Psychophysical and Clinical Investigations Of Ocular Discomfort

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.

I understand that my thesis may be made electronically available to the public.

Abstract

Purpose

To investigate ocular surface sensations, specifically ocular discomfort using psychophysical and clinical techniques. The measurement of discomfort on the ocular surface has been limited to the use of traditional rating scales until recently. This thesis focuses on the scaling of discomfort using a psychophysical approach and also investigates the less explored area of the influence of blur on ocular discomfort.

The specific aims of each chapter are:

Chapter 2: To evaluate the difference thresholds of the central cornea in lens and non-lens wearers.

Chapter 3: To devise a novel scale for ocular discomfort, relating subjective estimation of discomfort arising from contact lens wear to discomfort produced by the pneumatic stimuli delivered by a modified Belmonte esthesiometer.

Chapter 4: To evaluate the influence of blur on ocular comfort while systematically manipulating vision using habitual refractive correction, induced spatial and optical blur, and under the absence of visual structure.

Chapter 5: To examine if subjects rate discomfort and intensity of suprathreshold pneumatic stimuli differently when viewing clear and defocused targets and to examine the suprathreshold scaling of stimuli under the same visual conditions.

Methods

Chapter 2: The mechanical sensitivity of the central cornea was determined in 12 lens wearers and 12 non-lens wearers using a modified Belmonte pneumatic esthesiometer. The mechanical threshold of the central cornea was first estimated using the method of limits. Then, a series of systematically increasing stimuli were presented, with the first stimuli being 25% less than the threshold. The subjects were asked to compare the intensity of each stimulus with the preceding one and report if any difference in intensity was detectable. The intensities at which the subjects perceived an increased intensity from the previous was recorded. The difference threshold (DL) was the differences between the stimulus intensities at which an increase was perceived and five DLs were measured for each subject. Weber's constants that relate the size of the difference thresholds to the stimulus intensity were derived for each DL level and repeated measures ANOVA was used to compare the Weber's constants in the lens and non-lens wearing groups.

Chapter 3: Twenty seven participants were enrolled for this magnitude matching study. Soft (HEMA) contact lenses of eight different lens designs varying in base curve and diameter were fit on all participants. The study was conducted on two separate days with four lenses randomly assigned on each day. The assigned soft contact lens was placed on the chosen eye and the sensations were measured using a numerical rating scale. Following this, the subjects were asked to regulate the intensity of the pneumatic stimulus using the control dial in order to match the discomfort from the stimulus to the discomfort from contact lens wear. At the completion of magnitude matching, ratings of sensations were again recorded. Pearson product moment correlation was used to correlate the objective esthesiometer matches to the subjective ratings of discomfort reported by each participant. The method of least log squares was used to derive the power exponents as defined by Stevens' power law and analyze the psychophysical functions. Repeated measures ANOVA was used to investigate the effect of lens sequence and session on ocular discomfort with contact lens wear. The impact of lens type and time on discomfort was studied using linear mixed modeling.

Chapter 4: Twenty emmetropic subjects rated ocular comfort, vision and sensation attributes (burning, itching and warmth) under conditions of normal vision, spatial blur and dioptric defocus, each session lasting for five minutes. Subjects viewed digital targets projected from a distance of 3m, and ocular surface sensations, vision were rated using magnitude estimation. Dioptric defocus was produced using +6.00DS contact lenses and equivalent spatial blur was created by spatially blurring the targets. Clear target images were used during dioptric defocus and blurred images during spatial blur session. Comfort was also rated under the absence of visual structure in fifteen of the participants using a ganzfeld and black occluders. Repeated measures ANOVA was used to compare vision and comfort ratings between the different experimental conditions.

Chapter 5: Twenty one participants were enrolled. Ocular discomfort was produced by delivering mechanical stimuli from a pneumatic esthesiometer, and participants were asked to rate the intensity of stimulus and the discomfort induced by it under clear and defocused visual conditions. Esthesiometry was performed on one eye while the fellow eye viewed either a clear or blurred 6/60 fixation target through a trial lens. For the clear visual condition, the trial lens contained +0.25DS over their distance refractive correction and for the defocused condition, an additional +4.00DS was used. Mechanical thresholds from the central cornea were estimated using ascending methods of limits and then stimuli that were 25%, 50%, 75% and 100 % above threshold were presented in random order. Participants rated intensity and discomfort of each stimulus using a 0-100 numerical scale where 0 indicated no sensation and 100 indicated highest imaginable intensity/discomfort. There were 3 sessions with clear visual conditions and 3 sessions with defocus, in random order.

Results

Chapter 2: The functions relating Weber's constants to stimulus intensities were slightly different in lens and non-lens wearing groups, although the absolute thresholds were similar. Repeated measures ANOVA revealed a significant main effect of DL level on Weber's constant ($p<0.001$), with the Weber's fraction at the first DL being higher than the following DLs. A significant main effect of the group type was also observed, with the lens wearers showing higher Weber's constants than the non-lens wearers ($p=0.02$) However, there was no interaction between DL level and lens wearing group on Weber's constants ($p=0.38$).

Chapter 3: The average and individual psychophysical functions appeared to follow Stevens' power function, with mechanical and chemical stimuli giving rise to different power exponents. Examination of the individual transducer functions revealed that only about half of the subjects were able to match the contact lens sensations to the pneumatic stimulus discomfort, with both mechanical and chemical stimulation. The lens types did not have any impact ($p=0.65$) on the session or sequence in which the lens was presented, although an effect of session and sequence on discomfort was observed. The average discomfort ratings produced by the different lens types were similar. There appeared to be significant effects of time ($p<0.001$) on the reporting of discomfort with lens wear, with the discomfort upon lens insertion rated to be higher than after lenses settling.

Chapter 4: Ratings of vision under spatial blur and dioptric defocus were significantly different ($p<0.001$) from normal vision condition. Vision with dioptric defocus was rated worse ($p<0.001$) than spatial blur. Significant differences in comfort were observed between normal vision and blur, including spatial blur ($p=0.02$) and dioptric defocus ($p=0.001$). However, there was no significant difference ($p=0.99$) in comfort between spatial blur and dioptric defocus. Comfort remained unchanged between normal vision, occluders and ganzfeld although vision was absent in the later two conditions.

Chapter 5: There was no significant difference in mechanical thresholds under clear and defocused conditions with a paired t-test ($p=0.66$) and similar results were obtained with repeated measures ANOVA, with no significant difference in discomfort ($p=0.10$) and intensity ($p=0.075$) ratings between the two visual conditions. However, paired t-test between the derived exponents under clear and defocused conditions showed significant differences for discomfort ($p=0.05$) and no significant difference for the ratings of intensity ($p=0.22$). Comparison of exponents between discomfort and intensity showed a significant difference in both clear ($p=0.02$) and defocus conditions ($p<0.001$).

Conclusions:

Chapter 2: The differential sensitivity of the ocular surface can be successfully measured with a pneumatic esthesiometer and it appears that Weber's law holds true for corneal nociceptive sensory processing. There are subtle differences in mechanical difference thresholds between lens and non-lens wearers suggesting the possibility of different neural activity levels in the two groups.

Chapter 3: Subjective ratings of discomfort can be scaled by corneal esthesiometry in a selective group of people. In the subset of subjects with poorer correlations, perhaps the pneumatic mechanical stimulus was too localized and specific to match the complex sensations experienced while wearing contact lenses. However, there is also a group of subjects who are poor at making judgments about ocular comfort. Hence, the use of special sensory panels should be considered when ocular comfort is the primary outcome.

Chapter 4: There does seem to be an association between clarity of vision and ocular comfort, although the pathways for pain and vision are perhaps exclusive. Interactions between vision and other senses have been reported, but a similar inter-sensory interaction between pain and vision is yet to be clearly demonstrated. The decreased comfort observed in this study might perhaps be due to nocebo or Hawthorne effects.

Chapter 5: Suprathreshold scaling of pneumatic stimuli can vary with the viewing conditions, with defocus associated with higher exponents than clear visual conditions. However, the ratings of comfort appear to be similar under both the conditions. If defocus does affect comfort, it is subtle and does not affect the sensory components, but tiny effects through the affective aspect of pain can contribute to the differences in power exponents. The differences in the perception of comfort do not appear to be attributable to the differences in threshold or sensory intensity.

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Dedication

To my mom, dad, sister, loving husband and my little one

Mom,

If not for your love, support and courage

I would not have come this far!

Table of Contents

AUTHOR'S DECLARATION ii
Abstract iii
Acknowledgements ix
Dedication xi
Table of Contents xii
List of Figures xv
List of Tables xvii
List of Symbols and Abbreviations xviii
Chapter 1 Introduction and Literature review 1
1.1 Pain overview 1
1.1.1 Transmission of pain 2
1.1.2 Affective dimension of pain 5
1.1.3 Theories of pain 5
1.2 Sensory innervations of the cornea 8
1.2.1 Functional properties of ocular sensory neurons 10
1.3 Psychophysical techniques of detection and discrimination 13
1.3.1 Methods of psychophysical measurement 16
1.4 Psychophysical scaling 21
1.4.1 Indirect scaling techniques 22
1.4.2 Direct scaling techniques 23
1.4.3 Psychophysical scaling in ocular surface literature 26
1.4.4 Subjective ratings of pain 27
1.5 Measurement of ocular surface sensations 30
1.5.1 Pneumatic esthesiometers 31
1.5.2 Comparison of Cochet-Bonnet and pneumatic esthesiometers 34
1.5.3 Sensations arising from the ocular surface 35
1.5.4 Physiological variations in corneal sensitivity 36
1.5.5 Corneal sensitivity and soft contact lens wear 37
1.6 Ocular discomfort with contact lenses 40
1.7 Vision with contact lenses 41

Chapter 2 Measurement of difference thresholds on the ocular surface 48
2.1 Introduction 48
2.2 Materials and methods.. 50
2.2.1 Subjects 50
2.2.2 The Belmonte esthesiometer 51
2.2.3 Procedures 52
2.2.4 Data analysis.. 52
2.3 Results 53
2.4 Discussion 56
Chapter 3 Psychophysical scaling of ocular discomfort with contact lenses 60
3.1 Introduction 60
3.2 Materials and methods.. 63
3.2.1 Subjects 63
3.2.2 Contact Lenses.. 63
3.2.3 The Belmonte esthesiometer 64
3.2.4 Numerical rating scale 65
3.2.5 Procedures 65
3.3 Data analysis.. 66
3.4 Results 67
3.4.1 Scaling of subjective and objective measurements of ocular discomfort..................... 67
3.4.2 Group average scale for ocular discomfort... 70
3.4.3 Multiple regression analysis of the relationship between ocular discomfort and other sensations.. 75
3.4.4 Session effect on ocular discomfort ratings 77
3.4.5 Effect on lens type on ocular discomfort 79
3.4.6 Effect of time on ocular discomfort ratings 81
3.5 Discussion 81
Chapter 4 Influence of vision on ocular comfort ratings.. 90
4.1 Introduction 90
4.2 Part one.. 93
4.2.1 Materials and methods... 93
4.2.2 Procedures 94

4.2.3 Data analysis 95
4.2.4 Results 95
4.2.5 Discussion 102
4.3 Part Two 103
4.3.1 Materials and methods 103
4.3.2 Results 106
4.4 Discussion 111
Chapter 5 Suprathreshold scaling of ocular discomfort with blur 116
5.1 Introduction 116
5.2 Materials and methods 118
5.2.1 Subjects 118
5.2.2 The Belmonte esthesiometer 119
5.2.3 Trial lenses and visual conditions 119
5.2.4 Procedures 119
5.2.5 Data analysis 120
5.3 Results 120
5.4 Discussion 125
Chapter 6 General Discussion and Conclusions 132
Bibliography 144
Appendix A 192

List of Figures

Figure 1-1: Illustration of the pathway for pain 4
Figure 1-2: Theories of pain 7
Figure 1-3: Illustration of morphologically distinct nerve fibre patterns in rabbits 10
Figure 1-4: Functional types of sensory neurons innervating the eye 13
Figure 1-5: Sample data showing Weber's fraction over a range of stimulus intensities 15
Figure 1-6: The psychophysical function for determining the absolute threshold using the method of constant stimuli 18
Figure 1-7: Example of discrimination scale relating the stimulus intensity with the number of JNDs above absolute threshold 23
Figure 1-8: Magnitude estimation of discomfort as a function of stimulus intensity on the human cornea 25
Figure 1-9: Construction of the pneumatic Belmonte esthesiometer 33
Figure 1-10: Custom software of the computer controlled Waterloo Belmonte esthesiometer 34
Figure 2-1: Mean absolute thresholds in lens and non-lens wearers 54
Figure 2-2: Mean difference thresholds in lens and non-lens wearers 54
Figure 2-3: Weber fractions for different stimulus intensities in the group of non-lens wearers...55
Figure 2-4: Weber fractions for different stimulus intensities in the group of lens wearers. 55
Figure 3-1: Corneal transducer function of a single participant with mechanical and chemical stimulation 68
Figure 3-2: Psychophysical scale for ocular discomfort: mean discomfort ratings are related to mean pneumatic mechanical stimulus strength 71
Figure 3-3: Psychophysical scale for ocular discomfort: mean discomfort ratings are related to mean pneumatic chemical stimulus strength 72
Figure 3-4: Group mean psychophysical scale (in log units) relating discomfort from contact lens wear and corneal esthesiometry with mechanical stimulation 73
Figure 3-5: Group mean psychophysical scale (in log units) relating discomfort from contact lens wear and corneal esthesiometry with chemical stimulation 73
Figure 3-6: Magnitude ordered psychophysical scale for ocular discomfort relating contact lens discomfort and mechanical pneumatic stimulus strength 74
Figure 3-7: Magnitude ordered psychophysical Scale for ocular discomfort relating contact lens discomfort and chemical pneumatic stimulus strength 75

Figure 3-8: Comparison of discomfort ratings across different sessions and lens sequence for mechanical and chemical stimulation 78
Figure 3-9: Discomfort ratings with lenses between mechanical and chemical stimulus sessions 78
Figure 3-10: Effect of lens type on session and sequence of lens presentation 79
Figure 3-11: Effect of different lens types on mean ocular discomfort ratings in mechanical session 80
Figure 3-12: Effect of different lens types on mean ocular discomfort ratings in chemical session 80
Figure 3-13: Mean discomfort ratings for all lens types at different measurement intervals. 81
Figure 4-1: Schematic design of part one of the experiment 95
Figure 4-2: Mean ocular sensation ratings in the right and left eyes under different experimental conditions 96
Figure 4-3: Mean numerical ratings of vision under different experimental conditions 98
Figure 4-4: Mean ratings of comfort under different experimental conditions 100
Figure 4-5: Plot illustrating the interaction of vision and comfort under different experimental conditions 101
Figure 4-6: Mean ocular comfort ratings in the right and left eyes 102
Figure 4-7: Schematic design of part two of the experiment 105
Figure 4-8: Mean ocular sensations in the right and left eyes under different experimental conditions 106
Figure 4-9: Plot illustrating the interaction of vision and discomfort under different experimental conditions 109
Figure 4-10: Mean ocular comfort ratings in the right and left eyes 110
Figure 4-11: Association between vision and comfort ratings under dioptric defocus 110
Figure 5-1: Mean mechanical threshold in clear and defocused visual conditions 121
Figure 5-2: Mean ratings of discomfort under clear and defocused conditions 123
Figure 5-3: Mean ratings of intensity under clear and defocused conditions 123
Figure 5-4: Mean discomfort and intensity ratings under clear visual condition 124
Figure 5-5: Mean discomfort and intensity ratings under defocused condition 125

List of Tables

Table 1-1: Literature review on corneal sensitivity measurements with contact lens wear 38
Table 1-2: Literature review on ocular discomfort with contact lenses 43
Table 3-1: Power exponents of individual psychophysical functions with mechanical stimuli 69
Table 3-2: Power exponents of individual psychophysical functions with chemical stimuli........ 70
Table 3-3: Summary of multiple regression statistics for the dependant variable: discomfort with contact lenses and flow rate for pneumatic stimulation 76
Table 4-1: List of experimental conditions that showed significant differences in ratings of vision between condition I and condition II.. 97
Table 4-2: List of experimental conditions that showed significant differences in comfort between condition I and condition II. 99
Table 4-3: List of experimental conditions that showed significant differences in vision between condition I and condition II 107
Table 4-4: List of experimental conditions that showed significant differences in comfort between condition I and condition II 109
Table 5-1: Mean power exponents for clear and defocused visual conditions............................ 122
Table 6-1: Sample size calculation... 133
Table 6-2: Post hoc power calculation 133

List of Symbols and Abbreviations

^	Raised to the power of
↑	Increase
↓	Decrease
ACC	Anterior Cingulate Cortex
ANOVA	Analysis of variance
C-B	Cochet-Bonnet esthesiometer
CCK	Cholecystokinin
CE	Constant error
CO_2	Carbon dioxide
CRCERT	The Cooperative Research Centre for Eye Research and Technology
CSF	Contrast sensitivity function
dk	Oxygen permeability
DL	Difference threshold
EW	Extended wear
H_2O_2	Hydrogen peroxide

HEMA	Polymacon
IASP	International association for the study of pain
IU	Interval of uncertainty
JND	Just noticeable difference
L_l	Lower limen
L_u	Upper limen
min	Minute
ml	Millilitre
MPDS	Multipurpose solution
NaCl	Sodium hydrochloride
NIBUT	Non-invasive tear breakup time
NRS	Numerical rating scale
PCV	Proportional directional control valve
PFC	Prefrontal Cortex
PI	Posterior Insula
PO	Parietal Operculum

PSE	Point of subjective equality
RGP	Rigid gas permeable lens
RL	Absolute threshold
SCL	Soft contact lens
SEP	Subepithelial plexus
SG	Substantia gelatinosa
St	Standard stimulus intensity
T	Transmission cells
VAD	Verbal analogue scale with descriptors
VAS	Visual analogue scale
VRS	Verbal rating scale

Chapter 1

Introduction and Literature review

Mild pain is referred to as ocular discomfort in the field of optometry, especially in the contact lens literature. Until recently, the source of ocular discomfort has been attributed to the activation of sensory nerve endings on the ocular surface. This thesis explores the sensory as well as affective dimension of pain and its contribution to the sensation of ocular discomfort.

1.1 Pain overview

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue-damage or described in terms of such damage"[1]. Pain is a subjective, perceptual experience that has two defining properties: 1) bodily sensation 2) an affective component. In 1900, Sherrington[2] proposed affect to be an attribute of all sensations, while Hardy, Wolff and Goodell[3] suggested that pain consists of sensory components related to stimulation of sensory nerve endings and reaction/processing components embodying distress and emotional reactions. Beecher[4] also had a similar view using the terms "primary" and "secondary" pain components. Tursky[5] referred to intensity (quantitative), sensory (qualitative) and reactive (agony, distress) components of pain. Melzack and Casey[6] proposed an interactive model and they described pain in terms of three hierarchical levels: a sensory-discriminative component (e.g., location, intensity, quality), a motivational–affective component (e.g., depression, anxiety), and a cognitive-evaluative component (e.g., thoughts concerning the cause and significance of the pain). Pain, therefore encompasses sensory, emotional, and cognitive components that contribute to the transmission and modulation of painful stimuli, mediated through the nociceptor neurons, the spinal cord processes, and the cerebral or brain processes.

Pain can be broadly divided into nociceptive, neuropathic, psychogenic, mixed, or idiopathic types of pain based on the clinical characteristics. Nociceptive pain is a consequence of the activation of nociceptive afferents of the sensory system by noxious stimuli and the pain can be measured by the methods applied in sensory physiology[7-9]. Neuropathic pain occurs as a result of direct injury or dysfunction of the central nervous system or the peripheral nerves[10]. The pain is sometimes disproportionate to the degree of tissue damage and it can occur without nociception, thus serving no protective function. The components of continued nociceptive pain may also coexist with a component of neuropathic pain. The experience of persistent pain can induce disturbances in mood (reactive depression or anxiety), impaired coping and other processes, which in turn can worsen pain and pain-related distress[11]. When pain is predominantly sustained by psychological factors, the phenomenon is termed as 'psychogenic pain' and when reasonable inferences about the supporting pathophysiology of a pain syndrome cannot be made, and there is no positive evidence that the etiology is psychiatric, the pain is referred to as "idiopathic".

1.1.1 Transmission of pain

Pain occurs as a result of primary activation of visceral or somatic nociceptors, by disease or trauma or from potentially damaging stimuli (nocigenic or nociceptive pain) or as a result of actual damage to the peripheral or central nervous system[7]. The structures involved in the complex process of pain include sensory receptors, their associated afferent nerve fibres, the dorsal horns, ascending and descending pathways, the reticular formation in the midbrain and medulla, the thalamus, the limbic system and the cerebral cortex. Nociceptors are specialized, free nerve endings that convert (transduce) a variety of stimuli into nerve impulses, which the brain interprets to produce the sensation of pain[8]. Based on the terminal of the nerve fibres, nociceptors can be classified as: a) C fibres that are small diameter, unmylineated nerves that conduct impulses slowly and b) Aδ fibres that are large diameter, mylineated and rapidly conducting nerves[7, 8, 12, 13]. The Aδ fibres mediate the fast, pricking quality of pain while the C fibres are responsible for the slower, burning quality of pain.

The physiology of normal pain transmission begins with the transduction of pain signals from the nociceptors to electrical information and conduction of electrical activity along the first-order afferent neurons to the central nervous system. Specific receptors are responsible for noxious mechanical, chemical and thermal stimuli and respond to stimuli of particular amplitude when applied to the receptor at the site. Sufficient stimulation of the receptor causes depolarization of the nociceptors and the nociceptive axon carries the electrical impulses from the periphery into the dorsal horn of the spinal cord to make connections directly, and indirectly, through spinal interneurons, with the second-order afferent neurons in the spinal cord. Second-order neurons ascend mostly via the spinothalamic tract up the spinal cord and terminate in higher neural structures, including the thalamus of the brain, thereby transmitting impulses from the spinal cord to the brain. Third-order neurons originate from the thalamus and transmit their signals to the cerebral cortex. Numerous supraspinal control areas—including the reticular formation, midbrain, thalamus, hypothalamus, the limbic system of the amygdala and cingulate cortex, basal ganglia, and cerebral cortex are involved in the modulation of pain. Neurons originating from these cerebral areas synapse with the neuronal cells of the descending spinal pathways that terminate in the dorsal horn of the spinal cord leading to the perception of pain[14, 15]. Figure 1-1 is an illustration of the pain pathway.

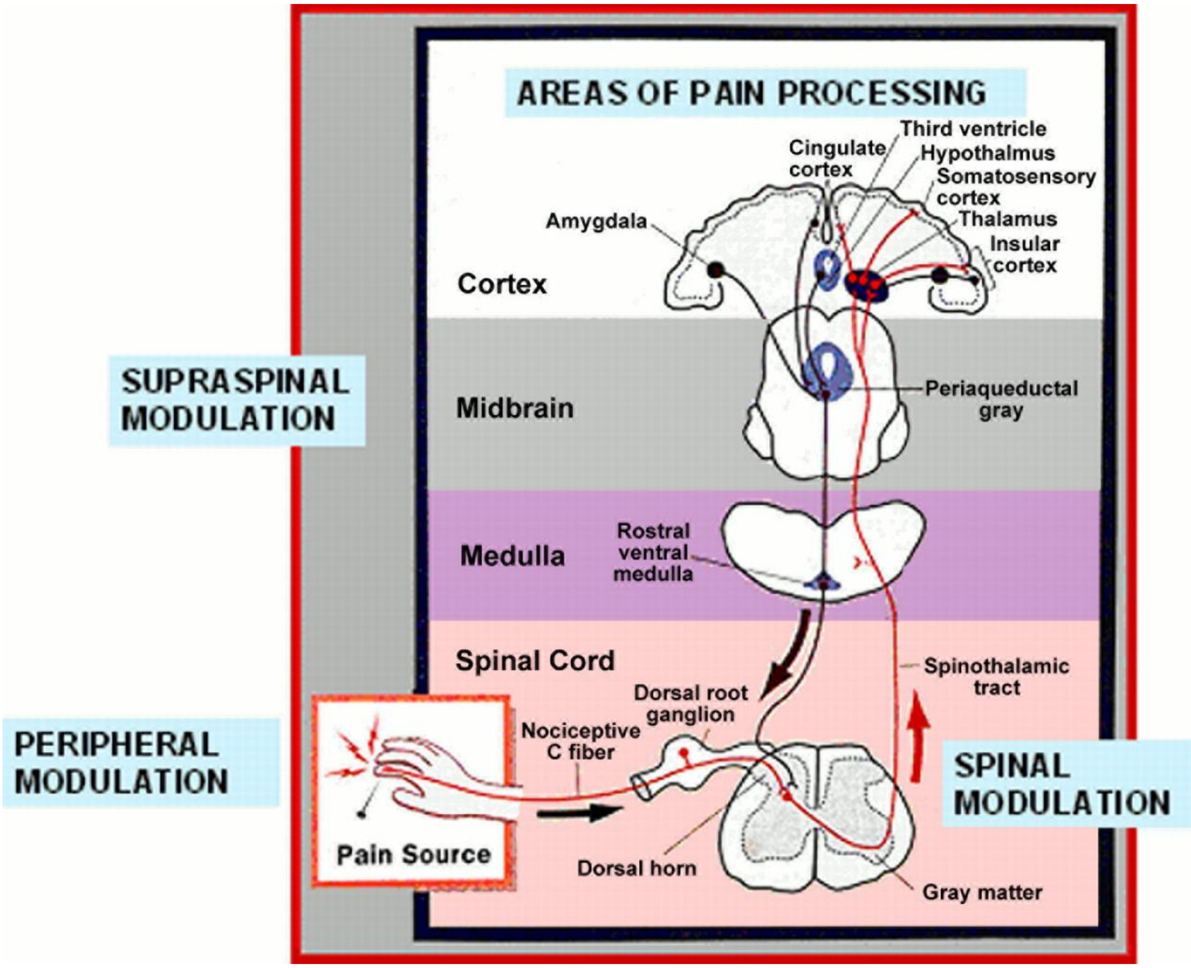

Figure 1-1: Illustration of the pathway for pain

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The trigeminal pathway involves the transmission of noxious stimuli from the face via the nerve fibres originating from the nerve cells in the trigeminal ganglion and cranial nuclei VII, IX, and X[8]. The nerve fibres enter the brainstem and move down to the medulla, where they innervate a subdivision of the trigeminal nuclear complex. From there, the nerve fibres ascend to enter the thalamus on the contra lateral side and the trigeminal information is sent to the primary sensory cortex.

1.1.2 Affective dimension of pain

The affective-motivational component is an essential part of pain sensation that encompasses: unpleasant sensations and emotional reactions, activation or arousal, stimulus-related selective attention, and a drive to terminate the stimulus causing the sensation[16]. Affective pain is associated with the medial nociceptive system, which in turn is connected to the limbic system. Administration of tranquilizers, the placebo effect and hypnotic suggestions may reduce the affective but not sensory component of pain[6]. Spinal pathways to the amygdala, hypothalamus, reticular formation, medial thalamic nuclei, and limbic cortical structures are the regions likely to be associated with the processes related to motivation and affect[17, 18]. Primarily, the activation of the anterior cingulate cortex is presumed to play an important role in the affective component of pain[18].

1.1.3 Theories of pain

1.1.3.1 Specificity theory

The specificity theory proposes pain to be an independent sensation and a result of activation of dedicated neural pathways[19, 20]. The nociceptors have thresholds at or near noxious levels and show an increase in activity with stronger noxious stimuli[21].

1.1.3.2 Intensity theory

The intensity theory presumes the intensity of stimulus and the response to be the main factors for the sensation of pain. Innocuous stimuli cause weaker activation of neurons while intense sensations involve strong stimuli and vigorous activation of neurons[20, 21]. This theory does not necessarily require nociceptors.

1.1.3.3 Pattern theory

This theory suggests that the pattern of discharge changes with different forms of stimulation[22] and individual neurons respond to stimuli with differing levels of intensity. The mode and location of stimulation can be indicated by the pattern of discharge from the afferent nerve fibres of a particular body region.

1.1.3.4 Gate control theory

Melzack and Wall[23] proposed that the nerve impulses are carried by the thin and thick diameter nerve fibres to the dorsal horn of the spinal cord that consists of 1) the cells of the substantia gelatinosa (SG) 2) the dorsal-column fibres that project towards the brain and 3) the first central transmission cells (T). A presynaptic gate in the SG controls the balance of activity between the thick and thin fibres. When there is more small fibre activation than the large fibres, the gate opens leading to nociception and when more large fibres are activated, the presynaptic gate is closed serving normal somatosensory input. Descending pathways from the brain close the gate and diminish pain perception. The gate control theory is illustrated in Figure 1-2.

1.1.3.5 The body self neuromatrix

The body self neuromatrix[24] encompasses a widely distributed neural network that includes parallel somatosensory, limbic and thalamocortical components that subserve the sensory-discriminative, affective-motivational and evaluative-cognitive dimensions of pain. The architecture of the neuromatrix is determined by sensory and genetic factors. The pattern of nerve impulses i.e., ‘neurosignature’ output of the neuromatrix, is produced by the neural programs genetically built into the neuromatrix and determines the qualities and properties of the pain experience. The neurosignature pattern is modulated by a combination of: 1) sensory inputs 2) visual and other sensory inputs 3) cognitive and emotional inputs from other areas of the brain 4) intrinsic neural inhibitory modulation in the brain 5) body's stress regulation system. This framework of pain provides equal importance to genetic influences and neural-hormonal mechanisms of stress to the multidimensional experience of pain, in addition to the sensory processes.

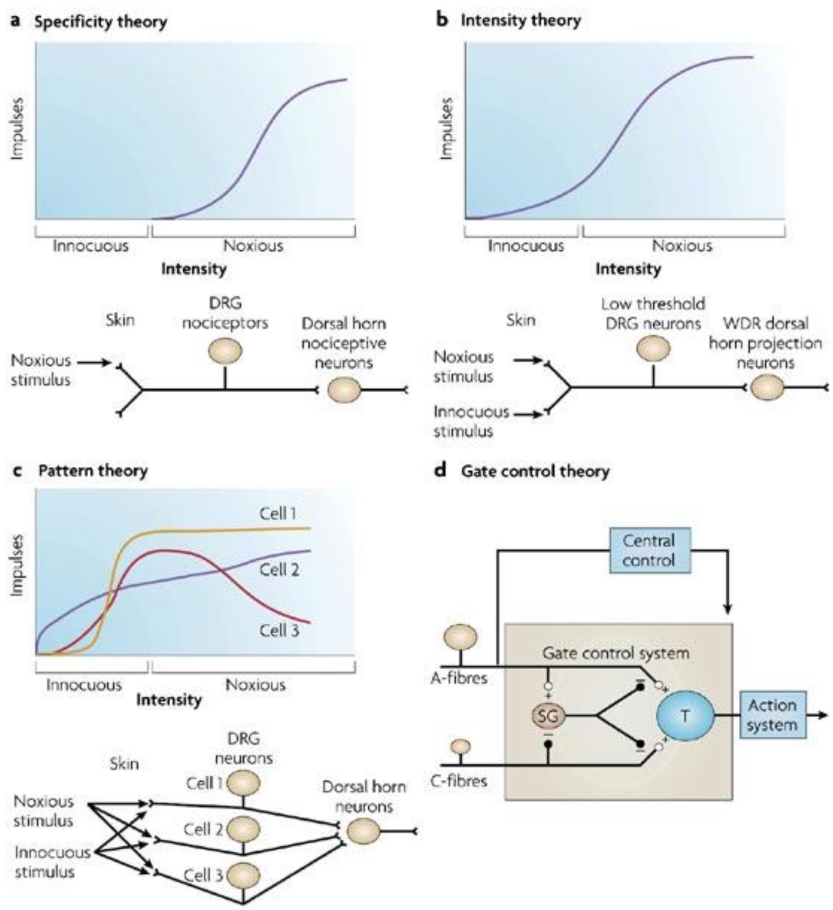

Figure 1-2: Theories of pain

1.2 Sensory innervations of the cornea

The cornea is one of the densely innervated structures in the human body, with innervation 20-40 times more than the tooth pulp and 300-400 times higher than the skin[25]. Most of the corneal nerves have a sensory origin from the ophthalmic branch of the trigeminal nerve, while a part of the inferior cornea receives innervation from the maxillary nerve. Corneal layers adjacent to the Descemet's membrane and endothelium are devoid of nerve fibres. Thick nerve bundles from the ciliary nerves enter the mid stroma through the corneosceral limbus in a radial pattern[26, 27]. These nerve fibres lose their myelin sheath within 1 mm of entering the stroma and are then surrounded by Schwann cell sheaths[28]. The nerve fibres subdivide di-or-trichotomously into smaller branches forming a sub epithelial plexus (SEP) between the anterior stroma and Bowman's layer. The SEP is sparse and patchy containing two types of nerve fibres: 1) thick, straight nerves with a dichotomous branching pattern and 2) tortuous, highly anastomotic nerves with a beaded appearance[29, 30]. The SEP is observed in the peripheral cornea with decreased or no presence in the central cornea[31]. From the SEP, the nerves turn 90^0 and enter into the Bowman's membrane where they once again subdivide into smaller branches and run parallel to the corneal surface. The Bowman's membrane contains smooth and beaded nerve fibres which again turn 90^0 to enter into a dense basal leash located between the Bowman's membrane and the epithelium, where the long curvilinear nerves converge onto a whorl like pattern 1-2 mm inferonasal to the corneal apex[26, 29, 31-33]. The nerve fibres that pass through the corneal apex run in the 12-6 hr direction while the other nerve fibres that do not pass the corneal apex run in 7-1, 5-11 and 3-9 hr direction[27]. Morphologically the epithelial leashes consist of both straight and beaded nerve fibres. The beaded nerve fibres are afferent sensory terminals that turn 90^0 perpendicular to the cornea and terminate in the corneal epithelium as free nerve endings[28, 34, 35]. Based on light microscopy and electrophysiological studies on rabbit[25, 36] and rat[37, 38], the free nerve endings on the epithelium belong to the Aδ or C type fibres.

Ling et al.[39] proposed the sensory terminals of the rat and rabbit corneas to be similar those of humans and these animals can be models to study the structural and the corresponding functional properties of the nerve terminals in humans. The basal leash formation and intraepithelial terminals in the cat were found to be qualitatively the same as those in rabbit[25] and human corneas[34]. MacIver and Tanelian[36, 40] identified two types of morphologically different nerve fibres arising from the SEP and terminating in the epithelium of rabbits. The type I fibres were short, vertically projecting and approaching within 5µm of the epithelium while the type II endings were long slender processes parallel to the surface at a depth of 10-20 µm. Based on the conduction velocities of these nerve terminals, type I endings were classified as C fibres (slow conduction velocities < 2 m/s) and type II as Aδ fibres (velocity of >1.5 m/s). Aδ fibres were found to be mylineated and C fibres to be unmyelinated.

Figure 1-3 illustrates the morphologically distinct nerve fibre pattern in rabbit corneas.

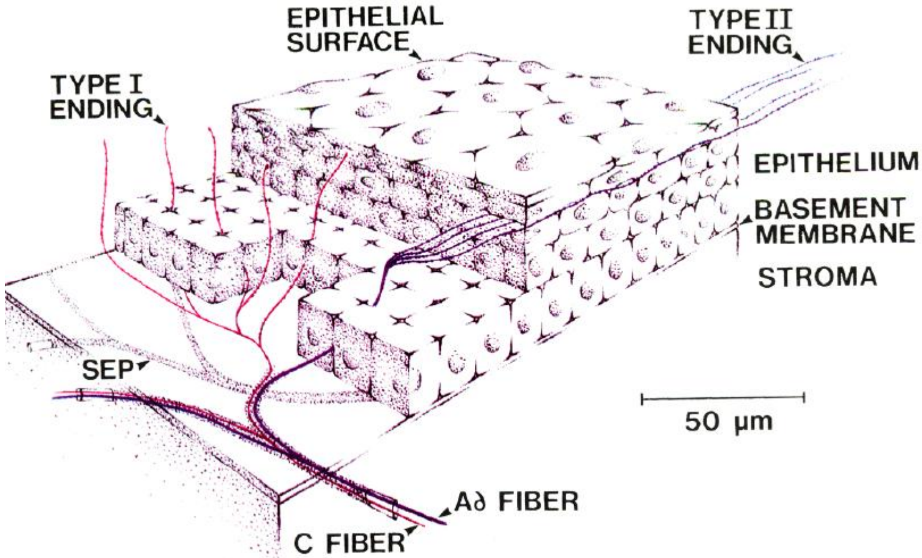

Figure 1-3: Illustration of morphologically distinct nerve fibre patterns in rabbits

Reprinted from The journal of neurophysiology, Vol 69, No. 5., MacIver MB, Tanelian DL, Free nerve ending terminal morphology is fiber type specific for Aδ and C fibers innervating rabbit corneal epithelium:1779-1783. Copyright 1993, with permission from The American physiological society.

1.2.1 Functional properties of ocular sensory neurons

Electrophysiological studies on cat[37, 38, 41-43] and rabbits[40, 44] propose that corneal sensory neurons can be divided into different subclasses by their conduction velocities, modality of stimulus that preferentially activates them, and the resulting sensation[45-47]. A graphical representation of the functional types of the sensory neurons innervating the eye is illustrated in Figure 1-4 and the classification of ocular sensory neurons based electrophysiological studies is presented below.

1.2.1.1 Mechanosensory neurons: These myelinated Aδ neurons are excited mainly by mechanical forces, firing one or few impulses in response to short or sustained indentation of the corneal surface. Mechanosensory neurons contribute to 20% of the total neurons innervating the cat's cornea and about 2/3 in the rabbit. These neurons mainly signal the presence of the stimuli rather than detecting the intensity of the stimulus and moving stimuli excites these neurons more than stationery stimuli. Electrical stimuli parallel to the long axis of the receptive area produce maximum activation, perhaps suggesting a directional sensitivity to these types of fibres. Mechanosensory neurons can possibly mediate short acute pain produced by a mechanical stimulus in contact with the corneal surface[46].

1.2.1.2 Polymodal neurons: About 70 % of the corneal sensory neurons in cat belong to the polymodal nociceptor class. Most of them have C fibre endings but few of them also have Aδ terminals with large receptive fields. These neurons are activated by mechanical forces, chemical irritants and heat over 39-40^0 C. Polymodal neurons respond to stimuli with an irregular continuous discharge that is roughly proportional to the intensity of the stimulus. So, in addition to signaling the presence of the stimulus, they also code stimulus intensity. These neurons are silent at rest and fire occasional spikes at very low frequency (0.06/sec in Aδ , 0.1/sec in C fibres).

Response to mechanical forces: Polymodal neurons irregularly discharge similarly to mechanosensory neurons, but have a spontaneous activity and lower mechanical threshold than mechanosensory nociceptors. The characteristics of tonic discharge, fatigue during repeated stimulation and post discharge with high intensity stimulus distinguish the unmylineated C neurons from the Aδ polymodal neurons[45].

Response to temperature changes: Aδ and C polymodal neurons are excited when temperature exceeds 39-40^0 C. Upon temperature elevation, there is an accelerating train of impulses, whose frequency reaches a peak and then gradually returns to the lower maintained level. With sustained heating of the cornea, the impulse discharge gets irregular. When temperature drops to basal level, the firing stops transiently and when temperature crosses the noxious level causing tissue damage, there is an irregular low frequency background discharge[37, 41, 48]. Polymodal neurons are not reactive to cold. Temperatures below 20^0 C silences or diminishes the activity of these neurons.

Responses to chemicals: Afferent neurons showing sensitivity to mechanical stimuli and if they also responded to acetic acid and hyperosmolar NaCl, then they are classified as polymodal[38, 41, 43]. The C polymodal neurons are reactive to exogenous chemical irritants and endogenous chemical mediators that are released during tissue damage and inflammation with a discharge of impulses that is roughly proportional to the proton concentration.

1.2.1.3 Mechano-heat neurons: These bimodal afferents belong to the Aδ group that exhibit high sensitivity to mechanical forces and thermal stimulation but do not respond to chemicals.

1.2.1.4 Cold-sensitive receptors: 10-15% of corneal neurons are cold receptors belonging to both Aδ and C groups giving rise to low frequency discharges. Cold neurons discharge spontaneously at the rest and increase their firing rate when the temperature of the cornea decreases around 33^0 C. The firing rate also increases when the temperature of the cornea drops due to evaporation of the tears or application of a cold drop or blowing cold air on the corneal surface[41]. The neurons are transiently silenced upon warming. Corneal receptor fibres can detect temperature variations of 0.1^0 or less and encode it as a sensation of cooling.

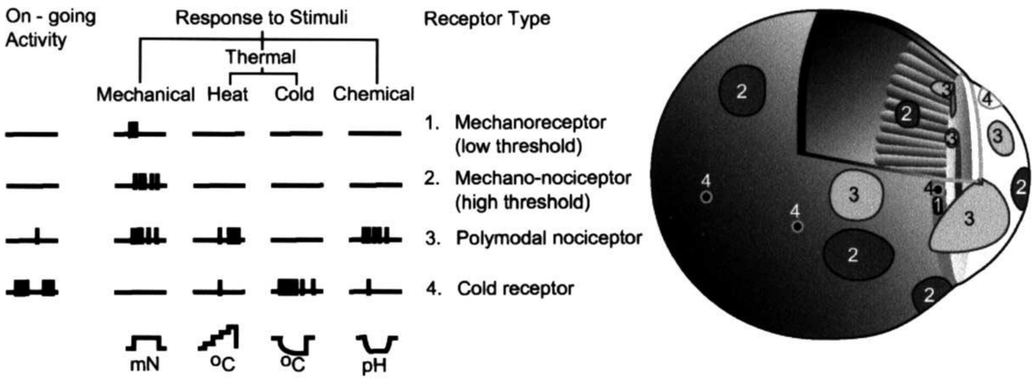

Figure 1-4: Functional types of sensory neurons innervating the eye

Reprinted from Experimental Eye Research, Vol 78, Issue 3. Belmonte, Acosta MC, Gallar J, Neural basis of sensation in intact and injured corneas:513-525. Copyright 2004, with permission from Elsevier.

In rabbit corneas, MacIver and Tanelian[40] identified four types of modality specific neurons: 1) slow adapting C fibre cold receptors 2) C fibre chemosensitive units 3) high threshold mechano-heat receptors belonging to Aδ fibres 4) rapidly adapting Aδ mechanosensitive units. A different group of neurons known as "silent nociceptors" was also observed that was activated by endogenous chemicals released during local inflammation, but insensitive to mechanical and thermal stimuli[40].

1.3 Psychophysical techniques of detection and discrimination

Fechner[49] in the year 1860 coined the term "psychophysics" describing the relationship between 'sensation' in the psychological domain and 'stimulus' in the physical dimension. Psychophysics was designed to determine the relationship between the internal sensory events and perceptual responses to the external stimuli[50]. The measurement of sensory threshold plays a pivotal role in the assessment of any sensory system. Threshold is a boundary value in the stimulus continuum that indicates the presence of a stimulus or a difference in the stimulus response[50]. Thresholds can be categorized into: 1) Absolute threshold (RL) that refers to the presence of the stimulus and 2) Difference thresholds (DL) that indicates the change in the stimulus.

Absolute threshold is defined as the smallest amount of stimulus energy necessary to produce a sensation[51]. When a sensory threshold is reached, the stimulus needs to be increased or decreased by a certain amount to sense a change in the stimulus. The amount of change in a stimulus ($\Delta\varphi$) required to produce a just noticeable difference (JND) is called the difference threshold[51]. Typically, greater change ($\Delta\varphi$) is required to detect changes in higher intensity stimuli than stimuli of lower intensities. According to Weber's law, the increase or decrease in the intensity of the stimuli that is just noticeably different ($\Delta\varphi$) is always a constant fraction (c) of the starting intensity of the stimulus (φ)[51].

$$(\Delta\varphi)/\ \varphi = c$$

Figure 1-5 illustrates the Weber's fraction over a range of stimulus intensities on sample data.

Weber's law holds true for a wide range of the intensities. However, Weber's fraction tends to be high at lower stimulus intensities, possibly because of the noise in the sensory system or the stimulus. To accommodate the noise factor, Weber's law has been modified to:

$$(\Delta\varphi)/\ \varphi+a=c$$

where 'a' is a constant that has a small value, representing the amount of noise when $\varphi = 0$. At lower stimulus intensities, the constant 'a' will be a significant factor, but it decreases in significance as the intensity increases and may also be omitted for higher stimulus values without influencing the data appreciably[52].

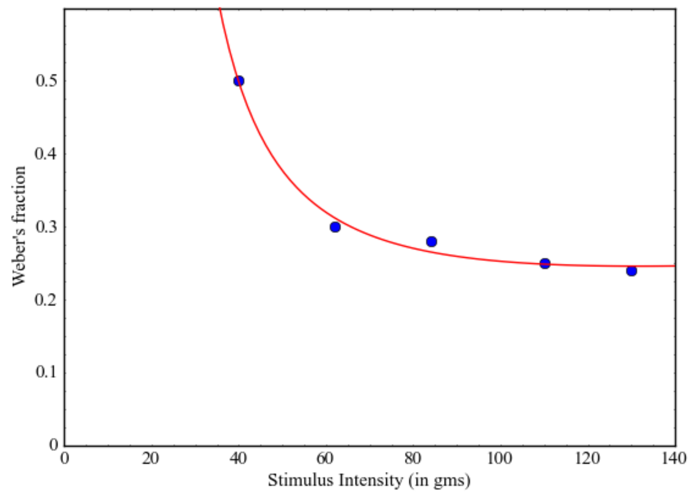

Figure 1-5: Sample data showing Weber's fraction over a range of stimulus intensities

Sensitivity is unique to each sensory system, and within each sensory modality, the stimulus dimension differs in intensity, quality, extension and duration. Although, discrimination threshold ($\Delta\varphi$) cannot be compared across the various sensory systems and stimulus dimensions, their relative sensitivities can be compared by means of Weber's fraction[51].

Thresholds can vary with time due to the influence of external and internal sources[51]. Hence, several measurements of the threshold value are obtained and averaged to estimate the sensory threshold of a particular system. External sources of variation can be due to the random fluctuations in the stimulus itself or the environment/experimental settings in which the test is conducted. Internally, noise in the neurological system can be one of the contributors for the variations, along with other factors like psychological bias and attention.

1.3.1 Methods of psychophysical measurement

1.3.1.1 Method of constant stimuli

The procedure involves typically presenting a set of 5-9 stimulus intensities repeatedly throughout the experiment[53]. The range of stimuli is chosen from previous observations in such a way that the lowest stimulus is seldom perceived and the highest stimulus intensity is almost always detected, with the threshold located somewhere within the selected range of stimuli. As the stimulus intensity is increased from low to high, the likelihood of the stimulus being detected also gets higher. Therefore, in the method of constant stimuli, each stimulus is randomly presented several times and the number of yes and no responses for each stimulus is recorded. The proportion of yes response for each stimulus value is computed and a graph called 'psychometric function' is plotted with stimulus intensity in the abscissa and the proportion of yes responses in the ordinate. Absolute threshold is the stimulus intensity for which the proportion of yes response is 0.5 or 50%[53]. An example of the psychometric function is in Figure 1-6. If there is no direct stimulus intensity corresponding to the 50% proportion of correct response, a psychometric curve is drawn connecting all the data points. The absolute threshold is estimated from the curve by noting the stimulus intensity that corresponds to the 0.50 point[53]. The psychometric curve as illustrated in Figure 1-6 is generally an S shaped function, also called an ogive.

The measurement of difference threshold with the method of constant stimuli involves a standard stimulus and a set of comparison stimuli. The standard stimulus has a fixed value and the comparison stimuli consists of a range of 5, 7 or 9 stimulus values that are equally distributed above and below the standard stimulus with equal step intervals[53]. The values of the comparison stimuli are chosen in such a way that the stimulus with the greatest magnitude is always judged higher than the standard and the stimulus of the lowest value is almost always judged less than the standard. Each comparison stimuli is then paired several times with the standard stimulus in random order and the observer identifies the stimulus with greater magnitude. The proportion of times each comparison stimulus is judged greater than the standard stimulus is noted and a psychometric function relating the intensity of the comparison stimulus and the proportion of "greater responses" is plotted forming an ogive[53].

In order to control the effects of time error, the standard stimulus is presented first in one half of the trials and second on the other half of the trials. Spatial errors are avoided by presenting the standard stimulus to one receptor area on half of the trials and to another receptor area on the other half of the trials.

When the comparison stimulus is judged equal to the standard stimulus, the proportion of greater response will be 0.5 and is known as the point of subjective equality[53] (PSE). The comparison stimulus value at PSE ideally should correspond to the value of standard stimulus, but it seldom does. The difference between PSE and the standard stimulus is called the "constant error" (CE), which reflects the influence of uncontrolled factors like spatial and time errors making the measurements consistently high or low by a certain amount. Since PSE represents the lack of discrimination between the standard and comparison stimulus, and 0 or 1.0 represents perfect discrimination, the intermediate points 0.25 and 0.75 are used to identify the DL. The lower DL is the difference between the PSE and the stimulus intensity at 0.25 point and the upper DL is the difference between the PSE and the stimulus intensity at the 0.75 point[53]. The upper and lower DL values are then averaged to obtain one DL for a particular standard stimulus.

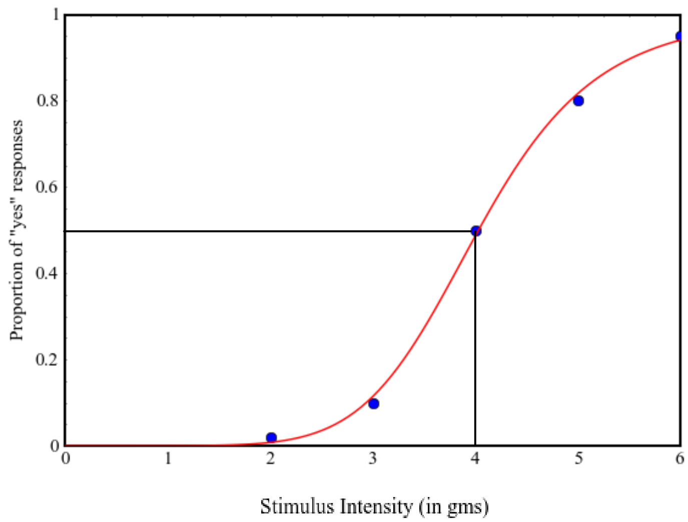

Figure 1-6: The psychophysical function for determining the absolute threshold using the method of constant stimuli

1.3.1.2 Method of limits

The method of limits is a highly efficient and a less time consuming procedure[51]. The range of stimulus values for the method of constant stimuli is often determined using the method of limits.

The method of limits is the procedure of presenting stimuli well above or below the threshold and successively changing the stimulus intensity in small equal amounts until the boundary of sensation is obtained[53]. The stimuli are typically presented several times in an ascending or descending fashion. In an ascending series trial, the starting stimulus is below threshold and the stimulus intensity is gradually increased until the observer reports the presence of the sensation. In a descending series trial, the starting intensity is well above threshold and the intensity is gradually decreased in equal interval steps until it is no longer perceived. The series is terminated once the transition point in sensation is obtained. The transition point obtained for each ascending and descending trial is considered to represent the threshold and the average of all the transition points is designated as the absolute threshold[53].

Two types of errors can be encountered with the method of limits[51]. Error of habituation occurs when the observer develops a tendency of repeating the same response even after the threshold point is reached. This error affects the results by falsely increasing the threshold in ascending trials and falsely decreasing the threshold in descending trials. The error of expectation occurs when the observer anticipates the arrival of the stimulus and prematurely reports the change in sensation before it actually happens. In this case, the thresholds are falsely low in ascending trials and falsely high in descending trials. When the error of habituation and the error of expectation are of equal magnitude, they may cancel each other, but this condition is unlikely. The error of expectation can be avoided by varying the starting point of the stimulus in each trial, so that the observer will not be able to judge the number of steps required to achieve the threshold. Avoiding excessively long trials can prevent the error of habituation[53]. Preliminary training and careful instructions can also help to eliminate or minimize the errors associated with the method of limits.

The difference threshold is measured by presenting a pair of standard and comparison stimulus simultaneously or successively[53]. The comparison stimulus is changed by a small amount in the direction of the standard stimulus and the observer is asked to report if the comparison stimulus is greater, lesser, or equal in magnitude compared to the standard stimulus. The stimuli can be presented in an ascending or a descending fashion. During each series, whether ascending or descending, two transition points are obtained: the upper limen and the lower limen. In an ascending trial, the lower limen (L_l) is the transition point at which the "less" response changes to "equal" and the upper limen (L_u) is the point at which the "equal" response changes to "greater".

For the descending trial, the upper limen (L_u) is the point at which “greater” response changes to “equal” and the lower limen (L_l) is the point at which “equal” response changes to “lesser”. The series is terminated when both the transition points are reached. The ascending and descending series are repeated several times and the upper and lower limen values are averaged. The range of stimulus intensities over which the observer does not perceive any difference between the comparison and the standard stimulus is called the interval of uncertainty (IU) and is computed by subtracting the mean lower limen from the mean upper limen[53] ($IU= L_u - L_l$). The difference limen or the difference threshold (DL) is the half of IU[53] ($DL=1/2\ IU$). The point of subjective equality (PSE) is calculated by the addition of the mean upper and lower limen and dividing it by half [$PSE=1/2(L_u + L_l)$].

The measurement of difference threshold can also be affected by the errors of habituation and expectation. The methods to control for these errors are the same as discussed earlier with the measurement of absolute threshold. Since a pair of stimuli is used to measure the DL, care must also be taken to avoid time and space errors by executing procedures as suggested in the section of method of constant stimuli.

1.3.1.3 Method of adjustment

The method of adjustment requires the observer to adjust of the intensity of the stimulus in order to obtain the threshold[51]. The starting point of the stimulus is placed either very high or low and the observer is asked to increase the stimulus until it is perceptible or decrease the intensity until it is no longer perceptible. The stimulus intensity is generally continuous although it can be varied in discrete steps. The trials are conducted several times in ascending and descending series and the absolute threshold is the average of all the transition points[53].

During the difference threshold measurements with the method of adjustment, the observer is required to adjust the comparison stimulus equal to the standard stimulus. The observer sometimes overestimates and sometimes underestimates the standard stimulus by a considerable amount. However, most often the matches tend to cluster around the standard stimulus intensity. When enough trials are administered, the frequency distribution of comparison stimulus settings approximately follows a normal distribution. The mean of the distribution or the mean of all the settings of the comparison stimulus is the point of subjective equality[53] (PSE). The constant error is computed by subtracting the standard stimulus intensity (St) from the PSE[53] (CE=PSE-St). The measure of dispersion like standard deviation is used to indicate the difference threshold[53] (DL).

The disadvantages[51, 52] with the method of adjustment are: 1) The results can be inaccurate when the stimulus can only be varied in discrete steps and not continuously variable 2) It is difficult to counterbalance or measure the stimulus order effects in experiments that necessitate the standard stimulus to be presented first followed by the comparison stimuli 3) The observer's motors skills may play a role in the judgments along with the amount of time devoted to each judgment. 4) It is difficult to maintain constant conditions in the experiment since the observer modulates the stimulus intensity in this procedure.

1.4 Psychophysical scaling

Thresholds, both absolute and differential involve the physical dimension of stimuli without any information about the resulting sensation[54]. A complete picture of a sensory system is obtained when both the input and output side of the system can be quantified and related. The stimulus intensity and the resulting sensation do not always stand in a one to one relationship and hence the changes in stimulus intensity and the corresponding changes in sensation have to be studied experimentally. Psychophysical scaling refers to the process of quantifying mental events, especially sensation and perception and determining how the quantitative measures of mental events are related to the quantitative measures of the physical stimuli[55]. A psychophysical relationship called the psychophysical magnitude function is established when the magnitudes of a sensory attribute is plotted against the corresponding physical values of the stimulus[54]. The psychophysical magnitude function perhaps helps us to understand the operation of sensory system and is unique to each sensory modality and stimulus condition.

Psychophysical scaling techniques may be subdivided into three types[54, 56]. 1) Discrimination techniques: where subjects make ordinal discrimination judgments of stimuli. 2) Equisection/Bisection scaling: where subjects adjust stimuli to partition the sensory continuum into equal intervals 3) Magnitude estimation: in which the subjects make direct numerical estimations of the sensation magnitudes produced by various stimuli. In magnitude production, the subjects adjust stimuli to match numbers presented by the experimenter.

Although, each method generates an estimate of sensory magnitude, each involves a different type of perceptual response from the observer.

1.4.1 Indirect scaling techniques

Discrimination scales are based on the principle that the difference between the psychological magnitudes of two stimuli increases as a function of the observer's ability to discriminate between them[54]. Fechner[49] assumed the JNDs to be psychologically equal and used the difference threshold as a measure of sensation magnitude. This assumption along with Weber's statement that the size of the DL is proportional to stimulus intensity, led to the formation of Fechner's discrimination scales. Using JND as a unit of sensory magnitude, Fechner suggested that sensory magnitude could be measured by counting the number of JNDs a stimulus is above absolute threshold and the psychological magnitude function will be the number of JNDs above absolute threshold as a function of stimulus intensity[49]. An example of the discrimination scale is illustrated in Figure 1-7.

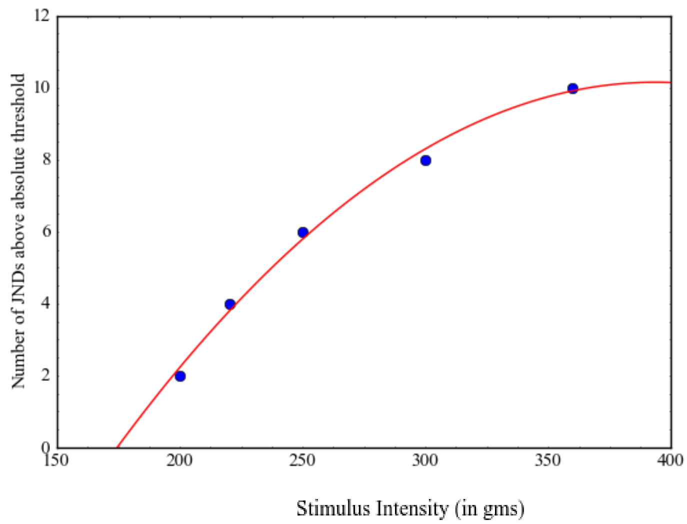

Figure 1-7: Example of discrimination scale relating the stimulus intensity with the number of JNDs above absolute threshold

Another method of indirect scaling utilizes the comparative ability of the observers. Thurstone[57] in 1927 proposed the law of comparative judgment using the analysis of paired comparison judgments. A psychophysical scale between two stimuli is constructed by evaluating the proportion of times one stimulus is judged greater than the other with respect to some attribute.

1.4.2 Direct scaling techniques

Direct scaling involves the observers' judgments of sensations being directly converted to measurements of sensory magnitude. Stevens[58, 59] work on direct ratio scaling of sensation is a landmark in psychophysical scaling. In magnitude estimation, the subjects assign numbers to the sensation magnitudes produced by various stimuli. The estimation can be conducted with a standard reference modulus or a modulus free method. In the former one, the observer is presented with a standard stimulus and told that it produces a sensation of certain numerical value (modulus) such as 10. On subsequent trials with other stimuli, the observer assigns numbers to the sensation relative to the value of the modulus. In the modulus free method, there is no modulus defined to the observer and they are free to use any number. The stimuli are typically randomly presented and the observer assigns number to the sensation in proportion to their magnitudes.

Stevens[60] in 1957 proposed that the form of the relationship between sensation magnitude and stimulus intensity was a power function, which became known as the Power law that is stated as:

$$\Psi = k\,(\Phi)^{b}$$

where Ψ is the sensation magnitude, Φ is the stimulus intensity, k is an arbitrary constant determining the scale unit and b is the power exponent that depends on the sensory modality and stimulus conditions. The value of the power exponent partly determines the shape of the function where Ψ is plotted against Φ. The relationship is positively accelerated when the exponent is greater than 1.00 and negatively accelerated when less than 1.00. An example of the Stevens power function plot is shown in Figure 1-8.

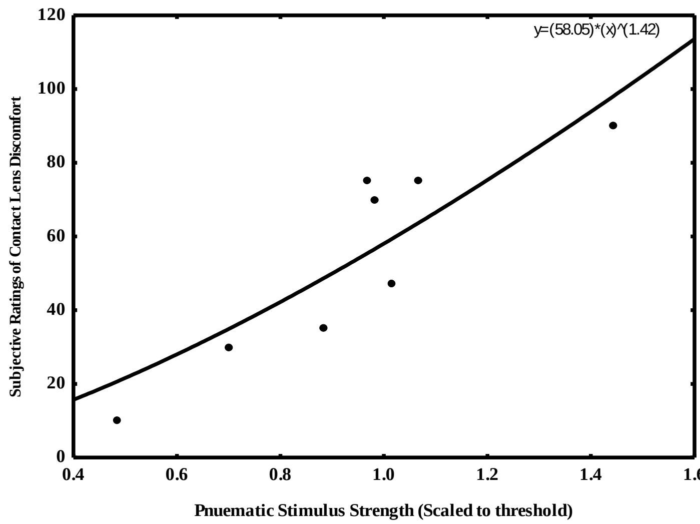

Figure 1-8: Magnitude estimation of discomfort as a function of stimulus intensity on the human cornea

Magnitude matching can be theoretically used to observe the validity of the data obtained from magnitude estimation[56]. The objective is to have the observer judge the sensory magnitude of two different modalities on a single, common scale. Stimuli that have the same scale values should be judged subjectively equal when they are directly matched. In cross modality matching, the observer adjusts the intensities of stimuli from different modalities to match the sensation magnitudes[56].

The other methods of direct scaling are partition scaling, category scaling, ratio production and ratio estimation[54, 56]. In partition scaling, the observer makes judgments about the sensory differences among the stimuli. The observer either attends to several stimuli along a physical continuum and partitions them into a number of categories that are psychologically equal or matches another stimulus to be a fraction of a reference (e.g., half as intense). In category scaling, the observer is presented with large set of stimuli and the task is to assign them into specified number of categories. The categories are usually specified in numbers (1,2,3) or as adjectives (such as low, medium, high).

Ratio production and ratio estimation are similar suprathreshold techniques[56]. In ratio production, the observer is required to adjust a variable stimulus while observing a standard stimulus so that both the sensations are in a prescribed ratio. With ratio estimation, the observer responds to two stimuli by estimating the apparent ratio between them. Ratio estimation is used as a means of testing validity of the scales produced by ratio production.

1.4.3 Psychophysical scaling in ocular surface literature

Psychophysical scaling on the ocular surface was initially carried out with a Cochet-Bonnet esthesiometer and the judgments of sensation were recorded using magnitude estimation with a free modulus. The relationship between the apparent magnitude of corneal sensitivity to the pressure applied on the cornea was found to be a power function with an exponent of 1.01[61]. Since magnitude estimation could slightly underestimate the value of the exponent[62], the authors predicted the exponents to represent a lower bound. Later studies[43, 63-65] on psychophysical scaling were conducted using non-contact pneumatic stimuli. Feng[63] reported the corneal transducer function for mechanical and chemical stimuli to be 0.82 and 1.08 respectively. A similar study by Belmonte[64] revealed the intensity-response curves with an exponent of 0.58 for mechanical and 0.63 for chemical stimuli. Chen[43] also reported the relationship between CO_2 concentration and magnitude of pain to follow Stevens' power function with an exponent adjusted to 1.12. A study[66] on sensory transduction in central and peripheral corneal locations indicated exponents of 1.38 and 1.19 for mechanical stimuli and 0.97 and 0.96 for chemical stimuli respectively.

1.4.4 Subjective ratings of pain

Rating scales are used to record the subjective experience of pain and help to understand the extent of pain in addition to clinical measurements. The expression of pain can be done through simple verbal questioning in a clinical setting to the use of specifically designed pain measurement tools like questionnaires or rating scales. Questionnaires aid in multidimensional assessment of pain, involving sensory, afferent, emotional, social and cultural aspects of pain, while rating scales usually have a one-dimensional structure mainly evaluating the pain intensity[67]. Since pain involves cognitive as well as emotional components in addition to intensity, the effects of all the components tend to spread over the entire scale regardless of the magnitude of actual sensations[68].

Rating scales can be of continuous or categorical type.

1.4.4.1 Continuous rating scales

The visual analogue scale (VAS) is a horizontal or vertical line of uniform thickness and of a given length (often 10 centimeters) whose ends are labeled with words descriptive of the maximal and minimal extremes of the dimension being measured[69]. The subjects respond to the VAS by making a mark across the line at a position that represents their current perception of the attribute under investigation and the scale is scored by measuring the distance from minimal end of the scale to the subject's mark. The VAS offers the potential of being simple and easy to construct, easy to administer and score, suitable for repeated and frequent uses[69]. It is suitable for use by untrained staff[70] and needs little motivation for completion by the subjects[71]. It is also a reliable, valid and sensitive measure of pain[69, 72]. It is approximate to a ratio scale and independent from the language except for the anchor labels[73-75]. VAS scales are unidimensional, but a combination of rating scales can be used to scale more than one dimension of pain. The sensory as well as affective dimensions of pain have been shown to be recorded using VAS[76, 77].

The difficulties associated with VAS are the clustering of scores usually near the midpoint or extreme ends of the scales, suggesting that the subjects do not always make use of the full range of scale[78]. Another problem is the tendency of the investigator to treat the score as interval or ratio level scaling in statistical analysis without the evidence that the subjects actually use the numbers in that way. McCormack et al.[69] and Carlsson[79] have questioned the ease of use of VAS as the scales necessitate the conversion of a complex subjective experience to a visuospatial judgment.

Numerical rating scales (NRS) consist of a range of numbers usually from 0 to 10 or 0 to 100, from which the subjects report a number that closely represents the pain they experience. The lower end of the scale '0' corresponds to "no pain" while the upper number represents "pain as bad as it can be". The number reported by the subject as representing their pain intensity is the score for the NRS. Numerical scales are easier to administer and show better compliance than the VAS[80, 81]. A study[80] comparing six methods of pain intensity measurements suggests the use of 101-point numerical rating scale among the other scales used in the study.

1.4.4.2 Categorical scales

The subjects are asked to rate the stimulus on a structured, categorized scale that indicates pain intensity or emotional aspects of pain. The scale may describe the frequency (never, sometimes, often, always) or severity (mild, moderate, severe) of the symptoms using 3-11 categories. Guyatt et al.[82] has suggested that a seven category scale is sufficient to demonstrate a change in function perhaps mainly due to the ease of administration and interpretation of the seven point scale. Verbal rating scale (VRS) consists of a list of adjectives that describe different levels of pain. The adjectives indicate varying levels of pain from no pain to increasing levels. The lowest score 0 is attributed to the absence of pain, the next one with a score of 1 and so on with each consecutive adjective given a number higher than the previous. The subject's pain score will be the number associated with the adjective that best describes their pain. The simple and clinically used verbal rating scales consist of the adjectives: none, mild, moderate and severe[83].

Heft and Parker[84] proposed that the category scale items are not equally spaced when labeled with words commonly used to describe pain. When categories of pain descriptors are employed, it is difficult to specify the size of each category and the categories can be misinterpreted to have equal intervals. The categorization may falsely imply a rank ordered scaling, although the VRS is ordinal. According to Grunberg et al.[85], the verbal descriptors given to the categories may cause confusion or a different meaning may be assigned to the descriptors by the study participants. The other drawback is that the scores from the scale can be analyzed only by using non-parametric ranking statistics[86].

Despite the problems, rating scales are used to study subjective experiences, as the scales are simple, easy and economic for the subjects to use and comprehend. In measuring symptoms with contact lens wear, both category rating scales/likert scales and visual analogue scales have been employed, but the justification for the use of a particular scale may not always be specified. Tu doit et al.[72] for example, compared three types of rating scales: VAS with two anchors, VAD (VAS with 20 intervals and descriptors) and LRS (Likert rating scale) in order to determine a suitable scale to record subjective responses to contact lens wear. The results support the use of a VAS to measure contact lens handling due to their high construct validity, reliability, good responsiveness and least variability in ratings.

1.5 Measurement of ocular surface sensations

The earliest measurement of corneal sensitivity was done by Von Frey in 1894 using varying lengths of horse hair attached to a glass rod by wax[87]. Later the technique was modified by Boberg Ans[88] and Cochet-Bonnet[89] by using nylon monofilament in the place of horse hair to measure the sensitivity of the cornea.

The Cochet-Bonnet esthesiometer[89] consists of a nylon thread attached to a probe, which is handheld or mounted on an apparatus. The mechanical force caused by the thread against the cornea, identified by bending of the thread, indicates the sensitivity of the cornea. In the test procedure, the nylon thread is perpendicularly brought closer to the eye to touch the cornea and the subject reports the presence of the thread verbally or by using a buzzer. A magnifier attached to the apparatus is used to monitor the bending of the thread upon touching the cornea. The longest thread length (6cm) is used first as represents the lowest stimulus intensity. If the thread is not felt, the length is then decreased in 0.5cm steps until the participant feels the presence of the thread. The test procedure is usually carried out with the 0.12 mm diameter filament[90], although 0.08 mm diameter thread is also used. Several measurements are taken for each thread length and the length with 50% positive response is converted to mechanical pressure by a calibration scale provided with the instrument.

The drawbacks of Cochet-Bonnet esthesiometer are discussed in several studies[90-94]. It has a truncated stimulus intensity range[93], with most of the stimuli being suprathreshold. The stimulus is also localized due to the fine end of the tip stimulating fewer corneal nerve endings. The sensitivity measurements can be affected by humidity, environmental conditions and age of the thread[95, 96]. There can be epithelial surface deformations due to the application of nylon thread and patient apprehension plays a major role by falsely increasing the sensitivity[94, 96, 97].

1.5.1 Pneumatic esthesiometers

The development of pneumatic esthesiometers[64, 94, 98, 99] succeeded the Cochet-Bonnet type with better stimulus characteristics, mode of stimulation and higher range of stimulus intensities. The Belmonte esthesiometer and its two other variations are described below. The structure of the pneumatic Belmonte esthesiometer and the modified Waterloo Belmonte esthesiometer are illustrated Figures 1-8 and 1-9 respectively.

The Belmonte esthesiometer[64] consists of two gas cylinders, one containing air and other with 98.5% CO_2. Both are connected using a pressure regulator and a unidirectional regulator to a directional control valve (PCV) that electronically adjusts the flow of air and CO_2 separately. This generates the output gas mixtures with a controlled proportion of CO_2 and air. The final flow of air is adjusted by a flowmeter and transferred to a probe (PB) mounted on a slit lamp holder. The probe contains a temperature-controlling device comprising of a thermode, a servo regulator and a Peltier cell (^{0}C) that warms or cools the gas and a three-way solenoid valve that directs the output of gas (EV). During stimulation, the gas mixture is transiently directed to the tip of the probe by means of a pulse generator that changes the direction of flow from the electronic valve towards the ocular surface, producing a short pulse of gas with defined CO_2 concentration, temperature and flow rate for a specified period of 1-10 seconds. When no stimulation activity, the gas flowing through the valve is diverted back to the probe and enters a CO_2 meter where the concentration of the gas mixture is monitored.

The CCERT Belmonte esthesiometer[98] was built on the above principle with few modifications. The electronic flowmeters and temperature controllers are different from the Belmonte esthesiometer. The inner diameter of the probe is smaller (0.5mm) and a heating coil is present at the tip of the probe to deliver the stimulus at the corneal temperature. The temperature sensor helps to maintain a constant temperature independent of the airflow and ambient temperature. The esthesiometer also consists of an optical range finder in the probe that helps to maintain an aligned distance of 4mm between the probe and the eye. There are also two laser pointers to find the correct working distance when non-reflective areas of the ocular surface are stimulated.

The Waterloo Belmonte esthesiometer[99] was built using the CCERT Belmonte esthesiometer as a platform. The modified Belmonte esthesiometer developed at the University of Waterloo provides computer-controlled combinations of air, CO_2 flow and temperature. Also, a custom software is used to input the psychophysical method and stimulus attributes for the computerized functioning of the test procedure and a button box is used to record the participants' responses. The distance between the probe and ocular surface, and its orthogonal alignment are constantly monitored using a calibrated video camera.

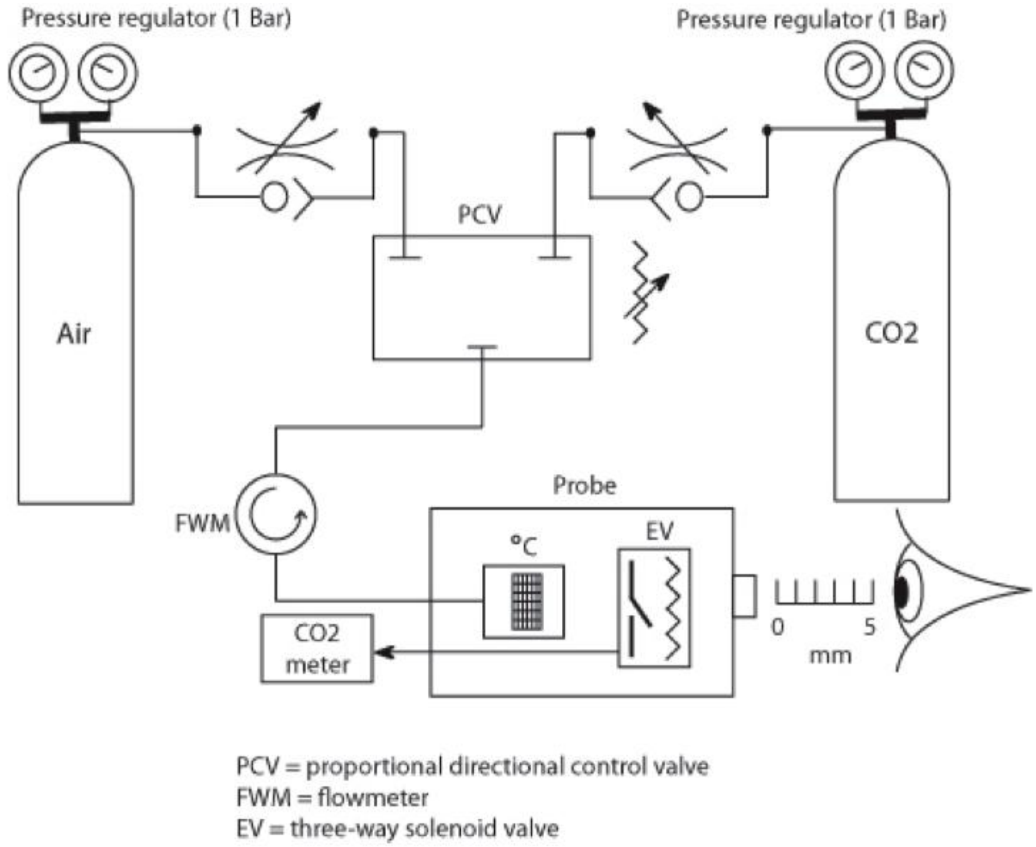

Figure 1-9: Construction of the pneumatic Belmonte esthesiometer

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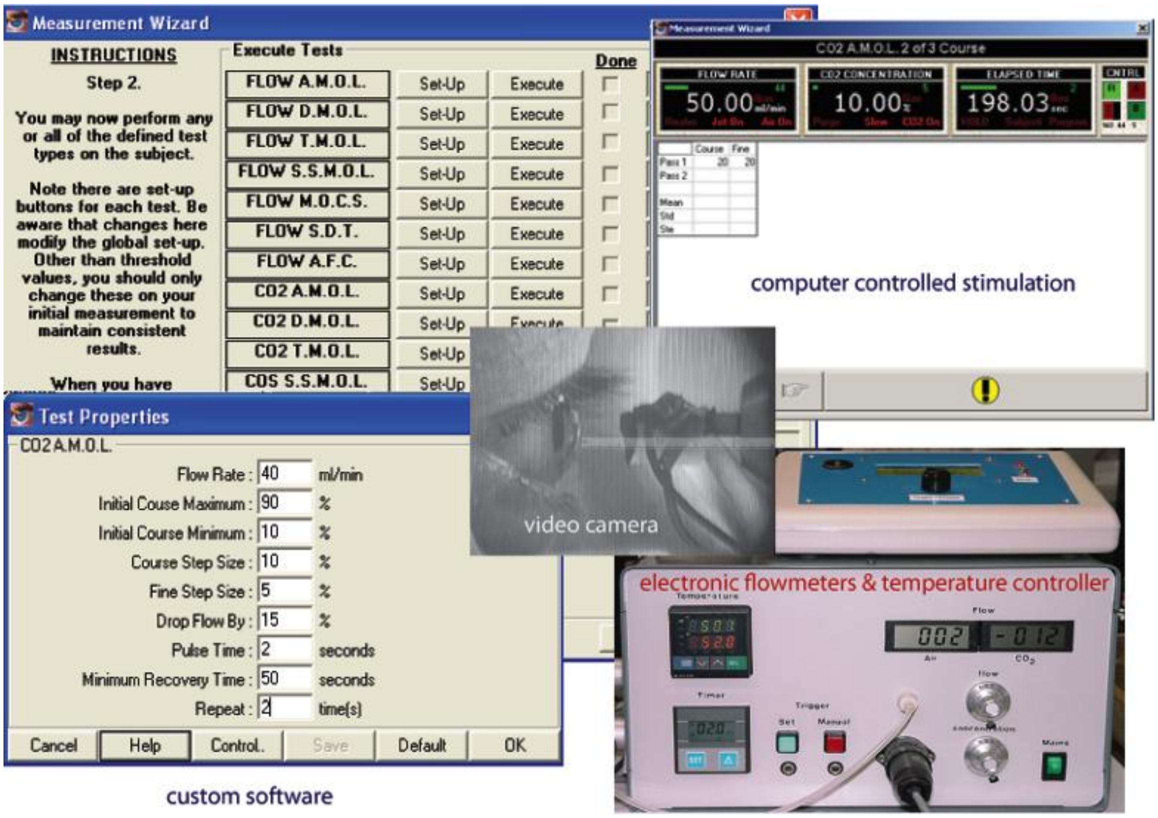

Figure 1-10: Custom software of the computer controlled Waterloo Belmonte esthesiometer

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1.5.2 Comparison of Cochet-Bonnet and pneumatic esthesiometers

The Cochet-Bonnet esthesiometer consists of a nylon thread providing mechanical force[89] on the cornea, likely activating the Aδ mechanosensory nociceptors. The area of stimulation by the esthesiometer is also smaller activating fewer nerve terminals. The pneumatic esthesiometers have the ability to activate mechanosensory as well as polymodal and cold receptors with the modulation of mechanical pressure, CO_2 and temperature[45]. A wider range of stimulus intensities and a larger area of stimulation can be obtained with the air jet instruments[93]. Due to the non-contact nature of the probe, patient apprehension and damage to the epithelium can potentially be avoided. Sensitivity to stimulation with the Cochet-Bonnet is measured in length of nylon filament (cm) while the pneumatic esthesiometer is in flowrate (ml/min). The units used to describe corneal sensitivity are also different, with pressure in millibars (mbars) for the Cochet-Bonnet esthesiometer and ml/min for the pneumatic esthesiometer[90, 93]. The measurement scale of the Cochet-Bonnet esthesiometer represents the corneal sensitivity directly (i.e., a long thread length indicates a high sensitivity), while the stimulus pressure measured with the pneumatic esthesiometer describes the threshold (i.e., a low number indicates a low threshold). The pneumatic esthesiometers provide better repeatability of measurements, superior stimulus reproducibility and control over stimulus characteristics more than the Cochet-Bonnet esthesiometers[90, 98, 100].

1.5.3 Sensations arising from the ocular surface

Irritation and cold are the predominant sensations that occur when delivering mechanical, chemical and temperature stimuli on the ocular surface[42, 64, 101]. Mechanical stimulation gives rise to an acute sharp sensation that is scratchy and irritating[99, 101] possibly due to the activation of the mechanosensory Aδ and low threshold mechanical polymodal nociceptors. Reduction in corneal pH by a chemical stimulus can cause burning and stinging pain[42, 43, 64, 102] which may be due to the stimulation of polymodal nociceptors and the pain lasts longer even after the stimulus is removed. Temperature changes are sensed similar to chemical stimulus along with an irritation and warmth component[42, 101, 103, 104]. During cooling of the cornea with cold air or test measurements conducted at room temperature (20^0 C) activates the cold receptors creating a “cooling sensation”. The cold sensation can gradually change to irritation as the temperature is increased from 20^0 to 50^0 C [42, 99, 105].

1.5.4 Physiological variations in corneal sensitivity

Measurements of sensitivity across the cornea with a Cochet-Bonnet esthesiometer[87, 89] suggests a reduction in threshold in the center compared to the peripheral locations, while studies[65, 98] conducted using a pneumatic esthesiometer reveal slight or no change in thresholds across the cornea. Rozsa and Beuerman[25] proposed that the corneal sensitivity across the cornea corresponds to the organization of nerve density. But, a recent study[106] on human subjects revealed no correlation between the sub basal nerve density and sensitivity. Like other biological functions, corneal sensitivity also exhibit diurnal variations, with the thresholds being highest upon awakening and lowest in the evening[98, 107, 108]. The diurnal change in sensitivity may be due to the reduced oxygen tension at the epithelial surface when the eye is closed[92]. A reduction in sensitivity with increase in age after 50 years is reported in few studies[109-111] and the decline is attributed to the reduced stimulus transduction mechanism and/or the presence of arcus senilis. Gender is also shown to have a significant effect on sensitivity, with females exhibiting higher sensitivity compared to males[109, 112].When women after menopause are compared to men, the gender differences in sensitvity are not observed, indicating that the hormonal changes that occur during menstruation and pregnancy[113, 114] can possibly alter the corneal sensitivity in females. Studies conducted on individuals with blue irides reveal varying results with a reduction[109] or no change in sensitivity[115, 116]. However, investigation on heterochromic eyes shows no difference in sensitivity between the eyes[117], suggesting that there is no association between iris color and sensitivity. In addition, exposure to ultra violet radiation can also be one of the factors to cause a decline in corneal sensitivity function[92].

1.5.5 Corneal sensitivity and soft contact lens wear

In earlier studies with tactile stimulation, a decline in sensory function was observed with contact lens wear and the reduction was found to be associated with the duration of lens wear[118-120], oxygen permeability[121, 122], and lens type[123, 124]. With the newer silicone hydrogel lenses, a slight increase or no change in sensitivity is observed with lens wear. The mechanisms that may cause a change in sensitivity[125] are: 1) mechanical stimulation by the contact lens 2) alteration of corneal metabolism due to decreased oxygen transmission and 3) corneal acidosis.

Table 1-1 summarizes the studies on corneal sensitivity measurements with contact lens wear.

Table 1-1: Literature review on corneal sensitivity measurements with contact lens wear

Author	Lens type	Instrument	Results	Other notes
Knoll HA[123] (1970)	SCL, Hard lens, non lens wearers	Cochet-Bonnet	↓ Sensitivity with hard lens	No difference between soft lens and non lens wearers
M Millodot[126] (1974)	SCL	Cochet-Bonnet	↑ Sensitivity	N/A
M Millodot[118] (1976)	SCL-Adapted lens wearers	Cochet-Bonnet	↓ Sensitivity	
M Millodot[119] (1977)	Hard lens	Cochet-Bonnet	↓ Sensitivity	Sensitivity decreases with duration of lens wear
M Millodot[120] (1978)	Hard lens	Cochet-Bonnet	↓ Sensitivity	
A Polse[127] (1978)	Hard lens	Cochet-Bonnet	↓ Sensitivity	No association between corneal edema and sensitivity
Larke JR[128] (1979)	SCL-EW	Cochet-Bonnet	↓ Sensitivity	

Bergenske P[124] (1987)	Hard lens wearers refitted with RGP	Cochet-Bonnet	↑ Sensitivity with RGP refit	
Velasco MJ[122] (1994)	SCL	Cochet-Bonnet	↓ Sensitivity	Decreased sensitivity lower in 38% water content lenses than 55%
Toit, R Du[129] (2001)	SCL	Pneumatic	No change	After 6 months interval
Murphy PJ[125] (2001)	Non lens wearers, RGP, SCL	Pneumatic	↓ Sensitivity in lens wearers	No difference between RGP and SCL
Patel SV[130] (2002)	Non lens wearers, all lens wearers	Cochet-Bonnet	↓ Sensitivity in lens wearers	No association between sensitivity and nerve fibre density
Stapleton[98] (2004)	Unadapted wearers- No lens , SCL, SH	Pneumatic	No difference in corneal sensitivity	Room temperature threshold lower than eye temperature
P Situ[65] (2010)	Adapted lens wearers-no lens, SH	Cochet-Bonnet, pneumatic	↑ Sensitivity with SH refit	

1.6 Ocular discomfort with contact lenses

The success of contact lenses has been reported to be attributed to the comfortable experience with lens wear among the various other aspects. Patients' expectations with lens wear can be understood from survey studies conducted on dissatisfied and lapsed contact lens wearers. The information from surveys combined with the clinical and research findings enhances our understanding about the mechanisms of ocular comfort.

The primary factors reported in survey studies for lens dissatisfaction and discontinuation are: ocular symptoms of discomfort and dryness[131-134], preference for another corrective modality[132], inconvenience with contact lenses and poor vision[131, 132]. The possible predictive factors for lens discontinuation are found to be: the age of starting lens wear, lower myopic prescription and reduced wearing time[131, 132]. Symptoms such as dryness, grittiness, itching, soreness are also more often observed more in contact lens wearers than in non-lens wearers[135, 136].

In a study[133] attempting to fit lapsed lens wearers with a modified lens design and replacement modality, 77% of the sample could successfully wear lenses again. The initial reason for lens discontinuation in the study participants was discomfort, specifically dryness-related discomfort. After re-fitting, the lens wearing time was seen to significantly increase and improvements in limbal, bulbar hyperemia and corneal staining were observed along with better comfort, decreased dryness and fewer uncomfortable hours of lens wear[137]. Unfortunately, patients cited vision problems rather than discomfort to discontinue lenses again[133].

Diurnal increase in severity of discomfort, dryness, and visual changes are observed with the worsening of symptoms in the evening[138]. Dumbleton et al.[139, 140] also reported a diurnal change in comfort, but no differences in comfort scores were seen between the five different types of silicone hydrogel lenses used in that study. Comparison of ocular comfort at different times of the day in hydrogel, silicone-hydrogel, gas permeable and non-lens wearers revealed decreased comfort in all the groups towards the end of the day[141], suggesting the presence of ocular or general fatigue that might contribute to the decreased comfort and the end of the day discomfort might not be solely related to contact lens wear. The frequency of ocular symptoms of tiredness, itchiness, watering, pain, aching, excessive blinking and burning have also been observed to have similar rates of occurrence in soft, gas permeable and spectacle wearers[142].

The lens related effects that can lead to discomfort are: lens dehydration, osmolality, wettability, lubricity, and the effects of protein and lipid deposition. The edge profile, rigidity, base curve and movement of lenses may also contribute to the lens related effects. However, modifications to the lens material, design, replacement frequencies and care systems may improve the lens wearing experience[134]. To be satisfied, contact lens wearers expect comfort, clarity of vision and longer wearing times when lenses are to be used as a primary modality of vision correction.

Table 1-2 summarizes the studies on contact lens discomfort and its associated factors.

1.7 Vision with contact lenses

Visual complaints are common in contact lens wearers along with other ocular complaints. However, studies that investigate the measurements of contrast sensitivity function (CSF) and visual acuity with contact lenses report varying results[143-146]. Few studies using

Snellen acuity[143, 147] and contrast sensitivity charts[145, 148] do not reveal a direct relationship between different contact lenses and reduced visual performance while other authors[144] propose decreased CSF for higher spatial frequencies. However, dynamic measures of vision after blinking suggest visual changes to occur during contact lens wear. Ridder and Tomlinson[149] observed transient fluctuations in contrast sensitivity following a blink, with a significant loss of CSF occurring with spherical soft contact lens wear compared to spectacles. Thai et al.[150] also reported the CSF to be significantly reduced for middle to high spatial frequencies when the pre-contact lens tear film dries and breaks up. The possibility of pre-corneal tear film break up in contact lens wearers is proposed to account for the intermittent blurred vision and may also act as a stimulus for blink. Timberlake et al.[151] suggests that the light scatter produced by the changes in hydration levels of the lens or changes in the quality of the tear film might cause variations in visual performance with soft lens wear. Deposit formation on HEMA lenses[152] and use of lower content lenses[146] are also proposed to be associated with reduced contrast sensitivity. However, the interaction between vision and ocular discomfort is still not completely understood. Papas et al.[153] proposed an association between vision and comfort, with a decrease in comfort during increased levels of blur. To explore the concept of vision and comfort interaction in detail, further studies are required.

Table 1-2: Literature review on ocular discomfort with contact lenses

Author	Lens Type	Sample size	Variables in study	Results	Other notes
Bradley[174] (1979)	Hydrogels	24	Lens thickness	Greater changes in corneal sensitivity, increased corneal thickness over 6- months of wearing period	
Efron[156] (1986)	Hydrogels	10 unadapted subjects	Contact lens power, water content	Negative correlation between comfort and water content No correlation between lens power and comfort	
Efron[167] (1988)	Hydrogels	Survey on 104 lens wearers	Water content	Symptom of dryness associated with lower water content lenses	
Brennan[135] (1989)	Hydrogels	104	Symptomatology with contact lenses	Dryness was reported more than scratching and watering. Symptoms were reported by patients wearing lenses for more than 6 months and toric lenses	

Pritchard[158] (1995)	Hydrogels	19	Lens dehydration	Dehydration of lenses over 7 hour period does not affect lens movement and dryness	
Young[173] (1996)	Hydrogels	2065 soft lens trial fittings	Lens fitting characteristics	Subjective comfort is of some limited value in assessing loose fitting lenses and not tight fitting lenses	
Lebow[159] (1997)	Hydrogels	100	Comparison of material properties between Proclear and Acuvue lenses	Better comfort, decreased post blink movment, better fit with Proclear	Increased dehydration with Acuvue lenses
Fonn[157] (1999)	Hydrogels	20 symptomatic and asymptomatic lens wearers	Lens dehydration	No correlation between lens dehydration and subjective dryness and comfort	Symptomatic group had reduced wearing time, decreased comfort, increased dryness rating and reduced NIBUT
McNamara[172] (1999)	Hydrogels	23	Lens diameter	Larger diameter associated with higher comfort scores	

Inaba[162] (2000)	Daily disposables	127 subjects (45 subjects wore 1-Day Acuvue Lenses), 82 subjects wore other types of soft lenses)	Comparison of etafilcon A (1-Day Acuvue) and nelfilcon A (Focus Dailies)	Subjective preference for 1-Day Acuvue lenses	
Dumbleton[171] (2002)	Silicone hydrogels	95	Base curve	Better comfort with steeper base curve	
Guillon[169] (2006)	Silicone hydrogels and hydrogels	24	Wettability	Silicone hydrogel (galyfilcon A) had better wettability and comfort than alphafilcon A (hydrogel). Wettability was found to be associated with comfort	

Brennan[160] (2006)	Silicone hydrogels	56	Comparison of galyfilcon A and lotrafilcon A lenses	Galyfilcon lenses showed better overall daily wear clinical performance than lotrafilcon A	
Epstein[166] (2006)	Disposable lens weare	8	Lens care products	ReNu MultiPlus was associated with decreased comfort during midday and end-of-day. There was also significant reduction in corneal sensitivity compared to OPTI-FREE Express	
Walker[161] (2007)	Daily disposable	282	Comparison of etafilcon A (1-Day Acuvue) and nelfilcon A (Focus Dailies)	1-Day Acuvue showed higher mean comfort scores, better end of the day comfort, longer wearing time, better fitting pattern and ease of removal	
Andrasko[168] (2008)	Silicone hydrogels	30	Solution toxicity	Some solution/lens combinations cause excessive corneal staining 2 to 4 hours after lens insertion. Patients with high levels of corneal staining experience decreased comfort	
Santodomingo Rubido[170] (2008)	Silicone hydrogels	26	Base curve	No difference in comfort between 8.3 and 8.6 base curve lens	

Wilcox[163] (2010)	Silicone hydrogels	10	Lens care products	Lens care products change corneal staining and comfort responses during wear. Lotrafilcon lenses had decreased comfort, increased burning/stinging, increased lens awareness on insertion	
Zhao[164] (2010)	Silicone hydrogels		Protein and cholesterol deposition on lenses	Amount of protein or cholesterol extracted from lenses was not associated with corneal infiltrative or mechanical adverse event during wear and was only very weakly correlated with insertion comfort of lenses	
Keir[165] (2010)	Silicone hydrogels	26	Lens care systems (H_2O_2 and MPDS)	H_2O_2 resulted in longer reported comfortable wearing time than MPDS. No difference in overall ratings of comfort, dryness and vision between solutions	
Chen[155] (2010)	n/a	Symptomatic lens wearers, asymptomatic lens wearers (20 in each group)	Tear menisci	Comfort linearly associated with decreased tear volume after 10 hours	

Chapter 2

Measurement of difference thresholds on the ocular surface

2.1 Introduction

The measurement of sensory threshold plays a pivotal role in the assessment of any sensory system as it serves to be an important indication of the health of the system. Thresholds can be categorized into absolute thresholds and difference thresholds. Absolute threshold is the smallest amount of stimulus energy necessary to produce a sensation[1]. When the sensory threshold is reached, the stimulus needs to be increased or decreased by a certain amount to sense a change in the stimulus. The amount of change in a stimulus ($\Delta\varphi$) required to produce a just noticeable difference (jnd) in sensation is called the difference threshold[1] (DL).

Weber in 1846[2] proposed that heavier weights are difficult to discriminate than two relatively lighter weights, and the size of the DL is linearly related to the stimulus intensity. The relationship between the difference threshold and the stimulus intensity is referred to as the Weber's law, which states that the change in stimulus intensity that can be discriminated ($\Delta\Phi$) is a constant fraction (c) of the starting intensity of the stimulus (Φ).

$$(\Delta\Phi)=c\Phi$$

The physical value corresponding to DL is $\Delta\Phi$.

The size of the Weber's fraction is unique to each sensory dimension and can be compared across different modalities and conditions. Experiments have been conducted in vision[3], hearing[4-8], smell[9] and tactile sensation[10-12] to study the sensory discrimination differences. Weber's fractions were found to range from 0.3 for the pitch of pure tones[13] to 25 for odor intensity[9], and the size of the fraction was hypothesized to be associated with the ability of the sensory system to detect differences. Vision and hearing were observed to be keenest senses, while taste and smell were found to be the dullest[1].

The ocular surface thresholds ever reported have been absolute thresholds. Early detection thresholds were estimated using Cochet-Bonnet type (C-B) esthesiometers[14] with threshold determined by the touching the cornea with a fine nylon filament. The procedure of tactile stimulation suffered from several drawbacks[15-17] and it has now been succeeded by the pneumatic esthesiometers. Measurements of absolute threshold with the pneumatic esthesiometer are found to be reliable and repeatable[16, 18, 19]. However, there is a discrepancy in the absolute thresholds reported by different studies. The contributing factors for the variability include [15, 16, 18-20]: differences in psychophysical techniques employed, the characteristics of the instrument used, the time of the day the measurements were obtained, the type of stimuli used, the distance of the probe from the ocular surface and the duration of the stimulus.

Investigations of the impact of contact lens wear on corneal sensitivity have had varying results. Depression of corneal sensitivity was noted in earlier studies using tactile stimulation[21-23] and the factors contributing to the reduction were hypothesized to include the use of low dk lenses[24], decreased oxygen permeability[23, 24], duration of contact lens wear[22, 25, 26] and type of lenses worn [27, 28]. Measurements with the pneumatic esthesiometers have shown mixed results. In a study comparing non contact lens wearers, soft and rigid gas permeable lens wearers, a difference in sensitivity was observed between lens and non-lens wearers[29], while there was no difference between soft and rigid lens wearers. Stapleton et al.[18] demonstrated no difference in corneal sensitivity between non lens wearers and users of low DK and high DK lenses after six hours, while increases in sensitivity were observed in subjects using silicone hydrogel lenses[30]. The possible mechanisms underlying the changes with contact lens wear were proposed be 1) mechanical effect of the lens 2) decreased oxygen supply 3) change in pH of the cornea that may cause a reduction in the sensory nerve function[29].

On the ocular surface, the investigation of just noticeable inter-ocular comfort difference with different contact lenses has been undertaken[31]. The results were that the subjects were able to detect clinically significant changes in comfort with a difference of 7- 8 units of the numerical ratings between the two eyes. This study perhaps provides some sort of preliminary information about the discrimination capacity of the ocular surface, but contact lenses are not a source of fixed stimulus strengths that can be quantified, so traditional discrimination data cannot be determined as the stimulus intensity is not related to the sensory difference. Therefore, to investigate the difference thresholds of the ocular sensory neurons, suprathreshold stimuli of quantifiable intensities needs to be utilized. The purpose of the present experiment was to measure the difference thresholds of the central cornea using a modified Belmonte pneumatic esthesiometer and to investigate if there are any differences in thresholds between contact lens wearers and non-lens wearers.

2.2 Materials and methods

2.2.1 Subjects

24 participants were enrolled for the study; 12 were soft contact lens wearers and 12 were non-lens wearers. The age of the participants ranged from 21 to 33. All the subjects were in good ocular and systemic health. Contact lens wearers wore either daily or bi-weekly disposable hydrogel or silicone hydrogel lenses and were asked to cease lens wear the night before the test

procedures were performed. The subjects had a history of lens wear for more than a year and wore lenses for at least 3 days a week for a minimum of 5 hours a day. The study was approved by University of Waterloo Ethics Research committee. Subjects in good health were chosen in the study in order to establish a baseline for difference thresholds measurements on the ocular surface.

2.2.2 The Belmonte esthesiometer

The construction of the computer controlled Belmonte esthesiometer has been described in various studies [20, 32, 33]. The modified Belmonte esthesiometer was used to deliver mechanical and chemical stimuli to the central cornea. It contained computerised flow controllers mixing air and CO_2 as well as controlling the stimulus temperature. The distance between the ocular surface and the tip of the esthesiometer probe was continuously monitored by a calibrated video camera. Custom software was used to enter the appropriate psychophysical technique, stimulus modality and duration of the stimulus, and to record the subjects' responses from a button box. The mechanical stimuli consisted of a series of air pulses with flow rate ranging from 0 to 200ml/min. The temperature of the stimulus was set at 50^0 C, which translated to 33^0 C at the ocular surface[34].

2.2.2.1 Flow rate calibration

The Belmonte esthesiometer used in this study has been calibrated previously[35]. Briefly, the flow rate of air from the Belmonte esthesiometer was calibrated using a custom electronic calibrator developed at the School of Optometry, University of Waterloo. The calibrator consists of 2 mechanical and 2 thermal sensors (the calibrator was pre-calibrated using laser trimming resistors which were manufactured by Linear Technology and Maxium, USA). The mechanical calibration was performed under normal conditions with ambient temperature between 20-24^0 C and humidity of 30-40%. The calibration of flow rate was done from 20 to 200 ml/min at 20, 30, 40 and 50^0 C respectively. The electronic calibrator was positioned at a distance of 5mm from the tip of the probe and for each flow rate, the measurement was taken three times and averaged.

2.2.3 Procedures

The measurement steps and the procedure involved with esthesiometry were described to the subjects. All the measurements were carried out on the randomly selected eye. Mechanical detection threshold of the central cornea was first determined using the method of limits. The initial stimulus intensity was 10 ml/min and increased in 10 ml/min step until the participant reported the presence of the pneumatic stimulus. The detection threshold was then fine tuned by decreasing the flow rate by 20 ml/min and then increasing in 5 ml/min steps until the presence of stimulus was once again reported. This procedure was done three times and the absolute threshold was an average of the three measurements. Following the measurement of absolute threshold, a series of systematically increasing stimuli (in 5ml increments) were presented, with the first stimulus being 25% less than the absolute threshold. The subjects were asked to compare the intensity of each stimulus with the preceding one and report if any difference in intensity was detectable. The intensities at which the subjects perceived an increase from the previous stimulus were recorded. The difference threshold (DL) was the differences between the stimulus intensities at which an increase was perceived and five DLs were measured for each participant.

2.2.4 Data analysis

Statistical analysis for this study was performed with Statistica 9.0 (Statsoft Inc. Tulsa, OK, USA). Independent sample Student's t-test was used to compare the absolute thresholds between lens and non-lens wearers. Repeated measures ANOVA was employed to compare the difference thresholds between lens wearers and non-lens wearers. $P \leq 0.05$ was considered to be statistically significant for all the tests.

Bilinear functions using least squares non-linear regression were fit to the group data of lens and non-lens wearers to plot the Weber's fractions for different stimulus intensities.

2.3 Results

Comparison of mean absolute thresholds in the lens and non-lens wearing groups (illustrated in Figure 2-1) did not show any statistically significant difference [t (df =22) =-1.89, $p=0.07$]. Repeated measures ANOVA revealed a significant main effect of DL level on the Weber's constant, with the Weber's constant at the first DL being higher than the following DLs. The Weber's constant for the second DL was also statistically different from the last DL ($p<0.001$). A significant main effect of the group type was also observed with the lens wearers showing higher Weber's constants than the non-lens wearers [F (df =1, 22) = 5.66, $p=0.02$]. However, there was no interaction between DL level and lens wearing group on Weber's constants [F (df=4, 88) = 1.05, $p=0.38$]. The results from the repeated measures ANOVA are illustrated in Figure 2-2. The bilinear fit of the Weber's constants in the lens and non-lens wearing groups are presented in Figures 2-3 and 2-4.

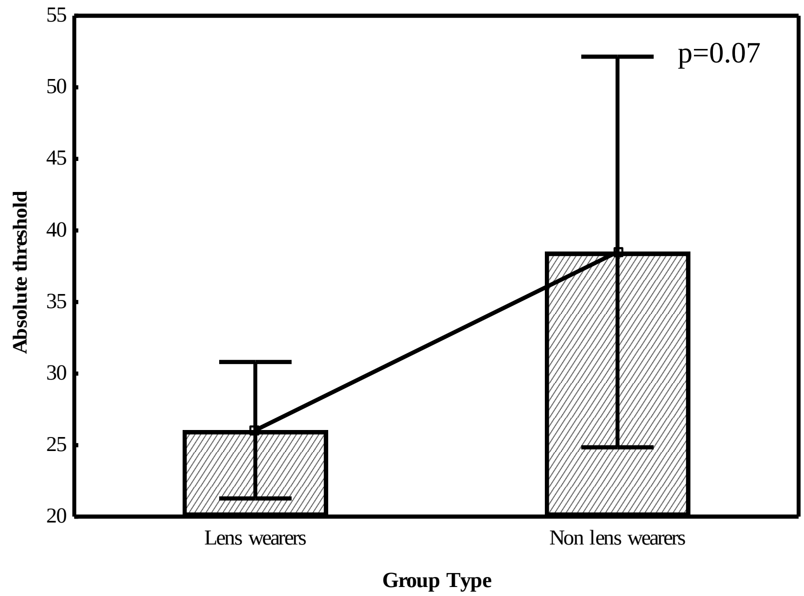

Figure 2-1: **Mean absolute thresholds in lens and non-lens wearers**

Vertical bars denote 95%CI of mean thresholds

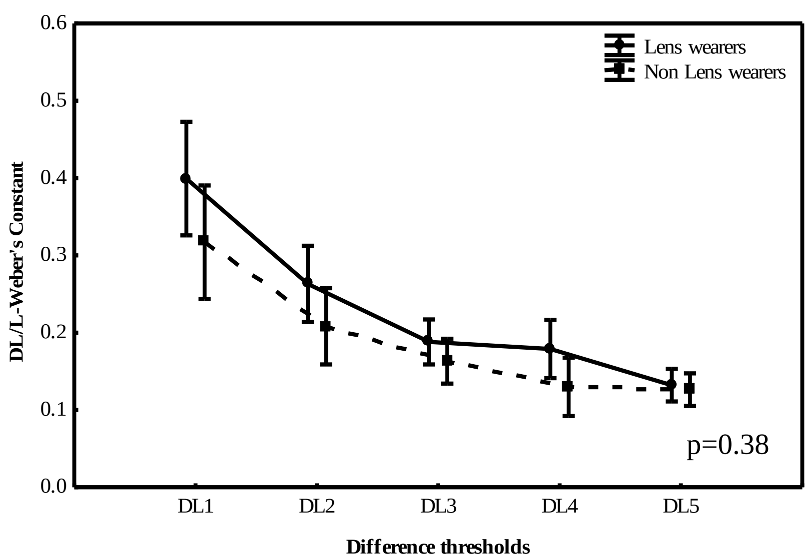

Figure 2-2: **Mean difference thresholds in lens and non-lens wearers**

Vertical bars denote 95%CI of mean thresholds

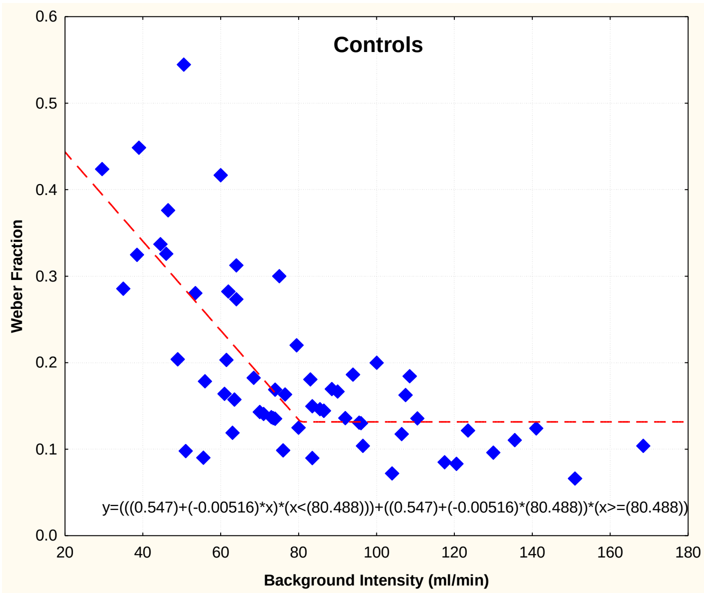

Figure 2-3: Weber fractions for different stimulus intensities in the group of non-lens wearers. The continuous line represents the bilinear line of best fit with a quadratic polynomial.

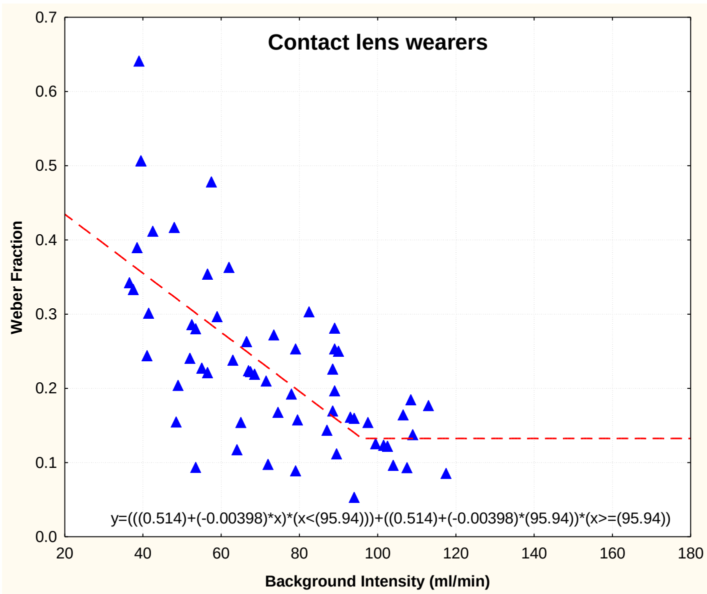

Figure 2-4: Weber fractions for different stimulus intensities in the group of lens wearers. The continuous line represents the bilinear line of best fit with a quadratic polynomial.

2.4 Discussion

The results of the study indicate that the difference thresholds of the central cornea can be successfully measured using a pneumatic esthesiometer. Previously, various investigators[15, 17-20, 32, 33] have measured the absolute thresholds of the central and peripheral cornea as well as the conjunctiva. The responses of the ocular surface to suprathreshold stimulation with different stimulus modalities have also been documented[20, 36-38]. These investigations demonstrated that the pneumatic esthesiometer can be effectively employed to study the sensory processing on the ocular surface. The present study sets another milestone by providing insight on how the ocular surface detects differences in stimulus intensities.

The Weber's fraction is a useful index of sensory discrimination for comparison across different modalities and stimulus conditions. In this experiment, the Weber's fraction ($\Delta\Phi/\Phi$) approaches a constant value for high intensities and it increases rapidly for low stimulus intensities close to the absolute threshold. A similar phenomenon has been observed in the discrimination of auditory tones[6] and tactile vibration[11]. Different Weber's fractions have been reported using vibrotactile stimuli[11, 39], the variations hypothetically occurring due to the differences in methodology and stimulus conditions. In a study[6] that investigated the intensity discrimination of auditory tones, the Weber's fraction was found to rapidly decrease with an increase in stimulus intensity and the fraction was found gradually to decrease without becoming a constant. This deviation from the Weber's law for low intensity stimuli is known as the "near miss" of the Weber's law[7]. Discrimination experiments in loudness and noise[8] also demonstrated the Weber's constant to be higher with stimulus intensities closer to threshold that became a constant with increasing levels of intensity. The increase in Weber's constant towards the lower intensity stimuli can be due to the presence of noise in the stimulus or sensory noise, a continuous random fluctuation in the activity levels of the neurons that carry signals from the ocular surface to the central nervous system[1]. The background noise is observed to be present even in the absence of the stimulus[40]. Since sensory noise is present as spontaneous activity in the nervous system as a background to stimulation, the level greatly influences the value of $\Delta\Phi$ for very low stimulus intensities. For a stimulus to be perceived, the ocular neurons should respond strongly enough to the stimulus and distinguishable from the action potentials produced by the sensory noise. The measurement of absolute threshold is also regarded as a measure of difference threshold as it denotes the stimulus strength required to increase the neural activity level above the sensory noise(when there is no background) by some critical amount in order to be perceived[40]. Hence, both the absolute and differential threshold involves the discrimination of differences in neural activity levels. If the presence of sensory noise around the detection thresholds is taken into account, Weber's law holds true for the difference thresholds of the ocular surface as well.

Another important finding in this study is the absence of differences in absolute threshold between lens and non-lens wearers, while the difference thresholds were higher in lens wearers than non-lens wearers. Recent studies on ocular surface sensitivity in silicone hydrogel contact lens wearers have demonstrated no changes in sensitivity[18] or an increased sensitivity[30] with lens wear. Contact lenses have been hypothesized to depress the sensitivity of the cornea by the mechanical effects of the lens against the ocular surface or cause a change in corneal metabolism perhaps due to hypoxia[29], along with compromise of the tear film with lens wear[41-43]. A combination of these factors might alter the equilibrium of the ocular surface, causing a change in sensory input in contact lens wearers possibly increasing the neural noise in lens wearers and thereby giving rise to increased Weber's constant. The shift in neural activity levels between lens and non-lens wearers can also be observed in the bilinear fit of the pooled data as illustrated in

Figures 2-3 and 2-4. The relatively fewer data points for stimulus intensities higher than 120ml/min were because only 5 DLs were measured for each participant. Despite this apparent limit, there still were two statistical components to the bilinear fits as illustrated in Figure 2-4. Another explanation for the observed differences is that the discrimination of pneumatic stimuli itself may be processed differently in the central nervous system for lens and non-lens wearers due to the differences in ocular surface physiology. The increased level of noise in lens wearers during discrimination, especially for low intensity stimuli such as the stimuli provided by contact lenses, may also be the reason why participants find it difficult to differentiate comfort experienced with different lens types.

The inability to detect a difference in absolute thresholds between lens and non-lens wearers can be due to the small size of the study. The increased variance in the absolute thresholds of non-lens wearers (Figure 1-1) can also perhaps cause the non-significant statistical difference in detection thresholds between the two groups, while indeed there might have been actual differences existing between them. In other sensory dimensions[12, 44], difference thresholds were found to be similar even in the presence of different absolute sensitivity. When vibrotactile intensity discrimination was measured by three methods, it was observed that regardless of the sensory channel excited by each method, the DL functions were the same[12]. This non-difference in DL functions by different methods indicates that the neural processes responsible for the DL must have been the same for each channel or the whole process operates at a level in the central nervous system that integrates information across the psychophysical channels. The discrimination of vibrotactile stimuli was also observed to be similar in the presence of pain and non painful conditions, supporting the hypothesis that the effect of pain on tactile sensation is a sensory rather than a cognitive process, and the mechanisms governing tactile sensitivity are different from that of discrimination[44]. On the ocular surface, the suprathreshold sensory processing is shown to be different for mechanical and chemical stimulus modalities[20, 32, 36], and varying locations[45], but the influence of contact lens wear on suprathreshold stimuli is yet to be studied. At suprathreshold levels, as in discrimination of pnuematic intensities, the stimulus comparisons are based on the differences in the sensation magnitude of two stimuli whereas absolute threshold involves the difference between no sensation and presence of a sensation (ie. the detection of stimulus from the background). Detection thresholds might be hypothesized to occur when a stimulus produces sufficient change in neural activity that is different from spontaneous activity (or neural noise when there is no stimulus). During discriminiation, there is a combination of neural noise and stimulus driven neural activity (as well as stimulus noise perhaps) and discrimination threshold is reached when a decision can be made by the observer that the neural activity has increased (or decreased for decrement thresholds) and is different. Hence, the two measurement types can fundamentally involve different mechanisms of sensory processing and the detection and discrimination tasks may not co-vary.

In conclusion, this study demonstrates that the difference thresholds of the ocular surface can be evaluated using a pneumatic esthesiometer. If as anticipated, the psychophysical results reflect neural activity of the receptors, of the neurons and the central processing complex, then the results demonstrate that ocular sensory neural processing is altered by contact lens wear, as exhibited by the differences in difference thresholds for pneumatic stimuli and a change in ocular surface physiology could possibly be observed with difference threshold measurements. To understand the sensory processing on the ocular surface better, the test of difference thresholds should be included in studies that investigate ocular comfort between different lens types.

Chapter 3

Psychophysical scaling of ocular discomfort with contact lenses

3.1 Introduction

Measurement of comfort is an essential part of contact lens evaluation. Traditionally, comfort assessment involves the use of subjective rating scales. Visual analogue scales (VAS) are commonly utilized[1-8] to record reactions from observers, as are category scales[9, 10]. Numerical ratings are similar to VAS providing reliable and valid results[11-13], where the subjects assign numbers corresponding to the magnitude of sensation. In the psychophysical domain, numerical ratings can be regarded as the method of magnitude estimation, which is used to derive sensation magnitudes. Although these measures provide subjective estimates of the underlying sensation, there are no objective quantifications to anchor the subjective findings. The objective quantification with pneumatic stimuli can help minimize the variability in the subjective ratings of comfort by providing an estimate of ocular discomfort that the participant might experience and serves as a form of ***Master scaling***[14]. Assistance can perhaps be derived from the area of psychophysics to fill in this inadequacy.

A variety of psychophysical scaling procedures can be utilized to systematically measure the psychological responses to physical properties of objects. Psychophysical scaling refers to the process of quantifying mental events, especially sensation and perception, and then relating these to quantitative measures of physical stimuli. The interesting feature is that the stimulus and the resulting sensation do not always have a one to one relationship, but rather they could be power functions. Stevens[15] in 1957 postulated the “power law” that states that the subjective magnitude of sensation grows approximately as a power function of the stimulus intensity. The power law is represented by the general function $\psi = k\Phi^n$ in which ψ is the sensation magnitude, Φ the physical stimulus strength and k is the scaling constant. The power exponent is denoted by 'n' and characterises the rate at which the sensation grows as a function of physical stimulus intensity. Each sensory dimension has a unique exponent that ranges from 3.5 for electric shock to 0.33 for brightness[16].

Psychophysical scaling can also be approached by cross modality matching where an observer adjusts the stimulus magnitude on one continuum to achieve a magnitude match on another continuum[17, 18]. In cross modality matching, one domain is selected as the standard and the other continuum is adjusted until an equal sensation is achieved. A psychophysical scale is constructed when the stimulus intensities of two modalities carrying equal sensations are matched to each other. Another method called 'magnitude matching' was developed by Stevens and Marks[19] where the sensory magnitudes of two different modalities are separately quantified by magnitude estimation and then the intensities that carry the same sensory magnitudes are matched. Stevens[20, 21] conducted experiments using cross modality matching to match the sensations arising from the force of a handgrip to equate sensations of varied magnitude on nine different perceptual continua. In another study[22], the loudness of sound was matched to intensities of sensations on ten other perceptual continua. A similar approach has been undertaken in clinical patients, where ear function was evaluated by adjusting the vibration on a fingertip to match the loudness estimates with normal hearing and those with conductive or neural loss[23]. Three distinctly different loudness functions were observed, with hearing affected by neural loss having steeper functions compared to normals, and those with conductive hearing loss gave rise to slopes similar to normals but displaced higher up on the intensity scale. Cross modality matching has also been used to test the effectiveness of medications, where the intensity of discomfort was scaled by adjusting the loudness of noise presented through earphones[24].

On the ocular surface, scaling of corneal sensations has been performed using tactile as well as pneumatic stimuli. Corneal stimulation with the Cochet-Bonnet esthesiometer[25] revealed the power exponent to be 1.01. Later studies[26-29] using the pneumatic Belmonte esthesiometer related the pneumatic stimulus strength to the resulting sensation magnitude to derive the power exponents for ocular surface sensations. Feng[26] reported the corneal power exponents to be 0.82 and 1.08 for mechanical and chemical stimulus respectively while a similar study by Belmonte[27] revealed intensity-response curves with an exponent of 0.58 for mechanical and 0.63 for chemical stimulus. Chen et al.[28] also found the relationship between CO_2 concentration and pain magnitude to follow Stevens' power function with an exponent adjusted to 1.12. A study[29] on sensory transduction in central and peripheral corneal locations showed an exponent of 1.38 and 1.19 for mechanical stimuli respectively. For chemical stimulation, the exponents were 0.97 and 0.96 for the central and peripheral locations respectively.

In the present study, the ocular surface response to suprathreshold stimulation is evaluated in a unique way using contact lenses. To understand how the contact lens induced sensations are matched to physical stimuli delivered by the Belmonte esthesiometer, I performed the following experiment which examined the discomfort arising from wearing contact lenses of different designs matched to the stimuli from the pneumatic esthesiometer. An equal sensation function was created by matching the discomfort from contact lens wear to the magnitude of sensation produced by the pneumatic stimuli from the modified Belmonte esthesiometer and then, the dimension of each contact lens was related to the strength of the pneumatic stimulus. The primary purpose of this study was to devise a novel scale for ocular discomfort using contact lenses and corneal esthesiometry as two different modalities. Along with the process of scaling, the effects of lens sequence, lens types and time on ocular discomfort ratings were also explored. The hypothesis of this experiment is that psychophysical scaling can be an effective technique to relate the discomfort from contact lens wear to the discomfort from pneumatic stimuli delivered by a Belmonte esthesiometer.

3.2 Materials and methods

3.2.1 Subjects

27 participants were enrolled in this experiment; 14 were lens wearers and 13 were non contact lens wearers. Four subjects from Chapter 2, four subjects from Chapter 4 and eleven subjects that were enrolled for Chapter 5 were included in this study. The age of the participants ranged from 21-33. All the subjects were free of ocular and systemic diseases. Contact lens wearers were wearing either daily or a bi-weekly disposable hydrogel or silicone hydrogel lens. The subjects had a history of lens wear for more than a year and wore lenses for at least 3 days a week for a minimum of 5 hours a day. Contact lens wearers were asked to cease lens wear the night before the test procedures were performed.

3.2.2 Contact Lenses

Soft contact lenses (38% polyHEMA) of plano refractive power and center thickness of 0.15mm were ordered from Custom Contact Lenses Inc., (Scarborough, Ontario, Canada). Three base curves and three lens diameters were utilized in the study. The base curves were: 8.2, 8.7, and 9.2 mm and lens diameters were 13.8, 14.2, and 14.5mm.

Slit lamp biomicroscopy was performed before lens insertion and after lens removal to evaluate the ocular surface health. Fluorescein dye was used to examine the presence of any corneal and conjunctival staining due to lens wear. The fitting characteristics of all the lenses were recorded by a slit lamp video camera. The centration of the contact lens, coverage, lens movement and lens lag were the parameters that were documented.

There were three set of lenses available for each lens type and the lenses were sterilized by overnight soaking in a hydrogen peroxide system (Clear Care, CIBA VISION, Duluth, GA) before reuse.

3.2.3 The Belmonte esthesiometer

The computer controlled Belmonte esthesiometer and its construction has been described in various studies[27, 30, 31]. In brief, the modified Belmonte esthesiometer was used to deliver mechanical and chemical stimuli to the central cornea. It contained computerized flow controllers mixing air and CO_2 as well as controlling the stimulus temperature. The distance between the ocular surface and the tip of the esthesiometer probe was continuously monitored by a calibrated video camera. Custom software was used to select the appropriate psychophysical technique, stimulus modality, and duration of the stimulus. The subject's responses were recorded from a button box.

The mechanical stimuli consisted of series of air pulses with flow rate ranging from 0 to 200ml/min. Chemical stimuli comprised of 0 to 90% CO_2 mixed with air, with the flow rate of air set at 75% of the mechanical threshold. The temperature of the stimulus was set at 50^0 C, which translated to 33^0 C at the ocular surface[32].

3.2.4 Numerical rating scale

The magnitude of sensations (discomfort, burning, itching, scratchiness, warmth and cold) was recorded using a 0-100 numerical rating scale where 0 indicated the absence of sensation and 100 represented the most intense sensation.

3.2.5 Procedures

The measurement steps and the test procedure involved with esthesiometry were described to the subjects. The mechanical threshold of the randomly chosen eye was first estimated using the ascending method of limits. Three measurements were taken and the threshold was an average of them. The subjects were then instructed on the psychophysical method of adjustment, where the intensity of the pneumatic stimulus had to be adjusted to match the discomfort arising from the contact lens that would be placed on the eye soon after. The participant used a control dial to regulate the intensity of stimulus, in order to achieve an equal magnitude of discomfort in both the eyes.

The assigned soft contact lens was then placed on the fellow eye and the sensations were measured using a numerical rating scale. Following this, the subjects were asked to regulate the intensity of the pneumatic stimulus using the control dial in order to match the discomfort from the stimulus to the discomfort from contact lens wear. At the completion of magnitude matching, ratings of sensations were again recorded. The fitting characteristics of the contact lens was then assessed and documented using a slit lamp video camera. Lenses were removed and the ratings were once again reported. The same procedure was followed with the placement of the next assigned contact lens.

Four contact lenses were used in each session with a 10-minute interval between the measurements with each lens type. Each session lasted for approximately one hour. Subjects were assigned eight lenses for the study, randomized from the total pool of nine lenses. The first four lenses were used in the first session and the remaining four lenses were tested in the second session. All subjects had to undergo two sessions with mechanical stimuli and two sessions of chemical stimulation. The order of lenses was maintained the same for mechanical and chemical sessions to enable comparison across the two sessions.

3.3 Data analysis

Numerical estimates of ocular discomfort and their corresponding pneumatic stimulus intensities were used for analysis using Statistica 9.0 (Statsoft Inc. Tulsa, OK, USA). Stevens' power functions[15] were fit to each individual subject's data and for the arithmetic mean of all participants for each lens type. All analyses were done with both arithmetic and geometric means[33]. Since the pattern of results was identical with both estimates of ratings, arithmetic means are presented for the purpose of simplicity. The method of least log squares was used to derive the power exponents and analyze the psychophysical functions. The group mean of all the subjects' sensation magnitudes and their corresponding stimulus intensities was used to derive the master scale of ocular discomfort. Magnitude ordered scaling of contact lens discomfort ratings and its respective pneumatic stimulus strengths was also performed.

Repeated Measures ANOVA was used to investigate the effect of lens sequence and session on ocular discomfort with contact lens wear. Linear mixed modeling using IBM SPSS 19 (SPSS Inc., Chicago, IL) was used to test the influence of lens types on ocular discomfort due to sequence or session effects. The impact of time on discomfort with lens wear was also studied using linear mixed modeling. Multiple regression was performed to identify the sensations most predictive of ocular discomfort. $P<0.05$ was considered to be statistically significant in all the tests.

Ratings of discomfort that were obtained at magnitude match were used for analysis throughout the study except for the investigation of time on discomfort, where discomfort from different time periods was utilized.

3.4 Results

The average and individual psychophysical functions appeared to follow Stevens' power function, with mechanical and chemical stimuli giving rise to different power exponents. Examination of the individual transducer functions revealed that only about half of the subjects were able to match the contact lens sensations to the pneumatic stimulus discomfort, with both mechanical and chemical stimulation. The lens types did not have any impact on the session or sequence in which the lens was presented, although an effect of session and sequence on discomfort was observed. The average discomfort ratings produced by the different lens types were similar. There appeared to be significant effects of time on the reporting of discomfort with lens wear, with the discomfort upon lens insertion rated to be higher than after lenses settling.

3.4.1 Scaling of subjective and objective measurements of ocular discomfort

Non-linear estimation of ocular discomfort from contact wear and its corresponding mechanical pneumatic stimulus match gave rise to well behaved power functions in fourteen out of twenty seven participants. The correlation coefficient 'r' ranged from 0.60 to 0.88 for mechanical stimulation. Chemical stimulation also showed a similar pattern with eleven participants exhibiting a well-fit power function. The correlation coefficient in this group ranged from 0.65 to

0.96. In the subset of participants that showed poor correlations the ‘r’ value ranged from 0.05 to 0.77 for mechanical and 0.05 to 0.63 for chemical stimulation. The participant’s data that showed an ‘r’ value of 0.77 for mechanical stimulation was associated with a negative exponent and hence regarded as a poor fit power function.

Figure 3-1 shows the corneal transducer function for mechanical and chemical stimulation in a single participant. The power exponents in the group of participants that demonstrated well-fit functions with mechanical and chemical stimulation are tabulated in Table 3-1 and 3-2 respectively.

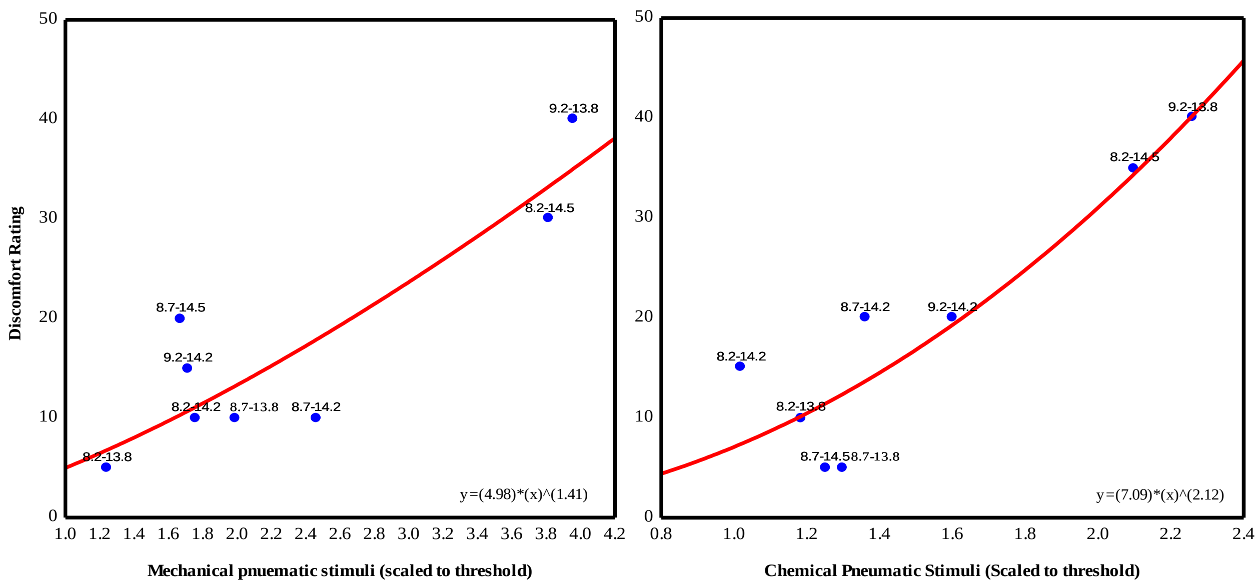

Figure 3-1: **Corneal transducer function of a single participant with mechanical and chemical stimulation**

Table 3-1: **Power exponents of individual psychophysical functions with mechanical stimuli**

Participant id	Mechanical power exponents	Range of numbers used
14	0.37	40-80
22	0.64	15-70
4	0.88	10-70
17	1.05	30-90
21	1.20	5-15
24	1.41	5-40
1	1.58	30-100
13	1.80	2-30
3	1.82	10-90
2	2.17	20-85
6	2.27	10-50
8	2.37	0-80
9	2.60	15-35
25	3.54	5-50

Table 3-2: Power exponents of individual psychophysical functions with chemical stimuli

Participant id	Chemical power exponents	Range of numbers used
1	0.67	10-50
15	0.72	8-30
9	1.00	3-20
13	1.53	10-60
5	1.69	0-45
18	1.83	15-90
3	1.91	5-95
24	2.12	5-40
12	2.76	0-25
2	2.79	10-90
8	3.74	0-25

3.4.2 Group average scale for ocular discomfort

The group mean scale was constructed by calculating the arithmetic mean of pneumatic stimulus intensities and their corresponding discomfort ratings for each lens type. The results are presented in Figures 3-2 and 3-3 for mechanical and chemical stimulation respectively. The power exponent for the group was 1.06 for mechanical and 0.79 for chemical transducer functions. Figures 3-4 and 3-5 are another representation of the group average psychophysical function for mechanical and chemical stimuli respectively, with a common y-axis representing the mean discomfort ratings and a double x-axis representing the mean esthesiometer settings and the contact lens types.

Magnitude ordered scaling was done by ordering the contact lens discomfort based on their magnitudes (irrespective of the contact lens design) and then relating the magnitude ordered contact lens discomfort with their corresponding pneumatic stimulus strengths. Figure 3-6 and 3-7 represents the magnitude ordered scaling of ocular discomfort with power exponents of 1.34 and 0.89 for mechanical and chemical stimulation respectively. The error bars are not displayed in Figures 3-2 to 3-7 as the error bars masked the other data points in the figure, making the scale unclear.

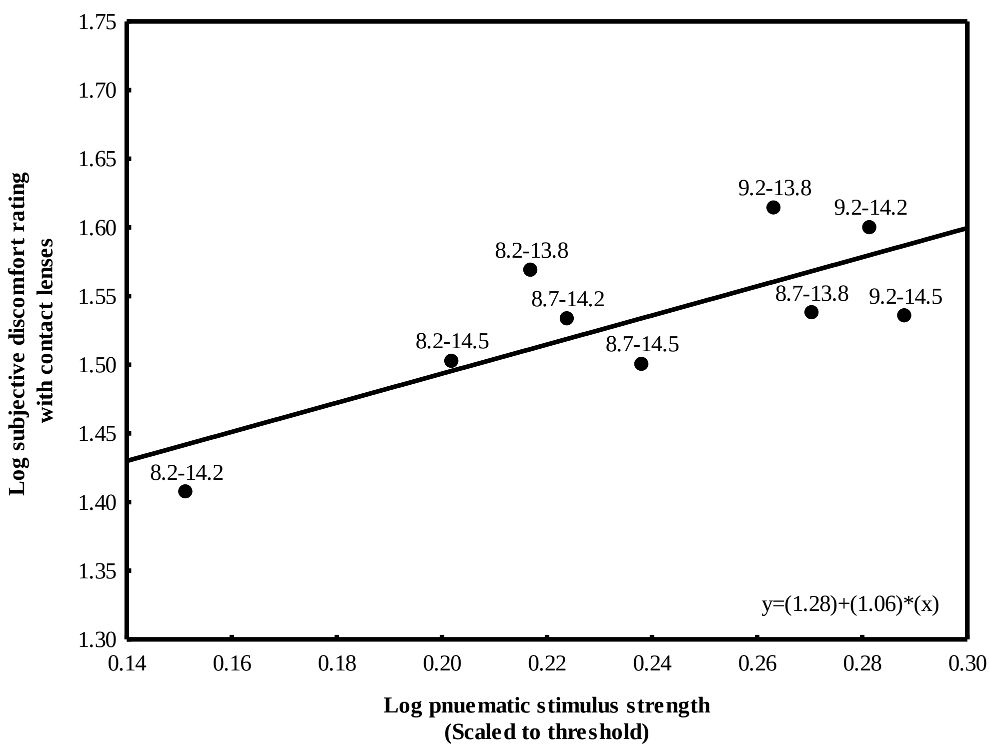

Figure 3-2: Psychophysical scale for ocular discomfort: mean discomfort ratings are related to mean pneumatic mechanical stimulus strength

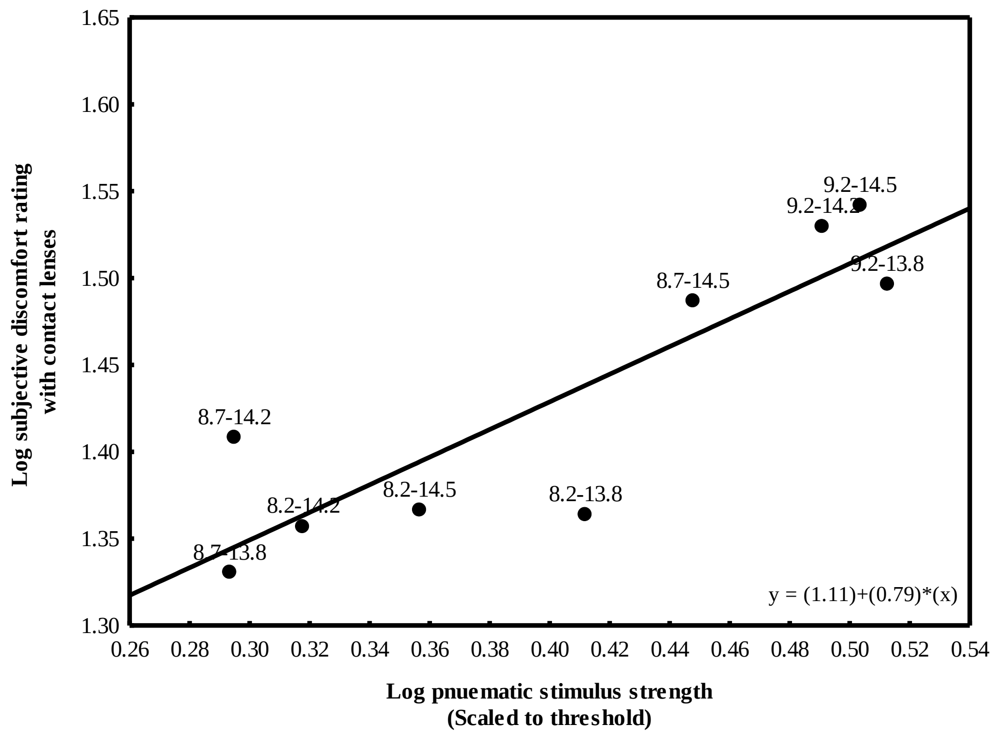

Figure 3-3: Psychophysical scale for ocular discomfort: mean discomfort ratings are related to mean pneumatic chemical stimulus strength

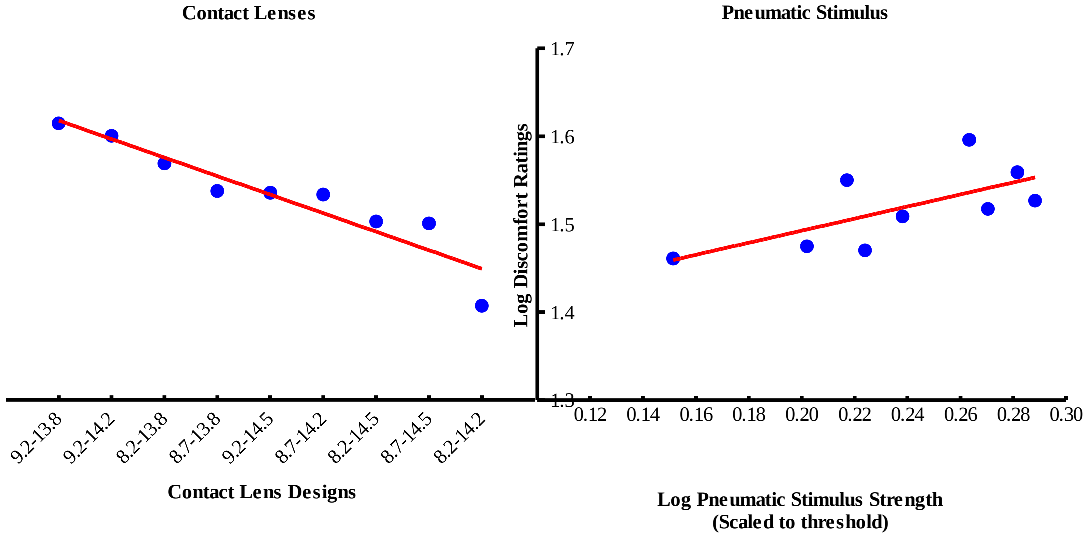

Figure 3-4: Group mean psychophysical scale (in log units) relating discomfort from contact lens wear and corneal esthesiometry with mechanical stimulation

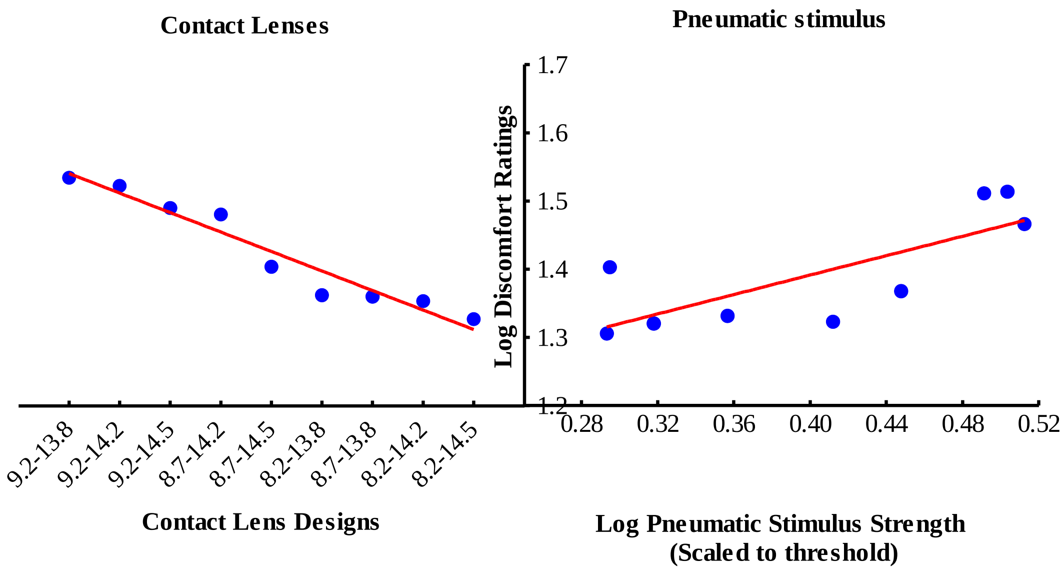

Figure 3-5: Group mean psychophysical scale (in log units) relating discomfort from contact lens wear and corneal esthesiometry with chemical stimulation

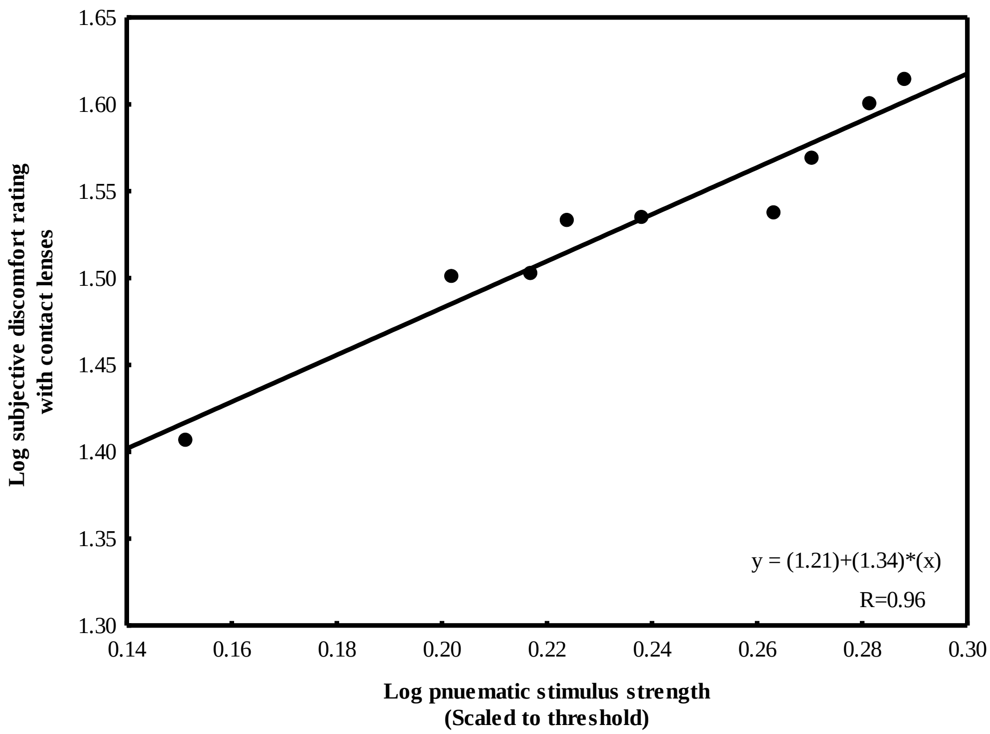

Figure 3-6: Magnitude ordered psychophysical scale for ocular discomfort relating contact lens discomfort and mechanical pneumatic stimulus strength

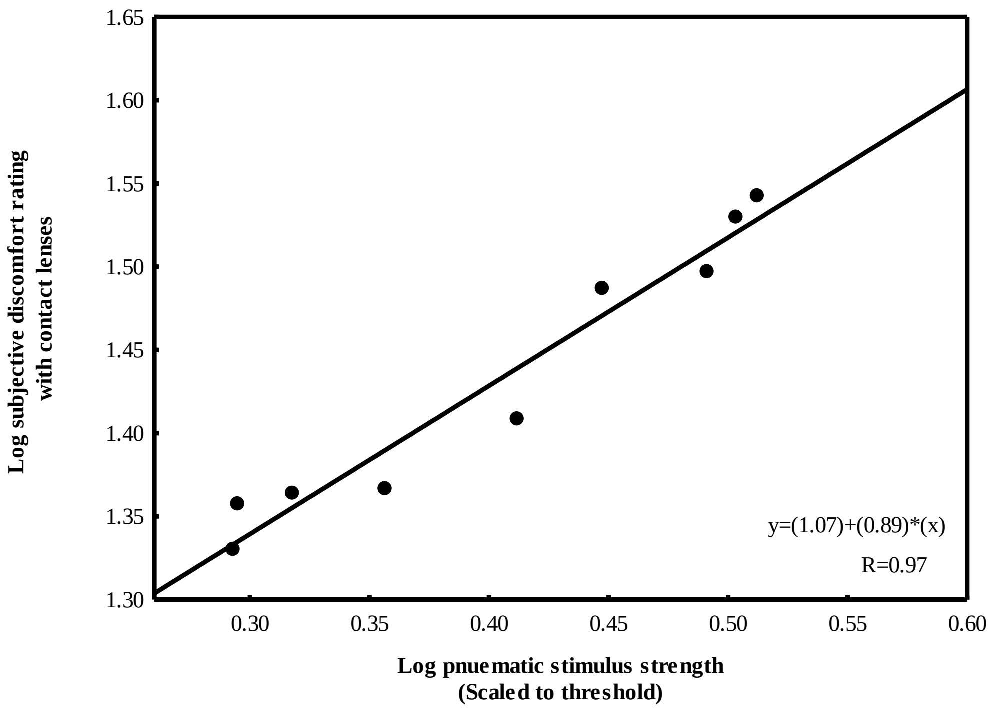

Figure 3-7: Magnitude ordered psychophysical Scale for ocular discomfort relating contact lens discomfort and chemical pneumatic stimulus strength

3.4.3 Multiple regression analysis of the relationship between ocular discomfort and other sensations

Multiple regression analysis of sensation attributes on ocular discomfort demonstrates that scratching and burning were jointly predictive of discomfort from contact lens wear. The flow rate of mechanical stimuli to obtain an equal magnitude match was predicted by the sensory component of scratching, while the flow of chemical stimuli was predicted by burning, itching, and scratching. The summary of regression analysis is presented in Table 3-3.

Table 3-3: **Summary of multiple regression statistics for the dependant variable: discomfort with contact lenses and flow rate for pneumatic stimulation**

Regression summary for dependent variable: discomfort with lenses – Mechanical session			
	Regression Coefficient	**Standard Error**	**p-value**
Scratching	0.57	0.059	<0.001
Burning	0.37	0.05	<0.001

Regression summary for dependent variable: discomfort with lenses – Chemical session			
	Regression Coefficient	**Standard Error**	**p-value**
Scratching	0.54	0.06	<0.001
Burning	0.36	0.05	<0.001

Regression Summary for dependent variable: flow rate with mechanical stimuli-Mechanical session			
	Regression Coefficient	**Standard Error**	**p-value**
Scratching	0.32	0.08	<0.001

Regression summary for dependent variable: flow rate with chemical stimuli-Chemical session			
	Regression Coefficient	**Standard Error**	**p-value**
Burning	0.23	0.07	<0.001
Itching	-0.28	0.10	<0.001
Scratching	0.37	0.097	<0.001

3.4.4 Session effect on ocular discomfort ratings

Measurements during the mechanical session revealed a significant main effect [F (df (1, 26) =6.14, p= 0.01] of session number on contact lens discomfort. Post hoc analysis with Tukey HSD indicated the lenses presented in the first session to be rated higher in discomfort than the lenses in the second session. With chemical session, a significant main effect of lens sequence [F (df (3, 78) = 4.57, p=0.005] was observed with the lens in the first sequence to be rated higher than the lenses in the following sequences. However, there were no significant interaction effects of session number and sequence on discomfort, with p=0.30 [F (df (3, 78) =1.23] for mechanical and p=0.13[F (df (3, 78) = 1.92] for chemical sessions. The results of the effects of lens sequence and session number on discomfort ratings are illustrated in Figure 3-8.

The lens types and the sequence of lens presentation were the same for mechanical and chemical sessions. Hence, the lens discomfort ratings were compared between mechanical and chemical stimulus sessions. In the first session, a significant main effect of lens sequence [F (df (3, 78) = 3.60, p= 0.01] was observed, with the first lens being rated higher than the lens at the fourth sequence. The second session did not show any main effect of lens sequence. No significant interaction effects (with p value at least 0.11) were observed between lens sequence and type of stimulus session (mechanical/chemical) for the first [F (df (3, 78) = 0.49, p =0.68] as well as the second session [F (df (3, 78) = 2.07, p=0.11]. Figure 3-9 represents the lens discomfort ratings between the mechanical and chemical stimulus sessions.

Mechanical session **Chemical session**

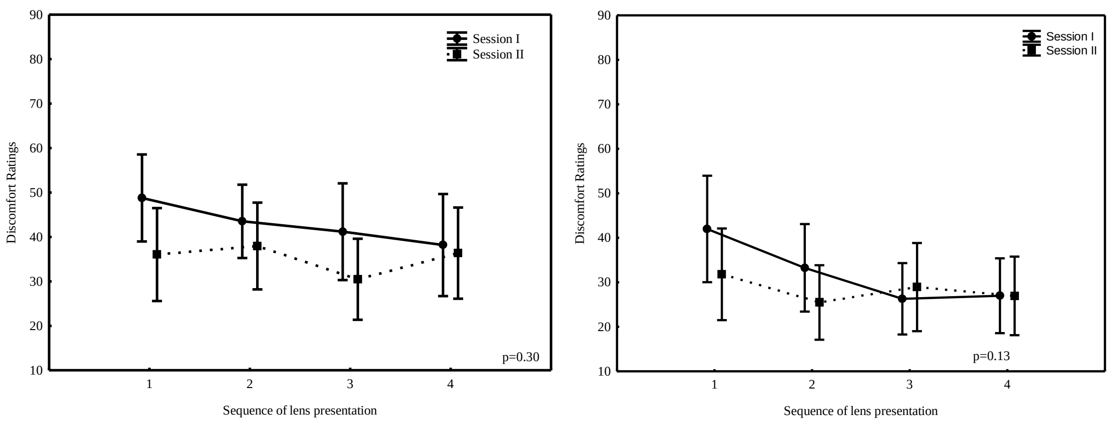

Figure 3-8: Comparison of discomfort ratings across different sessions and lens sequence for mechanical and chemical stimulation

First Session **Second Session**

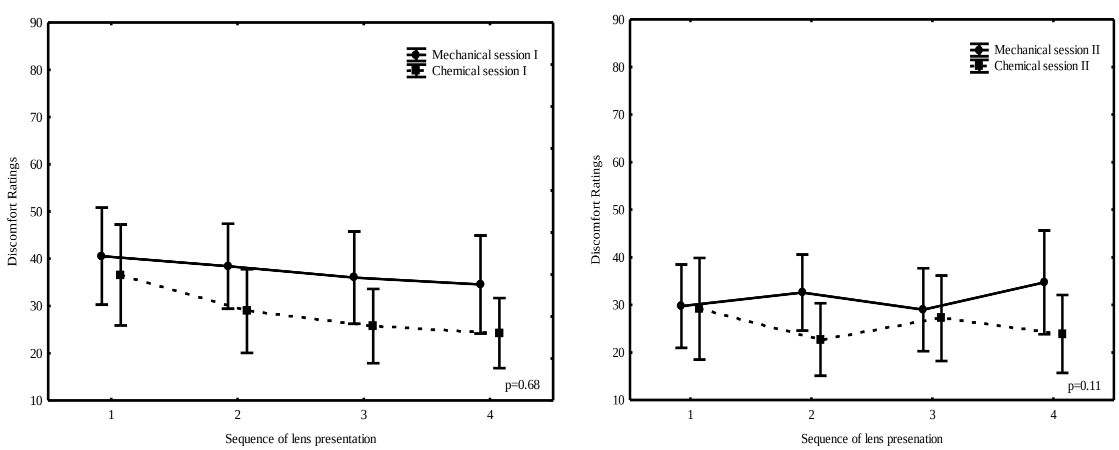

Figure 3-9: Discomfort ratings with lenses between mechanical and chemical stimulus sessions

The impact of lens type on session and lens sequence was further clarified using linear mixed models. The model included random effects of lens type on sequence and session. The fixed effects included lens type, lens sequence, and session. Results as presented in Figure 3-10 reveal no significant effects (p=0.651) of lens type on session and sequence.

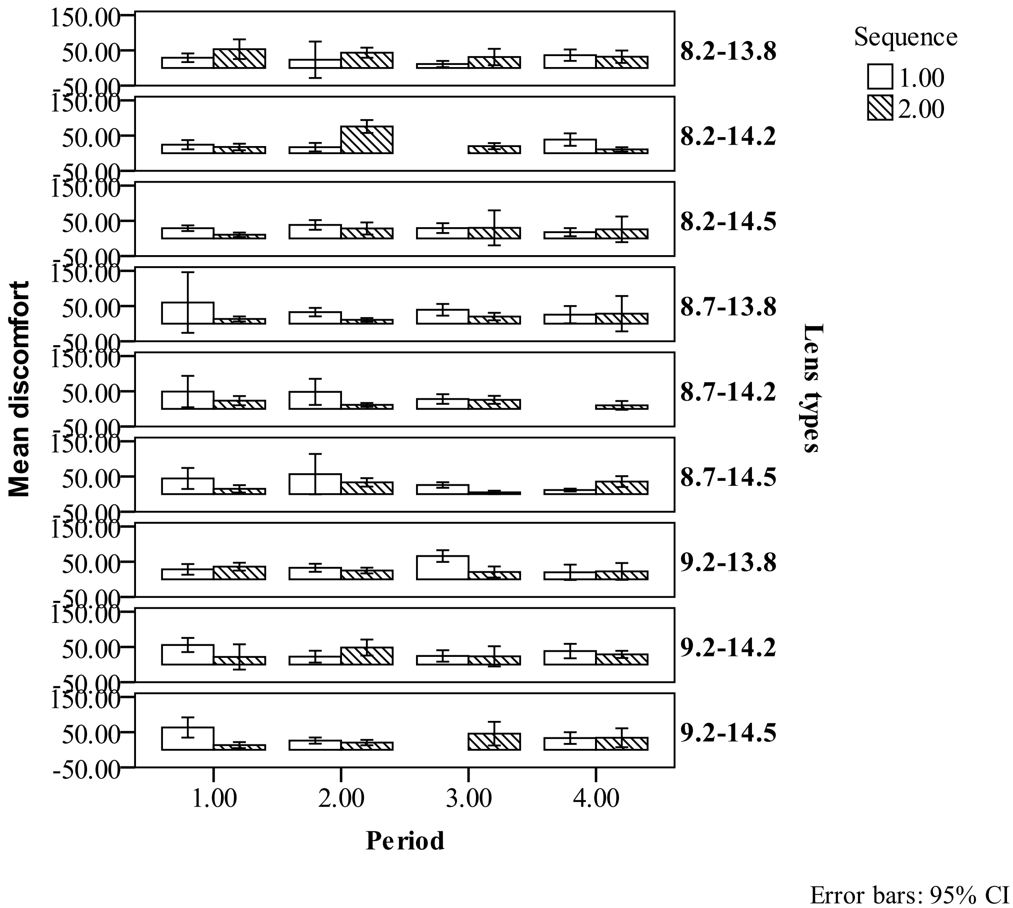

Figure 3-10: Effect of lens type on session and sequence of lens presentation

3.4.5 Effect on lens type on ocular discomfort

Linear mixed modeling of different lens types on discomfort showed no significant difference between the lens types used in the study (p=0.22) during the mechanical session. However, a significant effect (p=0.04) of lens type on discomfort was observed in the chemical session. The results are illustrated in Figures 3-11 and 3-12.

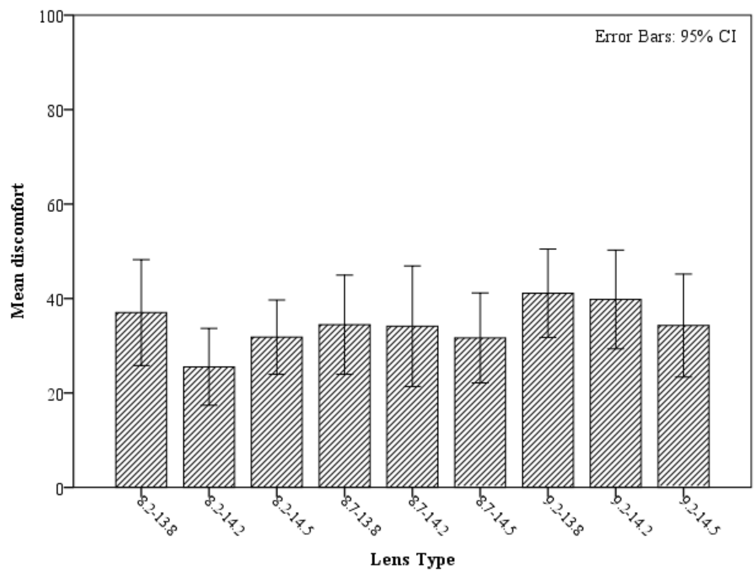

Figure 3-11: Effect of different lens types on mean ocular discomfort ratings in mechanical session

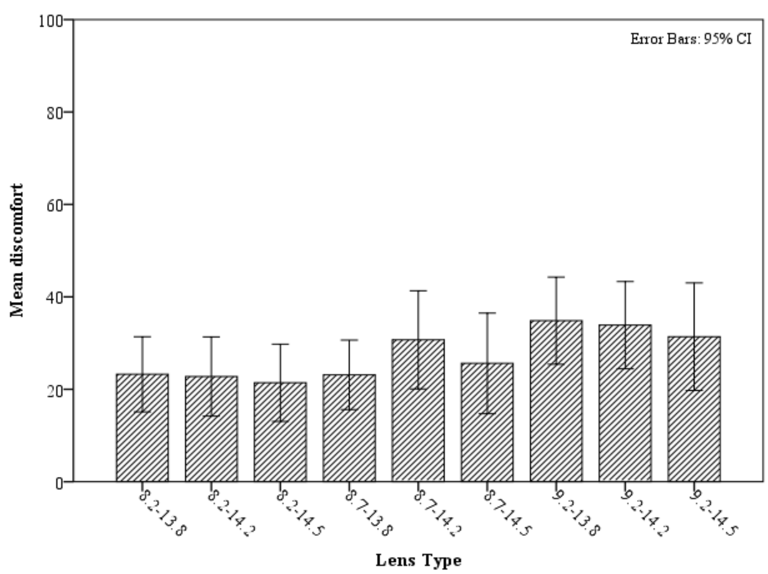

Figure 3-12: Effect of different lens types on mean ocular discomfort ratings in chemical session

3.4.6 Effect of time on ocular discomfort ratings

Linear mixed modeling showed a significant difference ($p<0.001$) in the ratings of discomfort from the time of insertion to lens settlement (i.e., at magnitude matching) and lens removal. The results are presented in Figure 3-13.

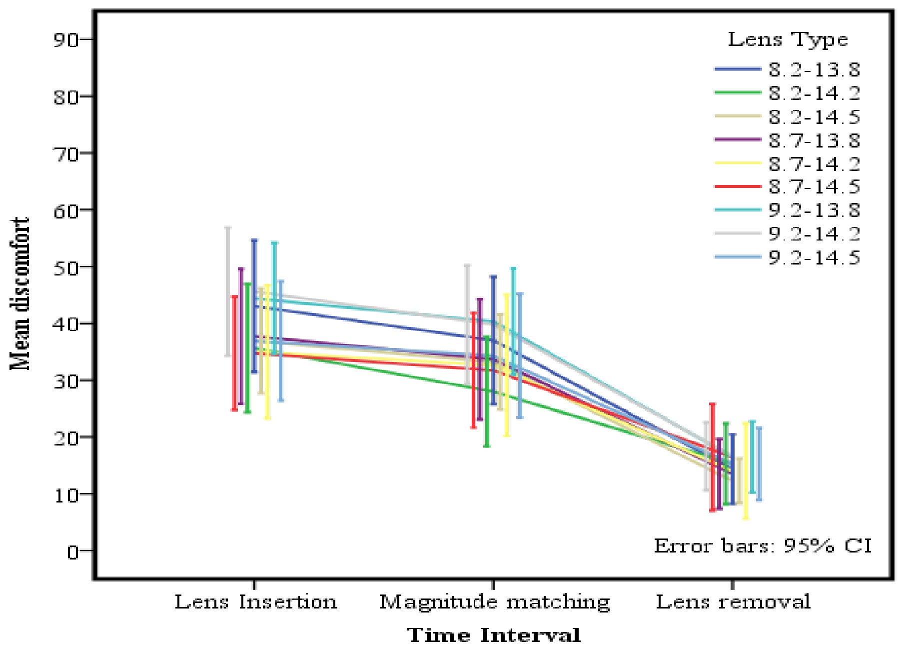

Figure 3-13: Mean discomfort ratings for all lens types at different measurement intervals.

3.5 Discussion

The purpose of the study was to scale ocular discomfort from contact lens wear to the discomfort produced by the pneumatic esthesiometer. In general, the study demonstrated that magnitude matching could be utilized to construct psychophysical scales for ocular discomfort. However, a sensory panel exists where only specific participants were able to perform the magnitude matching. The sequence and session in which the lens is presented can have a considerable effect on the ratings of discomfort, with the first lens being rated higher in discomfort than the following lenses.

Psychophysical scales have been constructed using magnitude matching or cross modality matching in various sensory dimensions [19, 22, 34-36]. The theory underlying the scale construction is that the physical dimensions of two different sensory modalities can be matched to each other when an equal magnitude function is established between them. Though the psychophysical scales provide adequate description of the underlying sensory dimension, there are inter-individual variations that are exhibited by the differences in the values of the power exponent. The differences are because the magnitude estimates of sensations can vary substantially between individuals. The inter-subject differences have been observed and discussed in many sense modalities[37-49]. Marks[49] and Stevens[48] have expressed that individual subject's data adhere to the power functions, while others[50, 51] have indicated the power functions to be poor. Pradham et al.[51] observed the individual psychophysical functions to not follow power laws, although averaging individuals' data yielded a power function.

Inter-individual differences are also evident in this study, where only about half of the subjects were able to successfully match the magnitude of sensation from contact lens wear to the pneumatic stimulus. The three eminent reasons leading to the discrepancy between the individuals[52] are: 1) subject's use of numerical estimates 2) operating characteristic of the subject's sense organs or perceptual differences and 3) subject's modulus or reference (see page 24). The latter two factors are unlikely to be the cause, as the sensory perceptual differences do not vary as widely as the individual exponents[53] and the changes in the subject's modulus would theoretically affect the multiplicative constant and not the exponent[44].

Participants vary in their judgments of magnitude estimation and with the use of numbers including the range and type of numbers used. Preference for a particular number[54, 55] such as multiples of 5 or 10, the absolute size of the number chosen and whether the numbers are linearly related to sensation magnitude are also the factors that contribute to the subjective differences[33]. Also, subjects have a tendency to shorten the range of the variable they can control, introducing response bias in the measurements. Rule [37, 56] and Mackeley[37] have proposed that the inter-individual variability can occur due to differences in subject's response strategies, with some using a narrow range of numbers and some using an extended range, while others [43, 47, 57] indicated the important source of response bias to be the subjects' interpretation and handling of numbers used in scaling experiments. A study on individual loudness measurements in 11 observers that showed varying transducer functions[48] assumed the auditory system of all the observers to operate similarly and the differences in transducer function were attributed to the different numerical estimates of loudness. Gescheider[58, 59] also proposed that the variability of individual magnitude judgments exceeds the variability of the underlying sensory processes, making it unlikely for the sensory differences to cause the variations in psychophysical functions. The regression towards the mean effect[53, 60] is also probable in either the numbers used in magnitude estimation or the physical continuum adjustment in cross modality matching.

The inexperience of the subjects has been reported to have a minor role to play in inter-subject differences as untrained inexperienced subjects can perform well at matching tasks[53] and subjects who clearly understand the instructions to judge qualitatively different stimuli may also find it difficult to make absolute comparisons in magnitude matching[35]. The numerical estimates reflect the judgmental abilities of the participant, with no right or wrong to the responses of the subjects and only training is necessary to recognize the stimulus. However, the inexperience of the participants in magnitude estimation can be seen as relatively small group exponents[61].

From the stimulus perspective, the range of stimulus intensities utilized, the distribution of the presentation of different stimulus intensities and the number of available response categories can influence the responses from the participants[62-64]. In this study, some of the subjects could not perceive a difference in sensation intensity between the different contact lenses, as observed by similar discomfort ratings or by the use of short range of numbers. The base curves used in the study were 8.2, 8.7, 9.2 and the diameters were 13.8, 14.2, and 14.5. The combination of steep base curve with smaller diameter lenses and flat base curve with larger diameters could have stabilized the lens on the eye leading to better centration and comfort[65]. Tight fitting lenses with smaller base curves can be as comfortable as well fitting lenses or even better than the well fitting lenses immediately upon insertion for a short period of time[1, 3], while the loose fitting lenses tend to cause discomfort due increased movement of the lens. The use of lower water content hydrogel lenses also might have enhanced the comfort[9]. Hence only fewer lenses than expected would have produced an uncomfortable sensation and the range of contact lenses that produced enough discomfort to perceive a difference in intensity between them might have been substantially reduced.

The fitting pattern of each contact lens design is specific to an individual's corneal dimensions and discomfort is related to the fitting pattern. Averaging of responses from the participants for each lens type may not reflect the actual psychophysical scales, as there are inter-individual differences in how subjects scale stimuli and the fit of a lens is unique to an individual. The average psychophysical scale constructed with lens type as a sensory modality and its matching pneumatic strength may not precisely specify the form of the relationship, although it has been shown that averaging can remove the differences across subjects and enable to derive a common scale for any sensory dimension[53]. Instead, the magnitude ordered method of scaling could be a better technique for scaling discomfort as it is relative to subject's preference of lens type. The contact lenses used in this study were only a medium for producing discomfort and scaling need not be based on the design of the lenses. It would be recommended to order the contact lens discomfort based on its magnitude and scale it to the corresponding pneumatic stimulus strength irrespective of the contact lens design. Another alternative would be to scale discomfort for each individual subject with respect to the lens design.

The sensations elicited in the study by the mechanical and chemical forces are in accordance with other studies that characterize the sensations with pneumatic stimuli[28, 31, 66-68]. Morphologically, the corneal nerve fibers terminate as thin myelinated Aδ type fibers or unmyelinated C type endings [69, 70]. They can be functionally classified into different types based on their transduction properties, the modality of stimulus they preferentially activate and the quality of sensation evoked by each type of neuron[68, 71, 72]. Based on the electrophysiological studies on cats[28, 68, 73-75] and rabbits[70, 76], the mechanosensory neurons belong to the Aδ fibers that are excited mainly by mechanical forces in contact with the corneal surface and are responsible for the short acute pain signaling the presence of the stimuli rather than the intensity. The polymodal neurons comprise both Aδ and C fibers and react to mechanical forces, chemicals, and temperature changes. The mechanosensory neurons have slightly higher thresholds than polymodal and show adaptation to repeated stimulation. The equivalent human psychophysical channels have been hypothesized to be comprising of non noxious cold channel producing a cooling sensation, a noxious heat channel mediating thermal heating pain, a chemical channel that causes burning or stinging pain, a mechanical channel and an itch channel[66].

The air from the pneumatic stimuli can perhaps activate the Aδ mechanosensory fibers causing scratching sensation while CO_2 recruits the polymodal neurons that evoke low threshold Aδ nerves as well as C fibers giving rise to sensations of scratching and burning[28, 31, 66-68]. Suprathreshold stimulation of the ocular surface with a contact lens can trigger both the mechano and polymodal nociceptors giving rise to sensations of scratching and burning. Mechanically, the contact lenses cause friction to the corneal surface, while the physiological changes that occur due to lens wear may can cause a chemical interaction. The study also demonstrates the mechanical and chemical channels to be exclusive as depicted by different power exponents and by the quality of sensation produced by each modality. Other studies[26, 27, 30] have also proposed the corneal transducer functions to have different power exponents for mechanical and chemical stimulation and the differences in exponents might perhaps be due to underlying sensory differences with mechanical and chemical stimulation.

Another finding in the study is the impact of the session and sequence of lens presentation on discomfort ratings. The lenses presented in the first session and/or the first sequence tended to produce higher discomfort than the lenses used in the following session/sequences. However, the participants rated the lenses similarly in the mechanical and chemical stimulus sessions. A similar study[77] on heat pain thresholds showed marked differences in first session measurements compared to the subsequent three sessions. The first session bias could not be eliminated, although training stimuli were used before the actual measurement. In psychophysical scaling studies, sequential dependencies can occur because of the influence of the sequence of stimuli, particularly the immediately prior stimuli. There can be effects of assimilation, where the subjects give higher ratings when the preceding stimulus is higher and a lower rating when the preceding stimulus is lower than the one judged. The contrary happens with a contrast effect i.e., the stimulus is judged lower when followed by a higher intensity stimulus. Assimilation is observed to occur in both absolute judgments and categorical judgments [78-81]. The characteristic of both assimilation and contrast may give rise to a "centering effect" that can also be associated with sequential dependency problems[82].

Adaptation to the lenses used in the study can also be another possibility for the session/sequence effects. As there is no sensory stimulus to the cornea before the placement of the contact lens, the insertion of the first lens would have triggered an immediate, higher sensory response causing increased discomfort ratings. Upon further placement of lenses, the ocular surface may have adjusted to the sensory input with a decreased firing rate and may perhaps cause lower discomfort. It has been proposed that the cornea adapts to suprathreshold mechanical stimuli[83] and the effects are prominent in asymptomatic contact lens wearers than the symptomatic group[84]. Adaptation to the lenses is also the reason for the asymptomatic group to be free of ocular symptoms. In this present study, since the contact lenses were randomly allotted to the sessions and sequences, the adaptation effects will not be pertained to any particular lens type. The non-adaptation to any specific lens type is also supported by the finding from linear mixed modeling of lens type on session and sequence, the test results showing no significant differences.

The improvement in comfort with time, from lens insertion to magnitude matching can also be explained by the mechanism of adaptation. There are physiological changes in the tear film and lens surface occurring during the first few minutes of lens wear that can affect how the lens feels initially[2] and then the lens settles giving rise to improved comfort. Contact lenses have been shown be settle within 30-45 seconds of insertion in adapted lens wearers and the settled comfort is found to be greater than comfort at insertion[2]. The sustained interaction of the contact lens to the corneal surface might have led to adaptation and hence alleviated the symptoms of discomfort.

Contact lenses were chosen as a means of suprathreshold stimulation as they can activate the corneal sensory nerves due to friction on the ocular surface especially during the initial period of lens wear. The mechanical aspect of the lens along with the physiological changes that occur due to the interaction of tear film with contact lenses will disrupt the normal functional equilibrium of the sensory input and thereby give rise to unpleasant sensations. The initial comfort with contact lenses also significantly influences a person's perception of contact lenses and impacts the success of contact lens wear[9, 85]. Hence, the discomfort from contact lens wear was scaled within few minutes of lens insertion. It was expected that the fitting characteristics of the different contact lens designs would provide varying amounts of discomfort. Nevertheless, the soft contact lenses used in the study might not have provided an adequate range for the participants to sense a substantial difference between them. The study was carried out with eight lenses from the total pool of nine lenses to balance the number of lenses in each session, with four lenses in the first session and four lenses in the second session. The reason for using linear mixed modeling for statistical analysis of the data is that it mitigates the absence of few data points for each lens type, due to the random dropout of one lens design for each participant.

In summary, the subjective ratings of comfort can be scaled by corneal esthesiometry in a selective group of people (defined in this experiment statistically). In the subset of people with poorer correlations, perhaps the pneumatic stimulus was too localized and specific to match the complex sensations experienced while wearing contact lenses. In addition, perhaps there is also a group of subjects who are simply poorer at making judgments about ocular comfort. Magnitude matching is a valuable procedure that can provide considerable information about the perceptual changes across individuals and groups. Although, the mean data can adequately illustrate the power law, a deeper understanding of the psychophysical judgment can be obtained by studying the individual subject's psychophysical functions. Measurements of comfort on different days or with lens designs can encounter a potential possibility of session effect, which should be carefully considered. The comfort with contact lenses tends to improve with time, which can perhaps be due to adaptation effects.

Chapter 4

Influence of vision on ocular comfort ratings

4.1 Introduction

Contact lens wear is one of the successful modalities for refractive correction among other alternatives such as spectacle wear, laser refractive surgery and orthokeratology. Despite the popularity of contact lenses, reports of dissatisfaction with lens wear are not uncommon. Reports[1-4] of the reasons for lens discontinuation in lapsed lens wearers suggests the primary reason for dissatisfaction to be ocular symptoms of discomfort and dryness. The other reasons include preference for another corrective modality[1], inconvenience with lens wear due to maintenance/handling difficulties and poor vision with lenses[2]. Lens related effects such as reduced oxygen transmissibility, lens dehydration[5], water content changes[6], change in osmolality[7], poor wettability[8], protein/lipid deposition on the lenses[9] are shown to be associated with the etiology of discomfort. The base curve of the lens[10], diameter[11] and fitting characteristics of the lenses[12] also tend to contribute to the symptoms of discomfort, and so these lens related clinical variables might contribute to discontinuation. Continuous modifications to the lens design, lens materials, and care systems are performed in the quest for comfortable contact lens wear.

Increase in discomfort and dryness towards the end of the day is a common complaint of contact lens wearers[13-16]. In a study[13] investigating comfort in lens and non-lens wearers over the course of the day, a reduction in comfort was observed in both the groups, suggesting the role of ocular and general fatigue in the end of the day discomfort. Dumbleton et al.[14, 15] also reported a diurnal change in comfort, but no differences in comfort scores were observed between the five different types of silicone hydrogel lenses used in the study. In a multicenter study reported by Begley et al.[16] a diurnal change in discomfort was seen along with similar changes in vision. 19% of contact lens wearers reported moderate to intense ocular discomfort in the morning that tripled (56%) in the evening. Similar moderate to intense visual changes also increased by approximately 25 % in the evening. The paralleling of discomfort and visual changes towards the end of the day gives rise to the question of whether vision and comfort are related. Although studies have been conducted to investigate the physiological changes that accompany contact lens wear and the resultant discomfort, very little is known about the impact of vision on ocular discomfort.

Measurements of visual acuity and contrast sensitivity function (CSF) with contact lenses reveal mixed results[17-20]. Few studies[19, 21, 22] suggest no difference in CSF between lenses and spectacles, while others indicate decreased CSF in the mid and high spatial frequencies[18]. However, dynamic measurements of vision with blink reveal decreased visual function with contact lenses. Ridder and Tomlinson[23] have indicated transient fluctuations in contrast sensitivity following a blink, with a significant loss of contrast sensitivity with spherical soft contact lens wear compared to spectacle wearers. Thai et al.[24] also reported the CSF to be significantly reduced for middle to high spatial frequencies when the pre-contact lens tear film dries and breaks up. The study suggests the possibility of pre-corneal tear film break up in contact lens wearers to account for intermittent blurred vision and to be a stimulus for blink in these individuals. This view is again supported by Liu et al.[25] proposing that blurry vision symptoms reported by contact lens wearers were caused by poor quality of the retinal image due to tear film breakup. While

Timberlake et al.[26] attributed variations in visual performance with soft lenses to the light scatter produced by the changes in hydration levels of the lens or changes in the quality of the tear film. Deposit formation on HEMA lenses[27] and use of lower content lenses[20] were also observed and hypothesized to cause reduced contrast sensitivity function.

The intermittent reduction in vision with blink and the decrement in vision as reported by contact lens wearers being one of the causative factors for ocular discomfort is suggested by a few clinical anecdotes that vision and comfort are related. Papas et al.[9] reported an influence of vision on comfort with greater discomfort with increasing levels of blur experimentally altered using defocusing contact lenses. Discomfort ratings were found to be worse for blurred conditions compared to occlusion and full correction. The drawback of the above study is that blur was introduced using contact lenses and comfort was assessed during lens wear, which would itself be a source of discomfort. Hence, to avoid the impact of the contact lens on ocular discomfort, I conducted this study in both lens and non-lens wearing conditions. The effect of blur was also studied by experimentally inducing spatial blur and dioptric defocus. Therefore, the primary objective of this study was to evaluate the ratings of comfort and other sensations under the presence of blur and absence of visual structure. It was hypothesized that ocular comfort can be influenced by the changes in vision. In order to comply with the different experimental conditions in the study and avoid patient fatigue/boredom, I conducted this study in two parts.

4.2 Part one

4.2.1 Materials and methods

4.2.1.1 Subjects

Twenty participants with age ranging from 24 to 51 years were enrolled for the study. Subjects were emmetropic non contact lens wearers with good ocular and systemic health. The right eye was always the test eye, while the fellow eye was occluded with an eye patch.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and ethics clearance was obtained from the University of Waterloo, Office of Research Ethics (Waterloo, Ontario, Canada). Informed consent was obtained from each participant.

4.2.1.2 Visual targets

A collection of 10 common scenic real life pictures were arranged on a Microsoft PowerPoint (Microsoft Office 2007, Microsoft Corporation, Redmond, WA) presentation and served as visual targets for the experiment. The presentation was projected on a clear white wall using an overhead projector and was viewed from 3 meters. Each slide was viewed for 30 seconds with immediate transition. The same set of pictures was used for all participants, but the order was random.

There were two sets of visual targets used for the study; spatial blurred targets and clear targets. Spatial blur was created by spatially filtering the pictures to a nominal +6.00DS equivalent defocus as defined by VOL-CT software (Sarver Associates, Chicago, IL).

4.2.1.3 Contact lenses

Dioptric defocus was achieved by using Focus® Dailies (CIBA Vision, Duluth, GA) contact lenses of +6.00DS refractive power. The base curve of the lens was 8.6mm with a diameter of 13.8mm. Lenses were allowed to settle for 15 minutes after insertion followed by slit lamp bio-microscopy to assess the lens centration, movement and lens lag.

4.2.1.4 Numerical ratings

The magnitude of comfort, burning, itching, warmth and vision was reported using a 0-100 numerical rating scale. 0 indicated 'no sensation' and 100 represented 'most intense underlying sensation'. Vision was also rated from 0 to 100 where 0 represented 'clear vision' and 100 indicated 'vision as bad as it can be'.

4.2.2 Procedures

The experimental design of part one of the study is illustrated in Figure 4-1.

There were three experimental conditions in the study: normal vision, spatial blur and dioptric defocus. Subjects viewed the corresponding targets for each condition from a distance of 3 meters without any other light, with each condition lasting for five minutes. Towards the end of each experimental condition, the subjects were asked to rate their vision and sensations of both their eyes using the numerical rating scale. Ratings were also recorded at the start and end of the experiment, and immediately after the contact lenses settled.

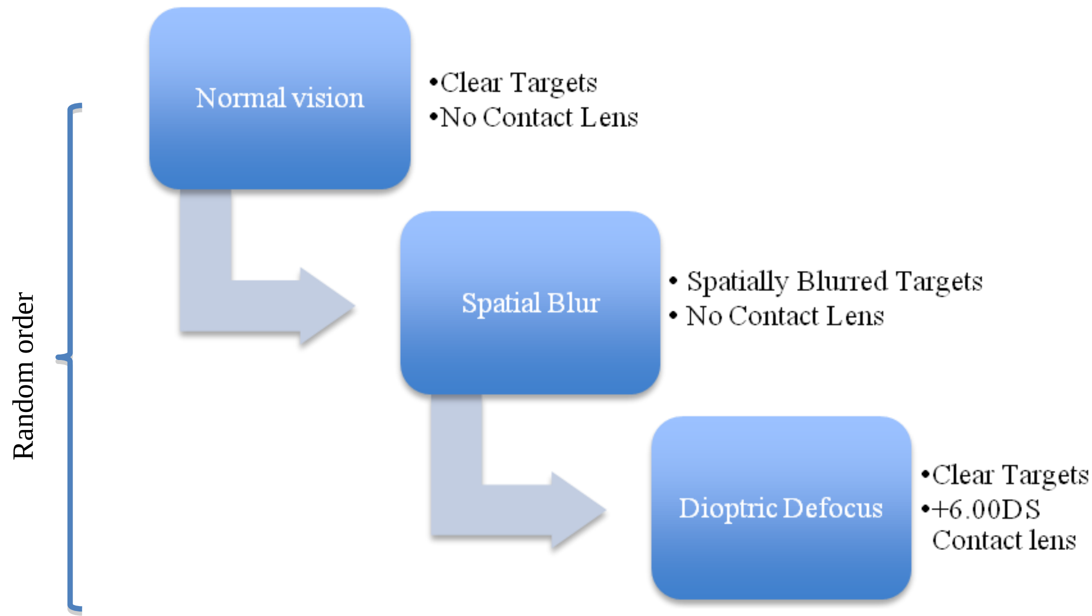

Figure 4-1: Schematic design of part one of the experiment

4.2.3 Data analysis

Statistical analysis was performed using Statistica 7 (Statsoft Inc. Tulsa, OK, USA). Repeated measures ANOVA and post hoc analysis with Tukey HSD were used to compare the ratings of vision, comfort and other sensations under different experimental conditions. In addition, the right eye ratings were compared to the left eye ratings. $P \leq 0.05$ was considered to be statistically significant.

4.2.4 Results

Ratings of burning, itching, and warmth were unaltered between all experimental conditions while vision and comfort ratings were reduced during dioptric defocus and spatial blur conditions. The results of the study are presented in three sections: ocular sensations (burning, itching, warmth), vision and comfort.

4.2.4.1 Ocular sensations

Ratings of burning, itching and warmth in the test eye demonstrated no significant difference [F(df=10, 190)=1.73, p=0.07] under the different experimental conditions. There was also no significant difference between the right and left eye ratings, with p-values at least 0.75. The results of ocular sensation measurements are presented in Figure 4-2.

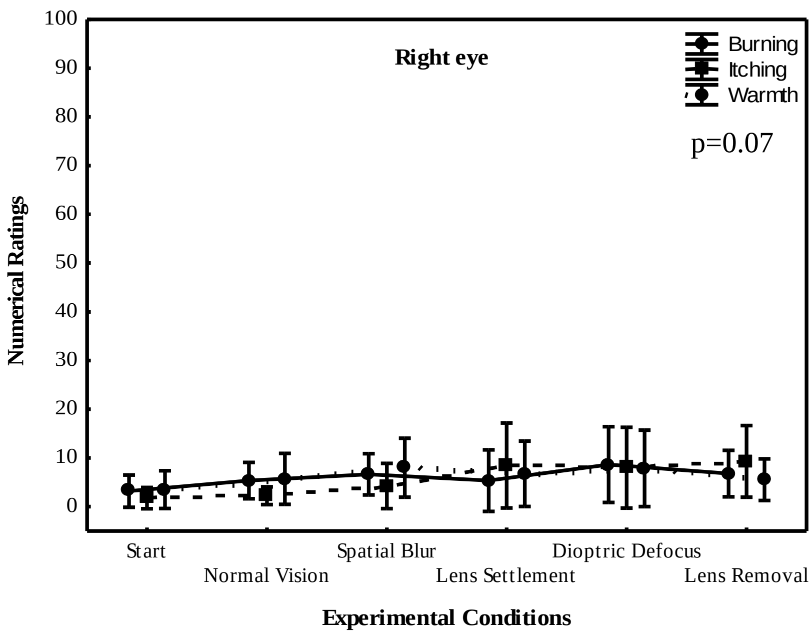

Figure 4-2: Mean ocular sensation ratings in the right and left eyes under different experimental conditions

Vertical bars denote 95% CI of mean ratings

4.2.4.2 Vision

Figure 4-3 illustrates the ratings of vision under different experimental conditions.

Significant differences (p=0.001) were observed with spatial blur and dioptric defocus from the ratings under normal vision conditions. Vision with dioptric defocus was worse (p=0.001) than with spatial blur.

Vision with contact lenses, during both lens settlement and dioptric defocus was the same (p=0.39). There were also no significant differences between normal vision condition and the ratings recorded at the start (p=0.17) and end of the experiment (p=0.39).

The experimental conditions that revealed significant differences in vision are summarized in Table 4-1.

Table 4-1: List of experimental conditions that showed significant differences in ratings of vision between condition I and condition II

Experimental Condition I	**Experimental condition II**	**p-values from post hoc analysis**
Start of the experiment	Spatial blur	p<0.001
Start of the experiment	Dioptric defocus	p<0.001
Normal vision	Spatial blur	p<0.001
Normal vision	Dioptric defocus	p<0.001
Spatial blur	Dioptric defocus	p<0.001

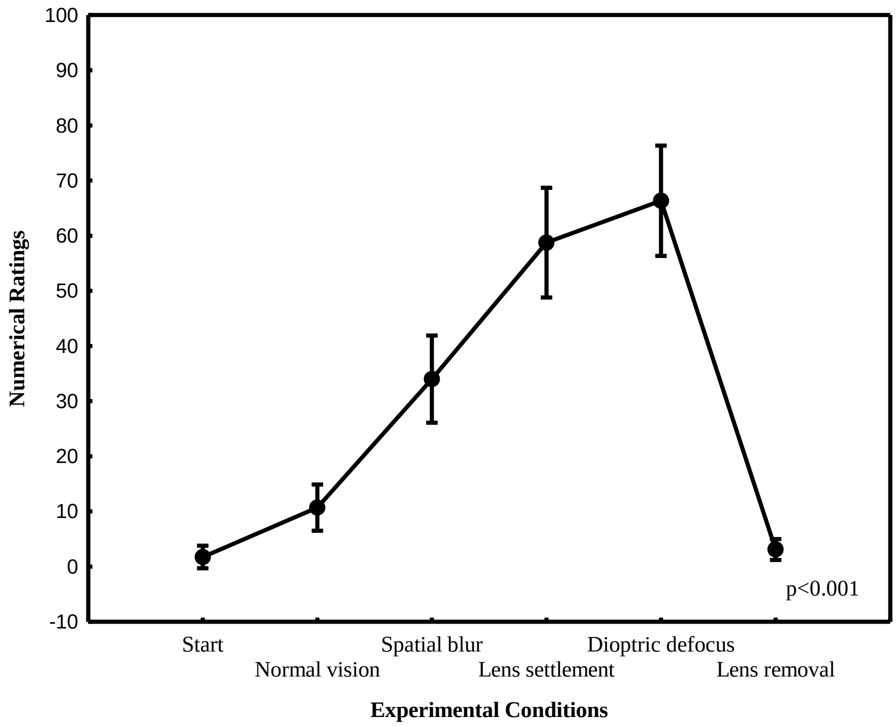

Figure 4-3: Mean numerical ratings of vision under different experimental conditions

Vertical bars denote 95% CI of mean ratings

4.2.4.3 Ocular comfort

The results of ocular comfort ratings are presented in Figure 4-4. Table 4-2 summarizes the experimental conditions under which significant differences in comfort were observed.

Comfort remained the same under normal vision conditions and at the start and end of the experiment. There were significant differences between normal vision and blurred conditions, including spatial blur (p=0.02) and dioptric defocus (p=0.001). However, there was no significant difference (p=0.99) between spatial blur and dioptric defocus. Comfort with contact lenses after settling tended to remain the same during all experimental conditions (all p-values at least 0.17) except for the start of the experiment (p=0.004). After lens removal, ratings improved to close to the level at the start of experiment. Comfort experienced in the right and the left eyes were significantly different with spatial blur (p=0.001) and dioptric defocus (p=0.001), with no differences under other experimental conditions. The interaction between vision and comfort is graphically presented in Figure 4-5. Ratings of comfort in the right and left eyes are presented in Figure 4-6.

Table 4-2: List of experimental conditions that showed significant differences in comfort between condition I and condition II.

Experimental Condition I	Experimental condition II	p-values from post hoc analysis
Start of the experiment	Spatial blur	p<0.001
Start of the experiment	Dioptric defocus	p<0.001
Normal Vision	Spatial blur	p=0.02
Normal Vision	Dioptric defocus	p=0.001

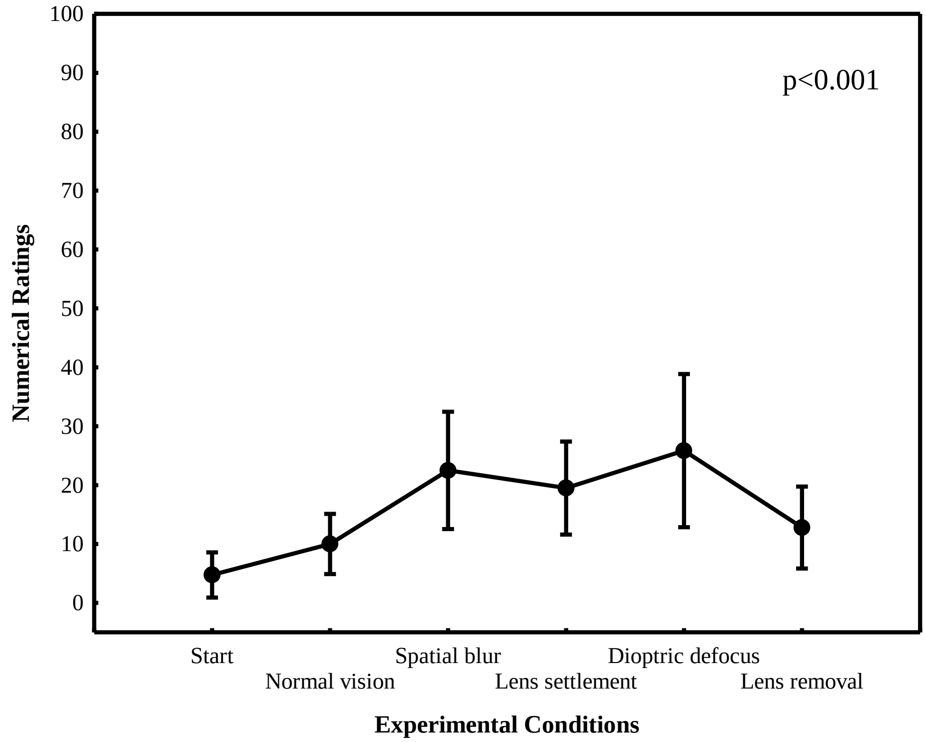

Figure 4-4: Mean ratings of comfort under different experimental conditions

Vertical bars denote 95%CI of mean ratings

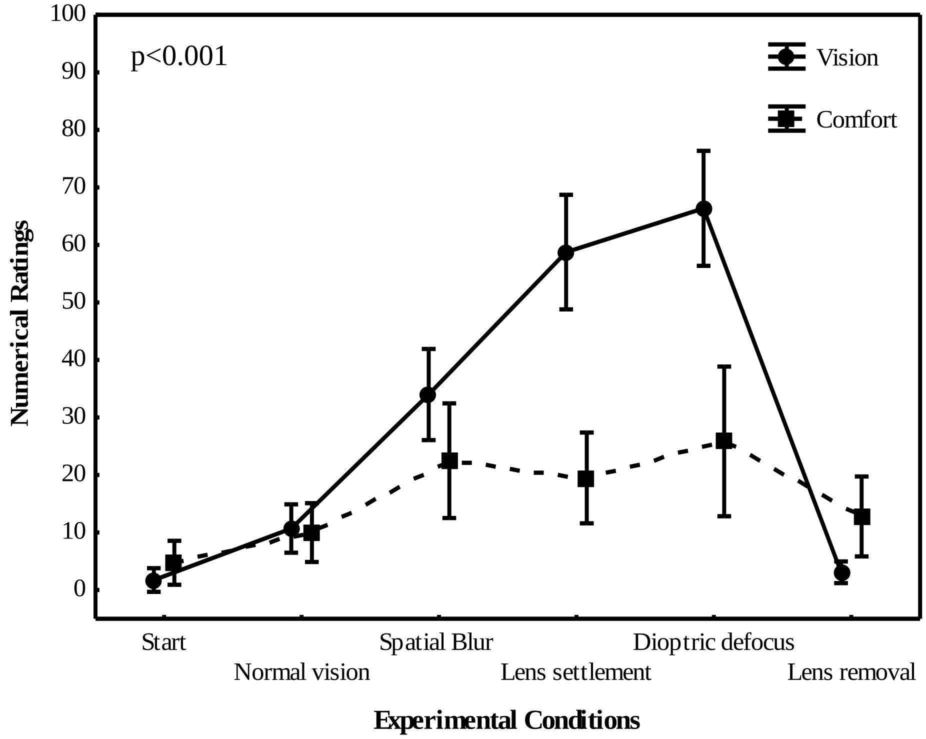

Figure 4-5: Plot illustrating the interaction of vision and comfort under different experimental conditions

Vertical bars denote 95%CI of mean ratings

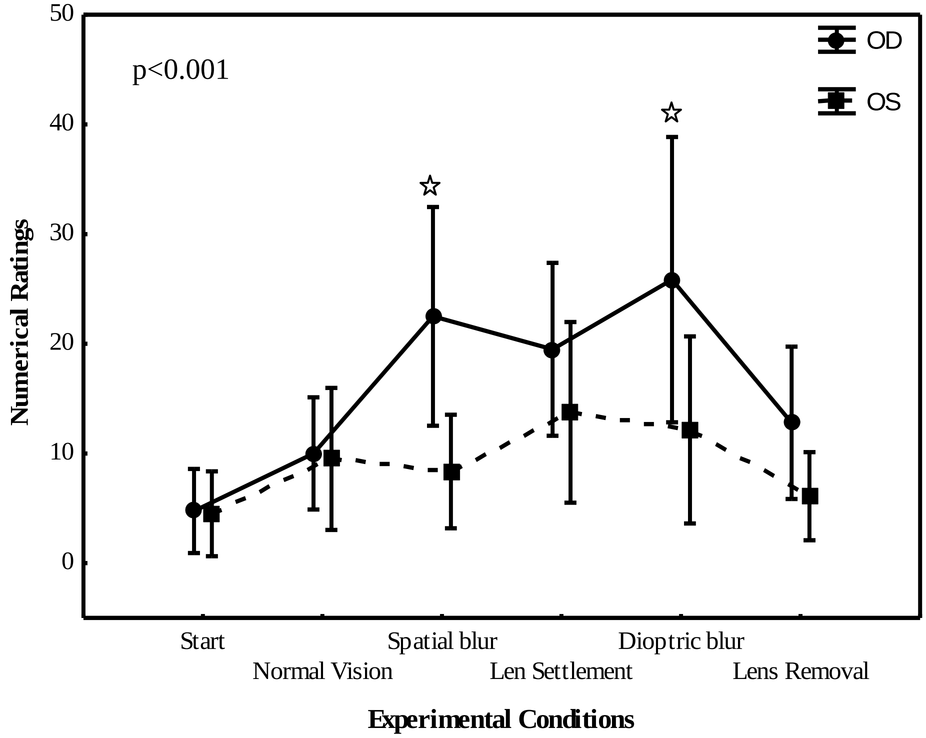

Figure 4-6: Mean ocular comfort ratings in the right and left eyes

Vertical bars denote 95%CI of mean ratings.

☆Indicates a significant difference

4.2.5 Discussion

The investigation of the influence of vision on ocular comfort suggests that comfort ratings are reduced in the presence of spatial blur and dioptric defocus. Inter ocular differences in comfort were also observed with the introduction of blur. However, though vision was rated worse with dioptric defocus than spatial blur, comfort remained the same during the two conditions, suggesting that vision and comfort may not co-vary with each other.

The pathways for the transmission of pain sensation and the visual pathway are mutually exclusive and there are no reports of sensory integration between the two. To further explore the impact of vision on ocular comfort, the study was extended to part two. In the next study, comfort was also assessed under conditions of complete absence of visual structure. To examine the effects of contact lenses on ocular comfort ratings, a +0.50DS lens was also used in addition to the +6.00DS lens. The +0.50DS lens was used during the normal vision conditions as well as with spatial blur to observe if the presence of blur influenced the ratings during the two conditions.

The methods and results of the part two of the study are detailed below.

4.3 Part Two

4.3.1 Materials and methods

4.3.1.1 Subjects

Fifteen participants from part one of the study were used in part two. The age of the participants ranged from 24 to 51 years. All subjects were in good ocular and systemic health. The right eye was always the test eye and the fellow eye was occluded with an eye patch.

The study was conducted in accordance with the guidelines of Declaration of Helsinki and ethics clearance was obtained from the University of Waterloo, Office of Research Ethics (Waterloo, Ontario, Canada). Informed consent was obtained from each participant.

4.3.1.2 Visual targets

The same set of visual targets from part one of the study was used in part two.

4.3.1.3 Contact lenses

Contact lenses of +0.50DS and +6.00DS (Focus® Dailies®, CIBA Vision, Duluth, GA) were used. The base curve of the lenses was 8.6mm with a diameter of 13.8mm. Lenses were allowed to settle for 15 minutes followed by slit lamp bio-microscopy to assess the lens centration, movement and lens lag.

4.3.1.4 Numerical ratings

The magnitude of comfort, burning, itching, warmth and vision was recorded using a 0 to 100 numerical rating scale. 0 indicated ‘no sensation’ and 100 represented ‘the most intense sensation’. Vision was also rated from 0 to 100, where 0 represented ‘clear vision’ and 100 indicated ‘vision as bad as it can be’.

4.3.1.5 Procedures

The experimental design for part two of the study is illustrated in Figure 4-7.

There were three experimental conditions in the study: normal vision, spatial blur and dioptric defocus. The participants wore either a +0.50DS or +6.00DS contact lens during each experimental condition. Subjects viewed the corresponding visual targets for each condition from 3 meters without any other light. The experimental conditions were presented in random order, with each condition lasting for five minutes. Towards the end of each experimental condition, the subjects were asked to rate their vision, comfort and other sensations in both their eyes using a numerical rating scale. Ratings were also recorded at the start and end of the experiment, and after the contact lenses were settled.

Absence of visual structure was simulated using a ganzfeld and a black occluder. The purpose of the ganzfeld was to provide an illuminated structure-less field target. Participants viewed the ganzfeld with no fixation target for five minutes. A black occluder was also used to eliminate vision for five minutes. Vision, comfort and the other sensations were rated after five minutes while viewing the ganzfeld or wearing the occluder. The order of occluded or ganzfeld viewing were randomized.

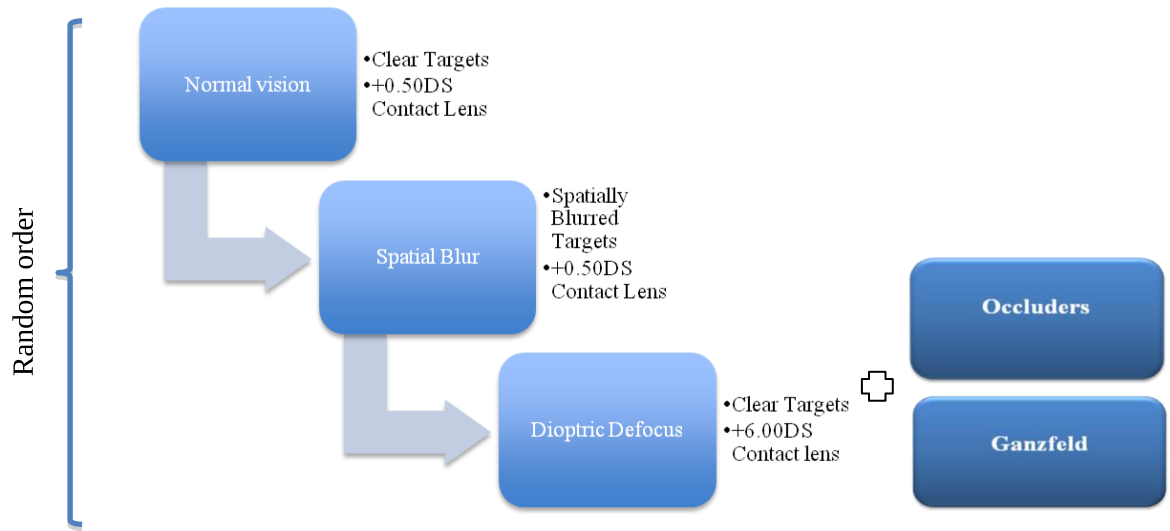

Figure 4-7: Schematic design of part two of the experiment

4.3.1.6 Data analysis

Statistical analysis was performed using Statistica 7 (Statsoft Inc. Tulsa, OK, USA). Repeated measures ANOVA and post hoc analysis with Tukey HSD were used to compare ratings of vision, comfort and other sensations between the different experimental conditions. Measurement of sensations from the right and the left eyes were also compared. Pearson product moment correlation was done between vision and comfort ratings under all the experimental conditions.

$P \leq 0.05$ was considered to be statistically significant.

4.3.2 Results

Comfort and vision were reduced during target viewing under conditions of spatial blur and dioptric defocus. Although, vision was rated less with dioptric defocus than spatial blur, there were no differences in comfort between the two conditions. Comfort was not affected when viewing the ganzfeld or when occluded. The results of the study are presented in three sections: ocular sensations (burning, itchiness, and warmth), vision and comfort.

4.3.2.1 Ocular sensations

Ratings of burning, itching, warmth were found to be unchanged (all p-values atleast 0.07) under all the experimental conditions in the test eye. No significant difference was observed (all p-values atleast 0.43) when ratings of burning, itching and warmth from the right and left eyes were compared. The mean ocular sensations in the test eye are presented graphically in

Figure 4-8.

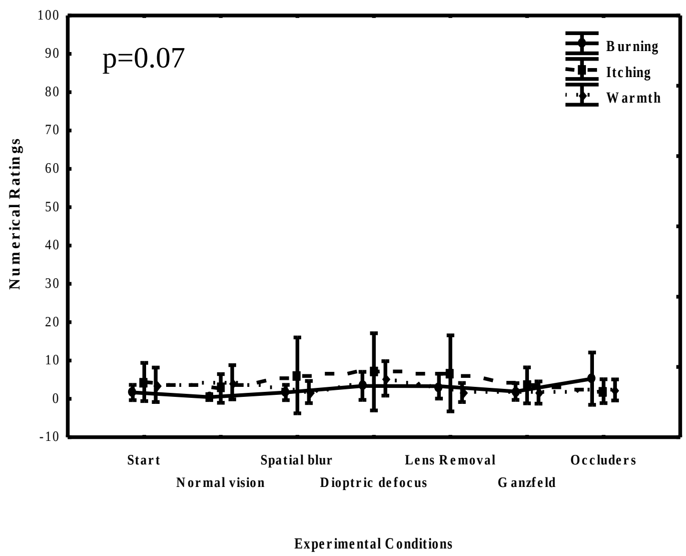

Figure 4-8: **Mean ocular sensations in the right and left eyes under different experimental conditions**

Vertical bars denote 95% CI of mean ratings

4.3.2.2 Vision

Figure 4-9 illustrates the ratings of vision under the different experimental conditions.

Ratings of vision under dioptric defocus and spatial blur were significantly different (p<0.001) from the ratings under normal vision conditions. There were also significant differences (p<0.001) between dioptric defocus and spatial blur. Vision was rated to be similar under conditions of normal vision and ganzfeld, while the ratings with occluder were significantly different (p<0.001) from all other experimental conditions. The list of experimental conditions that revealed significant differences in vision are summarized in Table 4-3.

Table 4-3: **List of experimental conditions that showed significant differences in vision between condition I and condition II**

Experimental Condition I	**Experimental Condition II**	**p-values from post hoc analysis**
Normal vision (with +0.50DS contact lens)	Spatial blur (with +0.50DS contact lens)	p<0.001
Normal vision (with +0.50DS contact lens)	Dioptric defocus (with +6.00DS contact lens)	p<0.001
Spatial Blur	Dioptric defocus	p<0.001
Ganzfeld	Dioptric defocus	p<0.001
Occluder	Normal Vision	p<0.001
Occluder	Spatial Blur	p<0.001
Occluder	Dioptric defocus	p<0.001
Occluder	Ganzfeld	p<0.001

4.3.2.3 Ocular comfort

The results of comfort ratings under the different experimental conditions are presented in Figure 4-9 and the experimental conditions that revealed significant differences in comfort are summarized in Table 4-4.

Comfort remained unchanged (p-values atleast 0.72) between normal vision, spatial blur, ganzfeld and occluders. However, significant difference was observed between dioptric defocus and normal vision (p=0.003), ganzfeld (p=0.008), occluders (p= 0.002). There was no significant difference (p=0.28) in comfort between spatial blur and dioptric defocus.

The ratings of comfort from the right and the left eyes revealed significant differences with spatial blur (p=0.003) and dioptric defocus (p<0.001), with no difference during all other experimental conditions. The results of the right and left comfort are illustrated in Figure 4-10.

Pearson product moment correlation revealed a significant correlation (p=0.01) between vision and comfort under the condition of dioptric defocus with r=0.76. No significant correlation was obtained during all other experimental conditions. The results of the Pearson product moment correlation between vision and comfort ratings under dioptric defocus are presented in Figure 4-11. The relatively low degrees of freedom precludes partitioning the analysis into two subsets within which this linear correlation appears to differ.

Table 4-4: **List of experimental conditions that showed significant differences in comfort between condition I and condition II**

Experimental Condition I	**Experimental Condition II**	**p-values from post hoc analysis**
Normal vision (With +0.50DS contact lens)	Dioptric defocus	p=0.003
Ganzfeld	Dioptric defocus	p=0.008
Occluder	Dioptric defocus	p=0.002

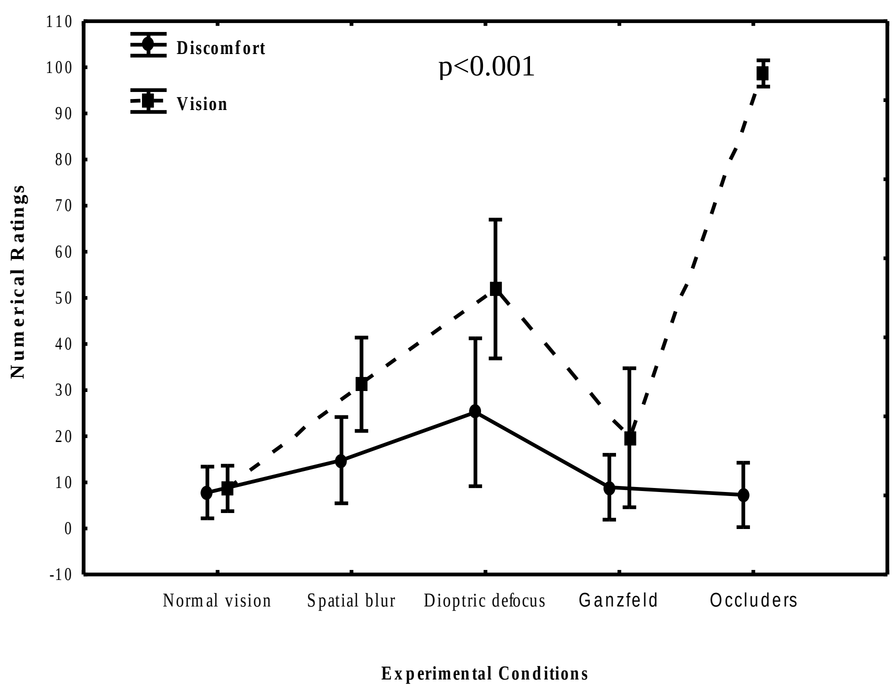

Figure 4-9: Plot illustrating the interaction of vision and discomfort under different experimental conditions

Vertical bars denote 95% CI of mean ratings

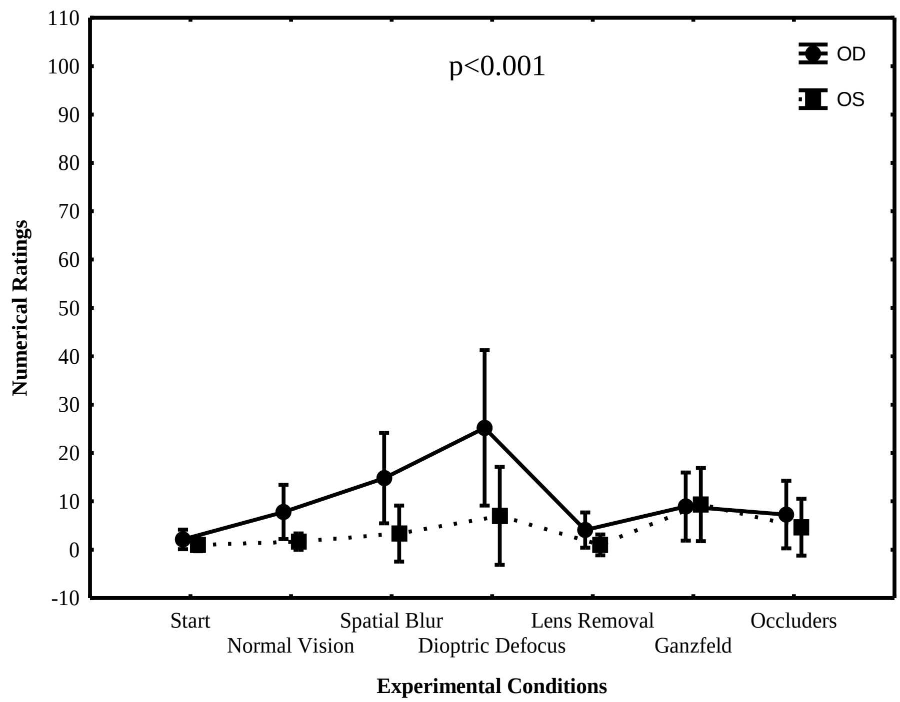

Figure 4-10: Mean ocular comfort ratings in the right and left eyes

Vertical bars denote 95% CI of mean ratings

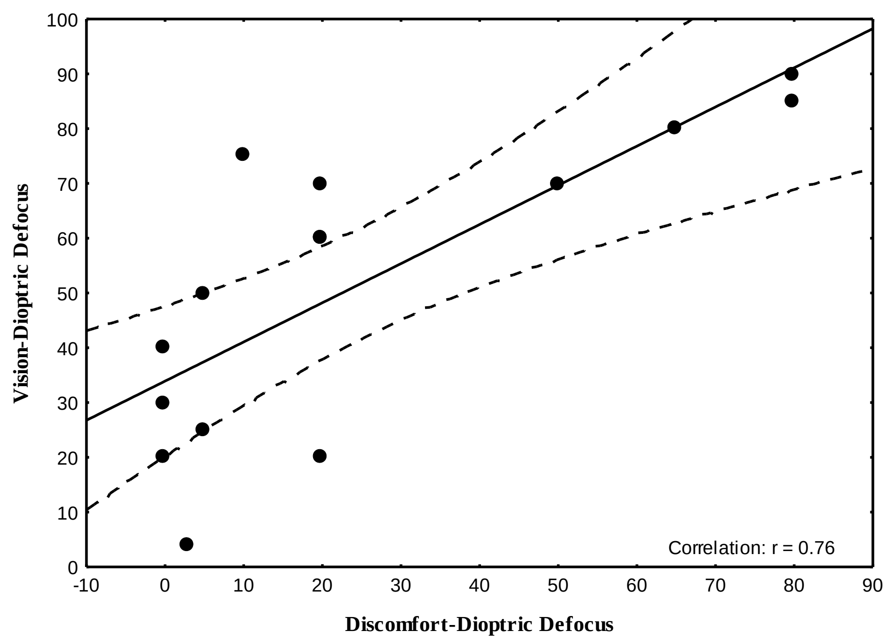

Figure 4-11: Association between vision and comfort ratings under dioptric defocus

4.4 Discussion

Discomfort has been the primary complaint of contact lens wearers. Although there are many reasons for discomfort, the putative influence of blur or decreased vision on ocular discomfort is poorly understood. Hence, this study was carried out to study the interaction of vision on the ratings of ocular discomfort. The results of both the part one and part two of the study suggest that comfort and vision are reduced under spatial blur and dioptric defocus. The differences in comfort in the right and left eyes during experimental conditions of spatial blur and dioptric defocus also reiterate that the participants experience a reduction in comfort with the induction of blur, while the other experimental conditions that did not have inter-ocular differences in clarity did not demonstrate a between eye difference in comfort rating. Although vision was rated to be worse with dioptric defocus compared to spatial blur, there were no differences in comfort between the two conditions. The change in vision ratings between the two blur conditions did not seem to co-vary with the reduction in comfort. Also, when the presence of visual structure was removed by the use of occluders and ganzfeld, comfort seemed to be unaffected and appeared similar to normal vision conditions. This non co-variation of vision and comfort gives rise to the speculation that the decrement in comfort with the induction of blur might perhaps be an experimental effect.

The pathways for the transmission of pain and the visual pathways are mutually distinct with separate receptor organs and different lobes of the brain controlling the output. The visual information from the environment is processed by the receptors in the retina that transduce the visual input to neuronal signals and is transmitted via the optic nerves of each eye to the primary visual cortex in the occipital lobe of the brain[28]. On the contrary, the pathway for pain involves the transmission of nociceptive signals from the receptor organ to the primary somatosensory cortex[28, 29] via the dorsal horn of the spinal cord, medulla, reticular formation in the midbrain and the thalamus. The transmission, processing of vision and pain occurs at different areas of the brain and a sensory integration between them is poorly understood. However, studies on olfactory tasks and audition propose integration between these two senses and vision. Studies exploring the relationship between vision and olfaction have demonstrated that visual objects can modulate the neural processing of odours, and orbitofrontal cortex can be a potential substrate for the integration of visual and olfactory stimuli[30, 31]. Vice-versa, odours can also affect visual processing by attracting attention to the odour source[32]. The visual cortex is also observed to be activated during pure olfactory tasks suggesting the possibility of unimodal perceptual tasks to be influenced by the processing of other unrelated sensory information in the brain[31]. Similarly, a cross modal relationship between vision and audition has also been reported[33-35]. Animal studies suggest the presence of multisensory neurons and integration of visual, auditory, and somatosensory signals in the superior colliculus of the midbrain[36-38]. But, the extent to which the multisensory mechanisms defined in the superior colliculus can be generalized to the cortical processes and integration between vision and somatosensation is yet to be understood.

Pain is a subjective perceptual experience consisting of not only the sensory nociceptive component, but also affective and cognitive factors[39-42]. The changing visual conditions in the study and the consciousness of being in an experiment might have triggered the affective dimension of pain causing the participants to anticipate a decrease in comfort upon the introduction of blur. The nocebo effect is a phenomenon where anticipation and expectation of a negative outcome may induce worsening of a symptom. Brain imaging studies suggest activation of specific brain regions during anxiety that correlate significantly to the subjective reports of pain. Anticipation of pain activates the anterior cingulate cortex (ACC), the prefrontal cortex

(PFC) and the posterior insula (PI)[44, 45]. These regions are observed to overlap with those involved in the processing of afferent sensory information[46]. The ACC is found to be involved in mediating the affective components associated not only with painful stimulation, but also with attention and anticipation of pain[44, 45, 47, 48]. Sawamoto et al.[49] proposed that the expectation of painful stimuli intensifies the perceived unpleasantness of innocuous thermal stimulation, along with activations in the ACC, parietal operculum (PO) and PI. In another study by Koyama et al.[50], an increase in activation of the thalamus, PI, PFC and ACC was observed as the magnitude of expected pain was also increased. Similarly, Keltner et al.[51] also observed the level of expected pain to alter the perceived intensity of pain along with the activation of different brain regions. Pharmacological studies[52, 53] suggest that anticipatory anxiety activates the Cholecystokinin(CCK) A and B receptors systems that facilitate pain transmission. The brain mechanisms involved in the expectations of pain are proposed to strongly interact with the regions involved in processing afferent nociceptive information and thereby can considerably alter the subjective experience of pain[50].

The awareness of the participant being studied can also be one of the contributing reasons for the reduced comfort with blur. The first ‘Hawthorne effect’ was noted in an industrial study that was conducted to investigate the influence of illumination on production in different factory situations[54]. The increase in productivity of the workers with worsening of the working conditions was due to the attention received by the participants that influenced their improved behavior. The findings of the Hawthorne study serves as an indication that people can change their behavior whenever they know that they are being observed. Although, there are many controversies around the first Hawthorne study that took place, the existence of “Hawthorne Effect” is accepted and referred to as an increase in productivity or other outcome caused by the participation in the study. Hence, the changing visual conditions in the study might have simulated a Hawthorne effect, influencing the participants to rate ocular comfort to be worse under the presence of blur. The affective and cognitive biases might have produced a halo effect affecting an individual's response to the experiment and contrary to our expectations, the experience of discomfort is distorted by spurious visual cues.

The ocular discomfort reported with contact lens wear might be influenced by the ocular surface conditions and may not relate to vision itself. The psychological fatigue at the end of the day might result in longer blink duration and blink incompleteness exposing the sensory nociceptive terminals[55]. The increased activity of the sensory nerve terminals in the exposed surface during reduced blinking and a less effective distribution of pre-corneal tear film may allow discomfort and poor vision to appear together, but may not be associated with each other.

The subjects in this experiment were emmetropes. This was to minimize the variability in the effects of defocus. There is no biological reason to believe that emmetropes and ametropes would differ in their response to the stimuli used in this experiment and so there are no reasons to limit the generalizability of these results to ametropes.

In conclusion, a reduction in comfort is observed during conditions of spatial blur and dioptric defocus which might perhaps be due to anxiety induced pain transmission or a Hawthorne effect. The multisensory integration between the sensation of pain and visual signals is yet to be fully understood. The Hawthorne effect is difficult to control in experiments as prior consent has to be obtained and the participants are well aware of their participation in an experiment. One potential way to understand if comfort is altered due to an anxiety component of the affective aspect of pain might be to conduct further studies where the subjects' responses are recorded under mild tranquilization.

Chapter 5

Suprathreshold scaling of ocular discomfort with blur

5.1 Introduction

The response of the ocular surface to suprathreshold stimulation using pneumatic stimuli has been investigated in several studies[1-4]. Selective stimulation of the cornea with controlled mechanical, chemical and thermal stimuli evoke sensations proportional to the magnitude of applied stimuli. The magnitude of sensations can be recorded using magnitude estimation where subjects assign numbers to stimuli that correspond to the sensation magnitude. The relationship between stimulus intensity and the magnitude of the resulting sensation is demonstrated by the power function[5] and represented by a subjective stimulus-intensity curve. The value of the exponent in the power function is unique to each sensory modality and determines the curvature of the function. Exponents have been derived for about a dozen perceptual continua to understand the operation of the sensory system[6]. High exponents (steeper slope) indicate that the sensation grows more rapidly as the stimulus intensity is increased and for a sensory continuum with low exponents (flatter slope), the sensation grows less rapidly[7].

The cornea is densely innervated by sensory nerves from the ophthalmic branch of the ipsilateral trigeminal nerve[8]. The nerves fibres branch extensively within the different layers of the cornea and terminate as free nerve endings on the superficial layer with overlapping receptive fields[9-11]. Studies on cat[9, 12, 13] and rabbit[14-16] have reported the nerves endings to be of the Aδ or C fibre types. The Aδ fibres are mylineated and fast conducting while the C fibres are unmylineated and slow conducting. The ocular sensory neurons can be functionally classified into mechano nociceptors, polymodal nociceptors and cold receptors based on the modality of stimuli that activates them and the quality of sensation evoked by each type of neuron[17-19]. Mechanonociceptors are often activated by mechanical forces parallel to the corneal surface and mainly signal the presence of the stimuli rather than its absolute intensity[9, 20]. The polymodal nociceptors react to mechanical forces, chemical irritants and noxious heat in proportion to the intensity of stimulation[3, 12, 14-17]. The cold receptors are activated when the normal temperature of the cornea decreases around 33^0C and are sensitive to temperature changes of 0.1^0 degrees or less[12, 17].

The sensations evoked by the different classes of the sensory afferents are largely unknown, but it may depend on the modality of stimulus acting on the cornea. Irritation is proposed to be the primary sensation evoked on application of mechanical forces, acid, heat and cold[21]. Mechanical stimuli can cause acute sharp sensation of irritation, and scratching when a foreign body is in contact with the cornea or conjunctiva causing local tissue damage[22]. With the activation of polymodal nociceptive fibres, subjects can experience a blended sensation that possesses an identifiable quality but dominated by an irritation component[21] and the sensation evoked by CO_2 are often described in terms of stinging and burning pain[2, 17, 21, 23]. Moderate cold stimulation of the cornea yields an innocuous cooling sensation that becomes irritating with lower temperatures[17].

The presence of a contact lens on the ocular surface alters the sensitivity of the cornea and conjunctiva due to the mechanical stimulation of the lens, altered metabolic function due to reduced corneal oxygen and carbon dioxide gaseous exchange, and a change in corneal pH[24-26]. Contact lens wearers primarily complain of discomfort and dryness[27-30]followed by difficulty with contact lens maintenance and poor vision[27, 28]. Symptoms of dryness, grittiness, itching, soreness are also observed in lens wearers than non-lens wearers[31, 32] and concomitant changes in vision and ocular discomfort are reported, especially towards the end of the day[33]. There are anecdotes of comfort and vision being related, but whether the sensation of discomfort and the decrease in vision co-vary with each other remains largely unknown. Papas et al.[34] reported an interaction of vision and comfort with decreased comfort accompanying increasing level of blur. In one of my previous studies that aimed to investigate the influence of vision on ocular comfort ratings, a reduction in comfort was observed under conditions of spatial blur and dioptric defocus. Since there have been no reports of sensory integration between vision and pain, it was speculated that the presence of discomfort with blur might be related to non-sensory factors such as the nocebo related effects or possibly due to Hawthorne effect. To explore the concept of vision and comfort further, this study was conducted to examine how people respond to suprathreshold stimulation of cornea with and without the presence of blur. The hypothesis of this experiment is that the relationship between the sensation magnitude and the intensity of the stimulus is a power function and the size of the power exponent is different in clear and defocused visual conditions.

5.2 Materials and methods

5.2.1 Subjects

21 participants, both lens and non lens wearers with age ranging from 21 to 54 years were enrolled for the study. All the subjects were in good ocular and systemic health. Contact lens wearers were asked to cease lens wear from the night before the experiment. The study was conducted in accordance to the guidelines of the Declaration of Helsinki and ethics clearance was obtained from the University of Waterloo, Office of Research Ethics (Waterloo, Ontario, Canada). Informed consent was obtained from each participant.

5.2.2 The Belmonte esthesiometer

The construction of the computer controlled Belmonte esthesiometer has been described in detail previously[2, 4, 23]. The esthesiometer contained computerized flow controllers mixing air and CO_2 as well as controlled the stimulus temperature. The mechanical stimuli consisted of series of air pulses with flow rate ranging from 0 to 200ml/min. The temperature of the stimulus was set at 50^0 C, which translated to 33^0 C at the ocular surface[35]. The distance between the ocular surface and the tip of the esthesiometer probe was monitored continuously by a calibrated video camera. Custom software was used to enter the appropriate psychophysical procedure, stimulus modality, duration of the stimulus and to record the subjects' responses from a button box.

5.2.3 Trial lenses and visual conditions

Trial lenses were placed in a lens holder in front of the non-test eye to provide the necessary visual conditions for the study. For the clear visual condition, the trial lens contained +0.25DS over the subject's distance refractive correction and for the defocused condition an additional +4.00DS was used. There were three sessions with clear visual conditions and three sessions with defocus, randomly presented.

5.2.4 Procedures

The esthesiometry test procedure was first explained to the participants. Measurements were conducted on one eye (randomly chosen), while the fellow eye viewed a 6/60 fixation target through the trial lens from a distance of 3 meters. The mechanical threshold of the central cornea was determined using the ascending method of limits[36]. The measurements were taken thrice and the absolute threshold was an average of the three measurements. Then mechanical stimuli that were 25%, 50%, 75%, and 100 % greater than the threshold were presented in random order. Participants rated the discomfort and intensity of each stimulus using a 0-100 numerical rating scale. For the intensity scale, 0 corresponded to ‘no pain’ and 100 indicated the ‘most intense imaginable’. For the discomfort scale, a rating of 0 indicated ‘no discomfort’ and 100 indicated the ‘worst discomfort imaginable’. Suprathreshold stimuli were presented thrice for clear visual condition and dioptric defocus, with each condition presented randomly and the ratings of discomfort and intensity were recorded.

5.2.5 Data analysis

Statistical analysis was performed using Statistica 9.0 (Statsoft Inc. Tulsa, OK, USA) and $p \leq 0.05$ was considered to be statistically significant for all the tests. Paired sample t-test was used to compare the absolute thresholds during clear and defocused visual conditions. The numerical estimates of intensity and ocular discomfort under the two visual conditions were compared using repeated measures ANOVA.

Non-linear regression using the method of least squares was used to plot the relationship between the ratings of discomfort and the respective stimulus intensities. The exponent ‘n’ and scaling constant ‘b’ were derived for each subject by the fitting the data to the power function $y=bx^n$ (where y is the sensation magnitude, b is the scaling constant, x is the stimulus intensity and n is the power exponent). Paired sample t-test was used to compare the difference in size of the power exponents under clear and defocused visual conditions.

5.3 Results

Comparison of absolute thresholds for mechanical stimulation of the central cornea during clear and defocused conditions revealed no significant difference [t (df =20) =-4.33, p=0.66]. The results are illustrated in Figure 1-1.

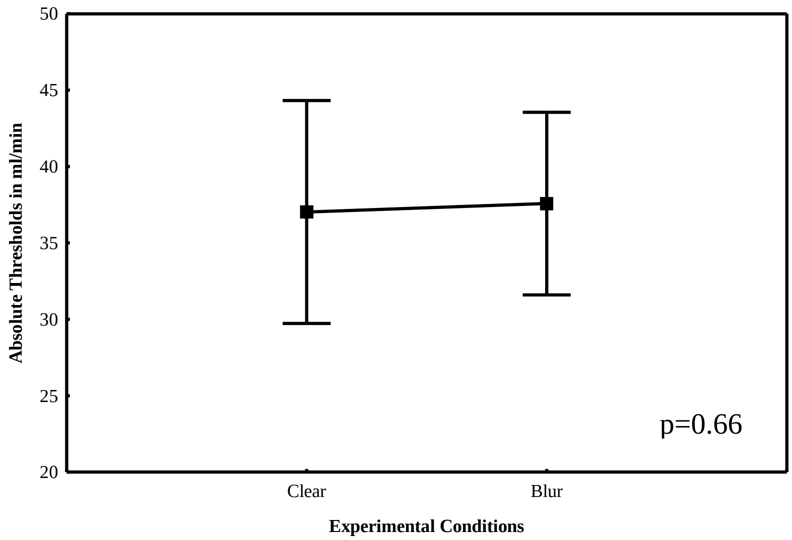

Figure 5-1: Mean mechanical threshold in clear and defocused visual conditions

Vertical bars denote 95% CI of mean ratings

The relationship between the ratings of discomfort and the respective stimulus intensities was monotonic and was used to estimate the exponents defined by Stevens' power law using non-linear regression. Paired t-test revealed significant differences between the derived exponents for discomfort [t (df =17) =-0.11, p=0.05] under clear and defocused conditions. However, no significant differences were observed for the ratings of intensity [t (df =17) =-1.26, p=0.22]. Comparison of exponents between discomfort and intensity showed a significant difference in both clear [t (df =17) =-2.49, p=0.02] and defocus conditions [t (df =17) =-0.17, p<0.001]. The mean power exponents obtained for the clear and defocused conditions are presented in Table 5-1.

Table 5-1: Mean power exponents for clear and defocused visual conditions

	Exponents Clear visual condition	**Exponents Defocused visual condition**	**p- value**
Discomfort ratings	0.96	1.08	0.05
Intensity ratings	0.82	0.90	0.22
p-value	0.02	<0.001	

Analysis of the subjective ratings of suprathreshold stimuli under clear and defocused visual conditions using repeated measures ANOVA revealed no significant main effect of visual condition on the ratings of both discomfort [F (df=1,17) =0.38, p=0.54] and intensity [F (df=1,17) =1.10, p=0.30]. As expected, a significant main effect of stimulus strength was observed, with a progressive increase in ratings with an increase in stimulus strength. However, there was no interaction effect of the visual condition and stimulus strength on the ratings of both discomfort [F (df =3, 51) =2.15, p=0.10] and intensity [F (df =3, 51) =2.42, p=0.075]. Figures 5-2 and 5-3 illustrate the discomfort and intensity ratings for suprathreshold stimuli under the two visual conditions in the study.

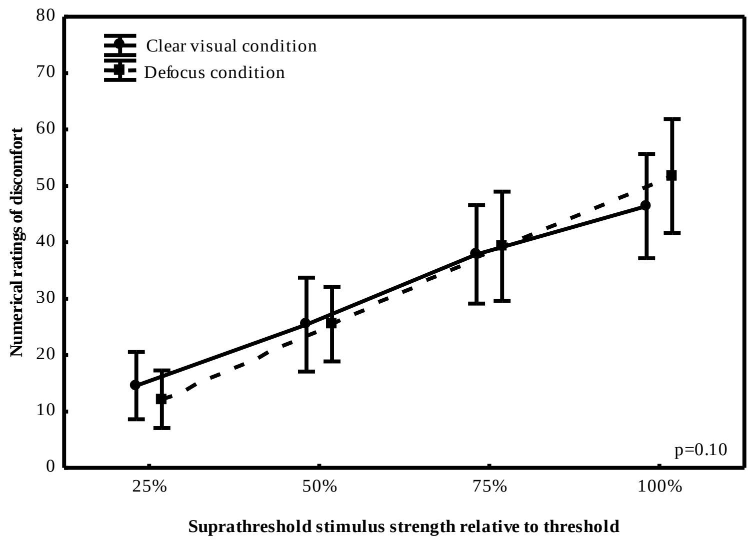

Figure 5-2: Mean ratings of discomfort under clear and defocused conditions

Vertical bars denote 95% CI of mean ratings

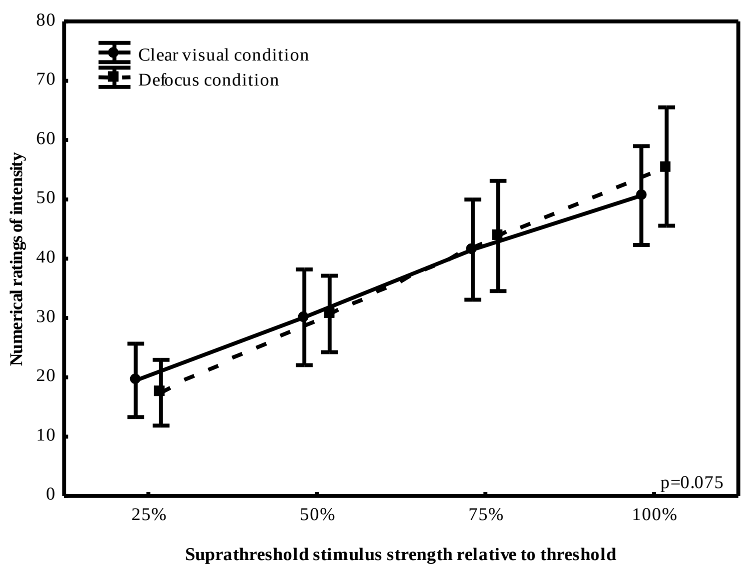

Figure 5-3: Mean ratings of intensity under clear and defocused conditions

Vertical bars denote 95% CI of mean ratings

Comparison of discomfort and intensity ratings revealed a significant main effect ($p<0.001$) of the rating type (whether discomfort/intensity) and stimulus strength on the subjective ratings under both clear and defocused visual conditions. Intensity of the stimuli was found to be rated higher than discomfort at all stimulus strengths with the Tukey HSD post hoc analysis. However, there was no interaction between rating type and stimulus strength under clear [F (df= 3, 51)=0.25, $p=0.85$] and defocused [F (df= 3, 51)=0.46, $p=0.70$] conditions. Figures 5-4 and 5-5 illustrate the comparison between discomfort and intensity ratings for suprathreshold stimuli under clear and defocused conditions.

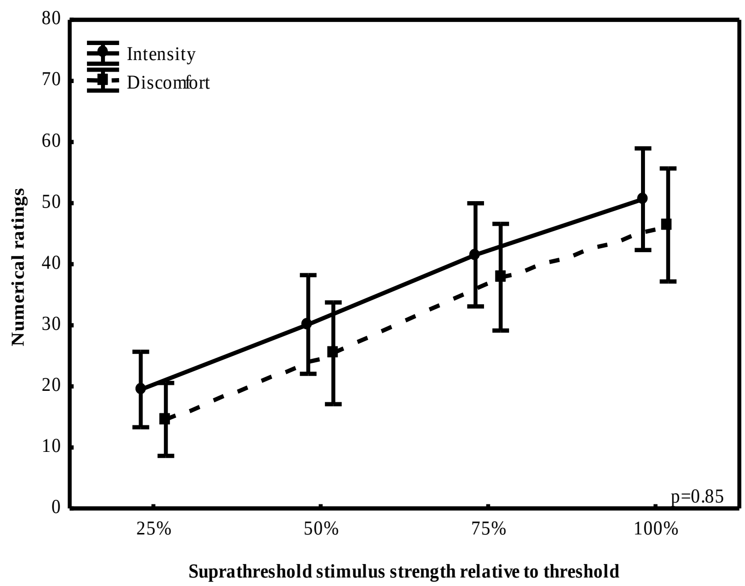

Figure 5-4: Mean discomfort and intensity ratings under clear visual condition

Vertical bars denote 95% CI of mean ratings

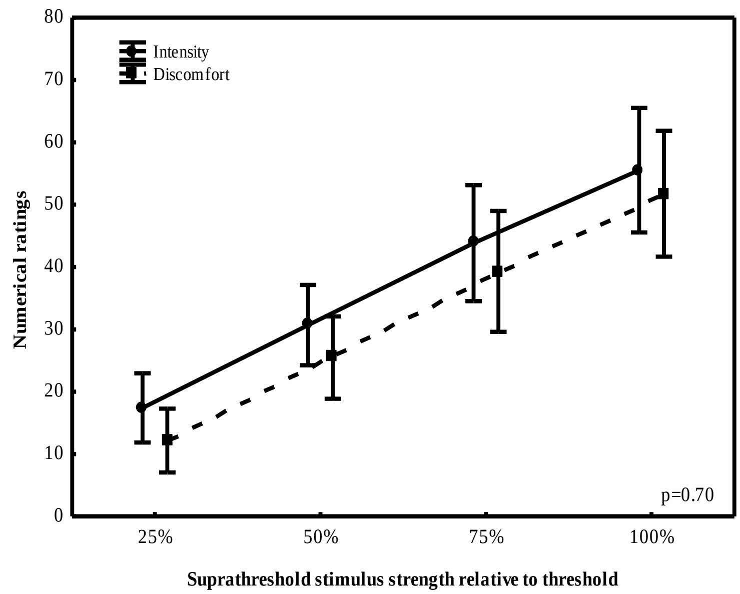

Figure 5-5: Mean discomfort and intensity ratings under defocused condition

Vertical bars denote 95% CI of mean ratings

5.4 Discussion

This present study investigated the sensory transducer functions of the central cornea while the participants viewed a clear or a defocused target. The results suggest that the suprathreshold scaling of pneumatic mechanical stimuli are similar under the two visual conditions. Psychophysical magnitude functions relate the magnitude of sensations to the intensity of the stimuli, with the form of relationship represented by a power function[5]. The power exponent is unique to each sensory dimension and characterizes the rate at which sensation grows as a function of the physical stimulus intensity[37]. The transmission of information through the sensory nervous system can be understood from the psychophysical magnitude functions, as well as inferences can be made about the transduction of stimulus energy into neural impulses by the receptors, the coding of neural impulses and the operation of the judgmental processes in the central nervous system[38].

Previously, studies[1-4] have been conducted to investigate the magnitude of sensations relative to the intensity of stimulus applied on the ocular surface. However, the perception of ocular surface sensations under differing visual conditions has not yet been reported. The investigation of the ocular sensations under clear and defocused visual conditions is important to clarify the anecdotal reports of the co-variation of comfort and vision, and to understand if ocular sensations change with a change in visual conditions. The results of the study demonstrate that the psychophysical magnitude functions for discomfort vary under clear and defocused conditions with different power exponents, implying that the processing of discomfort can differ with the induction of blur. However, the exponents for discomfort under both the conditions are close to one (0.96 for clear and 1.08 for defocus), indicating that there may not be huge differences in sensory processing under clear vision and defocus. The results of repeated measures ANOVA also support the hypothesis that the ratings of discomfort and intensity do not change with the defocus and clear vision. Since, the strengths of the suprathreshold pneumatic stimuli that were presented to the cornea were the same during both the conditions, the processing of the sensory information should also be similar. However, there can be the other dimension of pain, the affective component that can influence the processing of pain information in the brain.

The visual targets used in the study and the change in visual conditions could have perhaps caused distraction of attention, altering the perception of discomfort. However, in a single visual condition the subjects were able to perform suprathreshold scaling in an efficient manner, showing an increase in magnitude of sensations with an increase in stimulus strength.

Distraction is the process of attending to information unrelated to the painful stimulus[39] and psychological manipulation such as distraction can alter the perceived intensity or emotional reaction to a painful stimulus. Studies[40-42] designed to investigate pain on manipulation of attention suggest that subjects rate pain lower when they direct their attention away from the painful stimulus. Measurement of intensity and unpleasantness of thermal pain under different conditions of attention suggests that when a subject focused his attention on noxious heat stimuli, the pain is perceived to be more intense and more unpleasant than when his attention is diverted[42]. It was also observed that both the sensory and affective pain responses were altered in a similar manner by direction of attention, suggesting that the effects can occur at an early stage of sensory processing. Another study[39] on external and internal focusing of attention suggests the external focusing reduced pain ratings and can help to deal with short-term pain. During the clear visual condition, the subjects would have focused their attention more on the targets than the pneumatic stimuli, as the targets appear clear and hence rate discomfort lower. In defocused conditions, since the targets appeared blurred, there is a possibility of the subjects to deviate their attention on the pneumatic stimuli than on the visual targets and hence feel the discomfort to be higher.

In the defocused visual conditions, it is also probable that the participants could have fixated on the esthesiometer probe with the test eye rather than using their fellow eye to focus on the visual target. However, none of the participants in this study was a high myope for the probe to appear clear at 5cm distance and the addition of +4.00DS in defocused condition would relax the eye's accommodative facility causing the esthesiometer probe to also appear blurred. Hence, the participants would have fixated on the visual targets than the esthesiometer probe, as the targets tend to appear clear than the probe. The participants were also constantly reminded and asked if they were fixating at the letter target.

Another explanation for the observed differences in power exponents under the two conditions is that the defocused condition could have also possibly created a nocebo like effect (discussed in more detail in Chapter 4), driving the participants to anticipate an increase in discomfort with defocus.

At the level of higher order processing in the brain, the sensory experiences of vision and pain have separate receptor organs and different regions of the brain are responsible for the perception of pain and vision. In addition, the lack of electrophysiological evidence on the sensory integration between vision and pain leads to the speculation that the sensation of pain/discomfort and vision may not be related to one another in sensory terms. However, studies on olfaction[53-55] and audition[56-58] show integration between these two senses and vision. The visual cortex is observed to be activated during pure olfactory tasks suggesting the possibility of unimodal perceptual tasks to be influenced by the processing of other unrelated sensory information in the brain[54, 59]. Studies on animals suggest the presence of multisensory neurons and integration of visual, auditory, and somatosensory signals in the superior colliculus of the midbrain[60-62], but the extent to which the multisensory mechanisms defined in the superior colliculus can be generalized to humans, and the integration between vision and somatosensation is yet to be understood.

The results of the repeated measures ANOVA suggest that the rating of discomfort and intensity do not change with differing conditions in the study. Suprathreshold scaling using Stevens' power functions and repeated measures ANOVA essentially tests two different aspects of the perception of discomfort. The power functions demonstrate the rate of growth of sensation with change in stimulus intensities whereas repeated measures ANOVA compares the mean of the discomfort ratings under the two conditions. Since the power exponents were derived for each individual participant and a paired t-test was performed to investigate the differences in exponents under clear and defocused conditions, the change in psychophysical magnitude functions would provide more information on the processing of ocular surface sensations than just the comparison of means.

The absence of difference in detection thresholds, the similarity in ratings of discomfort (as observed with repeated measures ANOVA) and the strength of the nociceptive input (strength of the pneumatic stimuli) being the same in both the visual conditions, suggest that the processing of sensory components on the ocular surface may not influence the ratings of discomfort with blur. However, there can be a tiny affective aspect of pain or a higher order sensory integration between vision and pain that can influence discomfort under blur, that is evident with the small difference in power exponents between the clear and defocused conditions.

Another interesting finding in this study is that the ratings of intensity and discomfort were dissimilar, and the pain intensity was rated higher than the discomfort ratings. Studies[42, 63] have revealed that pain intensity and pain-unpleasantness are two distinct dimensions of pain and they can have different relationships to the nociceptive stimulus. Pain is multidimensional, consisting of sensory, cognitive, and affective dimensions[64]. The sensory aspects of pain vary in intensity, locus, duration and quality whereas the affective aspect of pain is presumably a function of cognitive and motivational variables influenced by psychological factors[65]. The term sensory intensity usually indicates the magnitude of sensation and the affective label is applied to emotional/motivational variables like unpleasantness, discomfort, distressing or intolerable[65]. Few investigators[66-68] have demonstrated that pain descriptor scales can provide independent measures of the three pain dimensions and it is possible to initiate an alteration in one dimension while leaving the others relatively unchanged. Based on the estimates of unpleasantness and intensity from different types of stimuli, it can be possible to classify the stimuli that would be suitable for assessing sensory-discriminative and affective aspects of pain perception[69]. In a study[69, 70] assessing the psychophysical relationship of pain sensation intensity and pain-unpleasantness to heat stimuli, pain unpleasantness ratings were found to be less than the pain intensity ratings, and both intensity and unpleasantness were altered by attention. Positively accelerating power functions with exponents of 3.0 and 3.5 were obtained for pain intensity and pain-unpleasantness respectively. The differences in exponents of affective to sensory ratings of nociceptive stimulus intensity were speculated to occur due to brevity of the stimulus. In this study, subjects were able to scale suprathreshold stimuli by evaluating both the perceived intensity and discomfort. The difference in exponents between intensity and discomfort might possibly be because they reflect two different dimensions of pain. Some types of patients are observed to make greater use of sensory words while some display greater use of affective word groups to describe their pain[71]. When subjects were exposed to chronic pain or under conditions of threat to health or life, affective ratings of VAS are found to be higher than the less threatening conditions even when both types of patients gave identical sensory-intensity VAS ratings[70]. The affective dimension of clinical pain is usually influenced by psychological contextual factors. Since the subjects enrolled for the study were clinically normal, the intensity of the stimulus might have been perceived higher than discomfort (the component of pain that reflects affect). The emotional and cognitive factors that influence the sensation of pain might be less in this set of participants, causing intensity to be rated higher than the discomfort. Although, sensory-discriminative and affective aspects of pain maybe separable, it is unlikely that completely independent afferent pathways are responsible for processing these two aspects of pain[69].

In summary, this study results suggest that the suprathreshold pneumatic stimuli can be scaled differently under clear and defocused visual conditions. Any differences in the perception of comfort does not appear to be attributable to the differences in detection threshold or sensory intensity, but a tiny affective aspect of pain or a higher order sensory integration between vision and pain may influence the ratings of discomfort with blur.

Chapter 6

General Discussion and Conclusions

The experiments in this thesis were designed to study ocular discomfort using psychophysical scaling and clinical measures. Our understanding of the ocular surface sensitivity has been limited to the knowledge of absolute thresholds of the cornea and conjunctiva. The awareness of how people differentiate stimuli when strengths greater than the absolute thresholds are applied on the ocular surface is not present. Hence, the first experiment (Chapter 2) in the thesis focuses on the measurement of difference thresholds of the central cornea to mechanical stimuli. The third chapter involves direct psychophysical scaling techniques (magnitude estimation and magnitude matching) to understand how subjects scale ocular discomfort, and if subjective and objective measures of discomfort can be related to construct a novel scale for discomfort. The understanding of ocular discomfort is furthered in the fourth chapter by using subjective rating scales that are traditionally used in the clinic to measure pain or discomfort. The ratings of ocular discomfort are evaluated under different visual conditions (normal vision, blur and absence of visual structure), the intent of which is to gain knowledge on the interaction of vision and ocular discomfort. In chapter five, the investigation of the influence of blur on ocular discomfort is advanced by scaling suprathreshold stimuli produced by a pneumatic esthesiometer in the presence of blur and normal vision.

The sample size calculation for each chapter in the thesis is presented in Table 6-1. Since there was no previous literature available for Chapter 2, Chapter 4 and Chapter 5, sample sizes were calculated for three effect sizes (1, 1.5 and 2) and an effect size of 1.5 was chosen to decide on the sample size for the study. The study detailed in Chapter 3 was primarily descriptive and a pure pilot study. Due to the complex nature of the study and wear of different types of discomfort producing lenses, it was difficult to retain participants and hence there were unequal number of subjects in the lens and non lens wearing groups. Nevertheless, the statistically significant inferential testing conducted in this chapter does indicate that the experiment was ***not*** generally underpowered due to sample size.

Table 6-1: Sample size calculation

Chapter No.	Outcome variable	Effect size	Required total Sample size	A Priori Power
Chapter 2	Weber's Constants	1	34	0.80
Chapter 4	Comfort	1.5	18	0.80
Chapter 5	Discomfort	2	12	0.80

Table 6-2: Post hoc power calculation

Chapter No.	Outcome variable	Effect size	Sample size	Post hoc power
Chapter 2	Weber's Constants	1.43	12 in each group	0.91
Chapter 4	Comfort	1.41	20 subjects	0.99
Chapter 5	Discomfort	1.41	21 subjects	0.99

The first experiment (Chapter 2) demonstrated that the difference thresholds of the central cornea can be successfully measured using a pneumatic Belmonte esthesiometer and that the lens and non-lens wearers exhibit dissimilar difference thresholds. The study also revealed that Weber's law holds true for the sensitivity of the ocular surface. The Weber's fraction approached a constant value for high stimulus intensities, while it increased rapidly for intensities close to absolute threshold. A similar phenomenon has been reported in discrimination of auditory tones[1, 2] and tactile vibration[3], and the variation in Weber's constant was attributed to the differences in methodology and stimulus conditions. The presence of sensory noise, which is a continuous random fluctuation in the activity levels of the neurons that carry signals from the ocular surface to the central nervous system might have contributed to the discrepancy in Weber's constant observed in this chapter. It is also proposed that the difference between lens and non-lens wearers can perhaps be because the operation characteristics of the sensory system for difference thresholds are different in both the group of subjects. In other sensory dimensions[4, 5], differential sensitivity were found to be similar even in the presence of different absolute sensitivity. Measurement of difference thresholds using different methods yielded similar DL functions indicating that the neural processes responsible for the DL must have been the same for each channel or the whole process operates at a level in the central nervous system that integrates information across the psychophysical channels[5]. A combination of mechanical lens effects and changes in corneal metabolism with lens wear can alter the equilibrium of the ocular surface, causing a change in sensory input in contact lens wearers. The alteration in ocular surface physiology can possibly contribute to increased noise in the neural activity levels of the lens wearers thereby giving rise to increased Weber's constant.

At suprathreshold levels, as in discrimination of pnuematic intensities, the stimulus comparisons are based on the differences in the sensation magnitude of two stimuli whereas absolute threshold involves the difference between no sensation and presence of a sensation (i.e., the detection of stimulus from the background). In absolute threshold measurements, the neural activity needs to be changed from background noise to an increase in neural activity and in difference threshold measurements, the neural activity produced by the two stimuli should be substantially different in addition to the background noise for a change in sensation to be perceived. The two measurement types may fundamentally involve different mechanisms of sensory processing and, the detection and discrimination tasks may not relate to one another. The difference in ocular surface physiology between lens and non-lens wearers can also lead to dissimilar processing of sensory information for differentiating pneumatic stimuli in the central nervous system and hence lens wearers have higher difference thresholds than non-lens wearers.

Repeatability measurements were not performed in this experiment. If repeatability had been too poor, there would not have been significant effects and the pattern of difference thresholds as observed in lens and non lens wearers may not have been found.

Chapter 3 explores the scaling of ocular discomfort by using direct psychophysical scaling techniques of magnitude estimation and magnitude matching to construct an ocular discomfort scale that relates discomfort arising from contact lens wear to the discomfort produced by pneumatic stimuli. The results propose that the average and individual psychophysical functions appear to follow Stevens' power functions, with the mechanical and chemical stimuli giving rise to different power exponents. However, examination of the individual transducer functions revealed that a sensory panel can exist where only specific participants are able to perform magnitude matching.

The inter-subject differences observed in this chapter were found to in accord with several studies in other sense modalities[6-18]. The subject's use of numerical estimates were proposed to be the primary reason for the variation in power exponents and the inter-individual variability can occur due to the differences in subject's response strategies, the subjects' interpretation and handling of numbers used in scaling experiments[6, 12, 16, 19, 20]. The range of stimulus intensities utilized, the distribution of the presentation of different stimulus intensities and the number of available response categories can also influence the responses from the participants[21-23].

In this experiment, some of the subjects were not able to perceive a difference in sensation intensity between the different contact lenses, the non-differences observed as similar discomfort ratings or by the use of short range of numbers. The combination of steep base curve with smaller diameter lenses and flat base curve with larger diameters could have stabilized the lens on the eye leading to better centration and comfort[24] and there might have been fewer lenses to produce an uncomfortable sensation.

The results of the experiment suggests that the averaging of responses from the participants for each lens type may not reflect the actual psychophysical scales as there are inter-individual differences in how subjects scale stimuli and the fitting pattern of each contact lens design is specific to an individual's corneal dimensions, which in turn relates to discomfort. The average psychophysical scale constructed with lens type as a sensory modality and its matching pneumatic strength may not precisely specify the form of the relationship, although averaging can remove the differences across subjects and enable to derive a common scale for any sensory dimension[25]. Instead, the magnitude ordered method of scaling is proposed to be a better technique for scaling discomfort as it is relative to the subject's preference of lens type. Contact lenses were only used as an instrument for producing discomfort and scaling need not be based on the design of the lenses. From the results, it would be recommended to order the contact lens discomfort based on its magnitude and scale to the corresponding pneumatic stimulus strength irrespective of the contact lens design.

The sensations elicited by the mechanical and chemical forces in this chapter were found to be in accordance with other studies that characterize the sensations with pneumatic stimuli[26-30]. The air from the pneumatic mechanical stimuli evoked a scratching sensation while CO_2 gave rise to sensations of both scratching and burning. Suprathreshold stimulation of the ocular surface with a contact lens also produced sensations of scratching and burning, probably due to the trigger of both the mechano and polymodal nociceptors. Mechanically, the contact lenses can cause friction to the corneal surface, while the chemical interaction that occurs with lens wear can cause physiological damage. The mechanical friction with silicone hydrogel lenses can be because of the increased modulus of elasticity, and with the hydrogel lenses, the conformity of the lens to the corneal surface leaves a decreased amount of tear film between the lens and the cornea causing friction.

The study also demonstrated that the mechanical and chemical channels could be exclusive as there are differences in power exponents and the quality of sensation produced by each modality. Other studies[31-33] have also proposed the corneal transducer functions to have different power exponents for mechanical and chemical stimulation and the differences in exponents might perhaps be due to underlying sensory differences with mechanical and chemical stimulation.

Chapter 3 also discusses the impact of the session and sequence of lens presentation on discomfort ratings. The lenses presented in the first session and/or the first sequence were observed to produce higher discomfort than the lenses used in the following session/sequences. However, the participants rated the lenses similarly in the mechanical and chemical stimulus sessions. Adaptation to the lenses was considered a possibility for the session/sequence effects. As there is no sensory stimulus to the cornea before the placement of the contact lens, the insertion of the first lens could have triggered an immediate higher sensory response causing an increase in discomfort ratings. Upon subsequent placement of lenses, the ocular surface would have adjusted to the sensory input with a decreased firing rate and may perhaps cause lower discomfort. The cornea can adapt to suprathreshold mechanical stimuli[34] and the effects are seen more prominently in asymptomatic contact lens wearers than the symptomatic group[35]. Since the design of the contact lenses were randomly allotted to the sessions and sequences, the adaptation effects were not pertained to any particular lens type. The improvement in comfort with time, from lens insertion to magnitude matching can also be explained by the mechanism of adaptation.

The reasons for ocular discomfort have been studied extensively[24, 36-42] and measures are taken to alleviate the symptoms and provide a satisfied lens wear experience. The contribution of poor/decreased vision to ocular discomfort in not known and hence the thesis have furthered clinically to study the effects of vision on the ratings of ocular discomfort. Traditional methods of comfort measurement using subjective rating scales were used in Chapter 4. The results suggest that ocular comfort is reduced under spatial blur and dioptric defocus conditions. However, when visual structure was removed by the use of occluders and viewing of ganzfeld, comfort seemed to be unaffected and appeared similar to normal vision conditions. This lack of alignment between vision and comfort gave rise to the speculation that the decrement in comfort with the induction of blur might perhaps be related to non-sensory factors such as the nocebo related effects or possibly due to Hawthorne effect.

Based on the finding that ocular discomfort increases with spatial blur and dioptric defocus, further investigations (Chapter 5) were carried out to understand if the ocular surface sensations evoked by suprathreshold mechanical stimulation, change under the presence of blur. The inferences from Chapter 4 are further strengthened by the findings from Chapter 5, as the intensities of stimuli applied to the ocular surface are known and similar in both clear and defocused conditions.

Previously, studies[30-33] have been conducted to investigate the magnitude of sensations relative to the intensity of stimulus applied on the ocular surface. However, the perception of ocular surface sensations under differing visual conditions has not yet been reported. The results of Chapter 5 suggest that the psychophysical magnitude functions can behave differently under clear and defocused conditions with different power exponents, implying that the processing of ocular surface sensations vary with the induction of blur. However, the exponents for discomfort under both the conditions are close to one (0.96 for clear and 1.08 for defocus), indicating that there may not be huge differences in sensory processing under clear vision and defocus. The results of repeated measures ANOVA also support the hypothesis that the ratings of discomfort and intensity do not change with defocus and clear vision. Since the strengths of the suprathreshold pneumatic stimuli that were presented to the cornea were the same during both the conditions, the processing of the sensory information should also be similar. However, there can be the other dimension of pain, the affective component that includes anticipation, distraction that can influence the processing of pain in the brain.

The visual targets used in the study can cause distraction of attention as well as nocebo like effects influencing the ratings of discomfort with blur. Studies[43-45] designed to investigate pain on manipulation of attention suggest that subjects rate pain lower when they direct their attention away from the painful stimulus. During the clear visual condition, the subjects would have focused their attention more on the targets than the pneumatic stimuli as the targets appear clear and hence rate discomfort to be lower. In defocused conditions, since the targets appeared blurred, there is a possibility of the subjects to deviate their attention on the pneumatic stimulus than on the visual targets and hence feel the discomfort to be higher.

The defocused condition could have also possibly created a nocebo like effect (discussed in detail previously in Chapter 4) driving the participants to experience decreased comfort.

The higher order processing of the sensory experiences of vision and pain in the brain are discussed previously in Chapter 5.

The results of the repeated measures ANOVA suggest that the rating of discomfort and intensity do not change with differing conditions in the study. Suprathreshold scaling using Stevens' power functions and repeated measures ANOVA essentially tests two different aspects of the perception of discomfort. The power functions demonstrate the rate of growth of sensations with changes in stimulus intensity, whereas repeated measures ANOVA compares the mean discomfort ratings under the two conditions. Since the power exponents were derived for each individual participant and a paired t-test was performed to investigate the differences in exponents under clear and defocused conditions, the change in psychophysical magnitude functions would provide more information on the processing of ocular surface sensations than the comparison of means. The results from Chapter 3 also suggests that averaging of subjects' responses may not be a suitable technique to scale ocular comfort due to the presence of inter-subject variability in the use of numerical estimates and judgment of stimuli. The psychophysical magnitude functions provide more insight by revealing that a tiny affective aspect of pain can account for the differences in power exponents observed and thereby influence the perception of discomfort under blur.

Another interesting finding in Chapter 5 is that the ratings of intensity and discomfort were dissimilar and pain intensity was rated higher than the discomfort. Studies[45, 62] have revealed that pain intensity and pain-unpleasantness are two distinct dimensions of pain and they can have different relationships to the nociceptive stimulus. The term sensory intensity usually indicates the magnitude of sensation and the affective label is applied to emotional/motivational variables like unpleasantness, discomfort, distressing or intolerable[63]. The difference in exponents between intensity and discomfort might possibly be because they reflect two different dimensions of pain. Although, sensory-discriminative and affective aspects of pain maybe separable, it is unlikely that completely independent afferent pathways are responsible for processing these two aspects of pain[64].

The absence of difference in detection thresholds, the similarity in the ratings of discomfort (as observed with repeated measures ANOVA) and the strength of the nociceptive input (strength of the pneumatic stimuli) being the same in both the visual conditions, suggest that the sensory processing of nociception on the ocular surface may not influence the increase in discomfort with blur. However, the affective aspect of pain or a higher order sensory integration between vision and pain can influence the perception of discomfort under blur.

The results from the series of the experiments in this thesis propose that a special sensory panel can exist which has to studied closely. The techniques for identifying the sensory panels can be complex and yet to investigated. Whether the psychophysical scaling and ratings are dependent upon the individual's sensory response of the ocular surface or the subject's use of numbers/judgment has to be completely understood. Subjects may perhaps be classified based on their ability to perform the scaling tasks and the use of subjective ratings scales. Investigation of such separate group of participants can help us understand the scaling of discomfort in more detail. I could not employ sensory panel analysis in this series of experiments due to the small sample size.

The results of this dissertation help to advance our understanding of the perception of ocular discomfort. Clinically, Chapter 2 emphasizes the importance of difference threshold measurements and perhaps this can be a basis for testing response differences between contact lenses. Chapter 3 establishes the ocular discomfort scales that equate the subjective reports of discomfort to quantitative pneumatic stimulus strengths and so perhaps if this method of scale development were adopted, a better understanding of the participants' reports of discomfort might be possible. The clinical implications of Chapter 4 and 5 are related to the much contemplated view that is whether vision influences comfort. The affective aspect of mild ocular pain and not sensory pain was proposed to play a role in the reduction of vision under blur.

The experiments in this thesis could have been performed differently by sampling the subjects in a different manner, since it was observed that only half of the subjects were able to perform the magnitude matching tasks and the subjective reports of discomfort showed inter-individual variation. Further studies based on the sensory panels can be perhaps be conducted using rating scales and/or magnitude estimation/matching. To understand the influence of the affective aspect of pain on the perception of discomfort, there could have been steps undertaken to measure discomfort under conditions of varying anxiety levels or arresting the experience of affective pain using tranquilizers. Electrophysiological tests such as functional magnetic resonance imaging and pain evoked potentials can also be used to attempt to understand pain processing in the brain and classify the subjects based on its findings. A thorough understanding of the influence of blur on ocular discomfort can also be achieved by employing electrophysiological recordings from the brain when the subjects view defocused targets.

In addition to the scaling of sensory dimension of pain, the cognitive and emotional aspects of pain should also be explored for example using standardized questionnaires while subjects are experiencing discomfort. A model can perhaps be developed that includes the sensory, affective, and cognitive recordings to create an index for ocular discomfort.

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Chapter 1

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