CRCERT- Belmonte esthesiometer as a platform, an automated Belmonte esthesiometer has been developed at the University of Waterloo, with computer-controlled mixing of air and CO_2 flow rate and temperature.[54] Additionally, a calibrated video camera continuously monitors the distance between the cornea and the tip, and the orthogonal alignment of the tip of the esthesiometer and the ocular surface. Custom software monitors/ controls stimuli and collects the responses provided by the participants. The type of response depends on the psychophysical method and a few of the psychophysical methods are described below.

1.6 Psychophysics:

Fechner coined the term "psychophysics" and described psychophysics as "exact science of the relations between body and soul" which identifies the relationship between the internal sensory events and perceptual responses to the external stimuli.[55–57] More recently, psychophysics has been defined as "the analysis of perceptual processes by studying the effect on a subject's experience or behavior of systematically varying the properties of a stimulus along one or more physical dimensions".[58]

1.6.1 Classical methods of psychophysical measurements:

The classical psychophysical methods utilize the concept of thresholds which plays a crucial role in the assessment of the sensory system. The threshold is used as a quantifier of the

performance of the sensory system and it is defined as a quantity at which the stimuli or the change in the intensity of the stimuli is detected 50% of the time.[59,60] Two types of thresholds are used in classical methods: absolute and difference thresholds. The absolute threshold which is also a detection threshold is defined as the value (intensity of the stimulus) in the sensory continuum at which the stimulus is just detected. The difference threshold is defined as the amount of change in the intensity of the stimulus that is needed for the stimulus to be detected as different from the reference stimulus. The classical psychophysical methods which can be used to estimate thresholds are the method of adjustment, constant stimuli, and limits.[56,57] Since only detection tasks were used in this thesis, the descriptions below for each psychophysical method are only based on the detection task.

In the method of adjustment, participant is asked to adjust the intensity of the stimulus until it is barely detectable while increasing the intensity from an undetectable stimulus (ascending) or decreasing the intensity from an easily detectable stimulus (descending). In this method, the stimulus is always present and the intensity of the stimulus is continuously adjusted using keys, knobs, or joysticks until the stimulus is barely detected. There is a higher chance of error in this method due to the possible habituation and adaptation to the stimuli. This method is used rarely in corneal sensitivity studies. In addition to the drawbacks mentioned above, the continuous presence of pneumatic corneal stimuli can artificially induce evaporative dryness on the corneal surface resulting in an artificially induced irritation or discomfort.[56,57]

The method of constant stimuli is one of the classical psychophysical methods that have been used to measure thresholds. In this method, a series of pre-determined stimuli are presented in random order multiple times and a threshold is then calculated by estimating the 50% probability (most common) of detection. It is a time-consuming experiment as each intensity in the pre-determined stimulus range is tested multiple times. There are possibilities of fatigue and adaptation effects when this method is used.[56,57]

The method of limits is similar to the method of adjustment but the stimulus is presented based on the response provided by the subject for each trial.[56,57] The initial intensity of the stimulus

is either lowest (ascending) or strongest (descending) depending on the method. The intensity is either increased or decreased depending on the response in pre-determined steps. Different step sizes are employed to obtain the absolute threshold. This was proposed to reduce the time taken to obtain threshold compared to the method of constant stimuli. Often this method has two different step sizes, one (larger step size) to get gross thresholds and the other (smaller step size) to get absolute threshold. Initial step sizes are larger until the first change in response is obtained and then the trials are repeated with smaller step sizes to obtain absolute thresholds. The trials in smaller step sizes will be similar to the larger step sizes, but it will start from one or two steps before the changeover point in the larger step size trials. This procedure is usually repeated several times to improve the accuracy of the threshold and the experiments start from the first step (lowest intensity (in ascending methods) or strongest intensity (in descending methods)) every repetition.

The aforementioned methods are generally referred to as classical psychophysical methods. A relatively recent modification of the classical methods of limits is the staircase method, an extension of the method of limits, in which rules are used to adjust the steps and number of reversals (transitions from yes to no or no to yes) to calculate the threshold.[56,57,61] This method (in simpler form) is likely to use fewer steps to calculate the threshold compared to the method of limits. Similar to the method of limits, the staircase has ascending and descending methods. One of the main advantages of the staircase methods is that multiple staircase experiments could be performed in the same session. The staircase method will have different step sizes depending on the number of reversals and responses provided by the participant. The staircase may have bigger steps initially until the response change is observed, followed by a smaller step size and there is an option to indicate how many reversals for each step size. For example, an experiment could be conducted with 8,4,2,1 step sizes, where the first set of trials follow 8 steps, followed by 4 steps in the reversal, and then 2 and 1 until the required number of reversals is completed. Each response change is a reversal, and the end of the experiment is decided by the number of reversals set by the examiner. The threshold for the staircase experiment is usually calculated by taking an average of ‘x’ number of reversal intensities.

Each reversal is the same as repeating the method of limits but in much shorter intervals and steps. There are many modified staircase methods available and the main modification is in the form of conditions that are set to each step based on which the experiment either moves forward or backward (reversal). For example, a condition can be that out of 2 trials of the same step, participants should correctly identify both trials to move forward, or else a reversal will happen. This particular method is indicated as the 2UP 1DOWN staircase method. Though manual stimulus presentations are possible, often staircase method is conducted using computer programs.[56,57]

In addition to classical methods, the sensory characteristics of the ocular surface have been evaluated using psychophysical scaling where the relationship between a quantitative mental event (output) and physical stimuli (input) is evaluated.[56,57] There are other psychophysical methods that don't apply the concept of threshold to analyze the sensory processing of different stimuli and one of those is the signal detection theory.

1.6.2 Signal detection theory (SDT):

A detection model known as signal detection theory or detection theory was created by combining the high threshold theory of detection and signal decision theory that separates the detection of the stimuli based on sensory and decision processes.[62–64] The sensory process explains the sensory representation of the physical stimuli (amount of separation of the stimulus from noise) given by the detectability (d') and the decision process is given by the criteria which explain the bias associated with the detection of the stimuli. Detectability is proposed to reflect the physiological condition of the nervous system, while decision criteria reflect the cognitive aspect of sensation (how much a subject is willing to report a sensation).[62–64] People holding conservative criteria will reveal higher thresholds because they are reluctant to respond "Yes" to a stimulus unless it produced a notable change in the perception, while those who hold liberal decision criteria will reveal lower thresholds supposing the stimuli have the same detectability. Many factors affect the choice of criteria, such as emotional conditions (e.g. anxiety), personality, as well as cognitive factors.[62–64] In SDT experiments, instruction,

stimulus probability and pay-off conditions all can change subjects' criteria choice. There has been a fair amount of research into pain using SDT and the authors of those studies have proposed that sensation of pain has both physiological and psychological components. [65–69] For example, work on the effects of instruction and placebo using SDT has demonstrated that subjects changed their criteria instead of detectability when their anticipation of the stimuli differed.[65,68,70,71] If only classical psychophysical methods were used, the results of this work would have lead researchers to conclude that subjects' thresholds increased after placebo use and positive instruction, suggesting that each had analgesic effects.[65,68,70,71]

According to SDT, to elicit a response for a given trial, the sensory process first detects the stimulus and this is then followed by the decision process (influenced by multiple factors) that shifts the response either in favor of the signal or noise.[62,72] There are a few types of SDT available but in this thesis, only the basic yes-no and rating SDT methods are used.

1.6.2.1 Yes-No SDT:

Participants, for each trial in this method, identify with a yes/no response whether the neuro-sensory effect is from the distribution of signal (S+N) (stimulus was present) or from the distribution of noise (stimulus was absent). For brevity, the "signal + noise" distribution will be referred to as "signal" in this thesis. The hit rates (HR) (proportion of signal trials correctly identified as a signal), and false alarm rates (FAR) (proportion of catch trials incorrectly identified as a signal) are calculated based on these responses. The detection theory estimates (d' and criteria) are calculated using the HR and FAR.[82] The *d',* in standard deviation units, is the distance between the means of signal *(z(HR)*) and noise distribution (z*(FAR)*) (Equation I) and it is a parametric estimate based (in the original detection theory) on the assumption that both signal and noise distributions are Gaussian normal distributions (Figure 1.2 A). A_z is the non-parametric estimate of detectability that doesn't use gaussian normal distribution assumption in the calculation. The criterion (*c*) and likelihood ratio (*β*) are the estimates of bias.[33,57,82] The location of the criterion on the decision axis indicates the general tendency of the participants to respond yes or no during the experiment. The criterion, in standard deviation

units, is the distance between the neutral point (where there is no bias) and the location of the criterion (Equation II). β is the other form of bias determination which estimates how likely the participant would have responded "yes" to each trial (Equation III).

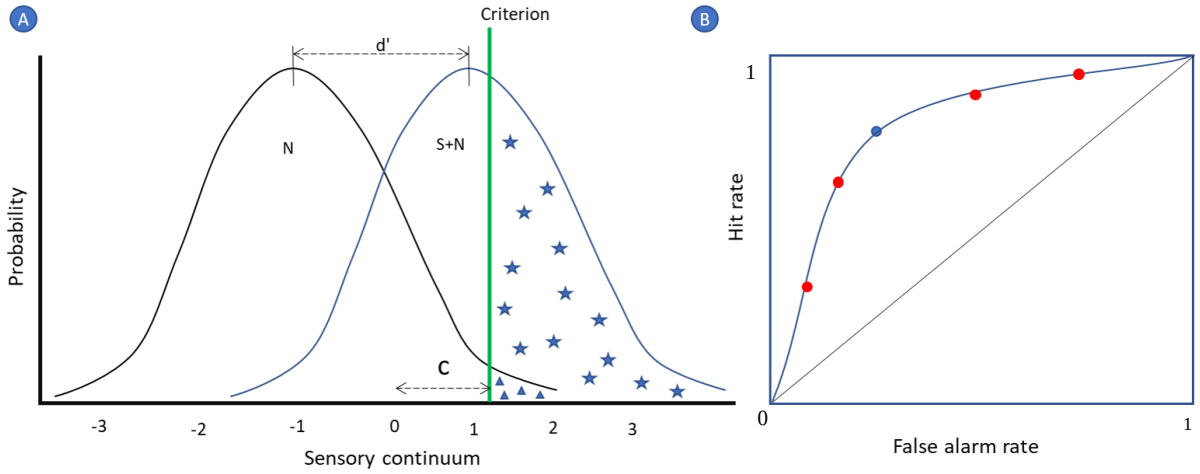

Figure 1.2:(A) Distribution of signal and signal + noise showing the d', location of criterion and c. The area highlighted with the star represents the correct identification of the signal and the triangle represents the incorrect identification of the noise as signal. In a rating experiment, multiple criterion lines will be present relative to the number of ratings used. (B) ROC curve with false alarm on x-axis and hit rate on y-axis. The blue dot represents one possible data point if yes-no response was used to determine SDT parameters and red points indicate one possible combination of data points if the response was based on 5 (4 criteria) ratings.

$$d' = z\,(HR) - z\,(FAR) \quad \text{(I)}$$

$$c = -0.5\left(z\,(HR) + z\,(FAR)\right) \quad \text{(II)}$$

$$\beta = \exp\left(0.5(z\,(FAR)^2 - z\,(HR)^2)\right) \quad \text{(III)}$$

SDT assumes that participants have fixed detectability when asked to detect a stimulus of certain intensity.[62,63,73] However, response bias may vary the participant's response depending on their willingness to report "yes" or "no" to each trial. If d' is invariable, then there is more than one pair of hit and false alarm rates that could produce the same detectability for the

stimulus intensity tested. Though the same detectability is obtained, the difference between the pairs produces different response biases.[62,63,73] Based on this concept, all possible hit, and false alarm rates can be estimated using a function called receiver operating characteristics (ROC) curve where hit rate and false alarm rates are plotted against each other (Figure 1.2 B).[62,63,73] Both metrics have a range between 0 and 1 indicating the proportion of each metric. The hit rate of "0" indicates a poor hit rate where the participant did not identify any signal trial as signal and "1" indicates that all signal trials were correctly identified as signal. On the other hand, a false alarm rate of "0" indicates a good performance where participants correctly identified all catch trials as noise and "1" indicates that all catch trials were incorrectly identified as a signal. The graph is bounded by the range of proportions of hit and false alarm rates and the ROC curve connecting (0,0) and (1,1) through the data point indicates the detectability. All the points on the ROC curve are possible pairs of hit and false alarm rates (different response biases), for each level of d'(they are also called isosensitivity lines). The diagonal connecting (0,0) and (1,1) is the chance line where d' is equal to 0 and the hit and false alarm rates are always equal. In the simplest model of SDT, it is assumed that each stimulus has its own detectability along a sensory continuum. The ROC curve could be used to compare different variables, stimuli, signals, or outcomes from different experiments.[62,63,73]

As mentioned earlier, each point on the ROC curve represents a different bias due to the change in the hit and false alarm rate pair. In a simple yes-no SDT experiment, only one point on the ROC can be measured in an experiment as the criterion *changes* cannot be evaluated. To measure changes in criterion or different points on the ROC curve in a single experiment, a rating SDT method is needed.

1.6.2.2 Rating SDT:

In rating SDT, participants respond to each trial with a confidence rating instead of yes/no. For example, in a detection task, participants respond to each trial using a scale of 1(most certainly signal was not presented) to 5 (Most certainly signal was presented) for how confident they are that they detected a signal. These rated responses allow criterion changes during the

experiment to be evaluated and these ratings are also used to identify different points of the ROC curves. A rating task with 5 ratings will provide 4 (n-1) points for the curve and the number of ratings is decided by the examiner beforehand depending on the number of trials and criteria evaluated (Figure 1.3).[62,63,73]

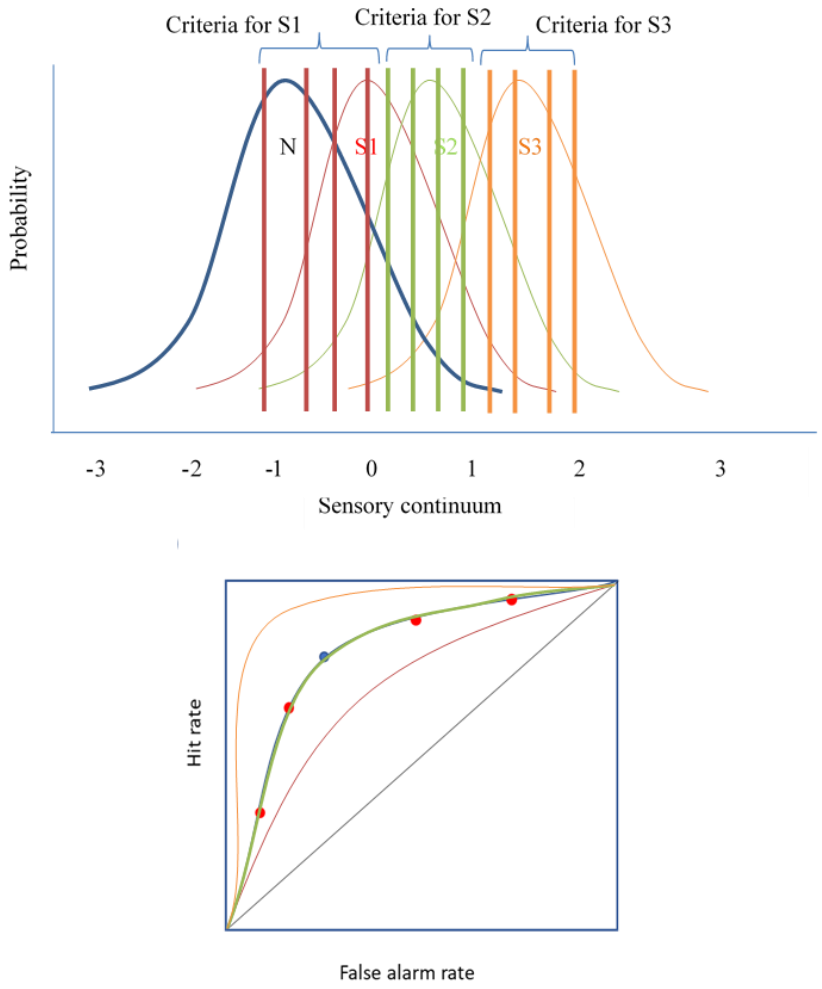

Figure 1.3: Schematic representation of multi-stimulus multi- criterion SDT. (Top figure) Gaussian distribution for 3 signals and a noise with 4 criteria for each stimulus. Signals are indicated with different colors and the distance between the noise and each signal distribution gives detectability of that signal; (bottom figure) ROC curves for each of the signal with criteria indicated only for S2. Please note the criterion levels were chosen separately for each stimulus pair.

The hit and false alarm rates in the rating task are obtained by considering a cut-off at each level and estimating the hit and false alarm rates at each level. For example, in a 5-point rating scale, the first point on the ROC curve is obtained by having the cut-off at rating 1 where the rating of 1 for signal trial as incorrect detection (No) by the subject and all other ratings cumulatively as correct detection of a signal (Yes). The total number of ratings from 2-5 divided by the total number of signal trials will be the hit rate. Similarly, a rating of 1 in the catch trial will be considered as the correct detection of noise trial (No) and the cumulative frequency of all other ratings will be considered as false alarms. Hit rate and false alarm rates are calculated for each stimulus and the remainder of the ROC will be extrapolated similar to the yes/no task. For a stimulus with 5 rating responses, there will be one d' and 4 (which is n-1) criterions calculated.[62,63,73]

1.7 Ocular surface sensation and SDT:

The ocular surface sensory processing of different types of stimuli has been evaluated by both physiological and psychophysical methods on animal and human corneas.[2,7,9] As summarized inTable 1-1, corneal sensory processing has been evaluated only using classical psychophysical techniques such as the method of limits, method of constant stimuli, or (more recently) staircase techniques.[8,31,49,53,54,74–76] The detection threshold is used as the measure of ocular surface sensation even though the thresholds have been found to vary.[53,74,75,77–79] The comparison of thresholds between groups[9,79,80] with or without dry eye disease (among others)[22,80–82] often produced conflicting results. Factors such as age, usage of contact lenses, iris color, environmental factors, corneal eccentricity, and diurnal variations have been associated with corneal sensitivity alterations.[10,83–86] Interestingly viewing the esthesiometer during the experiment has been shown to alter corneal sensitivity.[87] Similarly, studies on thermal pain have shown that seeing the physical stimuli could affect the criterion.[88] In addition to these factors, failure to control the observer's criterion could be a crucial drawback in the classical psychophysical methods that could possibly affect all the threshold measurements.[57,89] The observer's criterion (constant for that participant but, of course,

different between observers) during a psychophysical experiment, may lead to biased observations as it can be set based on multiple factors that are available to observers at the time of the experiment including previous experience, instruction characteristics, signal probability, stimulus intensity or presumed tolerability to pain.[57,63,67,68,89,90]

Theoretically, when a 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. In classical psychophysics, to overcome these drawbacks, the decision criterion is assumed to be fixed (and therefore cannot be assessed, only the threshold is estimated) and the participants might either 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.

As mentioned earlier, the separation of sensory and decision-making components could be obtained using SDT and has been used in the examination of responses to painful stimuli.[66,67,91–93] Though SDT has not been used in ocular surface sensory processing studies before, the utility of SDT in somatic, dental, and other areas of pain perception has been demonstrated in several studies.[65,68,88,92,94–104] Therefore, I designed the experiments reported in this thesis, to measure the detectability and criterion of different stimuli using signal detection theory and to compare these parameters between different clinical groups of participants.

Table 1-1: List of studies with different types of esthesiometer.

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
1960	Kenshalo D[105]	Method of limits (ascending and descending); thermometer	The cool, warm, and hot thresholds of lip, forehead, and conjunctiva were similar
1963	Schirmer K[106]	Did not mention, Schirmer esthesiometer	Threshold decreases with an increase in the amount of contact surface. Pressure, friction and area of contact are the main variables affecting thresholds
1968	Millodot M[107]	Magnitude estimation method; Cochet-Bonnet esthesiometer (C-B)	The judgment of corneal sensitivity to the pressure applied is controlled by the power function with an exponent of 1.01
1970	Larson W[51]	Did not mention, Electromechanical esthesiometer	Comparison between electro-mechanical and C-B esthesiometer.
1972	Millodot M[83]	Ascending method of limits (adjusted); C-B	Normal eyes become more sensitive by evening
1974	Millodot M[108]	Ascending method of limits (adjusted); C-B	Menstruation causes lower corneal sensitivity

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
1975	Millodot M[109]	Ascending method of limits (adjusted); C-B	Blue irises have the most sensitive corneas
1975	Millodot M[110]	Ascending method of limits (adjusted); C-B	Hard contact lens wearing causes corneal edema and decreased sensitivity
1977	Millodot M[111]	Ascending method of limits (adjusted); C-B	Pregnant women have lower corneal sensitivity
1977	Millodot M[112]	Ascending method of limits (adjusted); C-B	Corneal sensitivity decreases gradually throughout life
1978	Polse A[113]	Descending method of limits; C-B	Sensitivity decrease is related to mechanical adaptation
1979	Millodot M, O'Leary D[114]	Ascending method of limits (adjusted); C-B	Loss of corneal sensitivity and increase in corneal thickness with lid closure
1980	Millodot M, O'Leary D[115]	Ascending method of limits (adjusted); C-B	Corneal sensitivity reduced with 2.1% to 3.15% partial oxygen pressure
1980	Tanelian D, Beuerman R[116]	Electrically controlled thermal apparatus (saline bath and saline jet) Ascending method of limits; C-B	No irreversible sensory change of corneal sensitivity. There was a decrease in sensitivity induced by contact lens wear which cannot be attributed to simple adaptation

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
1984	Draeger J[117]	Electronic optical esthesiometer (psychophysical methods were not clear); C-B	There are age and sex-specific differences of corneal sensitivity, and genetic difference to local anesthetic benoxinate
1994	McGowan D et al.[118]	Ascending method of limits; C-B	The lower lid margin is more sensitive than the upper lid, no difference on tarsal conjunctiva, large inter-subject variation
1999	Vega J, Simpson T[54]	Method of constant stimuli; Belmonte esthesiometer	A high correlation between day 1 and 2; contact lens caused 55% sensitivity decrease; and 155% decrease by topical anesthetic; central cornea was significantly more sensitive than the temporal conjunctiva
2000	Battat L, et al.[119]	Constant stimuli; C-B	Cornea sensitivity decreased after LASIK

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2001	Yen M, et al.[120]	Ascending method of limits; C-B	Ocular surface sensitivity and tear production decreased after temporary punctual occlusion in normal subjects and will return to normal after 14 to 17 days.
2003	Feng Y, Simpson T[74]	Ascending method of limits; Modified Belmonte	The central cornea is more sensitive than the temporal conjunctiva
2003	Du Toit R et al.[121]	Ascending method of limits; Belmonte esthesiometer	Diurnal variation in corneal sensitivity and thickness may be physiologically regulated by the hypoxic conditions caused by eye closure.
2004	De Paiva C, Pflugfelder S[122]	Method of levels; Modified Belmonte	Dry eye patients have higher corneal sensitivity
2004	Roszkowska A[84]	Ascending method of limits; C-B	Age-related decrease of corneal sensitivity
2004	Murphy P et al.[123]	Double-staircase method of limits; NCCA	A gradual reduction in corneal sensitivity with increasing age in both non-diabetic and diabetic subjects.

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2004	Adatia F et al.[124]	Did not mention; C-B	Reduced corneal sensation correlated with increasing severity of Sjogren's. Patients with advanced corneal staining likely to have fewer dry eye symptoms
2004	Feng Y, Simpson T[36]	Ascending method of limits; Modified Belmonte	There are 5 psychophysical channels on the human cornea, and they are independent
2005	Stapleton F, Tan M[125]	Method of constant stimuli; Belmonte esthesiometer	The cornea is more sensitive than the conjunctiva; the conjunctiva is more sensitive to thermal stimuli
2005	Golebiowski B, Stapleton F[53]	Unequal staircase technique (Garcia-Perez Staircase (GPS)); Belmonte esthesiometer	Unequal staircase technique (Garcia-Perez Staircase (GPS)) is as accurate as Method of Constant Stimuli (MOCS), and GPS is more repeatable and less time consuming

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2005	Henderson L, et al.[126]	Ascending method of limits Method of constant stimuli; Modified Belmonte	Age, gender and iris color are not predicting factors for corneal mechanical, chemical and thermal sensitivity
2005	Feng Y, Simpson T[127]	Ascending method of limits; Modified Belmonte	Corneal and conjunctival sensory channels are not independent
2005	Bourcier T et al.[128]	Method of levels; Belmonte esthesiometer	Patients with dry eye exhibited corneal hypoesthesia after mechanical, thermal, and chemical stimulation which might be related to damage to the corneal sensory innervation
2006	Chang Y[129]	Descending method of limits; C-B	No sensitivity change on the cornea after strabismus surgery but conjunctiva

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2006	Stapleton F et al.[130]	Unequal staircase technique (Garcia-Perez Staircase (GPS)); Belmonte esthesiometer	Nerve morphology was associated with a mechanical threshold after LASIK surgery; chemical sensitivity appeared to be unaffected after LASIK
2006	Acosta M et al.[131]	Method of levels; modified Belmonte	Corneal and conjunctival thresholds to mechanical and chemical stimuli increased with age. Premenopausal women were more sensitive to corneal stimulation than men of similar ages
2007	Situ P et al.[132]	Ascending method of limits and constant stimuli; Modified Belmonte	Sensitivity across cornea only varied slightly and different from what was reported with Cochet-Bonnet
2008	Golebiowski B, Stapleton F[86]	Unequal staircase technique (Garcia-Perez Staircase (GPS)); Belmonte esthesiometer	Females are more sensitive than males on both cornea and conjunctiva; increase of corneal sensitivity with age in female subjects

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2008	Tuisku I et al.[133]	non-standard psychophysical method; modified Belmonte	The mechanical detection threshold was low in the primary Sjogren's group compared to normal
2010	Situ P, Simpson T[134]	Ascending method of limits and scaled stimulus presentation; Modified Belmonte	Noxious mechanical and chemical stimuli evoked significant tear secretion. Central mechanical corneal stimulation is the most effective stimulus-position pairing and appears to be the major sensory driving force for reflex tear secretion
2010	Situ P et al.[135]	Ascending method of limits; modified Belmonte	Corneal sensitivity changed in adapted lens wearer when lenses were refit after a no-lens interval and during lens wear with different care regimens
2010	Chen J et al.[136]	Ascending method of limits; modified Belmonte	Both mechanical and cold receptors on the human cornea show adaptation to repeated suprathreshold stimuli

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2010	Gallar J et al.[137]	Method of minimum stimulus; Belmonte esthesiometer	Corneal sensitivity in eyes with HSV keratitis had mechanical forces and heat significantly impaired
2011	Chen J, Simpson T[138]	Ascending method of limits and rating; modified Belmonte	Adaptation was found to suprathreshold mechanical stimuli in the asymptomatic group but not in the symptomatic group.
2011	Golebiowski B et al.[77]	Ascending method of limits and rating; modified Belmonte and C-B	No association between the sensitivities obtained with two esthesiometers
2012	Tesón M et al.[139]	Method of levels; standard and new prototype Belmonte	No difference between the eye and between the instruments. Men had significantly higher chemical thresholds than women.
2014	Basuthkar S, Simpson T.[140]	Detection (ascending method of limits) and difference thresholds; Modified Belmonte	Differential sensitivity of the ocular surface can be measured and Weber's law holds for corneal nociceptive sensory processing

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2014	Navascues-Cornago M et al.[141]	Ascending method of limits; C-B	The marginal conjunctiva was the most sensitive of all the conjunctival regions
2015	Situ P et al.[142]	Ascending method of limits; Modified Belmonte (Indiana)	Calibration and repeatability were performed. Repeatable cool stimuli thresholds
2015	Chao C et al.[143]	Ascending method of limits; C-B	Repeatability was good at the central cornea on the same day and 3-months apart. Not repeatable for conjunctival thresholds
2015	Martín-Montañez V et al.[144]	Method of levels, Belmonte esthesiometer	CL wearers with higher corneal sensitivity to mechanical stimulation reported more end-of-day dryness with habitual CL wear.
2015	Wu Z et al.[145]	Not indicated; Modified Belmonte	A dose-response relationship between increased surface stimulation and blinking in healthy subjects

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2016	Spierer O et al.[80]	Ascending method of limits; modified Belmonte	Mechanical detection and pain thresholds measured on the cornea are correlated with dry eye symptoms and ocular pain.
2016	Kaido M et al.[146]	Not mentioned clearly. A type of descending methods probably; C-B	Corneal sensitivity for blinking and pain evoked by increased stimuli was higher in the symptomatic group compared to normal
2016	Nosch D et al.[147]	Forced-choice double-staircase; NCCA	Significant interactions between corneal sensitivity, NIBUT, OST and blink frequency
2019	Alabi E, Simpson T[148]	Ascending method of limits and scaled stimulus presentation; Modified Belmonte	The conjunctiva of the stimulated eye becomes significantly redder than the unstimulated eye for stimulus types. The intensity is greater for chemical stimuli

Year	Author(s)	Psychophysical method and instrument	Author(s)'s major finding(s)
2019	Situ P et al.[149]	Ascending method of limits; Modified Belmonte	The intensity and coolness rating to cool stimuli decreased following STARE trials, while it increased for mechanical and chemical stimuli
2020	Alabi E; Simpson T[150]	Ascending method of limits and scaled stimulus presentation; Modified Belmonte	No difference in the pupil size between stimulated and unstimulated contralateral eye in mechanical and chemical experiments
2020	Situ P et al.[151]	Ascending method of limits; Modified Belmonte	Corneal sensitivity and symptoms, but not tear meniscus height, increased diurnally in symptomatic CL wearers.

1.8 Psychological variables:

Non-sensory factors such as fear, anxiety, motivation, personality, depression, self-confidence have been shown to affect or influence the decisions made during the perception of painful stimuli.[68,94,152–158] Though not reported before, based on my experience of conducting experiments using the pneumatic esthesiometer, its setup induces anxiety (and in some participants even fear) perhaps due to the proximity of the esthesiometer nozzle (or the nylon filament, if using a C-B device), its sharpness (the delivery nozzle is a tiny syringe-like tube) and also the expectation of irritation and discomfort after stimulation. Therefore, I included

measurements of anxiety. In addition to the anxiety measures, I also decided to evaluate the general decision-making of the participants since the criterion in SDT provides experimental decision-making. General decision-making was included, and the working hypothesis was that there would be an association between these decision-making metrics and experimental decision-making as reflected in SDT criteria outcomes. These associations have never been explored before.

1.8.1 Anxiety:

Anxiety is defined as the psychological state in which an individual's sense of uneasy suspense and distress is triggered by ambiguous circumstances.[159] It is a complex multidimensional psychological state representing a series of interrelated cognitive, emotional, somatic, and behavioral reactions.[159] Though it is projected as a negative emotion, it is actually an adapted defensive mechanism that motivates the individual to adapt to the environment and detect potential threats to safeguard from potential bodily harm or psychological distress. Unfortunately, the same safeguard mechanism could misdirect the individual to work against themself failing to perform the tasks that they intended.[159]

Anxiety has been shown to influence the decisions made during pain measurements which may be due to the amygdala, which plays a key role in emotional responses such as anxiety and depression and also an important role in modulating the emotional component of pain.[68,94,154,156,157,160,161] Perhaps partly because of the anxiety-inducing components of esthesiometry and also because the painful stimuli are being delivered, no experiments have been conducted to evaluate the effect of anxiety on ocular surface sensory processing.

Many instruments have been developed to psychometrically assess anxiety and I chose to use the State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA) questionnaire, an extension of the State-Trait Anxiety Inventory (STAI). Even though STAI has been widely used in psychological research to measure anxiety compared to STICSA, I chose the STICSA questionnaire because it addressed the limitations of STAI and was developed to measure both

cognitive and somatic components of the state and trait anxiety.[162–164] In addition, related to the experiments in this thesis, participants can experience both cognitive and somatic components of anxiety due to the stimulus and instrument characteristics. I hypothesised that state and trait aspects would vary differently as the experiment progressed.

The STICSA questionnaire has 21 items for state and 21 items for trait components and the participants respond using a 4-point Likert scale for each item on the questionnaire (Appendix B). The items in the questionnaire are the same for both state and trait components, however, the participants are asked to respond based on the general situation during the administration of the trait questionnaire and based on that instance during the administration of the state questionnaire. The questions are then categorized based on cognitive and somatic components while scoring and the total score for each component is calculated for both state and trait.

1.8.2 Decision-making:

Janis and Mann[165–168] suggested that decision-making is not a simple process of following certain pre-determined stages but suggested seven criteria to evaluate or make high-quality decisions. The seven criteria are: "*1. Thoroughly canvas a wide range of alternative courses of action, 2. Survey the full range of objectives to be fulfilled and the values implicated by the choice, 3. Carefully weigh whatever is known about the costs and risks of negative consequence, as well as the positive consequence, that could flow from each alternative, 4. Intensively search for new information relevant to further evaluation of the alternatives, 5. Correctly assimilate and take account of any new information or expert judgment to which one is exposed, even when the information or judgment does not support the course of action initially preferred, 6. Re-examine the positive and negative consequences of all known alternatives, including those originally regarded as unacceptable, before making a final choice, and 7. Make detailed provisions for implementing or executing the chosen course of action, with special attention to contingency plans that might be required if various risks were to materialize*". They also emphasized that confidence has a huge role in the decision-making

process and time pressure and pessimistic feeling causes individuals to not follow all the decision-making criteria.

Decision-making is a common term that has folksy interpretation as well as somewhat variable interpretation in the disciplines in which the task is measured. For example, within psychophysics it would typically refer to a choice about a sensory event[57] (e.g. its detection) whereas in marketing it might refer to how many clicks occur when browsing a webpage[169]. The most common portrayal of decision-making is one that interprets the action as a rational choice.[170–172] In experiments examining decision making as an outcome, typically, the main goal is to study the choices made in different scenarios (how a scenario influences a decision).[155,173–180] The SDT decision characteristics are in the form of biases that are specific to the human experimental condition, particularly when participants are under some pressure to provide correct responses. This of course is true for the psychophysical experiments described in this thesis. A decision-making questionnaire designed to evaluate how individuals approach different scenarios, was compared to bias metrics derived from the decisions made in psychophysical experiments of signal detection. I hypothesized that the general decision-making described by Janis and Mann[167,168], and those occurring in my psychophysical experiments in this thesis would be associated. My concern, within the pertinent chapter in this thesis, is what are the influences of the dimensions of general decision-making (derived using a standardized instrument[166]) on the sensory decisions (that is how to do the associations vary). The Melbourne decision-making questionnaire was chosen and it provides scores for four decision-making categories: vigilance, buck-passing, hypervigilance, and procrastination.[166]

In summary, the main aim of the thesis is to measure the detectability and criteria of different pneumatic stimuli and to compare the SDT metrics between different groups. In addition to the psychophysical measurements, anxiety and general decision-making are to be evaluated and to analyze the relationship between psychological and psychophysical measures.

Chapter 2
Calibration of Chemical Pneumatic Stimuli

Chapter 2 was published as follows:

A New Method to Calibrate the Carbon Dioxide (Chemical) Stimuli of Pneumatic Esthesiometer Externally

Varadharajan Jayakumar, Trefford L. Simpson

Translational Vision Science & Technology 2019;8(5):4

	Jayakumar	**Simpson**
Experimental design	Y	Y
Data collection	Y	-
Data analysis	Y	Y
Write-up publication	Y	Y

2.1 Introduction:

Esthesiometers have been used in estimating the sensitivity of various sensory systems such as skin, particularly for measuring the touch sensitivity/ pain sensitivity, each of which depends on the amount of pressure applied on the surface of interest.[1] Like other sensory systems, the sensitivity of the ocular surface has also been measured using esthesiometers.[2–11] Von Frey[12] developed the horsehair based esthesiometer to measure the mechanical sensitivity of the ocular surface.[13] The esthesiometer's filaments are of certain length and diameter to exert a pre-calibrated amount of pressure on the ocular surface.[12] The fundamental principle of stimulating mechanical sensitivity with a filament proposed by Von Frey was widely accepted and many versions of the esthesiometers were developed to quantify corneal sensitivity; in ophthalmic research, perhaps the most significant of them is the Cochet-Bonnet (CB) esthesiometer that is used clinically as well as in research settings.[2,4,6,14,15] However, the filament stimuli are unidimensional, as they measure the mechanical sensitivity of a localized area with a narrow dynamic range of stimulus intensity. Other limitations that have been documented include perceptible filament producing an anxious response when brought closer to the eyes[16] and a variable/inconsistent pressure was being applied to the ocular surface due to the bending of the filament.[3,17,18] Even though a number of devices were developed with the limitations of the CB esthesiometer addressed[3,7,14,15,19], clinically, CB esthesiometer is still the most frequently used esthesiometer. Other esthesiometers have been developed to measure corneal sensitivity, including Lele and Weddell's[3] infrared heated air stimulus, Schirmer's[14] esthesiometer with a broader contact surface, Larson's[15] electro-mechanical esthesiometer, and Tanelian and Beuerman's[7] heated saline jet, and there has been a report of CO_2 laser ocular surface esthesiometer.[19]

Based on the reports of cutaneous polymodal nociceptor's responsiveness to chemical stimuli, such as acetic acid and capsaicin, Belmonte's group[8,20–24] recorded the single unit electrical activity of cat and rabbit corneas by using the same chemical stimuli and developed a pneumatic esthesiometer for human participants. CO_2 has been identified as an ideal stimulus

for the human ocular surface chemical sensitivity experiments because of the sustained reduction in the pH of the ocular surface, unlike a buffered response obtained by an acetic acid stimulus.[9] In a number of studies, corneal chemoreception using the CO_2 was measured and illustrated, perhaps, the importance of measuring chemical sensitivity.[9,24–29] What emerged over a series of corneal physiological and psychophysical experiments was the demonstration of the utility of a pneumatic esthesiometer capable of measuring responses to mechanical, chemical and thermal stimulation, and linking hypotheses were developed and empirically supported that in humans there are channels with similar attributes to the neural behavior reported in rabbit and cat corneas.[9,24,25,30,31] Also, the experiments demonstrated that in animals (mainly cat and rabbit, initially), polymodal nociceptors were found to form a majority (about 70%) of corneal receptors, with mechanonociceptors (20%) and cold receptors (10%) forming the remaining corneal receptor population.[32] It was hypothesized that these polymodal subgroups form the main peripheral sensory input from the cornea for the detection of nociceptive chemical, thermal, and mechanical stimuli.[1,32,33]

There are different versions of pneumatic esthesiometers described in the literature[10,24,25,27,34–37] all of which were custom built or modified versions of Belmonte's design that delivers air/CO_2 to the ocular surface. There are few reports on the calibration of the flow rate and temperature of the pneumatic stimulus.[25,38–40] However, and perhaps because of technical issues, there are no reports on the calibration of CO_2 stimulus of the pneumatic esthesiometer.[41,42] The CO_2 is controlled and calibrated internally either in the control box where the gas mixing occurs or at the nozzle with a closed-loop tube sampling CO_2 sensors.[24,25] Even though the CO_2 is internally calibrated, the $\%CO_2$ in the stimulus is unknown/not calibrated when it reaches the ocular surface (the place at which the pneumatic stimulus actually operates). The gases are not restricted to a closed column and so the stimulus has to interacts with the air in the environment between the nozzle and the ocular surface. The physical chemistry at the level of ocular surface will be different from the tip of the

esthesiometer, but it is unclear how much of CO_2 is retained by the possible laminar flow (or otherwise) within the stimulus column.[10]

Previously, the only way to measure $\%CO_2$ in the stimulus externally was to use solid electrolyte sensors which were typically difficult to use and have long and short term drift effects, making the measurements less reliable over time.[43] Recent advancements in the CO_2 sensors have made them more reliable to measure at ambient conditions and offers wider concentration detection range. These are solid-state nondispersive infrared (NDIR) sensors that are portable sensors that use a low-power infrared light-emitting diode and detector to estimate the CO_2 levels.[43] Because these sensors have not been used previously for the calibration of esthesiometer stimulus, in this work, we initially determined the feasibility of using the sensor for calibration of the esthesiometer stimulus and then calibrated the CO_2 stimuli at different concentrations, flow rate, and working distances.

2.2 Materials and methods:

2.2.1 Waterloo modified Belmonte esthesiometer:

The construction of the Belmonte esthesiometer has been discussed in detail by Belmonte et al. [24]. The essential components of an esthesiometer are the gas inputs, control box, and nozzle. The gas inputs to the control box are regulated at 5psi from both the medical air and CO_2 cylinders. The control box houses the electronic controls for manual input and flow meters/ gas mixers to prepare the stimulus. Our esthesiometer (Waterloo version) has been extensively modified to include automation of flow control, mixing, and stimulus delivery (as well as the audio prompts and subject data collection) (Figure 2.1 and Figure 2.2). [44] The stimulus is delivered through the nozzle mounted on an adjustable mount, controlling x, y, z position, and yaw. The tip/nozzle of the esthesiometer was wrapped with a coil thermostat to control the temperature of the stimulus delivered (Figure 2.1 and Figure 2.2). A calibrated camera viewing system mounted on the side of the esthesiometer allows the examiner to position the tip at the desired working distance and partly control/monitor the stimulus

orthogonality relative to the ocular surface. To create a chemical stimulus, the flowmeters in the control box regulate the mix of medical air and CO_2 to a specified concentration and flow rate. The manual/automated inputs provided to create a stimulus include the flow rate (mL/min), nominal CO_2 concentration (%; 0% in case of mechanical and cold stimulus) and duration of the stimulus (seconds). The temperature of the stimulus is maintained throughout the experiment at either 50℃ (translating to approximately 33℃ at the ocular surface for mechanical and chemical stimulation) or room temperature for the cold stimulus. The nominal concentration is the $\%CO_2$ set by the observer/software for a given flow rate that would occur at the tip of the esthesiometer when the stimulus is presented.

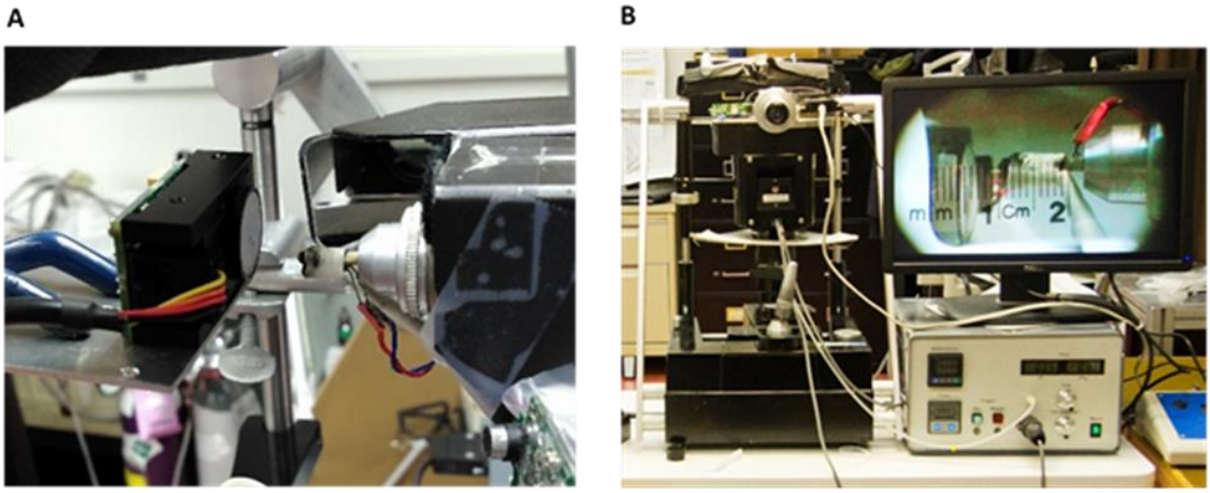

Figure 2.1: (A) Setup of modified Belmonte esthesiometer and COZIR CM-0041 CO2 sensor; and (B) the esthesiometer setup with the control box and calibrated viewing system.

2.2.2 Carbon dioxide sensor:

A portable CO_2 sensor (COZIR CM-0041) from CO2Meter.com was used (Figure 2.3).[45] (According to the manufacturer, the CO2 sensor (CM-0041) has been discontinued. The GC-0016[45] is the recommended replacement for the CM-0041, as both the models use the same COZIR 100% CO_2 sensor.) This compact, low power, diffusion sampling sensor uses NDIR technology with gold-plated optics to measure ambient CO_2 concentration. The measurement

chamber is covered by a 100% CO_2-permeable membrane for the CO_2 molecules to enter the chamber. The information reviewed before choosing this particular type of sensor was its accuracy, sampling rate, optimal operating condition, and the ability to detect concentration from 0 to 100%. The COZIR CM-0041 sensor detects $\%CO_2$ from 0 to 100% with an accuracy of ± 70 ppm or ± 5% of the reading at a sampling rate of 2 Hz. Also, the optimal operating condition for this sensor was between 0 to 50°C/ room temperature and atmospheric pressures between 950 mBar and 10 Bar. It could be used for an instantaneous measure of $\%CO_2$ or for fixed interval measure with the inter measurement timing ranging from every second to every 30 minutes. The session data containing the time and concentration (ppm) could be exported to a spreadsheet using the supplied data logger software. The sensor was pre-calibrated when purchased, and before each experimental session, the initial measurement of ambient room $\%CO_2$ was 1300 ± 100 ppm (average of 3 trials). In addition, as is reported later, when the stimulus was set to deliver 100% CO_2 and the sensor was at the tip of the esthesiometer, it consistently reported 100% CO_2.

2.2.3 CO_2 sensor design:

The sensor design as explained in the manufacturer's manual.[45] The COZIR sensor uses an infrared LED light source and a detector (Figure 2.3C)[43] that is mounted on the bridgeboard facing the gold plated parabolic reflector at the bottom (Figure 2.3D). The active measurement area is the area between the bridgeboard and reflector. The LED is operated at 4.3μm, as this wavelength is similar to the absorption spectra of CO_2. The infrared light from the LED passes through the gas in the active area and reflects back to the detector by the reflector. The amount of light reaching the detector depends on the concentration of the CO_2 inside the active area, and the rate of absorption or the proportion of light reaching the detector is used in the calculation of the $\%CO_2$ at a given moment.

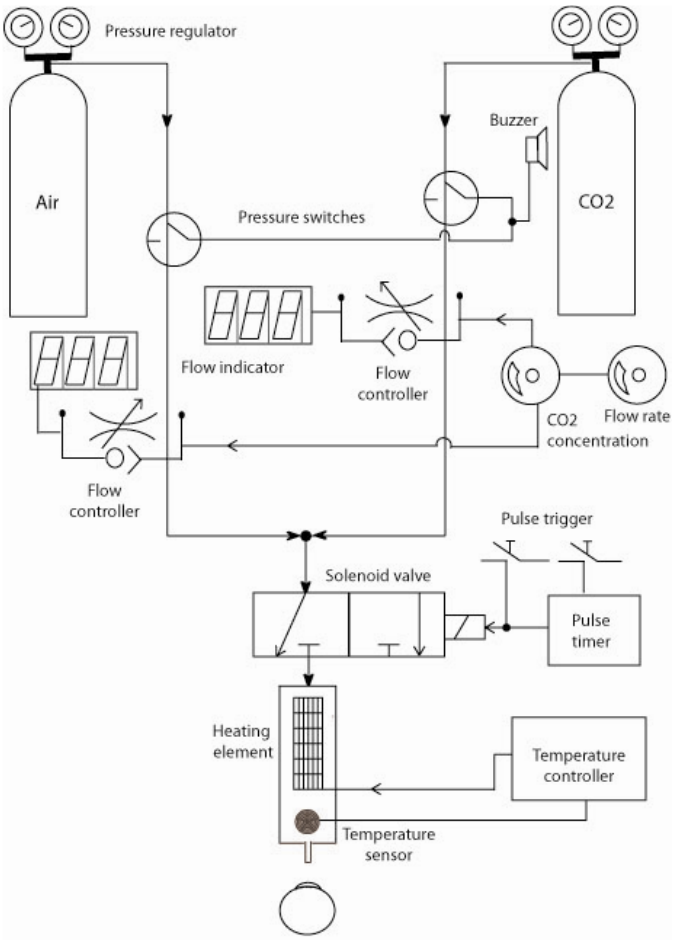

Figure 2.2: The Waterloo modified Belmonte esthesiometer (adapted from the thesis of Situ[44])

2.2.4 Experimental setup:

The sensor was removed from its original plastic enclosure (Figure 2.3B) and mounted on the chin rest by using metal clamps for easier positioning of the sensor orthogonal to the tip of the esthesiometer (Figure 2.1A). A calibrated measuring scale was used to adjust the working distance between the tip of the esthesiometer and front face of the sensor (Figure 2.1B). The air vents in the room were partially blocked, and the room doors were closed to avoid air draft affecting the flow of the jet between the tip and sensor. The room setup was similar to the experiments with human participants performed in the lab. Due to the stimulus

dimension and low flow rates used in the experiment, the stimulus duration for the trials was 99.9 seconds each (maximum time of the device) allowing the active area to get saturated with the stimulus being presented. The working distance, flow rate, and nominal concentrations were changed systematically according to the experiment. The $\%CO_2$ inside the active area of the sensor was logged every second. Between each trial, a breathing time of 2 minutes was used to allow the concentrations inside the chamber to return to ambient conditions. Each trial was repeated three times to measure repeatability. The concentration was measured at room temperature.

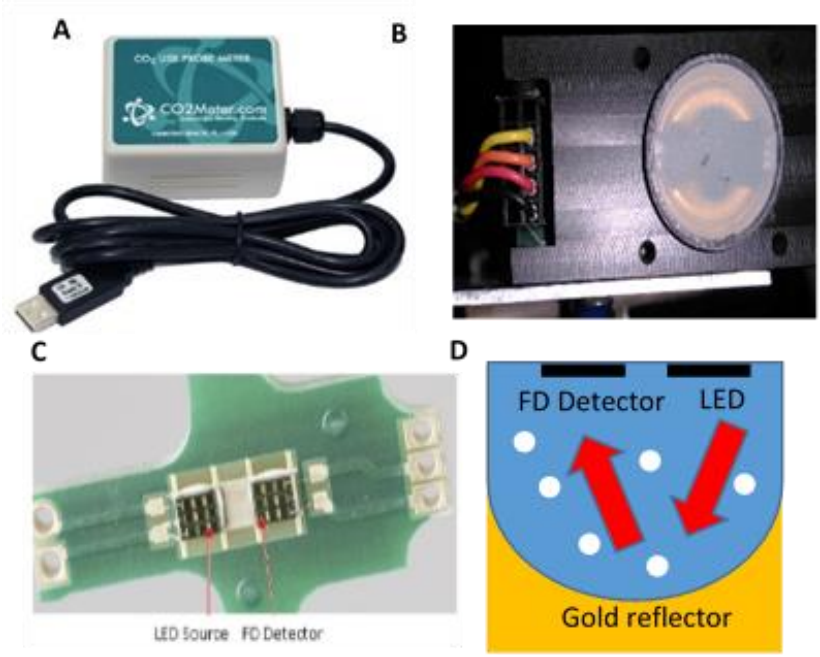

Figure 2.3 (A): COZIR CM-0041 portable carbon dioxide sensor [45] (adapted with permission from CO2Meter.com (Appendix B)); (B) CO_2 sensor without the protective case; (C) the bridgeboard containing LED source and detector to measure CO_2 concentration (reference 43 ,included using creative commons attribution license 4.0); and (D) Schematic representation of the measurement chamber of the CO_2 sensor and CO_2 detection mechanism (source: adapted from reference 43 using creative commons attribution license 4.0).

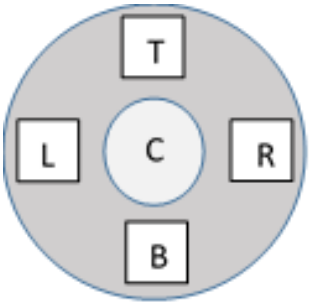

Figure 2.4: Location of area tested on the surface of the sensor indicated with the labels; C, center; L, left; R, right; T, top; B, bottom.

Experiment 1: Identifying an optimal location on the surface of the sensor to deliver corneal pneumatic stimuli

The diameter of the front face of the sensor is larger than the esthesiometer tip (stimulus column) as well as the active measurement area inside the sensor. Because the sensor is designed to detect ambient conditions, it was unclear what effect it would have on the detection of the $\%CO_2$ in the stimulus column. As seen in Figure 2.3B, the front face of the sensor with a bridgeboard (black shadow in the middle) obscures the entry of the stimulus into the sensor. Therefore, the tip of the esthesiometer was placed at five different locations on the surface of the collector (no loss in the CO_2), and a stimulus of 100% CO_2 at 100 mL/min flow rate was delivered directly to the active area. The locations were center, left, right, top and bottom half of the sensor surface (Figure 2.4).

Experiment 2: Effect of flow rate and working distance for a maximum nominal CO_2 concentration

This experiment was conducted to determine the concentration at the ocular surface plane with a constant stimulus concentration of 100%, and the flow rate varied at 3-, 5-, and

10- mm working distances. The flow rates used were 50, 100, 150 and 200 mL/min, and the flow rates were increased methodically from lowest to highest at each working distance.

Experiment 3: Estimation of %CO_2 reaching the ocular surface at smaller intervals of flow rate and concentrations

In this experiment, all three components were changed to obtain their respective observed %CO_2. The flow rate and concentration were varied in smaller steps at 3 predetermined working distances similar to experiment 2. The flow rates used were between 20 mL/min and 100 mL/min in 20 mL/min steps, whereas the concentrations were from 0 to 100% in 20% steps.

2.2.5 Data analysis:

The maximum concentration achieved within each trial was extracted and used in the analysis. The data were analyzed using R statistics (version 3.4.3)[46] in R studio (version 1.1.383)[47]. Linear models were obtained using "lme4," [43] and the test-retest repeatability was obtained using "irr" package[48,49]. The plots were produced using "ggplot2"[50]and "cowplot"[51] packages of R statistics.

2.3 Results:

2.3.1 Determining the feasibility and the location of stimulus delivery:

The feasibility was evaluated by delivering a 100% CO_2 stimulus at a flow rate of 100 mL/min directly to the surface of the sensor. When delivered, the stimuli could still fill the active area with 100% CO_2 when the tip was orthogonally positioned right against the surface in the top and bottom quadrants of the sensor. Even though the diameter of the esthesiometer tip/stimulus was smaller than the diameter of the collector, the stimulus could still saturate the chamber with 100% CO_2, validating the use of the sensor in calibration. At locations other than the top and bottom quadrants, the observed %CO_2 reached only 30% for a 100 %CO_2 stimulus,

indicating a larger loss in the CO_2 reaching the active area. As discussed in the construction of the sensor, the presence of bridgeboard may have (where the photodiode detector and LED are located) restricted/limited the CO_2 molecules from entering the chamber, resulting in lower observed concentration. Because the CO_2 molecules tend to rise when released, the stimuli for the experiments were delivered to the bottom half of the sensor for natural circulation of CO_2 inside the active area of the sensor.

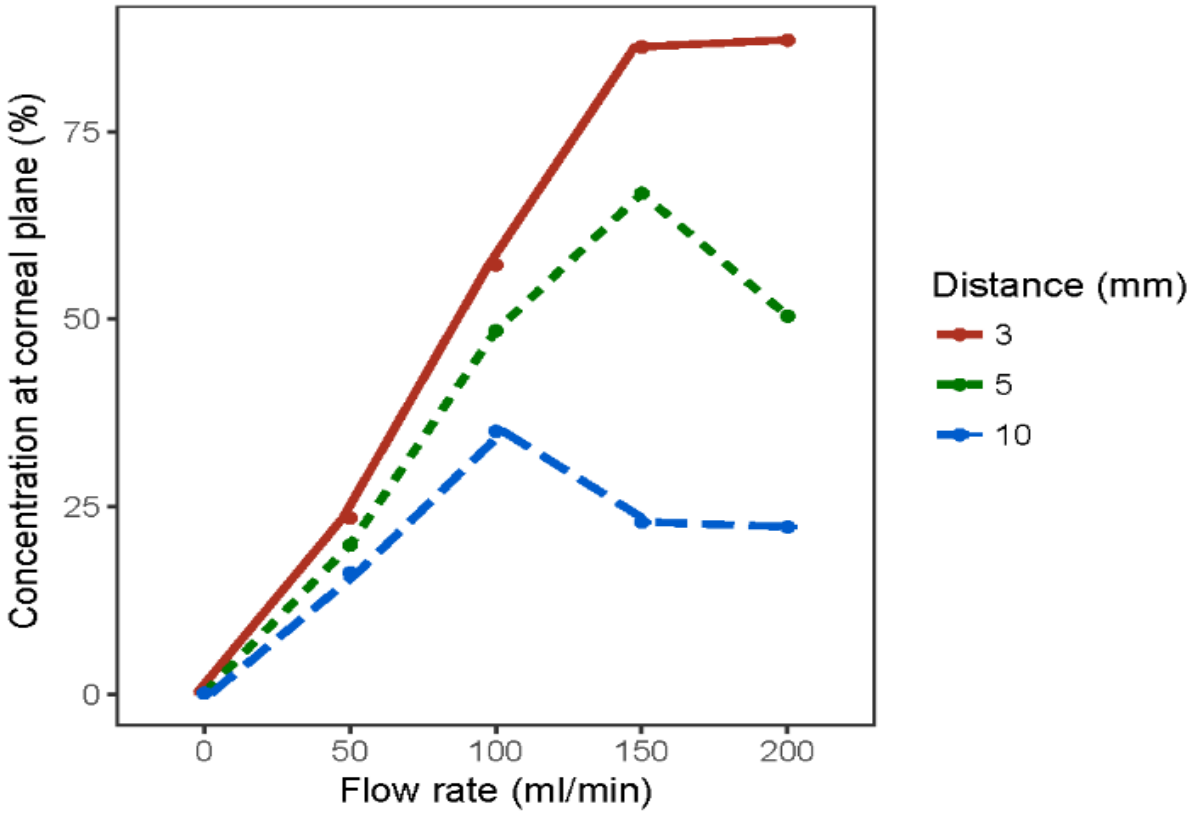

Figure 2.5: The observed concentration was plotted against the flow rate of the stimuli delivered with a concentration of 100% CO_2. The colored lines indicate the working distance (distance between the sensor and esthesiometer tip) used in the trial.

2.3.2 Determining the observed CO_2:

The experiment with a fixed concentration (100% CO_2) and a variable flow rate showed a progressive increase in the observed %CO_2 with increasing flow rates, but the observed %CO_2 were relatively low at larger working distances compared to 3-mm working distance (Figure 2.5). The %CO_2 were strongest when the sensor was positioned 3 mm away from the tip, whereas the lowest was observed at 10mm. A maximum concentration of 87.2% was obtained for a stimulus with the flow rate of 200 mL/min at 3mm. Compared to low flow rates that had a linear increase in the %CO_2, the amount of CO_2 reaching the active measurement area lessened or plateaued at the strongest flow rates (150 and 200 mL/min) of the esthesiometer. In the subsequent experiment with the concentrations measured for flow rates within the usual test range and nominal %CO_2 set at smaller steps, the rate of increase in the observed %CO_2 corresponding to the nominal %CO_2 was lower when the flow rates were lower and the sensor was positioned farther from the esthesiometer tip. There was a progressive increase in the variability of the observed %CO_2 between flow rates with increasing nominal concentration resulting in a fan-like distribution of values at each working distance (Figure 2.6). Both flow rate of the stimulus and working distance were found to be significantly important factors ($P < 0.001$) to determine the observed %CO_2 reaching the ocular surface/ sensor. Because the test-retest repeatability of each stimulus intensity was high with zero or small standard deviations for each mean (intraclass correlation coefficient [ICC] = 1), a nomogram was created using the average values so that the %CO_2 at the ocular surface plane could be obtained based on the nominal concentration, working distance, and flow rate (Table 2-1).

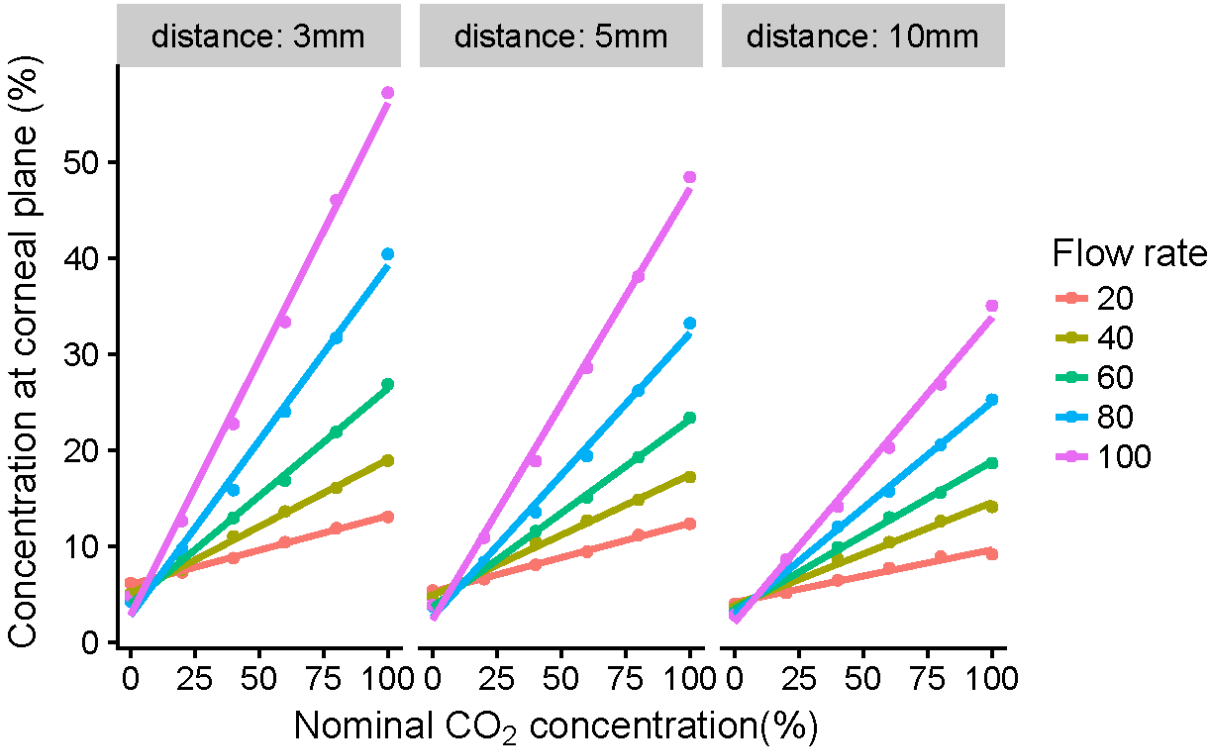

Figure 2.6: The observed concentration was plotted against nominal concentration. The linear fits were plotted for each working distance and flow rate.

		Nominal %CO_2				
Flow rate (mL/min)	**Distance (mm)**	**20**	**40**	**60**	**80**	**100**
20	**3**	7.32	7.64	8.44	9.77	12.66
	5	6.62	7.23	7.61	8.39	10.93
	10	5.18	5.96	6.78	7.52	8.67
40	**3**	8.8	11.06	13	15.88	22.75
	5	8.1	10.44	11.6	13.58	18.88
	10	6.51	8.7	9.92	12.07	14.15
60	**3**	10.45	13.64	16.85	24.02	33.37
	5	9.46	12.71	15.1	19.4	28.58
	10	7.75	10.45	13.03	15.73	20.3
80	**3**	11.91	16.1	21.93	31.73	46.02
	5	11.21	14.86	19.29	26.22	38.11
	10	8.94	12.65	15.6	20.58	26.88
100	**3**	13.09	18.94	26.87	40.41	57.02
	5	12.38	17.23	23.4	33.22	48.43
	10	9.2	14.14	18.67	25.27	35.05

Table 2-1: Nomogram to obtain observed concentration at the ocular surface plane for a given nominal concentration, flow rate, and working distance.

2.4 Discussion:

Pneumatic esthesiometry is currently the only way to examine chemo nociception on the human ocular surface. These experiments are more time-consuming than other pneumatic esthesiometry experiments because of the necessity to remove the gas from the previous trials. There is currently only one esthesiometer specifically designed with a vacuum component to do this without slowing down the experiments, [52] and its CO_2 characteristics have also not been experimentally determined. In this study, we examined the feasibility of using a relatively inexpensive portable CO_2 sensor to calibrate the chemical (CO_2) stimuli of our pneumatic esthesiometer at the ocular surface plane. The research question arose because, perhaps, the CO_2 stimuli were internally calibrated, and the composition of the stimulus is unknown when it reaches the ocular surface. Because the stimulus released from the esthesiometer interacts with the environment before reaching the area of interest, calibrating the stimulus at the ocular surface would help in improving the experimental design to measure chemical sensitivity.

2.4.1 Feasibility:

The feasibility was primarily tested because the column of gas produced by the esthesiometer was limited (diameter at the nozzle tip is 0.5mm) and in our esthesiometer, the stimulus column (from the nozzle tip to the ocular surface) was 5 mm long, whereas the front face of the collector was 20mm in diameter. It was unclear that the CO_2 measuring device would be able to reliably detect/measure the gas within the limits of the gas column, and in addition, if it were able to, what would be the characteristics of the column (or at least the characteristics of CO_2 within the column) determined by the sensor. Calibration of the esthesiometer using the sensor seemed generally viable based on the results obtained for both medical air (0% CO_2) and 100% CO_2 stimuli. The CO_2 measurements were accurate (based on readings with zero added and 100% CO_2 columns) and repeatable, even though there was a mismatch between the sensor output and nominal stimulus specifications.

	3 mm		5 mm		10 mm	
Flow rate (mL/min)	**Equation**	**r^2**	**Equation**	**r^2**	**Equation**	**r^2**
20	6.07 + 0.073*x	0.997	5.3 + 0.0713*x	0.998	4.2 + 0.0547 *x	0.977
40	5.12 + 0.139*x	0.998	4.93 + 0.125*x	0.996	3.91+ 0.107*x	0.992
60	4.07 + 0.224*x	0.998	3.75 + 0.195*x	0.999	3.51 + 0.153*x	0.997
80	2.84 + 0.364*x	0.993	2.69 + 0.295*x	0.993	2.99 + 0.221*x	0.999
100	2.87 + 0.532*x	0.995	2.4 + 0.448*x	0.995	2.16 + 0.317*x	0.995

Table 2-2: Linear regression equations to calculate observed concentration based on flow rate, working distance and empirical concentration (x)

2.4.2 Relationship between concentration, flow rate, and working distance:

A linear relationship was observed between nominal and observed concentrations for flow rates up to 100 mL/min depending on the working distance (Figure 2.5 & Figure 2.6). There was a reduction in the observed $\%CO_2$ at high flow rates (Figure 2.5), which might be due to the turbulence in the stimulus or disruption in the laminar flow of the stimulus allowing the CO_2 to diffuse out of the stimulus column. The decrease in the $\%CO_2$ was more pronounced when the sensor was placed away from the esthesiometer. Of course, the interaction between the stimulus air-column and surrounding air is to be expected and has been shown using Schlieren imaging of the mechanical stimulus, which showed turbulence fringes at higher flow rates.[10] From our perspective when using pneumatic esthesiometry to measure psychophysical sensory performance, fortunately, the flow rate for chemoreception trials would never be more than 100mL/min in our experiments. To minimize the mechanical sensory effect while

measuring chemical thresholds, the flow rate of the stimulus would always be set at half of the mechanical (flow) thresholds and the maximum flow rate for the Waterloo modified esthesiometer is 200mL/min. Although there were suggestions that the relationships can be more complicated with some non-linearities at higher flow rates, both of these attributes (the general "simple relationships" as well as the departure from what is expected) highlight the importance of understanding how the air column behaves to understand the sensory attributes of the tissue being examined when doing pneumatic esthesiometry, in our instance, of the ocular surface.

2.4.3 Repeatability:

The study by Tesón et. al[31] found that the chemical thresholds were the least repeatable thresholds among the corneal sensory measurements, with a variability of 18.06% and ICC of 0.49. This is the only study that measured repeatability of the chemical threshold. Many internal and external factors have been found to vary the ocular surface sensitivity.[53] Calibration could be a factor that is closely related to the stimulus characteristics for the variability in the sensation perceived by the participants. In our study, we found that the chemical stimuli itself is repeatable (ICC=1) considering the flow rate and working distance remain constant between the trials. When the flow rates were increased, there was an increase in the observed concentration at the ocular surface plane even though the concentration delivered remained same (Figure 2.5). This phenomenon was easily noticeable at higher nominal concentrations, and a similar phenomenon was observed with the working distance which was discussed earlier. In a human ocular sensitivity experiment, the working distance will remain constant among all participants, but the flow rate is different between participants based on the mechanical thresholds. There might be a confounding factor in the form of flow rates that may reduce the repeatability of the chemical thresholds in human participants. The information on the difference in the flow rate of chemical stimuli were not available in the study by Tesón et al[31].

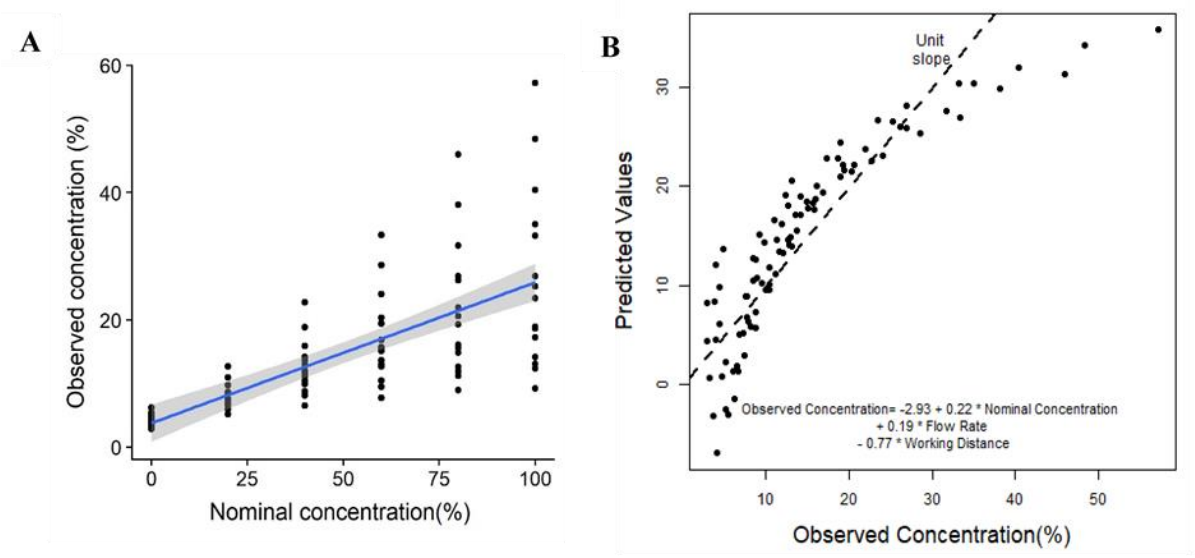

Figure 2.7 (A) The observed concentrations were plotted against the nominal concentrations and a linear fit was added with flow rate and working distance as factors; (B) The predicted values were plotted against the observed concentrations in the scatter plot. The $\%CO_2$ was predicted using the linear equation annotated in the figure and compared with the observed concentration from the sensor. Ideally, all points would be on the y=x function (dotted line).

2.4.4 Complexity of regression models:

One of the aims of this study was to create a regression model that predicts the observed concentration based on the nominal concentration, flow rate, and working distance. Mixed modeling and nonlinear multiple regression models were attempted to create the expected models. Partly due to very poorly behaved error distributions and fan-like distribution of observed values, the predictability of the models was poor especially at higher concentrations (Figure 2.7). Because of the residual errors, simple linear regression lines were fitted to data for each flow rate at each working distance. The r-square for all the linear regression lines were more than 0.95, indicating good fit (Table 2-2).

2.5 Limitations:

Even though we were able to calibrate the chemical stimuli, there is still an inability to measure the $\%CO_2$ in the stimulus column instantly, and the temperature of the stimulus was also not same as the one used in a regular experiment. The inability for an instantaneous measure of concentration in the stimulus column might be due to the size of the measurement chamber and diffusion model of the sensor. In this study, we overcame the limitation by delivering the stimulus for an extended period to saturate the measurement chamber with the stimulus presented, and the maximum concentration attained within the trial was used as the observed concentration. The saturation of the gas inside the chamber can be monitored in the real-time graph of the data logger software provided. As soon as the chemical stimulus was on, the observed $\%CO_2$ increased sharply from the baseline (ambient level) until it plateaued or slowed the increase in the concentration with time. The plateauing was apparent at high flow rates and closer working distance. The plateau indicated the saturation of the $\%CO_2$ inside the chamber and there was no evidence of CO_2 pooling inside the chamber, as the $\%CO_2$ started dropping instantaneously after the stimulus was off. The $\%CO_2$ inside the chamber returned to ambient levels within half a minute from the stimulus was off.

In this study, the temperature of the stimulus was not the same as the one for human ocular surface chemoreception experiments because the NDIR sensor used in this experiment uses infrared LED to detect the concentration. A change in the temperature of the stimulus might affect the performance of the sensor as well as the temperature of the stimuli would, themselves, require additional calibrations. The 50°C temperature at the nozzle is designed explicitly for a stimulus delivered from a 5-mm working distance (as it translates to 33°C or normal ocular surface temperature when it reaches the ocular surface) and it may not translate to the ocular surface temperature at other working distances. As this calibration study explored the effects (among others) of other working distances to characterize the CO_2 in the stimulus, altering the thermal gradient would alter the sensor performance.

The sensor setup in this manuscript does not exactly reflect a human ocular surface experiment. The facial features like nose and deep eye socket might provide a more closed environment affecting the air circulation and altering the dispersion of the CO_2 from and surrounding air into the stimulus air column. In addition, body temperature and the thermal gradient surrounding the body might be expected to influence these flows, in addition to the physical structure of facial features. We have previously shown that blocking the flow from and into the column by using a tube (obviously) does affect the distribution of measured CO_2[54]; there was an increase in the CO_2 reaching the sensor. This might better control the concentration of the CO_2, but it cannot be implemented clinically because of the effect of the tube on the cornea and eye lids. Future calibrations more accurately simulating the ocular surface environment (including different brow and nose characteristics and eye socket depths and ocular temperature) would provide information about the influences that these theoretical variables would have over the stimulus air column.

2.6 Recommendations:

We would like to suggest a 5-mm working distance for ocular surface sensory processing experiments with the pneumatic esthesiometer. This particular working distance is recommended because the 3-mm working distance is too close to the eye and the esthesiometer tip will touch the eye lid/lashes, producing discomfort and false responses from the participants. On the other hand, longer working distances have the primary disadvantage of not being able to provide sufficient CO_2 concentrations at the eye to enable consistent measurements of thresholds, and other experimentation also requires higher amounts of CO_2 delivery e.g., adaptation experiments[55,56].

2.7 Summary:

Calibration of the CO_2 in the air column of a pneumatic esthesiometer is critical: There is a systematic reduction in the $\%CO_2$ reaching the ocular surface plane that depend on working distance and flow rate. The measures of CO_2 were repeatable for all stimulus combinations. It is evident that in pneumatic esthesiometers, it is necessary to standardize the chemical

stimulus, as both working distance and flow rate could change the amount of CO_2 reaching the ocular surface.

2.8 References:

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Chapter 3

Analyzing Ocular Surface Sensory Processing using Yes-No Signal Detection Theory

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

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	Jayakumar	**Simpson**
Experimental design	Y	Y
Data collection	Y	-
Data analysis	Y	Y
Write-up publication	Y	Y

3.1 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.[1–4] When a stimulus is detected, the impulses from the corneal nerve terminals are transmitted to the brain (somatosensory cortex) through an afferent trigeminal pathway and a reaction is elicited (among others) in the form of ocular surface discomfort, pain, and tearing, hyperemia and pupillary dilation.[1–5] The corneal nerves have been theorized to protect the corneal surface from the factors that can harm the corneal integrity and the nerves are bombarded continuously with multiple types of stimuli.[3] Since there are no electrophysiological studies conducted to evaluate human/primate corneal neuro-physiology, the concepts have been adapted from the cat, rabbit and guinea-pig corneal neurophysiological studies.[3,6–11] Based on conduction velocities and presence of myelin sheath surrounding the neuron, the corneal neurons have been classified into two types: a thinly myelinated fast conducting Aδ-fibers and an unmyelinated slow conducting C-fibers.[4,7–9,12,13] The electrophysiological studies on cat and rabbit corneas have identified three functional types of sensory nerve fibers present in the cornea that conduct nerve impulses either through Aδ or C-fibers.[3,10,11,14,15] The proportion of nerve fibers in the cornea have been found to vary significantly between the different species and was approximately found to be approximately 70% of polymodal nociceptors, 20% mechano-nociceptors, and 10% cold receptors in cat and rabbit corneas.[2,3,16,17] The cold thermo-receptors and polymodal nociceptors have 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.[13,15,18] The sympathetic and parasympathetic innervations of approximately 10-15% have been identified using histochemical methods in the rabbit and cat corneas, but the existence of these fibers in nonprimate corneas have been suggested to be scarce.[10] The neuro-physiology of the corneal sensory fibers have been mainly obtained on the cat corneas, with some information from rabbit, guinea pig, and other rodents.[3,4,11,19–21] Since there is no systematic neurophysiological examination on the effects of human corneal stimulations, the

presence of receptors/channels in the human cornea has been evaluated psychophysically.[22] Feng and Simpson[22] have identified multiple corneal psychophysical channels in the human cornea and the detection of the human corneal and conjunctival stimuli have been shown to be complex due to the interdependence of the components of the ocular surface sensory processing system (both within and between the cornea and conjunctiva).

Generally, cold receptors are the non-noxious thermoreceptors that detect a drop in the temperature of the anterior ocular surface. The cold receptors' impulse frequencies increase when the surface temperature drops.[3,4,23] The evaporation of the tear film has been found to be a probable physiological basis for the reduction in the surface temperature and as little as 0.1°C downward change has been reported to alter the impulses from the cold receptors.[4,17,23] The polymodal nociceptors detect a wide range of noxious mechanical, chemical and thermal stimuli, whereas the low threshold mechano-nociceptors detect only the noxious mechanical forces.[3,24] The polymodal nociceptors have a higher mechanical threshold compared to the mechano-nociceptors and, in humans, polymodal nociceptors are hypothesized to produce the stinging/burning sensation, whereas mechano-nociceptors produce a sharp discomfort/irritation.[18]

The sensitivity of the ocular surface is usually measured with an esthesiometer, and most commonly used clinical instrument is the Cochet-Bonnet esthesiometer[25], while the pneumatic esthesiometer such as the Belmonte esthesiometer is frequently used in research settings.[3,18,26–28] Traditionally, corneal sensitivity has been estimated using a classical psychophysical technique such as the method of limits, a method of constant stimuli or (more recently) staircases stimuli.[3,12,26,27,29–32] The detection threshold (generally, the statistically lowest stimulus intensity reliably detected by the participants[33]) has frequently been used to measure ocular surface sensation.[27,29,31,34–36] However, these thresholds have been found to vary and often produced conflicting results when compared between groups[2,28,36] with or without dry eye disease (among others).[4,28,37,38] The density of the corneal nerves has been reported to be lower in participants with dry eye[37,39–43], but conflicting results have been

reported for corneal sensitivity in dry eye.[28,34–37] Feng and Simpson[22] have shown as many as five possible psychophysical channels in the human cornea that are dependent on each other for stimulus detection at the threshold level. Factors such as age, usage of contact lenses, eye color, environmental factors, corneal eccentricity, and diurnal variations have been associated with corneal sensitivity alterations.[44–48] Other aspects of ocular surface sensory processing that has also been examined using pneumatic esthesiometry include adaptation to the stimuli[49–51], difference thresholds[52] and hypersensitivity[38,53,54].

Corneal detection thresholds have been widely used as an estimator of corneal sensory characteristics, but there is a possible drawback in the classical psychophysical methods used in the measurement of thresholds.[33,55] 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.[33,55] 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.[56,57] 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. In classical psychophysics, the decision criterion is assumed to be fixed (and therefore cannot be assessed, only the threshold is estimated). However, in an experiment, the participants might either 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.[33,55] Non-sensory factors such as anxiety, personality, or previous experiences have been reported to influence the criterion while detecting the painful stimuli.[58–61]

The separation of sensory and decision-making components of pain perception could be obtained using a modern psychophysical method such as signal detection theory(SDT).[62–65]

SDT has been used in the examination of responses to the painful stimuli since pain is subjective and the perception of pain could vary.[62–64,66,67] There are also reports that have questioned the use of SDT in pain literature.[68,69] However, the utility of the SDT in somatic, dental and other areas of pain perception has been demonstrated in several studies.[59,66,77–81,68,70–76] 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.[82]

Linking propositions, as explained by Teller[83], are used in this study to understand the relationship between the psychophysical data of human ocular surface sensitivity and the electrophysiological studies on cat and rabbit corneas. In making these links in this paper, we acknowledge the scientific tenuousness of relating primate human & conscious data being related to primarily extracellular neural behavior measured in unconscious non-primates. Since, currently, these are the only corneal electrophysiological data, all we are able to do is test specific linking hypotheses attempting to account for our data based on these extant results.

In this paper, Bayesian analysis is used in analyzing the psychophysical data against the linking propositions. 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 hypothesis while interpreting the results in terms of the probability (in this instance) using the Bayes factor (BF).[84–86]

The main aim of this study is to test the utility of an SDT approach to obtain *d'*, *c* and *lnβ* of the supra-threshold corneal pneumatic stimuli in "normals". Also, we tested the applicability of different linking propositions based on non-primate neuro-physiology experiments to the psychophysical data from the human cornea.

3.2 Hypothesis:

1) The detection theory estimates of supra-threshold stimuli are different between the stimulus types

3.2.1 Restrictive hypothesis for Bayesian testing:

2) If the human corneal sensory mechanism has a difference in the level of nociception, then detection theory estimates of the nociceptive stimuli are different from the non-nociceptive stimuli
   ((Chemical= Mechanical) ≠ Cold)

3) If the human corneal sensory mechanism has a difference in the nerve conductance, the detection theory estimates of the mechanical stimuli (myelinated Aδ fibers) are different from the rest (unmyelinated C fibers)
   ((Chemical= Cold) ≠ Mechanical)

4) If the detection of the stimulus is based only on the chemical composition of the stimulus, then the detection theory estimates are different for chemical stimuli compared to other stimuli
   ((Cold (ml/min) = Mechanical (ml/min)) ≠ Chemical (% CO_2))

3.2.2 The rationale for using restrictive hypotheses:

We have used the concept of linking propositions in this study to test the concepts from the electrophysiological findings in non-primate corneas against the human corneal psychophysical data because the electrophysiological studies cannot be performed in the human corneas and the applicability of the theories from the non-primate corneas to the human corneas are unknown. The linking hypotheses 2, 3, and 4 are tested against the general alternative hypothesis of all the stimulus types being significantly different from each other. Hypothesis 2 tests the nociception theory, as the non-primate studies have shown that

nociceptive receptors detect the mechanical and chemical stimuli compared to cold stimuli by the non-nociceptive cold receptor. Hypothesis 3 tests the nerve conductance theory, as studies have shown the mechanical detection is primarily done by faster conducting Aδ fibers producing a sharp pain, whereas other stimuli are detected using slower conducting C fibers. Hypothesis 4 evaluates the stimulus chemical composition, as some authors have questioned the mechanical properties of pneumatic stimuli and have preferred using the cold stimuli in the 'mechanical' experiments.

3.3 Methods:

3.3.1 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.

3.3.2 Subjects and study protocol:

Experiments were conducted to measure the *d'*, *c* and β of supra-threshold 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 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[27] was used to deliver pneumatic stimuli to the center of the corneal surface (Figure 3.1). After the end of each visit, the ocular surface was evaluated using slit-lamp biomicroscopy and fluorescein staining.

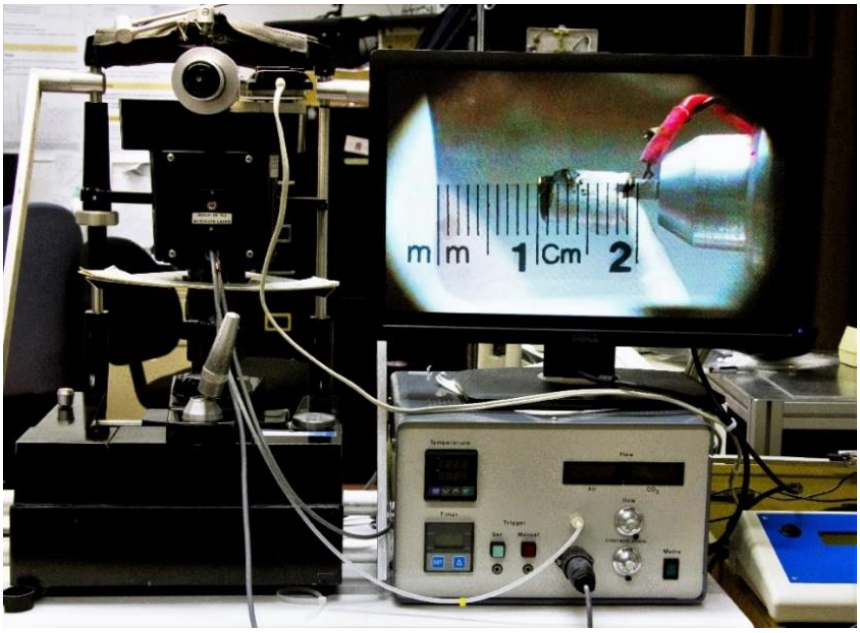

Figure 3.1: The control box and alignment video camera setup of a Waterloo modified Belmonte pneumatic esthesiometer

3.3.3 Esthesiometry:

The stimuli were presented using the Waterloo Belmonte esthesiometer and the stimulus types used were mechanical, chemical and cold.[26,51,52] The mechanical stimulus was medical air heated to 50°C (which translates to approximately 33°C at the ocular surface[52,87]). The 'cold' (non-noxious) stimulus was room temperature medical air that was estimated to reduces the corneal surface temperature by 1.4°C.[87] 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' estimates with the chemical stimulus. The carbon dioxide 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.

Mechanical and cold stimuli were delivered for 3-seconds and chemical stimuli were delivered for 2-seconds. 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). Participants could blink freely between trials. The inter-trial interval for mechanical & cold stimuli was approximately 10 seconds; for chemical stimuli, it was at least 30 seconds. 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 supra-threshold pneumatic corneal cold stimuli.

This experiment included two study visits and 9 out 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. A supra-threshold stimulus of the 1.5x 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 the visits.

Experiment 2: Detectability of the nociceptive supra-threshold pneumatic corneal stimuli.

Twenty participants (ten for each type of stimulus) were recruited. The nociceptive stimuli used were mechanical and chemical 1.5x threshold stimuli, and were tested on two separate study visits. For the mechanical stimuli, the threshold was derived initially by averaging two AMOL estimates. For the chemical experiments, the mechanical thresholds 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). Similar to cold SDT experiment, the mechanical SDT experiment was conducted using a 1.5x threshold as the stimulus. The chemical SDT experiment was conducted using a 1.5x CO_2 threshold stimulus. A stimulus probability of 40% was used in both the mechanical and chemical SDT experiments. There were 100 trials in the mechanical experiment, whereas only 50 trials were presented in the chemical experiment. The reduction in the number of trials was primarily due to longer inter-stimulus intervals needed to prepare, deliver, and purge chemical stimuli.

3.4 Analysis:

3.4.1 Signal detection theory analysis:

Theoretically, participants were required to separately identify the distribution of the neuro-sensory effect when the stimulus was present (the "signal") from the distribution of the neuro-sensory effect when the stimulus was absent (the "noise"). The *yes/no* responses were compiled for each participant separately for each stimulus type, the hit rates (HR) (the proportion of signal trials correctly identified as a signal) and false alarm rates (FAR)

(proportion of catch trial incorrectly identified as a signal) were calculated. Using the HR and FAR, the detection theory estimates were calculated using the formula in excel spreadsheet.[82]

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 non-parametric estimation of detectability. Bias is determined (among others) using the criterion (*c*) and likelihood ratio (*β*).[33,57,82] 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).

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

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

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

Bayes Factor (BF_{10})	Support for alternate hypothesis (Jeffreys) [92]
1-3	Anecdotal
3-10	Substantial
10-20	Strong
20-30	Strong
30-100	Very strong
100-150	Decisive
>150	Decisive

Table 3-1: Jeffreys interpretation of Bayes factor (BF_{10}).

3.4.2 Statistical data analysis:

The detection theory estimates for the cold stimuli from two different stimulus probabilities were compared using the Bayesian paired t-test and the detection theory estimates 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 estimates of detection theory. Alongside Bayesian analysis, appropriate NHST analyses were also conducted for comparison. R software[88,89] was used in the analysis: The BayesianFirstAid[90] R package was used to obtain Bayesian probabilities and highest-density interval (HDI) estimates for paired t-test and correlations. The prior used by "BayesianFirstAid" package for Bayesian posterior estimation was an exponential distribution.[84,90] Bayes factors were also estimated using the BayesFactor[91] R package for both paired t-tests and analyses of variance (ANOVAs). The prior distribution to calculate Bayes factor was a non-informative Jeffrey's prior on means of the distribution and a Cauchy prior with *r scale* = $\sqrt{2}/2$ (or) 0.707 on standardized effect size.[91] The 95% HDI obtained using the Bayesian estimation of posterior probabilities provides an estimate of the range of values between which the highest probability density of the data located [84] and the BF provides a ratio of the probability of the data favoring one hypothesis relative to another.[85] The BF obtained from the analysis were interpreted with Jeffrey's scaling for Bayes factors (Table 3-1).[92] 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). The variance of the paired samples was tested using the Bonett-Seier test of scales for paired samples using the PairedData R package.[93] The violin plots (vioplot R package) were used in place of regular boxplots as it provides distribution of the data along with the boxplot.[94] Multiple comparisons (restrictive hypotheses 2, 3 & 4) between the stimulus types were tested by taking advantage of the BF analysis as explained by Morey[95–97].

3.5 Results:

3.5.1 Thresholds:

Even though the main aim of the study was to evaluate the detection theory estimates, 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 threshold (± SE) for visit 1 and 2 were 27.43 ± 3.79 and 31.14 ± 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 (Figure 3.2A). The variance of the paired differences between the visits was in the range of 9.04 to 1540 $(ml/min)^2$ (Figure 3.2B). The NHST equivalent student paired t-test of the thresholds was not significantly different between the visits (p = 0.62). The average thresholds (± SE) for the mechanical and chemical stimuli were 34.8 ± 4.6 ml/ min @ 50°C and 20.8 ± 3.7 $\%CO_2$ respectively. The threshold between the stimulus types could not be compared due to the difference in the unit of measurement.

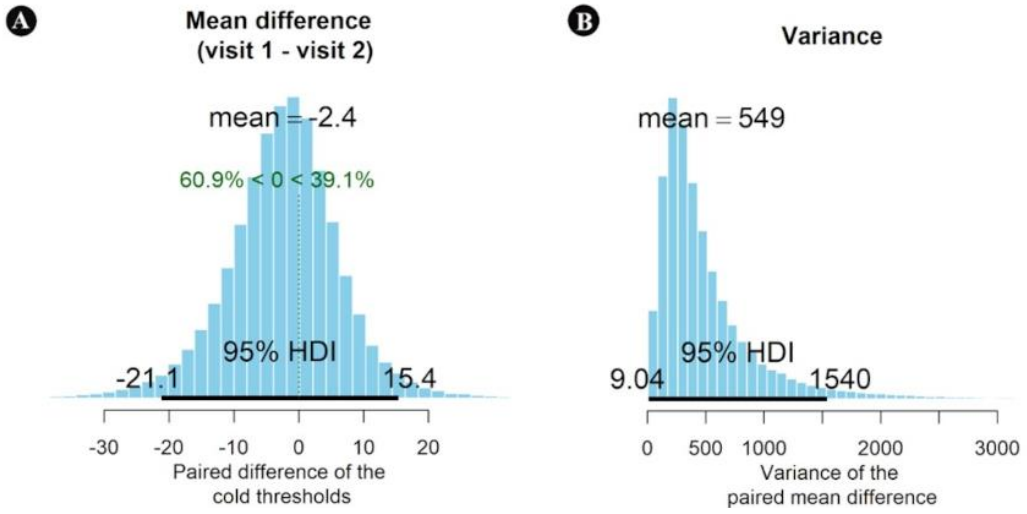

Figure 3.2: The Bayesian posterior distribution of paired differences of the thresholds between visits (A) and variance of the paired threshold differences (B).

3.5.2 Detectability:

The average (± SE) d' for the supra-threshold cold stimulus for the experiment with 40% and 60% stimulus probabilities were 0.60 ± 0.13 and 1.05 ± 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 (Figure 3.3). The NHST paired student 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 (Figure 3.3B). 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 ranged from 0.198 to 5.52 square units (Figure 3.3B).

The average *d'* of the noxious supra-threshold mechanical and chemical stimuli with 0.4 stimulus probability were 1.65 ± 0.37 and 1.14 ± 0.4, respectively (Figure 3.3). The *d'* of all three-stimulus types were compared using a Bayesian one-way ANOVA. A factor (BF_{10}) of 1.55 indicated an anecdotal/mild favoring of the data towards 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). While testing the restrictive hypothesis (#2) 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 $BF_{10} = 1.27$. The restrictive hypothesis (#3) tested the difference in the *d'* based on the type of nerve fibers (Aδ vs. C) used by the receptors. Similar to the results of the hypothesis (#2), 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 (#4) based on the chemical combination of the stimulus with BF_{01}'s of 2.76 and 4.29 respectively. The NHST analysis using ANOVA showed no significant difference (F (2,26)= 3.25; p = 0.06) between the *d'* of the stimulus types.

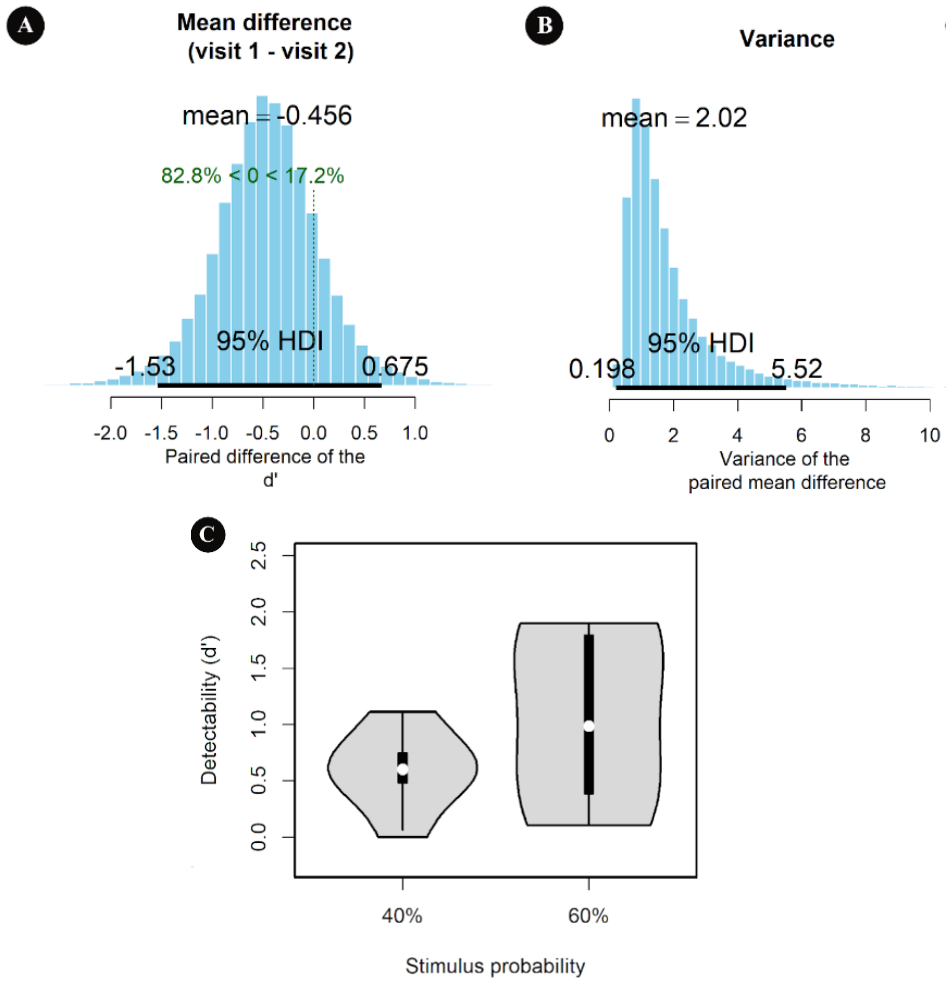

Figure 3.3: A) Histogram of the predicted posteriors using the default prior distribution for the paired mean differences of detectability along with the HDI. (B) The variance of the paired differences of the *d'* of cold stimuli between 2 stimulus probabilities. C) The boxplot (center) and density distribution (grey shaded area) of the original data represented using violin plots.

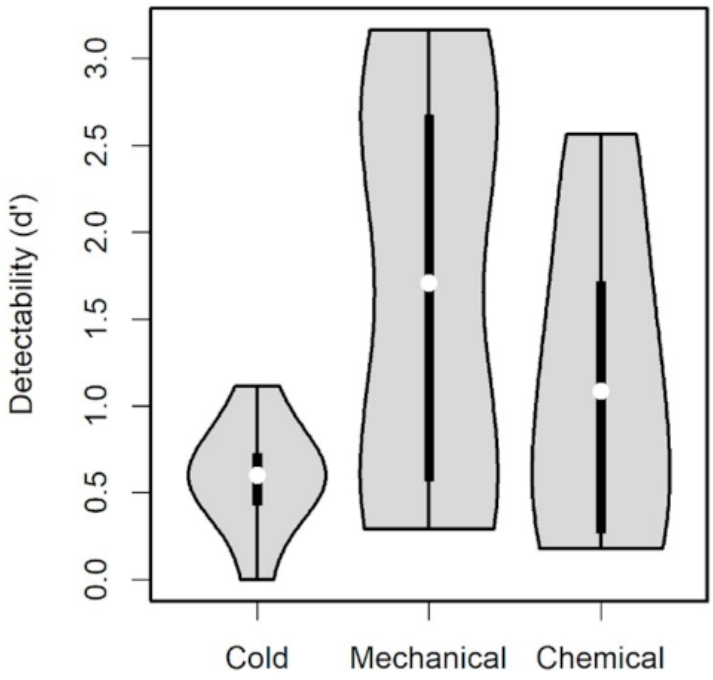

Figure 3.4 : The *d'* of the supra-threshold stimuli at 40% stimulus probability for three stimulus types are presented as boxplots in the middle of the violin plot. The white dot in the middle of the box plot represents the median with the edges of the box representing the quartiles. The outlines of the violin plot represent the kernel density curves, i.e., the width of the shaded area represents the proportion of data located there.

3.5.3 Bias estimates:

The average *c* (± SE) for the cold supra-threshold stimulus with an experiment stimulus probability of 40% and 60% were 0.33 ± 0.09 and 0.54 ± 0.13 respectively. The average *lnβ* (± SE) for the cold supra-threshold stimulus were 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 (Figure 3.5).

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 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.

The average (± SE) criterion with 40% stimulus probability for the mechanical, chemical and cold stimuli were 0.58 ± 0.097, 0.37 ± 0.13 and 0.33 ± 0.09 respectively. The comparison of *c* between the stimulus types produced a BF_{10} of 1.08, suggesting the data neither favored the null nor the alternate hypothesis. Similar to *d'*, the restrictive hypotheses were tested against the null and alternative hypothesis for the bias estimates as well. The *c* was anecdotally in favor of nociception (#2) and nerve fiber type (#3) restrictive hypothesis by a BF_{10} of 1.19 and 1.7 respectively against the null hypothesis; 1.09 and 1.57 respectively against the default alternate hypothesis. The *c* did not support the hypothesis based on the chemical composition hypothesis (#4) 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 (#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 hypotheses. The NHST one-way ANOVA of criterion showed no significant difference ($p = 0.09$) between stimulus types (Figure 3.6). 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 ($p = 0.03$).

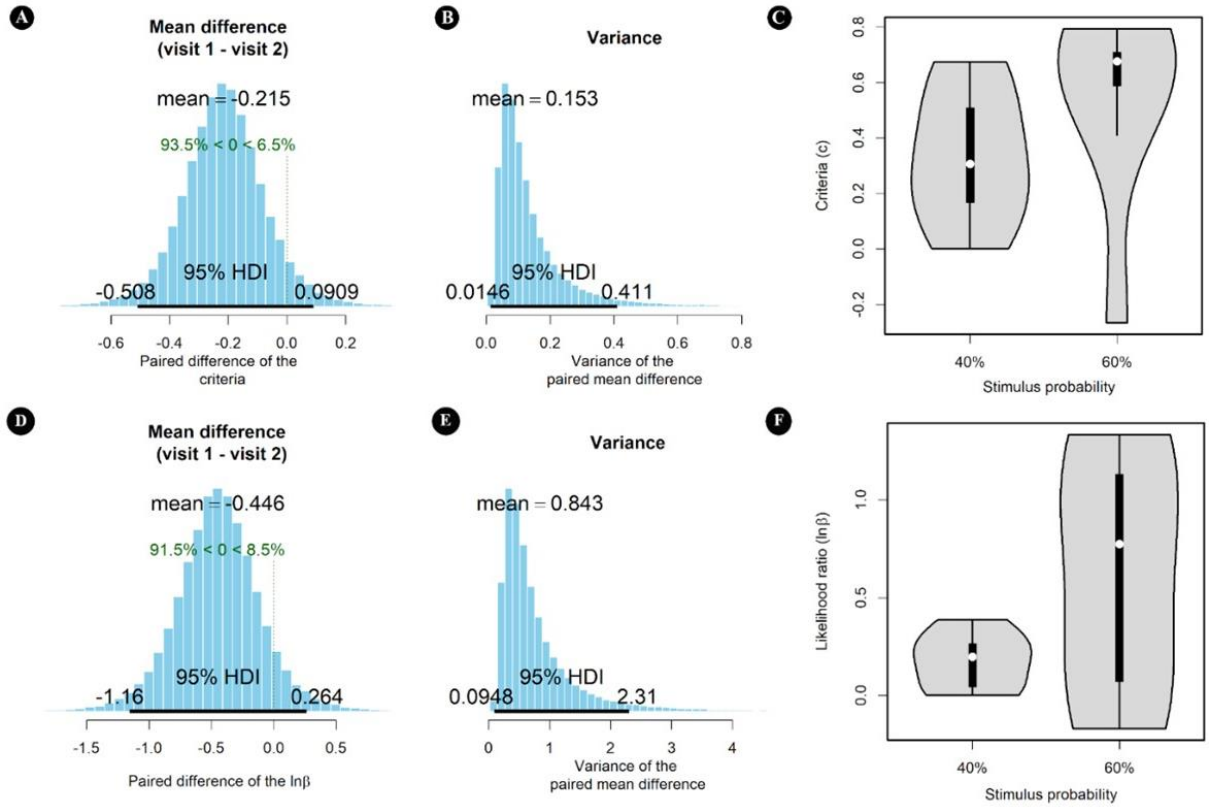

Figure 3.5: The posterior Bayesian probabilities and HDI for paired mean criteria (A) and lnβ (D) differences; the posterior distribution of the variance of paired difference (B and E); The violin plots for original data of criteria (*c*) and lnβ (F). Each plot compares the values obtained using the 40% and 60% stimulus probabilities.

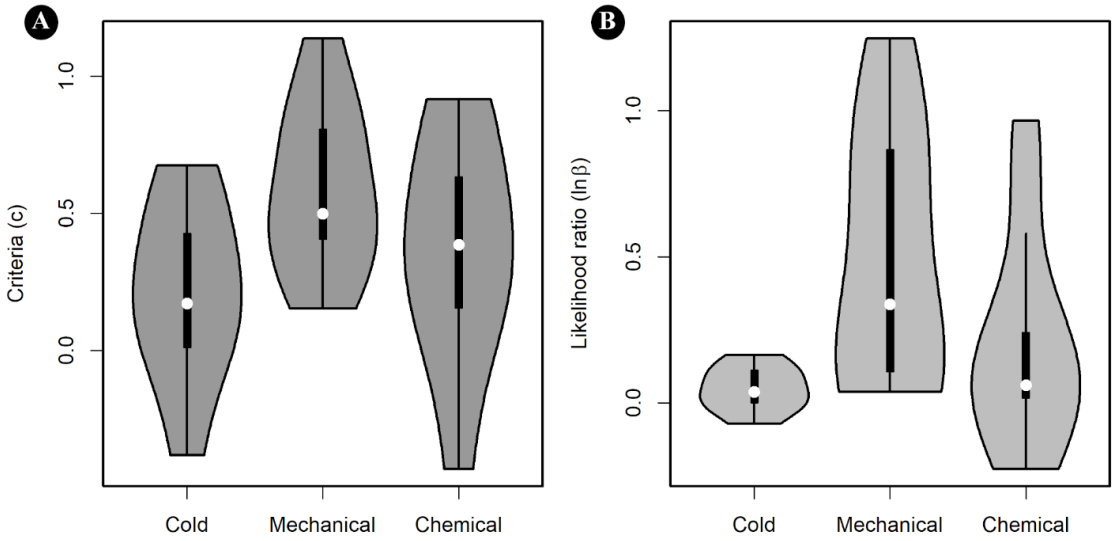

Figure 3.6: Violin plot with boxplot in the middle of the violin plot. The violin plot representing the distribution, median and quartiles of the c (A) and lnβ (B) for supra-threshold stimulus types. The frequency distribution of the data is given by the kernel density curve on either of the boxplot.

3.5.4 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 (Figure 3.7). 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. Anecdotal 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 (Figure 3.8) 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, $p = 0.017$).

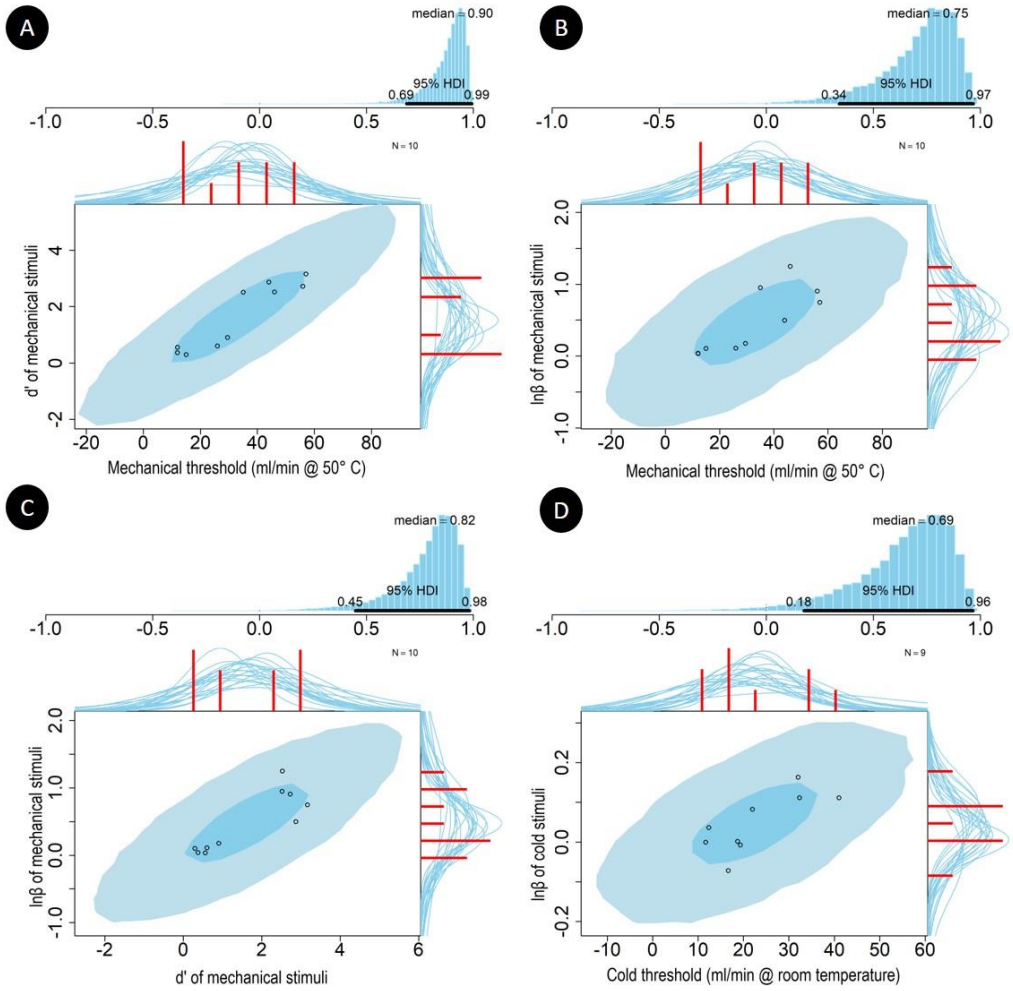

Figure 3.7: Bayesian estimation of Pearson correlation to obtain the relationship between the threshold, d', c and lnβ for each stimulus type. Data that favored the relationship have been shown in graphs between (A) threshold and d' of mechanical stimuli, B) threshold and ln*β* of mechanical stimuli, C) *d'* and ln*β* of mechanical stimuli, and D) threshold and ln*β* of cold stimuli.

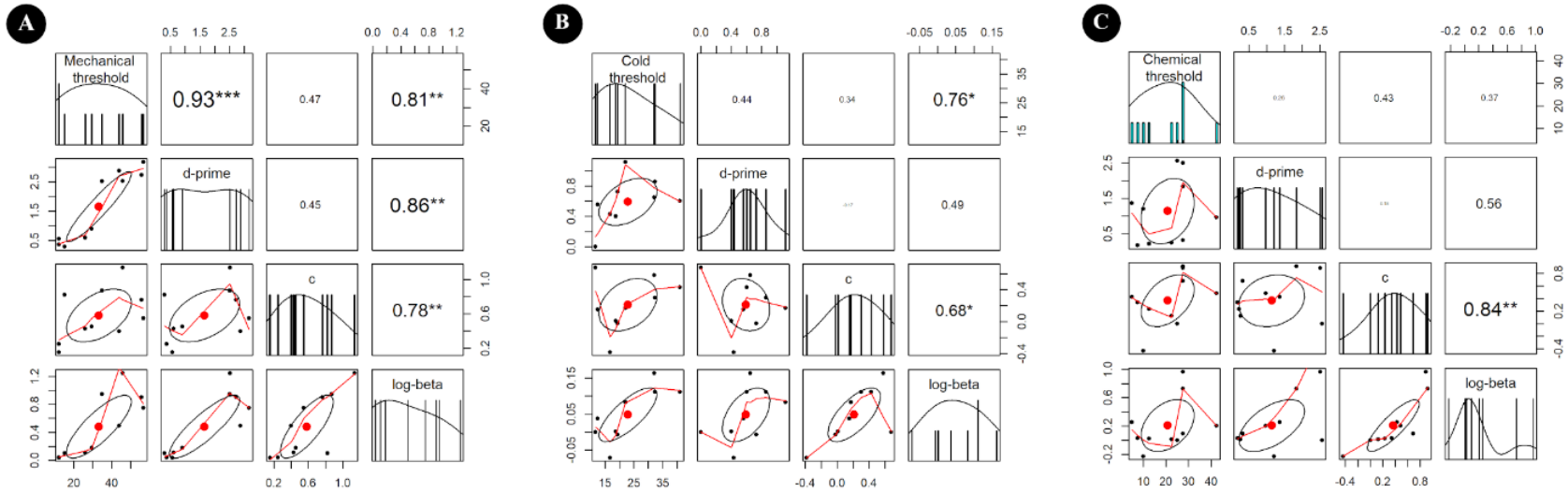

Figure 3.8: Correlation matrix with Pearson correlations to analyse the relationship between the thresholds, d', c and lnβ for A) mechanical, B) cold and C) chemical stimuli. The scatter plot with loess line fit and correlation ellipses providing the relationship between the variables analyzed. The numbers represent the correlation coefficient values with variable font size indicating the strength of the relationship along with stars indicating the significance.

3.6 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 estimates from human participants were in favor of theories based on non-primate corneal neurophysiology. We also showed that the detection theory estimates favored responses to different types of stimuli being independent of each other, based on chemical composition and temperature.

The literature on using SDT to study pain has indicated a need for careful selection of the stimulus to obtain *d'* and bias.[68,98] 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 either used stimuli scaled to detection thresholds[99–103] or stimuli of predefined intensities.[98,104] The advantages and disadvantage of both methods were discussed in the thesis by Tan[98]. 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 esthesiometry, 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 (supra-threshold) stimuli to examine pain.[64,105] 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 the calculating SDT parameters. Participants could also adapt to the strong stimulus if multiple presentations were presented, altering the perceived intensity as the experiment progressed.[51,53] On the other hand, a weak stimulus may not be readily detected, resulting in a higher FAR and lower HR.[106] Also, in the previous corneal sensitivity experiment in our lab, with the same instrument and stimulus, participants categorized the 1.5x detection threshold stimuli as mild to moderately intense.[50,51] Therefore,

pilot experimentation and theoretical considerations led us to use the stimulus intensity of 1.5x 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 estimates, 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. Only 5 out of 30 participants took extra breaks during the experiment, which were mostly due to non-experiment related factors. Mild corneal staining was observed for 3 participants at the end of the experiment with the mechanical supra-threshold stimulus, but no discomfort, irritation, or pain sensations 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 non-primate corneal neuro-physiology 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 estimates 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 as 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 neurophysiological 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 (1.5x threshold) to keep the perceived sensation similar across participants and stimulus types psychophysically.[98] 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 towards the conservative side, indicating a cautious approach by the participants in their responses to the supra-threshold stimuli. There is only one previous report of ocular surface sensing based on SDT (in contact lens wearers) by Beuerman and Rozsa[103], 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 electrophysiological studies on non-primate corneas, but no similar studies on the human cornea and a general assumption is 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 (that also, have been reported to have little background activity).[3,4,18,21,23,24] This sort of distinction between painful and non-painful stimuli has been proposed before.[107]

Our linking hypothesis explicitly assumes similar functioning in primate as in non-primate corneas.[108] In reports about corneal sensitivity, the authors appear to assume similar animal-human linking hypotheses in reaching conclusions about the human cornea.[3,12,18] 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 and this is the first time the theory has been psychophysically tested directly in human participants.

Similar to nociception theory, the psychophysical data also supported the nerve conductance theory. Since histo-chemical[109] 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 presence these fibers[109], the Aδ- and C- fibers have been assumed to be present in the human cornea similar to the non-primate cornea.

As described in the methods, the mechanical and cold stimulus use medical air at different temperatures, whereas the chemical stimulus contains a mixture of CO_2 and medical air. Cold stimuli have been used to evaluate corneal sensitivity and it has been debated about whether this is also contaminated by a mechanical stimulus.[28,36,43,110,111] According to a study by Nosch et.al [110], room temperature plus 10 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 and suggested that if the stimulus was outside of this range (room + 10 degrees) there would be a thermal component in a pneumatic mechanical stimulus. We tested the hypothesis with the assumption that if the mechanical stimulus had a cold component, then the mechanical and cold would be detected similarly by the participants. However, our psychophysical data did not favor this hypothesis.

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 $ln\beta$ (Figure 3.7). Even though there were no obvious grouping of the data in the mechanical threshold, we observed two groups of participants in the *d'* of mechanical stimuli. Participants either had a low *d'* or high

d' and the participants who had lower *d'* had a low threshold and lower bias using *lnβ* or vice versa. A similar decrease in *d'* and bias has been seen in SDT literature that analyzed the effect of anxiety [58,68,105,112–117], though 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 higher threshold which in turn increased the detectability in SDT (since we used threshold from the AMOL to obtain supra-threshold 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 state earlier can affect the signal detection metrics.

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Chapter 4: Detection Theory and Psychological Aspects of Ocular Surface Sensory Processing

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	Jayakumar	**Simpson**
Experimental design	Y	Y
Data collection	Y	-
Data analysis	Y	Y
Write-up publication	Y	Y

4.1 Introduction:

The yes-no SDT experiment in the previous chapter (Chapter 3) involved a detection task, in which participants detected the presence of a signal (supra-threshold stimulus) against the background noise. The yes-no SDT experiment demonstrated the feasibility of using one-interval two response (yes-no) design signal detection theory (SDT) to analyze the ocular surface sensory processing (OSSP) of pneumatic stimuli. However, there were a few limitations in the experiment that needed to be addressed, such as the assumption of fixed criterion, detection indices obtained only for a single signal intensity, and longer experiment duration if needing to test each intensity separately in a similar protocol. The yes-no SDT assumes that participants use a single criterion throughout the experiment when responding "Yes" or "No" to a trial, similar to the assumed single (and fixed) criterion in a classical psychophysical method but with the ability to estimate bias.[1–3] However, if the participants vary their criterion during the experiment, the variation cannot be distinguished/evaluated due to the two response design. Pay-off matrices or changes in instructions provided before the experiment have been reported in the literature to control/ alter the criterion assumed by the participants.[1–3] However, these restrict the participants from choosing their criterion independently during the experiment. Also, in a normal/clinical/experimental environment, the cornea receives multiple stimuli of different types and intensity at the same time. For example, in a clinical environment, participants may have to detect the stimuli of different intensities while they are already experiencing discomfort from the pre-existing dry eyes or factors such as the draft winds and dry airconditioned environment[4,5]. The limitations make the yes-no one-interval SDT design less efficient, but the flexibility of SDT is that the same experiment could be conducted with variable criteria and multiple stimuli instead of a single stimulus intensity yes-no design. The SDT experiment with variable criteria is usually referred to as a multi-criterion or rating SDT experiment. In rating SDT experiments, instead of reporting a yes/no detection response, participants rate their confidence with which they detected a signal compared to the background noise.[1–3,6–8] Each level is then 'converted' to a yes-no design to obtain different criteria adopted by the participants during the experiment, which will be similar to conducting multiple yes-no experiments with different pay-off matrices. The either ends of the rating scale (1 and 5, if 1-5 rating scale is used) represent the most conservative or most lax criteria used by the participants during the experiment, but participants can

independently choose and vary their criterion during the experiment.[2,7–9] Also, the detection indices could be estimated for multiple intensities within a single rating SDT experiment and it is referred to as multi-stimuli rating SDT (MSDT) in this thesis.[2,9]

MSDT experiments with pneumatic stimuli have never been conducted to examine OSSP. In the only previously reported OSSP study using MSDT, detection of thermal waterjet corneal stimuli was obtained from rating responses, but the results were reported as though the experiment was conducted as a yes-no SDT experiment.[10] Studies have used MSDT in other areas such as studies on audition, pain and memory.[2,3,9,11–13] The concepts of SDT from the pain literature will be applied and evaluated in this study. OSSP is similar to somatic pain processing despite using the trigeminal pathway and partly because of its initiation with similar pain receptors.[14–19]

According to the International Association for Study of Pain, pain is an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[20,21], and recently Williams and Craig[22] defined pain as "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components." Studies have often found that psycho-social entities such as anxiety, fear, personality, confidence, decision-making, self-esteem and stress affect the perception of painful stimuli.[23–25] Similar issues have been suggested in the literature of corneal sensitivity[17], but have never been addressed before.

According to SDT, to elicit a response for a given trial, the sensory process first detects the stimulus and this is then followed by the decision process (influenced by multiple factors) that shifts the response either in favor of signal or noise.[2,8] Both psychological and physiological factors have been shown to alter the detectability and bias.[26] Specifically, the detectability is linked with stimulus parameters such as the intensity, and the bias is associated with motivational, attitudinal and learning factors that influence the decision process.[27,28] Anxiety has been shown to affect the d-prime and response bias.[27–30] Similarly, decision-making has been an essential factor addressed in literature from various disciplines. The Melbourne Decision-Making Questionnaires (MDMQ II) is a redesigned Flinder's decision-making questionnaire to address motivational effect, cognitive styles and personality

components on decision-coping style.[31] Similarly, anxiety has been shown to affect decision-making.[25,32–36] Both anxiety and decision-making are processed in the amygdala, insular cortex, and prefrontal cortex.[36] The involvement of the amygdala in pain processing has also been studied in recent years, as the nociceptive pathway passes through the amygdala before it reaches the thalamus and cortex.[37,38] Even though there does not appear to be enough evidence of one influencing the other, in recent studies, it has been proposed that anxiety influences decision-making due to the shared pathways.[36] It is unclear whether these psychological factors affect the detection of corneal stimuli because these predictor variables have never been explored in experiments examining corneal sensory processing. In addition, corneal esthesiometry is considered an anxiety-inducing technique due to the proximity of the esthesiometer to the eye and anticipatory effect pertaining to the severity of the impending stimuli.

In addition to psychological factors, the factors such as gender, symptoms and contact lens usage have been evaluated frequently in ocular surface sensitivity studies. Studies have shown differences in the perception of pain with gender.[39–41] There are no studies that evaluated the pain perception in symptomatic participants and participants who use contact lenses. There is no literature available on the noise levels in these conditions, but I speculate that participants might have elevated background noise levels against which the signal needs to be detected. The speculated elevation in noise levels is either due to discomfort or contact lens use and the level of noise might be different depending on the level of adaptation (chronic or acute). SDT studies have shown that clinical conditions (chronic or acute) affect the detection indices.[26,42–44]

The initial aim of this experiment was to evaluate the feasibility of using MSDT to understand the OSSP, and once feasibility was established, to compare detection theory estimates between different groups, and examine the non-sensory decision and anxiety factors and then, analyze the relationship between the psychological factors and psychophysical outcomes of detection thresholds, d_a, and criterion. Also, evaluate the effect of different factors on detection theory indices.

4.1.1 Research questions:

- Are the indices of detection different between stimulus types and intensities?
- Is there any interaction of groups (based on symptoms and contact lens use) in the detection of pneumatic stimuli?
- Do psychological factors such as anxiety and decision-making show any relationship with the outcomes of psychophysical methods used in this study?

4.1.2 Hypothesis:

- The detectability of stimulus intensities is different between each other.
- The detectability is different between stimulus types.
- The bias adopted by the participants is different between stimulus types but constant within each of the stimulus types.
- The detectability of the stimulus is the same, but bias is different between non-contact lens wearers and contact lens wearers.
- The detectability of the stimulus is the same, but bias is different between an asymptomatic and symptomatic group of participants.
- The decision-making and anxiety have no effect on the sensory estimates.
- The decision-making and anxiety scores have an effect on the bias adopted by the participants.

4.2 Methods:

Forty-one participants were recruited in the study using convenience sampling from the students and staff community of the University of Waterloo. The study was conducted according to the guidelines of the Declaration of Helsinki and ethics approval was obtained from the University of Waterloo, Office of Research Ethics (Waterloo, Ontario, Canada). Informed consent was obtained from each participant and participants were allowed to discontinue at any stage of the study. The screening and recruitment of the participants were performed on the first study visit. On arrival, participants filled the questionnaire on dry-eye symptoms using the DEQ-5 questionnaire and the history of contact lens usage was also

recorded. The ocular surface was screened for any active signs of inflammation or infection. The scores from the DEQ-5 questionnaire was later used in the analysis by grouping them into asymptomatic and symptomatic participants. Participants who wore their contact lenses at least three days per week were grouped under the contact lens wearer group, otherwise under non-contact lens wearers. There were only soft contact lens wearers in this study and the lens wearers were instructed not to wear their contact lenses on the day of their study visits. The visits were scheduled to occur at the same time of the day (± 30 min) to reduce diurnal variation affecting the measurement.

4.2.1 Stimulus characteristics:

The stimulus types used in this experiment were mechanical, chemical, and cold (or cool, room temperature). A Waterloo Belmonte pneumatic esthesiometer was used to deliver each stimulus to the center of the anterior corneal surface. The mechanical stimulus was medical air, heated to 50°C (converts to 33°C at the corneal surface) at the nozzle, and the cold stimulus was a room-temperature medical air. The flow rate of the stimulus was either increased or decreased to alter the intensity of the output, depending on the response provided by the participants. In the case of the chemical stimulus, the flow rate of the stimulus was kept constant at half of the mechanical threshold to remove any mechanical effect influencing the judgment. The ratio of carbon dioxide mixing with the medical air was changed at a given flow rate to produce a chemical stimulus. The % CO_2 in the stimulus defines the intensity of the chemical sensation induced. The flow meters in the control box of the esthesiometer regulates the flow of medical air and CO_2 to the desired concentration and flow. The temperature of the chemical stimuli was the same as the mechanical stimuli. The preparation and delivery of the stimulus were automated using the custom software according to the psychophysical procedure conducted. Each stimulus type was randomly assigned to one of the 3 study visits at the start of the first study visit. Each visit was approximately an hour long and was separated by at least a day to avoid fatigue effects and allow ‘recovery’ of the ocular surface and the pain processing system.

4.2.2 Ascending method of limits:

Though it is an MSDT experiment, the detection thresholds were calculated to use as a baseline for the following MSDT experiment. At the start of the visit, detection thresholds for the assigned stimulus was measured using the ascending method of limits (AMOL). An average of three measures was considered as a threshold. The duration of the chemical stimulus was 2 seconds, and mechanical and cold stimuli were 3 seconds long. The inter-stimulus interval for cold and mechanical stimuli were 10 seconds; for chemical stimuli, the inter-stimulus interval was 30 seconds (to enable purging of the stimulus in preparation for the subsequent stimulus). The oral instructions were provided by me before the start of the experiment, followed by the automated audio prompts for each trial. The training was provided. Participants were advised to blink between each trial. Participants responded yes/no to each trial using the button box and the responses were recorded in the software. If the difference in detection thresholds between 3 measures were larger than 15ml/min or 15%, the experiment was repeated another day. If the thresholds were still variable, the participants were excluded from the study.

4.2.3 Detectability experiment:

The signal intensities for the MSDT experiments were scaled based on their respective corneal detection thresholds and the signals (in the analysis and report) were referred based on relative intensity to the threshold. The scaled intensities are described later in the methods. Instructions for the detectability experiment were accompanied by a short demonstration of the trial sequence. 'Neutral' instructions were scripted and delivered to all participants at the start of the experiment, in an attempt to minimize examiner induced bias and variability. The stimulus probabilities and feedbacks, indicating the correctness of the response were not provided to the participants. Instead, audio feedback confirmed each button press. Participants rated each trial using the button box and the number of button presses was stored as the rating for each trial. Participants were advised to blink between stimulus presentations.

4.2.3.1 Cold and mechanical detectability experiment:

The cold and mechanical MSDT experiments consisted of 100 trials with random presentations of a signal or a noise stimulus. Each experiment consisted of four signal

intensities of 20 trials each and a noise stimulus of 20 trials. The signal intensities (scaled based on detection thresholds) were a sub-threshold (0.5x threshold), a threshold and two supra-threshold (1.5x and 2x threshold) intensities. The noise stimulus was a catch trial with no stimulus. If the estimated threshold for cold or mechanical stimulus was between 15 ml/min and 20 ml/min, a flow rate of 10 ml/min was used as the intensity of the sub-threshold stimulus. If the threshold was below 15 ml/min, the trials involving sub-threshold stimulus were replaced with the blanks (catch trials) as the flow rate of 50% threshold would be well below the esthesiometer's reliable output range of 10-200 ml/min. On a given trial, either a signal (one of the four scaled stimulus intensities) or a noise (blank stimulus) trial was randomly presented, and the instructions for the noise trials were exactly the same as signal trials.

The inter-stimulus interval and presentation time was the same as the threshold experiment. A confidence rating scale of 5 ratings was used by the participants to respond to each trial. Breaks were provided after 50 trials by default or whenever participants pause the experiment using a button box.

1	2	3	4	5
Definitely "No" signal was not presented	*Probably "No"* signal was not presented	Not sure/ Uncertain	*Probably "Yes"* a signal was presented	*Definitely* "*Yes*" signal was presented

Table 4-1: The confidence rating scale used by the participants to respond to a mechanical or a cold stimulus trials.

4.2.3.2 Chemical detectability experiment:

Chemical MSDT experiment consisted of 50 trials with random presentations of either a signal or a noise stimulus. There were two signal intensities (the threshold and the 2x threshold) of 20 trials each and 10 noise trials. Unlike cold and mechanical MSDT experiments, the noise/catch trial for chemical stimuli were not completely blank stimuli; instead, a medical air stimulus with 0% CO_2 added at the same flow rate as signal trials. A confidence rating of 4 ratings was used by the participants to respond to each trial. Breaks were provided after 25 trials by default or whenever participants pause the experiment using a button box.

1	2	3	4
Definitely "No" signal was not presented	*Probably "No"* signal was not presented	*Probably "Yes"* a signal was presented	*Definitely* "*Yes*" a signal was presented

Table 4-2: The confidence rating scale used by the participants to respond to a chemical stimulus trials.

4.2.4 Anxiety and decision making:

The decision-making scores were obtained at the start of the first study visit using the Melbourne Decision-Making Questionnaire II (MDMQ II). The decision-making was evaluated before the start of the experiment, followed by DEQ-5 and anxiety questionnaires. The anxiety was evaluated using the State-Trait Inventory for Cognitive and Somatic Anxiety questionnaire (STICSA). There were two components of anxiety measured: Trait (anxiety in general) and state (anxiety at that instance). The STICSA-trait questionnaire was administered only once and it was administered after the DEQ-5 questionnaire on the first study visit. Participants were instructed to respond based on how they feel in general. The instructions for the threshold experiment were provided, followed by the state anxiety questionnaire to respond based on how they feel at the particular instance after the instructions. The anxiety questionnaires were obtained before and after each threshold measurements in each study visit.

4.3 Data analysis:

The rating data for each participant was exported to Microsoft Excel spreadsheet. The RscorePlus software (v.5.6.1)[45] was used to calculate the detection theory parameters. These were based on assumptions of Gaussian signal and noise distributions. The RscorePlus data input file had the information on the number of rating categories, a number of signals (including catch trials), participant id, commands specific for SDT analysis along with the response frequency for each rating category. The commands included code for collapsing data in case of unsuccessful analysis, treatment of zero frequencies and type of the SDT experiment. For this study, the SDT indices were calculated with a SINT (single-interval experiment paradigm) SDT protocol and zero frequencies were replaced with 1/number of rating categories to eliminate errors due to zero frequencies. The hit rate (HR) and false alarm rate (FAR) were calculated by cumulating the rating responses of n ratings for (n-1) decision

criteria similar to the yes-no procedure. The HR and FAR was used in the calculation of detection theory parameters. The outputs included the detection theory parameters for each signal and formatted datasheet for creating detection theory graphs using R. The equations used in calculating each detection theory parameter as provided by the software manual are listed below:[45]

$$d' = z(HR) - z(FAR) \qquad \text{(Equal variance model)}$$

$$d_a = \sqrt{\frac{2}{1+b^2}} \,.(z(HR) - b.z(FAR)) \qquad \text{(Unequal variance model)}$$

$$A_z = z^{-1}\left[\frac{d_a}{\sqrt{2}}\right]$$

$$c = -0.5\ (z(HR) + z(FAR))$$

$$X_c = -z(FAR)$$

$$\ln(\beta) = \frac{[z(FAR)^2] - [z(HR)^2]}{2}$$

The d_a and d' are numerically the same if the variance of the Gaussian distribution of noise and signal + noise are the same.[45,46] The standardized criterion, X_c, gives the bias status of the participants for the whole SDT experiment (each stimulus type), whereas criteria (c and *ln*β) gives independent bias indices for each stimulus intensity used inside the MSDT experiment. The A_z provides the area under the curve estimate for each signal. The receiver operating characteristics (ROC) curves were plotted for individual and cumulated (grouped) data. The cumulated data ROCs were plotted by using the rating data obtained by adding the response frequencies of each stimulus rating category across all the participants within the group as though a single participant received all the trails (Figure 4.1). For example, all 3600 trials (720 catch and 2880 signal trials) for mechanical stimuli were received by a single participant compared to 100 trials each by 36 participants. The R programming codes provided in the RscorePlus software package[47] were used in plotting the ROCs, zROCs and Gaussian distributions reported in this chapter.

Participant id	Stimulus type	Rating 1	Rating 2	Rating 3	Rating 4	Rating 5
1	Cold sub-threshold	5	2	1	0	2
2	Cold sub-threshold	2	3	3	2	0
3	Cold sub-threshold	5	5	0	0	0
Group detection indices using the cumulated ratings data		12	10	4	2	2

Figure 4.1: Example for the cumulated ratings to calculate group detection indices and draw group ROC curves.

To analyze the bias between the types of stimulus, the multiple criterion data from the rating dataset were collapsed to a single criterion yes-no type analysis due to the difference in the rating scales between the stimulus types used by the participants to respond to the trials. The ratings were accumulated based on 'liberal' and 'strict' criteria. In case of the 'liberal criterion', a rating of 1 (definitely "no" there was no signal presented) was used as the frequency of "no" response and ratings of more than 1 were cumulated as the frequency of "yes" response which would be similar to criterion 1 from the rating analysis. In the case of the 'strict criterion', a rating of 5 (definitely "yes" there was signal) was used as the frequency of "yes" response (rating 4 for chemical stimuli) and the ratings of less than 5 were cumulated as the frequency of "no" response which would be similar as criterion 4 (criterion 3 for chemical) from the rating analysis. Both the standardized criterion (X_c) of the Gaussian distribution and the biases for individual stimulus types were used for the analysis between stimulus types.

The detection theory indices were analyzed using a mixed-model analysis of variance (mixed-model ANOVA) ('lmerTest' package[48]) and paired sample t-test in R. The post-hoc/contrast analysis for the mixed-models were performed using the "psycho" package.[49] Several R packages were used in sorting, rearranging and analyzing data, and in creating and

exporting graphs.[48,50–66] An alpha value of $p \leq 0.05$ was assumed to be significant in all the analyses conducted.

4.3.1 Outline of the analysis conducted:

Parameters from the experiment:

- Stimulus types: Cold, mechanical, and chemical
- # of stimulus intensities: Cold- 4, Mechanical- 4, Chemical- 2
- # of rating categories: Cold- 5, Mechanical- 5, Chemical- 4
- Groups: CL use (2), symptoms (2), symptoms & CL (4)
- Detection theory parameters: d_a, A_z, criteria (c and $ln\beta$), X_c
- Decision-making components: Vigilance, buck-passing, procrastination, and hypervigilance
- Anxiety components: Trait & State- Cognitive and somatic anxiety

Outline of analyses:

Rating SDT (Paragraph 4.4.2)

- Summary statistics for threshold, detection theory parameters, decision-making scores, and anxiety scores
- Comparisons of the detection theory parameters between stimulus intensities within each stimulus type and between stimulus types
- Comparisons of the detection theory parameters between groups based on factors
- Correlation between detection thresholds and detection theory parameters

Decision-making (Paragraph 4.4.5)

- Comparisons of the decision-making scores between the 4 categories and analysis of the interaction between groups based on factors
- Correlations between the detection thresholds and DM scores
- Correlations between the detection theory parameters and DM scores

Trait anxiety (Paragraph 4.4.6)

- Comparisons of the trait anxiety scores between the 2 anxiety components and analysis of the interaction between groups based on factors
- Correlations between the detection thresholds and trait anxiety scores, and interaction between groups based on factors
- Correlations between the detection theory parameters and trait anxiety scores
- Correlation between decision-making and trait anxiety scores

State anxiety (Paragraph 4.4.7)

- Mixed model analysis of change in anxiety over the course of the experiment and analysis between groups based on factors
- Comparisons of the state anxiety scores between the two components and between the pre- and post-AMOL scores
- Comparisons between the pre- and post- AMOL state anxiety scores and interaction of groups based on factors
- Correlations between the detection thresholds and state anxiety scores (pre & post) and the interaction of groups based on factors
- Correlations between the detection theory parameters and state anxiety scores (pre & post)
- Comparisons of the state anxiety scores between anxiety components (pre & post)
- Comparisons of the state anxiety scores between groups (pre & post)
- Correlations between the detection thresholds and state anxiety scores (pre & post)
- Correlations between the detection theory parameters and state anxiety scores (pre & post)

4.4 Results:

Forty-one participants were recruited in this study. The mean (± SD) age group of the participants was 30.20 ± 7.44 (range: 19 to 50) years. Five participants were discontinued at different stages of the study: Three discontinued due to variable detection thresholds obtained while repeating the AMOL and 2 participants discontinued due to high threshold. As

mentioned earlier, the detection theory indices for all participants and groups were calculated in two formats: 1) calculated using the summed rating data (for each rating) within the group/all participants and 2) calculated from each participant's rating data. Along with the detection theory indices, 135 sets of ROCs, z-ROCs and gaussian distributions were plotted (individual participant: 108 (3 stimulus type * 36 participants); groups: 27 (3 stimulus * 1 all participants + 3 stimulus * 2 groups based on symptoms + 3 stimulus * 2 groups based on contact lens usage + 3 stimulus * 4 groups of both symptoms & contact lens)). Since this chapter consists of a large number of analyses, the format of the result section has been categorized in sub-sections based on detection thresholds, SDT indices, and psychological indices. Under each sub-section, there are summary statistics, followed by comparisons between stimulus types, comparisons with other study variables, and finally the interactions of factors as listed in outline above (4.3.1).

4.4.1 Detection thresholds:

The average (±SE) detection thresholds for cold, mechanical, and chemical stimuli were 26.01 ± 2.10 (ml/min@ room temperature), 28.60 ± 2.25 (ml/min @ corneal temperature), and 24.83 ± 2.30 (%). Within each stimulus type, the detection thresholds were compared between groups based on gender, contact lens wear and symptoms using the independent t-test. The mechanical detection thresholds were significantly different between the groups based on gender ($t(27.6) = -2.06$, $p = 0.049$) and the cold detection thresholds were significantly different between the groups based on symptoms ($t(31.75) = -2.28$, $p = 0.03$) (Figure 4.2).

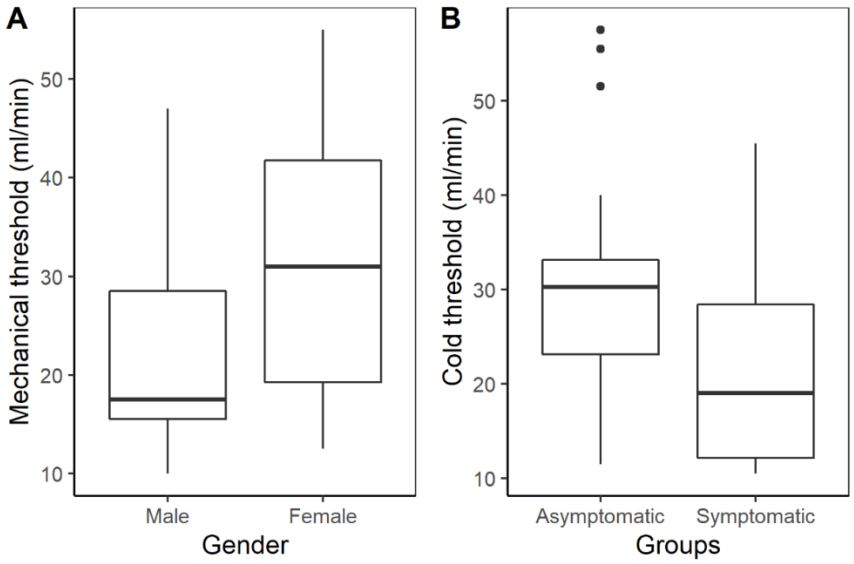

Figure 4.2: Boxplot for mechanical detection thresholds compared between gender (A) and cold thresholds compared between groups based on symptoms (B)

4.4.2 Comparisons of detection theory indices between stimulus types:

4.4.2.1 Detectability:

The average (±se) d_a of each stimulus type and intensity are listed in Table 4-3. Since the sub-threshold and 1.5x threshold intensity stimuli were not used in the chemical MSDT experiment, the d_a was analyzed independently for each intensity level between stimulus types. A paired sample t-test was conducted to compare the d_a between cold and mechanical stimuli of sub-threshold and 1.5x threshold intensity. The d_a's of both sub-threshold and 1.5x threshold intensity were not significantly different between the stimulus types ($p > 0.05$). On the other hand, a mixed-model analysis was conducted to compare the d_a's between the stimulus types of threshold and 2x threshold intensity. The d_a's of the threshold intensity stimuli were not significantly different between the stimulus types ($F(2, 70) = 2.988$, $p = 0.057$), though the box plot showed a higher d_a for chemical stimuli in comparison to cold and mechanical stimuli (Figure 4.3). The d_a's of the 2x threshold intensity was not significantly different between stimulus types. A similar analysis for the A_z also showed similar comparisons as the d_a. No significant main effect or interactions of factors were observed for both d_a and A_z (all $p > 0.05$).

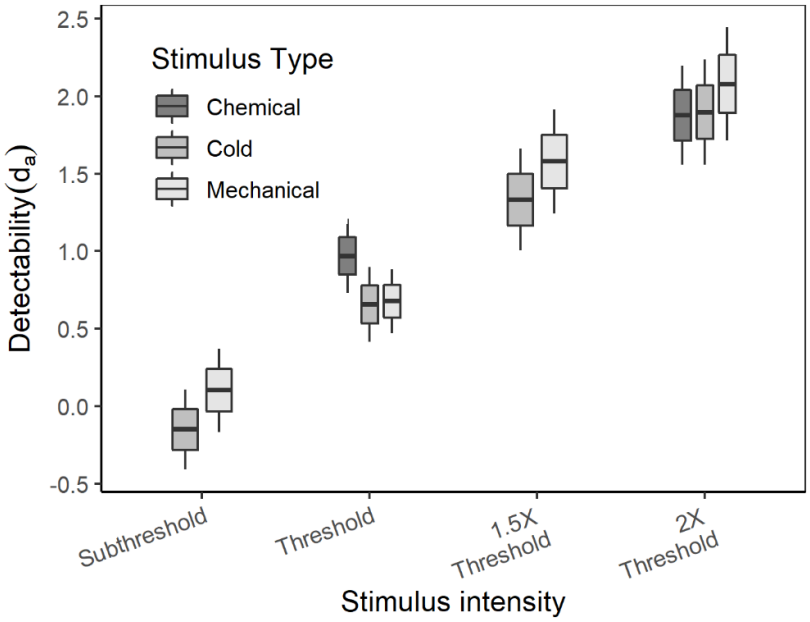

Figure 4.3: Comparison of d_a between stimulus intensities and stimulus types.

SDT Parameters	Stimulus intensity	Cold (non-noxious)	Mechanical (noxious)	Chemical (noxious)
Detectability (d_a) (mean ± SE)	Sub-threshold	-0.15 ± 0.13	0.10 ± 0.14	NA
	Threshold	0.66 ± 0.12	0.68 ± 0.11	0.97 ± 0.12
	1.5x threshold	1.33 ± 0.17	1.57 ± 0.17	NA
	2x threshold	1.90 ± 0.17	2.08 ± 0.19	1.88 ± 0.16

Table 4-3: Average (±SE) d_a for all three stimulus types and stimulus intensities.

4.4.2.2 Standardized / Decision Criterion (X_c):

Mixed model analyses between stimulus types were conducted only for the most liberal (X_c1) and most strict (X_c 4) criterion levels. A significant main effect of stimulus types ($F(2,70) = 22.93$, $p < 0.001$) was observed for the standardized criterion level 1 (X_c1) (assumption of the liberal observer), whereas no significant effect was observed for standardized criterion 4 (X_c4) (an assumption of the strict observer) (Figure 4.4). Contrast analysis of X_c1 showed that the criterion used for chemical stimuli was significantly different from the cold and mechanical stimuli ($p < 0.001$). No main effect or interaction of factors was observed for both X_c1 and X_c4.

4.4.2.3 Criterion (*c*) for each stimulus intensity:

4.4.2.3.1 Assuming a liberal criterion (c1) for collapsing into yes/no paradigm:

A significant main effect of stimulus types was observed for the *c*1 of threshold ($F(2,70) = 27.15$, $p < 0.001$) and 2x threshold intensity stimuli ($F(2,70) = 20.30$, $p < 0.001$) (Figure 4.5). The contrast analysis of the *c*1 of threshold intensity stimulus indicated a significant difference between all three stimulus types. However, for *c*1 of 2x thresholds intensity stimuli, only the chemical stimuli were different from the other two stimulus types. The *c*1's of the sub-threshold and 1.5x threshold intensity stimuli were not significantly different between the two stimulus types (chemical was not tested) (all $p > 0.05$). Compared to cold and mechanical stimuli, the participants assumed the stricter criterion (at *c*1) to respond to the chemical stimuli.

4.4.2.3.2 Assuming a strict criterion (*c*4) for collapsing into yes/no paradigm:

A significant main effect of stimulus type was observed only for the *c*4 of threshold intensity stimuli ($F(2,70) = 9.41$, $p < 0.001$) and the contrast analysis showed the *c*4's of the chemical stimuli were significantly more liberal in comparison to other two stimulus types (Figure 4.5). The *c*4's of other intensities was not significantly different between the stimulus types ($p > 0.05$).

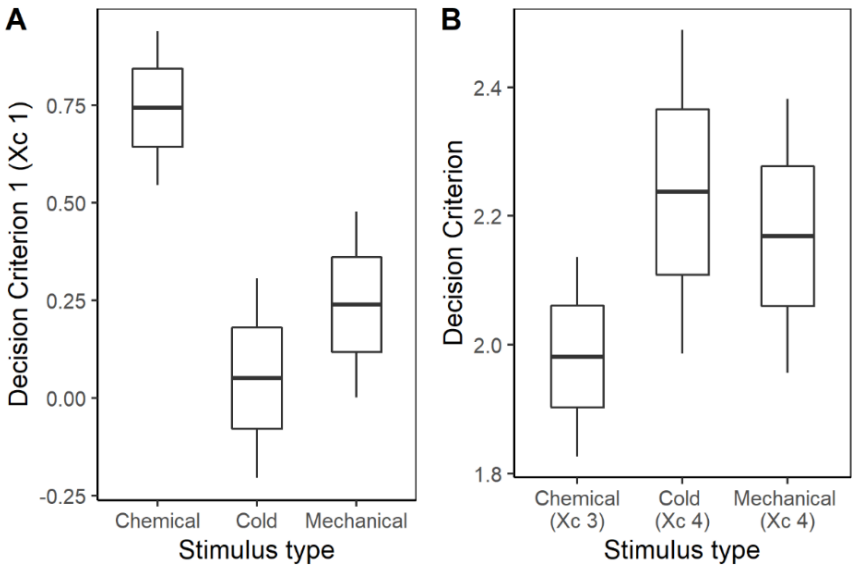

Figure 4.4: Comparison of decision criterion (X_c) between stimulus types considering liberal condition(A) and strict condition (B). At liberal criteria, the X_c are significantly different between stimulus types.

4.4.3 Within Stimulus comparisons:

4.4.3.1 Cold stimulus:

The ROC curves plotted using the cumulated ratings showed a good separation in the d_a between the scaled stimulus intensities (Figure 4.6). The ROC curve of cold sub-threshold intensity stimuli was inverted, indicating a negative d_a. The z-ROC curves for all stimuli were almost parallel to the chance line and only the z-ROC of the sub-threshold intensity stimuli was below the chance line similar to the ROC curve. The slopes of the supra-threshold z-ROC were less than 1, but the curves did not cross each other or other curves within the stimulus type. A mixed-model analysis was conducted to compare the d_a of the cold stimuli between the intensities. A significant main effect of stimulus intensity ($F(3,130) = 29.91$, $p < 0.001$) was observed for d_a between the cold stimulus intensities (Figure 4.7). The contrast analysis showed that the d_a of each intensity was significantly different from the other. Similarly, the analysis of the area under the curve was also found to be significantly different between the intensities ($F(3,94.96) = 129.91$, $p < 0.001$).

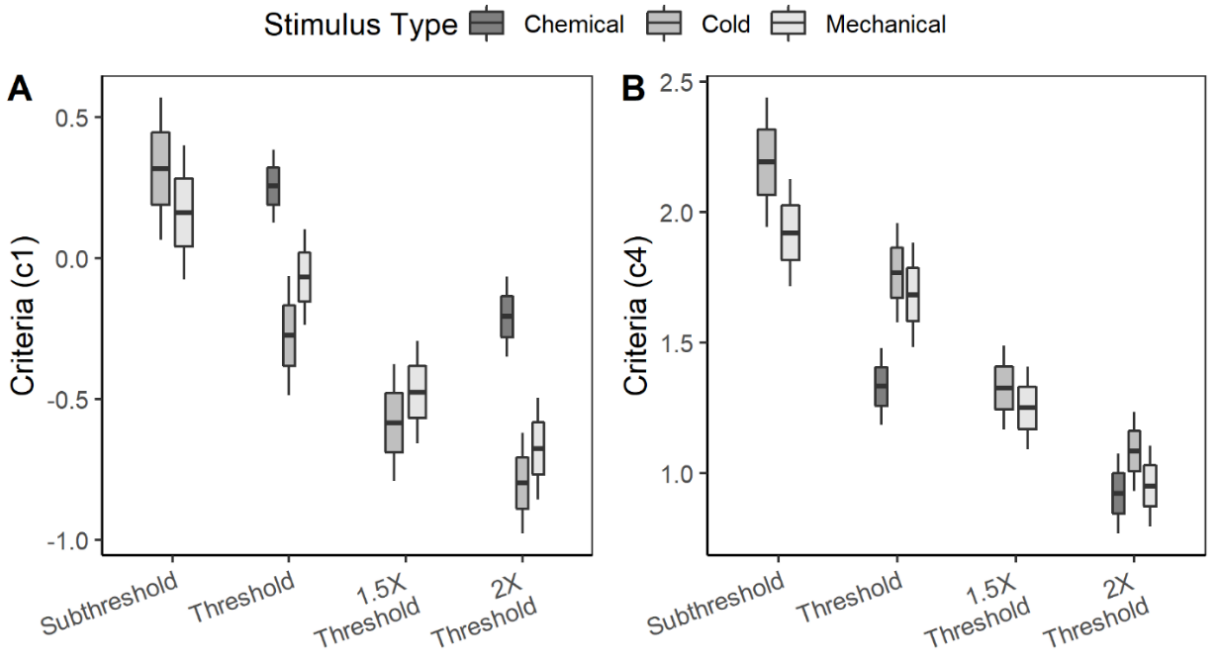

Figure 4.5: Boxplot of *c*1 (A) and *c*4 (B) for all the stimulus intensities and stimulus types. Note: in plot B for chemical stimuli, *c*3 was used as criteria in place of *c*4, as *c*3 is the strictest criteria for chemical stimuli.

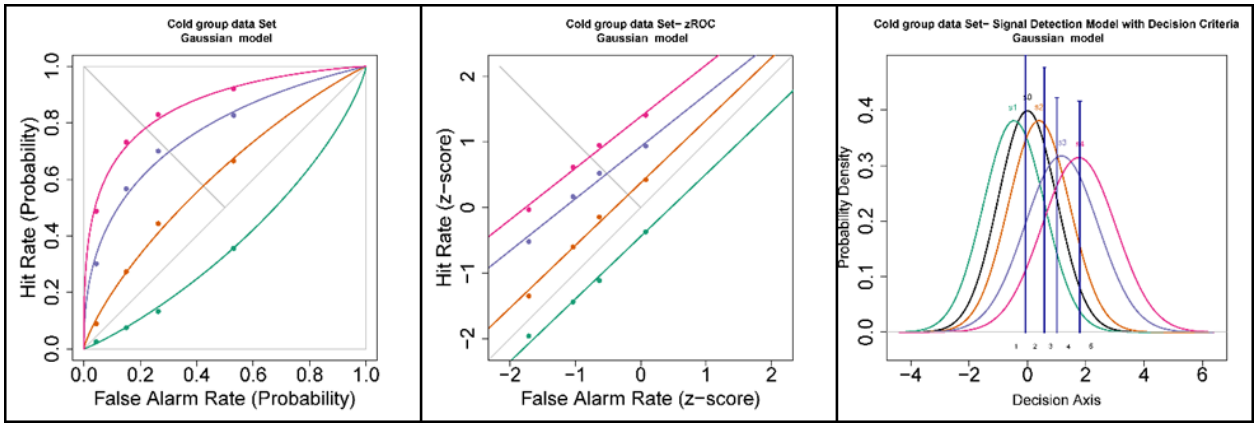

Figure 4.6: ROC and Gaussian distribution for the cold stimuli. The green line represents the sub-threshold stimuli followed by orange (threshold), purple (1.5x threshold) and pink (2x threshold). The black line (S_0) in density functions represent the noise distribution.

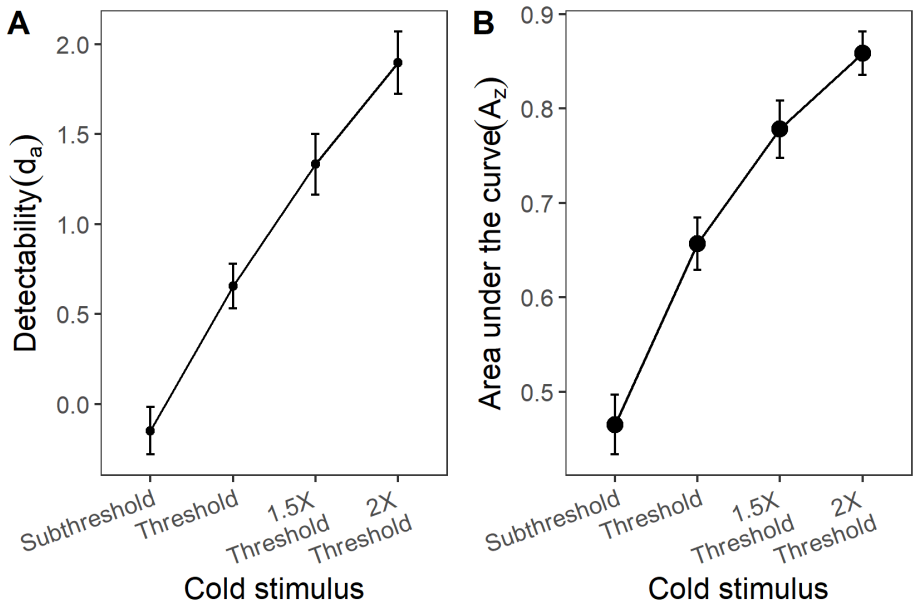

Figure 4.7: The d_a and A_z transducer functions for cold stimuli.

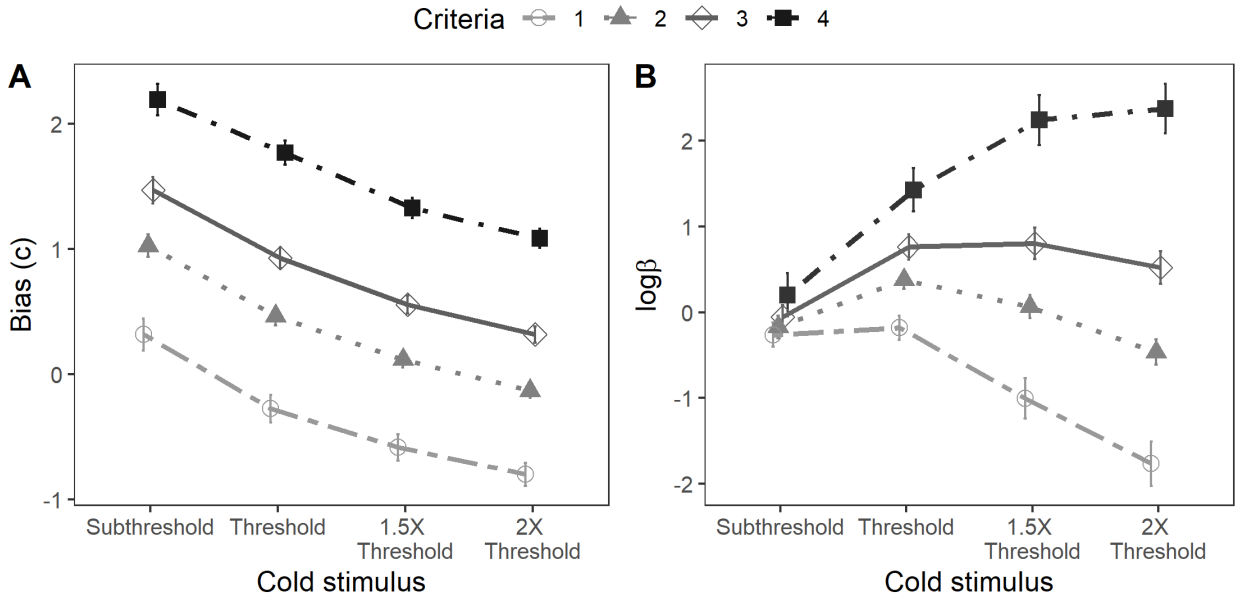

Figure 4.8: The bias function for *c* (A) and *lnβ* (B) of cold stimulus. The lines represent the 4 (n-1) criteria derived from the 5 rating responses from the participants for each stimulus intensity. Lighter to darker grey represent the lowest to highest criterion respectively.

A mixed-model analysis was conducted to compare the *c* between the stimulus intensities within each stimulus type. Significant main effects of criterion (F (3,77.35) = 131.32, $p < 0.001$) and stimulus intensity (F (3,106.8) = 130.96, $p < 0.001$) were observed, indicating the bias was different between the four *c* levels and intensities. Though there were main effects, no interactions were observed between the *c* and stimulus intensities. Mixed-model analysis of bias using $ln\beta$ also showed a significant main effect of β criterion (F (3,95.94) = 15.34, $p < 0.001$) and stimulus intensity (F (3,104.83) = 32.5, $p < 0.001$) similar to *c*. However, a significant interaction was also observed between the β criterion and intensity (F (9,285.85) = 51.59, $p < 0.001$) (Figure 4.8).

Mixed-model analyses for the d_a and A_z with factors showed no significant main effect or interactions of the groups (all $p > 0.05$), though the main effect of the stimulus intensity was observed on all analyses ($p < 0.05$). The ROCs using cumulated data for groups based on symptoms and contact lens usage are shown in Figure 4.9 and they showed slight variations in the curves between the types of groups. Even though there were no significant effects of groups, there was a significant interaction of the study visit in the comparison between *c* criterion level and intensities for cold stimulus (F (18, 268.05) = 1.97, $p = 0.012$).

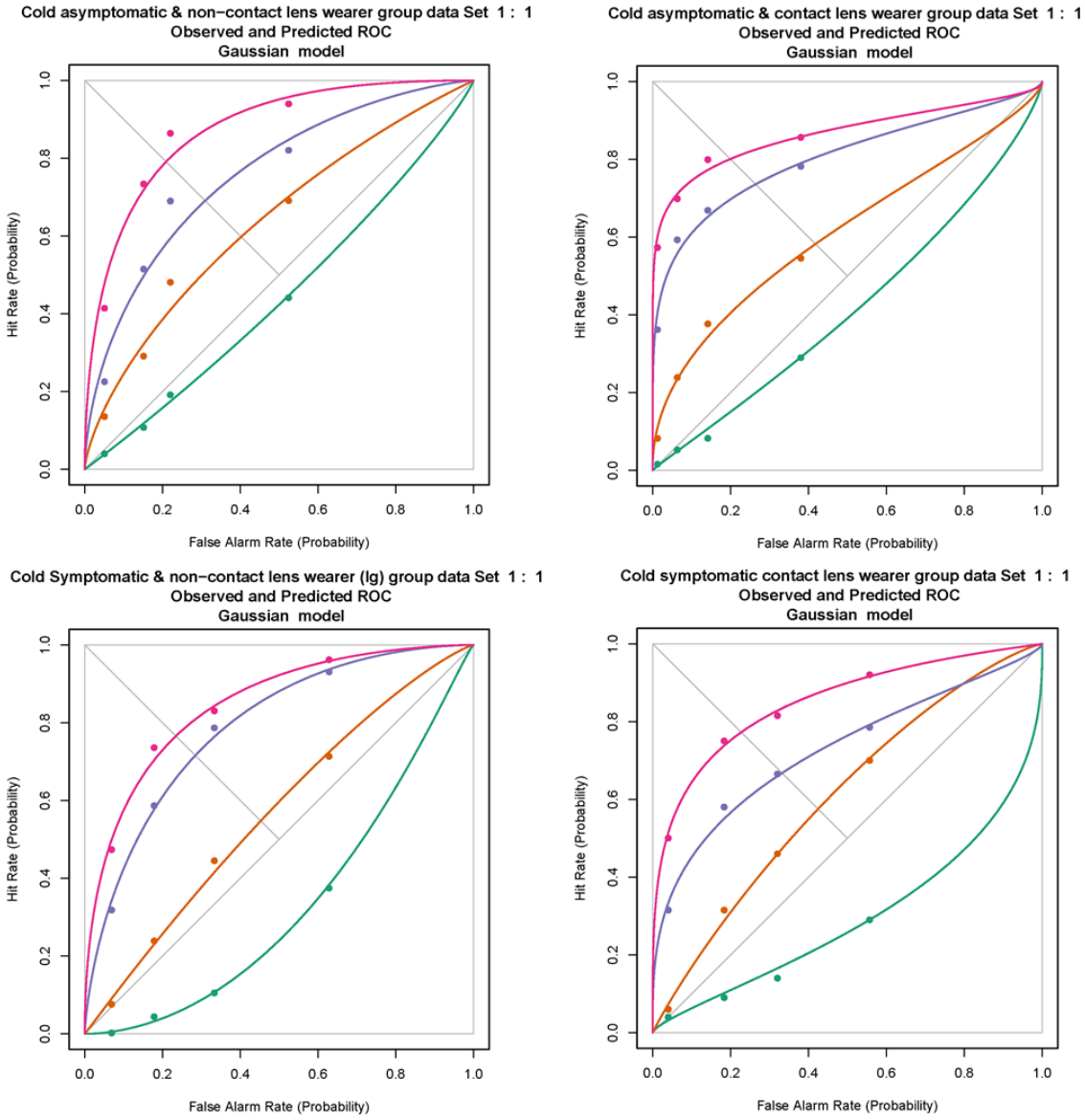

Figure 4.9: ROCs for cold stimuli for groups based on symptoms and contact lens wear.

4.4.3.2 Chemical stimulus:

The ROC for the cumulated ratings of all participants showed good separation between the d_a's of the threshold and 2x threshold intensity chemical stimuli (Figure 4.10). The slope of the z-ROC of the 2x threshold intensity stimuli was parallel to the chance line, whereas the slope was slightly less than 1 for threshold intensity stimuli. A paired sample t-test was conducted, and a significant difference was observed between the d_a's of the threshold (0.97 ± 0.12) and 2x threshold (1.88 ± 0.16) intensity stimuli; t (35) = -5.93, $p < 0.001$ (Figure 4.11). Similarly, the A_z was also significantly different between the two stimulus intensities (t (35) = -5.41, $p < 0.001$) (Figure 4.11). No significant main effect or interactions of the groups based on factors were observed in the detection of chemical stimuli. The cumulated ratings ROCs for groups based on symptoms and contact lens usage are shown in Figure 4.14 and they showed variations in the curves between the types of groups.

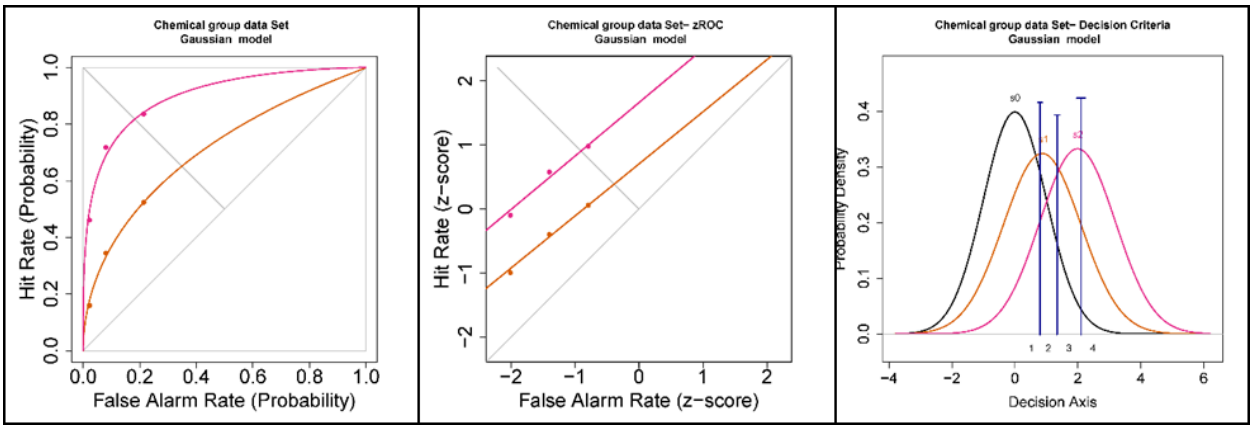

Figure 4.10: ROC and Gaussian distribution for the chemical stimuli. The orange line represents the threshold stimuli followed by pink (2x threshold). The density functions in black (s_0) represent the noise distribution.

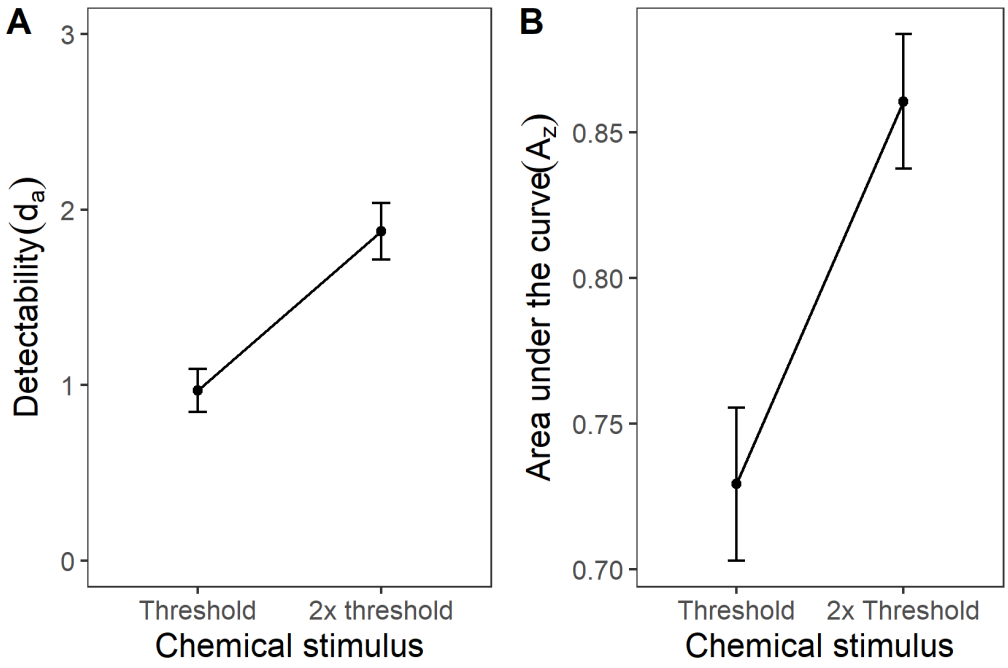

Figure 4.11: The transducer function for d_a and A_z of chemical threshold and 2x threshold stimuli.

The bias (*c* and *lnβ*) presumed by the participants in detecting the chemical stimuli was analyzed using mixed model analysis. Significant main effects were observed for the bias estimated using the *c* criterion between the criterion levels (F (1,55.89) = 33.69, $p < 0.001$) and between the stimulus intensities (F (2,76.43) = 161.77, $p < 0.001$) (Figure 4.12). There was no significant main effect of factors, although a few significant interactions were observed. The subgrouping of participants based on symptoms produced a significant interaction with the stimulus intensities (F (1,53.01)= 6.1, $p = 0.017$). The asymptomatic participants were more liberal to say "yes" to a supra-threshold stimulus in comparison to the symptomatic participants (Figure 4.13). There was also a three-way interaction observed for bias between stimulus intensity, *c* criterion levels and contact lens wear (F (2,67.39)= 8.17, $p < 0.001$). When the participants were further sub-divided based on both contact lens wear and symptoms, there was a significant interaction between the stimulus intensity and subgroups (F (3,48.42)= 4.48, $p = 0.008$), and there was a significant three-way interaction between stimulus intensity, *c* criterion levels and the subgroups (F (6,63.39)= 4.16, $p = 0.002$) (Figure 4.13).

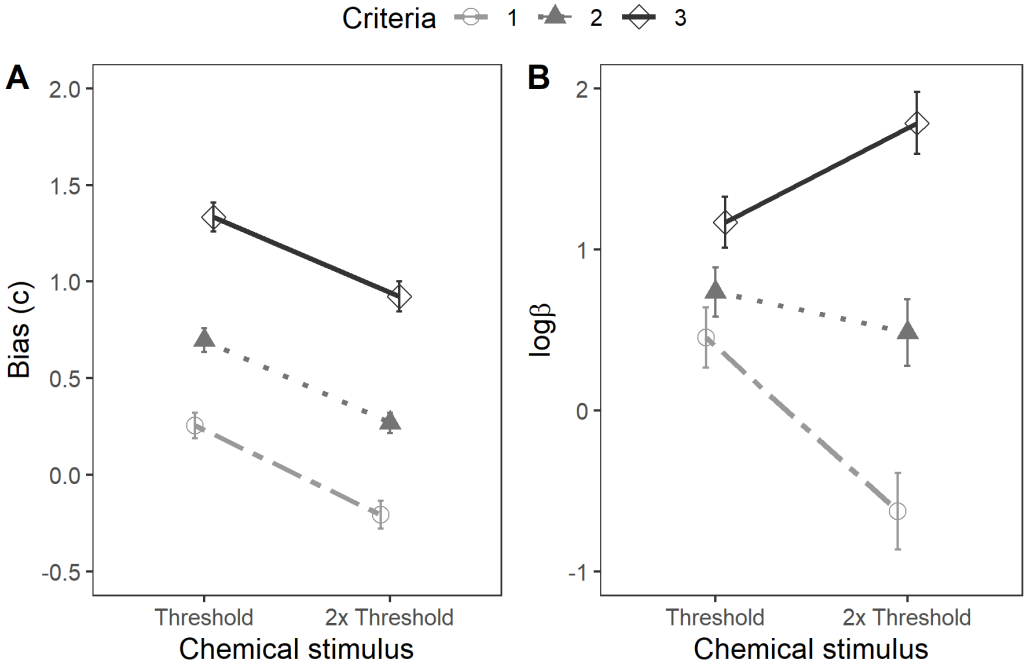

Figure 4.12: The bias function for *c* and *lnβ* of chemical threshold and 2x threshold stimuli.

Mixed-model analyses of bias using *lnβ* were conducted to compare the bias between the stimulus intensities and the lnβ criteria. A significant main effect of *lnβ* criterion was observed ($F(2,70) = 52.1$, $p < 0.001$) along with a significant interaction between the stimulus intensities and *β* criterion ($F(2,70) = 19.68$, $p < 0.001$). However, lnβ bias was not significantly different between the stimulus intensities (Figure 4.12). A three-way significant interaction was also observed between intensity, β criteria levels and groups based on symptoms ($F(2,170) = 4.32$, $p = 0.015$). There was also a significant two-way interaction for bias between the stimulus intensities and groups based on both contact lens wear and symptoms ($F(1,170) = 7.78$, $p = 0.006$).

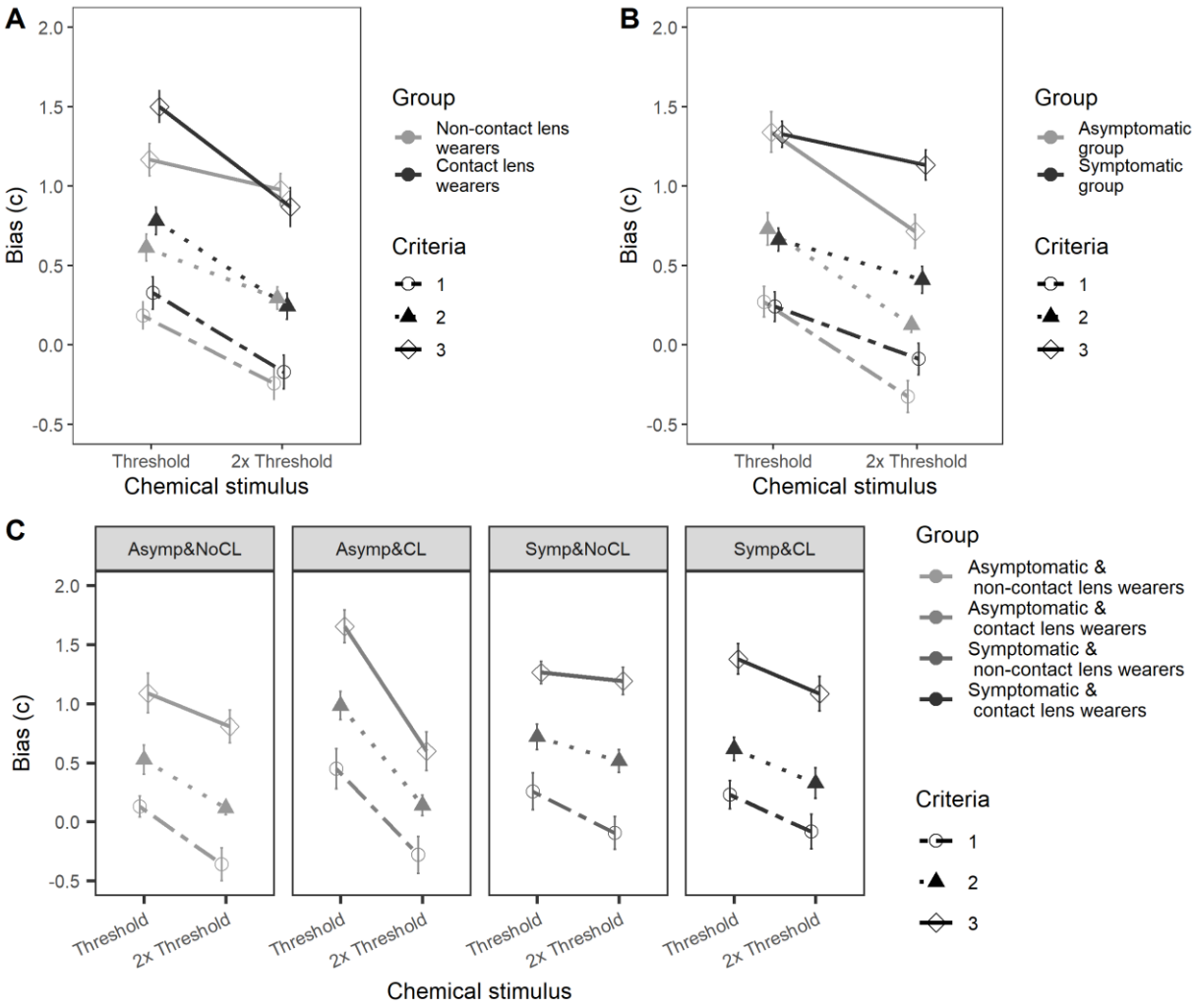

Figure 4.13: The bias (*c*) comparisons for different subgroup based on; A) contact lens wear, B) symptoms score, and C) combination of contact lens wear and symptom score

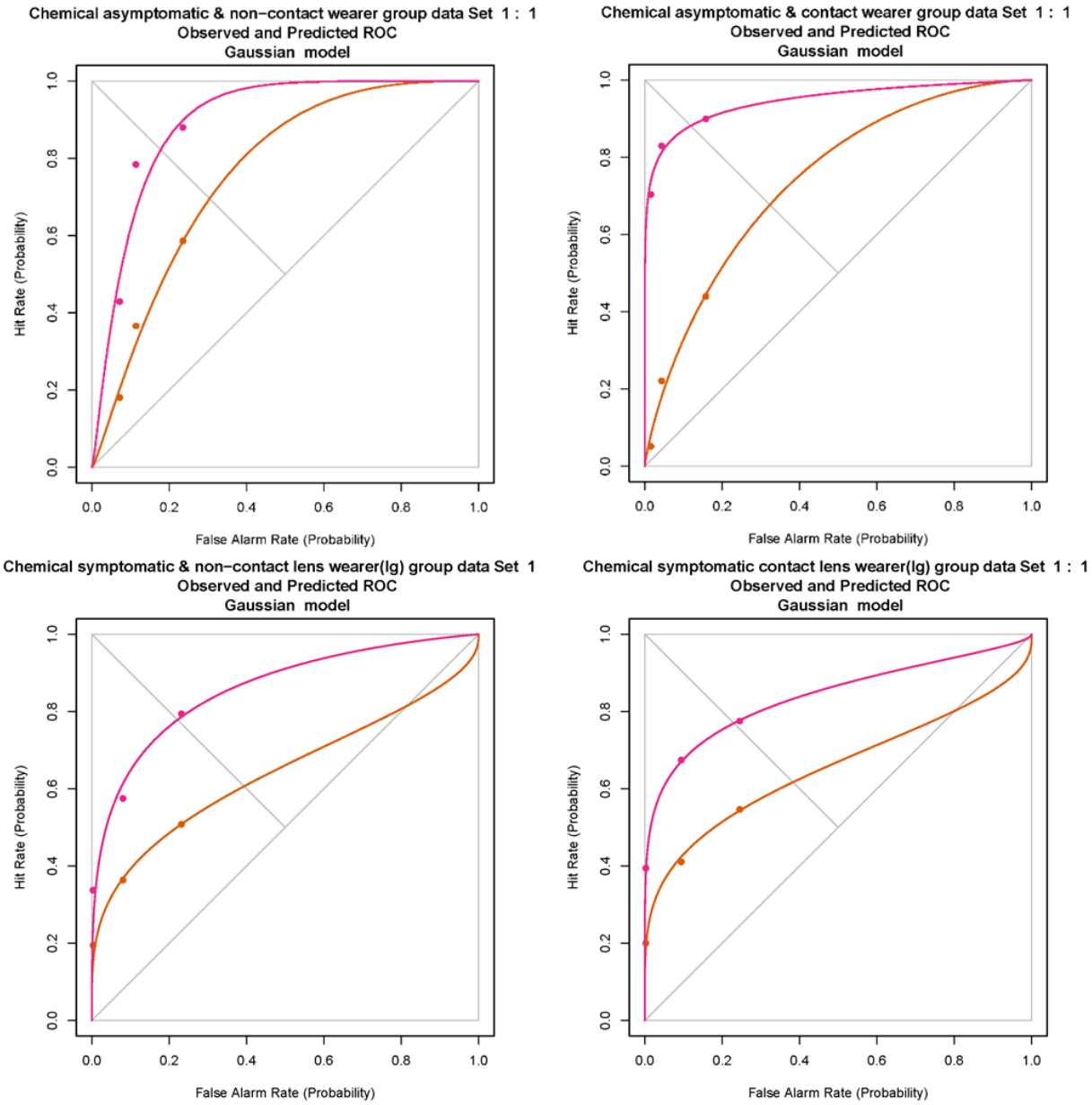

Figure 4.14: ROCs for chemical stimuli for groups based on symptoms and contact lens wear.

4.4.3.3 Mechanical stimulus:

Similar to the cold and chemical stimuli, there was good separation between the ROC curves of different stimulus intensities (Figure 4.15). The slopes of z-ROC were less than one and the z-ROC of sub-threshold intensity crossed the chance line. The mixed-model analysis showed that the d_a's of the mechanical stimuli were significantly different between the intensities used in the experiment (F (3,100.92) = 66.46, $p < 0.001$) (Figure 4.16). No other significant main effect or interaction with the factors were observed. The cumulated data ROCs for subgroups based on symptoms and contact lens usage is shown in Figure 4.19 and showed variations in the ROC curves between groups. A mixed-model analysis of the A_z showed a similar significant main effect of the intensities (F (3,100.63) = 60.96, $p < 0.001$) (Figure 4.16). Also, a significant interaction of group based on symptoms was observed for A_z between the stimulus intensity and the groups (F (3,97.6) = 3.089, $p = 0.031$) (Figure 4.17). When the groups were further divided based on both contact lens use and symptoms, a significant interaction was observed between the intensity of the stimulus and group was observed for A_z (F (6,95.38) = 2.86, $p = 0.013$) (Figure 4.17).

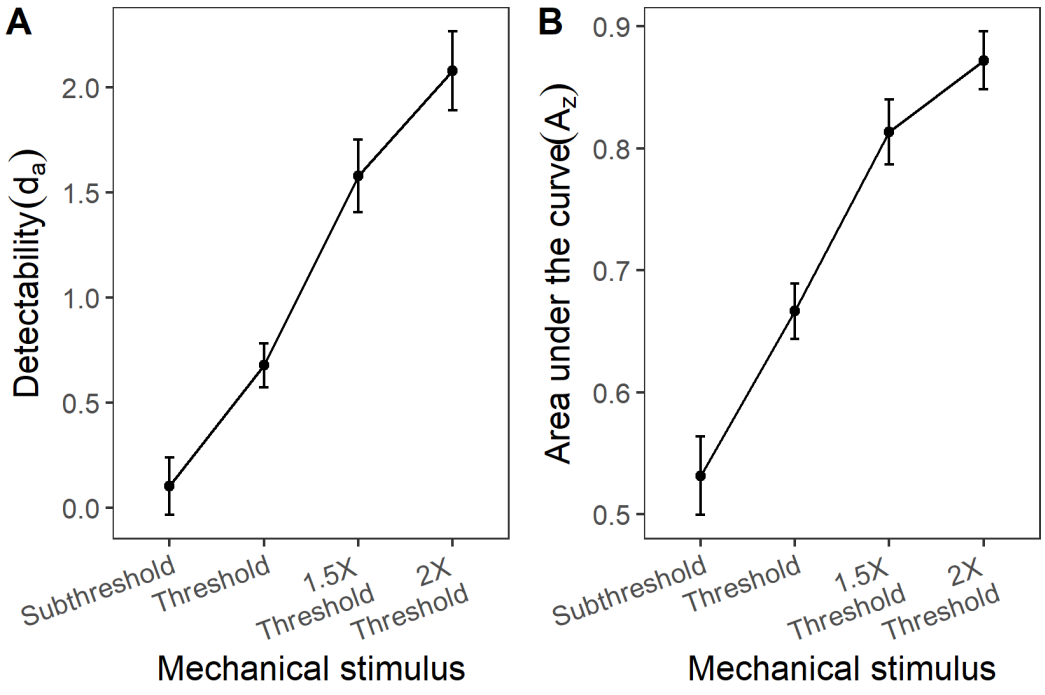

Figure 4.15: The transducer function for d_a and A_z of mechanical stimuli.

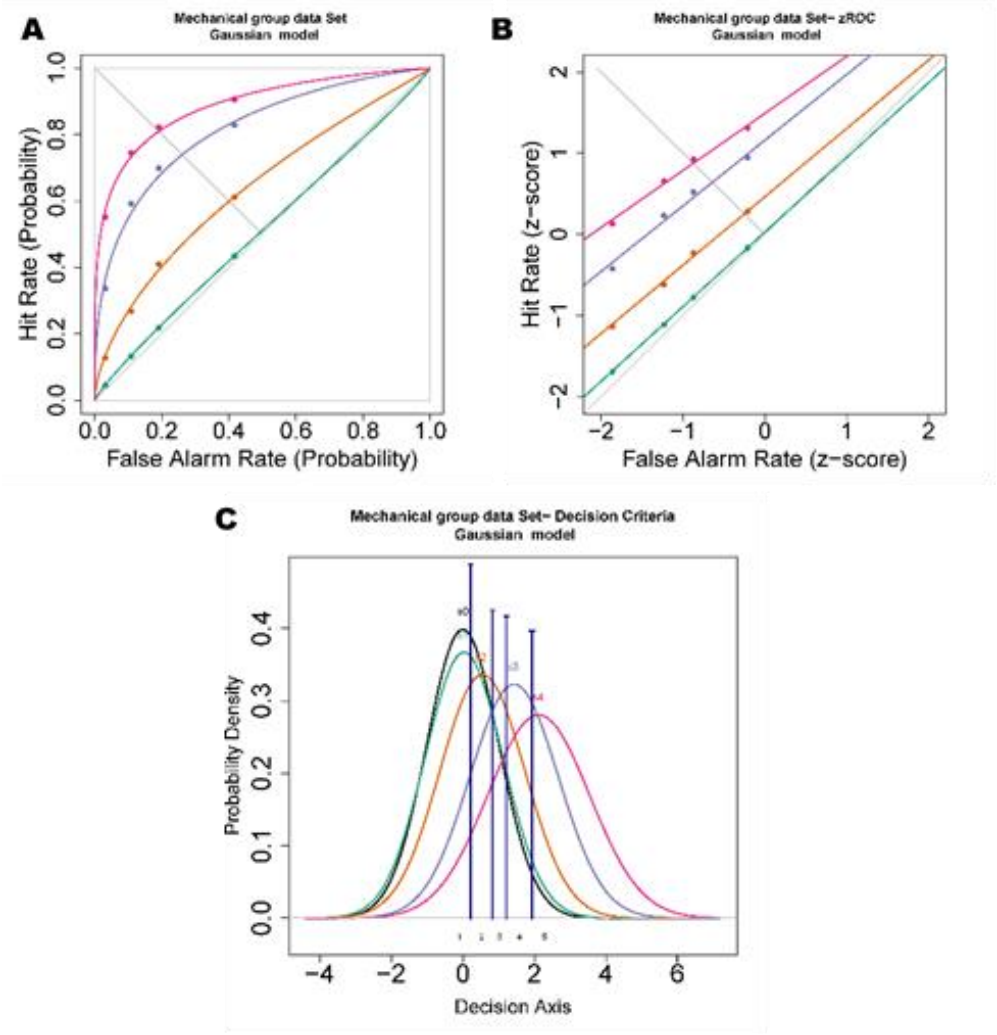

Figure 4.16: ROC, zROC and Gaussian distribution for the mechanical stimuli.

The bias (*c* and *lnβ*) to respond to the mechanical stimuli was similar to the cold and chemical stimuli. Significant main effects of intensity (F (3,101.52)= 84.03, $p < 0.001$) and *c* criterion (F (3,105.23)= 198.69, $p < 0.001$) were observed for mechanical stimuli indicating that the bias changed with the intensity of the stimuli and the bias was significantly different between the criterion levels (Figure 4.18). No other significant interactions were observed. The analysis of bias using lnβ showed main effect of stimulus intensity (F (3,101.64) = 7.56, $p < 0.001$) and lnβ criterion (F (3,105) = 49.44, $p < 0.001$) and a significant interaction between the stimulus intensity and lnβ criterion (F (9,304.08) = 38.38, $p < 0.001$) (Figure 4.18).

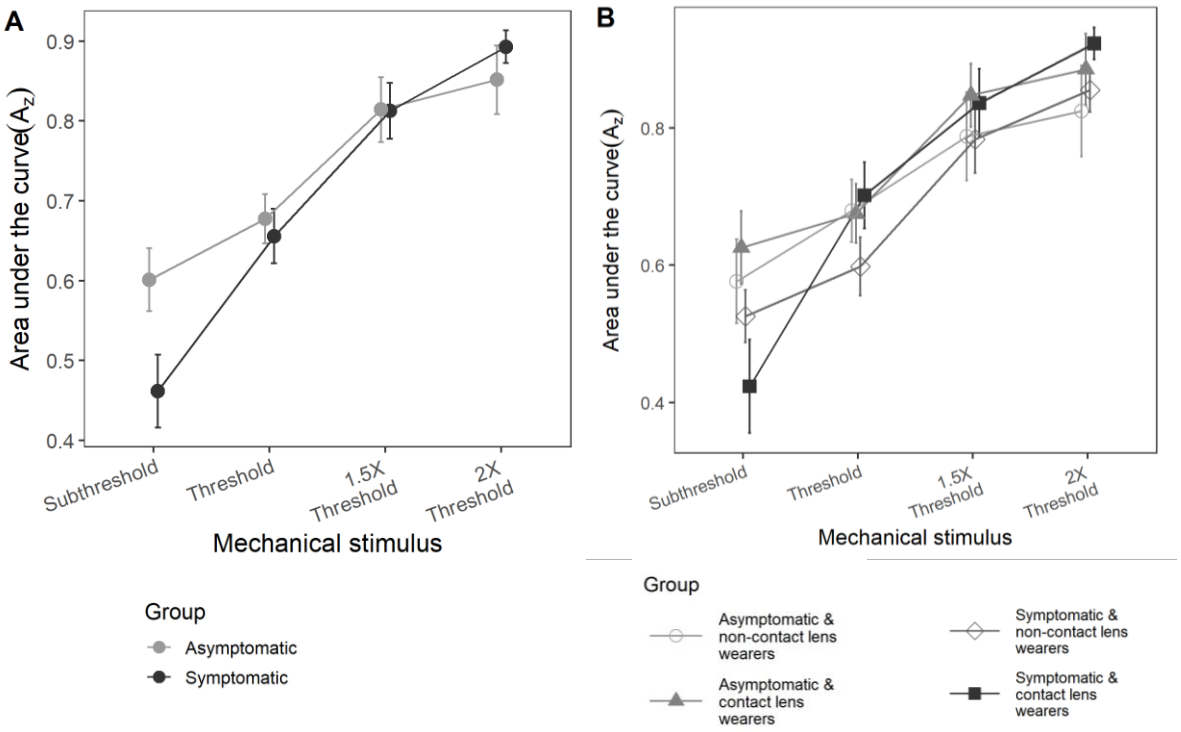

Figure 4.17: The mean (SE) A_z for subgroups based on (A) symptoms, and (B) symptoms and contact lens wear

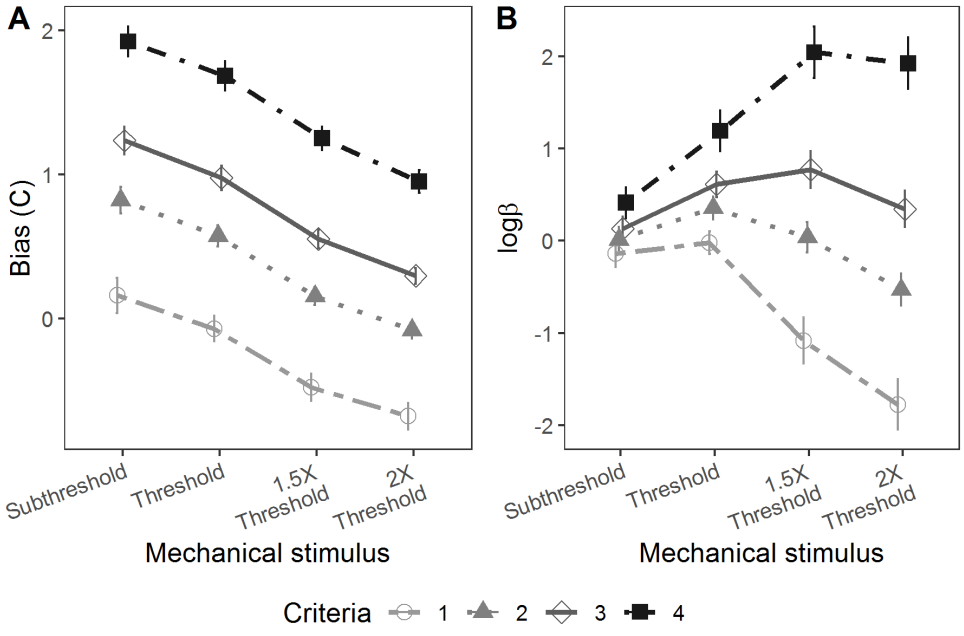

Figure 4.18: The bias function for mechanical stimuli using (A) *c* criterion and (B) *lnβ* criterion plotted against the stimulus intensity

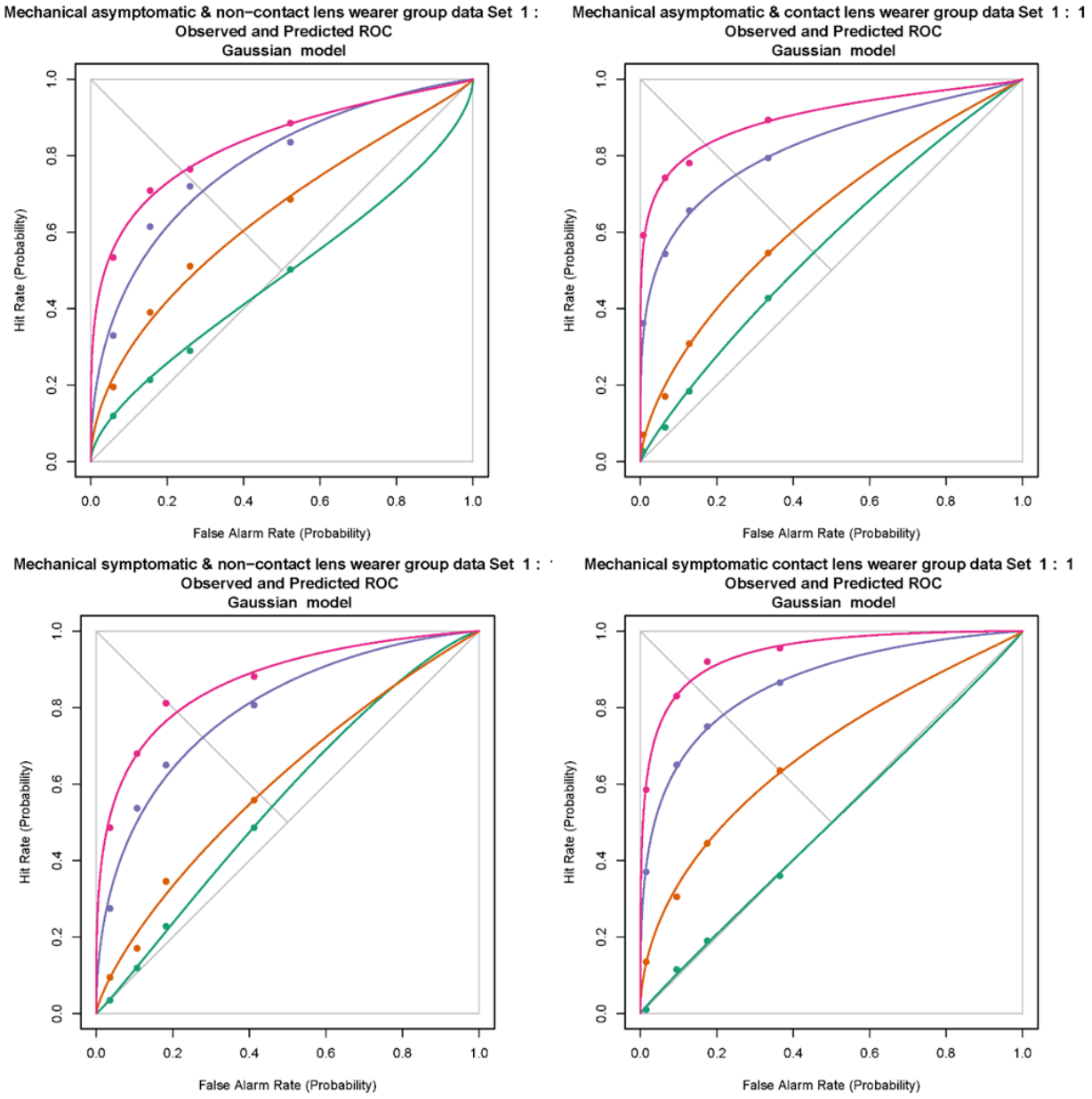

Figure 4.19: ROCs for mechanical stimuli for groups based on symptoms and contact lens wear

4.4.4 Correlation between detection thresholds and detection theory parameters:

The correlations between threshold and detection theory indices were conducted using Spearman correlations for each stimulus type. A significant positive relationship was observed between the cold detection thresholds and d_a of the cold threshold intensity stimuli (Figure 4.20), indicating a high detectability of threshold intensity stimuli with high baseline detection thresholds. The detection thresholds were positively correlated with the d_a of sub and supra-threshold stimulus intensities for all three stimulus types ($p < 0.05$) (Figure 4.20, Figure 4.21, Figure 4.22). The *c* (2,3) and *lnβ* (2,3,4) for the cold stimuli showed a significant positive correlation with the threshold (Figure 4.23 & Figure 4.25). Similarly, the criterion (1 & 2) of the chemical threshold stimuli was positively correlated with the chemical threshold (Figure 4.24).

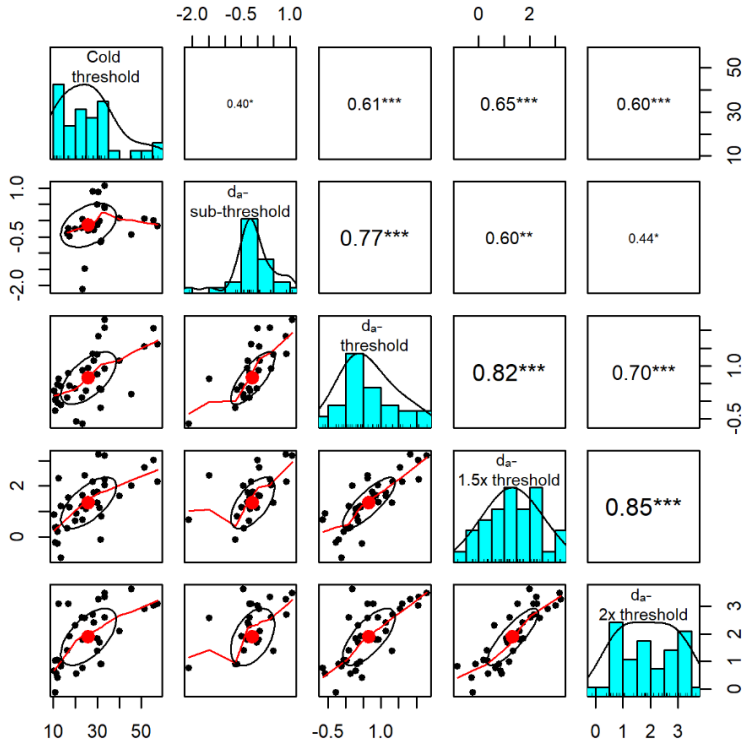

Figure 4.20: Correlation matrix for cold stimuli comparing corneal thresholds with the d_a of different stimulus intensities

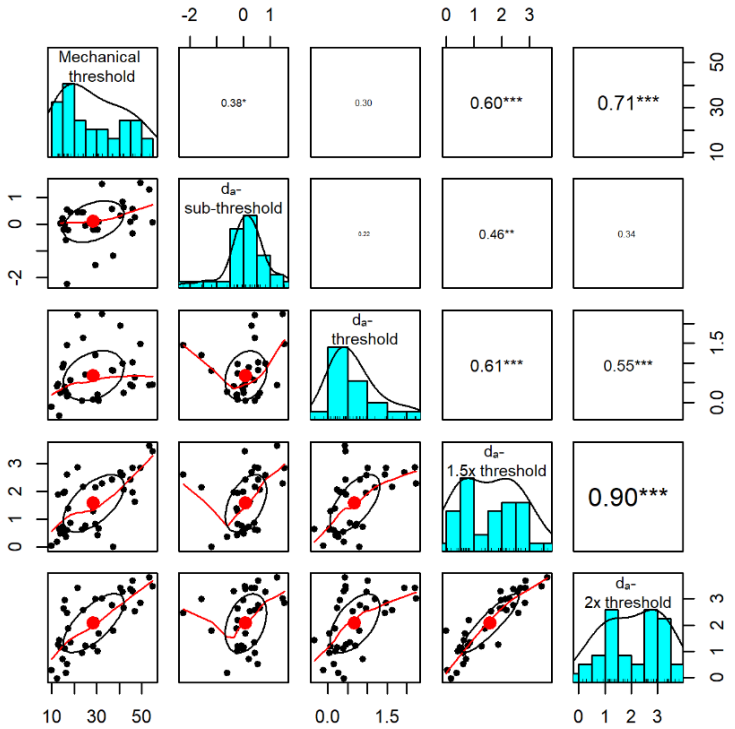

Figure 4.21: Correlation matrix for mechanical stimuli comparing corneal thresholds with the d_a of different stimulus intensities

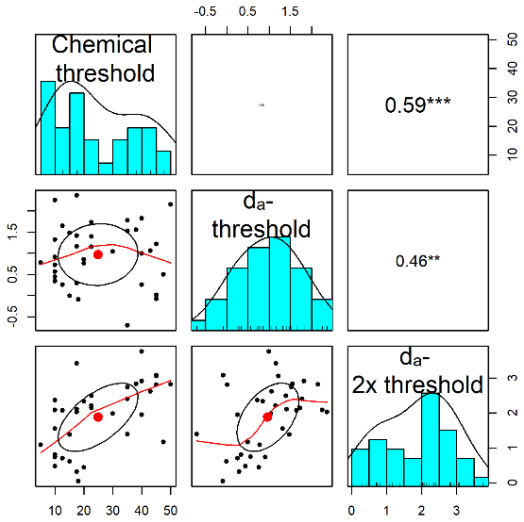

Figure 4.22: Correlation matrix for chemical stimuli comparing corneal thresholds with the d_a of different stimulus intensities

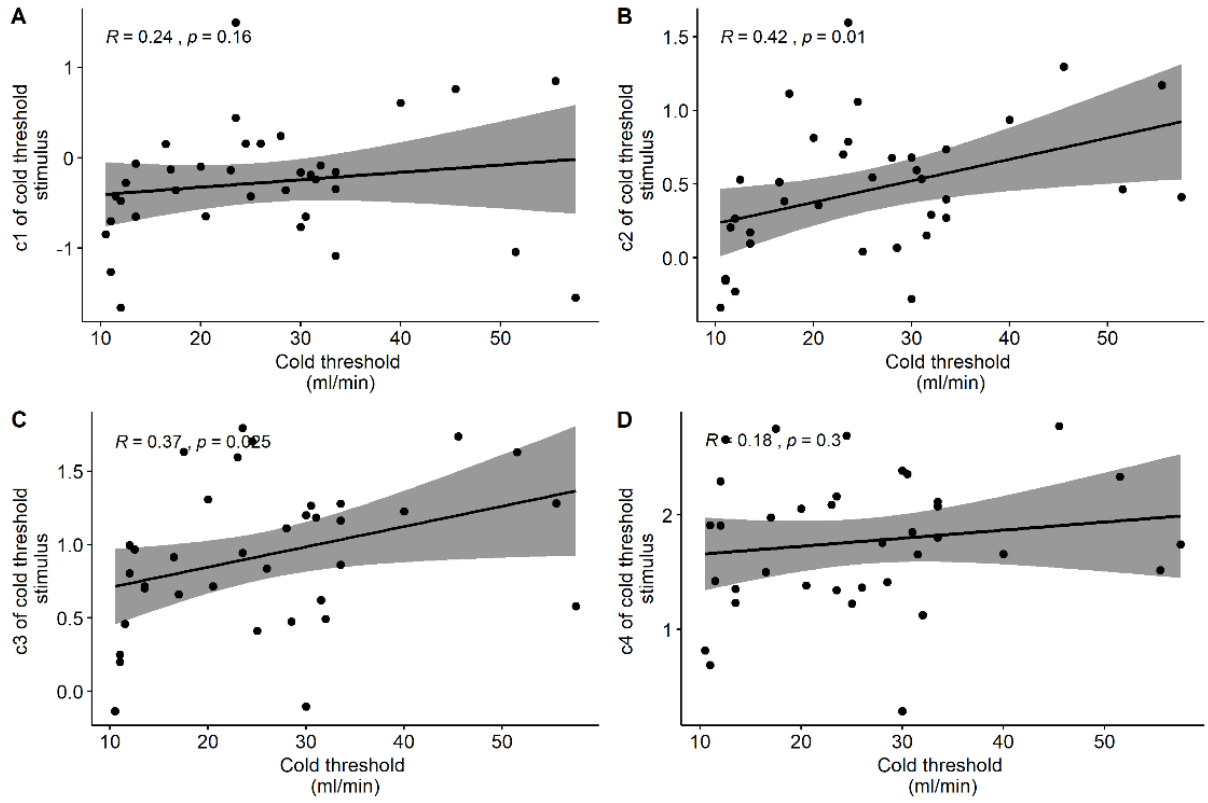

Figure 4.23: Correlation between the cold threshold and the *c* of cold threshold intensity stimuli

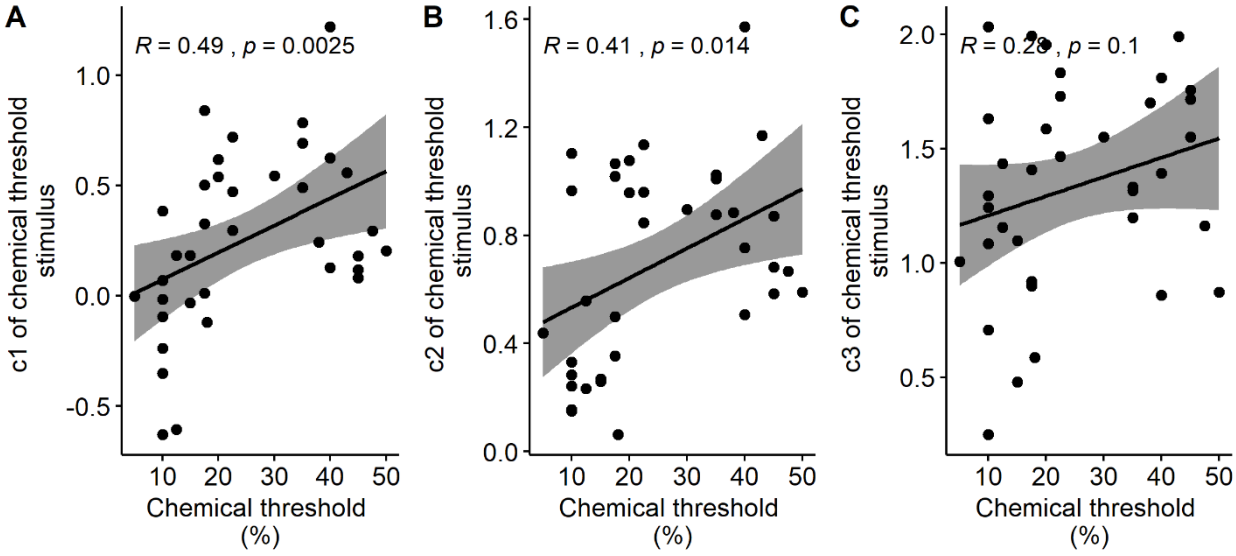

Figure 4.24: Correlation between chemical threshold and the *c* for chemical threshold intensity stimuli

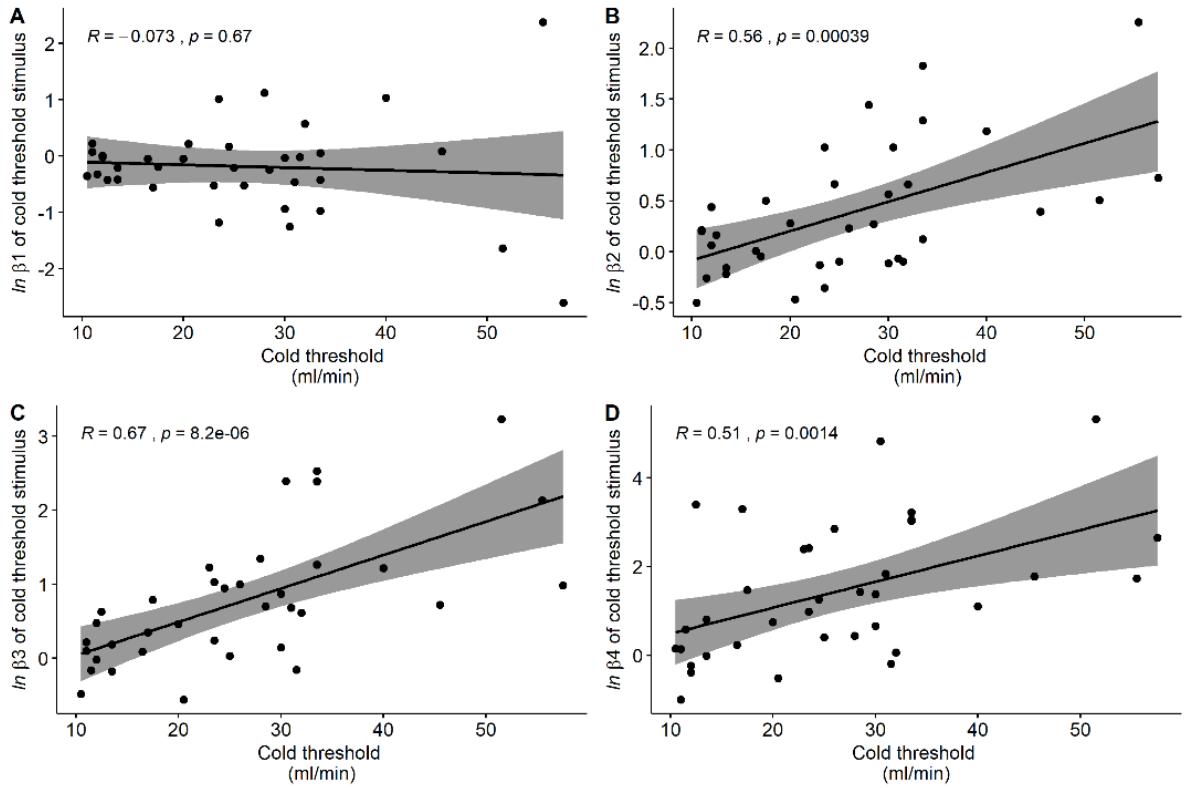

Figure 4.25: Correlation between the cold threshold and *lnβ* of cold threshold intensity stimuli

4.4.5 Decision-making:

The average (±se) DM scores of the participants and groups are listed in Table 4-4. The profile of DM scores for each participant in the study is shown in Figure 4.26 and the profile indicates that the majority of the participants had more vigilance score compared to other DM types. A mixed-model analysis of DM scores showed a significant difference in the scores between DM types ($F(3,105) = 121$, $p < 0.001$). The contrast analysis of the DM types showed that the vigilance scores were significantly different from all other DM types ($p < 0.001$) (Figure 4.28). Also, the procrastination scores were significantly different from hypervigilance scores ($p = 0.005$). Spearman correlations between the DM parameters were conducted (Figure 4.27) to analyze the relationship between the DM types and interactions with groups. The buck-passing, hypervigilance, and procrastination scores were significantly correlated with each other ($p < 0.01$), but the vigilance scores were not correlated with other DM types. No significant main effect or interactions of groups were observed.

Scale (items)	Overall	Gender		Symptoms		Contact Lens	
	(n=36)	Male (n=13)	Female (n=23)	Asymptomatic (n=18)	Symptomatic (n=18)	Non-contact lens wearers (n=18)	Contact lens wearers (n=18)
Vigilance (6 items)	9.89 (0.30)	9.46 (0.57)	10.13 (0.51)	10.06 (0.46)	9.72 (0.40)	10.06 (0.43)	9.72 (0.44)
Buck-passing (6 items)	3.22 (0.39)	2.39 (0.56)	3.70 (0.51)	3.00 (0.58)	3.45 (0.54)	3.11 (0.53)	3.34 (0.59)
Hyper-vigilance (6 items)	4.03 (0.36)	3.69 (0.61)	4.21 (0.44)	4.22 (0.50)	3.83 (0.51)	4.28 (0.50)	3.78 (0.52)
Procrastination (6 items)	2.56 (0.40)	2.31 (0.71)	2.70 (0.49)	2.67 (0.66)	2.45 (0.48)	2.34 (0.45)	2.78 (0.68)

Table 4-4: Mean (SE) of the scores for each DM component. The mean (SE) of the scores for groups based on gender, contact lens use and symptoms.

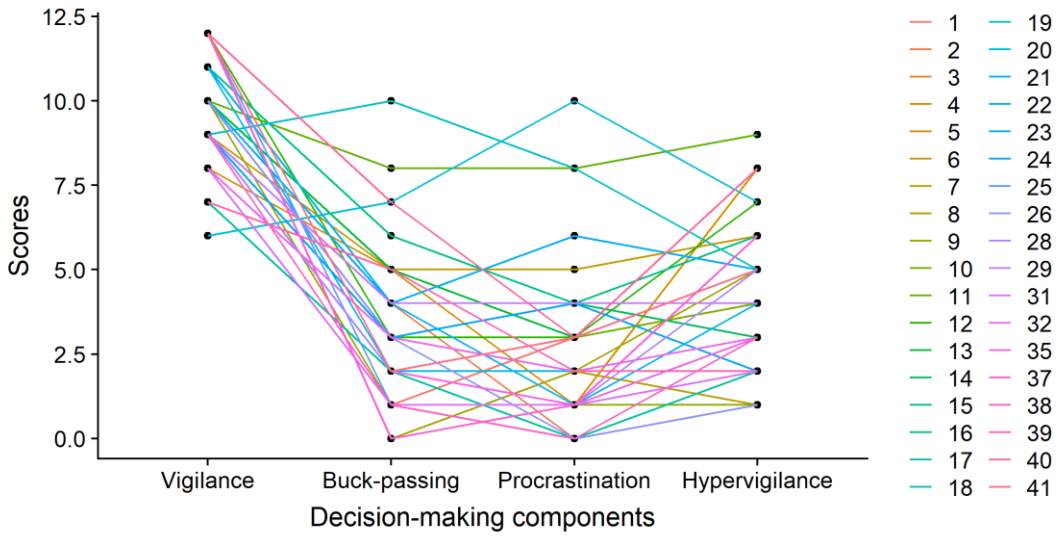

Figure 4.26: Profile of DM scores for each DM components.

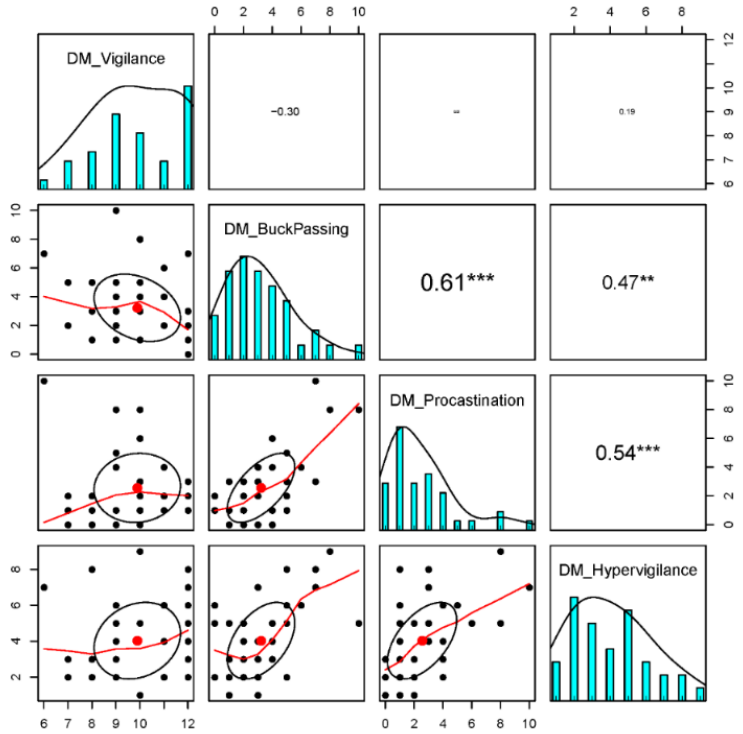

Figure 4.27: Correlation matrix between DM parameters.

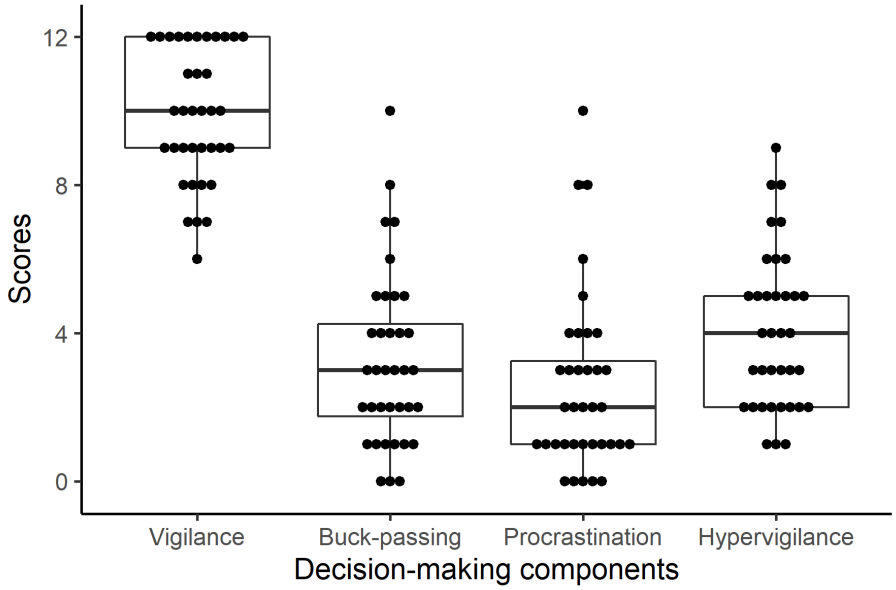

Figure 4.28: Boxplot representing the average scores for each DM item from the MDMQ2 questionnaire.

4.4.5.1 Correlation between DM scores and corneal detection thresholds:

The relationship between the DM scores and the corneal detection thresholds were analyzed along with interactions of factors using Spearman correlations. A significant negative relationship was observed between the vigilance scores and the chemical detection thresholds (ρ= -0.35, p = 0.04) (Figure 4.29).

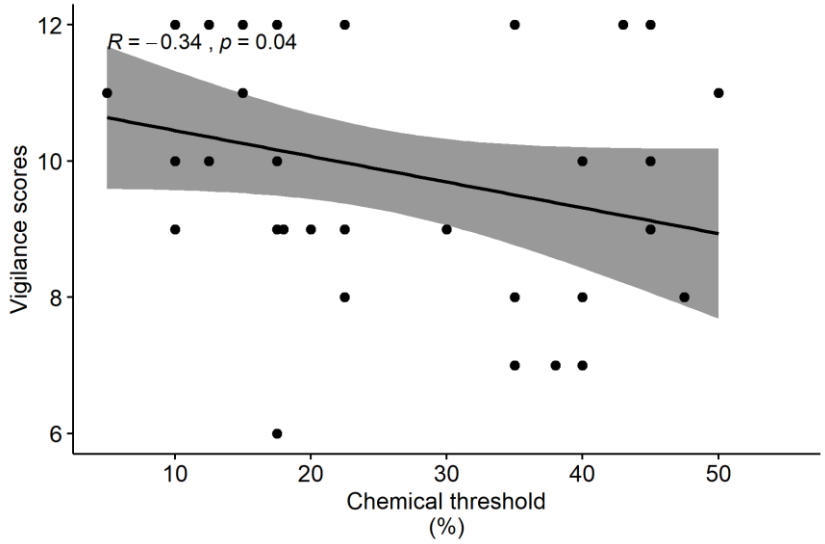

Figure 4.29: Correlation between chemical thresholds and vigilance DM scores.

4.4.5.1.1 Group interactions:

A significant negative correlation was observed in the symptomatic group of participants between vigilance score and detection thresholds of chemical (ρ= -0.7, p = 0.001) and cold (ρ= -0.61, p = 0.007) stimuli (Figure 4.30), whereas a significant positive relationship was observed in the asymptomatic group between vigilance scores and cold detection thresholds (ρ= 0.51, p = 0.029). A significant positive correlation was observed in the male group of participants between procrastination scores and mechanical detection thresholds (ρ= 0.66, p = 0.013) (Figure 4.31).

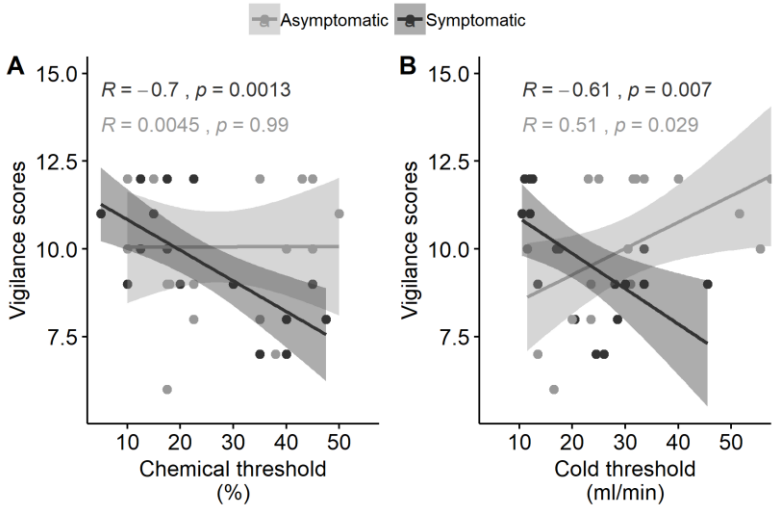

Figure 4.30: Correlations by group between vigilance scores of the participants and their thresholds.

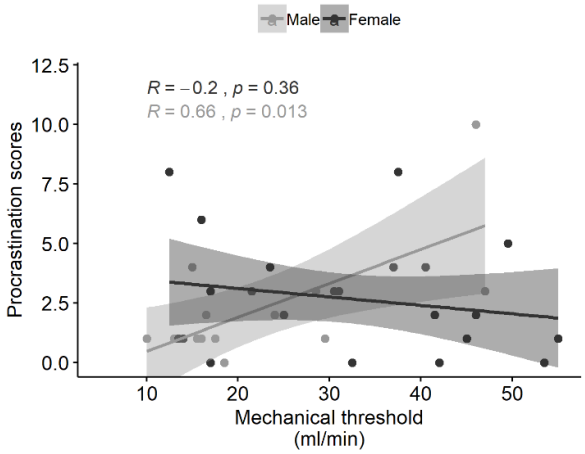

Figure 4.31: Correlation between mechanical threshold and procrastination scores.

4.4.5.2 Correlation between DM scores and d':

The relationship between the d_a and DM were analyzed using Spearman correlations. Only 1 out of 40 (4 decision scales * d_a of 10 stimulus intensities (4 intensities each for cold & mechanical stimuli; 2 for chemical)) correlation analyses conducted were significantly correlated. A significant positive relationship (Figure 4.32) was observed between buck-passing DM scores and d_a of the mechanical threshold intensity stimuli (ρ=0.33, p = 0.049).

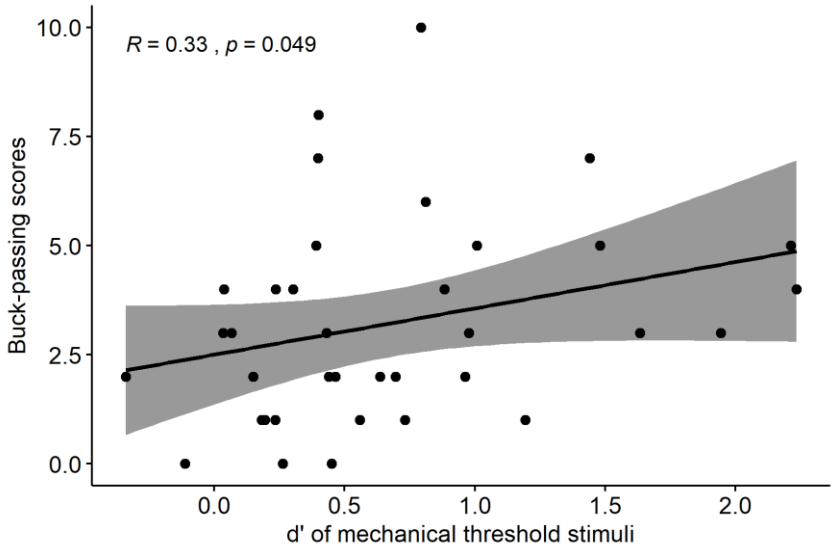

Figure 4.32: Correlation between the d_a of the mechanical threshold stimuli and buck-passing scores of the participants.

4.4.5.3 Correlation between DM and bias:

The relationships between the DM and criteria were analyzed using Spearman correlation (Table 4-5). For cold and mechanical stimuli, there were four criteria for each intensity tested from the 5-rating scale. There were 64 correlations (4 stimulus intensity * 4 criteria each * 4 DM types) each for mechanical and cold stimuli. 2 out of 64 correlations for mechanical stimuli and 9 out of 64 correlations for cold stimuli showed significant relationships. For chemical stimuli, there were three criteria for each intensity from the 4-rating scale. Only 1 out of 24 (2 stimulus intensity * 3 criteria each * 4 DM types) analyzed was significantly correlated.

DM type	Stimulus type and intensity	Criterion	Spearman correlations
Vigilance	Mechanical threshold	*c*1	ρ= -0.37, *p* = 0.025
Vigilance	Mechanical 1.5x threshold	*c*3	ρ= -0.34, *p* = 0.046
Vigilance	Cold threshold	*c*1	ρ= -0.37, *p* = 0.029
Buck-passing	Cold threshold	*c*4	ρ= 0.43, *p* = 0.0097
Buck-passing	Cold 1.5x threshold	*c*4	ρ= 0.33, *p* = 0.05
Buck-passing	Cold 2x threshold	*c*4	ρ= 0.37, *p* = 0.026
Procrastination	Cold threshold	*c*4	ρ= 0.44, *p* = 0.008
Procrastination	Cold 1.5x threshold	*c*4	ρ= 0.46, *p* = 0.0047
Procrastination	Cold 2x threshold	*c*4	ρ= 0.39, *p* = 0.019
Procrastination	Chemical Threshold	*c*1	ρ= -0.37, *p* = 0.026

Table 4-5: List of significant relationships between the *c* obtained for each stimulus type and DM scores

Most of the significant relationships were observed either for *c*1 or *c*4 of the criterion level. The *c*4's for cold threshold, 1.5x, and 2x threshold intensity stimuli were significantly correlated with the buck-passing and procrastination DM scores ($p < 0.05$) (Figure 4.33).

Similar to the analysis of the *c*, for *lnβ*, there were 64 correlations analyzed each for mechanical and cold stimuli. There were 24 correlations analyzed for chemical stimuli. 6 out of 64 and 3 out of 64 correlations analyses conducted were significant for mechanical and cold stimuli, respectively. Unlike *c*, most of the significant relationships were observed for either sub-threshold or threshold intensity stimuli (Table 4-6). 1 out of 24 correlation analyses conducted was significant for chemical stimuli. The *lnβ*4 of 2x chemical threshold intensity stimuli was significantly correlated with the buck-passing DM scores (ρ= -0.35, $p = 0.034$).

DM type	Stimulus type and intensity	Log-Likelihood ratio	Spearman correlations
Vigilance	Mechanical threshold	lnβ1	ρ= -0.43, p = 0.0087
Vigilance	Mechanical threshold	lnβ2	ρ= -0.37, p = 0.026
Vigilance	Cold sub-threshold	lnβ1	ρ= 0.52, p = 0.0063
Vigilance	Cold sub-threshold	lnβ4	ρ= -0.5, p = 0.0089
Buck-passing	Cold sub-threshold	lnβ4	ρ= 0.53, p = 0.0051
Buck-passing	Chemical 2x threshold	lnβ4	ρ= -0.35, p = 0.034
Hypervigilance	Mechanical sub-threshold	lnβ1	ρ= -0.45, p = 0.011
Hypervigilance	Mechanical sub-threshold	lnβ2	ρ= -0.44, p = 0.012
Procrastination	Mechanical sub-threshold	lnβ1	ρ= -0.44, p = 0.012
Procrastination	Mechanical sub-threshold	lnβ2	ρ= -0.41, p = 0.021

Table 4-6: List of significant relationships between *lnβ* and DM scores

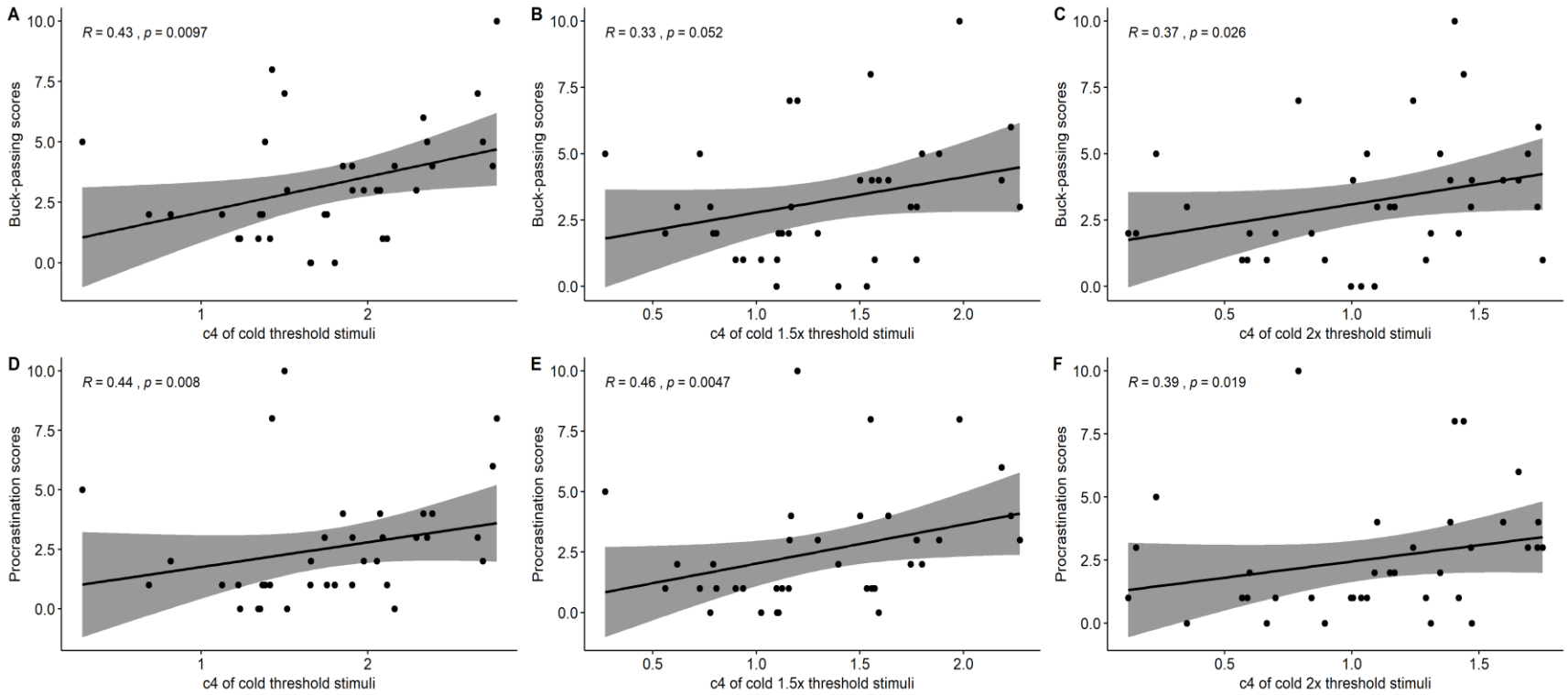

Figure 4.33: (Top row) Correlation between buck-passing scores and *c*4 of cold stimuli. (Bottom row) Correlation between procrastination scores and *c*4 of cold stimuli.

4.4.6 Trait Anxiety:

Paired t-test analysis showed a significant difference between the cognitive and somatic scores of trait anxiety (t (35) =4.0536, $p < 0.001$). The average scores for cognitive and somatic components of trait anxiety were 17.92 ± 0.94 and 14.58 ± 0.50, respectively (Figure 4.34(A)). A significant positive relationship was observed between the cognitive and somatic components of trait anxiety (Spearman's ρ= 0.483, $p < 0.001$) (Figure 4.34(B)). No significant interactions of factors were observed.

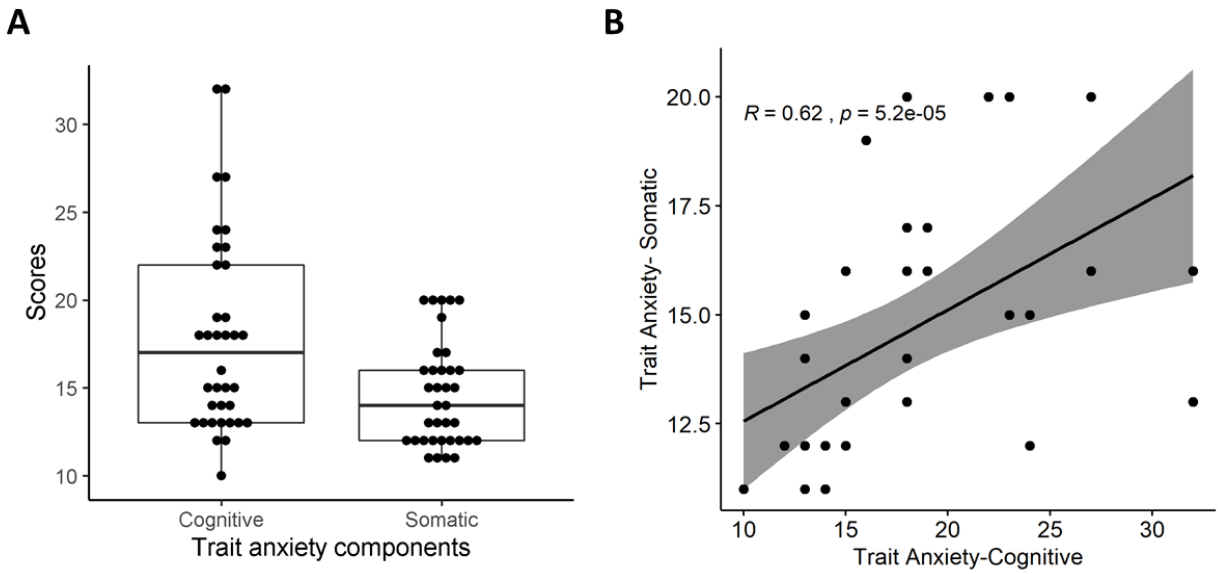

Figure 4.34: (A) Comparison between cognitive and somatic trait anxiety scores using boxplot; (B) correlation between cognitive and somatic trait anxiety scores.

4.4.6.1 Correlation between trait anxiety and detection thresholds:

The correlations between the trait anxiety scores and detection thresholds were evaluated along with group interactions. Even though there were no significant relationships between the detection thresholds and the trait anxiety scores, a significant interaction of gender (Figure 4.35) was observed in the relationship between the mechanical detection thresholds and trait anxieties (cognitive, F (1,32) = 15.599, $p < 0.001$; somatic, F (1,32) = 5.468, $p = 0.026$).

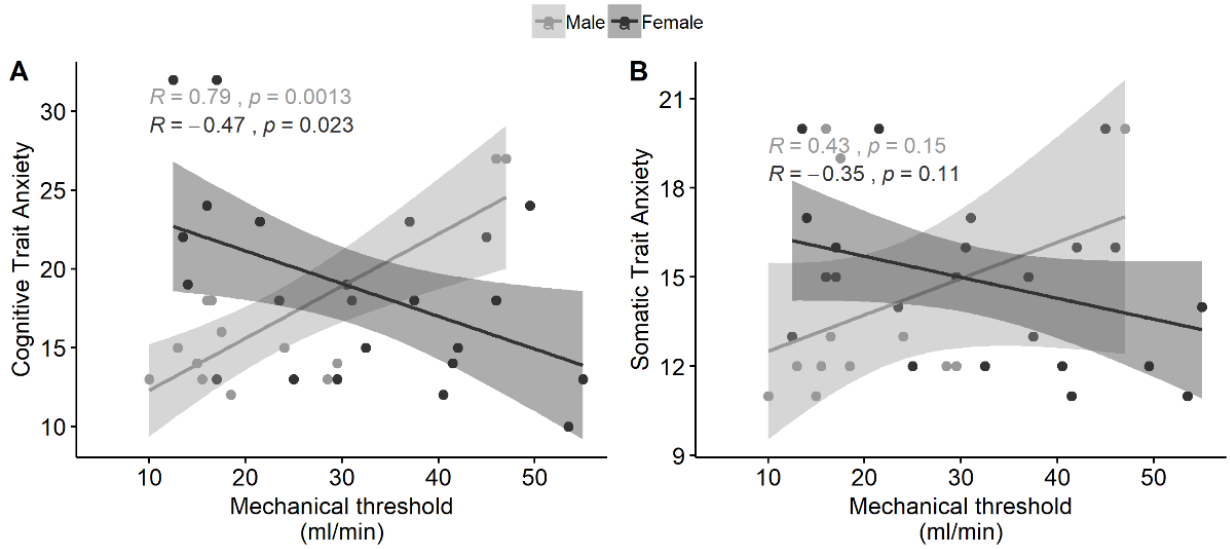

Figure 4.35: The interaction of gender in the association between the mechanical threshold and trait anxiety scores.

4.4.6.2 Correlation between trait anxiety and d_a:

20 (2 trait anxiety types * d_a of 10 stimulus intensities (4 intensities each for cold & mechanical stimuli; 2 intensities for chemical stimuli)). Spearman correlation analyses were conducted and there were no correlations or interactions of groups observed between the trait anxiety scores and d_a.

4.4.6.3 Correlation between trait anxiety and bias:

There were 32 Spearman correlations (4 stimulus intensity* 4 criteria each * 2 trait anxiety types) conducted between the trait anxiety scores and bias for mechanical and cold stimuli. 12 out of 64 correlation analyses conducted were significant with most of the relationships observed for the *c*1's of cold stimuli. A notable observation is that the *c*1 of cold sub-threshold, threshold, 1.5x threshold, and 2x threshold stimuli were negatively correlated with the cognitive trait anxiety scores (Figure 4.36). Similarly, the *c*1 of the cold threshold, 1.5x threshold, and 2x threshold stimuli were negatively correlated with the somatic trait anxiety scores (Figure 4.37). There were 16 (2 stimulus intensity* 4 criteria each * 2 trait anxiety types) relationships analyzed for chemical stimuli and there were no correlations observed. The significant relationships are listed in Table 4-7.

Similar to *c*, there were 80 correlation (32 cold, 32 mechanical and 16 chemical) analyses conducted for *lnβ* and 5 significant relationships were observed. The *lnβ*1 and *lnβ*2 of mechanical sub-threshold stimuli were significantly correlated with cognitive trait anxiety (ρ= -0.37, p = 0.036, ρ= -0.38, p = 0.033). *lnβ*1 of mechanical 2x threshold correlated with somatic trait anxiety (ρ= -0.38, p = 0.024). *lnβ*1 of cold 1.5x threshold correlated with somatic trait anxiety (ρ= -0.38, p = 0.021). *lnβ*2 of cold 2x threshold correlated with somatic trait anxiety (ρ= -0.35, p = 0.034).

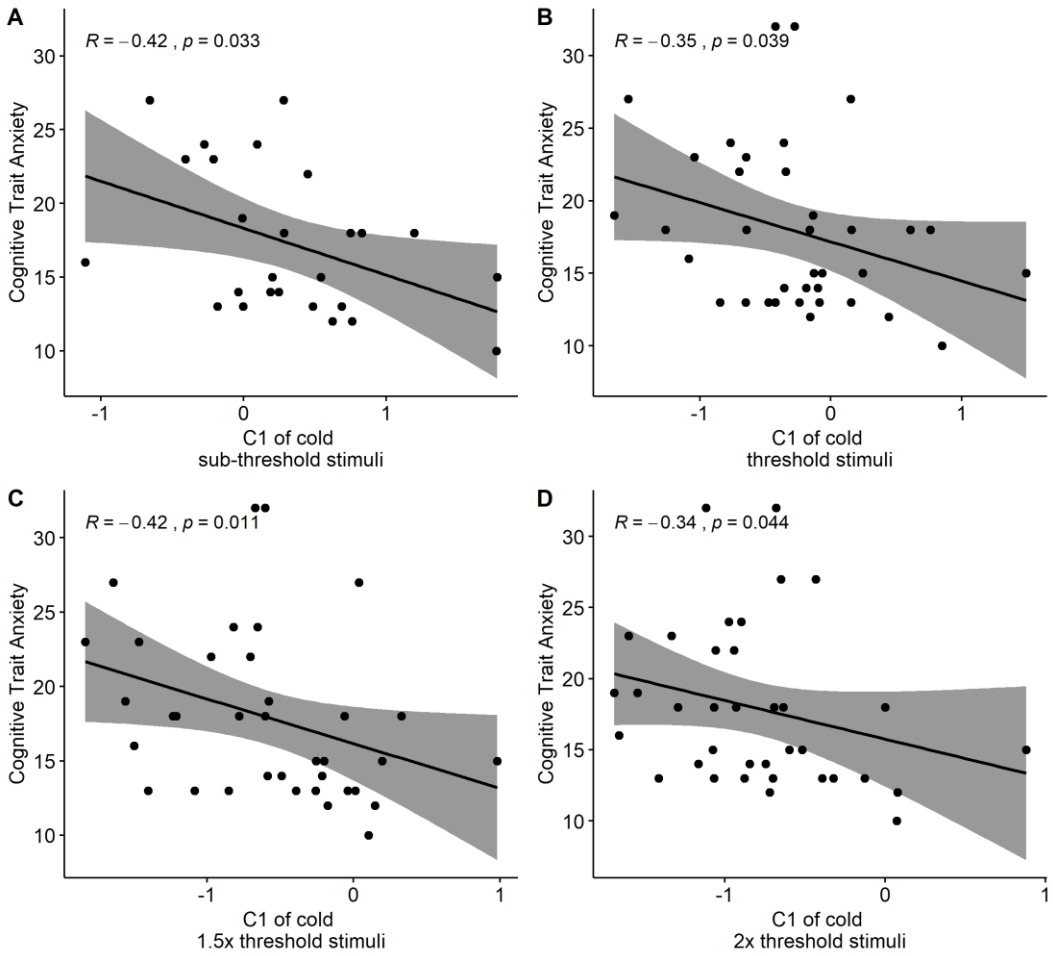

Figure 4.36: Spearman correlation between *c*1's of cold stimuli and cognitive trait anxiety scores.

Anxiety type (Trait)	Criterion	Stimulus type and intensity	Relationship between variables	Spearman Correlations
Cognitive	*c*1	Cold sub-threshold	Negative	ρ= -0.42, p = 0.033
Cognitive	*c*1	Cold threshold	Negative	ρ= -0.35, p = 0.039
Cognitive	*c*1	Cold 1.5x threshold	Negative	ρ= -0.42, p = 0.011
Cognitive	*c*1	Cold 2x threshold	Negative	ρ= -0.34, p = 0.044
Somatic	*c*1	Cold threshold	Negative	ρ= -0.47, p = 0.004
Somatic	*c*1	Cold 1.5x threshold	Negative	ρ= -0.59, p < 0.001
Somatic	*c*1	Cold 2x threshold	Negative	ρ= -0.47, p = 0.004
Somatic	*c*2	Cold 1.5x threshold	Negative	ρ= -0.45, p = 0.007
Somatic	*c*4	Cold sub-threshold	Positive	ρ= 0.46, p = 0.019
Somatic	*c*1	Mechanical 1.5x threshold	Negative	ρ= -0.37, p = 0.027
Somatic	*c*1	Mechanical 2x threshold	Negative	ρ= -0.44, p = 0.007
Somatic	*c*2	Mechanical 2x threshold	Negative	ρ= -0.34, p = 0.045

Table 4-7: List of significant correlations observed between the *c* and trait anxiety scores.

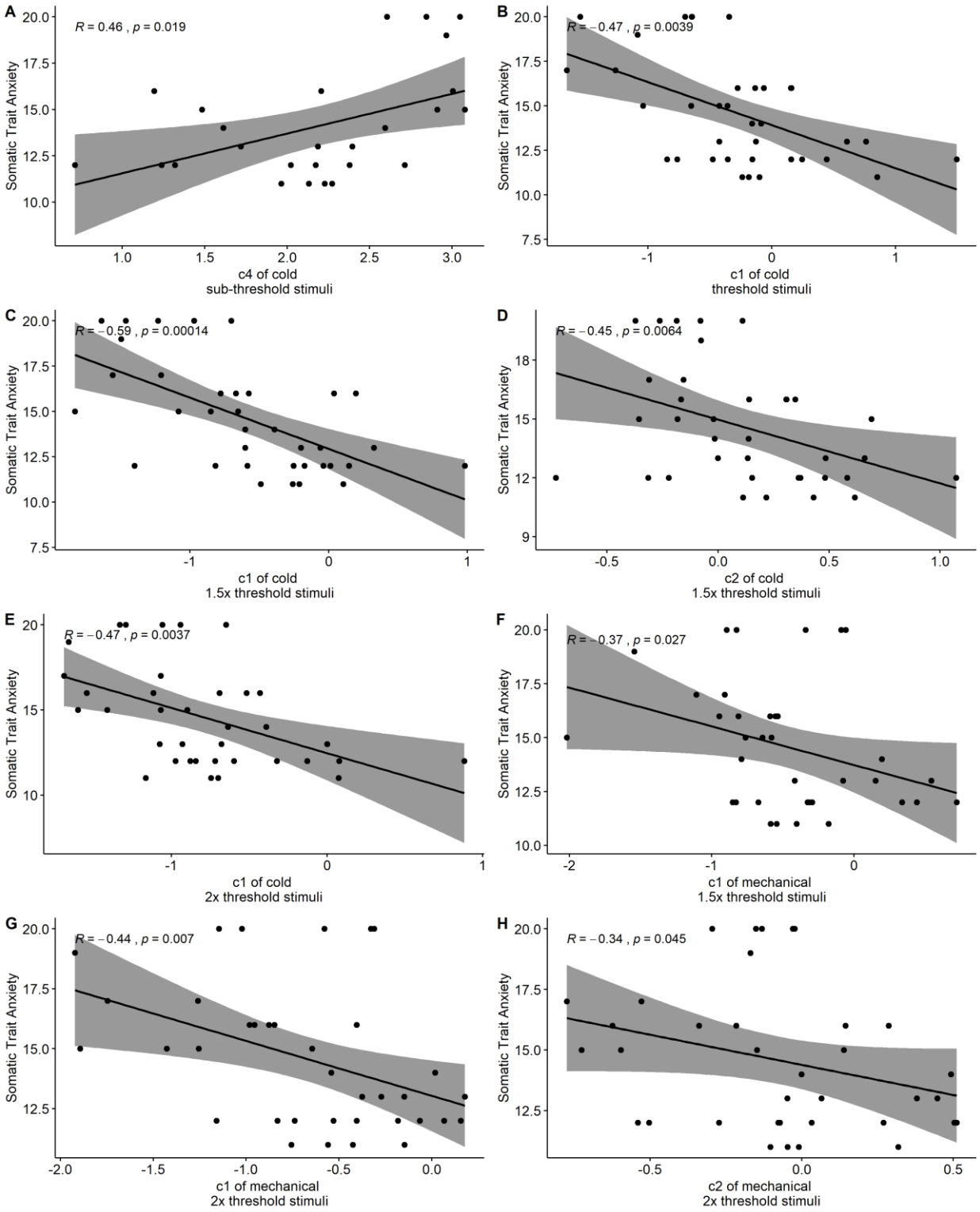

Figure 4.37: Spearman correlation between the somatic trait anxiety scores and *c*'s of cold and mechanical stimuli.

4.4.7 Correlation between DM and trait-anxiety:

Spearman correlation analyses were conducted to evaluate the relationship between the DM and trait anxiety scores (Figure 4.38). The vigilance scores were not significantly correlated with any of the DM categories and trait anxiety scores. The cognitive trait anxiety scores were significantly correlated with the buck-passing ($\rho = 0.48$, $p = 0.003$), procrastination ($\rho = 0.55$, $p < 0.001$) and hypervigilance ($\rho = 0.76$, $p < 0.001$) DM scores. The somatic trait anxiety scores were not correlated with DM scores.

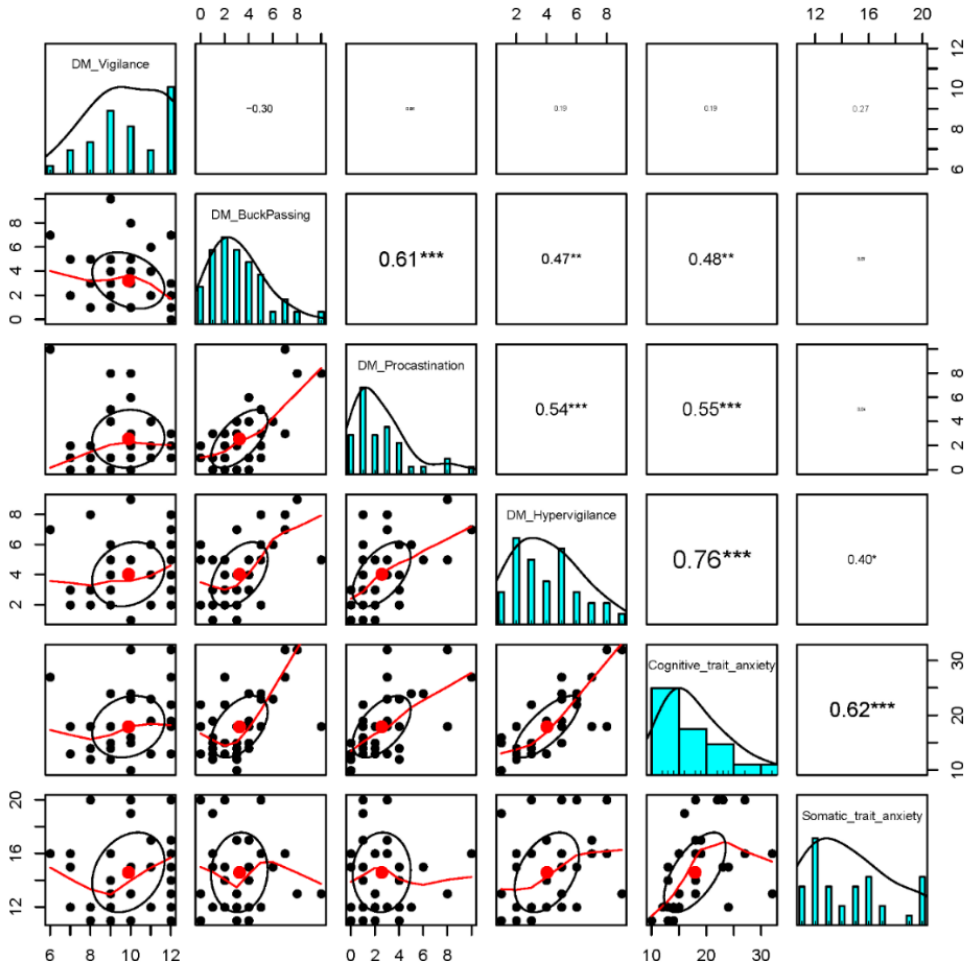

Figure 4.38: Spearman correlation between DM and trait anxiety scores.

4.4.8 State anxiety:

Similar to the trait anxiety scores, the state anxiety scores were also analyzed. Since the state anxiety questionnaires were administered before (pre) and after (post) each threshold experiment, the relationships were analyzed for both pre- and post-experiment scores. Data were analyzed using mixed model design with two within-subject factors (6 questionnaires (from 3 study visits) and 2 anxiety types (cognitive and somatic)) and subject ID as a random variable. A significant main effect of anxiety type was observed in the state anxiety scores ($F(1,385) = 6.05$, $p = 0.014$) (Figure 4.39). The somatic state anxiety scores were found to reduce significantly at the end of the three study visits ($F(5,175) = 2.57$, $p = 0.029$) compared to the start of the first visit, but the cognitive anxiety scores remained constant. The interaction of groups based on gender, symptoms and contact lens use was also analyzed and multiple significant two-way interactions were observed between the anxiety type and factors. Gender ($F(1,374) = 17.16$, $p < 0.001$) (Figure 4.40) , contact lens use ($F(1,374) = 21.14$, $p < 0.001$) (Figure 4.41), and symptoms ($F(1,374) = 8.64$, $p = 0.004$) (Figure 4.42) showed significant two way interactions with the type of state anxiety.

Paired t-test analyses were conducted to compare the state anxiety scores between pre- and post- threshold experiment for each stimulus type, and no significant differences were observed (Figure 4.43).

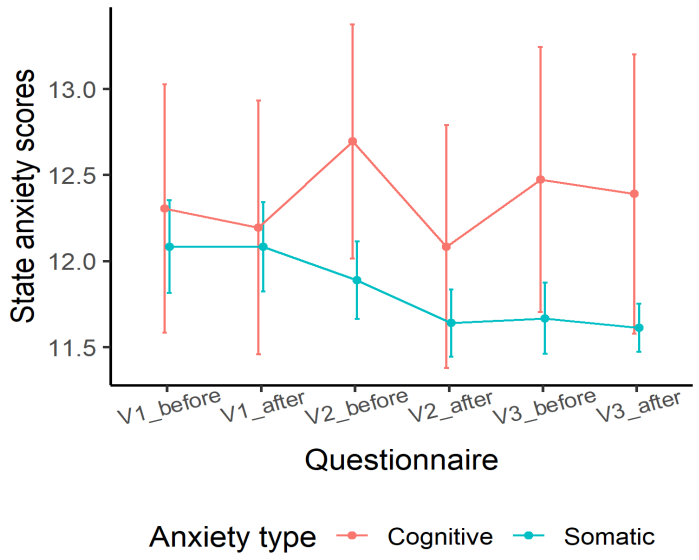

Figure 4.39: The mean (±se) state anxiety scores for cognitive and somatic state anxiety at each visit (pre- & post- threshold measures).

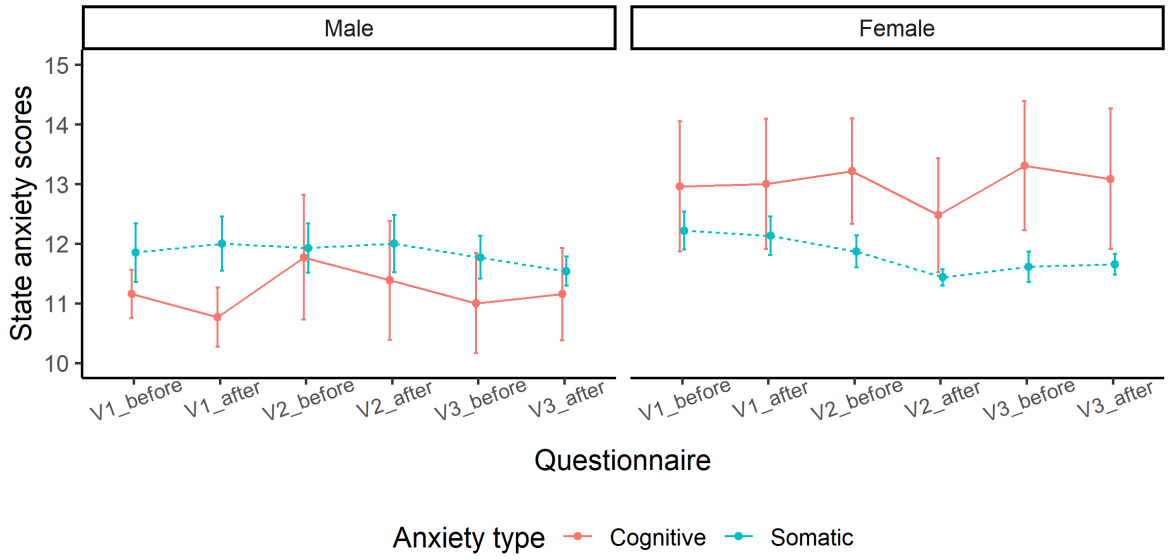

Figure 4.40: The mean (±se) state anxiety scores for cognitive and somatic state anxiety with interaction of gender at each visit (pre- & post- threshold measures).

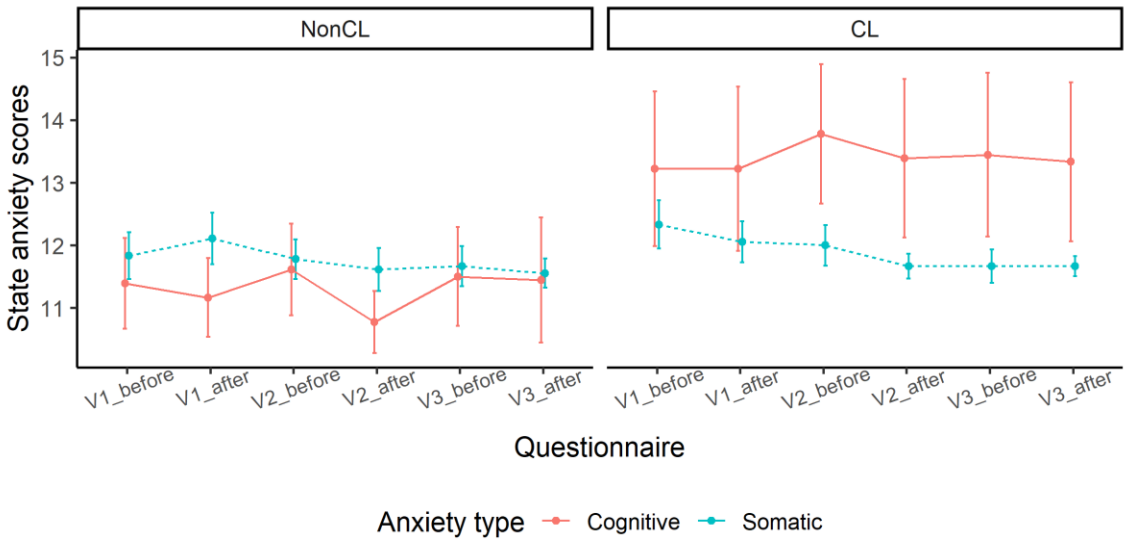

Figure 4.41: The mean (±se) state anxiety scores for cognitive and somatic state anxiety with interaction of contact lens use at each visit (pre- & post- threshold measures).

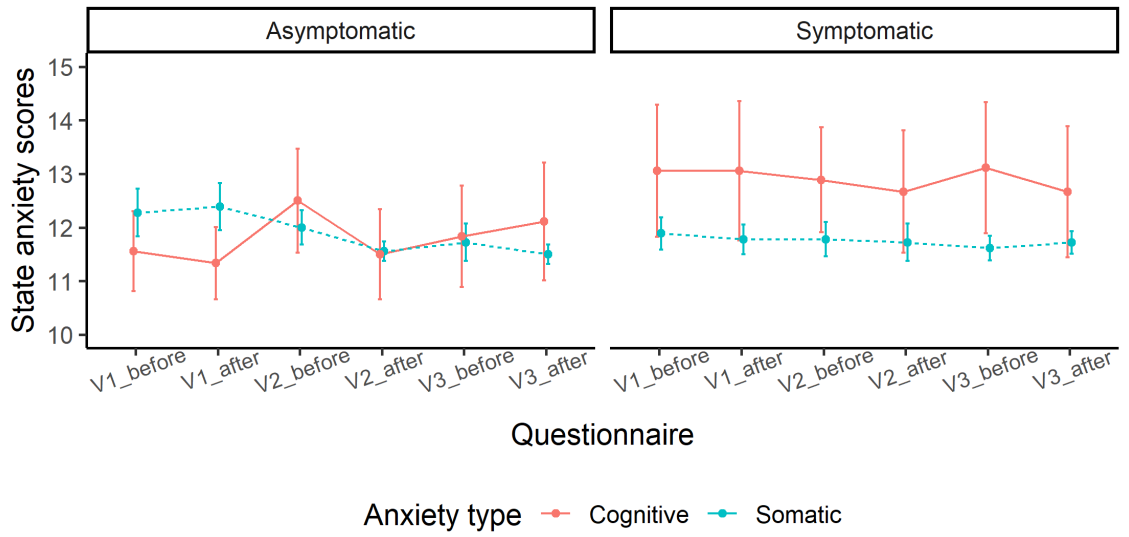

Figure 4.42: The mean (±se) state anxiety scores for cognitive and somatic state anxiety with interaction of symptoms at each visit (pre- & post- threshold measures).

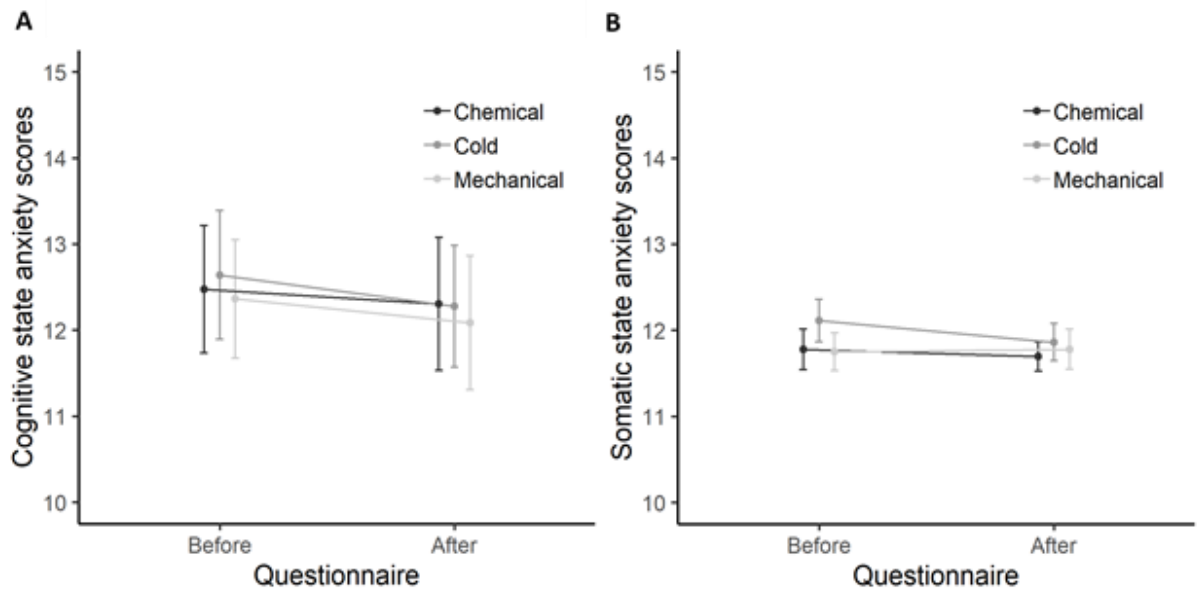

Figure 4.43: The cognitive (A) and somatic (B) state anxiety scores for different stimulus types before and after the threshold experiment.

4.4.8.1 Analysis based on starting stimulus for each participant:

The starting stimulus was different for each participant as the stimulus types have been randomly assigned to each study visit. For each stimulus, the change in anxiety scores along the study was evaluated using mixed-model analysis and no significant main effect or interaction with groups was observed (Figure 4.44).

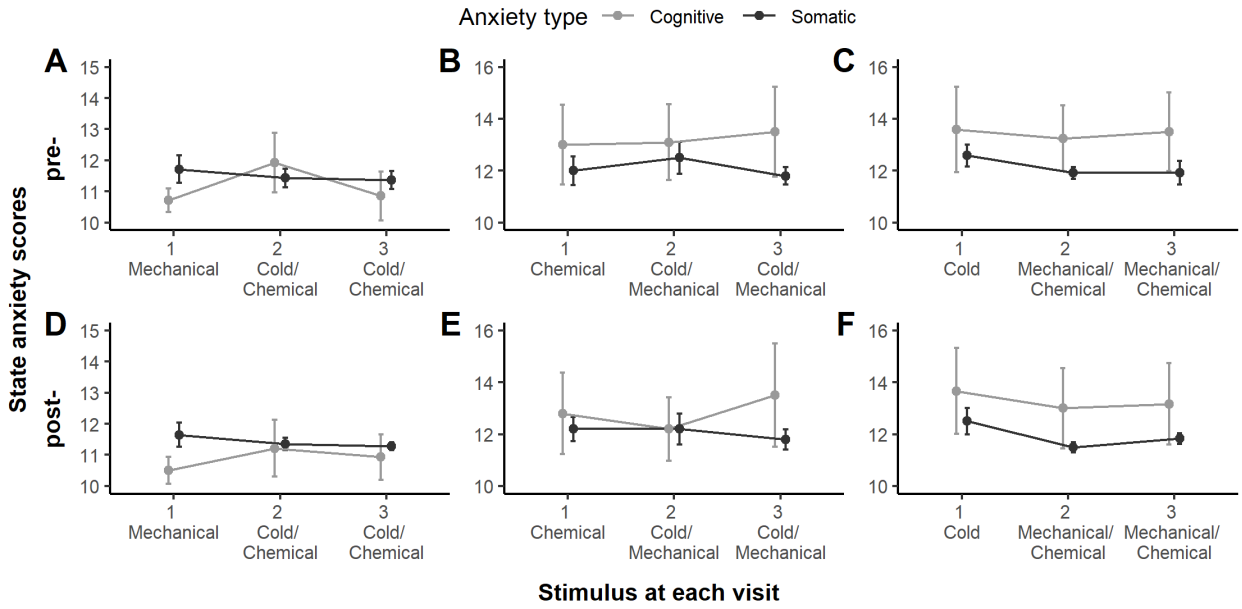

Figure 4.44: Analysis based on starting stimulus for pre- (top row) and post- (bottom row) threshold measure's state anxiety scores. The first column is for the group started with a mechanical stimulus, the middle column for participants started with a chemical, and the last column is for the group with a cold stimulus.

4.4.8.2 Relationship between the state anxiety scores and detection thresholds:

No significant relationships were observed between the pre- scores and detection thresholds, although a significant interaction of gender was observed in the relationship between cognitive state anxiety scores (pre) and mechanical detection thresholds ($p < 0.05$). A similar interaction of gender was observed in the relationship between cognitive state anxiety scores (pre) and cold detection thresholds (Figure 4.45). A similar relationship was also observed for post- scores (all $p < 0.05$) (Figure 4.46). The contact lens group showed a significant negative relationship between chemical detection thresholds and cognitive state anxiety scores (pre (ρ= -0.49, $p = 0.039$); post (ρ= -0.51, $p = 0.029$)) (Figure 4.47).

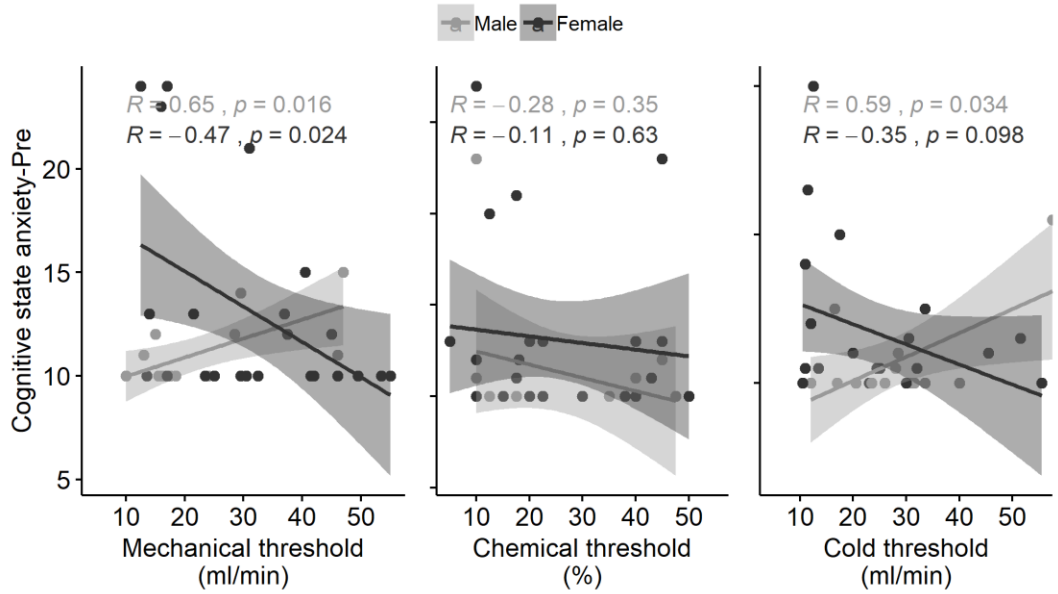

Figure 4.45: Interaction of gender in the relationship between cognitive state anxiety scores (pre) and thresholds of stimulus types.

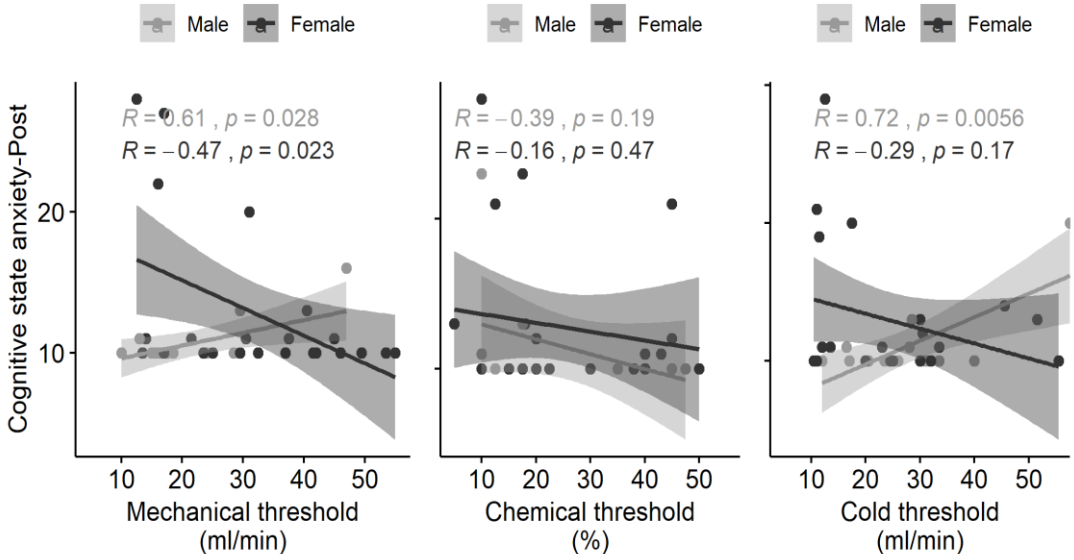

Figure 4.46: Interaction of gender in the relationship between cognitive state anxiety scores (post) and thresholds of stimulus types.

4.4.8.3 Relationship between the state anxiety scores and d_a:

Similar to the correlation analyses with trait anxiety scores, the relationships between the state anxiety scores (cognitive and somatic) and d_a of each stimulus type and intensity were analyzed using Spearman correlations. There were 16 correlations each (4 stimulus intensity * 1 d_a * 2 anxiety types * 2 measures (pre & post)) for mechanical and cold stimuli. Similarly, for chemical stimuli, there were 8 correlations (2 stimulus intensity * 1 d_a * 2 anxiety types * 2 measures (pre & post)) analyzed. No significant relationships were observed between the state anxiety scores and d_a of cold, chemical and mechanical stimuli (0 out of 40 correlations).

4.4.8.4 Relationship between state anxiety scores and bias:

The relationship between the criterion and state anxiety scores were evaluated. There were 64 Spearman correlations each (4 stimulus intensity * 4 criteria each * 2 anxiety types * 2 measures (pre & post)) for mechanical and cold stimuli. 10 out of 132 correlations showed a significant relationship for mechanical and cold stimuli. For chemical stimuli, there were 24 correlations (2 stimulus intensity * 3 criteria each * 2 anxiety types * 2 measures (pre & post)) analyzed and there were no significant relationships observed. Similar to the trait anxiety, the significant relationships were observed only for $c1$ or $c4$ (Table 4-8). The somatic state anxiety scores were negatively correlated with the $c1$ of cold sub-threshold, threshold, and 1.5x threshold stimuli ($p < 0.05$).

Pre/post	Criterion	Stimulus type and intensity	Anxiety type (State)	Relationship between variables	Spearman correlations
Pre	c4	Mechanical Threshold	Cognitive	Positive	$\rho = 0.33$, $p = 0.049$
Pre	c4	Mechanical 2x threshold	Cognitive	Positive	$\rho = 0.35$, $p = 0.036$
Pre	c1	Mechanical threshold	Somatic	Negative	$\rho = -0.34$, $p = 0.04$
Post	c4	Mechanical 2x threshold	Cognitive	Positive	$\rho = 0.34$, $p = 0.045$
Pre	c4	Cold sub-threshold	Somatic	Positive	$\rho = 0.4$, $p = 0.042$
Pre	c1	Cold 1.5x threshold	Somatic	Negative	$\rho = -0.37$, $p = 0.025$
Post	c1	Cold threshold	Cognitive	Negative	$\rho = -0.34$, $p = 0.041$
Post	c1	Cold sub-threshold	Somatic	Negative	$\rho = -0.44$, $p = 0.025$
Post	c1	Cold threshold	Somatic	Negative	$\rho = -0.42$, $p = 0.01$
Post	c1	Cold 1.5x threshold	Somatic	Negative	$\rho = -0.36$, $p = 0.031$

Table 4-8: List of significant correlations between the state anxiety scores and criterion for pre- and post-AMOL anxiety measures.

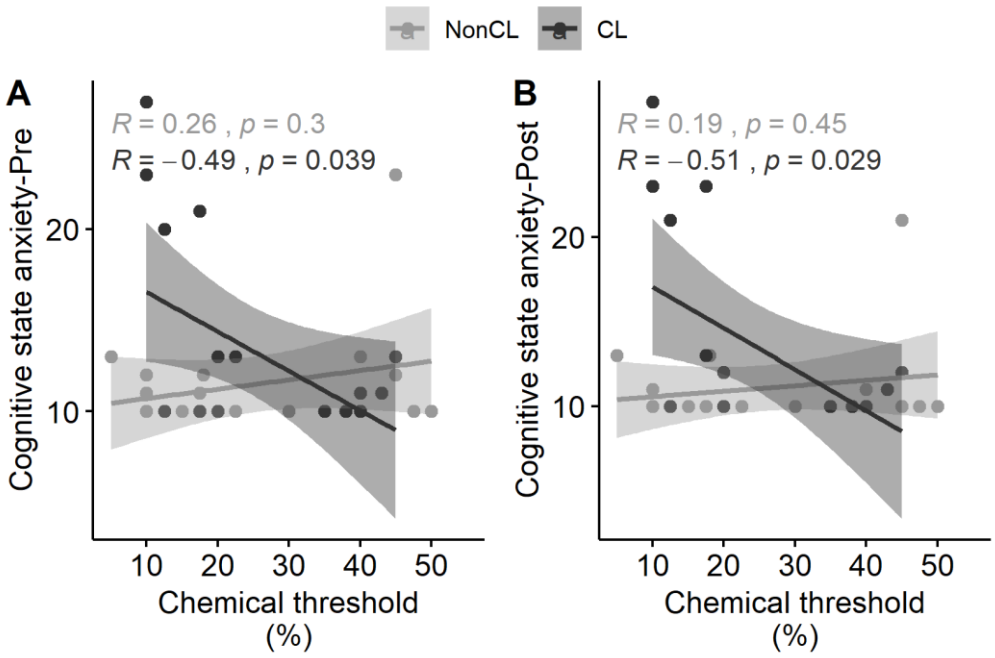

Figure 4.47: Interaction of contact lens use in the relationship between cognitive state anxiety scores (A-pre, B-post) and thresholds of stimulus types.

Similar to the c, there were 156 Spearman correlations analyzed for *lnβ*. Only 5 of 156 the correlations were significant. The *lnβ*1 of mechanical sub-threshold stimuli was negatively correlated with the cognitive state anxiety scores (pre) (ρ= -0.43, p = 0.014). Similarly, *lnβ*1 of mechanical sub-threshold stimuli was negatively correlated with the state cognitive anxiety scores (post) (ρ=-0.4, p = 0.022). Unlike the *c*, only one significant correlation was observed for cold stimuli. The *lnβ*1 of cold 2x threshold stimuli was negatively correlated with the cognitive state anxiety scores (post) (ρ= -0.34, p = 0.045). Also, *lnβ*1 of chemical threshold stimuli was correlated with the cognitive state anxiety scores (pre) (ρ=-0.36, p = 0.03) and the *lnβ*1 of chemical 2x threshold stimuli was correlated with the somatic state anxiety score (post) (ρ= -0.33, p = 0.048).

4.5 Discussion:

The primary purpose of this experiment was to determine the feasibility of conducting an MSDT experiment using pneumatic ocular surface stimuli. The previous chapter (Chapter 3) revealed that SDT could be used in a simple form (yes/no), but there were a number of drawbacks discussed in the chapter which might be overcome if multiple stimulus intensities were used and having participants use multiple criteria. Provided the MSDT method generally was feasible, and it was possible to reliably estimate the detection indices for different types and intensities of pneumatic corneal stimuli, the effect of clinical and psychological predictors on the OSSP of pneumatic stimuli could be examined using those outcomes. It is evident from the results that both d_a and bias indices can be estimated consistently and there is a systematic change in the detection indices in relation to the intensity of the stimuli. The interaction of clinical factors was observed only in the experiments with chemical stimuli. The results from psychometric analyses showed hidden relationships of the bias with the psychological indices that could not be evaluated using the classical psychophysical method. Overall, this study demonstrates the feasibility of utilizing MSDT to analyze OSSP and also demonstrates the feasibility and importance of measuring the psychological indices in psychophysical experiments. This is the first study to utilize and report an OSSP experiment with the MSDT protocol and the first OSSP study to analyze the interactions of sensory, clinical and psychological factors in the same group of participants.

4.5.1 Feasibility of MSDT:

Although this chapter is about signal detectability (and in signal detection theory, "thresholds" do not exist), the detection thresholds (used in scaling stimuli for MSDT experiments) obtained in this study were consistent with previous studies that measured corneal detection thresholds as a primary outcome measure.[67–71] The similarity in the detection thresholds externally validates the measures obtained in previous experiments. The MSDT data for all pneumatic stimuli used in this study followed the assumptions of SDT, which were evident in the ROC curves and Gaussian distributions reported in the results (Figure 4.6, Figure

4.9 and Figure 4.10). The ROC curves obtained were well behaved (with low residuals for each ROC line) for all stimulus types and the curves (both in ROC and z-ROC space) for intensities within each stimulus type did not overlap, indicating independent detectabilities for the scaled intensities. The z-ROC curves were almost parallel to the chance line, indicating the adherence of the obtained data to Gaussian assumptions of SDT and equal variance. Though the number of trials for each participant in this study was less than a typical SDT study, the d_a's calculated were similar using both cumulated rating data method and the average of the individual detectabilities (Table 4-9). This similarity in the d_a between the two methods indicates that the group detectability can be computed either way for ocular surface stimuli scaled based on detection thresholds. It also implies that the extrapolations used in place of zero frequency rating categories to calculate detectability did not considerably affect the detectability of the group. These results collectively point to the feasibility of using MSDT (with intensities scaled based on detection thresholds) in analyzing the OSSP of the pneumatic stimuli.

Another metric of feasibility is the number of participants who could not complete the experimental protocol. It is not useful if a large proportion of participants cannot do the experiments, even if the data from (a smaller number of) participants are well behaved. Two participants could not complete all the experiments due to their high baseline detection thresholds, and three participants could not complete due to variable detection thresholds. Since the strongest stimuli produced by esthesiometer is 200 ml/min or 100% (chemical), the supra-threshold stimuli cannot be scaled for high threshold participants. While considering the complex and noisy nature of the OSSP system, the results were remarkably consistent and indicative of feasible study methods.

Stimulus type	Stimulus intensity	d_a using cumulated rating data	Average d_a calculated from the d_a of each participant
Cold	Sub-threshold	-0.46	-0.15 ± 0.13
	Threshold	0.40	0.66 ± 0.12
	1.5x threshold	1.17	1.33 ± 0.17
	2x threshold	1.77	1.90 ± 0.17
Mechanical	Sub-threshold	0.03	0.10 ± 0.14
	Threshold	0.55	0.68 ± 0.11
	1.5x threshold	1.43	1.57 ± 0.17
	2x threshold	2.11	2.08 ± 0.19
Chemical	Threshold	0.87	0.97 ± 0.12
	2x threshold	1.99	1.88 ± 0.16

Table 4-9: Comparison of d_a obtained using cumulated and individual rating data

4.5.2 Detection theory indices:

The d_a (obtained from ROC using cumulated data) of all three stimulus types, which were scaled based on their respective detection thresholds, showed a systematic increase in the detectability of the stimuli with an increase in the intensity of the stimuli. Similar increases in the average d_a have observed in the transducer functions e.g., in vision [72] (generally d' vs. stimulus intensity) plotted using the individual participant data. Though the d_a was different between the intensities within each stimulus type, they were not different between the stimulus types.

The two types of bias indices (*c* and $ln\beta$) calculated in this study showed distinct characteristics. The "bias functions" plotted for each rating level between the amount of bias

and stimulus intensity showed significant separation between the levels for *c*, but not for *lnβ*. The vertical separation of criterion levels in *c* was similar for all the intensities within the stimulus type, indicating a proportional shift in criterion with an increase in stimulus intensity (Figure 4.8 (A), Figure 4.12 (A) and Figure 4.18 (A)). In contrast, the *lnβ* showed a dependency on the detectability of stimulus as there was an increase in the vertical separation of *β* criterion levels with an increase in stimulus intensity (Figure 4.8 (B), Figure 4.12 (B) and Figure 4.18 (B)). The *lnβ* levels were less separated and close to zero (no bias) for sub-threshold stimuli but separated for 2x threshold stimuli. The differences in the dependency of *c* and *lnβ* are somewhat scientifically problematic, because, ideally, the bias metrics should be approximately independent of stimulus intensity. Still, the criteria used by participants should be different (so, using conservative and liberal criteria should be consistent throughout the experiment). The optimal performance of *c* and the less-than-optimal performance of *lnβ* is illustrated in Figure 4.8, Figure 4.12, and Figure 4.18, suggesting that the former should be used rather than the latter.

4.5.2.1 Detectability:

The d_a of the corneal pneumatic stimuli was proposed to be different between the intensities and between the stimulus types. The difference in detectability between the stimulus intensities was proposed from the basics of SDT. SDT defines the sensory process as a continuous output, and the detectability depends on the strength of the signal against random noise, unlike the high threshold theory that defines the stimulus as always detectable once it crosses a threshold (and not detectable below threshold).[8] The change in the detectability with stimulus intensity was evident in this study for all three types of stimuli, something reported previously in other senses. [e.g., 73–75] Since MSDT studies are not available for comparison, the tendency of the participant's responses in classical psychophysics and psychophysiology literature has been compared to the detectability obtained using MSDT which may be directly related to the detectability of the stimulus. Alabi and Simpson[71,76,77] have observed a similar dose-effect increase in the autonomic responses such as redness, pupillary response, and

accommodation for pneumatic stimuli. Situ et. al[78] also reported an increase in the tear meniscus height as a response to an increase in the stimulus intensity of pneumatic corneal stimuli. Studies have also shown a similar increase in the discomfort rating with visual analog scales.[79–85]

The difference in detectability between stimulus types was proposed from the results of the Yes/No SDT experiment (Chapter 3), in which it was shown that the detectability of supra-threshold intensity stimuli was different between the three stimulus types. However, the difference was not apparent in the MSDT experiment when compared to the Yes-No SDT experiment (reported in chapter 3). The average detectability of the threshold intensity stimuli was relatively low for noxious mechanical (0.68) stimuli in comparison to noxious chemical (0.97) or non-noxious cold (0.66) stimuli. Also, the average d_a of the 1.5x mechanical threshold intensity stimuli was similar to the yes/no study but with lower variability. The d_a of the cold 1.5x threshold intensity stimuli was higher in the MSDT experiment (1.33 ± 0.17) than the yes/no SDT study (0.60 ± 0.13). The observed variation in the detectability between yes-no and MSDT experiments might be due to the difference in the type of SDT, as shown by Clark and Mehl[12]. Higher stimulus probability (though different intensities) and having more detectable stimuli has been shown to encourage participants to say "Yes" more to the trials (a liberal criterion).[86] Also, a similar increase in the detectability of the cold supra-threshold stimuli was observed in the yes/no experiment with higher stimulus probability. Future work with the same group of participants performing both yes-no and MSDT or rating SDT could provide more information on the actual differences in the detectability of ocular surface stimuli between the types of SDT protocols.

Among all the stimulus intensities, only sub-threshold stimuli had negative detectabilities indicating difficulty in detecting the stimuli from the background noise. The negative detectabilities were obtained often for cold sub-threshold stimuli compared to mechanical sub-threshold stimuli. The average d_a of cold sub-threshold stimuli was negative, while the average d_a of mechanical sub-threshold stimuli was slightly more than zero. In SDT

literature, a negative d_a generally indicate that the participant did not understand the experiment/instructions resulting in higher false alarm rate compared to hit rate. However, in this experiment, participants performed well for all other stimulus intensities as no negative d_a's were observed for other stimulus intensities. It is evident that there is difficulty in detecting the cold sub-threshold stimuli and the sub-threshold stimuli appear to be either suppressing the background noise or it is being detected as noise. The only way to confirm the above speculation will be by using the electrophysiology and observing the changes in single nerve recordings which was not available for this study.

4.5.2.2 Bias indices:

To my knowledge, this is the first study to analyze both overall experiment bias and biases for each stimulus intensity in the same experiment. In addition, the biases were also compared between stimulus types for both overall experiment bias and bias for each intensity.

Between stimulus type:

The standardized bias (X_c) or the overall bias for each experiment was different between the stimulus types (4.4.2.2). Similar differences were observed when *c*'s for threshold and 2x threshold intensity stimuli were compared between all three stimulus types (both most liberal and strict *c*) (4.4.2.3). The biases were noticeably different for the chemical stimuli and the difference might have been due to several factors such as nature, intensity and duration of the perceived sensation, trial/experiment duration, and the number of ratings. Though both mechanical and chemical stimuli are noxious in nature, the sensation produced by the chemical stimuli is probably more apparent , easily identifiable[87] and perceived longer than the sensation produced by the mechanical stimuli. Chemical stimuli produce a stinging/ burning sensation, and they may last longer on the eye as the carbonic acid from the dissolved CO_2 may take some time to disappear from the ocular surface. Also, the chemical stimuli are detected by the polymodal nociceptors and the nerve impulses are conducted through the slow conducting C-fibers, which may prolong the sensation perceived.[82,87]

In addition to the physiological differences, there were also a few experimental differences in chemical experiment due to longer stimulus preparation time, which may have affected their bias as well. The number of trials and signal intensities were reduced to keep the duration and signal probability of the chemical experiment consistent among all stimulus types. The number of ratings were also reduced to 4 to avoid ratings with no associated responses. The effect of these changes is unknown and needs further experimentation with different experimental methods to estimate the effect of each parameter on the resultant bias.

Within stimulus type:

The relationship between stimulus intensity (in relation to detection thresholds) and bias has not been evaluated before, but the bias has been shown to shift with detectability due to the larger separation between the distributions.[2,3,7] Though the two types of bias (*c* and *lnβ*) estimated are supposedly measuring the same bias, studies have shown both to be different from each other.[2,3,7,8,88] However, often only one type of bias metric was reported in previous SDT studies.[2,3,7,8,88] In this thesis, both bias indices were evaluated, and both showed a systematic change in the amount of bias within the stimulus type, but the interaction of criterion levels with stimulus intensities was observed only for lnβ. Both *c* and *lnβ* indicated that the participants, in general, adopted stricter criteria during the experiments, though these criteria shifted towards liberal criteria for higher intensities.

Of the two types of bias estimated, *c* showed an equivalent shift in bias towards being more liberal for all criterion levels with an increase in the stimulus intensity and the *lnβ* (which is known to be affected by the detectability of the stimuli[7]) showed an increase in the separation of *β* criterion levels with an increase in stimulus intensity. A dependency of *lnβ* with stimulus intensity was also observed in this study as there were significant interactions between *lnβ, β criterion* and stimulus intensities for all three stimulus types. A diverging fan-like distribution was seen for lnβ due to the larger separation/variation between the *β* criterion levels for stronger stimulus intensities compared to almost overlapping levels for sub-threshold stimuli,

indicating possibility of large criterion shifts to respond to stronger stimulus intensities. This indicate that future studies should adopt a stricter control of criteria to detect esthesiometer stimuli.

4.5.3 Effects of symptoms and contact lens usage on detection theory estimates:

The interactions of two clinical factors, contact lens usage and symptoms of dry eye, in the detection of ocular surface stimuli was analyzed in this study due to increase in the prevalence of dry eye and contact lens discontinuations related to discomfort. There are contrasting reports on the effect of these factors on ocular surface sensitivity.[69,89–104] If only the experiments with Belmonte esthesiometers are considered, the mechanical detection thresholds have been shown to be negatively associated in symptomatic participants[96] and the symptomatic contact lens wearers have been shown to have higher cold detection sensitivity compared to asymptomatic contact lens wearers[92,95,97]. In addition, studies comparing signs and symptoms of dry eye also showed contrasting results.[69,93,96,105–116] The sensory etiology or physiological mechanism of both dry eye and contact lens related discomfort still remains unclear. This section of the thesis analyses the interaction of the factors in the association between stimulus intensity and detection indices. Both sensory and decisional aspects of these groups were analyzed.

The d_a's for mechanical and cold stimuli types were not affected by the predictor variables. Surprisingly, there were difference in d_a's for chemical stimuli. These chemical stimuli are distinctive producing a burning sensation, and perhaps the contact lens wearers are adapted to the stinging sensation arising from the contact lenses and /or lens solution.

For bias, the interactions were different between symptoms factors and contact lens wear; Contact lens wearers had similar bias to controls (non-contact lens wearers) for the supra-threshold stimuli, but their bias was different for less intense stimuli. Symptomatic participants had similar bias to controls (asymptomatics) at threshold but different bias for supra-threshold stimuli. In both analyses, the non-control group had stricter biases compared to the controls,

and unfortunately, reasons for these differences are unclear and needs more experimentation perhaps with a wider range of lens wearers and symptoms would make these differences more apparent.

4.5.4 Effects of gender on detection theory estimates:

The d_a has been shown to be different between gender in pain studies.[39,117–120] However, in this study, no effects of gender were observed for any detection theory indices. The interactions were observed only for the bias in the chemical stimuli experiment.

4.5.5 Are the detection thresholds a good baseline for MSDT experiments?

The detection thresholds were used as a baseline for this SDT experiment so that the scaling of the stimuli will be similar for all participants. The effectiveness of detection thresholds as a baseline was examined using the association between detection thresholds themselves and d_a for the stimuli at threshold intensities for all subjects. Ideally, d_a will be unrelated to the detection threshold. This is demonstrated in the observation of the detection thresholds and d_a of the threshold intensity stimuli were not correlated for noxious mechanical and chemical stimuli. There was however a positive correlation observed for the non-noxious cold stimuli. This positive correlation indicates that participants with higher detection thresholds had higher detectability (easily detected the threshold intensity stimuli). It is possible that participants adopted a stricter criterion (waiting until stimulus was more obvious) during the threshold measurements, which artificially inflated their measured detection thresholds. Since the estimated detection thresholds would be in the supra-threshold intensity range, the detectability of the stimulus may have been higher than the participants with no bias. The above speculation is supported by the positive relationships seen between the cold detection thresholds and a few of the bias metrics obtained for cold threshold stimuli (Figure 4.23 and Figure 4.25). Though all bias metrics were not significant, it is important to note that the bias assumed by participants during threshold experiments might have been of any amount and may even have varied during the experiment. In addition, the detection thresholds were

positively correlated with d_a's of all other supra-threshold intensities within the stimulus type. The effect was seen for observed even for the mechanical and chemical stimuli, which did not have significant correlations with d_a's of threshold intensity stimuli. Among others, a probable reason for the correlation is the linear scaling of the stimulus intensities, which produces higher intensity (supra-threshold) stimuli for participants with high detection thresholds. Further analysis/experimentation is needed to analyze the best scaling method for MSDT experiments, as well as finding an optimal way to obtain detection threshold with least amount of bias.

4.5.6 Psychological parameters:

The general validity of the psychological indices obtained in this study was evaluated and both psychological parameters obtained were comparable to their respective validation studies. The DM scores of this study group were similar to the experiment conducted by Mann et. al[121] on 2002 participants from six different countries. In our study group, the vigilance scores were higher compared to other DM components and positive correlations were observed between the buck-passing, hypervigilance and procrastination scores. The vigilance scores were not correlated with other DM scores. Similar observations were also reported by Mann et. al[121]. Similar to DM scores, the trait and state anxiety scores demonstrated external validity when compared to the validation studies by Ree et al.[122] and Grös et al.[123] A positive correlation was observed between the cognitive and somatic trait anxiety scores, which was also similar to the validation studies.[122,123] In the correlation analyses between DM and trait anxiety scores, significant correlations were observed only for the relationships involving cognitive trait anxiety scores. There were positive correlations between cognitive trait anxiety scores and scores of 3 DM components (procrastination, hypervigilance, and buck-passing) (Figure 4.38). Somatic trait anxiety and vigilance scores were not correlated with other variables. Surprisingly, there was no interaction of any factors, including gender, on both DM and trait anxiety scores.

The state anxiety scores were obtained before and after each threshold experiment, and no significant differences were observed between pre- and post- anxiety scores. Similarly, no interactions of factors were observed. There was no order effect in the anxiety scores as well, and scores were not dependent on the type of the stimulus. Though pre- and post-measurements did not show any difference, overall, there was a difference in the scores between the cognitive and somatic components of anxiety. The cognitive component remained the same until the end of the study, but the somatic component reduced significantly. Though the validation study by Ree et al.[122] showed an increase in anxiety after introducing stress, the cognitive component remained the same in their study as well. This reduction in somatic component indicates that a dimension of anxiety about the experiment, the esthesiometer and the stimuli (in any combination) decreased as the study progressed, though cognitively anxiety remained the same. There were also interactions of factors in how the anxiety changed during the study. The cognitive component of state anxiety was lower for male participants compared to females during the study. A similar observation was observed for non-contact lens wearers and contact lens wearers. This was surprising because contact lens wearers who are habituated to experiencing closer objects, still had more cognitive and somatic anxiety than non-contact lens wearers. Interactions were observed between the asymptomatic and symptomatic groups of participants as well.

4.5.7 Relationship between psychological and psychophysical parameters:

The psychological components were evaluated to analyze the relationship between the psychological and psychophysical variables. The inclusion of evaluating psycho-social factors in the experiments measuring pain was suggested in pain literature as well.[22] There were many significant associations between psychological and psychophysical parameters (Table 4-10). Most of the associations were observed between the criteria and psychological parameters: Both DM and anxiety scores showed these relationships. The significant relationships were with either C1s or C4s and the relationships were positive in case of C4 and negative in case of C1 and this was consistent for all the significant relationships observed. The reasons for

these complex relationships are unclear, but I speculate that the psychological differences between the participants becomes manifest when they are forced to assume the most (extreme) strict or liberal criterion and their underlying makeup becomes manifest. For example, the negative correlation of C1 of the cold threshold stimuli with vigilance score could indicate that the participants who are more vigilant assumed a stricter liberal bias because they don't say yes unless they are more certain about it. This tendency also translates to C4 where they show a positive correlation (i.e., participants who are more vigilant adopts stricter criteria).

There were significant correlations between the cold and chemical detection thresholds with the DM vigilance scores. None of the other relationships with the psychological parameters were significant. The correlations were dependent on whether the subjects were symptomatic or asymptomatic. The cold thresholds were negatively correlated with the vigilance scores for symptomatic group, but they were positively correlated for the asymptomatic group. A possible reason for the positive correlation is that people who are more vigilant tend to adopt stricter criterion. The opposite relationship in the symptomatic group could be a result of habituation to the pre-existing discomfort that is more likely to occur in participants who are less vigilant. A similar negative relationship was observed between the chemical threshold of symptomatic group and vigilance scores. Because there was no correlation with mechanical stimulus, the possible implication is that the habituation is due to a chemical/ cold stimulus.

Similar to the DM scores, an interaction of gender was observed in the correlation between mechanical detection thresholds and cognitive scores of trait and state anxiety. Male participants with higher cognitive anxiety had a high mechanical threshold, whereas the female participants with high cognitive anxiety had a low threshold. A gender difference in corneal sensitivity has been shown before, but the contribution of psychological components has never been obtained. Our study shows that there is a possible confounding variable in the form of anxiety affecting the responses. A similar observation has been seen in other pain studies.[39,40,117–120,124,125]

Stimulus	DM	Trait Anxiety	State Anxiety	
			Pre	Post
Cold Sub-Threshold	lnβ1 (-) Vigilance lnβ4 (+) Vigilance lnβ4 (+) Buck-passing	c1 (-) Cognitive c4 (+) Somatic	c4 (+) Somatic	c1 (-) Somatic
Cold Threshold	c1 (-) Vigilance c4 (+) Buck-passing c4 (+) Procrastination	c1 (-) Cognitive c1 (-) Somatic		c1 (-) Cognitive c1 (-) Somatic
Cold 1.5x Threshold	c4 (+) Buck-passing c4 (+) Procrastination	c1 (-) Cognitive c1 (-) Somatic c2 (-) Somatic lnβ1 (-) Somatic	c1 (-) Somatic	c1 (-) Somatic
Cold 2x Threshold	c4 (+) Buck-passing c4 (+) Procrastination	c1 (-) Cognitive c1 (-) Somatic lnβ2 (-) Somatic		lnβ1 (-) Cognitive
Mechanical Sub-Threshold	lnβ1 (-) Hypervigilance lnβ2 (-) Hypervigilance lnβ1 (-) Procrastination lnβ2 (-) Procrastination	lnβ1 (-) Cognitive lnβ2 (-) Cognitive	lnβ1 (-) Cognitive	lnβ1 (-) Cognitive
Mechanical Threshold	c1 (-) Vigilance lnβ1 (-) Vigilance lnβ2 (-) Vigilance		c1 (-) Somatic c4 (+) Cognitive	
Mechanical 1.5x Threshold	c3 (-) Vigilance	c1 (-) Somatic		
Mechanical 2x Threshold		c1 (-) Somatic c2 (-) Somatic lnβ1 (-) Somatic	c4 (+) Cognitive	c4 (+) Cognitive
Chemical Threshold	c1 (-) Procrastination		lnβ1 (-) Cognitive	
Chemical 2x Threshold	lnβ4 (-) Buck-passing			lnβ1 (-) Somatic

Table 4-10: Summary of significant relationships between the bias from SDT and psychological parameters. (+) indicates a significant positive correlation and (-) indicates a significant negative correlation.

4.5.8 Limitations

There were a few instrument and psychophysical method related limitations in this experiment. The instrument related limitations were the Belmonte esthesiometer's stimulus range and the time taken to prepare the chemical stimuli. The Waterloo Belmonte esthesiometer has a reliable–stimulus flow rate range of 10-200 ml/min. In addition, the maximum concentration of added CO_2 in chemical stimuli can be only 100%. Since the MSDT experiment has stimuli of intensities at detection threshold, as well as sub-threshold (0.5x detection threshold) and supra-threshold (1.5x and 2x detection threshold) levels, the limitations arise when the scaled intensities fall outside the stimulus range available. For example, if the participant has a high chemical detection threshold of 70%, both supra-threshold intensities (105% and 140%) are outside the physical range of concentrations possible. Similarly, if the participant has high mechanical detection threshold of 115 ml/min, the 2x supra-threshold (230 ml/min) stimuli would be outside the stimulus range available from the Waterloo Belmonte instrument. The stimulus range cannot be increased and the options available were not to test that particular intensity or not to use that participant data. But losing two stimulus intensities would affect both stimulus probability and overall duration of the MSDT experiment. So, the participants with high detection thresholds (2 of 41 participants recruited) were dropped from the experiment.

Similarly, there was also limitation with stimulus range for participants with low detection thresholds of cold or mechanical stimulus. The intensity of sub-threshold stimuli would be out of range of the esthesiometer if the detection thresholds were below 20ml/min. To overcome this limitation, for participants with detection thresholds between 15-20 ml/min, the intensity of the sub-threshold stimuli was set at 10 ml/min. If the detection thresholds were lower than 15 ml/min, then the sub-threshold stimuli trials were replaced with blank trials. The stimulus probability would be affected by the replacement of sub-threshold trials with blank trials but considering the low intensity of the stimulus, it was assumed it would not produce

larger difference to the stimulus probability. This would also keep the duration of the experiment constant across participants.

The limitation of longer time taken to prepare each chemical stimulus trial was addressed by using fewer intensities compared to cold and mechanical stimuli experiments. Fewer intensities also meant fewer trial to keep the overall time and stimulus probability similar as other two stimuli experiments. The number of ratings were reduced to avoid rating categories with zero frequency responses. An unavoidable (obvious) consequence of these changes was observed in the analysis when detection indices were compared between stimulus types due to difference in the number of ratings and number of intensities between stimulus types. Instead of overall comparison between all 3 stimulus types using ANOVA, analyses were obtained for each intensity. Similar analyses were conducted for bias as well. This modifications in the analyses did not alter the hypothesis tests possible (except for those tested with the, perhaps, irrelevant omnibus F-test) but the principle concern was to keep the mechanical, thermal and chemical trials approximately equal length, in order to eliminate the possibility of participants showing different fatigue effects with different stimulus types, and therefore affecting the SDT decision metrics as well as the psychometric predictors.

In addition to the changes in number of trials, intensities and ratings for chemical experiment, there might be a general MSDT method limitation for all stimulus types used in this experiment. The MSDT parameters (number of trials, stimulus probability, number of intensities, number of catch trials and number of ratings) were assumed to be best for this experiment based on non-OSSP MSDT literature. There have never been studies to test the effects of different MSDT parameter combination on OSSP experiments. Since these would essentially be about signal detection theory, and my thesis used detection theory to examine ocular surface processes, the extensive experimental studies need to be conducted to analyze the effect of each parameter and find a best combination of MSDT parameters, which was beyond the scope of this thesis. The results do however demonstrate that the estimates/compromise parameters selected, allowed the revelations reported in the previous

chapter and so it seems that if not optimum, the parameters selected did not appear to mask the effects found.

Training was provided to participants to familiarize them to the experiment, audio prompts during the experiment and how to use the response button box. Participants were also trained to appreciate/recognize threshold intensities, prior to MSDT trials. Because of the inclusion of anxiety measurement between experiments, training was not separately provided for participants to familiarize themselves with each stimulus intensity. Future work may be needed to evaluate the exact effect of protracted training and also the effects of perceptual learning on the sensory and decision metrics used in this experiment. There has been no reports covering ocular surface processing that have ever raised/addressed this topic.

4.5.9 Summary:

MSDT is feasible for analyzing ocular surface sensory processing and provides insight into the possible bias associated with the use of pneumatic stimuli. The detectability of scaled threshold intensities showed a systematic increase, and the bias varied within the stimulus type. With noxious and non-noxious pneumatic stimulation, detectability and criteria vary systematically with stimulus intensity, a result that cannot be derived using classical psychophysics. Both decision-making and anxiety showed relationships with the bias, which may influence the threshold measurements if not properly controlled.

Chapter 5
Discussion

The experiments in this thesis were about the sensory and decisional aspects of ocular surface sensory processes along with an evaluation of the effects of clinical and psychological factors. The objective of this thesis was to gain insight into the sensory mechanism underlying the detection of several ocular surface stimuli and the associated bias. Also, to relate these findings to a few clinical and psychological factors that may have an effect or an association with the sensory detectability and associated decisions. This is the first set of experiments with pneumatic corneal esthesiometer that have been conducted using signal detection theory examining the ocular surface sensory processing (OSSP) and a subset are also the first experiments to analyze the relationships between the psychological and psychophysical aspects of detecting ocular surface stimuli.

In addition to the sensory characteristics of the esthesiometer stimuli, some of the physical characteristics of the stimuli were also needed to be evaluated. There were studies on the calibration of mechanical and thermal components of the pneumatic stimuli but there were no similar studies available for the chemical stimuli.[1–4] In all previous works specifying additional CO_2 ('added CO_2' or 'CO_2 concentration' or '%CO_2'), the concentration of CO_2 in the chemical stimuli was nominal, measured internally by flow meters and reported by the dials on the instrument. This means the %CO_2 reflected the CO_2 concentration somewhere inside the instruments and not the concentration at the ocular surface. The speculated reasons since none of the articles explicitly described the reasons for using nominal CO_2 were the unavailability of proper calibration device and the assumption that smaller working distance and laminar flow of the gases will produce only a minimal drop in the concentration which is possibly insignificant. The concentrations have never been estimated at the ocular surface – how does concentration vary in the column between the tip of the esthesiometer and the ocular surface? With more advanced and portable CO_2 sensors available and the possibility of

obtaining instantaneous %CO_2 measurements, in Chapter 2 of this thesis, the calibration of the CO_2 stimuli was conducted at different working distances. Contrary to the beliefs, a larger and significant loss in the %CO_2 was observed even at the shortest working distance (Figure 2-5, 2-6). Also observed were even larger reductions in the concentration with an increase in the working distance (Figure 2-5, 2-6). Even with reduced concentrations, all the stimuli that were calibrated on this experiment had good test-retest repeatability indicating consistent stimulus flow rates and concentrations generated by the esthesiometer each trial and a consistent loss in the CO_2 to the surroundings while the stimulus is traveling from the esthesiometer nozzle to the testing surface. It is recommended from these results that the use of smaller working distances and lower flowrates (below 100 ml/min) are optimal for chemical stimuli experiments.

The initial intent of this calibration experiment in this thesis was to conduct data analyses in subsequent experiments using both the nominal and calibrated concentrations. Though this experiment provided insights about the physical characteristics of the chemical stimuli, there were a few limitations in the experimental design and CO_2 sensor used in this experiment that suggested the need for further experimentation before using the calibrated %CO_2 for analysis. Since the sensor worked on the principle of diffusion with a larger gas collection chamber compared to the volume of the stimulus delivered and continuous exchange of the gases inside the chamber, the stimulus had to be delivered for longer (99 seconds) than the usual stimulus duration of 2 or 3 seconds. Also, for calibration, a room temperature CO_2 was used instead of actual heated CO_2 stimuli due to the use of non-dispersive infrared (NDIR) technology to quantify the %CO_2 inside the gas chamber. The sensor may produce conflicting values with changes in the temperatures inside the chamber. Considering the limited choice of CO_2 sensors that were available for this type of application and the limitations highlighted before, calibrated concentrations were not part of further analyses in other experimental chapters and only nominal concentrations were used. A suggestion provided by the external examiner is to consider mass estimate of the stimuli (kg/min) delivered instead of flow rates

and concentrations. This is not done because volumetric flow has been used as a standard metric of pneumatic esthesiometry since its development by Belmonte et al.[5] (eg. Figure 2). On the other hand, even if it were mass and not volumetric flow that was the most accurate scale for the predictor variable, the transducer functions show (Figure 4.7, Figure 4.11 and Figure 4.15) how well-behaved detectability (the sensory outcome) versus flow (the predictor outcome) relationships are. This suggests that gains in rescaling the predictor variable would be modest. In addition, the mass unit addresses only one aspect of the stimuli tested (mechanical) but the esthesiometers also use chemical and thermal components which cannot be differentiated one from other if just volumetric unit is used.

Chapters 3 and 4 were experiments that were conducted with two different SDT methods to measure sensory and decisional components of ocular surface sensory processing. A basic yes or no single intensity SDT was used in Chapter 3 and a multi-criterion multi-intensity SDT was used in chapter 4. The primary reason for using SDT is that the sensory processing of the pneumatic stimuli could be estimated independent of the bias and the bias could be estimated in the same experiment as well, unlike classical psychophysical methods in which both are not feasible (classical theory simply does not include decision component estimation). Also, in classical psychophysical methods, the sensory estimates obtained in the form of thresholds are in different units depending on the type of stimulus tested. This impedes the comparison of results between the stimulus types. Whereas the sensory estimate of SDT, detectability or d', gives how detectable the given stimulus is from the background noise. d' is independent of bias and can be compared between different stimulus types provided the intensities are matched. There were multiple options provided in the literature to match the stimulus, but the viable options for OSSP experiments were matching with stimulus intensity or detection thresholds due to the complexity of the experiments and lack of relatively sophisticated instruments (esthesiometers). Matching the stimulus across stimulus types with a randomly chosen intensity is not feasible due to the difference in the units of measurements of each stimulus type, as well as possible physiological and neuro-physiological differences in

how each stimulus type is detected. For example, if the randomly chosen intensity was 50, a 50 ml/min cold stimulus is not the same as a 50 ml/min mechanical or 50% chemical stimulus. Similarly, choosing a specific intensity based on previous studies is also not optimal due to the wider detection threshold range in the studies even for a normal or asymptomatic group of participants.[4–19]

The other feasible option is to match the stimulus using the detection thresholds and this method has been used before in studies with esthesiometer to scale the intensities between participants such as using sub or supra thresholds stimuli to understand other aspects of OSSP.[15–17,20–23] However, though not explicitly stated in previous experiments, the thresholds were used to scale the intensities under the assumption that the bias was similar across the participants (there is no preference to say yes/no to the trials). The reason for this assumption is because of the limitation with the classical psychophysical methods with which bias could not be estimated.[24] The use of thresholds to match the stimuli across stimulus types is also not perfect because bias is unknown and it could alter the thresholds obtained. For example, a trigger happy participant could say "yes" to all the trials resulting in a completely different sensory threshold than actual. But since the main objective is to match the stimulus across the participants to find the sensory and decisional aspects of the stimulus, the detection thresholds were used as the baseline for the signal trials of SDT experiments.

In chapter 3 of this thesis, a basic yes-no SDT experiment was conducted to estimate the sensory and decisional aspects of 1.5x detection threshold intensities stimuli. Since this is the first of a kind experiment among ocular surface sensory processing experiments, relatively easily identifiable stimulus intensity was chosen based on the literature.[16,25,26] The experiment was conducted with a relatively 'conservative' signal probability of 40% in 100 trials of mechanical and cold stimuli, and 50 trials of chemical stimuli. The results from this experiment were that the supra-threshold stimuli (mechanical, chemical, and cool) were detected differently from each other, though the intensities were matched and scaled (Figure 3.4). However, the bias calculated was similar across stimulus types and the bias was towards the

stricter side of the criterion as the experiment designed (Figure 3.6). There also appeared to be some difficulty in the detection of supra-threshold stimuli by a few participants, resulting in lower average detectability for the group. In addition to estimating the sensory and decisional aspects, these SDT estimates also allowed testing specific theories that were based on previous literature on corneal neurophysiology.

As mentioned earlier, the comparison between the stimulus types was not feasible with detection thresholds. But with the SDT estimates, comparisons could be performed as d' and bias has the same units for all stimulus types. Based on the literature, three hypotheses were proposed (Section 3.2.1(restrictive hypothesis)) and the support for these hypotheses by the SDT estimates was analyzed using Bayesian analysis. The nerve conduction hypothesis tested the physiological theory that two kinds of nerve fibers exist in the human corneal sensory processing which is similar to other non-primate literature. The second hypothesis on the nociception tested the physiological theory that there are two kinds of pain perception (nociceptive and non-nociceptive) in the human corneal sensory processing similar to non-primate literature. The third hypothesis tested the physical characteristics of the esthesiometer stimuli in particular the similarity between mechanical and cold stimuli. Considering the current impossibility of performing in-vivo neurophysiology experiments on human corneas, the results provided a direct test of theories using psychophysical data obtained from human participants instead of electrophysiological data. The analyses showed support for both nerve conduction and nociception theories but did not find any support for using cold stimuli as a replacement for mechanical stimuli. The d' of cold and mechanical stimuli were different from each other. This indicates the presence of a similar neural mechanism in humans as in animals (as previously hypothesized by Feng and Simpson[17]) but there are still questions on the density of these receptors and their receptive fields and the higher-order processing mechanism of these pneumatic stimuli.

The chapter 3 experiments provided a lot of insights into the psychophysical, sensory, decisional, and neurophysiological aspects of ocular surface sensory processing of pneumatic,

however, there were a few limitations in the study to consider for further experimentation. The detection parameters were estimated only for supra-threshold stimuli that were scaled to 1.5x the detection threshold and the responses provided by the participants were binary (yes/no) which does not help in identifying the changes in the criterion that may have occurred during the experiment, as they reported the stimuli as only presence/absence. There was also a different group of participants for each stimulus type but the male to female ratio (roughly 6-7 male and 3-4 female) and age group was similar for all three stimulus types. Less than half the subjects were repeated for each stimulus type, and since there is no priori reason to suppose that d' would be correlated across stimulus types, unpaired analysis were used. This was later addressed in the MSDT experiments (chapter 4) were same set of participants participated in experiments of all three stimulus types. In addition, a lack of understanding of the empirical effect of psychological factors on sensory processing of pneumatic stimuli provided the impetus for the development of hypotheses related to the effects of decision making and anxiety on ocular surface sensing: This, in turn, resulted in the inclusion of psychometric instruments examining decision and anxiety predictors. What was therefore done was a multi-intensity multi-criteria SDT (MSDT) experiment (chapter 4), with additional assessments of effects of clinical (dry eye symptoms and contact lens wear) and psychological (decision and anxiety) predictors on the sensory and bias estimates.

There were a few basic theoretical predictions, based on detection theory that provide simple tests of internal validity of the experimental methods and/or outcomes, that can be examined in Chapter 4. First, the detectability of pneumatic stimuli increased systematically with an increase in the intensity of stimuli. Of course, this is a seemingly trivial result, but using the rating methods chosen and the intensities selected, there is no prior necessity for this to have been the case. Second, bias also changed systematically. These results were observed for all three stimulus types and they illustrate, for the first time, that systematic changes in both sensory and decisional aspects of ocular surface sensing are in line with what would be expected directly from signal detection theory.

These results are perhaps more crucial due to the lack of human corneal electrophysiological studies conducted to understand the noise characteristics, signal conductance, and higher-order processing of the stimuli. In addition to these issues, I speculated a noisy corneal sensory processing because the detection of the stimuli could be easily masked by the normal background process like the detection of tear film breakup, background activity of cold neurons, and detection of stimulations caused by blinking/ ambient room conditions. Contrary to speculations, the group's MSDT data for all three stimulus types followed the assumptions of SDT and the d_a for each stimulus intensity was significantly different from the other (Figure 4.3). The ROC curves from the group data showed a good separation of the curves between the stimulus intensities with very high R-square values (Figure 4.6, Figure 4.10, Figure 4.16). The slopes of the z-ROCs were very close to 1 as well. These indicate the adherence of data to Gaussian distribution and equal variance. However, the MSDT data of a few participants deviated from what might be predicted if the noise and signal + noise distributions were gaussian mainly when the false alarm rates were low resulting in crowding of all data points at one end of the distribution. This might be because there was a relatively low number of trials for each stimulus (especially for chemical stimuli) compared to the grouped data. The number of trials (when considered for individual intensity) was also lower than traditional SDT experiments which suggests using more number of trials.[27–29] More experiments examining the number of trials and intensities are needed to understand the effect of these parameters on the detection of pneumatic stimuli.

Among the ROC curves obtained for different stimulus intensities, the group ROC curve for the cold sub-threshold stimulus was slightly negative. Cold is a non-nociceptive stimulus and the sub-threshold intensity might be very difficult to differentiate from noise and so sometimes might be anticipated to produce a low negative d' in the same way as you might expect a stimulus that is difficult to differentiate from noise to produce a low positive d'. The data were not removed, as this change is happening only for this particular intensity among all others tested. In addition, cold receptors have a background activity in general and perhaps this

might have added more difficulty to detect a sub-threshold stimulus. Also, as is apparent in the figure of the cold transducer function (Figure 4.7) the slightly negative d' in no way detracts from the very good, almost perfectly linear relationship. Even though at the sub-threshold level an "almost impossible" detectability was estimated, the fact that its standard error of the estimate of the mean d' included zero, illustrates that its computed value should not be over interpreted. Finally, even though it is negative, there were also a number of significant relationships observed between the log-likelihood ratio for the sub-threshold stimulus and psychological parameters.

The MSDT experiments were also conducted with an aim of analyzing the effects of some clinical parameters. These were the presence of symptoms of dry eye, and contact lens wear. Both of these predictors have been shown to have contrasting effects on corneal sensitivity.[12,26,30–43] In my experiments, only cold thresholds were found to be different between the groups based on symptoms, and no effect of contact lens wear was seen for any of the stimulus type tested. In the comparison between stimulus intensities and d_a, neither symptoms nor lens wear showed significant interactions for any stimulus type but there were a few significant interactions observed in the comparison between stimulus intensity and bias. This indicates that there is no effect of the predictors on the detection of stimulus but the predictors might have an effect on the bias. This is significant because bias can influence the threshold in the classical psychophysical methods and that might be the source of contrasting results from the studies that evaluated the effect of predictors on corneal sensitivity.

The contact lens wearers used stricter bias compared to non-contact lens wearers for chemical stimuli of threshold intensity (Figure 4.13). However, the bias was similar for chemical stimuli of 2x threshold intensity. A similar but the opposite effect was seen in the comparison between groups based on symptoms. The symptomatic participants used stricter bias compared to asymptomatic participants for chemical stimuli of 2x threshold intensity and no difference in bias for threshold intensity stimuli. The above interaction was observed only for the chemical stimuli and similar effects were not observed for mechanical and cold stimuli.

The differences in bias was possibly due to the difference in the type of discomfort experienced by the two groups of participants. Both symptomatic participants and contact lens wearers experience some level of discomfort, but whether they experience a similar type of discomfort is unknown. I speculate that habituated contact lens wearers suppress the low-level discomfort and have a stricter bias when they respond to lower intensity stimuli as the sensation produced by the lower intensity stimuli might get suppressed or participants might think the sensation as a result of contact lens-related dryness. On the other hand, the symptomatic participants experience higher levels of discomfort and have a stricter bias in response to more intense stimuli. More experimentation is needed to further understand the bias in each of these groups.

Along with the MSDT OSSP experiment, anxiety and general decision-making were evaluated. I expected the results, using the instruments I selected, to be in line with previous validation work, therefore demonstrating both internal and external validity of the data I collected: Fortunately, and buttressing these expectations, both the anxiety and decision data were remarkably similar, in many ways, to the previous work used to demonstrate the instruments' validity.[44,45] Since these validation studies were not conducted on a Canadian sample, and in a way not resembling an experimental setting similar to my experiment, the external validity of the scores helped reassure me about the quality of the metrics I obtained. In general, my sample had higher vigilance scores compared to other dimensions of decision-making and had more cognitive trait anxiety compared to somatic trait anxiety. Though the somatic component of state anxiety declined with study visits, the cognitive component stayed the same throughout the study: This result was in accord with a broad theory that we have, that participants' anxiety *should* lessen during the experiment, as they get more familiar with the experimental procedures, and realize that the stimuli are less painful than their imagined stimulus intensity/painfulness *before* they began the experiments. This perhaps indicates that participants might feel less anxious in some ways as the study progressed, but at a cognitive level might understand that some aspects of their anxiety are unchanged: This difference (or perhaps even conflict in aspects of anxiety) might very well be expected to influence their

decisions, and so affect the psychophysical results, as was found. This theoretical expectation is again supported in the number of significant relationships observed between the anxiety and *bias/decisional* metrics but not with the *sensory* metrics. Consistent negative relationships were observed between anxiety and liberal bias metric (*c*1) indicating that more anxious participants adopted more liberal criteria. A few positive relationships were observed between anxiety and strict bias metric (*c*4) indicating that anxious participants were adopting stricter biases than less anxious participants. On the other hand, the decision-making showed a different relationship with bias metrics compared to anxiety. The bias for non-noxious cold stimuli had more positive relationships with DM metrics, while the bias for noxious mechanical and chemical stimuli showed all negative relationships with DM metrics. Of these relationships with the decision metrics, a majority of those relationships for the cold stimuli were observed for the stricter end of the bias (*c*4) whereas the relationships for nociceptive mechanical and chemical stimuli were observed for the liberal end of the bias (*c*1) (Table 4-5).

The state anxiety was measured before and after threshold experiments at each study visit and the progression of the state anxiety was evaluated along with the interaction of clinical factors. Both contact lens wearers and symptomatic participants have shown significant interaction in the progression of state anxiety levels with study visits. The cognitive and somatic components of state anxiety were similar for the control group (either asymptomatic or non-contact lens wearers), whereas the symptomatic group and contact lens wearing group had cognitive and somatic scores different from each other. The reason for these interactions is unknown and these relationships warrant future studies to analyze the effect of psychological parameters in OSSP and inclusion of psychological estimates in all OSSP studies.

In summary, I made a number of important scientific discoveries in my thesis: First, the column of air that is the pneumatic stimulus is more complex than has previously been assumed. The psychophysical results show for the first time that signal detection theory applies to complex stimulus intensities and criteria/biases adopted in my experiment. Also, contact lens wear and dry eye symptoms can be much more fully explored with these signal detection

methods than with traditional psychophysical tools. Finally, and importantly, relatively uncomplicated psychometric instruments may be used to show how complicated decision making and anxiety seem to be during these types of pneumatic esthesiometry experiments, and that these psychometric variables are related to detection theory detectability and bias outcomes estimated when ocular surface sensory processing occurs.

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Chapter 1:

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Appendix A Questionnaires

DEQ-5 Questionnaire:

DEQ 5

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, **how often** did your eyes feel discomfort?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   b. When your eyes felt discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

3. Question about **WATERY EYES:**
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total
___+___+___+___+___= ___

Melbourne Decision Making Questionnaire

PART II Name: Participant # Date:

Instructions:
People differ in the way they go about making decisions. Please indicate how you make decisions by ticking for each question the response which best fits your usual style.

When making decisions -		**True for me**	**Sometimes true**	**Not true for me**
1.	I feel as if I'm under tremendous time pressure when making decisions	[ ]	[ ]	[ ]
2.	I like to consider all of the alternatives	[ ]	[ ]	[ ]
3.	I prefer to leave decisions to others	[ ]	[ ]	[ ]
4.	I try to find out the disadvantages of all alternatives	[ ]	[ ]	[ ]
5.	I waste a lot of time on trivial matters before getting to the final decision	[ ]	[ ]	[ ]
6.	I consider how best to carry out the decision	[ ]	[ ]	[ ]
7.	Even after I have made a decision I delay acting upon it	[ ]	[ ]	[ ]
8.	When making decisions I like to collect lots of information	[ ]	[ ]	[ ]
9.	I avoid making decisions	[ ]	[ ]	[ ]
10.	When I have to make a decision I wait a long time before starting to think about it	[ ]	[ ]	[ ]
11.	I do not like to take responsibility for making decisions	[ ]	[ ]	[ ]
12.	I try to be clear about my objectives before choosing	[ ]	[ ]	[ ]
13.	The possibility that small things might go wrong causes me to swing abruptly in my preferences	[ ]	[ ]	[ ]
14.	If a decision can be made by me or another person I let the other person make it	[ ]	[ ]	[ ]

When making decisions -		**True for me**	**Sometimes true**	**Not true for me**
15.	Whenever I face a difficult decision I feel pessimistic about finding a good solution	[ ]	[ ]	[ ]
16.	I take a lot of care before choosing	[ ]	[ ]	[ ]
17.	I do not make decisions unless I really have to	[ ]	[ ]	[ ]
18.	I delay making decisions until it is too late	[ ]	[ ]	[ ]
19.	I prefer that people who are better informed decide for me	[ ]	[ ]	[ ]
20.	After a decision is made I spend a lot of time convincing myself it was correct	[ ]	[ ]	[ ]
21.	I put off making decisions	[ ]	[ ]	[ ]
22.	I cannot think straight if I have to make decisions in a hurry	[ ]	[ ]	[ ]

State-Trait Inventory for Cognitive and Somatic Anxiety- Trait Anxiety:

Ref _____ Date _____

STICSA
General Mood Questionnaire

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate *how often* each statement is true of you (eg, 1 = almost never, 4 = almost always**).** *Please read each statement carefully and circle the number which best indicates* **how often*, in general, the statement is true of you.***

	Almost never	Occasionally	Often	Almost always
In general.....				
1. My heart beats fast	1	2	3	4
2. My muscles are tense	1	2	3	4
3. I feel agonised over my problems	1	2	3	4
4. I think that others won't approve of me.	1	2	3	4
5. I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
6. I feel dizzy.	1	2	3	4
7. My muscles feel weak	1	2	3	4
8. I feel trembly and shaky	1	2	3	4
9. I picture some future misfortune.	1	2	3	4
10. I can't get some thought out of my mind.	1	2	3	4
11. I have trouble remembering things	1	2	3	4
12. My face feels hot	1	2	3	4
13. I think that the worst will happen.	1	2	3	4
14. My arms and legs feel stiff	1	2	3	4
15. My throat feels dry	1	2	3	4
16. I keep busy to avoid uncomfortable thoughts.	1	2	3	4
17. I cannot concentrate without irrelevant thoughts intruding	1	2	3	4
18. My breathing is fast and shallow	1	2	3	4
19. I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
20. I have butterflies in the stomach.	1	2	3	4
21. My palms feel clammy	1	2	3	4

State-Trait Inventory for Cognitive and Somatic Anxiety- State Anxiety- Version 1:

Q.1

Participant ID: _____ Study visit #_____

Name : _____ Date: _____

STICSA – State

Your mood at this moment

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate the degree with which each statement is self-descriptive of your mood at this moment (eg, 1= not at all, 4 = very much so). Please read each statement carefully and circle the number which best indicates how you feel right now, at this very moment, even if this is not how you usually feel

		Not at all	A little	Moderately	Very much so
In general.....					
1.	My heart beats fast	1	2	3	4
2.	My muscles are tense	1	2	3	4
3.	I feel agonised over my problems	1	2	3	4
4.	I think that others won't approve of me.. . . .	1	2	3	4
5.	I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
6.	I feel dizzy.	1	2	3	4
7.	My muscles feel weak	1	2	3	4
8.	I feel trembly and shaky.	1	2	3	4
9.	I picture some future misfortune.	1	2	3	4
10.	I can't get some thought out of my mind. . . .	1	2	3	4
11.	I have trouble remembering things	1	2	3	4
12.	My face feels hot	1	2	3	4
13.	I think that the worst will happen.	1	2	3	4

Q.1

14.	My arms and legs feel stiff	1	2	3	4
15.	My throat feels dry	1	2	3	4
16.	I keep busy to avoid uncomfortable thoughts. . . .	1	2	3	4
17.	I cannot concentrate without irrelevant thoughts intruding .	1	2	3	4
18.	My breathing is fast and shallow	1	2	3	4
19.	I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
20.	I have butterflies in the stomach.	1	2	3	4
21.	My palms feel clammy.	1	2	3	4

State-Trait Inventory for Cognitive and Somatic Anxiety- State Anxiety- Version 2:

Q.2

Participant ID: _____ Study visit #_____

Name : _____ Date: _____

STICSA – State

Your mood at this moment

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate the degree with which each statement is self-descriptive of your mood at this moment (eg, 1= not at all, 4 = very much so). Please read each statement carefully and circle the number which best indicates how you feel right now, at this very moment, even if this is not how you usually feel

		Not at all	A little	Moderately	Very much so
In general.....					
1.	My muscles are tense	1	2	3	4
2.	I can't get some thought out of my mind. . . .	1	2	3	4
3.	My heart beats fast	1	2	3	4
4.	I feel agonised over my problems	1	2	3	4
5.	I think that the worst will happen.	1	2	3	4
6.	I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
7.	I feel dizzy.	1	2	3	4
8.	I feel trembly and shaky.	1	2	3	4
9.	I think that others won't approve of me.. . . .	1	2	3	4
10.	I picture some future misfortune.	1	2	3	4
11.	My face feels hot	1	2	3	4
12.	I have trouble remembering things	1	2	3	4
13.	My arms and legs feel stiff	1	2	3	4

Q.2

14.	My muscles feel weak	1	2	3	4
15.	My throat feels dry	1	2	3	4
16.	My breathing is fast and shallow	1	2	3	4
17.	I keep busy to avoid uncomfortable thoughts. . . .	1	2	3	4
18.	I cannot concentrate without irrelevant thoughts intruding .	1	2	3	4
19.	My palms feel clammy.	1	2	3	4
20.	I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
21.	I have butterflies in the stomach.	1	2	3	4

State-Trait Inventory for Cognitive and Somatic Anxiety- State Anxiety- Version 3:

Q.3

Participant ID: _____ Study visit #_____

Name : _____ Date: _____

STICSA – State

Your mood at this moment

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate the degree with which each statement is self-descriptive of your mood at this moment (eg, 1= not at all, 4 = very much so). Please read each statement carefully and circle the number which best indicates how you feel right now, at this very moment, even if this is not how you usually feel	Not at all	A little	Moderately	Very much so
In general.....				
1. I picture some future misfortune.	1	2	3	4
2. My heart beats fast	1	2	3	4
3. My palms feel clammy.	1	2	3	4
4. My muscles are tense	1	2	3	4
5. I cannot concentrate without irrelevant thoughts intruding .	1	2	3	4
6. I feel agonised over my problems	1	2	3	4
7. I can't get some thought out of my mind. . . .	1	2	3	4
8. I think that others won't approve of me.. . . .	1	2	3	4
9. I keep busy to avoid uncomfortable thoughts. . . .	1	2	3	4
10. I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
11. My muscles feel weak	1	2	3	4
12. I think that the worst will happen.	1	2	3	4
13. I feel trembly and shaky.	1	2	3	4

Q.3

14.	I have trouble remembering things	1	2	3	4
15.	I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
16.	My face feels hot	1	2	3	4
17.	My throat feels dry	1	2	3	4
18.	I have butterflies in the stomach.	1	2	3	4
19.	My breathing is fast and shallow	1	2	3	4
20.	I feel dizzy.	1	2	3	4
21.	My arms and legs feel stiff	1	2	3	4

State-Trait Inventory for Cognitive and Somatic Anxiety- State Anxiety- Version 4:

Q.4

Participant ID: _____ Study visit #_____

Name : _____ Date: _____

STICSA – State

Your mood at this moment

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate the degree with which each statement is self-descriptive of your mood at this moment (eg, 1= not at all, 4 = very much so). Please read each statement carefully and circle the number which best indicates how you feel right now, at this very moment, even if this is not how you usually feel

		Not at all	A little	Moderately	Very much so
In general.....					
1.	My palms feel clammy.	1	2	3	4
2.	I have butterflies in the stomach.	1	2	3	4
3.	I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
4.	My breathing is fast and shallow	1	2	3	4
5.	I cannot concentrate without irrelevant thoughts intruding .	1	2	3	4
6.	I keep busy to avoid uncomfortable thoughts. . . .	1	2	3	4
7.	My throat feels dry	1	2	3	4
8.	My arms and legs feel stiff	1	2	3	4
9.	I think that the worst will happen.	1	2	3	4
10.	My face feels hot	1	2	3	4
11.	I have trouble remembering things	1	2	3	4
12.	I can't get some thought out of my mind. . . .	1	2	3	4
13.	I picture some future misfortune.	1	2	3	4

Q.4

14.	I feel trembly and shaky.	1	2	3	4
15.	My muscles feel weak	1	2	3	4
16.	I feel dizzy.	1	2	3	4
17.	I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
18.	I think that others won't approve of me.. . . .	1	2	3	4
19.	I feel agonised over my problems	1	2	3	4
20.	My muscles are tense	1	2	3	4
21.	My heart beats fast	1	2	3	4

State-Trait Inventory for Cognitive and Somatic Anxiety- State Anxiety- Version 5:

Q.5

Participant ID: _____ Study visit #_____

Name : _____ Date: _____

STICSA – State

Your mood at this moment

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate the degree with which each statement is self-descriptive of your mood at this moment (eg, 1= not at all, 4 = very much so). Please read each statement carefully and circle the number which best indicates how you feel right now, at this very moment, even if this is not how you usually feel	Not at all	A little	Moderately	Very much so
In general.....				
1. I have trouble remembering things	1	2	3	4
2. My face feels hot	1	2	3	4
3. I think that the worst will happen.	1	2	3	4
4. My arms and legs feel stiff	1	2	3	4
5. I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
6. I feel dizzy.	1	2	3	4
7. My muscles feel weak	1	2	3	4
8. I feel trembly and shaky.	1	2	3	4
9. I picture some future misfortune.	1	2	3	4
10. I can't get some thought out of my mind. . . .	1	2	3	4
11. My throat feels dry	1	2	3	4
12. I keep busy to avoid uncomfortable thoughts. . . .	1	2	3	4
13. I cannot concentrate without irrelevant thoughts intruding .	1	2	3	4

Q.5

14.	My breathing is fast and shallow	1	2	3	4
15.	I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
16.	I have butterflies in the stomach.	1	2	3	4
17.	My palms feel clammy.	1	2	3	4
18.	My heart beats fast	1	2	3	4
19.	My muscles are tense	1	2	3	4
20.	I feel agonised over my problems	1	2	3	4
21.	I think that others won't approve of me.. . . .	1	2	3	4

State-Trait Inventory for Cognitive and Somatic Anxiety- State Anxiety- Version 6:

Q.6

Participant ID: _____ Study visit #_____

Name : _____ Date: _____

STICSA – State

Your mood at this moment

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate the degree with which each statement is self-descriptive of your mood at this moment (eg, 1= not at all, 4 = very much so). Please read each statement carefully and circle the number which best indicates how you feel right now, at this very moment, even if this is not how you usually feel

		Not at all	A little	Moderately	Very much so
In general.....					
1.	My heart beats fast	1	2	3	4
2.	My muscles are tense	1	2	3	4
3.	I feel agonised over my problems	1	2	3	4
4.	I think that others won't approve of me.. . . .	1	2	3	4
5.	I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
6.	I feel dizzy.	1	2	3	4
7.	My muscles feel weak	1	2	3	4
8.	I feel trembly and shaky.	1	2	3	4
9.	I picture some future misfortune.	1	2	3	4
10.	I can't get some thought out of my mind. . . .	1	2	3	4
11.	I have trouble remembering things	1	2	3	4
12.	My face feels hot	1	2	3	4
13.	I think that the worst will happen.	1	2	3	4

Q.6

14.	My arms and legs feel stiff	1	2	3	4
15.	My throat feels dry	1	2	3	4
16.	I keep busy to avoid uncomfortable thoughts. . . .	1	2	3	4
17.	I cannot concentrate without irrelevant thoughts intruding .	1	2	3	4
18.	My breathing is fast and shallow	1	2	3	4
19.	I worry that I cannot control my thoughts as well as I would like to.	1	2	3	4
20.	I have butterflies in the stomach.	1	2	3	4
21.	My palms feel clammy.	1	2	3	4

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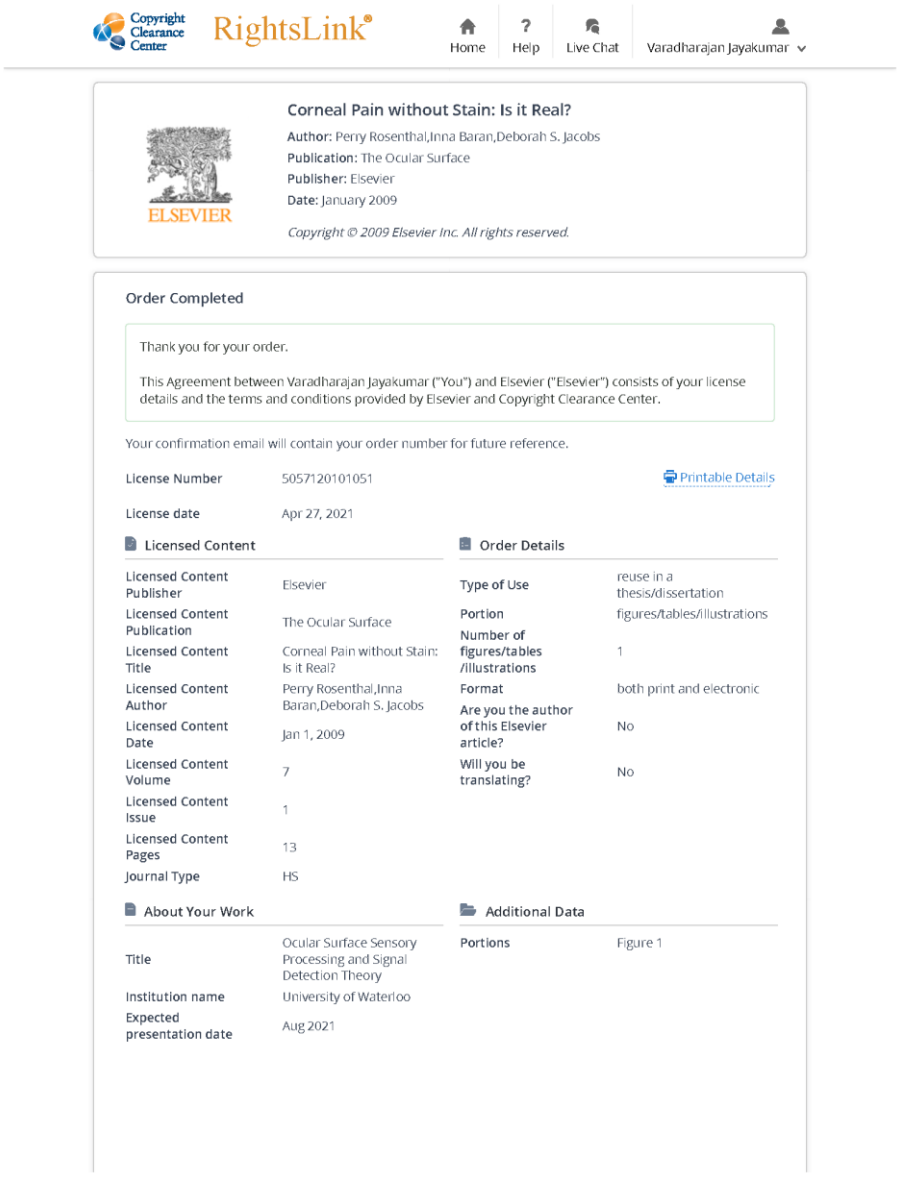

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Corneal Pain without Stain: Is it Real?

Author: Perry Rosenthal,Inna Baran,Deborah S. Jacobs
Publication: The Ocular Surface
Publisher: Elsevier
Date: January 2009

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varadhu Jayakumar

From: Situ, Ping <pingsitu@indiana.edu>
Sent: Tuesday, June 4, 2019 9:41 AM
To: varadhu Jayakumar
Subject: Re: Requesting permission to use a figure from your thesis

Varadhu,

Sure. I am happy to give you permission to use them.

Best regards,

Ping

From: varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca>
Date: Tuesday, June 4, 2019 at 9:29 AM
To: "Situ, Ping" <pingsitu@indiana.edu>
Subject: Requesting permission to use a figure from your thesis

Hi Dr. Situ,
This is Varadharajan Jayakumar from UWaterloo working with Dr. Simpson. Emailing you to request your permission to use the technical diagram of the modified Belmonte esthesiometer from your Ph.D. thesis (page# 24, Figure 2-4) in my manuscript. Please let me know if it is ok to use the diagram. Thank you.

Varadharajan Jayakumar

Copyright for the use of figure 2-3

Varadharajan Jayakumar

From: Morgan Morris <Morgan.Morris@co2meter.com>
Sent: June 28, 2019 2:03 PM
To: varadhu Jayakumar
Subject: RE: Requesting permission to use a photo from the website

Varadhu,

Not a problem.

Should you have any additional information feel free to reach out to me in the meantime.

Best of luck with the research!

Kind Regards,

Morgan

From: varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca>
Sent: Friday, June 28, 2019 1:47 PM
To: Morgan Morris <Morgan.Morris@co2meter.com>
Subject: RE: Requesting permission to use a photo from the website

Thank you Morgan. Thanks for all your help.

Varadhu

Morgan Morris <Morgan.Morris@co2meter.com> wrote:

Good Afternoon Varadhu,

I have checked in with our engineering and production department and they have concluded that the CM-0041, is a solid enclosure around the GC-0016 sensor module also known as the COZIR Wide Range Sensor 100%.

I have included the only documentation we have for this device above.

Please feel free to let us know should you need anything additional!

Kind Regards,

Morgan

From: varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca>
Sent: Thursday, June 27, 2019 4:45 PM
To: Morgan Morris <Morgan.Morris@co2meter.com>
Subject: RE: Requesting permission to use a photo from the website

Thanks. Also, does co2meters.com have an archive of older sensor models. Because, we purchased this sensor about 4 years ago and the model was CM-0041 (100% CO_2 sensor) and I could not find that model in your website now.

1

Varadhu

From: Morgan Morris <Morgan.Morris@co2meter.com>
Sent: Thursday, June 27, 2019 4:40 PM
To: varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca>
Subject: Requesting permission to use a photo from the website

Dear Varadhu,

Yes, if you could simply ensure you site www.co2meter.com and the correct sensor as "CM-0040 - https://www.co2meter.com/products/usb-probe-co2-sensor", we would just need a copy of the documentation once published.

Thank you again.

Kind Regards,

Morgan

From: varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca>
Sent: Thursday, June 27, 2019 4:25 PM
To: Morgan Morris <Morgan.Morris@co2meter.com>
Subject: Requesting permission to use a photo from the website

Hi,
We bought the Co2 sensor (model# CM-0041) from your website to use it in our research. I would like to use the photo of the CO2 sensor in my article. I have referenced the co2meter.com webpage. will that be enough? or do I have to obtain permission to use the photo?

Thanks,
Varadharajan Jayakumar

****

Varadharajan Jayakumar B.S. (Opt), M.Sc. (Vision Science)
Ph.D. Candidate |
School of Optometry & Vision Science | University of Waterloo
200 Columbia St. West, Waterloo, Ontario, N2L 3G1 | Canada
Tel: 519-888-4567 x38959

Permission for randomizing the question order in STICSA questionnaire:

Varadharajan Jayakumar

From: melissa ree <melissa.ree@optusnet.com.au>
Sent: July 6, 2015 8:58 PM
To: varadhu Jayakumar
Subject: Re: Regarding STICSA questionnaire

Hi Varadhu,

I dont think the questionnaire has been administered with different item order but it shouldn't make a difference to its validity.

Kind Regards,
Melissa

Dr Melissa J Ree
Clinical Psychologist

Jeffery&Ree Clinical Psychologists

Hamilton Psychology Practice
11 Hamilton St, SUBIACO,WA, 6008

Murdoch Specialist Centre
78 Farrington Rd, LEEMING 6149

Ph: 6267 6033 fax: 6161 1597
melissa.ree@optusnet.com.au
jefferyreeclinicalpsychologists.com

On 6 Jul 2015, at 10:44 pm, varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca> wrote:

Hi Dr. Ree,
Thanks again for sharing the questionnaire for my study. I finalised my study proposal few days back and I am planning to use the STICSA questionnaire multiple times during a study visit. I was wondering if I could randomise the order of the questions each time. Does randomising affect the validity of the questionnaire?

Regards,
Varadhu

From: varadhu Jayakumar
Sent: June-16-15 10:58 AM
To: melissa ree
Subject: RE: Regarding STICSA questionnaire

Thank you Dr. Ree.

Varadhu

From: melissa ree [mailto:melissa.ree@optusnet.com.au]
Sent: Wednesday, June 03, 2015 9:55 PM
To: varadhu Jayakumar
Subject: Re: Regarding STICSA questionnaire

Hello Varadhu,

No problem, all the best with your research.

Kind Regards,
Melissa

Permission to use MDMQ questionnaire:

Varadharajan Jayakumar

From: Leon Mann <leonm@unimelb.edu.au>
Sent: July 7, 2015 3:13 AM
To: varadhu Jayakumar
Subject: Melbourne Decision Making Questionnaire
Attachments: Cross-cultural Differences in Self-reported Decision-making Style and Confi... EBSCOhost.html; Mann et al JBDM 1997[3].pdf; MDMQUES.pdf; MDMQUES 1997 .SCORING KEY[1].pdf

Dear Varadhu
Thank you for your message.
You are welcome to use the Melbourne Decision Making Questionnaire in your research.
Coould you please let me know what you will be studying in your research.

I have attached the Questionnaire, scoring guide and two journal articles describing the Questionnaire and theoretical model .
Please keep me informed about the results from your study.
I'll be very interested.
Regards

Professor Leon Mann
University of Melbourne

From: varadhu Jayakumar <varadhu.jayakumar@uwaterloo.ca>
Date: Tuesday, 7 July 2015 12:36 am
To: Leon Mann <leonm@unimelb.edu.au>
Subject: RE: Regarding Melbourne decision making questionnaire

Hi Prof. Mann,
I am sending you this email as a reminder to your previous email regarding MDMQ sent on June 06th. Hope you had a nice journey back to Melbourne. It will be great if you could send me a copy of MDMQ when it is possible.

Thanks and regards,
Varadhu