Eye movement-based analysis in reading. A method for evaluating functional vision in normal ageing, presbyopia correction and in retinal diseases.

Ανάλυση οφθαλμικών κινήσεων κατά τη διάρκεια ανάγνωσης. Μέθοδος αξιολόγησης λειτουργικής όρασης στη φυσιολογική γήρανση, στη διόρθωση της πρεσβυωπίας και σε παθήσεις του αμφιβληστροειδούς.

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CONTENTS

List of Figures . . . vi

List of Tables . . . x

Abstract . . . xi

Περίληψη . . . xii

Acknowledgments . . . xiv

Publications . . . xv

1 INTRODUCTION . . . 1
- 1.1 Early visual processing . . . 1
  - 1.1.1 Retina . . . 1
  - 1.1.2 Binocular vision, Stereopsis . . . 3
- 1.2 Gaze system . . . 3
  - 1.2.1 Neuronal control systems that keep the fovea on target . . . 4
- 1.3 Extraocular muscles . . . 10
- 1.4 Eye movements during reading . . . 12
  - 1.4.1 Reading . . . 12
  - 1.4.2 Reading as a tool for visual performance evaluation . . . 13
  - 1.4.3 Eye-tracking during reading: technology and state of the art . . . 13
  - 1.4.4 Eye movement characteristics during reading . . . 15
  - 1.4.5 Perceptual span . . . 18
- 1.5 Age-related Macular Degeneration (AMD) . . . 19
  - 1.5.1 Pathophysiology and prevalence . . . 19
  - 1.5.2 Anti-Vascular Endothelial Growth Factor (Anti-VEGF) . . . 20
  - 1.5.3 Eye movements and reading in AMD and other macular diseases . . . 21
- 1.6 Presbyopia . . . 23
  - 1.6.1 Pathophysiology . . . 23
  - 1.6.2 Presbyopia correction . . . 23
  - 1.6.3 Presbyopia correction and oculomotor behavior . . . 26
- 1.7 Aim of the study . . . 26

2 EXPERIMENTAL SECTION . . . 28
- 2.1 Ethics . . . 28
- 2.2 Eye movements recordings . . . 28
- 2.3 Visual acuity . . . 30

2.4 Reading efficiency . . . 30
2.5 Reading material . . . 30
2.6 Eye movement parameters . . . 31
2.7 Ex-Gaussian fitting of fixation duration distributions . . . 32
2.8 Study I – Assessment of the test-retest reliability of eye movement parameters during text reading . . . 34
  2.8.1 Aim of the study . . . 34
  2.8.2 Participants . . . 34
  2.8.3 Reading material . . . 34
  2.8.4 Experimental procedure . . . 35
  2.8.5 Data analysis . . . 35
  2.8.6 Results . . . 35
  2.8.7 Discussion . . . 37
2.9 Study II - Patients with Age-related Macular Degeneration (AMD) . . . 41
  2.9.1 Aim of the study . . . 41
  2.9.2 Participants . . . 41
  2.9.3 Reading material . . . 42
  2.9.4 Experimental procedure . . . 43
  2.9.5 Data analysis . . . 43
  2.9.6 Results . . . 43
  2.9.7 Discussion . . . 48
2.10 Study III - Patients with presbyopia . . . 55
  2.10.1 Aim of the study . . . 55
  2.10.2 Participants . . . 55
  2.10.3 Reading material . . . 56
  2.10.4 Contact lenses . . . 56
  2.10.5 Experimental procedure . . . 56
  2.10.6 Data analysis . . . 58
  2.10.7 Results . . . 58
  2.10.8 Discussion . . . 68
2.11 Study IV – Effect of comprehension . . . 71
  2.11.1 Aim of the study . . . 71
  2.11.2 Participants . . . 71
  2.11.3 Reading material . . . 71
  2.11.4 Experimental procedure . . . 71
  2.11.5 Data analysis . . . 72
  2.11.6 Results . . . 72
  2.11.7 Discussion . . . 74

3 GENERAL DISCUSSION . . . 77

APPENDIX . . . 81

A APPENDIX 81

BIBLIOGRAPHY 84

LIST OF FIGURES

Figure 1.1 Fundus photography showing some distinctive areas of the retina. From Estudillo-Ayala et. al (2020)[1]. 2
Figure 1.2 Spatial distribution of rods and cones on the retina (From Osterberg 1935 [2]) 3
Figure 1.3 On the right, trajectories of saccadic eye movements during scanning the image shown on the left (From Yarbus 1968 [5]). 5
Figure 1.4 Saccade velocity as a function of saccade amplitude [8]. 6
Figure 1.5 Vergence system when looking near and far [3]. 7
Figure 1.6 Eye position during fixating on a small stimulus. Microsaccades, tremor and drift are displayed [9]. 8
Figure 1.7 Correlation of microsaccade magnitude with peak velocity [10]. 9
Figure 1.8 On the left, lateral view of a left eye and the extraocular muscles. On the right, a superior view of a left eye [3]. 10
Figure 1.9 The three axes of ocular motion [7]. 11
Figure 1.10 The extraocular muscles and their actions according to the eye position [7]. 11
Figure 1.11 Some current reading cards. 14
Figure 1.12 Developmental characteristics of eye movements during reading [11]. . 16
Figure 1.13 Single fixation duration as a function of Initial Fixation Position [4]. . . 18
Figure 1.14 Optical coherence tomography images of the macula in the eyes in age-related macular degeneration (AMD). (A) An eye with non-exudative or “dry” AMD with drusen between Bruch’s membrane and the retinal pigment epithelium (red arrows); (B) an eye with active exudative or “wet” AMD with subretinal (red arrow) and intraretinal fluid (white arrow) in the macula; (C) the same eye shown in B after receiving several intravitreal anti-VEGF injections with interval resolution of intraretinal and subretinal fluid. (reprinted from [85]). 21
Figure 1.15 MRI of the unaccomodated eye of a 26 year old person (left) and of a 49 year old person (right). In the older eye, increased lens thickness, reduced pupil diameter and anterior displacement of the uveal tract can be detected [107] (reprinted from [108]). 23
Figure 2.1 The experimental setup. 29
Figure 2.2 The EyeLink II system. 29
Figure 2.3 Reading cards used in the study. (a) the greek version of IReST and (b) one of the texts developed by the study group at the Laboratory of Optics and Vision for the purpose of the study 31

Figure 2.4 Performance categories of the Greek version of IReST (a) and their textual parameters (b). Circled in red the texts that were used in our study 32
Figure 2.5 Density functions of fixation durations fitted with ex-Gaussian, for high (solid line) and low (dashed line) frequency words. 33
Figure 2.6 Bland–Altman plots of the difference in VA (1st-2nd visit) as a function of the average VA. Three horizontal dotted lines: the upper limit of 95% and the mean and lower limit of the 95% of the difference. 37
Figure 2.7 Bland–Altman plots of the difference in Reading Speed and Number of Fixations as a function of their respective mean values. Three horizontal dotted lines: the upper limit of 95% and the mean and lower limit of the 95% of the difference. 38
Figure 2.8 Bland–Altman plots of the difference in Fixation Duration, Percentage of Regressions and ex-Gaussian parameters μ and τ as a function of their respective mean values. Three horizontal dotted lines: the upper limit of 95% and the mean and lower limit of the 95% of the difference. 39
Figure 2.9 Box plots of monocular near visual acuity for the dominant eye of the control group (left) and the affected eye of the AMD group (right) at both visits. Average values are shown in white. 45
Figure 2.10 Box plots of monocular passage reading speed (upper) and number of fixations (lower) for the RE of the control group and the affected eye of the AMD group at both visits. Average values are indicated in white. . . 50
Figure 2.11 Association between reading speed with visual acuity as measured in the treated eye. 50
Figure 2.12 Association of change in monocular passage reading speed (post-minus pre-treatment performance in wpm) with corresponding change in eye fixation parameters. Upper panel: fixation duration (left), number of fixations (middle) and regressions (right); Lower panel: ex-Gaussian parameters μ (left) and τ (right). Best-fitting linear regression curves are shown by dashed lines. 51
Figure 2.13 Relative refractive power of Acuvue CLs as a function of their semi-diameter. Image adopted from Kim E et al. (2017) [145]. 57
Figure 2.14 Near Visual Acuity (left) and stereoacuity (right) values in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC) and monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences. 60
Figure 2.15 Reading speed values in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences. . . 61

Figure 2.16 Number of forward fixations (left) and fixation duration (right) in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences. 61
Figure 2.17 Percentage of regressions (left) and blink rate (right) in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences. 62
Figure 2.18 Ex Gaussian parameters, μ and τ, in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences. 62
Figure 2.19 Associations of the change in reading speed with corresponding changes in number of fixations (upper panel), fixation duration (middle panel) and percentage of regressions (lower panel) between MON correction and FC condition. 64
Figure 2.20 The association of change in reading speed with corresponding change in near VA between MON and FC. 65
Figure 2.21 Reading speed values with monovision approach (MON), and multifocal contact lenses (MC) in high and low luminance. Whiskers represent 1.5 IQR. 66
Figure 2.22 Eye fixation parameters (number of forward fixations, fixation duration, percentage of regressions and blink rate) with monovision approach (MON) and multifocal contact lenses (MC) in high and low luminance. Whiskers represent 1.5 IQR. 67
Figure 2.23 Ex-Gaussian parameters μ and τ with monovision approach (MON) and multifocal contact lenses (MC) in high and low luminance. Whiskers represent 1.5 IQR. 68
Figure 2.24 Associations of the change in reading speed with corresponding changes in fixation duration (upper panel), number of fixations (middle panel) and ex-Gaussian μ (lower panel) between the two luminance conditions (low minus high) with MON correction. 69
Figure 2.25 Reading speed values in the two conditions tested: BASELINE and COMP. 73
Figure 2.26 (Number of forward fixations (upper left), Fixation duration (upper right), Percentage of regressions (down left) and blink rate (down right) in the two conditions tested: BASELINE and COMP. 74
Figure 2.27 Ex-Gaussian μ (left) and τ (right) in the two conditions tested: BASELINE and COMP. 75

Figure 2.28 The association between change in reading speed between the two conditions and concurrent change in eye fixation parameters (number of fixations, percentage of regressions and ex-Gaussian τ). 75

LIST OF TABLES

Table 2.1 Visual Acuity (VA) and eye movement parameters over two visits: mean (SD) values, average differences and Coefficient of Repeatability (CR) . 36
Table 2.2 Mean values of eye movement parameters, Coefficient of Repeatability (CR) and CR as a percentage of the mean value 40
Table 2.3 CRT, VA and reading performance parameters (SD) and differences between groups 44
Table 2.4 CRT, near visual acuity and reading fluency (SD) across visits and average differences for the two groups. 47
Table 2.5 Reading performance across visits and average differences for the two groups. 49
Table 2.6 Experimental procedure of Studies III and IV. NC: near corrected, FC: far corrected, Comp: comprehensive reading, low: low luminance 57
Table 2.7 VA, stereoacuity, reading speed and eye movement parameters (SD) in the four conditions of the study. 59
Table 2.8 Correlations of changes in reading speed with corresponding changes in near VA and in eye movement parameters between MON and FC and between MC and FC conditions. *: significant correlation. 63
Table 2.9 Reading performance with two kinds of CLs in high and low luminance levels. 65
Table 2.10 Correlations of changes in reading speed with corresponding changes in eye movement parameters between high and low luminance in MON and MC conditions. *: significant correlation. 67
Table 2.11 Reading performance parameters in BASELINE and COMP conditions. 73
Table 2.12 Correlations of changes in reading speed with corresponding changes in eye movement parameters between BASELINE and COMP conditions. *: significant correlation. 73
Table 3.1 Reading Speed and eye movement parameters in relation to various factors 80
Table A.1 Demographics of the participants of Study I. 81
Table A.2 Demographics of the participants of Study II. 82
Table A.3 Demographics of the participants of Study III. 83

ABSTRACT

Visual acuity assessment is the preferred first-line test among clinicians to evaluate the integrity of the visual system. However, simple measures of near acuity, while of interest, may provide only a partial indication of functional vision and of the effectiveness of surgical or optical corrections. Since many activities of daily living rely on reading it is not surprising that reading difficulty is the most common complaint among individuals with decreased vision, while it forms the primary reason for patients to seek referral to a low vision clinic and a strong predictor of vision-related quality of life.

Reading, however is a complex function. It requires a proper retinal image and intact retina to send information to the brain, where the image is analyzed for extraction of meaning. Thus it is difficult to evaluate functional vision based on reading performance. The evolution of eye trackers, new standardised reading tests and computational and statistical methods have given valuable tools to further analyse reading performance through eye movement parameters.

The aim of this work is to use eye movement analysis during text reading to evaluate functional vision under different conditions. It is divided into four studies involving: assessment of method repeatability, applications to age-related macular disease, anti-VEGF treatment, and presbyopia correction, as well as the study of reading comprehension.

A secondary aim is to find certain eye movement parameters that are distinctly affected under each condition and factor. In this context, the ex-Gaussian analysis is used to evaluate the fixation duration distribution.

The results highlight certain distinct effects of specific factors on eye movement and ex-Gaussian parameters. Ex-Gaussian parameter τ, the percentage of regression and the number of forward fixations were affected by cognitive (higher-level) processes while ex-Gaussian μ, fixation duration and the number of fixations were mainly affected by optical (lower-level) factors.

In the future, studies of specifically manipulated changes in certain factors have to be performed. More refined computational methods and machine learning approaches could provide more thorough analysis of eye movement parameters during reading.

ΠΕΡΙΛΗΨΗ

Η εξέταση της οπτικής οξύτητας αποτελεί το τεστ πρώτης γραμμής που προτιμάται από τους κλινικούς γιατρούς για την αξιολόγηση της ακεραιότητας του οπτικού συστήματος. Παρ΄ όλα αυτά, η εξέταση της κοντινής οξύτητας, αν και χρήσιμη, μπορεί να παρέχει μόνο μερική ένδειξη της λειτουργικής όρασης και της αποτελεσματικότητας μιας χειρουργικής ή οπτικής διόρθωσης. Αφού πολλές δραστηριότητες της καθημερινής ζωής στηρίζονται στην ανάγνωση, δε μας εκπλήσσει το ότι η δυσκολία στην ανάγνωση είναι το πιο σύνηθες παράπονο ατόμων με χαμηλή όραση και ότι αποτελεί τον βασικό λόγο που ασθενείς παραπέμπονται σε κλινική χαμηλής όρασης και ισχυρό προγνωστικό παράγοντα για την ποιότητα ζωής σχετικά με την όραση.

Η ανάγνωση παρ΄ όλα αυτά, είναι μια περίπλοκη διαδικασία. Απαιτεί καλή αμφιβληστροειδική εικόνα και ακέραιο αμφιβληστροειδή για να στείλει την εικόνα στον εγκέφαλο, όπου αναλύεται για την κατανόηση του μηνύματος. Εξού και είναι δύσκολη η αξιολόγηση της λειτουργικής όρασης με βάση την αναγνωστική συμπεριφορά. Η εξέλιξη των eye trackers, νέες τυποποιημένες κάρτες ανάγνωσης και νέες υπολογιστικές και στατιστικές μέθοδοι έχουν δώσει πολύτιμα εργαλεία για την περαιτέρω ανάλυση της αναγνωστικής συμπεριφοράς με τη χρήση παραμέτρων οφθαλμικών κινήσεων.

Σκοπός αυτή της εργασίας είναι η χρήση της ανάλυσης οφθαλμικών κινήσεων κατά την ανάγνωση κειμένου για την αξιολόγηση της λειτουργικής όρασης κάτω από διαφορετικές συνθήκες. Χωρίζεται σε τέσσερις μελέτες: έλεγχος επαναληψιμότητας της μεθόδου, μελέτη της επίδρασης της ηλικιακής εκφύλισης της ωχράς κηλίδας AMD και της αποτελεσματικότητας της anti-VEGF θεραπείας στις οφθαλμικές κινήσεις κατά την ανάγνωση και μελέτη της επίδρασης της πρεσβυωπίας και τεχνικών διόρθωσής της με φακούς επαφής, καθώς και μελέτη της επίδρασης της κατανόησης του κειμένου στις οφθαλμικές κινήσεις.

Ένας δεύτερος σκοπός είναι να βρεθούν συγκεκριμένες παράμετροι οφθαλμικών κινήσεων που επηρεάζονται σαφώς από την επίδραση κάθε παράγοντα. Σε αυτό το πλαίσιο, η ανάλυση ex-Gaussian χρησιμοποιείται προκειμένου να αξιολογηθεί η κατανομή της διάρκειας των σημείων προσήλωσης. Στη σχετική βιβλιογραφία, η ανάλυση ex-Gaussian στην κατανομή της διάρκειας των σημείων προσήλωσης έχει χρησιμοποιηθεί για τη μελέτη της επίδρασης πολλών παραγόντων στις οφθαλμικές κινήσεις. Είναι υπό συζήτηση αν η κάθε παράμετρος της κατανομής ex-Gaussian υποδηλώνει διαφορετική γνωσιακή διεργασία. Η μελέτη μας, έχει ως σκοπό να συμβάλει σε αυτή τη συζήτηση ελέγχοντας αυτές τις παραμέτρους κάτω από διαφορετικές συνθήκες.

Στη μελέτη για την επίδραση της ηλικιακής εκφύλισης της ωχράς κηλίδας AMD τα αποτελέσματα δείχνουν ότι οι ασθενείς με AMD είχαν σημαντικά χειρότερη οπτική οξύτητα και μεγαλύτερο πάχος αμφιβληστροειδή CRT από την ομάδα των υγιών συμμετεχόντων, καθώς επίσης και σημαντικά διαφορετικές τιμές στην ταχύτητα ανάγνωσης και σε όλες τις παραμέτρους των οφθαλμικών κινήσεων. Μετά από τρεις μήνες θεραπείας anti-VEGF, οι ασθενείς παρουσίασαν βελτίωση στην ταχύτητα ανάγνωσης και στον αριθμό των σημείων προσήλωσης. Αντίθετα, η οπτική οξύτητα παρέμεινε σχετικά σταθερή, στηρίζοντας την άποψη ότι η οπτική οξύτητα δεν είναι αρκετή για να αξιολογηθεί η λειτουργική όραση σε ασθενείς με χαμηλή όραση.

Η διόρθωση της πρεσβυωπίας με φακούς επαφής διαφορετικών σχεδιασμών (πολυεστιακοί και φακοί που παρέχουν μονοόραση), είχε σημαντικά αποτελέσματα στην οπτική οξύτητα, στην ταχύτητα ανάγνωσης και σε παραμέτρους των οφθαλμικών κινήσεων, όπως στον αριθμό των σημείων προσήλωσης και τη διάρκεια της προσήλωσης, καθώς επίσης και στην παράμετρο μ της ex-Gaussian. Παρ΄ όλο που η οπτική οξύτητα ήταν σημαντικά καλύτερη με την μονοόραση απ΄ ότι με τους πολυεστιακούς φακούς επαφής, καμία άλλη διαφορά δε βρέθηκε μεταξύ των δύο τρόπων διόρθωσης. Η ανάγνωση σε χαμηλή φωτεινότητα είχε σημαντική επίδραση σχεδόν σε όλες τις παραμέτρους των οφθαλμικών κινήσεων και στην παράμετρο μ της ex-Gaussian. Η επίδραση αυτή ήταν μεγαλύτερη στους πολυεστιακούς φακούς επαφής.

Στη μελέτη της επίδρασης της κατανόησης του κειμένου στις οφθαλμικές κινήσεις κατά την ανάγνωση, δώσαμε στους συμμετέχοντες δύο διαφορετικά σετ οδηγιών. Στο πρώτο σετ, καλούνταν να διαβάσουν το κείμενο σε έναν άνετο, γι΄ αυτούς ρυθμό ενώ στο δεύτερο σετ, καλούνταν να διαβάσουν το κείμενο έτσι ώστε να το καταλάβουν και να είναι σε θέση να απαντήσουν μετά σε ερωτήσεις κατανόησης του κειμένου. Τα αποτελέσματα έδειξαν ότι η δεύτερη συνθήκη σχετίζεται με χαμηλότερη ταχύτητα ανάγνωσης, μεγαλύτερο αριθμό σημείων προσήλωσης, μεγαλύτερο ποσσοστό κινήσεων προς τα πίσω (regressions) και υψηλότερη τιμή στην παράμετρο τ της ex-Gaussian. Η αύξηση του αριθμού των σημείων προσήλωσης μπορεί να προβλέψει σε σημαντικό βαθμό τη μείωση στην ταχύτητα ανάγνωσης.

Τα αποτελέσματα δείχνουν σαφή επίδραση συγκεκριμένων παραγόντων στις παραμέτρους οφθαλμικών κινήσεων και στις παραμέτρους της ανάλυσης ex-Gaussian. Η παράμετρος τ της ex-Gaussian, το ποσοστό των κινήσεων προς τα πίσω (regressions) και ο αριθμός των σημείων προσήλωσης μετά από σακκαδική κίνηση προς τα μπροστά, εξαρτώνται κυρίως από γνωσιακές διεργασίες, όπως η κατανόηση του κειμένου, ενώ η παράμετρος μ της ex-Gaussian, η διάρκεια και ο αριθμός των σημείων προσήλωσης επηρεάζονται κυρίως από οπτικούς παράγοντες, όπως η φωτεινότητα και η θόλωση. Ενδιαφέρον έχει το γεγονός ότι οι ασθενείς με AMD είχαν σημαντικά διαφορετικές τιμές από την ομάδα των υγιών, σε όλες τις παραμέτρους που μελετήθηκαν. Θα περιμέναμε η ηλικιακή εκφύλιση τηε ωχράς κηλίδας να επηρεάζει την όραση κυρίως μέσω οπτικών παρεμβολών στο επίπεδο του αμφιβληστροειδή επίπεδο. Φαίνεται όμως, ότι επηρεάζει την όραση σε τέτοιο επίπεδο, ώστε να μειώνεται η ικανότητα αναγνώρισης λέξεων και νοήματος, με αποτέλεσμα να υπάρχουν επιπτώσεις και σε γνωσιακό επίπεδο.

Στο μέλλον, θα πρέπει να πραγματοποιηθούν μελέτες με αλλαγές συγκεκριμένων παραγόντων, με κατά το δυνατόν, διαχωρισμό γνωσιακών και οπτικών παραγόντων, προκειμένου να εξαχθούν πιο ασφαλή συμπεράσματα σχετικά με τη συσχέτιση συγκεκριμένων παραγόντων με τη λειτουργία της όρασης κατά την ανάγνωση. Περισσότερο εκλεπτυσμένες υπολογιστικές μέθοδοι και προσεγγίσεις μηχανικής μάθησης μπορούν να δώσουν πιο λεπτομερή ανάλυση των παραμέτρων των οφθαλμικών κινήσεων κατά την ανάγνωση.

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PUBLICATIONS

This thesis includes work by the author that has been published. In particular, some data, ideas, opinions and figures presented in this thesis have previously appeared in:

Ktistakis E, Simos P, Tsilimbaris MK, Plainis S "**Efficacy of Wet Age-related Macular Degeneration Treatment on Reading: A Pilot Study Using Eye-movement Analysis**" published in *Optometry and Vision Science*, DOI: 10.1097/OPX.0000000000002064

1

INTRODUCTION

In this chapter, the basic concepts relevant to the thesis are described and the state of the art is presented.

1.1 EARLY VISUAL PROCESSING

Visual perception begins in the retina. Incoming light is focused by the optical elements of the eye, mainly the cornea and the lens, and projected to the outer layers of the retina. There, light is converted to electrical signal which is then sent through the optic nerve to thalamic and tegmental nuclei for further processing before reaching the visual cortex.

1.1.1 *Retina*

The retina covers the posterior pole of the eye and is the photosensitive layer where light is focused on and conversion of light energy to electrical signal takes place.

In vivo imaging of the retina using fundus photography reveals the following structures (Fig. 1.1):

- The macular lutea with a diameter of about 5mm (20° of visual angle), - The fovea, at the center of macular lutea with a diameter of about 1.5mm (5°) and the foveola at the center of the fovea (1°). The foveola is responsible for high resolution vision supported by the high density of cone photoreceptors. - The optic disk which is about 15° of visual angle nasally from foveola.

The retina contains five different neuronal cells: The photoreceptors, the horizontal, the bipolar, the amacrine and the ganglion cells. Every kind of these cells is responsible for a different function.

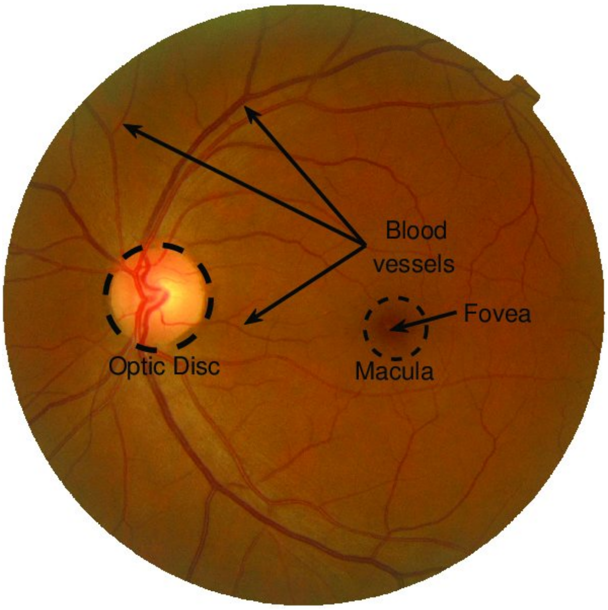


Figure 1.1: Fundus photography showing some distinctive areas of the retina. From Estudillo-Ayala et. al (2020)[1].

The photoreceptors are responsible for the conversion of light energy to a change in membrane potential. There are two kinds of photoreceptors, rods and cones. Cones are responsible for day vision and color processing, while rods for night vision. Cones provide higher acuity and better resolution than rods. Rods are very sensitive to light and therefore they function well in dim light when cones cannot be excited. Although rods are more sensitive to light than cones, they are "achromatic".

There are three types of cones distinguished by the range of wavelengths to which they are most sensitive, i.e. the S-cones which are most sensitive at 420nm, the M-cones sensitive at 534nm and the L-cones which are most sensitive at 564nm.

Figure 1.2 shows the density of rods and cones as a function of the retinal eccentricity. The cone density is higher at the center of the fovea, foveola, and decreases in the periphery. On the contrary, rod density is higher at about 20° from the center of macula lutea. Rods are absent from the foveola and only cones are present in this area. This is why the foveola has the highest resolution and spatial sensitivity. In addition, at the center of the fovea, each cone is connected to a single ganglion cell but at the periphery more than one cones and rods converge to a single cell.

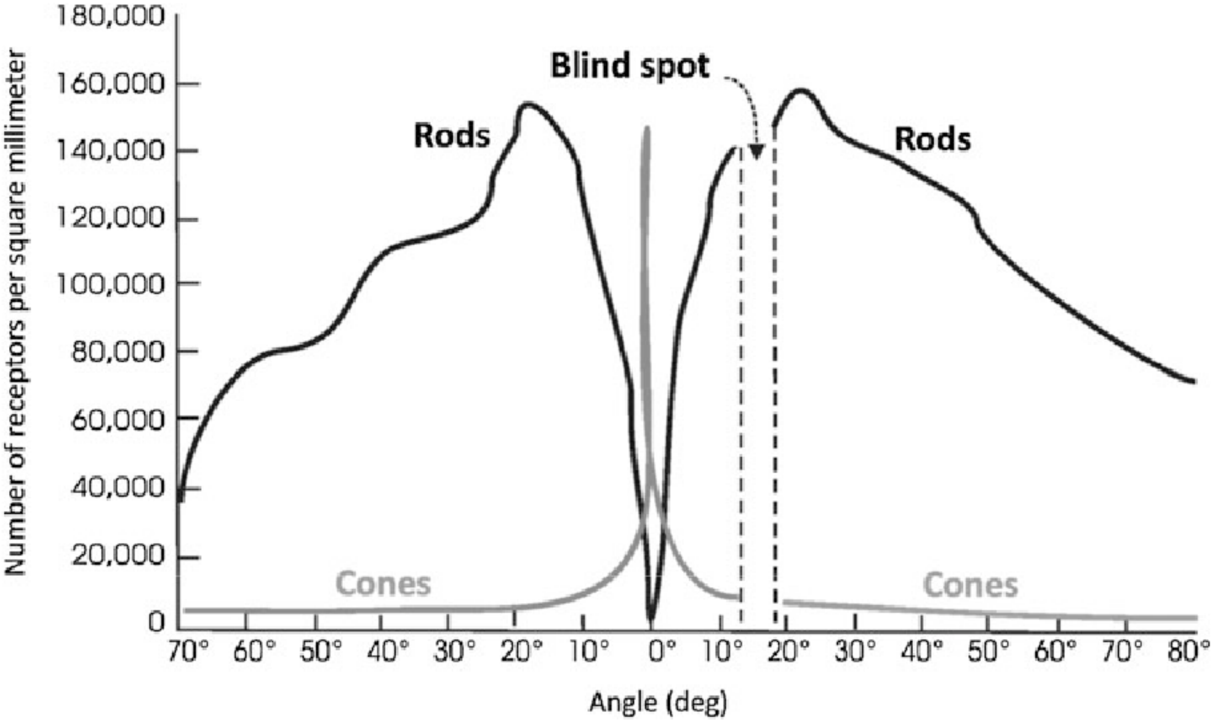


Figure 1.2: Spatial distribution of rods and cones on the retina (From Osterberg 1935 [2])

1.1.2 *Binocular vision, Stereopsis*

The retinal image is two-dimensional, however we perceive the world as tree-dimensional. The shift from two to three dimensions relies on both monocular and binocular cues. Monocular cues create far-field depth perception, while binocular cues create near-field depth perception. Stereoscopic vision is based on the fact that the two eyes are separated in the horizontal plane, thus each eye sees the world from a slightly different angle. When we fixate on a point, the convergence of the eyes cause this point to fall on identical spots of the fovea. The rest of the points (closer or further from the fixation point) however, fall on slightly different points of the retina of each eye. This difference is known as binocular disparity and it constitutes a vital cue for depth perception.

1.2 GAZE SYSTEM

The gaze system is responsible for the placement of a visual target on the fovea, where the resolution of the retina is optimal. It consists of two components: the oculomotor system and the head movement system. The first one moves the eyes in the orbits, while the latter moves the orbits in space.

1.2.1 *Neuronal control systems that keep the fovea on target*

We can outline five different movement systems, three of which keep the fovea on a visual target and two that stabilize the eye when the head moves [3].

- Saccadic eye movements move the fovea rapidly to a visual target
- Smooth pursuit movements keep the image of a moving target on the fovea
- Vergence movements move the eyes in opposite directions so that the image is positioned on both foveae
- Vestibulo-ocular movements hold images still on the retina during brief head movements
- Optokinetic movements hold images during sustained head rotation

All, but the vergence movements are conjugate movements. That means that both eyes move in the same direction and by the same amount. Vergence movements are disconjugate: the eyes move in different directions and sometimes by different amounts.

Finally, there is a sixth system, the fixation system which suppresses the eye movements in order to hold the eye still during intent gaze [3].

1.2.1.1 *The saccadic system*

Saccades are fast, ballistic, and conjugate eye movements [4]. They can be made not only towards a visual target but also towards auditory or tactile stimuli, or even towards memorized targets and verbal commands [3].

When exploring the world with our eyes, we do it in a series of fixations connected by saccades. The purpose of the saccades is to move the eyes as quickly as possible so that the image of an object is brought to the fovea [3]. Figure 1.3 shows the orbit of the saccades during scanning an image.

The target determines the amplitude and the direction of a saccade. On the contrary, its velocity and duration are not subject to voluntary control. Its velocity is strongly and positively

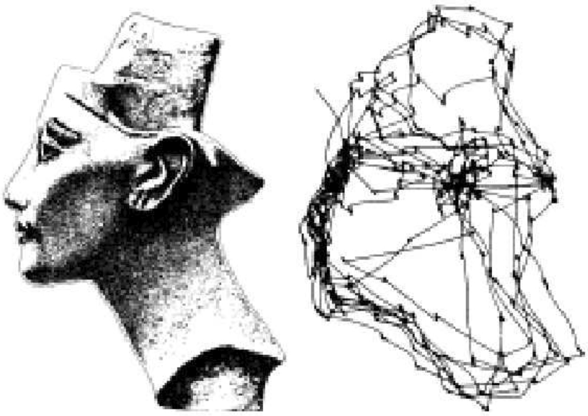


Figure 1.3: On the right, trajectories of saccadic eye movements during scanning the image shown on the left (From Yarbus 1968 [5]).

correlated to the amplitude of the saccade, i.e., the distance of the target from the current fixation point. Figure 1.4 shows this relationship.

Normally there is no time for visual feedback to modify the course of a saccade, thus corrections to the direction or the amplitude of a saccade are made by subsequent saccades [3].

The velocity and the duration of saccades of similar amplitude can highly vary even for the same individual. There are many factors that have predictable effect on saccadic velocity. Saccadic velocity can be reduced by certain drugs, fatigue or pathological states. Saccades are also affected in psychiatric patients and in people with affective and neurological disorders [4]. Saccades are also slower when made in complete darkness, when made in anticipation of targets moving in a predictable way or when made in the opposite direction of a visual stimulus [6]. Saccadic velocity is also affected by the direction of the movement and the initial and final orbital position. Saccades towards the center tend to be faster than the ones that are directed towards the periphery [6]. In healthy adults saccadic velocity ranges between 30-700°/sec, saccade duration between 30-100 ms, amplitude between 0.5-40° and latency between 150-250 ms (the sum of sensory and oculomotor processing time [7].

1.2.1.2 *The smooth pursuit system*

The smooth pursuit system consists of conjugate eye movements that track a slowly moving object so that its image is kept on the fovea. This is done by calculating how fast the target is moving and then moving the eyes accordingly [3]. Only animals with foveae make smooth pursuit eye movements and those that do not have, use their optokinetic eye movements in

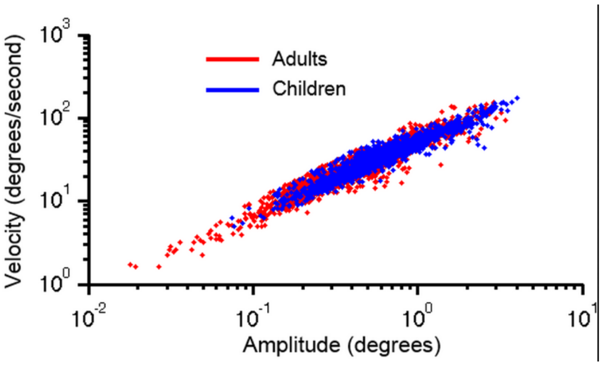


Figure 1.4: Saccade velocity as a function of saccade amplitude [8].

order to track objects of their environment. Although humans have both smooth pursuit and optokinetic movements, they rely mainly on the smooth pursuit [7].

A moving stimulus is needed to properly calculate eye velocity. This means that a verbal command or an imagined image cannot produce smooth pursuit. Smooth pursuit movements have a maximum velocity of about 100°/s and latency (initiation time) ranging between 100-130 ms [3, 7]. Drugs, fatigue, alcohol, and even distraction degrade the quality of these movements.

1.2.1.3 *The vergence system*

The vergence eye movements shift the gaze axes in depth so that the image of a target is kept simultaneously on both foveae. At any given time only a small portion of the visual field is in focus on the retina. When we look at something nearby, distant objects are out of focus and when we look at something far away, near objects are blurred. So, the vergence movements bring the new object of interest in focus. Figure 1.5 shows vergence movements when the viewer aims to look far and near.

As mentioned before, the vergence movements are the only disconjugate eye movements. That means that in order to move from a far to a near target, the eyes converge (i.e., rotate towards the nose) and in order to aim from a near to a far target, the eyes diverge (i.e., rotate towards the temples) [7].

Vergence is linked to the accommodation of the lens and to pupillary constriction. These three linked systems comprise the near response (or near triad), because they occur when we move our gaze from a far to a near target.

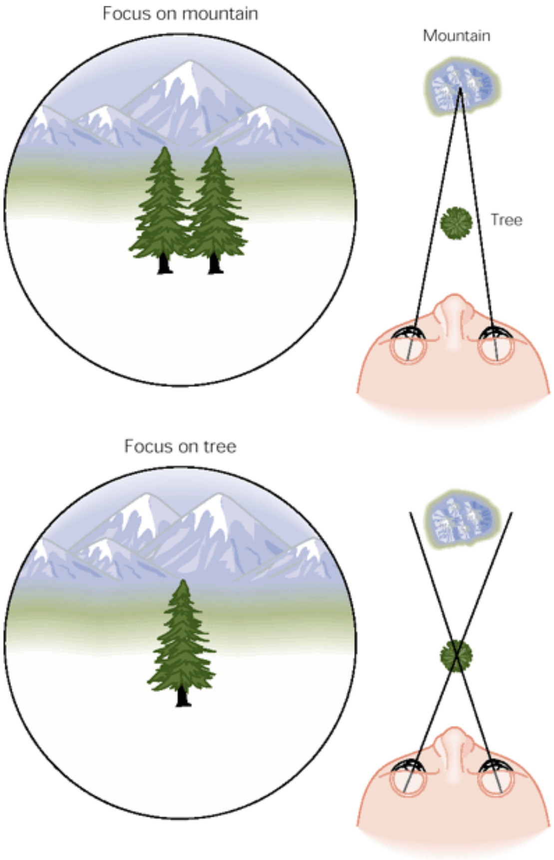


Figure 1.5: Vergence system when looking near and far [3].

The main stimuli for vergence are the retinal image blur and the retinal disparity. The retinal disparity is the slight difference of retinal position between the two eyes, used by the visual system, to create the sense of depth.

Vergence eye movements are very slow and last 1 second or even longer. This may be due to the fact that vergence, contrary to the saccades, is driven by visual feedback, which normally takes at least 80 ms. The speed of vergence movements may be also limited by how fast the lenses change shape (accommodation) and how fast the pupils constrict, since they all occur simultaneously [7].

The latency of the vergence movements is about 200 ms for retinal blur stimuli and 80-160 ms for retinal disparity stimuli [7].

1.2.1.4 *The vestibulo-ocular system*

The Vestibulo-Ocular Reflex (VOR) stabilizes retinal images during head movements by counter-rotating the eyes at the same speed as the head but in the opposite direction. Image stabilization based on vestibular input is much faster and more efficient than visual processing, supported by saccades, smooth pursuit and vergence movements which require cortical processing to be accurate and fast or even to initiate, because visual information takes about 100 ms to travel from the primary visual cortex through a series of brain structures, to the ocular motoneurons that move the eyes. On the contrary, vestibular information takes only about 7-15 ms to travel from the vestibular nuclei in the brainstem to the ocular motoneurons. This short latency allows the eyes to compensate for the rapid oscillation of the head [7].

1.2.1.5 *The optokinetic system*

The optokinetic system supplements the vestibulo-ocular system. The vestibular apparatus does not perfectly transduce ongoing head movement parameters and this is where the optokinetic system provides the central vestibular system with visual information that is used to stabilize the eyes [3]. The optokinetic reflex responds to very slow visual image motion and it builds up slowly so as to provide a motion signal that can take over as the vestibular signal decays.

1.2.1.6 *The fixation system*

It would be expected that vision would be most accurate when the eyes stay still. However, steady fixation doesn't really exist. Even during fixation there are small ocular movements: microsaccades, drifts and tremor. Figure 1.6 shows spontaneous changes in eye position during typical fixation. Although unstable fixation may result to visual degradation, there is now evidence that small fixational eye movements may improve perception.

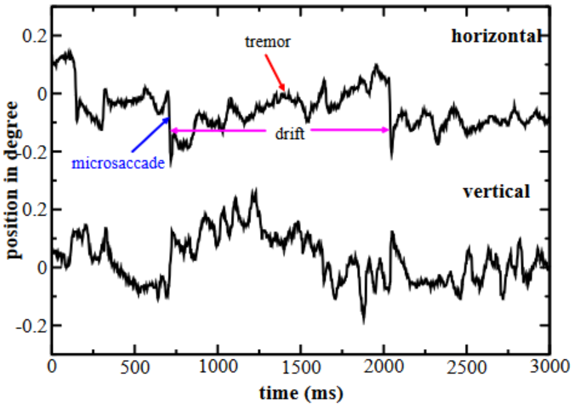


Figure 1.6: Eye position during fixating on a small stimulus. Microsaccades, tremor and drift are displayed [9].

Microsaccades are the fastest and largest fixational eye movements [4]. Their mean amplitude is about 6 arcmin and their upper limit is 1°. They occur at a mean frequency of approximately 120 Hz [7]. They move the retinal image in a distance of some hundreds of cones and they have a relatively constant duration of 25 ms and this is why a linear correlation of their velocity with their amplitude is being observed (Figure 1.7). Microsaccades are most possibly conjugate eye movements. Their main role is to correct shifts of the eyes caused by the drifts. They also play a role on the avoidance of the neuronal adaptation.

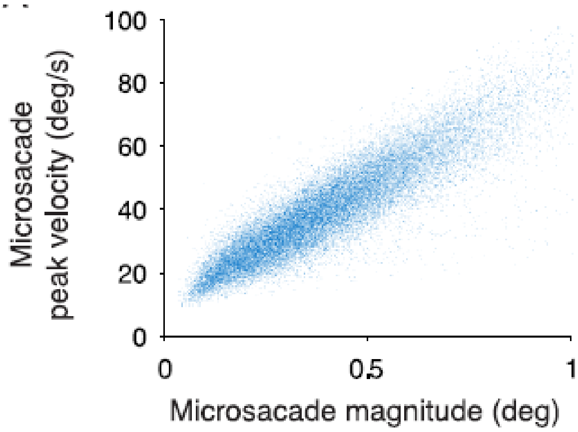


Figure 1.7: Correlation of microsaccade magnitude with peak velocity [10].

Drifts are small, winding motions that happen between the fast and linear microsaccades. Their velocity is less than 20 arcmin per second. They move the retinal image about 5-15 photoreceptors.

Their function is still debated. Although, they were first attributed to the instability of the extraocular muscles and to their antagonistic role with the microsaccades, recent studies have proposed that the drifts contribute to fixation's accuracy and that they prevent the image of a stable object from fading.

Tremor is a continuous, high frequency ocular motor activity that takes place during both microsaccades and drifts. Its frequency is about 50-100 Hz and its mean amplitude is less than 1 arcmin. Tremor is quite difficult to record because its amplitude and frequency are at the detection limits of conventional eye-traking equipmemt.

The role of tremor in vision is not yet defined. Its frequency is so high that the image's tremor is not recognizable by the eye. Tremor is different in each eye with a possible contribution to stereoscopic vision.

1.3 EXTRAOCULAR MUSCLES

The eye movements are controlled by a system of six extraocular muscles that form three complementary pairs. To understand how these muscles move the eyeball, it is essential to understand the geometry of the eye and the functions of the muscles.

There are four rectus (superior, inferior, medial, and lateral) and two oblique (superior and inferior) muscles attached to each eye. The recti originate at the apex of the orbit and insert on the sclera, anterior to the equator of the eye. The oblique muscles approach the eye from the antero-medial aspect and insert behind the equator. The extraocular muscles are presented in Figure 1.8.

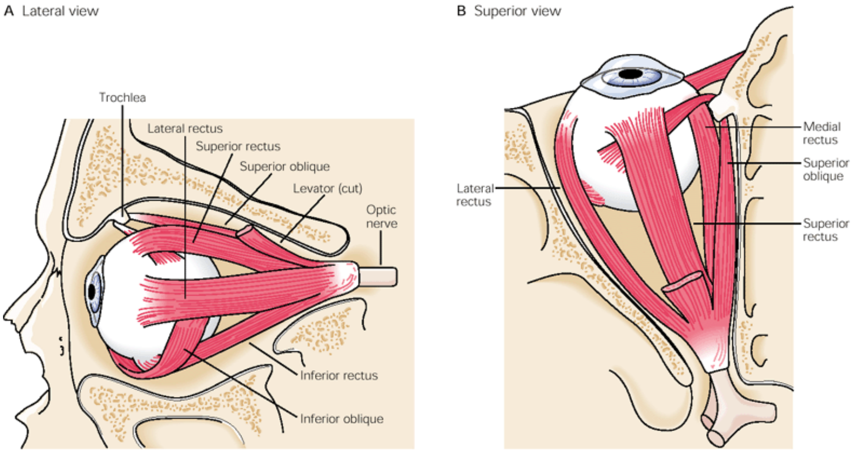


Figure 1.8: On the left, lateral view of a left eye and the extraocular muscles. On the right, a superior view of a left eye [3].

The eyeball rotates on three axes: horizontal, vertical, and torsional (Figure 1.9). Eye rotations are achieved by coordinated contraction and relaxation of the muscles.

The medial rectus adducts the eye while the lateral rectus abducts it. The rest of the muscles do not perform purely vertical or torsional rotations but a combination of the two. The proportion of torsional and vertical rotation performed by each muscle depends on the horizontal position of the eye in the orbit. Figure 1.10 shows the extraocular muscles and their actions according to the eye position.

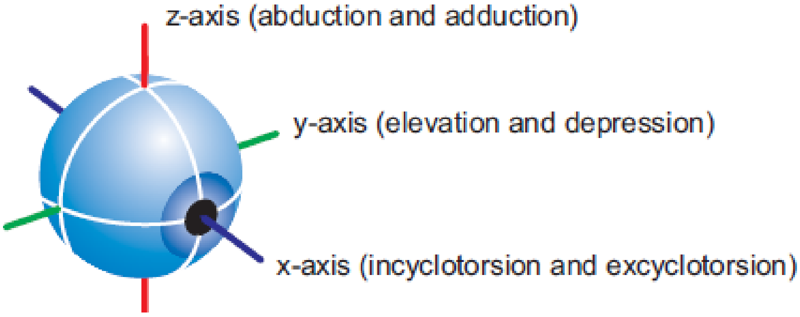


Figure 1.9: The three axes of ocular motion [7].

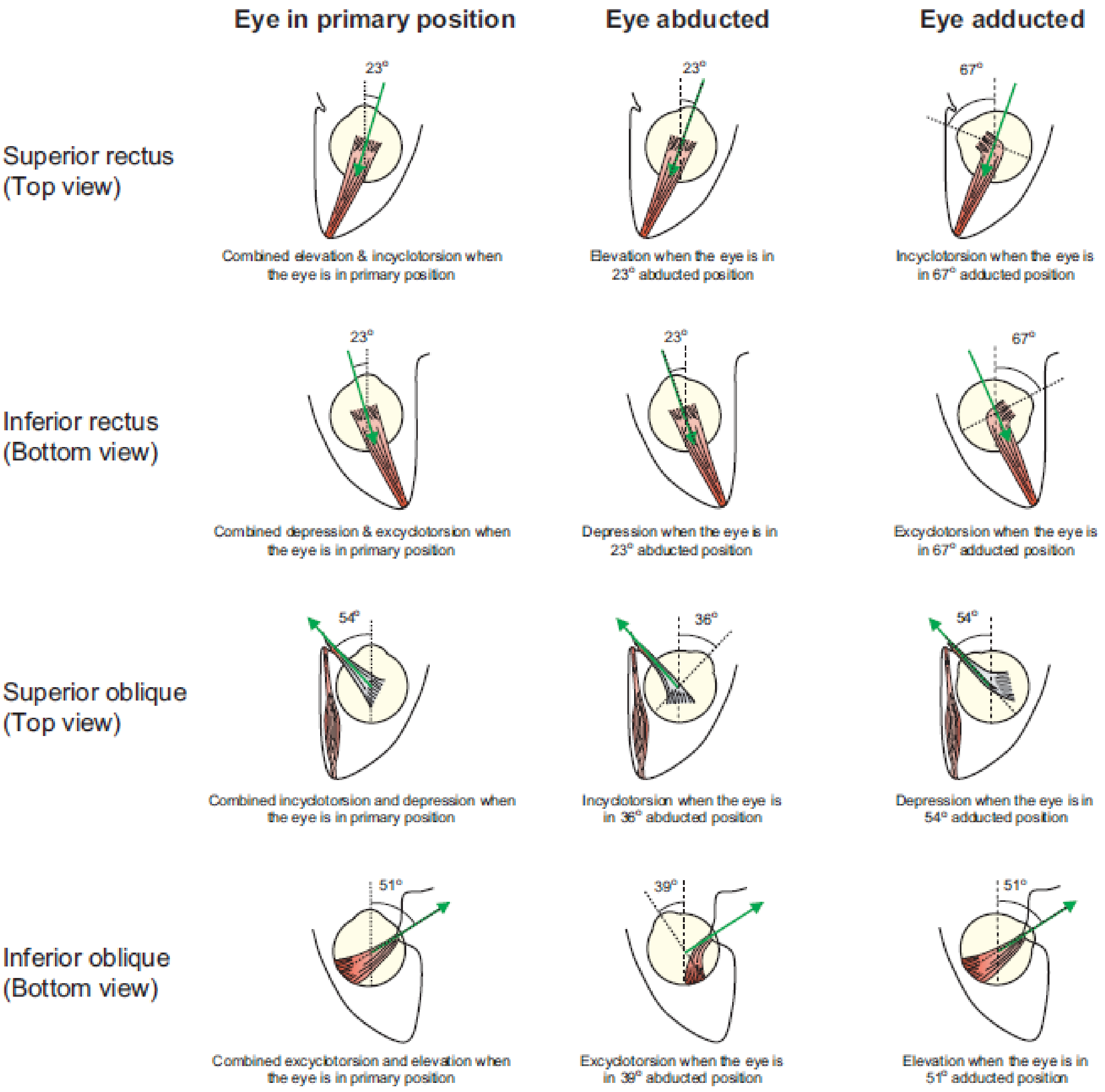


Figure 1.10: The extraocular muscles and their actions according to the eye position [7].

1.4 EYE MOVEMENTS DURING READING

1.4.1 *Reading*

There are many models to describe reading process and eye-movement control during reading, focusing on different classification criteria. Some models are focused on the control of eye movements during reading and whether they are controlled by low-level oculomotor strategies or influenced by higher level, cognitive processes [11]. Other models, are concerned on the relationship between eye movements and attention and whether words are processed serially or in parallel (cascaded processing [12, 13]).

Either way, reading is a complex function that is affected both by optical and cognitive factors. It requires a proper retinal image and intact retina to send information to the brain, where it is analyzed for message understanding [14]. Thus, it is affected by any optical factor that results in a non-proper retinal image, by any eye disease that influences the retina or any optical medium of the eye, but also by any higher-level cognitive factor that is linked with the processing of the information by the brain.

On the one hand, reading speed slows down when the letters are blurred [15, 16], when they are too small [17, 18], when they do not have enough contrast [19] or when binocular fusion is hampered [20]. On the other hand, it also slows down when bilinguals read in their second language compared to their primary language [21]. Reading speed also depends on demographic factors (such as age [22–24] and education level [25, 26]), overall processing speed as both a state and a trait characteristic [27], the extent of a person's vocabulary [28, 29] and other cognitive factors such as reading experience [27, 29]. It has also been shown that cognitive–linguistic processing affects greatly reading behavior, having an influence on many reading parameters [30].

Since many activities of daily living rely on reading, it is not surprising that reading difficulty is the most common complaint among individuals with decreased vision [31]. However reading performance tests are not used in clinical practice. Assessment of visual acuity remains the preferred test for low vision patients despite its suboptimal capacity to predict the extent of deficits in functional vision [32–35].

1.4.2 *Reading as a tool for visual performance evaluation*

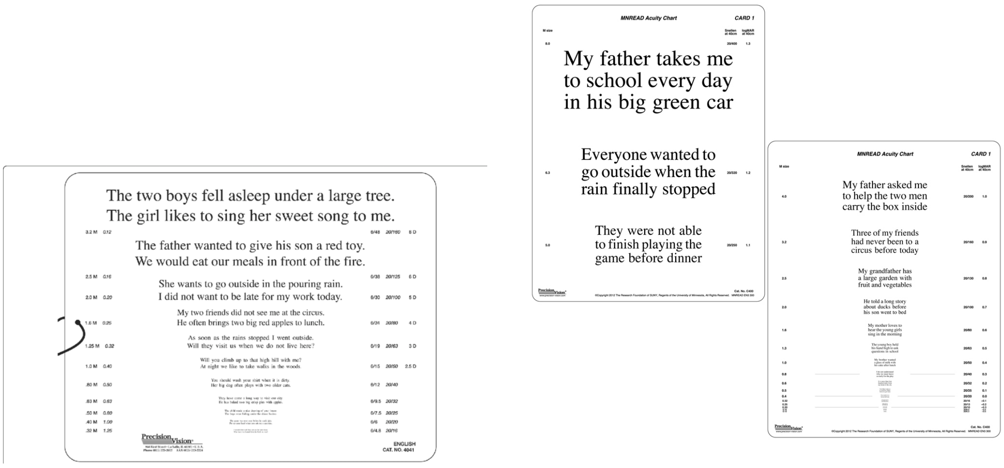
Reading ability is currently evaluated using a plethora of reading tests (available in several languages). Traditional reading tests usually have long paragraphs with small print and shorter ones with larger print, to allow determination of reading acuity. More recently developed cards follow the Bailey-Lovie principle [36] and have paragraphs of equal length; these include the MNread [37], Colenbrander and Radner [38, 39] cards. Standardized paragraphs allow comparison of the reading speeds for paragraphs of different print size. To test reading endurance, the International Reading Speed Texts (IReST) [40, 41] which provide longer segments of fixed size, or even very long stories developed for sustained reading [42], are probably the most appropriate. Although clinical reading tests are thoroughly standardized, there is a significant inter-individual variability in reading speed, as a function of various cognitive factors [25, 27–29] and age [22–24].

The question that rises is which test is the most appropriate to use. Although there are some standards for comparing tests, generally the optimal test will depend on what we want to measure [34]. When only optical factors are involved, visual acuity and reading acuity probably provide the most informative parameters, as optical deterioration of the foveal image predicts visual function. On the other hand, when retinal factors are involved, such as in maculopathies, it is preferable to evaluate reading performance (i.e. reading speed) using a continuous text, since reading ability requires a larger intact retinal area.

There are well-accepted standards for comparing the validity, reliability and responsiveness of the reading tests [34]. In most cases, the evaluation is restricted to test–retest variability and often limited to readers with normal vision. Few studies have made direct comparisons between tests, while comparing across studies is difficult when the testing conditions and characteristics of the participants differ. Figure 1.11 shows some of the most widely used current reading cards.

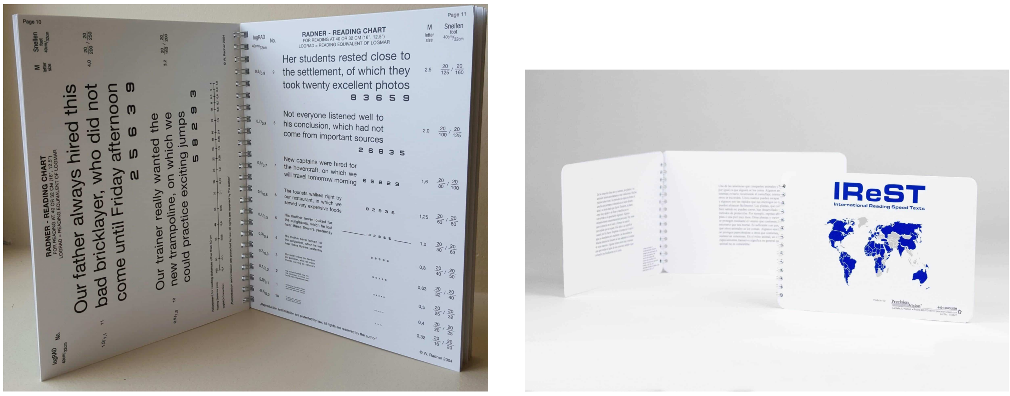
1.4.3 *Eye-tracking during reading: technology and state of the art*

Eye tracking is an experimental method of recording eye motion and gaze location across time. It has been used in various fields, primarily in psychology, but also in medicine, neuroscience, mathematics and computer science, education etc [43].



(a) Colenbrander reading chart

(b) MNRead chart



(c) Radner reading chart

(d) IReST

Figure 1.11: Some current reading cards.

Over the years, numerous techniques have been developed to record the eye movements. Three categories according to the physical characteristics of the eye which are used can be traced. Techniques i) based on reflected rays, ii) based on recording of the electrical impedance and iii) based on contact lenses. Most modern eye trackers use techniques based on reflected rays and are video-based. They shine infrared light into the eye, this light produces a reflection on the cornea and is identified by the eye tracking software. Pupil tracking and/or corneal reflection are used for recording. Then a calibration is performed, where the participant is instructed to look at a series of points at known locations on the screen. This calibration is tested in a validation stage. The gaze point can then be estimated from the relative positions of the pupil and corneal reflection.

Eye trackers vary in their sampling rate, reaching up to 2000 Hz. They also vary on whether they need the head to be stabilised via a chin rest or not, or whether they are stationary (with the infrared cameras set on a headband), portable (without a headband) or mobile (with cameras on glasses [44]), or whether they record one or both eyes.

Raw eye-tracking data is a series of samples that contain the point of gaze estimate for one or both eyes as an x and y screen position in pixels. Eye tracking software provides processed sampling data as fixation, saccade, blink and pupil size data.

For reading experiments, high sampling rate and head stabilisation with a chin rest are preferred, as accuracy for small eye movements and knowing which word is fixated, is important. Reading performance assessment with the use of eye-tracking can be challenging, particularly in special populations such as children or older adults, due to problems such as lack of concentration or calibration problems due to glasses or retinal scotomas [45]. The recent development of portable and mobile eye-trackers has facilitated the recordings in such populations.

In reading tasks, eye movement analysis is based on word, sentence or text level, and eye movement parameters are defined accordingly. In general, it is important to distinguish between first-pass and second-pass (i.e. re-reading part of the text) time for the region of interest [11]. Eye movement characteristics during reading are described in the next session.

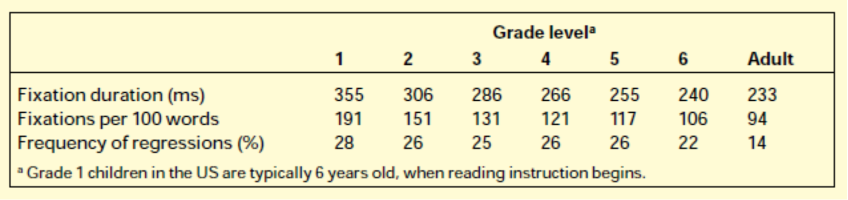
1.4.4 *Eye movement characteristics during reading*

When reading a text, efficient sensorimotor coordination is required for executing the sequence of fixations and saccades required to capture high-resolution images with the fovea. Eye movement efficiency develops almost in parallel with reading ability, in terms of speed and accuracy, as the child progresses from a beginner to a proficient adult reader [11]. Less skilled readers (e.g. children with reading difficulties) typically make more fixations of longer duration and shorter saccades than skilled readers [46–48].

For skilled readers, saccade amplitude and fixation duration average 7-9 letter spaces and 200-250 ms, respectively. Typically the eyes move forward from one word to the next, but they sometimes make an additional fixation on the currently fixated word (within-word refixation) or they move back (regression). The average percentage of regressions in the total number of saccadic movements is 10-15% for a skilled reader [11].

Regressions are a natural part of the reading process. When they are suppressed experimentally, by presenting texts one word at a time, comprehension falls dramatically [49].

There is considerable research on the factors that explain the considerable variability observed in saccade length and fixation duration. These factors include lexical and orthographic characteristics of a given word, type and syntactic complexity of the text read, visual conditions as well as several reader characteristics. For instance, reading experience in the course of reading acquisition is inversely related to saccade length and fixation duration (see Figure 1.12), whereas less experienced readers tend to make more fixations and more regressions than skilled readers. Detailed review of the effect of such characteristics on saccades and fixations is displayed in the following sections.



	Grade level[a]						
	1	2	3	4	5	6	Adult
Fixation duration (ms)	355	306	286	266	255	240	233
Fixations per 100 words	191	151	131	121	117	106	94
Frequency of regressions (%)	28	26	25	26	26	22	14

[a] Grade 1 children in the US are typically 6 years old, when reading instruction begins.

Figure 1.12: Developmental characteristics of eye movements during reading [11].

1.4.4.1 *Saccade length and percentage of regressions*

Saccade length can be measured in two ways: in degrees of visual angle and in number of letter spaces. It has been shown the saccade length, measured in letter spaces, remains constant if the text is read at different distances, even though the visual angle subtended by a letter space changes.

The probability of making a regression is highly dependent on the length of the prior, progressive saccade. More specifically, the longer the prior saccade, the higher is the probability of a regression. Regressions are also more likely to happen after a word that was skipped, especially if it's a long word [4]. About 70% of the regressions are towards one of the previous words (inter-word regressions). They are mainly small-amplitude saccades which bring the eyes right to the previous word. Sometimes however, longer regressions are made to more remote preceding words [4]. Finally, the length of regressive saccades is generally higher during monocular compared to binocular reading [50].

1.4.4.2 *Fixation duration*

The fact that some words are skipped and some others are fixated more than once, makes it difficult to measure processing time for a word [51]. There are various fixation duration-based parameters that are being used. Mean Fixation Duration underestimates the time the eyes spend on a word, that is the number of fixations on a specific word. Using Single Fixation Duration, we take into account just the words that are fixated only once. This is also problematic because there are words that are skipped and some that are refixated. Therefore, there are two measures that are mainly used. First Fixation Duration is the duration of the first fixation regardless of whether it is the only fixation of the word or the first of multiple fixations. Gaze Duration is the sum of all fixations on a word before moving to the next word. A final measure is also used. Total Time on a Word is the sum of all fixations including regressions. It cannot however, measure the initial processing time. In cases where the unit of analysis is not a word but a sentence or a text, it is appropriate to distinguish first pass reading time from the second-pass time [11].

Regarding fixation duration, it has been shown that it depends highly on both cognitive and optical factors. Word frequency has a great effect on it. Readers spend more time on lower frequency words than on higher frequency words. Words that are highly predictable from previous context are also fixated for less time. For this reason, function words are fixated only about 35% of the reading time, while content words are fixated about 85% of the time [11, 52]. Juhasz et al. showed that words with alternating case (e.g. AlTeRnAtInG cAsE) were fixated longer than those which were presented in normal case [53].

Monocular vision also affects fixation duration. Johansson et al. showed that monocular reading results in significant increase in fixation duration at 8.9% [54]. It has also been shown that the binocular advantage becomes more prominent in low contrast condition. Binocularity contributes increasingly to reading performance, by lowering the fixation duration, as stimulus contrast decreases [50]. Leyland et al. have also showed that partial word shading, produce longer gaze durations and that readers spend more time re-reading target words when they are partially shaded [55].

Fixation duration is also affected by the initial fixation location. As shown in Figure 1.13, fixation duration is longer when the fixation is near the center of short words and to the left of the center of long words. This phenomenon applies both to first fixations and refixations [4].

Fixation durations during text reading are not normally distributed; their frequency distribution always exhibits a pronounced right tail, i.e. an increased frequency of long fixations [56, 57]. Printed word frequency is one of the first factors examined in an attempt to account for the shape of this distribution. In one of the earliest studies, Staub et al. (2010) used ex-Gaussian fitting (please see also Section 2.7) and demonstrated that word frequency affected both the shift and the skew of the distributions [58]. This result has been replicated by Reingold et al. (2012) [59], who also showed that manipulation of the validity of parafoveal preview had

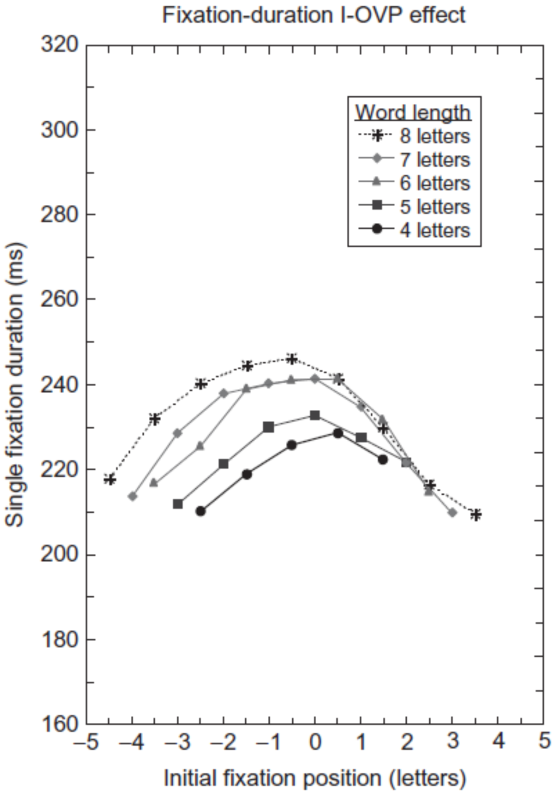


Figure 1.13: Single fixation duration as a function of Initial Fixation Position [4].

a similar effect. There are however, factors that affect only the μ parameter: predictability in context [60], lexical ambiguity [61], contrast of the text [62] and the landing position of the eyes within the word [59].

1.4.5 *Perceptual span*

Saccade length is also influenced by the length of perceptual span: The number of letters that can be extracted and effectively processed in a single fixation [4]. Although visual acuity is very high in the foveola (central 1 degree of vision), it is not as high in the parafovea (up to 5 degrees) and it's even poorer in periphery (region beyond the parafoveal). Several lines of evidence suggest that graphemic information is regularly extracted from parafoveal vision. Thus, readers often skip short function words or highly predictable words in a sentence [11]. Further, saccade length is influenced by both the length of the fixated word as well as the length of the next word in the sentence. The further the launch site of a saccade, the closer to the beginning of the word the landing site is. Also, if the beginning of a word contains an orthographically irregular segment, the initial landing position of the eyes shifts to the beginning of the word [11]. The perceptual span of a typical proficient reader is sufficient for word recognition which, in most cases, requires identification of up to about 7-8 letters to the right of the fixation [11], depending on the writing system and specific orthography. Perceptual span in not only parallel, but also vertical, thus readers also focus their attention in order not to acquire information from below the currently fixated line [63]. In turn, perceptual span affects fixation durations and overall text reading speed It has been indicated that if parafoveal information is denied, reading rates decrease rapidly [11].The capacity of the visual system to extract useful information from parafoveal words. This advantage gained by the availability of useful information in the parafovea is called ‘parafoveal-preview benefit’. There is however a great debate on the extent of this information gained. It is not clear yet whether we obtain from the parafovea just sublexical and phonological information or we also obtain higher-level lexical and semantic information [11].

1.5 AGE-RELATED MACULAR DEGENERATION (AMD)

1.5.1 *Pathophysiology and prevalence*

Age-related Macular Degeneration (AMD) is one of the most common causes of blindness in developed countries and affects about 20% of the population over 65% in the industrialized countries [64]. There are studies however, that show that AMD prevalence is declining due to improved lifestyle conditions and the introduction of anti-VEGF therapy [65]. Even when blindness is prevented, AMD can lead to low central vision and thus, impede activities that need high central resolution such as reading.

AMD is a disease that affects the macular region of the retina, causing progressive loss of central vision [66]. Early-stage AMD clinical signs may include yellow deposits on fundoscopy (drusen) and abnormalities of the retinal pigment epithelium while late-stage AMD can be neovascular (also known as wet or exudative) or nonneovascular (known as atrophic, dry, or non-exudative). In late AMD, loss of central visual acuity, leading to severe and permanent visual impairment and legal blindness, has a major impact on patient quality of life and functional independence [67].

High-contrast best-corrected visual acuity, using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, has formed a sensitive safety indicator for interventions in multi-center

/clinical trials in neovascular Age-related Macular Degeneration [68–70], but it has shown limited value as an end point when the goal is to identify early functional deficits in Age-related Macular Degeneration [71, 72]. Thus, alternative visual performance outcome measures beyond visual acuity have been proposed [73–75], especially when correlation for real life task performance is under investigation [34].

1.5.2 *Anti-Vascular Endothelial Growth Factor (Anti-VEGF)*

AMD is a disabling disease often ending up with significantly reduced vision requiring visual rehabilitation [76], however treatment based on anti-VEGF factors has achieved satisfactory results maintaining vision and improving the natural outcome of the disease [77, 78]. These anti-VEGF factors are administered through intravitreal injections and result in vessel regression, reducing the size of the choroidal neovascularization (CNV) area [79]. Anti-VEGF factors aim to the inhibition of the angiogenic protein VEGF, which is produced in the retina and increases retinal vascular permeability and promotes neovascularization [80]. More specifically, anti-VEGF agents block one or more isoforms of VEGF-A, the protein which is the main angiogenic factor of the VEGF family [81].

It has been shown that after 3-month anti-VEGF treatment of AMD, visual acuity improved by 5-7 letters [68, 69, 78, 82] and central retinal thickness (CRT) decreased by 150 to 175 μm) [70, 78]. Most of the improvement in mean visual acuity occurred during the first year of treatment (5-8.8 letters, depending on the dose regimen), with a little or no change during the second year. However, as anti-VEGF drugs do not eliminate neovascularization, treatment continues indefinitely for most patients [78] and the treatment schedule could be a burden to elderly patients [79]. Although, anti-VEGF drugs have shown a quite successful efficacy for more than 20 years, more than half of CNV patients are unresponsive to anti-VEGF agents [83] and thus, understanding the reasons for the variation in response among patients could lead to the development of methods to predict individual patient requirements [84]. Figure 1.14 shows optical coherence tomography images of the macula in AMD and after anti-VEGF treatment.

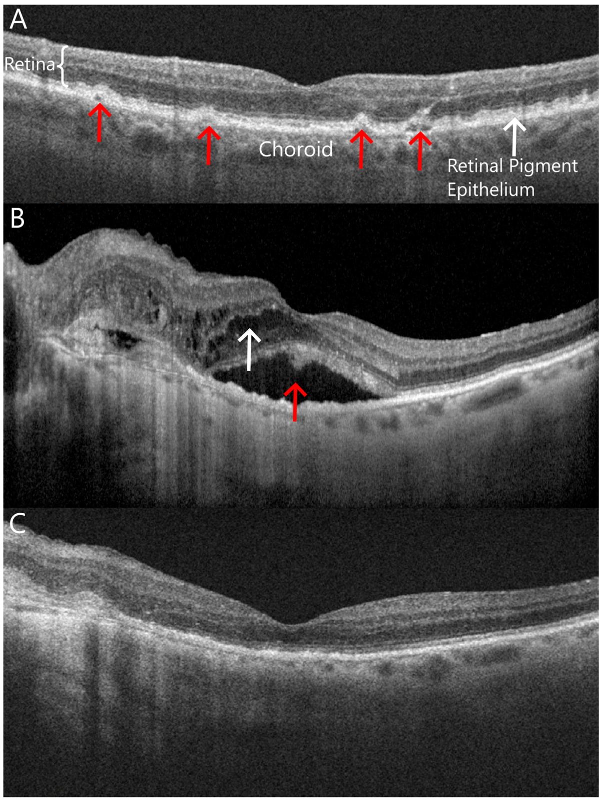


Figure 1.14: Optical coherence tomography images of the macula in the eyes in age-related macular degeneration (AMD). (A) An eye with non-exudative or "dry" AMD with drusen between Bruch's membrane and the retinal pigment epithelium (red arrows); (B) an eye with active exudative or "wet" AMD with subretinal (red arrow) and intraretinal fluid (white arrow) in the macula; (C) the same eye shown in B after receiving several intravitreal anti-VEGF injections with interval resolution of intraretinal and subretinal fluid. (reprinted from [85]).

1.5.3 *Eye movements and reading in AMD and other macular diseases*

Reading performance tests are not routinely used in clinical practice, which mainly relies on visual acuity measures, despite being a relatively poor predictor of functional vision impairment [32, 72]. This may be due to the fact that "aloud" and "as fast as possible" reading speed [34, 86], as measured with the currently available, single-sentences cards (i.e. MNread [37], Colenbrander and Radner [39] cards) may not be very relevant to real-life reading, which is typically silent and aims at comprehension [42, 87]. Thus sensitive reading measures that can be used as predictors of real-life reading function are highly desirable [34, 88, 89].

Although reading impairment in patients with Age-related Macular Degeneration is likely multi-factorial [89, 90], efficient reading is hampered due to the presence of retinal scotomas centrally, even compared to other low vision patients [34, 91–93]. As a result, patients with

Age-related Macular Degeneration tend to change their fixation to the near retinal periphery, a process known as eccentric viewing [94–96].

A significant decrease in reading speed has been reported in people with well-established age-related macular disease (AMD) [97] or newly developed AMD, even when their visual acuity is within normal limits [98]. A study by Varadaraj et al. showed statistical significantly lower reading speed in AMD patients compared to controls when reading out loud, but this difference was not shown when reading silently. This finding was combined however with lower comprehension scores in the AMD group [99].

Reading speed of AMD patients is reduced because reading ability requires a larger intact retinal area. Due to the scotomas and the subsequent eccentric viewing, reading becomes very difficult or even impossible and does not seem to depend on patient VA or sensitivity to contrast [97, 98]. This is mainly the result of shorter saccades and higher percentage of regressions, especially at low luminance levels [33]. In another study, information transfer rate, representing the combined effects of a reduced visual span and slower temporal processing of letters, was a better predictor of reading speed in AMD patients than visual span size [82].

The magnitude of the association between reading speed and fixation duration in AMD, remains unclear. Calabrese et al. (2014) studying reading performance in AMD and Stargardt patients, have found that they are negatively correlated [100]. Other studies have failed to show any correlation [33, 97, 101].

The relationship between VA and fixations in AMD patients has also been studied. Cacho et al. have found that visual acuity was significantly associated with Preferred Retinal Locus (PRL) distance but PRL distance only explained 10% of the variance in visual acuity. PRL distance was also found to be a significant but weak predictor of the difference in VA when measured with arrays of crowded letters compared to single letters presentations. Fixation quality was not a good predictor of this difference [102]. Patients with macular diseases have been found to have worse fixation stability than controls [103]. Patients with AMD seem to have good binocular ocular motor coordination during fixation, but monocular viewing can lead to disturbances in ocular motor control [96].

Eye-movement evaluation during reading, along with standardised reading cards and refined statistical and computational methods, could detect subtle changes in functional vision of patients with macular diseases, that conventional tests such as VA could not.

1.6 PRESBYOPIA

1.6.1 *Pathophysiology*

Presbyopia is an age-related deterioration in the focusing ability of the eye for near objects, hampering near vision resolution and thus, impeding activities such as reading. It is a normal feature of human visual physiology that can be detected as early as adolescence, although prevalence rises dramatically during the fifth decade of life, rendering remedial action necessary [104].

There are different definitions of presbyopia, a fact that leads to different estimations of the presbyopia prevalence [105]. However, a highly respected study by Holden et al. (2008) showed that there were 1.22 billion people with presbyopia in mid-2000 [106].

Over the years, two main theories regarding presbyopia development have risen. According to the first, cahnges in the crystalline lens are solely responsible for presbyopia. According to the second theory, presbyopia is mainly the result of the progressive weakening of the strength of the ciliary muscle. There is growing evidence suggesting that presbyopia is multifactorial in origin, involving gradually increasing lens stiffness in combination with changes in the ciliary muscle, the zonular fibers, the choroid, the iris and even the vitreous [107] (Figure 1.15).

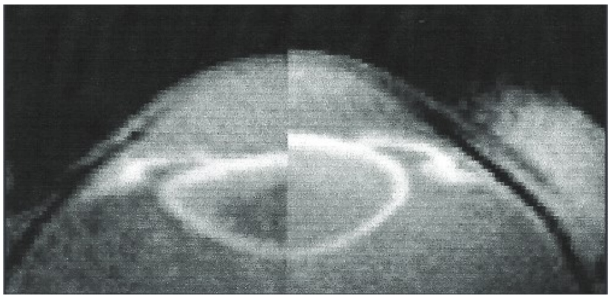


Figure 1.15: MRI of the unaccomodated eye of a 26 year old person (left) and of a 49 year old person (right). In the older eye, increased lens thickness, reduced pupil diameter and anterior displacement of the uveal tract can be detected [107] (reprinted from [108]).

1.6.2 *Presbyopia correction*

There are many options for the correction of presbyopia, including spectacles, contact lenses, and surgical procedures. Spectacles have been in use the longest with a variety of choices. They are also simple to use and with minor risks [109].

There are two general approaches to the correction of presbyopia with a spectacle lens: (1) single vision lenses worn during near-vision work and (2) multifocal lenses that provide a correction for both distance vision and close vision. On the other hand, correction of presbyopia with contact lenses include plenty of methods, with the most common ones being; (1) single-vision contact lenses for distance correction in combination with reading glasses, (2) monovision, with one eye being corrected optimally for distance and the fellow eye for near and (3) multifocal contact lenses [109, 110].

Studies have shown higher acceptance of multifocal contact lenses over monovision [111, 112]; however a significant percentage of presbyopes discontinue contact lens wear complaining of poor vision [113]. The success of presbyopia correction (with contact lenses or IOLs) strongly relies on blur interpretation and adaptation [114].

1.6.2.1 *Multifocal contact lenses*

Correcting presbyopia with contact lenses has long been a major challenge, since it is difficult to produce complex lens designs capable of providing sharp distance and near vision for every single visual task [110].

Multifocal contact lenses were first designed to correct presbyopia and can be manufactured in rotationally symmetrical or non-rotationally symmetrical form.

Multifocal contact lenses provide simultaneous image. This can be achieved with diffractive, annular (or zonal), aspheric or extended depth of focus (EDOF) designs and may be made as centre-near or centre-distance [114, 115].

Diffractive contact lenses are designed to provide a bifocal or multifocal effect over the full lens aperture by using the zero- and the first- order light from a blazed zone plate with parabolic profile on the back surface of the lenses [116]. Annular designs include a central circular zone, intended either for distance or near viewing, and one or more rings of near/intermediate or distance correction. Aspheric multifocal designs involve a progressive, rotationally symmetric, gradation of power from the centre to the edge of the optical zone. At least one aspheric lens surface is being used. The latest multifocal contact lenses design is the EDOF. These designs are usually similar to aspheric lenses, utilizing alterations of spherical aberration to generate their multifocality, but they also include other multiple higher order spherical aberration terms [117].

1.6.2.2 *Monovision correction*

Monovision is a method for correcting presbyopia, where one eye (usually the dominant eye) is corrected for distance vision and the other for near. Monovision is not used with spectacle lenses because the anisometropia acquired can cause differential prismatic effects and aniseikonia.

In monovision, the brain processes the focused retinal image from one eye, while suppressing the other eye's unwanted out-of-focus image. However, this suppression leads to deterioration of stereoacuity [110].

Low cost to the patient, as only single-vision lenses are required, and simple CL fitting are considered the main advantages of monovision [110]. The success rate of monovision has been reported to be between 70% and 76% [118].

1.6.2.3 *Evaluating the Effectiveness of Presbyopia Correction*

There are numerous tests to assess the quality of the optical image and therefore to evaluate the effectiveness of presbyopia correction. These tests are based on subjective, behavioural or objective methods. The subjective methods include visual perception tests and questionnaires. The preferred subjective test is visual acuity (a test to evaluate a person's ability to recognise small letters with precision) which can also be assessed for near vision. After visual acuity, contrast sensitivity is an important parameter of visual perception. Both visual acuity and contrast sensitivity tests are subject to various factors. Contrast loss may be the result of optical factors, such as refractive error, presbyopia, higher-order aberrations, or scatter, as from cataract and other opacities. Beyond the contrast reduction from less-than-perfect optical imaging, contrast perception depends on the sensitivity of the retinal receptors and on their neural connections. On top of that, since presbyopia is an age-related condition, it usually comes together with other pathological conditions such as macular degeneration and glaucoma. Thus, finding a contrast deficit is not helpful in establishing differential diagnosis, but it can be helpful in explaining the patients' complaints [14].

Another category of near-vision tests includes reading cards of continuous text. The main difference of these cards with small-letter charts is the fact that testing with small-letter charts evaluates only the foveal area. On the contrary, reading requires intact a larger retinal area. A number of parameters are evaluated using reading cards. The most common in clinical practise is reading acuity, the smallest letter size that the patient can read. Some, more sophisticated, parameters are reading speed and critical print size which is the smallest letter size for which the patient could read 90% of their maximum reading speed. Furthermore, with the use of an eye tracker, eye movement parameters can also be used; saccade length, fixation duration, number of fixations etc.

Other methods of evaluation of the effectiveness of presbyopia correction include subjective and objective measurement of the accommodation, visual reaction times, evaluation of perception of blur and dysphotopsia evaluation.

In clinical practise, visual acuity for near and reading acuity form the most usual tests for the evaluation of presbyopia.

1.6.3 *Presbyopia correction and oculomotor behavior*

Although presbyopia correction is evaluated with various tests, reading performance and especially in terms of eye movements is rarely considered [119]. In the few existing studies, multifocal and monovision CLs did not result in significant differences in aloud reading speed [120]. Further, monovision CL correction did not result in differences in eye movement parameters during reading when compared with correction for near [119], while eye movement parameters were recorded using multifocal CL correction during reading and there was a significant increase when compared with single vision CLs that provided correction for far [121].

While it is clear that presbyopia correction with CLs of any modality leads to better vision, and functional vision, compared to being uncorrected for near, it is not quite clear whether correction with multifocal or monovision CLs is as good as correction for near. Furthermore, it is not clear whether there is any difference between correction with multifocal and monovision CLs. These differences could be detected with eye movement analysis during reading.

1.7 AIM OF THE STUDY

Reading depends on various factors, making it very difficult to use as a robust tool. However, reading is one of the everyday activities that are most hampered in the presence of eye diseases, optical deficiencies and cognitive impairments. Three general categories of factors that affect functional vision and reading behavior can be detected; optical, retinal and cognitive. Thus, it is crucial to assess the way reading is affected by each of these categories of factors.

The aim of this study is to implement oculomotor analysis in reading using a video eye tracker in order to evaluate functional vision in healthy eyes but also in eye diseases. Ex-Gaussian analysis of the fixation duration distribution is also implemented. The ultimate scope of the study is to find certain eye movement parameters (biomarkers) that are differentially affected by certain factors. In order to do that, factors of different categories are tested.

Presbyopia following correction with the use of contact lenses is selected as an optical factor. In presbyopic patients the image on the retina is blurred and correction with contact lenses is used to answer to this effect. Due to the optical component of the factor, we expect the parameters that change due to blur, to change back when presbyopia is corrected with CLs. Ex-Gaussian parameter μ is expected to be affected as it is linked with low-level changes.

Age-related Macular Degeneration (AMD) is selected as a retinal factor. The effectiveness of anti-VEGF treatment is evaluated and the parameters that are improved will show in what extent the treatment reverses the damage on the retina. Vision is greatly hampered by AMD, thus effect of multiple eye movement parameters are expected to be affected.

The effect of the reader's comprehension is evaluated, being a cognitive factor. Two different sets of guidelines are given to the participants forcing them to read in different ways and thus, have different eye movement behavior. Apart from the percentage of regressions which is known to be linked with reading comprehension, ex-Gaussian τ is also expected to be affected.

Before these studies, the test-retest reliability of reading speed as well as of eye movement and ex-Gaussian parameters in silent passage reading is evaluated.

The studies that this Dissertation consists of are the following:

1. Study I - Assessment of the test-retest reliability of eye movement parameters during text reading
2. Study II - Patients with Age-related Macular Degeneration (AMD)
3. Study III - Patients with Presbyopia
4. Study IV - Effect of comprehension

2

EXPERIMENTAL SECTION

In this chapter, certain materials and methods that were common to the four studies included in this Dissertation are firstly described, followed by a separate presentation of the specific methods and results of each study.

2.1 ETHICS

Written consent was obtained from all participants after they received a written description of the study, which was conducted in adherence to the tenets of the Declaration of Helsinki. The study protocol had been approved by the University Hospital of Heraklion Research Ethics Committee.

2.2 EYE MOVEMENTS RECORDINGS

Eye movements were recorded during passage reading using video oculography (EyeLink II, SR Research Ltd, Canada). All measurements were performed with participants seated on a chair with their head stabilized by means of a chin rest to minimize head movements. The distance of the participant from the text was 40 cm. Figure 2.1 shows a participant and the experimental setup. Both binocular and monocular reading recordings were conducted, under two lighting conditions (chart background luminance about 50 and 5 cd/m^2), according to the needs of each study. Prior to each recording, a 5-point calibration/validation was achieved by presenting a small dot (0.3 deg) on the screen at 0 deg and at 10 deg vertically and horizontally. Eye position was sampled at 500 Hz using pupil tracking with an average accuracy of 0.5 deg and a spatial resolution of 0.01 deg.

Figure 2.1: The experimental setup.

The EyeLink II system consists of three miniature cameras mounted on a padded headband. One head-tracking camera was used to detect infrared markers in the world, while two eye cameras focus on the left and right eyes respectively. As we can see in Fig. 2.2, the system consists of a Host PC, a display PC, the headband and a PCI card. The Host PC connects to the headband and powers four infrared markers (for head tracking) that are mounted on the corners of Display PC's monitor. It also hosts the EyeLink II Host application where you can control the tracker and change the options of the recording. The Display PC runs experiment software for control of the Host PC and presents the stimuli to the monitor. The headband has the cameras which record the eye movements. Finally, the PCI card is connected with the headband and is hosted in the Host PC. It performs the powerful image processing required to achieve the high temporal and spatial resolution of the system.

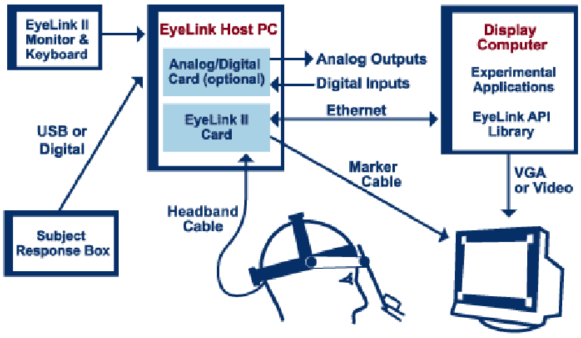


Figure 2.2: The EyeLink II system.

2.3 VISUAL ACUITY

Standardized visual (logMAR) acuity at 40 cm (“near” VA) and 4 m (“far” VA) was measured using the European-wide standardized logMAR charts (Precision Vision, USA) [122]. The charts for far recordings were held on a back-illuminated slim stand (Sussex Vision Ltd., UK) at 4 m distance (luminance was approximately 160 cd/m2). Near recordings took place in a well-lit room (chart background luminance was 70 cd/m2; illuminance at cornea was 75 lux). All subjects were asked to identify each letter starting from the upper left corner, and to proceed by row until they reached a row in which they could not correctly identify more than one letter. VA was derived in logMAR units from the calculation of correctly identified letters up to the last readable line

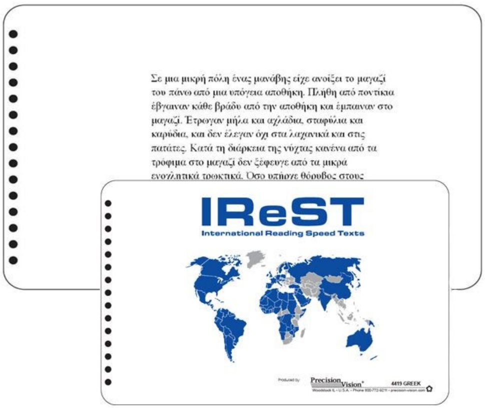
2.4 READING EFFICIENCY

Prior to passage reading performance measurements, word-level reading efficiency was assessed binocularly through a standardized test comprising two lists, one with relatively high-frequency words and a second one with phonotactically matched pseudowords [25]. Participants were asked to read each list aloud and as fast as they could without compromising accuracy. The number of words or pseudowords read correctly within 45 s was measured and then converted in words per minute.

2.5 READING MATERIAL

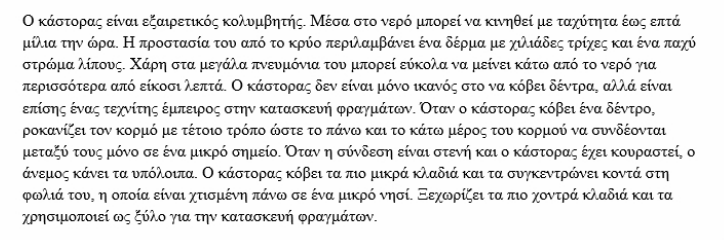
Two kinds of reading cards were used in this work; the Greek version [123] of the IReST [40, 41] (Figure 2.3(a)) and reading cards developed by the study group at the Laboratory of Optics and Vision for the purpose of the study (Figure 2.3(b)). A standard print size of 0.4 logMAR (1.0 M at 40 cm) was used in both kinds of reading cards.

The International Reading Speed Texts (IReST) set consists of 10 standardised paragraphs of approximately 140 words each. It is evaluated for repeated measurements within and between languages and is now available in over 17 languages. For the purposes of the study, the five



Σε μια μικρή πόλη ένας μανάβης είχε ανοίξει το μαγαζί
του πάνω από μια υπόγεια αποθήκη. Πλήθη από ποντίκια
έβγαιναν κάθε βράδυ από την αποθήκη και έμπαιναν στο
μαγαζί. Έτρωγαν μήλα και αχλάδια, σταφύλια και
καρύδια, και δεν έλεγαν όχι στα λαχανικά και στις
πατάτες. Κατά τη διάρκεια της νύχτας κανένα από τα
τρόφιμα στο μαγαζί δεν ξέφευγε από τα μικρά
ενοχλητικά τρωκτικά. Όσο υπήρχε θόρυβος στους

(a)



Ο κάστορας είναι εξαιρετικός κολυμβητής. Μέσα στο νερό μπορεί να κινηθεί με ταχύτητα έως επτά μίλια την ώρα. Η προστασία του από το κρύο περιλαμβάνει ένα δέρμα με χιλιάδες τρίχες και ένα παχύ στρώμα λίπους. Χάρη στα μεγάλα πνευμόνια του μπορεί εύκολα να μείνει κάτω από το νερό για περισσότερα από είκοσι λεπτά. Ο κάστορας δεν είναι μόνο ικανός στο να κόβει δέντρα, αλλά είναι επίσης ένας τεχνίτης έμπειρος στην κατασκευή φραγμάτων. Όταν ο κάστορας κόβει ένα δέντρο, ροκανίζει τον κορμό με τέτοιο τρόπο ώστε το πάνω και το κάτω μέρος του κορμού να συνδέονται μεταξύ τους μόνο σε ένα μικρό σημείο. Όταν η σύνδεση είναι στενή και ο κάστορας έχει κουραστεί, ο άνεμος κάνει τα υπόλοιπα. Ο κάστορας κόβει τα πιο μικρά κλαδιά και τα συγκεντρώνει κοντά στη φωλιά του, η οποία είναι χτισμένη πάνω σε ένα μικρό νησί. Ξεχωρίζει τα πιο χοντρά κλαδιά και τα χρησιμοποιεί ως ξύλο για την κατασκευή φραγμάτων.

(b)

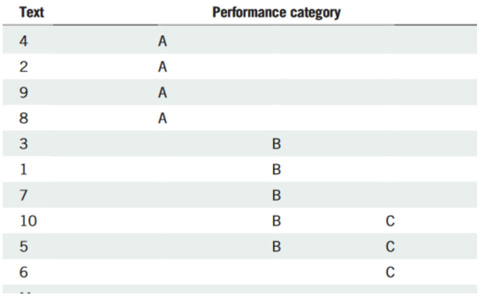
Figure 2.3: Reading cards used in the study. (a) the greek version of IReST and (b) one of the texts developed by the study group at the Laboratory of Optics and Vision for the purpose of the study

texts that belong to performance category B were used. For details regarding the texts, please see Figure 2.4, which shows Table 1 and an excerpt of Table 2 from Gleni A et al (2019) [123].

The reading cards that were developed by our group, consisted also of paragraphs of approximately 140 words. They were matched on average word frequency and word length. They were developed before the development of the Greek IReST and they were used because no standardised reading card with long paragraphs, in contrast to short sentences, existed at the time in Greek.

2.6 EYE MOVEMENT PARAMETERS

Reading performance was indexed by reading speed and by the following eye-movement based parameters which were derived by the Eye Link Data Viewer software; number of fixations, fixation duration, percentage of regressions and blink rate. Reading speed (in words/minute, wpm) was calculated by dividing the words for each paragraph of text by the time taken to read the paragraph. Fixations with duration between 75 and 1000 ms were included. Fixations with duration shorter than 75 ms were merged with neighbouring fixations if the



Text	Performance category		
4	A		
2	A		
9	A		
8	A		
3		B	
1		B	
7		B	
10		B	C
5		B	C
6			C

(a)

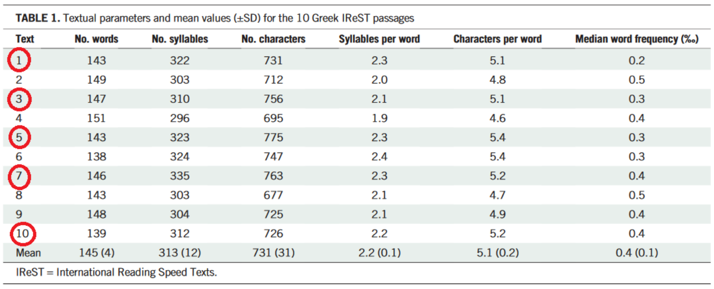


TABLE 1. Textual parameters and mean values (±SD) for the 10 Greek IReST passages

Text	No. words	No. syllables	No. characters	Syllables per word	Characters per word	Median word frequency (‰)
1	143	322	731	2.3	5.1	0.2
2	149	303	712	2.0	4.8	0.5
3	147	310	756	2.1	5.1	0.3
4	151	296	695	1.9	4.6	0.4
5	143	323	775	2.3	5.4	0.3
6	138	324	747	2.4	5.4	0.3
7	146	335	763	2.3	5.2	0.4
8	143	303	677	2.1	4.7	0.5
9	148	304	725	2.1	4.9	0.4
10	139	312	726	2.2	5.2	0.4
Mean	145 (4)	313 (12)	731 (31)	2.2 (0.1)	5.1 (0.2)	0.4 (0.1)

IReST = International Reading Speed Texts.

(b)

Figure 2.4: Performance categories of the Greek version of IReST (a) and their textual parameters (b). Circled in red the texts that were used in our study

latter were within an area of 1°. Since many studies have shown that the fixation duration distribution is not normal, the median fixation duration for each participant and each task was calculated. The average number of fixations per word was used, to allow comparisons across languages, varying considerably in mean word length. Only forward fixations were considered in calculating fixation duration and number of fixations per word. A fixation was considered regressive if the angle between the fixation and the previous one is greater than 135° or less than $-135°$. Blink rate was calculated as the number of blinks per minute of reading.

2.7 EX-GAUSSIAN FITTING OF FIXATION DURATION DISTRIBUTIONS

Ex-Gaussian distribution has been used for many years in the analysis of response time distributions [124–126] and more recently in fixation duration distributions [58, 61, 62] and in refractive error distribution [121, 127]. Ex-Gaussian distribution is a convolution of a normal and exponential distribution [124, 125]. MATLAB [128]-based algorithms were applied to assess the following three parameters i) the mean (μ) and ii) the standard deviation (SD) (σ) of the Gaussian distribution and iii) τ, which reflects the mean and the standard deviation of the exponential component, which has a rate $\lambda = 1/\tau$. The overall mean of the ex-Gaussian is $\mu + \tau$, and the overall standard deviation is $(\sigma^2 + \tau^2)^{1/2}$. Figure 2.5 shows the density function of the fixation duration distribution fitted with ex-Gaussian, for high (HF) and low (LF) frequency words [58].

All statistical analyses described in subsequent sections were performed using SPSS 27, Armonk, NY, IBM Corp.

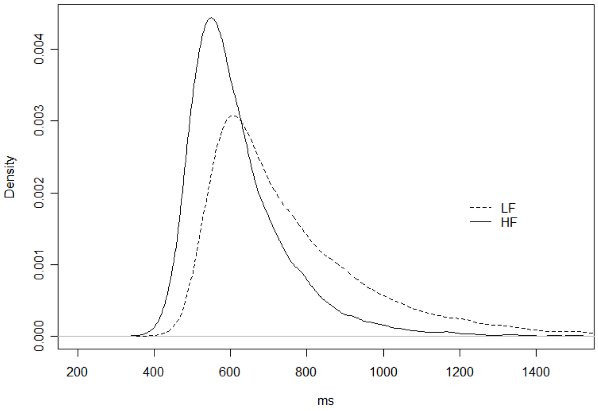


Figure 2.5: Density functions of fixation durations fitted with ex-Gaussian, for high (solid line) and low (dashed line) frequency words.

2.8 STUDY I – ASSESSMENT OF THE TEST-RETEST RELIABILITY OF EYE MOVEMENT PARAMETERS DURING TEXT READING

2.8.1 *Aim of the study*

The aim of the study is to evaluate the test-retest reliability of reading speed and eye movement and ex-Gaussian parameters in silent passage, binocular and monocular, reading. The study is based on the two visits during a three-to-four-month period that the participants made. The Bland–Altman method is used to compute the Coefficient of Repeatability of reading speed, fixation duration, number of fixations, percentage of regressions and ex-Gaussian parameters μ and τ.

A secondary aim is to investigate whether any eye-movement parameter is more stable than reading speed, and thus, more proper for functional vision evaluation.

2.8.2 *Participants*

Twenty middle aged and older adults, native speakers of Greek (8 women) aged 56 to 75 years (mean: 65, SD=6 years) who had attained an average of 12 (SD=4) years of formal education participated in the study, recruited through advertisements posted in the University Hospital and Medical School buildings (Table A.1).

Exclusion criteria for all participants included: any ocular disease or systemic pathology, spectacle-corrected visual acuity for far and near in each eye worse than 0.10 logMAR (0.8 decimal acuity equivalent), myopia > 5.0 D anisometropia > 2.50 D, clinically significant abnormal phorias, any history of refractive or other ocular surgery (cataract surgery was allowed if both eyes had been treated) and any neurological or psychiatric disorder which could affect reading performance.

2.8.3 *Reading material*

Reading speed and oculomotor performance was evaluated with two reading cards each displaying a passage of approximately 140 words (see section 2.5). A different card was used for each of the two reading conditions of the experiment (monocular and binocular) in a counterbalanced order across participants to prevent familiarity and learning effects.

2.8.4 *Experimental procedure*

All participants were assessed twice using identical procedures. The second visit took place three to four months following the first. On each visit, eye movement recordings were conducted in two conditions: binocular and monocular, with the dominant eye, reading. Reading efficiency was assessed at the beginning of the first visit.

Participants were instructed to read the text silently at a comfortable pace to understand the meaning of the passages and answer five simple multiple-choice questions.

2.8.5 *Data analysis*

The Bland–Altman method was used to assess agreement between the two reading sessions [129–131]. Coefficient of Repeatability (CR) and 95% limits of agreement are computed as the mean difference plus or minus 1.96 times its standard deviation. Coefficient of Repeatability is given by: $CR = 2\sqrt{(\Sigma d_i^2)/n}$, where d_i is the difference between two observations of a given participant and n is the number of participants [129]. 95% of the differences of two similar measurements will be less than the value of CR.

Paired t-tests were performed to compare the two visits on each parameter (the Shapiro-Wilk test showed that all variables followed normal distributions).

2.8.6 *Results*

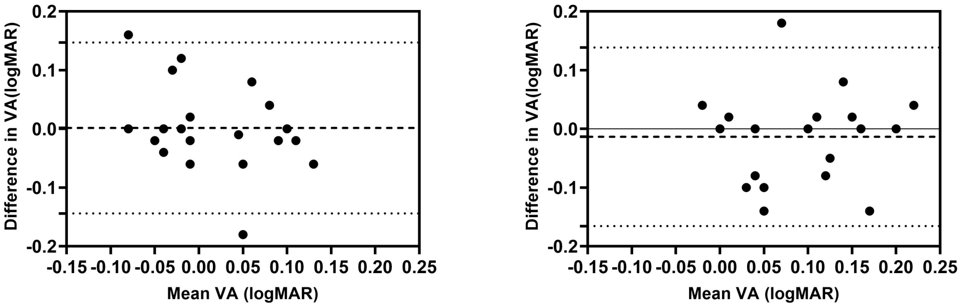
Average word (WRE) and pseudoword reading efficiency (PsWRE) in the present sample were very close to the population mean as indicated by z-scores of 0.20 (SD=1.0) and 0.10 (SD=1.1), respectively. Moreover, 5% and 10.0% of the participants scored below 1.5 SDs from the population average on WRE and PsWRE respectively. Average differences between the two visits in VA were practically zero either in binocular (mean dif: 0.00 wpm, CI: -0.03 to 0.04) or monocular viewing (mean dif: -0.01 wpm, CI: -0.05 to 0.02). See Table 2.1 and Figure 2.6.

Eye movement parameters also displayed notable stability over the two visits as indicated by very small average differences (which did not approach significance with the exception of monocular τ; see Table 2.1). As shown in the Bland-Altman plots in Figures 2.7 and 2.8 all but one participants demonstrated eye movement parameters within the 95% CI demonstrating adequate stability, with the exception of μ and monocular τ where two participants approached or exceeded this threshold. In our study, the CR was 60.8 wpm for binocular and 51.9 for monocular reading speed, 40 and 39 ms for binocular and monocular fixation duration, 0.21 and 0.29 fixations per word for binocular and monocular reading, 6.0 and 8.1% for binocular and monocular percentage of regressions.

Table 2.1: Visual Acuity (VA) and eye movement parameters over two visits: mean (SD) values, average differences and Coefficient of Repeatability (CR)

Feature	**1st visit**	**2nd visit**	**Mean Dif (95% CI)**	**p value**	**CR**
VA (B) (logMAR)	0.02 (0.06)	0.02 (0.09)	0.00 (-0.03 to 0.04)	0.929	0.14
VA (M) (logMAR)	0.09 (0.08)	0.10 (0.08)	-0.01 (-0.05 to 0.02)	0.446	0.15
RS (B) (wpm)	193.7 (46.7)	199.7 (57.6)	-6.1 (-20.4 to 8.2)	0.386	60.8
RS (M) (wpm)	182.5 (47.9)	184.3 (55.0)	-1.8 (-14.6 to 11.6)	0.776	51.9
Fix.dur. (B) (ms)	238 (38)	233 (40)	6 (-3 to 15)	0.199	40
Fix.dur. (M) (ms)	252 (46)	254 (48)	-2 (-12 to 7)	0.613	39
Fixations (B) (fpw)	0.93 (0.22)	0.92 (0.24)	0.02 (-0.03 to 0.06)	0.500	0.21
Fixations (M) (fpw)	0.97 (0.25)	1.00 (0.27)	-0.02 (-0.09 to 0.05)	0.510	0.29
Reg. (B) (%)	15.1 (5.8)	14.2 (5.8)	1.0 (-0.4 to 2.3)	0.159	6.0
Reg. (M) (%)	13.5 (6.0)	13.2 (4.8)	0.3 (-1.7 to 2.3)	0.735	8.1
μ (B) (ms)	176 (37)	170 (37)	7 (-4 to 17)	0.200	45
μ (M) (ms)	187 (49)	186 (49)	1 (-9 to 10)	0.879	38
τ (B) (ms)	73 (24)	79 (23)	-6 (-16 to 4)	0.210	42
τ (M) (ms)	75 (35)	82 (42)	-7 (-14 to 0.5)	0.065	33

Abbreviations: B: binocular, M: Monocular, RS: reading speed, Fix.dur: fixation duration, Reg: regressions, wpm: words per minute, fpw: fixations per word.
p value of tests comparing the two visits.



(a) Binocular VA

(b) Monocular VA

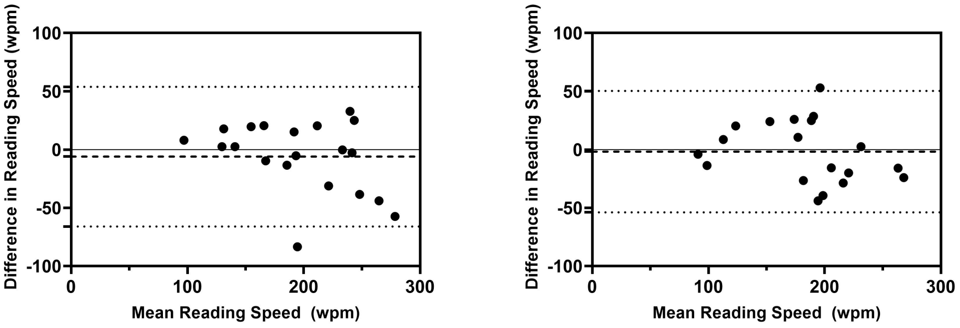
Figure 2.6: Bland–Altman plots of the difference in VA (1st-2nd visit) as a function of the average VA. Three horizontal dotted lines: the upper limit of 95% and the mean and lower limit of the 95% of the difference.

2.8.7 *Discussion*

The present study evaluated the temporal stability of eye movement parameters in silent reading of short passages used in Study II and similar to the ones used in Studies III-V. To investigate repeatability in reading speed and overall reading performance, measurements were repeated within a time interval of 3-4 months. Implementing eye movement recordings using a high-resolution video eye tracker allowed for the evaluation of reading speed (and a range of eye fixation parameters). Participants were asked to read the texts silently which, compared to oral reading, forms the preferred reading mode [132] and a prerequisite in real-life reading conditions [34, 87]. However, silent comprehensive reading exhibits higher variability compared to oral non-comprehensive reading [40, 41, 88].

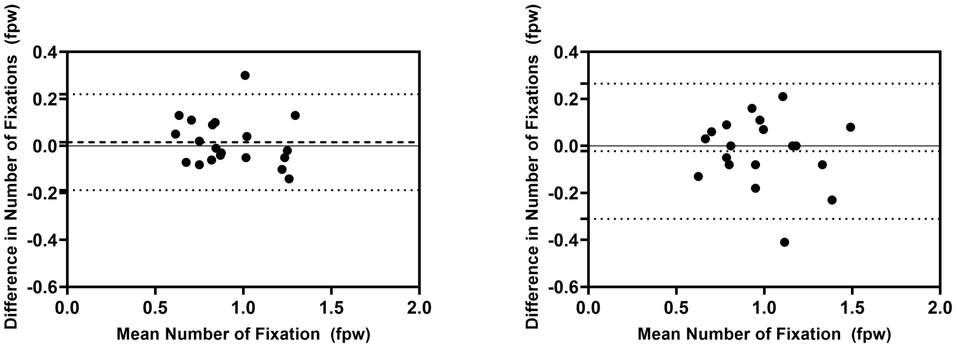
Participants of the study were of a certain age group, 56 to 75 years with a mean age of 65 years. Thus, our results are to be compared with studies with participants of similar age.

Traditionally, oral reading assessment was based on a series of single sentences of decreasing print size, to allow the determination of reading acuity. More recently developed cards follow the Bailey-Lovie principle [36], ensuring that sentences are of equal length; these include the MNread [37, 133], the Colenbrander and the Radner [38, 39] reading cards. Standardized sentences allow comparison of the reading speeds for paragraphs of different print size, but are susceptible to timing errors, due to their limited length [34]. For repeated measurements of reading speed, the International Reading Speed Texts (IReST) [40, 41], which consist of ten 150-word reading passages of fixed size, are probably the most appropriate to use, since paragraphs lead to lower variability compared to sentences [90]. For a thorough presentation



(a) Binocular Reading Speed

(b) Monocular Reading Speed



(c) Binocular Number of Fixations

(d) Monocular Number of Fixations

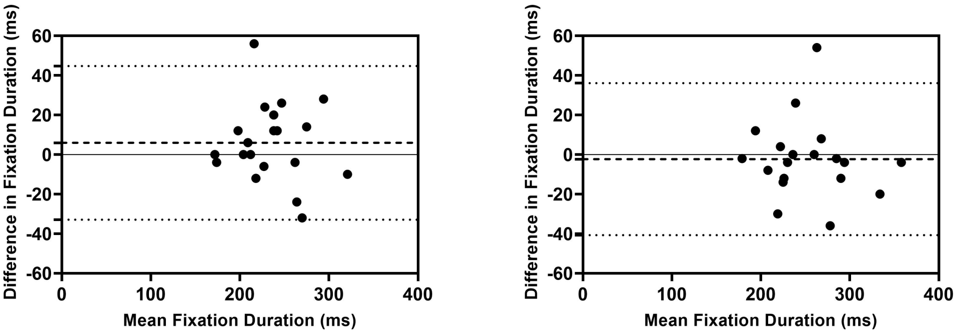
Figure 2.7: Bland–Altman plots of the difference in Reading Speed and Number of Fixations as a function of their respective mean values. Three horizontal dotted lines: the upper limit of 95% and the mean and lower limit of the 95% of the difference.

of the available continuous text reading tests and their measurement properties, please see Brusee T. et al. (2014) [134].

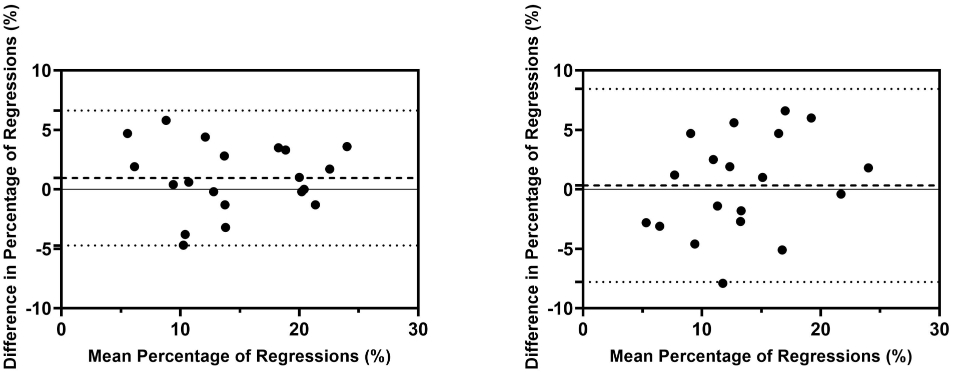
CR values obtained in Study I are similar and slightly better than those of Ktistakis E, et al. (2023) [135], although in that study the participants were younger (mean: 30 years) than in the present study (mean: 65 years).

Test–retest variability of oral reading speed has also been evaluated in ocular diseases, and more specifically in patients with maculopathies [88, 90] and glaucoma [136] and coefficient of repeatability for mean or maximum reading speed was still lower than that of mean silent reading speed in healthy (but older) population in our study.

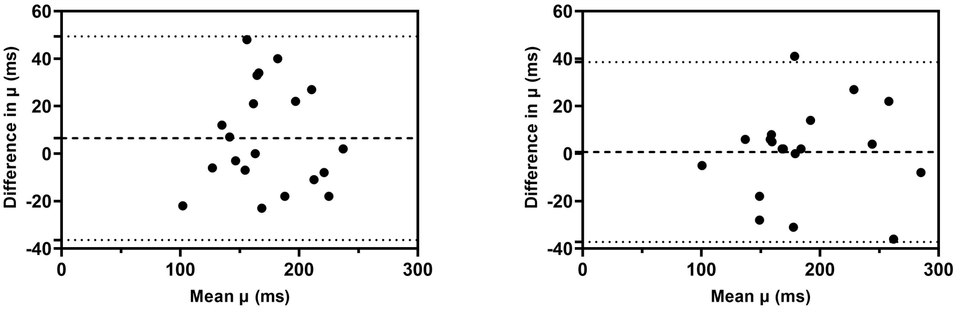
As far as the eye movement and ex-Gaussian parameters are concerned, CR as a percentage of mean value is lower in fixation duration, μ and in the number of fixations (only in binocular reading) than in reading speed (Table 2.2). This result shows that in the pursuit of good repeatability in silent reading, reading speed is not the best feature. Fixation duration seems to be the most stable feature. Regarding binocular reading, it seems that binocularity does



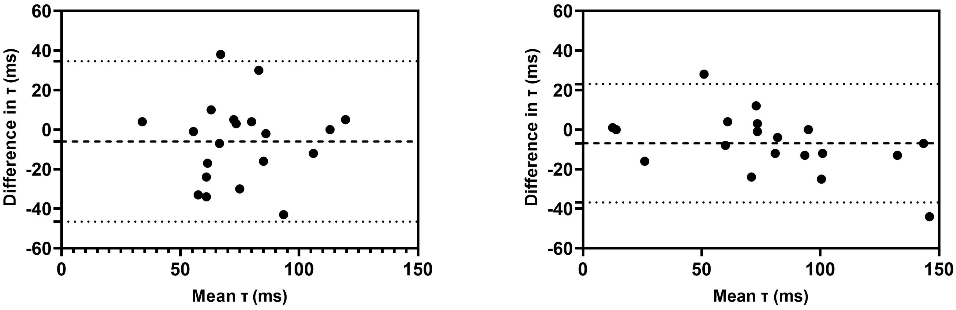
(a) Binocular Fixation Duration (b) Monocular Fixation Duration



(c) Binocular Percentage of Regressions (d) Monocular Percentage of Regressions



(e) Binocular μ (f) Monocular μ



(g) Binocular τ (h) Monocular τ

Figure 2.8: Bland–Altman plots of the difference in Fixation Duration, Percentage of Regressions and ex-Gaussian parameters μ and τ as a function of their respective mean values. Three horizontal dotted lines: the upper limit of 95% and the mean and lower limit of the 95% of the difference.

not provide significantly better repeatability in any parameter, apart from the percentage of regressions.

Some limitations of the study have to be taken into account. First of all, the participants were of a very narrow age range (56 to 75 years, mean: 65 years), making the study hard to compare with other studies. Secondly, the texts that were used were developed by the study group at the Laboratory of Optics and Vision for the purpose of the study and not some standardised reading cards, such as the IReST. This means that the test has limited application. Finally, a larger sample would have made our results more robust.

Table 2.2: Mean values of eye movement parameters, Coefficient of Repeatability (CR) and CR as a percentage of the mean value

Feature	**Mean**	**CR**	**Percentage (%)**
RS (B) (wpm)	196.7	60.8	30.9
RS (M) (wpm)	183.4	51.9	28.4
Fix.dur. (B) (ms)	236	40	16.9
Fix.dur. (M) (ms)	253	39	15.4
Fixations (B) (fpw)	0.93	0.21	22.6
Fixations (M) (fpw)	0.99	0.29	29.3
Reg. (B) (%)	14.6	6.0	41.1
Reg. (M) (%)	13.4	8.1	60.4
μ (B) (ms)	173	45	26.0
μ (M) (ms)	187	38	20.3
τ (B) (ms)	76	42	55.3
τ (M) (ms)	79	33	41.8

Abbreviations: B: binocular, M: Monocular, RS: reading speed, Fix.dur: fixation duration, Reg: regressions, wpm: words per minute, fpw: fixations per word.

2.9 STUDY II - PATIENTS WITH AGE-RELATED MACULAR DEGENERATION (AMD)

2.9.1 *Aim of the study*

The primary aim of the study is to evaluate the effectiveness of anti-VEGF treatment in wAMD patients by evaluating silent reading performance. Functional vision in AMD patients is hampered in a great extent, thus almost all eye movement parameters are expected to be affected, as compared to the control group.

Three months period is not enough for the anti-VEGF treatment to have great impact on the patients' vision and thus, reading behavior. However, an increase in reading speed and a decrease in some parameters, such as ex-Gaussian parameter μ and the number of fixations and the percentage of regressions due to shrinkening of the scotomas, are expected.

A secondary aim is to find certain parameters that account for the difference in reading speed due to anti-VEGF treatment.

2.9.2 *Participants*

Twenty wet AMD patients, native Greek speakers, who were scheduled to undergo anti-VEGF treatment in the Ophthalmology Department of the University Hospital of Heraklion were recruited in the study. Twenty participants without ocular pathology served as control.

Exclusion criteria for all participants included: any other ocular disease or systemic pathology, spectacle-corrected visual acuity for far and near in each eye worse than 0.50 logMAR in AMD patients and worse than 0.20 logMAR in controls, myopia > 5.0 D anisometropia > 2.50 D, clinically significant abnormal phorias, any history of refractive or other ocular surgery (cataract surgery was allowed if both eyes had been treated) and any neurological and psychiatric disorder which could affect reading performance.

The inclusion criterion of VA better than 0.50 logMAR in the treated eye has restricted the study to eyes with relatively good VA for wet AMD, but formed a prerequisite so the patients could perform the reading task.

Data from four patients were excluded from the analyses, due to deterioration of the disease to the extent that prevented them from reading the printed passage on the follow-up visit (n=3) and presence of retinal Pigment Epithelial Detachment (PED) in one patient, associated with a dramatic increase in CRT (333 nm).

The final patient data set comprised of 16 patients (10 women) aged 71 years (SD=8, range: 52 to 80 years) who had attained an average of 9 (SD=5) years of formal education. The sample included newly diagnosed (N=9) and patients with wAMD under anti-VEGF treatment in "Pro-re-nata" (when needed) protocol that had been relapsed (N=7). We considered a patient to have relapsed when he or she presented with deterioration in OCT (indexed by increased central macular thickness, CMT) or increase of intra-retinal fluid, or IRF) or increase of sub-retinal fluid SRF) alone or in any combination) along with VA deterioration (as long as VA is equal or better than 0.5 logMAR). Relapsed patients repeated the entire treatment protocol consisting of at least 3 monthly injections and PRN (i.e., when needed) afterwards. None of the patients discontinued the medication and no adverse drug reaction was observed. The demographics of the participants recruited are shown in Table A.2.

Participants in Study I (n=20) provided comparison data for Study II (For demographics of the control group see Table A.1). They were older than patients by 6 years on average (CI from 1 to 10, $p = 0.01$) and had attained slightly higher education level ($p = 0.08$). In addition, the two groups displayed comparable age- and education-adjusted word ($p = 0.1$) and pseudoword ($p = 0.4$) reading efficiency. This group was not a control group to test the controlled differential effect of an experimental intervention, but rather a sample of age-matched individuals with normal vision served to establish the temporal stability of eye movement measures and to show whether there are any learning effects.

2.9.3 *Reading material*

Reading speed and oculomotor performance was evaluated with three reading cards each displaying a passage of approximately 140 words (see section 2.5), the same that were employed in Study I. A different card was used for each of the two reading conditions of the experiment (monocular and binocular) in a counterbalanced order across participants to prevent familiarity and learning effects. Participants were instructed to read the text silently at a comfortable pace to understand the meaning of the passages and answer five simple multiple-choice questions.

2.9.4 *Experimental procedure*

Patients with AMD were measured on two different visits using identical procedures: the first visit took place immediately after diagnosis and before any therapeutic intervention for the naive patients and before initiation of therapy for relapse for the remaining patients. The second visit took place three to four months following the first visit, after they had completed their scheduled standard anti-VEFG treatment of three intravitreal ranibizumab injections (Lucentis, Novartis Pharma AG, Basel, Switzerland). Participants in the control group were assessed using identical material and procedures on two occasions three to four months apart. On each visit all participants had an OCT (Spectralis, Heidelberg Engineering, Germany) and Best Corrected Visual Acuity (BCVA) evaluation and were administered the reading efficiency tests prior to the passage reading session. Reading behavior measurements were conducted in two conditions: binocular reading and monocular reading with dominant eye.

Participants were instructed to read the text silently at a comfortable pace to understand the meaning of the passages and answer five simple multiple-choice questions.

2.9.5 *Data analysis*

Independent sample t-test with a 95% confidence interval (CI) for the mean difference is performed to assess the difference between the group of patients and the control group. Paired sample t-test is performed to evaluate within groups differences.

2.9.6 *Results*

2.9.6.1 *Group comparisons*

Table 2.3 shows mean values of all parameters as measured during the first visit of all participants of both groups and their respective differences. Patients' monocular values refer to the eye under treatment, while controls' monocular values refer to the dominant eye.

Independent sample t-test revealed that binocular (t(18.806)=-5.683, p<0.001) and monocular VA (t(23.651)=-6.339, p<0.001) were better in the control group compared to the patients with mean differences of 0.24 logMAR (95% CI from 0.15 to 0.32 logMAR) and 0.24 logMAR (95%

CI from 0.16 to 0.32 logMAR) respectively. CRT was also found to be statistically significantly higher in the patients group compared to the control group (t(19.097)=-2.473, p=0.023) with a difference of 40 μm (95% CI from 6 to 75 μm).

Differences between the groups were found to be statistically significant in reading speed and all eye movement parameters apart from the percentage of regressions in binocular reading (t(34)=-1.175, p=0.248). All ex-Gaussian parameters showed statistically significant differences between the groups, both in binocular and monocular reading.

Table 2.3: CRT, VA and reading performance parameters (SD) and differences between groups

Feature	**AMD Patients**	**Control Group**	**Mean Dif (95% CI)**	**p value**
CRT (μm)	325 (61)	285 (25)	40 (9 to 75)*	0.023
VA (B) (logMAR)	0.25 (0.16)	0.02 (0.06)	0.24 (0.15 to 0.32)*	0.000
VA (M) (logMAR)	0.33 (0.13)	0.09 (0.08)	0.24 (0.16 to 0.32)*	0.000
RS (B) (wpm)	103.1 (50.9)	193.7 (46.7)	-90.5 (-124.2 to -56.8)*	0.000
RS (M) (wpm)	69.4 (32.9)	183.9 (47.0)	-114.5 (-142.7 to -86.3)*	0.000
Fix. dur. (B) (ms)	314 (55.4)	238 (38.3)	76 (43 to 108)*	0.000
Fix. dur. (M) (ms)	377 (93.8)	252 (44.8)	125 (72 to 178)*	0.000
Fixations(B) (fpw)	1.35 (0.39)	0.93 (0.22)	0.41 (0.18 to 0.65)*	0.001
Fixations (M) (fpw)	1.70 (0.51)	0.96 (0.25)	0.74 (0.45 to 1.03)*	0.000
Regressions (B) (%)	17.5 (6.2)	15.1 (5.8)	2.40 (1.75 to 6.54)	0.248
Regressions (M) (%)	18.8 (7.2)	13.8 (5.9)	5.1 (0.62 to 9.51)*	0.027
μ (B) (ms)	224 (39)	176 (37)	48 (22 to 75)*	0.001
μ (M) (ms)	252 (87)	186 (48)	65 (19 to 111)*	0.007
τ (B) (ms)	129 (42)	73 (24)	56 (31 to 81)*	0.000
τ (M) (ms)	152 (60)	76 (34)	77 (42 to 112)*	0.000

Abbreviations: B: binocular, M: μonocular, RS: reading speed, Fix. dur: fixation duration
* significant difference

2.9.6.2 *Anti-VEGF treatment effect*

CHANGE IN CENTRAL RETINAL THICKNESS AND VISUAL ACUITY Paired sample t-test showed that near VA of the control group did not exhibit any changes between the two visits as measured binocularly (95% CI from -0.04 to 0.03 logMAR, p = 0.929) and monocularly (95% CI from -0.02 to 0.05 logMAR, p = 0.446).

Effectiveness of 3-month anti-VEGF treatment was anatomically indicated by a statistically significant reduction in CRT by 41±48 μm (95% CI from 16 to 66 μm, p = 0.004). Although the reduction in CRT following treatment correlated well with the change in VA (r = -0.71, p = 0.003), the improvement in near monocular and binocular VA was minimal and not statistically significant. VA difference was found to be on average 0.04 logMAR in both monocular (95% CI from -0.11 to 0.04 logMAR, p = 0.356) and binocular viewing conditions (95% CI from -0.09 to 0.02 logMAR, p= 0.163; see Table 2.4).

Figure 2.9 plots monocular visual acuity in AMD and control groups on both visits.

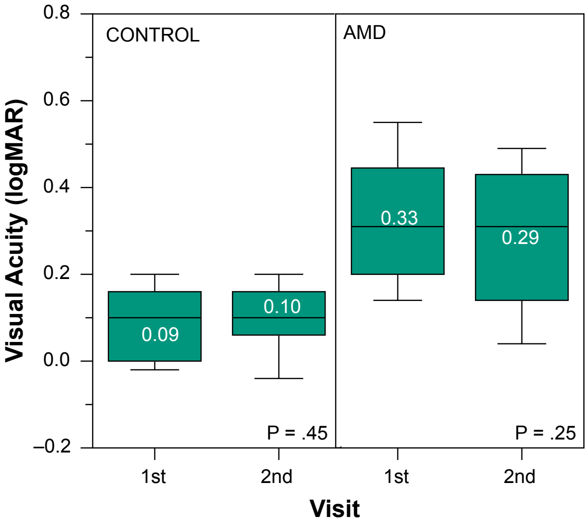


Figure 2.9: Box plots of monocular near visual acuity for the dominant eye of the control group (left) and the affected eye of the AMD group (right) at both visits. Average values are shown in white.

READING SPEED AND EYE FIXATION PARAMETERS The control group exhibited no differences in passage reading speed between the two visits, in both monocular (95% CI from -11.1 to 14.6 wpm, p = 0.8) and binocular viewing conditions (95% CI from -8.2 to 8 wpm, p = 0.4). In addition, no statistically significant difference was found in any eye fixation parameter in either binocular or monocular testing (see Table 2.5), suggesting minimal learning effects.

As far as the AMD group is concerned, improvement in passage reading speed was observed in 11/16 of patients which was accompanied by improvement in visual acuity in 8/11 patients (VA improved in one additional patient without concomitant improvement in reading speed). On average, passage reading speed improved from 69.4 to 85.3 wpm, i.e. by an average of 15.9±28.5 wpm (95% CI from 0.7 to 31.1 wpm, p = 0.041). Reading speed in binocular viewing did not change significantly between the two visits (see Table 2.5).

There was a significant reduction in the number of fixations per word, averaging 0.24±0.38 fpw (95% CI from 0.04 to 0.45 fpw, p = 0.023; see Figure 2.10). Reduction in the number of fixations during reading strongly correlated with the concurrent reduction in CRT (r = 0.71, p = 0.003). Change in the remaining eye fixation parameters with treatment was in the expected direction but did not reach significance (see Table 2.5).

As expected, improvement in monocular reading speed was closely associated with the concurrent reduction in CRT (r = -0.68, p = 0.004). Although near VA did not improve with treatment on a group basis, it was closely associated with the degree of improvement in monocular passage reading speed (r = 0.70, p = 0.003) (see Figure 2.11).

Regarding eye movement parameters, treatment-related changes in the number of fixations (r = -0.67, p = 0.006), average fixation duration (r = -0.65, p = 0.006), percentage of regressions (r = -0.52, p = 0.041) and ex-Gaussian parameter μ (r = -0.66, p = 0.005) were all significantly associated with the degree of improvement in monocular passage reading speed (see Figure 2.12).

FACTORS ACCOUNTING FOR DIFFERENCES IN READING SPEED AFTER ANTI-VEGF TREATMENT To further assess the joint contribution of change in monocular VA and in eye fixation parameters to the improvement in passage reading we computed two complementary hierarchical linear multiple regression models. Monocular VA was always entered in the first step. Due to collinearity concerns, fixation duration, percentage of regressions and parameter μ were not entered together in the same regression model. Model 1 included change in fixation duration, number of fixations per word, and percentage of regressions entered together in the second step. In Model 2, number of fixations per word and the ex-Gaussian parameter μ were entered together in the second step.

Both models were significant (p < 0.001) with the predictor variables accounting for 85 and 79% of the variance in reading speed improvement. Model 1 revealed that reductions in

Table 2.4: CRT, near visual acuity and reading fluency (SD) across visits and average differences for the two groups.

	AMD patients				**Control group**			
Feature	Before treatment	After treatment	Mean Difference (95% CI)	p value	Visit 1	Visit 2	Mean Difference (95% CI)	p value
CRT (μm)	325 (61)	284 (63)	-41 (-66 to -16)*	0.004	285 (25)	-	-	-
VA (B) (logMAR)	0.25 (0.16)	0.22 (0.15)	-0.04 (-0.09 to 0.02)	0.163	0.02 (0.06)	0.02 (0.09)	0.00 (-0.04 to 0.03)	0.9
VA (M) (logMAR)	0.33 (0.13)	0.29 (0.16)	-0.04 (-0.11 to 0.04)	0.356	0.09 (0.08)	0.10 (0.08)	0.01 (-0.02 to 0.05)	0.4
Words (z score)	0.10 (1.1)	-	-	-	0.20 (1.0)	-	-	-
Words/min	90.7 (12.3)	-	-	-	108.6 (13.2)	-	-	-
Pseudowords (z score)	-0.21 (1.3)	-	-	-	-0.05 (0.9)	-	-	-
Pseudowords/min	42.9 (12.2)	-	-	-	52.1 (11.2)	-	-	-

Abbreviations; B: Binocular, M: Monocular

[*] Statistically significant change ($p<0.05$)

fixation duration (B = -0.21, SE = 0.06, p = 0.006) and in the number of fixations per word (B = -30.92, SE = 11.03, p = 0.017) were significant predictors of improvement in reading speed even after controlling for the observed change in VA. Model 2 revealed that in addition to the reduction in the number of fixations, a reduction in the parameter μ significantly and independently predicted improvement in reading speed (B = -0.23, SE = 0.06, p = 0.002), even after controlling for the change in VA. The total amount of variance accounted for by eye movement parameters beyond that contributed by VA was 40% in Model 1 and 35% in Model 2. Finally, to facilitate comparisons with previous studies we performed supplementary analyses by excluding VA as a predictor of reading speed. These models indicated that eye fixation parameters alone can account for as much as 76% of the variance in the degree of improvement in reading speed.

To quantify the extent of therapeutic effects on retinal physiology and more specifically on the change in CRT, as predicted by the improvement in monocular VA and by the eye fixation patterns, we computed a complementary hierarchical, linear multiple regression model. Monocular VA was entered in the first step. Due to collinearity concerns, fixation duration, percentage of regressions and parameter μ were not entered together in the same regression model. The model included change in number of fixations per word, entered in the second step, and change in fixation duration in the third step.

Change in VA accounted for 50% of the variance in CRT improvement. When change in the number of fixations was added, the model accounted for 67% of the variance in CRT improvement. On the other hand, when fixation duration or percentage of regressions with parameter μ were added in the model, no statistically significant change in R^2 was observed. Moreover, reduction in the number of fixations (B = 55.92, SE = 22.30, P = 0.026) was a significant predictor of CRT improvement, even after controlling for the observed change in VA. Finally, we performed supplementary analyses by excluding VA as a predictor of CRT. The model indicated that the number of fixations alone can account for as much as 46% of the variance in CRT improvement.

2.9.7 *Discussion*

The main aim of the study was to assess the therapeutic effects of anti-VEGF treatment in wAMD patients by evaluating silent reading performance, which forms the preferred reading

Table 2.5: Reading performance across visits and average differences for the two groups.

	AMD patients				**Control group**			
Feature	Before treatment	After treatment	Mean Difference (95% CI)	p value	Visit 1	Visit 2	Mean Difference (95% CI)	p value
RS (B) (wpm)	104.1 (52.7)	108.3 (40.2)	4.2 (-19.2 to 27.7)	0.702	193.7 (46.7)	199.7 (57.6)	6.1 (-8.2 to 20.4)	0.4
RS (M) (wpm)	69.4 (32.9)	85.3 (33.5)	15.9 (0.7 to 31.1)*	0.041	182.5 (47.9)	184.3 (55.0)	1.8 (-11.1 to 14.6)	0.8
Fix. dur. (B) (ms)	318 (56)	318 (51)	0 (-26 to 26)	1.000	238 (38)	233 (40)	-6 (-15 to 3)	0.2
Fix. dur. (M) (ms)	377 (94)	362 (80)	-15 (-50 to 19)	0.359	252 (46)	254 (48)	2 (-7 to 13)	0.6
Fixations(B) (fpw)	1.32 (0.39)	1.29 (0.39)	-0.03 (-0.22 to 0.15)	0.7	0.93 (0.22)	0.92 (0.24)	-0.02 (-0.06 to 0.03)	0.5
Fixations (M) (fpw)	1.70 (0.51)	1.46 (0.44)	-0.24 (-0.45 to -0.04)*	0.023	0.97 (0.25)	1.00 (0.27)	0.02 (-0.05 to 0.09)	0.5
Regressions (B) (%)	17.9 (6.2)	17.8 (6.3)	-0.1 (-2.1 to 1.9)	0.9	15.1 (5.8)	14.2 (5.8)	-1.0 (-2.3 to 0.4)	0.1
Regressions (M) (%)	18.8 (7.2)	17.0 (7.9)	-1.8 (-4.7 to 1.0)	0.2	13.5 (6.0)	13.2 (4.8)	-0.3 (-2.3 to 1.7)	0.7
μ (B) (ms)	228 (37)	221 (40)	-7 (-27 to 13)	0.462	176 (37)	170 (37)	-7 (-16.7 to 3.7)	0.2
μ (M) (ms)	252 (87)	243 (58)	-9 (-40 to 23)	0.571	187 (49)	186 (49)	-1 (-10.0 to 8.6)	0.9
τ (B) (ms)	130 (43)	122 (42)	-8 (-31 to 15)	0.475	73 (24)	79 (29)	6 (-3.7 to 15.7)	0.2
τ (M) (ms)	152 (60)	147 (63)	-5 (-23 to 12)	0.528	75 (35)	82 (42)	7 (-0.5 to 14.3)	0.07

Abbreviations; B: Binocular, M: Monocular, RS: reading speed, fix. dur: fixation duration.

* Statistically significant change ($p<0.05$)

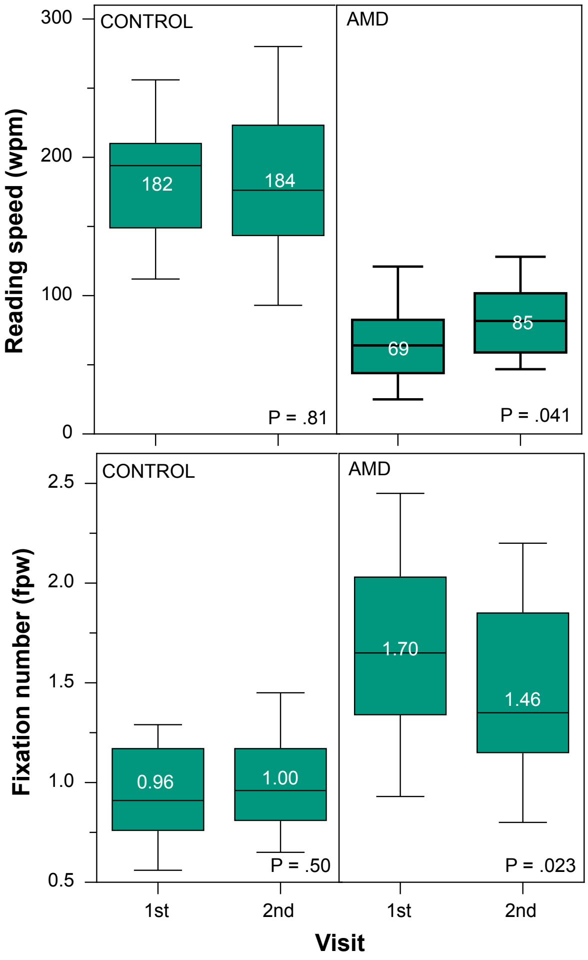


Figure 2.10: Box plots of monocular passage reading speed (upper) and number of fixations (lower) for the RE of the control group and the affected eye of the AMD group at both visits. Average values are indicated in white.

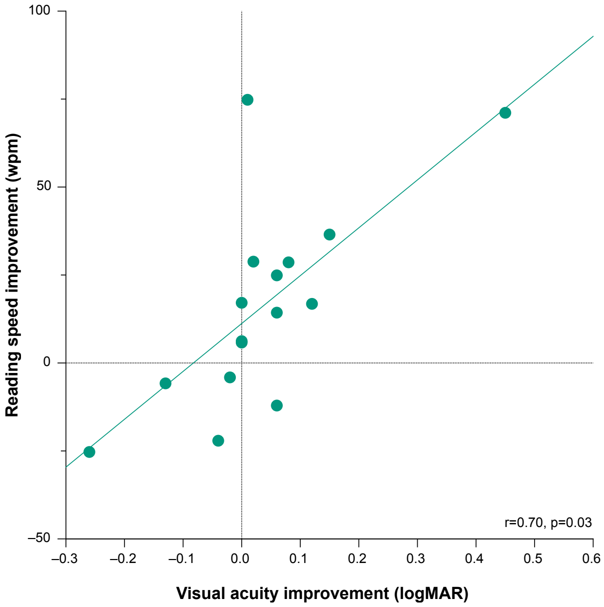


Figure 2.11: Association between reading speed with visual acuity as measured in the treated eye.

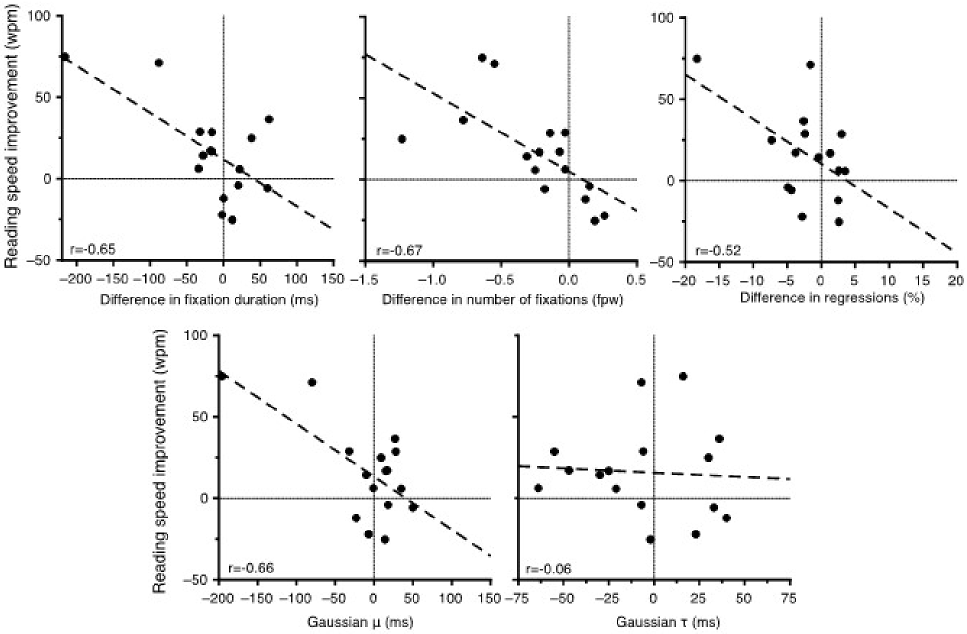


Figure 2.12: Association of change in monocular passage reading speed (post- minus pre-treatment performance in wpm) with corresponding change in eye fixation parameters. Upper panel: fixation duration (left), number of fixations (middle) and regressions (right); Lower panel: ex-Gaussian parameters μ (left) and τ (right). Best-fitting linear regression curves are shown by dashed lines.

mode [132] and a prerequisite in real-life reading conditions [34, 87]. This was achieved by implementing eye fixation analysis using a high-resolution video eye tracker, allowed for the evaluation of silent passage reading speed and a range of eye fixation parameters.

As expected, the patient group showed statistically significantly worse binocular and monocular VA than the control group, as a result of the statistically significantly higher CRT of the patient group. Similarly and in accordance with the literature [97, 98], the patient group showed statistically significantly different values from the control group, on all eye movement and ex-Gaussian parameters.

Following anti-VEGF treatment, monocular silent passage reading speed increased statistically significantly, from 69.4 to 85.3 wpm, while a concurrent significant improvement in the average number of forward fixations (0.24±0.38) was also observed. No significant treatment-related differences were found for other fixation parameters, i.e. fixation duration, ex-Gaussian parameters μ and τ of the fixation duration frequency distributions and regressions. The improvement both in reading speed and in the number of fixations was strongly correlated with the reduction in CRT following treatment. Improvement in monocular passage reading speed of the treated eye was also related to the improvement in near monocular VA. However, the average change in VA observed in the present study, after 3-month anti-VEGF treatment, was much smaller than has been reported by earlier clinical trials and observation studies [68, 69, 78, 82]. This may be due to the relatively small reduction in CRT (95% CI: 16 to 66 μm), compared to previous studies (average CRT is reduced by 150 to 175 μm) [70, 78]. Moreover, due to the exclusion criteria, most patients presenting for treatment in this study had relatively good VA (better than 0.5 logMAR) compared with the average patient being treated for wet AMD, which possibly limits the range of VA improvement resulting from anti-VEGF treatment. No statistically significant difference was found in visual acuity, reading speed and any eye fixation parameter in either binocular or monocular testing in the age-matched individuals with normal vision, suggesting minimal learning effects.

The second aim of the present study was to account for the observed improvement in monocular passage silent reading speed. Hierarchical multiple regression models highlighted treatment-related changes in three eye movement parameters as significant predictors of the degree of improvement in silent reading speed, even after controlling for near VA: average number of fixations per word, average fixation duration and ex-Gaussian parameter μ. It should be noted, however, that among these measures only the average number of fixations was statistically significantly reduced following treatment. Taken together these results suggest that improvement in reading speed reflected primarily a concomitant reduction in the number of fixations performed. The strong correlation found between silent reading speed and the number of fixations could be explained by a visual span expansion, which usually accompanies CRT shrinkage and is known to have a significant effect on reading performance in patients with maculopathy [82, 137].

The total effect of eye movement parameters on the change in treatment-related monocular passage reading speed in AMD patients was in the order of 76%. In a different setting (readers with simulated scotomas), the number of saccades and fixation duration accounted for as much as 94% of the total variance of reading speed [138]. While the debate on the relative importance of the number of saccades is ongoing, the majority of previous studies agree with current results by identifying forward saccade size, which is highly correlated with reduced fixations, as the best predictor of reading speed [33]. On the other hand, the role of fixation duration on predicting reading speed changes in AMD patients is not so clear. A negative association has been reported by Calabrese et al. in patients with AMD and Stargardt's disease [100], while others failed to show a significant association [33, 97, 101].

In interpreting these discrepancies, one should consider important methodological differences among studies, for example in the type of texts [73, 88, 90] and the reading mode, ie. silent vs reading aloud [42, 139]. In the present study reading speed was assessed during silent passage reading of continuous paragraphs instead of single sentences, at a comfortable pace, to simulate real-life reading conditions, while in most clinical studies participants were asked to read the texts out loud and as fast as they can. It is well known that parafoveal information contributes to faster silent reading speed through a reduction in both the duration and number of fixations, while reading slows down when parafoveal information is masked [140]. Although the lack of parafoveal information slows down reading speed in both oral and silent reading, the effects of parafoveal information are larger in silent than in oral reading, especially for faster readers [139]. Moreover, among glaucoma patients with bilateral VF loss, the greatest impact is present during silent reading than oral reading, over prolonged durations [42], and this association was independent of visual acuity.

In our study anti-VEGF, although effective in reducing CRT and improving monocular reading speed, did not result in a significant reduction in the ex-Gaussian parameters μ and τ. Although still under debate [141], most researchers agree that the location of the distribution of fixations during reading (μ) is primarily affected by optical factors, whereas the degree of skew of the distribution (τ) is primarily affected by cognitive factors [58–62]. However, a three-month anti-VEGF treatment is unlikely to be accompanied by significant changes in cognitive capacity and, further, it may have not dramatically affected the quality of the foveal image (as indicated by failure to improve near VA). In light of these considerations, lack of change in either μ or τ with treatment was expected. Interestingly, individual differences in the reduction of the μ parameter accounted for significant variance in the degree of improvement in reading speed. Given the near perfect correlation between change in average fixation duration and μ (r = 0.935), this finding may simply reflect the impact of the degree of reduction in fixation duration on the degree of improvement in reading speed.

Regarding VA, current results, in agreement with previous studies, hint that VA assessment is not sufficient to evaluate functional visual rehabilitation in low vision patients [97, 137]. The hierarchical linear multiple regression model revealed that change in VA accounted for 50% of the variance in CRT improvement and that, when change in the number of fixations is added, then the model can account for 67% of this variance. The joint contribution of VA and the number of fixations may reflect both foveal and parafoveal visual processing, which are known to be affected in AMD [89].

In interpreting the present results, several limitations need to be considered. First, the relatively small size of the patient group may have restricted statistical power to detect more subtle changes in VA and other eye fixation parameters. Second, the patients in this study are not fully representative of patients being treated for wet AMD, who show a larger degradation in VA. We purposely excluded patients with lower VA, since is known that roughly 25% of participants with late AMD are unable to read any words [73, 89] and the majority of them can only complete large-print standardized reading tasks [73]. Moreover, CRT and VA may not be the optimal indicators of the degree of retinal and functional impairment (i.e., foveal vision) of the affected eye, respectively. However, in some patients the retinal fluid is detected in parafovea and as a result, neither CRT nor VA are severely affected. Microperimetry [142] and functional tests, i.e. contrast sensitivity or retinal sensitivity [143, 144], which also consider the AMD patients' slow information transfer rate [82], may provide complementary indices of macular visual function and progression of the disease [70]. Finally, functional reading was not assessed using formally standardized passages, such as IReST, which are now available in Greek [123].

In this study, we showed that VA underestimates the improvement in functional vision after anti-VEGF treatment in patients with relatively good acuity, being treated for wet AMD. In addition, an appropriate eye-movement analysis in reading tasks with standardized texts may provide crucial information regarding the progress of eye diseases, especially maculopathies. Using this method in combination with other tests, may help eyecare specialists better evaluate functional vision and obtain useful information regarding parafoveal visual processing.

2.10 STUDY III - PATIENTS WITH PRESBYOPIA

2.10.1 *Aim of the study*

The scope of this study is to evaluate functional vision in presbyopic persons, before and after correction with multifocal and monovision contact lenses (CL), with the use of eye movement analysis during silent text reading. More specifically, the primary aim is to find eye movement parameters i) that are affected during reading due to uncorrected presbyopia and reverse when corrected with CLs and ii) that are affected by low luminance during reading. A secondary aim is to find the factors that account for the changes of reading speed after correction with CLs as well as the factors that account for the changes of reading speed between high and low luminance.

Reading performance is assessed in four conditions under high luminance level: i) correction for far (FC), ii) correction for near (NC), iii) correction with multifocal CLs (MON) and iv) correction with CLs that provide monovision (MC). Furthermore, reading performance is assessed under low luminance levels in two conditions: i) correction with multifocal CLs and ii) correction with CLs that provide monovision.

Reading performance in FC conditions is expected to be hampered as compared to NC condition, because of the blur effect. Most of the eye movement parameters are expected to be affected, apart maybe from the ones that are known to be affected mainly by cognitive factors, such as the percentage of regressions and ex-Gaussian τ. This effect is expected to reverse when the participants are corrected with the two CL modalities.

2.10.2 *Participants*

Thirty contact lens users with presbyopia participated in the study. The data from four participants was not included in the analyses (three early presbyopes with presbyopia onset < 44 years) and one who failed to use the multifocal CLs. The final sample comprised 26 (14 women) participants (aged 53±5 years, range 46 to 67). Their mean education level was 17±3 (range 12 to 23 years).

The exclusion criteria included: corrected visual acuity for far and near in each eye worse than 0.10 logMAR (0.8 decimal acuity equivalent) in each eye, myopia or hyperopia > 5.0 D, anisometropia > 2.00 D, astigmatism > 0.75 D, abnormal phorias.

The demographics of the participants recruited are shown in Table A.3.

2.10.3 *Reading material*

Five texts from the Greek version [123] of the IReST [40, 41] were used (see section 2.5). The same text was used in the test trial in all three visits while the other four were used randomly in each trial. Mean length of the texts was 144±3 words, each word consisted of 5.2±0.1 characters and mean word frequency was 0.32±0.08‰.

2.10.4 *Contact lenses*

Two different designs of contact lenses were used in the study: (i) multifocal CLs (1-DAY ACUVUE® MOIST Multifocal, with the addition that best-caters for each participant) and (ii) CLs providing monovision (single vision 1-DAY ACUVUE® MOIST). Both of them, by Johnson & Johnson Services, Inc.

According to the manufacturers, the 1-DAY ACUVUE® MOIST Multifocal CLs have a center-near aspheric design and three additions: low (+1.25), medium (+1.75) and high (+2.50). Kim E et al. have shown that these lenses have a gradual change in power between near and distance zones and that here is no distinct relative plus power to the distance prescription in the Lo addition (Figure 2.13) [145].

2.10.5 *Experimental procedure*

Testing was completed in three visits. Table 2.6 shows the reading conditions at three visits. On the first visit (baseline), measurements were performed for all participants with both eyes corrected for far (FC) wearing disposable single vision CLs and for near (NC) wearing readers on top of the lenses. For the next two visits conducted with time interval of two weeks, participants were assigned alternately according to their order of registration, to two groups of

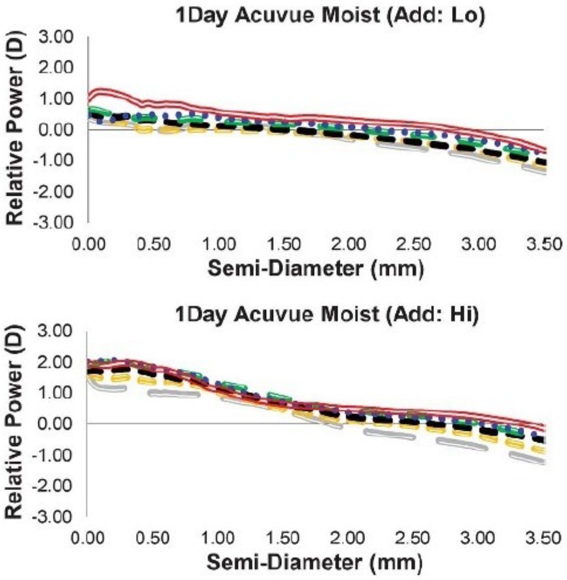


Figure 2.13: Relative refractive power of Acuvue CLs as a function of their semi-diameter. Image adopted from Kim E et al. (2017) [145].

	Visit 1	Visit 2	Visit 3
1	Test	Test	Test
2	FC	MC	MON
3	NC	MC low	MON low
4	NC Comp	-	-

Table 2.6: Experimental procedure of Studies III and IV. NC: near corrected, FC: far corrected, Comp: comprehensive reading, low: low luminance

13 persons. Participants in the first group wore single vision CLs creating monovision (MON) for the first two weeks and multifocal CLs (MC) for the next two weeks. Participants in the second group wore CLs in reverse order. FC condition is used as a negative control because reading a text at 40 cm when being corrected for far is expected to be worse than what is achieved when corrected for near.

The first trial of each visit was a familiarisation trial. The first visit comprised of three trials: 1) test trial, ii) best corrected for far (with contact lenses) and iii) best corrected for near (with readers on top of contact lenses). Visits 2 and 3 included the test trial and two reading behavior measurements in high and low luminance with the participants wearing contact lenses for presbyopia correction. Eye movements were recorded during binocular reading at two luminance levels (high and low photopic, 50 and 5 cd/m2 respectively). Thus, the effect of luminance was evaluated only in MC and MON correction.

Participants were instructed to read the text silently at a comfortable pace. In addition to eye movement measures, far and near logMAR visual acuity (VA) was measured with standardised ETDRS charts. Stereoacuity was measured using the Graded circle test and the random dot background in Randot stereopsis test.

2.10.6 *Data analysis*

Normality of all parameters was evaluated with the Shapiro-Wilk test. The Friedman test was used for the parameters (stereoacuity and blink rate) that were not normally distributed. For the rest of the parameters, Repeated Measures One-Way ANOVA was performed in order to evaluate the effect of condition (NC, FC, MON, MC). This analysis was conducted on data from high luminance condition.

To further assess the joint contribution of change in eye fixation parameters to the improvement in reading speed due to CLs (i.e. as compared to the FC condition), two complementary hierarchical, linear multiple regression models were computed. The number of fixations made was always entered in the first step. Due to collinearity concerns, fixation duration, percentage of regressions and ex-Gaussian parameter *tau* were not entered together in the same regression model. Model 1 included change in fixation duration entered in the second step. In Model 2, percentage of regression and the ex-Gaussian parameter *tau* were entered together in the second step.

For the effect of luminance, two-way repeated measures ANOVA was performed for reading speed and all eye movement parameters except blink rate as it does not follow normal distribution.

2.10.7 *Results*

2.10.7.1 *Effects of correction method*

Table 2.7 shows the mean values of all parameters in four conditions at high luminannce, except of stereoacuity and blink rate for which median (IQR: interquartile range) is presented.

The Friedman test revealed significant main effects of Condition both in stereoacuity and in blink rate ($x^2(3) = 25.029$, $p < 0.001$ and $x^2(3) = 8.123$, $p = 0.044$ respectively). For the rest of the parameters, Repeated Measures One-Way ANOVA revealed significant main effects for: far VA (F(2, 50) = 13.468, $p < 0.001$), near VA (F(3, 75) = 77.554, $p < 0.001$), reading speed (F(2.302,57.550) = 12.901, $p < 0.001$), fixations per word (F(2.066,51.661) = 7.809, p = 0.001), fixation duration (F(1.952,48.812) = 35.515, $p < 0.001$), percentage of regressions (F(3,75) = 3.672, p = 0.016), ex-Gaussian parameter μ (F(3,75) = 19.377, $p < 0.001$) and ex-Gaussian parameter τ (F(3,75) = 2.838, p = 0.044). Results of post-hoc pairwise comparisons (evaluated at Bonferroni-adjusted $p < 0.008$) are presented below.

Table 2.7: VA, stereoacuity, reading speed and eye movement parameters (SD) in the four conditions of the study.

	Condition			
Feature	**NC**	**FC**	**MON**	**MC**
Far VA (logMAR)	-	-0.09 (0.06)	-0.03 (0.08)	0.01 (0.11)
Near VA (logMAR)	-0.01 (0.08)	0.32 (0.10)	0.02 (0.10)	0.09 (0.10)
Stereoacuity (arcsec)	52 (40)	100 (130)	70 (135)	60 (30)
Reading speed (wpm)	258.7 (58.7)	196.5 (67.6)	236.2 (51.9)	240.4 (68.7)
Fixation duration (ms)	227 (31)	272 (45)	234 (25)	234 (30)
Fixations per word	0.78 (0.12)	0.89 (0.18)	0.80 (0.12)	0.80 (0.15)
Regressions (%)	8.1 (7.0)	10.2 (7.0)	11.0 (7.5)	11.0 (7.1)
Blink rate	4.8 (6.6)	7.5 (11.0)	7.7 (12.1)	4.5 (10.0)
Ex-Gaussian μ (ms)	173 (28)	203 (38)	172 (19)	174 (29)
Ex-Gaussian τ (ms)	64 (24)	81 (39)	76 (25)	72 (29)

Abbreviations; NC: near corrected, FC: far corrected, MON: monovision, MC: multifocal
All values are means (SD) with the exception of stereoacuity and blink rate values where median (IQR) values are reported.
All measurements were performed in high luminance settings (50 cd/m2).

Far VA was significantly better in the FC as compared to the MC and MON conditions ($p<0.001$ in both cases), but it was not different between the MC and MON condition (p=0.266).

Near VA was significantly improved in MC compared to FC condition by 0.23 logMAR (95% CI: from -0.31 to -0.15 logMAR, $p<0.001$), but worsened compared to NC condition by 0.10 (95% CI: from 0.03 to 0.17 logMAR, p=0.001). Near VA also significantly improved in MON compared to FC condition by 0.30 logMAR (95% CI: from -0.38 to -0.22 logMAR, $p<0.001$) and by 0.07 logMAR in MON compared to MC (95% CI: from -0.12 to -0.02 logMAR, p=0.005). There were minimal differences between MON and NC conditions (mean difference=0.03 logMAR, 95% CI: from -0.04 to 0.10 logMAR, p=1.000, see Fig. 2.14 left).

Post hoc analysis with Wilcoxon signed-rank tests (with a Bonferroni correction applied, resulting in a significance level set at $p < 0.008$) was conducted for stereoacuity and revealed significant improvement in the MC as compared to the FC condition (Wilcoxon signed-rank Z = -3.026, p = 0.002) and deterioration in the MON as compared to the NC condition (Z = -3.924, $p < 0.001$). Stereoacuity did not change significantly between MC and NC conditions (Z = -2.076, p = 0.038) and MON vs MC conditions (Z = -1.513, p = 0.130; see Fig. 2.14 right).

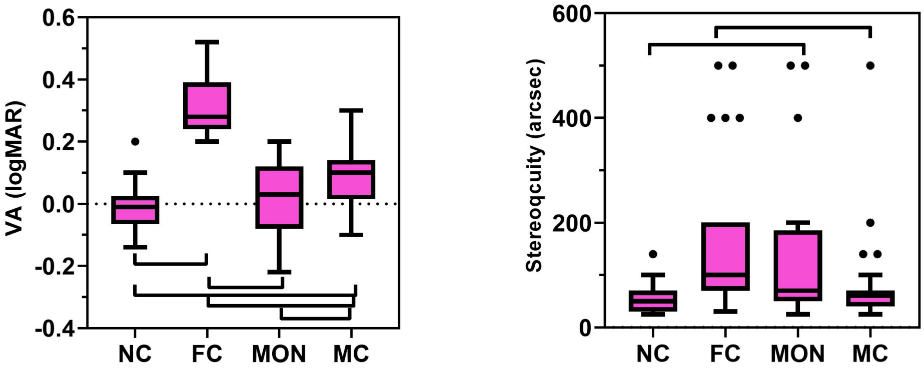


Figure 2.14: Near Visual Acuity (left) and stereoacuity (right) values in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC) and monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences.

Reading speed was significantly higher in MC and MON conditions as compared to the FC condition (mean difference = 44 wpm, 95% CI: 6 to 82, p = 0.018 and mean difference = 40 wpm, 95% CI: 7 to 73), p = 0.012 respectively). See Table 2.7 and Figure 2.15. Average reading speed was practically identical in the MC and MON condition (mean difference = 4 wpm, 95% CI, -25 to 33, p = 1.000) and slightly lower than in the NC condition, although this difference did not reach significance (mean difference =-18 wpm, 95% CI: -45 to 9, p = 0.375 and mean difference = -22 wpm, 95% CI: -46 to 1), p = 0.063 respectively).

The number of fixations per word significantly decreased only in the MON as compared to the FC condition (mean difference = -0.09 fpw, 95% CI: -0.17 to -0.01, p = 0.030). A similar degree of reduction in the MC as compared to the FC condition failed to reach significance (mean difference = -0.09 fpw, 95% CI: -0.18 to 0.0, p =0.065). All other pairwise comparisons did not approach significance ($p > 0.9$; Fig. 2.16, left).

Fixation duration significantly decreased in MC (mean difference = -38 ms, 95% CI: -54 to -23, $p < 0.001$) and MON (mean difference = -38 ms, 95% CI: -55 to -21, $p < 0.001$) as compared

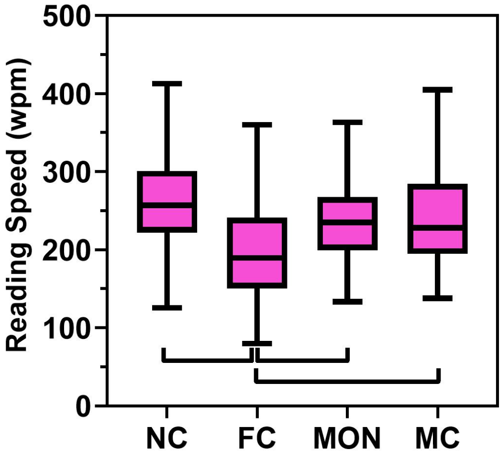


Figure 2.15: Reading speed values in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences.

to the FC condition. All other pairwise comparisons did not approach significance ($p > 0.2$; Fig. 2.16, right).

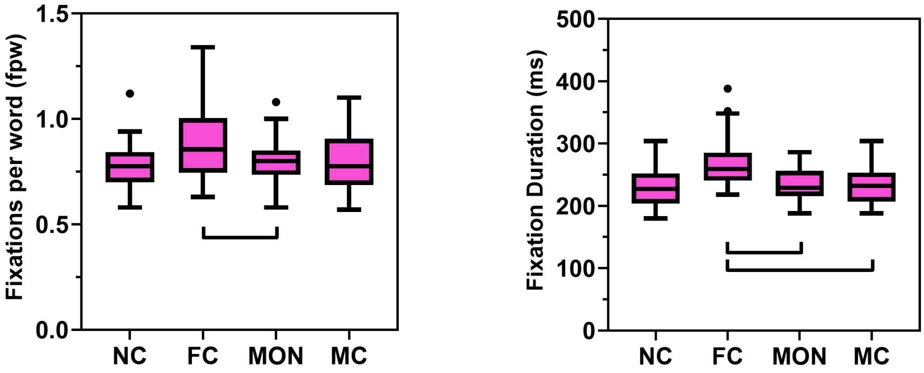


Figure 2.16: Number of forward fixations (left) and fixation duration (right) in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences.

No difference was found in the percentage of regressions in any pair among FC, MC and MON conditions. There was however, statistically significant increase both in MC (mean difference = 2.9 %, 95% CI: 0.8 to 5.0, $p = 0.004$) and in MON (mean difference = 2.9 %, 95% CI: 0.4 to 5.4, $p = 0.016$) condition as compared to the NC condition (Fig. 2.17 left).

Blink rate was significantly lower in the NC as compared to the FC condition (Wilcoxon signed-rank $Z = -2.688$, $p = 0.007$; Fig. 2.17 right).

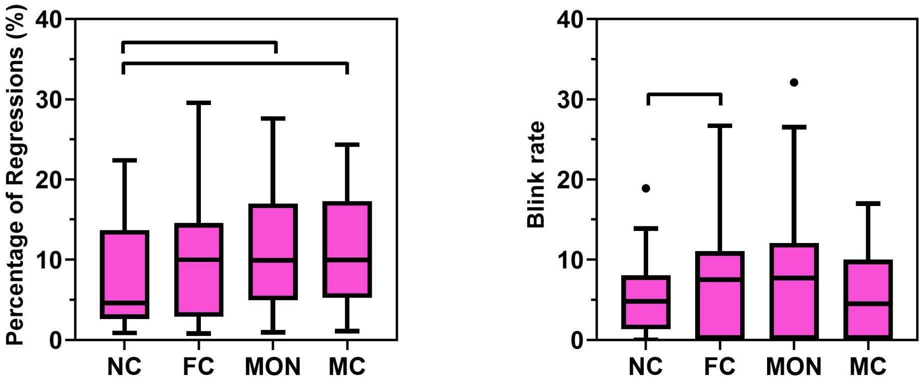


Figure 2.17: Percentage of regressions (left) and blink rate (right) in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences.

Figure 2.18 depicts the box plots of the ex-Gaussian parameters of fixations durations. The ex-Gaussian parameter μ was significantly lower in all conditions for near corrected vision compared to the FC condition: NC (mean difference = -30 ms, 95% CI, -46 to -13, p < 0.001), MC (mean difference = -29 ms, 95% CI: -45 to -13, p < 0.001) and MON (mean difference = -31 ms, 95% CI: -47 to -16, p < 0.001). No other significant difference was found in μ. Differences between conditions on the ex-Gaussian parameter τ did not reach significance (p > 0.09).

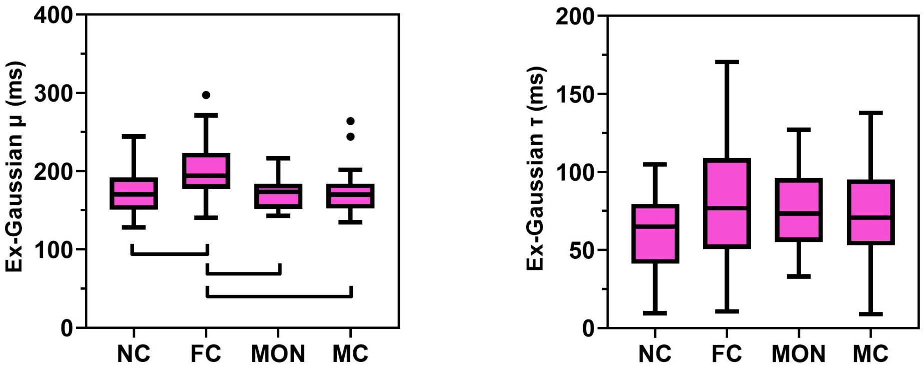


Figure 2.18: Ex Gaussian parameters, μ and τ, in the four conditions tested: single vision contact lenses with correction for far (FC), for near with readers (NC), with monovision approach (MON), and multifocal contact lenses (MC). Whiskers represent 1.5 IQR. Brackets indicate significant differences.

2.10.7.2 *Factors accounting for differences in reading speed when corrected with CLs*

As shown in Table 2.8 strong, significant associations between the degree of change in reading speed in the MON vs FC condition were found with concurrent changes in the number of

	VA	Fixation Duration	Fixations	Reg.	Blink rate	μ	τ
MON	r = -0.22 p = 0.29	r = -0.68* p < 0.001	r = -0.87* p < 0.001	r = -0.61* p = 0.001	r = -0.05 p = 0.80	r = -0.01 p = 0.97	r = -0.65* p < 0.001
MC	r = -0.33 p = 0.10	r = -0.84* p < 0.001	r =-0.44* p = 0.03	r = -0.82* p < 0.001	r = -0.34 p = 0.10	r = 0.19 p = 0.37	r = -0.59* p = 0.002

Table 2.8: Correlations of changes in reading speed with corresponding changes in near VA and in eye movement parameters between MON and FC and between MC and FC conditions.
*: significant correlation.

forward fixations (r = -0.87, $p < 0.001$), in fixation duration (r = -0.68, $p < 0.001$), ex-Gaussian τ (r = -0.65, $p < 0.001$) and the percentage of regressions (r = -0.61, p = 0.001).

The degree of improvement in reading speed in the MC as compared to the FC condition was strongly correlated with concurrent changes in the number of fixations (r = -0.84, $p < 0.001$) and in the percentage of regressions (r = -0.82, $p < 0.001$) and modestly correlated with concurrent changes in the ex-Gaussian parameter τ (r = -0.59, p = 0.002) and fixation duration (r = -0.44, p = 0.03). Figure 2.19 illustrates the association of the improvement of reading speed with concurrent changes in eye movement parameters with MON correction.

Improvement in reading speed in the MC or MON conditions as compared to the FC condition correlated weakly with concurrent improvement in near visual acuity ($p > 0.10$; Fig. 2.20).

Both models were significant ($p < 0.001$) in accounting for both sets of difference scores (MC minus FC and MON minus FC) with the predictor variables accounting for 72 and 80% of the variance in reading speed improvement with MC correction and 78 and 79% of the variance in reading speed improvement with MON correction. Model 1 revealed that the reduction in fixation duration remained a significant predictor of the improvement in reading speed only in the MON condition and only marginally (B=-0.28, SE=0.26, p = 0.04), while not in MC condition (B=-0.11, SE=0.30, p = 0.39). Model 1 revealed that the reduction in the percentage of regressions was significant predictor of the improvement in reading speed in MC condition (B=-0.38, SE=1.41, p = 0.007) and in MON condition (B=-0.28, SE=1.39, p = 0.034). Ex-Gaussian τ was not a significant predictor in either condition (B=-0.13, SE=0.21, p = 0.296 and B=-0.19, SE=0.24, p = 0.232 respectively). Both models showed that the decrease of the number of fixations was the strongest predictor of the improvement in reading speed accounting for

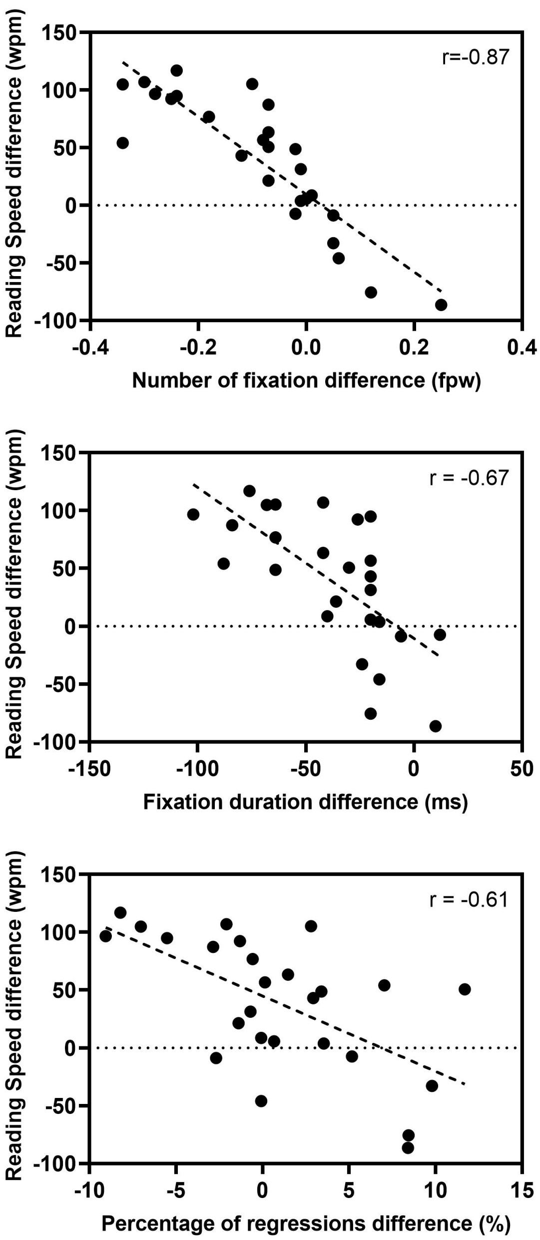


Figure 2.19: Associations of the change in reading speed with corresponding changes in number of fixations (upper panel), fixation duration (middle panel) and percentage of regressions (lower panel) between MON correction and FC condition.

as much as 71 and 74% of the variance in reading speed improvement with MC or MON correction, respectively.

2.10.7.3 *Effects of luminance*

Reading speed and eye movement parameters values at two luminance levels and with two CL corrections are demonstrated in Table 2.9.

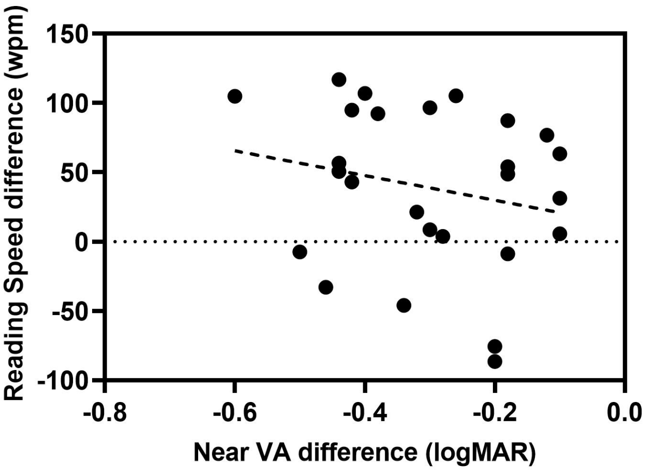


Figure 2.20: The association of change in reading speed with corresponding change in near VA between MON and FC.

The analysis showed a significant interaction between the modality of CL correction and luminance level (F(1,25) = 5.336, p = 0.029, η_p^2 = 0.176) on reading speed. Follow up simple main effects tests (one-way repeated measures ANOVA) revealed that reading speed improved significantly under high luminance levels with both MON (F(1,25)=15.62, p=0.001, η_p^2 = 0.375) and MC (F(1,25)=16.195, p<0.001, η_p^2 = 0.393) correction.

Interestingly, although reading speed was comparable between correction methods under high luminance (see Figure 2.15), reading speed was significantly higher using MON than MC at low luminance (F(1,25)=5.705, p=0.025, η_p^2 = 0.186, mean difference = 16.8 wpm, 95% CI, 2.3 to 31.2; Figure 2.21).

Table 2.9: Reading performance with two kinds of CLs in high and low luminance levels.

	High Luminance		**Low Luminance**	
Feature	MON	MC	MON	MC
Reading speed (wpm)	236.2 (51.9)	240.4 (68.7)	210.9 (54.8)	194.2 (67.4)
Fixation duration (ms)	234 (25)	234 (30)	272 (59)	291 (75)
Fixations per word	0.80 (0.12)	0.80 (0.15)	0.82 (0.15)	0.86 (0.20)
Regressions (%)	11.0 (7.5)	11.0 (7.1)	9.3 (5.7)	10.5 (6.2)
Blink rate	7.7 (12.1)	4.5 (10.0)	5.8 (6.7)	9.5 (9.1)
Ex-Gaussian μ (ms)	172 (19)	174 (29)	209 (54)	221 (57)
Ex-Gaussian τ (ms)	76 (25)	72 (29)	77 (32)	81 (46)

Abbreviations; MON: Monovision, MC: Multifocal.
All values are means (SD) with the exception of blink rate (median (IQR)).

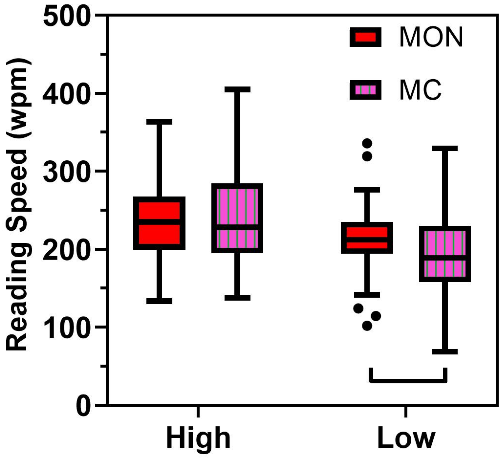


Figure 2.21: Reading speed values with monovision approach (MON), and multifocal contact lenses (MC) in high and low luminance. Whiskers represent 1.5 IQR.

High luminance was associated with less number of fixations (F(1,25) = 5.780, p = 0.024, η_p^2 = 0.188) and shorter ex-Gaussian parameter μ (F(1,25) = 23.019, p < 0.001, η_p^2 = 0.479).

The main effect of luminance was superseded by significant luminance by condition interactions for fixation duration (F(1,25) = 5.560, p = 0.025, η_p^2 = 0.185). A significant effect was found on fixation duration in both types of CLs (F(1,25)=16.425, p<0.001, η_p^2 = 0.387 for MON and F(1,25)=19.209, p<0.001, η_p^2 = 0.435 for MC).

Wilcoxon signed-rank test showed that luminance level elicited significant change in blink rate in MON condition (Z = -2.314, p = 0.021). In high luminance blink rate was 2.5 (95% CI, 0.5 to 4.5) greater than in low luminance. See Figures 2.22 and 2.23.

2.10.7.4 *Factors accounting for differences in reading speed between high and low luminance conditions*

As shown in Table 2.10, the change in reading speed due to luminance level (high minus low) correlated with corresponding change in fixation duration (MON: r = -0.61, p = 0.001, MC: r = -0.70, p < 0.001), with that of the number of fixations (MON: r = -0.53, p = 0.005, MC: r = -0.70, p < 0.001), of ex-Gaussian parameter μ (MON: r = -0.47, p = 0.02, MC: r = -0.62, p = 0.001). The correlation between change in reading speed and change in ex-Gaussian parameter τ was significant only in MC correction (r = -0.49, p = 0.01; see Figure 2.24).

A hierarchical, linear multiple regression model was computed in order to evaluate the joint contribution of change in eye fixation parameters to the decrease of reading speed due to low luminance. Due to collinearity concerns, fixation duration and ex-Gaussian parameter μ were

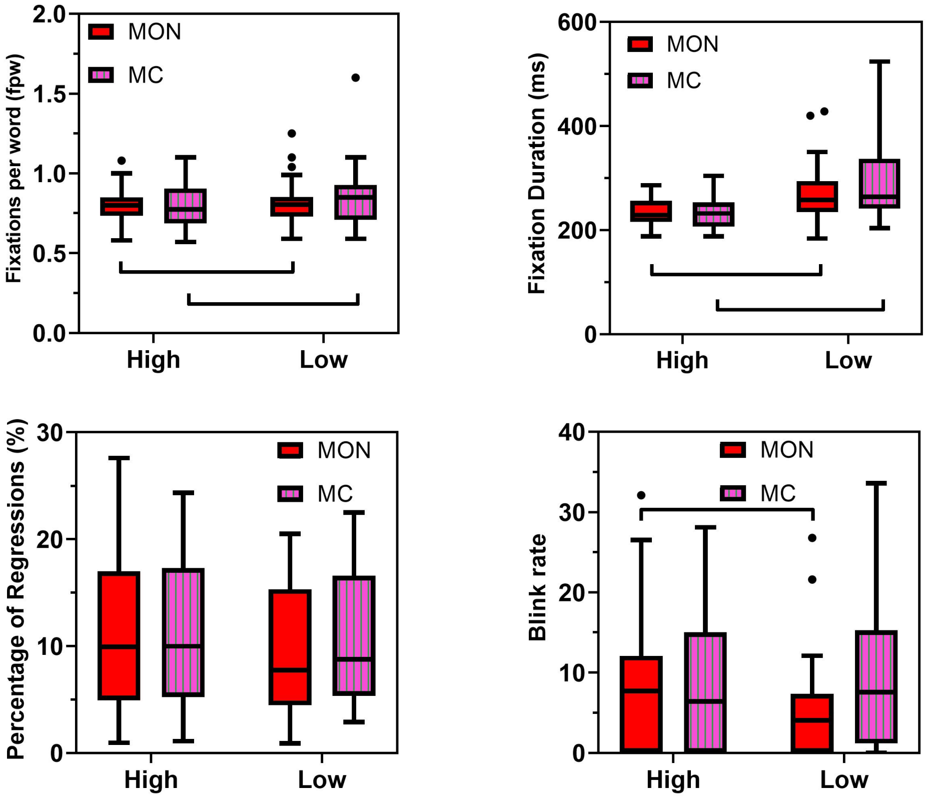


Figure 2.22: Eye fixation parameters (number of forward fixations, fixation duration, percentage of regressions and blink rate) with monovision approach (MON) and multifocal contact lenses (MC) in high and low luminance. Whiskers represent 1.5 IQR.

	Fixation Duration	**Fixations**	**Reg.**	**Blink rate**	μ	τ
MON	r = -0.61* p = 0.001	r =-0.53* p = 0.005	r = -0.30 p = 0.14	r = 0.02 p = 0.92	r = -0.47* p = 0.02	r = -0.28 p = 0.17
MC	r = -0.70* p < 0.001	r = -0.70* p < 0.001	r = -0.37 p = 0.07	r = -0.33 p = 0.11	r = -0.62* p = 0.001	r = -0.49* p = 0.01

Table 2.10: Correlations of changes in reading speed with corresponding changes in eye movement parameters between high and low luminance in MON and MC conditions. *: significant correlation.

not entered together in the regression model. The difference in the number of fixation made was entered in the first step and the difference in fixation duration was entered in the second step.

The model was significant ($p < 0.001$) in both conditions (MC, MON) with the predictor variables accounting for 67% of the variance in reading speed decrease in MC condition and 65% of the variance in reading speed decrease in MON condition. Inspection of regression coefficients revealed significant contributions by both the increase in the number of fixations

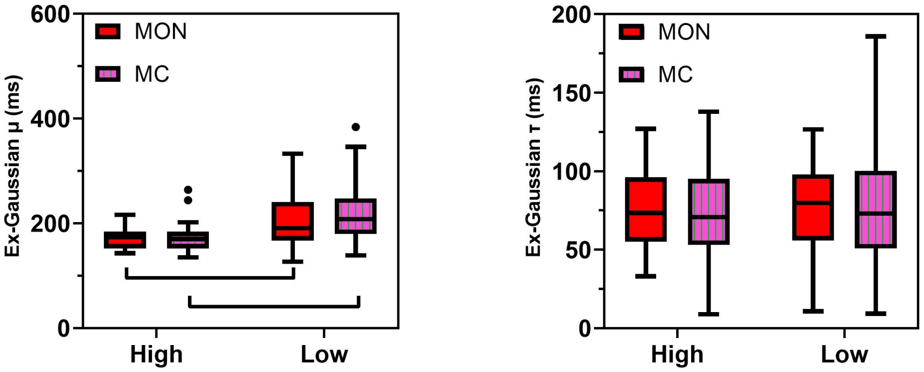


Figure 2.23: Ex-Gaussian parameters μ and τ with monovision approach (MON) and multifocal contact lenses (MC) in high and low luminance. Whiskers represent 1.5 IQR.

(MC: B=-0.483, SE=55.456, $p = 0.01$, MON: B=-0.509, SE=64.346, $p < 0.01$) and the increase in fixation duration (MC: B=-0.479, SE=0.118, $p = 0.02$, MON: B=-0.630, SE=0.081, $p < 0.01$).

2.10.8 *Discussion*

The main aim of the study was to evaluate reading performance in a presbyopic population corrected only for far with single vision CLs and also for near with monovision and multifocal contact lens correction, by recording eye movements during silent text reading.

Regarding the first aim of the study, results showed that both near visual acuity and reading speed improved significantly in both CL modalities compared to single vision contact lens, correction for far (FC condition). On the other hand, while VA in MC condition was found worse compared to best-corrected near vision (CLs combined with readers, NC condition), this was not the case for reading speed or any of the eye movement, apart from the percentage of regressions. Moreover, although monovision correction (MON condition) resulted in better VA levels at near compared to multifocal correction, this was also not reflected in any reading performance parameters.

Among eye movement parameters, fixation duration was found mainly improved with multifocal compared to single vision correction for far, followed by the number of fixations. No changes were observed in the parameter τ and only between NC and correction with CLs in the number of regressions, parameters that are linked mainly to cognitive factors [11]. The improvement of reading speed with the use of multifocal CLs compared to reading with

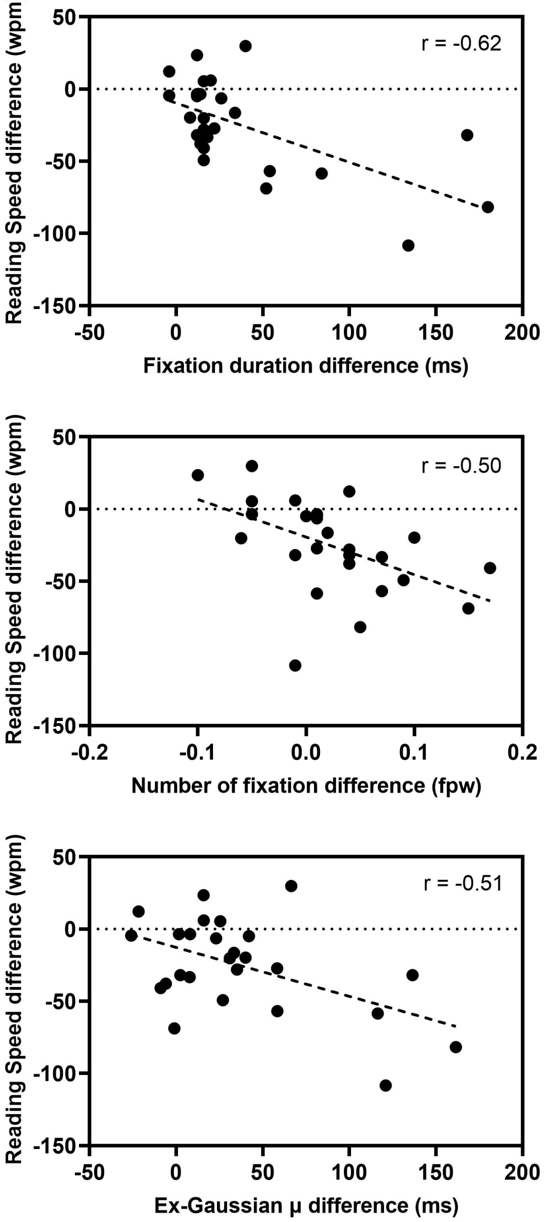


Figure 2.24: Associations of the change in reading speed with corresponding changes in fixation duration (upper panel), number of fixations (middle panel) and ex-Gaussian μ (lower panel) between the two luminance conditions (low minus high) with MON correction.

single vision correction for far, as well as the decrease of fixation duration and the number of fixations, was also observed in a recent study [121].

Regarding the second aim, the change in reading speed due to correction with CLs was mainly correlated with concurrent changes in the number of fixations, fixation duration and percentage of regressions. It is important to note that no correlation was found between the changes in visual acuity and improvements in reading speed. The lack of correlation between near VA and reading performance is not surprising and confirms previous results (for example, [97, 146]). Reading is known to be facilitated by parafoveal visual information [147–149] and it has been found to better correlate with extrafoveal visual performance and the crowding effect.

More specifically, the results in this study stress that the observed improvement in VA with multifocal correction cannot predict any enhancement in patients' reading performance, and this is frequently reported by contact lens users in clinical practice.

Effects of luminance levels also revealed interesting findings. Thus, low luminance negatively impacted reading speed in both MON and MC condition, although in greater degree in the MC vs MON condition. Low luminance was also associated with higher number of fixations, longer fixation duration and ex-Gaussian parameter μ for both modalities of CLs tested. Furthermore, fixation duration was found statistically significantly lower in MON than in MC condition in low luminance. No statistically significant effect of luminance on the percentage of regressions and on ex-Gaussian parameter τ was observed. Blink rate was significantly affected by the low luminance level only in MON condition.

The difference that was observed in reading speed due to low luminance was correlated with the differences in the number of fixations, in fixation duration and in ex-Gaussian parameter μ. A hierarchical, linear multiple regression model showed that the differences in the number of fixations and in fixation duration account for about 66% of the variance in reading speed decrease. In a recent study, saccade amplitude, fixation duration and regressive saccades together accounted for 90% of the variance in reading speed [150]. However it was not reading speed change due to luminance that was investigated, but reading speed under various background luminance and contrast levels.

2.11 STUDY IV – EFFECT OF COMPREHENSION

2.11.1 *Aim of the study*

The main aim of the study is to evaluate eye movement parameters during silent text reading with two different sets of guidelines. In the first condition, the participants were asked to read the text in a comfortable pace and in the second condition they were asked to read the sentences comprehensively. Thus, the effect of comprehension is evaluated. The percentage of regressions is known to be linked to comprehension and ex-Gaussian τ is linked to cognitive processes, so they are expected to differ between the two conditions.

A secondary aim is to find the eye movement parameters that account for the change in reading speed between the two conditions.

2.11.2 *Participants*

The present study involves analyses of additional recordings obtained from the group of Study III (see Table A.3). All trials were performed with the patients best corrected for near i.e wearing disposable single vision CLs (best corrected for far) and readers on top of the lenses (near correction).

2.11.3 *Reading material*

Three texts from the Greek version of the IReST [123] were used in a randomized order (see section 2.5. A fourth text was used for familiarisation with the procedure.

2.11.4 *Experimental procedure*

During the first visit of Study III, following a familiarization trial, participants were presented with two reading conditions. In the first trial the participants were asked to read the text silently in a comfortable pace (BASELINE condition). In the second trial they were asked to read the sentences comprehensively, as they would read a newspaper text to be able to answer questions regarding the meaning of the text afterwards (COMP condition) (Table 2.6).

2.11.5 *Data analysis*

Shapiro-Wilk normality test showed that reading speed, fixations per word and ex-Gaussian parameters τ and μ were normal distributions, while fixation duration, percentage of regressions and blink rate were not. Paired sample t-test was used for normal and Wilcoxon signed-rank test was used for non-normal distributions.

2.11.6 *Results*

2.11.6.1 *Differences between reading conditions*

Table 2.11 summarises the results of the study. Reading speed in the COMP condition was significantly lower than in the BASELINE condition (mean difference = -44.8 wpm, t(25) = -4.963, $p < 0.001$). Conversely, the following eye movement parameters were higher in the COMP condition: number of fixations per word (mean difference = 0.09wpm, t(25) = -5.399, $p < 0.001$) and percentage of regressions (mean difference = 3.4 %, Z = -3.213, p = 0.001), whereas the ex-Gaussian parameter τ was marginally significantly higher (mean difference = 10 ms, t(25) = 2.073, p = 0.049). The results are displayed in Figures 2.25, 2.26 and 2.27.

2.11.6.2 *Factors accounting for change in reading speed*

As shown in Table 2.12, the difference of reading speed between the two conditions was strongly correlated with the difference of the number of fixations per word (r = -0.866, $p < 0.001$) and modestly correlated with the differences of the percentage of regressions (r = -0.591, p = 0.001) and with the differences of ex-Gaussian parameter τ (r = -0.421, p = 0.032). These correlations are shown in Fig. 2.28.

Due to collinearity among the differences of number of fixations, percentage of regressions and ex-Gaussian parameter τ, a hierarchical, linear multiple regression model could not be computed. However, as displayed in the correlations table, the difference of the number of fixations alone is accounted for 74.9% of the variance of reading speed difference.

Table 2.11: Reading performance parameters in BASELINE and COMP conditions.

	Condition	
Feature	**BASELINE**	**COMP**
Reading speed (wpm)*	264.7 (66.0)	219.9 (50.3)
Fixation duration (ms)	221 (43)	223 (30)
Fixations per word*	0.77 (0.13)	0.86 (0.11)
Regressions (%)*	5.3 (10.7)	11.2 (8.2)
Blink rate	4.2 (3.8)	3.3 (4.5)
Ex-Gaussian μ (ms)	171 (27)	167 (27)
Ex-Gaussian τ (ms)*	63 (24)	74 (23)

Values are (mean [SD]) with the exception of fixation duration, regressions and blink rate (median [IQR]).
*: Features that exhibit significant differences.

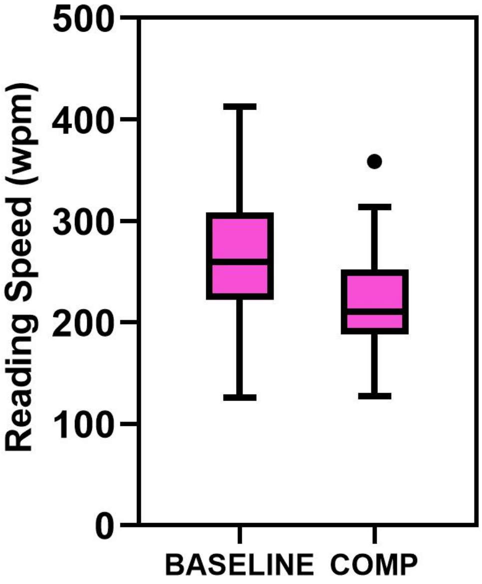


Figure 2.25: Reading speed values in the two conditions tested: BASELINE and COMP.

	Fixation Duration	**Fixations**	**Reg.**	**Blink rate**	μ	τ
Reading Speed	r = -0.12 p = 0.57	r =-0.87* p < 0.001	r = -0.59* p = 0.001	r = 0.04 p = 0.84	r = -0.05 p = 0.81	r = -0.42* p = 0.03

Table 2.12: Correlations of changes in reading speed with corresponding changes in eye movement parameters between BASELINE and COMP conditions. *: significant correlation.

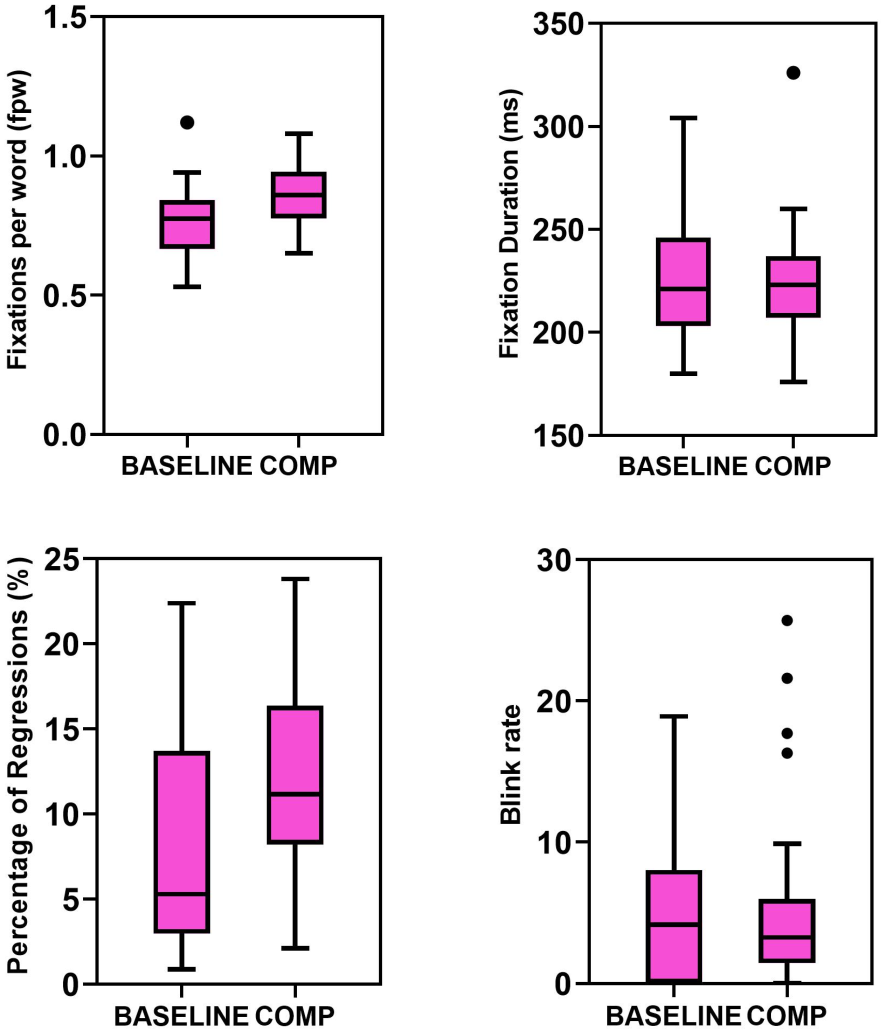


Figure 2.26: (Number of forward fixations (upper left), Fixation duration (upper right), Percentage of regressions (down left) and blink rate (down right) in the two conditions tested: BASELINE and COMP.

2.11.7 *Discussion*

Cognitive demands for text comprehension are reflected in various eye movement parameters, such as fixation duration, number of fixations and percentage of regressions [151]. Especially greater percentage of regressions is widely regarded as an indication of higher comprehension [49]. In the literature, text comprehension measures were shown to be affected by stimulus-related parameters (text type, word frequency, word length, lexical ambiguity etc) and specific instructions [152, 153].

In our study, we used similar texts and we changed the instructions to the participants. They were asked to read passages under two conditions: first, at a comfortable pace without

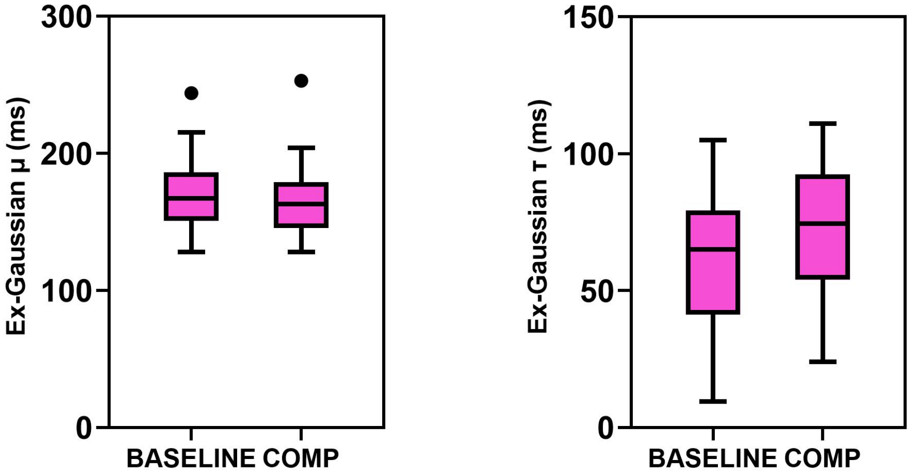


Figure 2.27: Ex-Gaussian μ (left) and τ (right) in the two conditions tested: BASELINE and COMP.

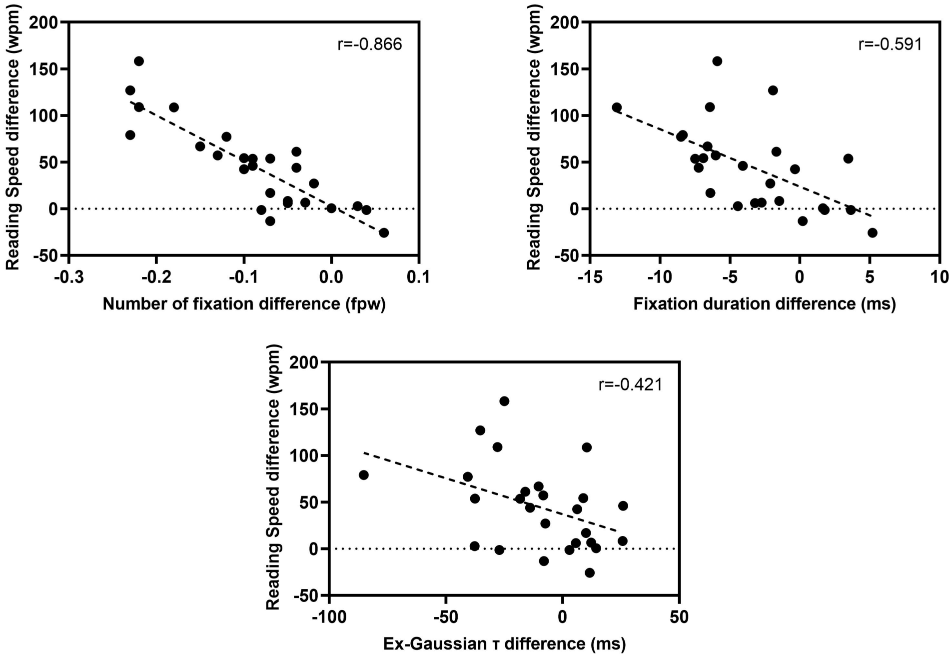


Figure 2.28: The association between change in reading speed between the two conditions and concurrent change in eye fixation parameters (number of fixations, percentage of regressions and ex-Gaussian τ).

emphasising the need to process text meaning and secondly, with a specific instruction for text comprehension in order to be able to respond to subsequent content questions. We found that the latter condition was associated with considerably slower reading speed, higher number of fixations, greater percentage of regressions and higher ex-Gaussian parameter τ. Importantly, the reduction in reading speed was largely accounted for by concurrent increase in the number of fixations.

These findings are in close agreement with Strukelj and Niehorster (2018) who employed very similar text reading conditions. They also reported reduced reading speed, greater average saccade amplitude and a higher percentage of long regressions to previous parts of the text and not on the current line [153] (they did not perform ex-Gaussian analyses of fixation duration distributions). In another study, slower reading speed, accompanied by higher fixation duration, number of fixations and ex-Gaussian parameters μ and τ were found during sentence reading for comprehension as compared to topic scanning [152]. In a study focusing on the impact of text difficulty during reading for comprehension, this parameter significantly affected reading time, probability of a regressive saccade, number of fixations and fixation duration. Moreoever, change in reading speed with text difficulty was primarily accounted for by corresponding change in the number of fixations rather than change in fixation duration [154].

To summarize, there is general agreement that reduced reading speed when reading for comprehension is accompanied by higher frequency of regressive eye movements, which suggests an increased tendency to reread previous words or even, initial portions of the text. Most of the studies also show that there is an increase of the number of forward fixations, reflecting a tendency to fixate on as many words as possible in order to process all or nearly all lexical/semantic elements of the passage which could be the topic of subsequent comprehension questions. Increased fixation duration is not a consistent finding across studies. In our study, fixation duration did not show a statistically significant change, however ex-Gaussian parameter τ did increase, indicating that there was an increase of fixations with high duration, without an increase of the mean value of fixation duration. This may reflect the need to fixate more on content words that provide syntactic cues, compared to small, functional words.

3

GENERAL DISCUSSION

The factors that affect reading performance can be divided into three categories: optical, retinal and cognitive. For example, low luminance, low contrast, small print size and narrowing of the pupil, increased opacity of the lens of the eye and loss of its elasticity due to ageing, are optical factors that affect reading behavior. Loss of photoreceptors and reduction of axons in the optic nerve because of ageing and abnormalities of the retinal pigment epithelium and neovasculararity because of macular diseases, such as AMD, are retinal/neural factors. Cognitive factors range from lexical knowledge (vocabulary), lexical retrieval, naming capacity and reading experience (which are in turn related to demographic characteristics such as age, gender, and education level) to stimulus characteristics such as word frequency, text complexity etc.

The scientific question that rises is whether we can distinguish the category of the effect by just the eye movement behavior evaluation. Are there distinct modes of influence of lower (optical and retinal) and higher (cognitive) level factors on eye movements?

A difficulty in this quest is the fact that some optical or retinal factors could affect vision to such an extent that the reader could not even identify letters and words that they are supposed to read, thus producing a higher level, cognitive, problem. For example, low mesopic luminance level may significantly disrupt visual processing and impair word recognition increasing cognitive effort (e.g. in guessing word identity from text context). Furthermore, some more general factors, such as age, cause both optical/retinal and cognitive changes.

In our study, AMD and anti-VEGF treatment were expected to mainly cause retinal changes in reading performance, presbyopia correction and luminance were expected to cause optical changes, whereas reading for comprehension was expected to affect cognitive factors. The present work took advantage of the explanatory power provided by ex-Gaussian analyses of eye movement parameters to help distinguish between the roles of low and high-level factors during text reading.

As explained in Section 2.7, ex-Gaussian distribution is a convolution of a normal and exponential distribution [124, 125] and it has been used for many years in the analysis of response time distributions [124–126]. Ex-Gaussian analysis uses three parameters that correspond to i) the mean (μ) and ii) the standard deviation (SD) (σ) of the Gaussian distribution and iii) τ, which reflects the mean and the standard deviation of the exponential component.

When initially introduced the ex-Gaussian analysis was linked to a processing model wherein each ex- Gaussian parameter reflected a distinct process jointly accounting for observed reaction times, one with normally distributed times and one with exponentially distributed times [155]. This approach was later challenged by Matzke D and Wagenmakers E-J (2009) using computational methods [141]. More recent studies assessing parameters during text reading have provided new evidence on the dissociation between μ and τ parameters consistent with the view that there may indeed be two processes contributing to the location and skew of distributions of eye fixations in reading [156]. Objections are still being raised though [157, 158].

Thus, word frequency affects both μ and τ [58], lexical predictability [60], lexical ambiguity [61], visual contrast [62], and the position of the eyes within the fixated word [59] affect only μ, while reading in a foreign language affects only τ, as long as both native and the foreign language are alphabetic [159].

Based on these results and the dissociation between μ and τ parameters, Staub and Benatar (2013) proposed that there are two distinct processes, processing difficulty and processing disruption, that influence the location and the skew of the fixation duration distribution respectively, and this is reflected in parameters μ and τ. They propose that a factor affects τ when it increases the likelihood of processing disruption instead of just causing processing difficulty. Physiological data seem to support this approach. Henderson JM et al. (2014) showed that differences in μ in a reading task were correlated with differences in the structural anatomy of the primary visual cortex, where early visual processing occurs [160] while Henderson JM et al. (2017) showed that τ is correlated with reading-related activity in frontal and parietal regions associated with attentional control, rather than occipital regions associated with perceptual processing [161].

This distinction in two stages of cognitive processing shares common ground with the distinction between low and high level factors addressed in the present work. Thus, τ was increased during reading for comprehension in agreement with the notion that this parameter reflects cognitive process involved in text reading. As shown previously, reading for comprehension also affects the percentage of regressions [154] and the number of forward fixations but not fixation duration, indicating that comprehensive reading demands more forward and regressive fixations without necessarily prolonging each fixation. However, when word identification is disrupted due to AMD, causing a more global "processing disruption", reading speed and all oculomotor parameters are negatively affected (including τ and μ) reflecting the increased cognitive burden during text reading incurred by both retinal and neuronal impairment. Three-month anti-VEGF treatment changed significantly only the number of fixations, a change which the improvement in reading speed was primarily reflected on.

On the other hand, low luminance, being a strictly optical factor, affects μ but not τ. The same applies to presbyopia correction which facilitates functional vision from an optical perspective. The link between optical factors and μ is in line with the results of White and Staub (2012) on visual contrast [62]. Low luminance and presbyopia correction also affected both the number of fixations and fixation duration. These three parameters predicted well the variance of reading speed change due to luminance or presbyopia correction.

Table 3.1 summarises all significant differences in the parameters that were investigated, under the influence of various factors.

The present work has shown that there may be indeed two cognitive processes that are projected in fixation duration distribution and ex-Gaussian parameters could distinguish these processes. However, apart from the fixation duration distribution, eye movement parameters during reading seem to be also subject to certain changes. This is a work in progress. First of all, studies of specifically manipulated changes in certain factors have to be performed. Factors, such as contrast, print size, age, the person's vocabulary and education level, could be investigated. Second, machine learning approaches could be tested in order to predict changes in different categories of factors, especially to differentiate eye diseases (presbyopia, cataract macular diseases, nystagmus) or neurological/ developmental/ psychiatric conditions (Parkinson's disease, dementia, multiple sclerosis, depression, bipolar disorder, schizophrenia, dyslexia).

Table 3.1: Reading Speed and eye movement parameters in relation to various factors

Feature	**AMD**	**anti-VEGF**	**NC**	**MON**	**MC**	**Low Lum**	**Comp**
RS	⇓	⇑	⇑	⇑	⇑	⇓	⇓
Fix dur	⇑	-	⇓	⇓	⇓	⇑	-
Fpw	⇑	⇓	⇓	⇓	-	⇑	⇑
Regressions	⇑	-	⇓	-	-	-	⇑
Ex-Gaussian μ	⇑	-	⇓	⇓	⇓	⇑	-
Ex-Gaussian τ	⇑	-	-	-	-	-	⇑
Blink rate	N/A	N/A	⇓	-	-	⇓	-

Abbreviations: RS: reading speed, Fix dur: fixation duration, fpw: fixations per word, NC: near corrected compared to FC, MON: monovision compared to FC, MC: multifocal compared to FC, Low Lum: low luminance compared to high luminance, Comp: comprehensive reading.

⇑: statistically significant increase, ⇓: statistically significant decrease, -: no statistically significant difference, N/A: not applicable.

A

APPENDIX

Table A.1: Demographics of the participants of Study I.

Participant	**Gender**	**Age (years)**	**Education level (years)**	**Number of words**	**Number of pseudowords**
1	F	72	12	104	41
2	M	68	6	53	26
3	M	61	16	89	50
4	M	65	8	92	45
5	F	66	6	80	26
6	M	59	9	64	26
7	M	57	16	85	50
8	M	68	6	67	26
9	F	65	6	90	44
10	M	70	9	70	34
11	M	75	16	62	28
12	M	64	12	75	39
13	F	56	16	93	41
14	M	70	8	95	48
15	F	69	16	91	45
16	M	71	16	90	42
17	F	61	12	89	45
18	M	56	20	94	45
19	F	63	12	62	36
20	F	64	12	82	47

Table A.2: Demographics of the participants of Study II.

Participant	Gender	Age (years)	Education level (years)	Number of words	Number of pseudowords
1	F	77	3	69	33
2	F	78	12	64	29
3	M	67	6	59	34
4*	M	67	6	82	36
5	F	74	12	81	43
6	F	67	16	81	27
7	F	77	6	54	29
8	F	52	3	69	42
9	F	76	6	50	29
10	M	59	12	99	56
11	M	67	8	75	30
12	M	67	6	64	29
13	M	78	16	57	30
14	M	70	18	82	37
15	F	73	6	54	16
16	F	80	8	60	25
17*	F	68	12	84	44
18*	F	70	8	59	28
19	F	72	6	69	27
20*	M	69	6	74	38

Table A.3: Demographics of the participants of Study III.

Participant	Gender	Age (years)	Near Add (D)	Words	Pseudowords
1	M	49	1.75	124	64
2	F	50	2.00	96	48
3	F	53	2.00	94	41
4*	F	49	1.50	84	44
5	M	49	1.50	94	51
6	M	57	2.00	94	45
7	M	49	1.50	103	51
8	F	53	1.50	102	44
9	F	50	2.00	97	55
10	M	55	2.00	106	44
11	M	49	1.50	82	49
12	M	53	1.50	109	52
13	F	54	2.00	90	47
14	M	46	1.50	100	46
15	F	53	2.00	92	47
16*	M	43	0.50	110	37
17	F	61	2.00	89	48
18	F	56	2.00	97	40
19	F	49	1.50	98	59
20	F	55	2.00	82	53
21	F	54	2.00	96	53
22	F	63	2.00	79	33
23	M	67	2.00	75	39
24*	F	44	0.50	95	60
25	M	49	1.50	87	41
26	F	52	1.50	83	44
27*	F	44	0.75	105	50
28	M	47	1.50	86	47
29	M	51	1.50	100	56
30	F	47	1.50	89	54

*: excluded participants

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