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1 2 3	Spatial attention and central crowding in primary open angle glaucoma							
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ABSTRACT

Clinical relevance: Measuring the impact of spatial attention on signal detection in damaged
parts of the visual field can be a useful tool for clinicians in ophthalmology.

Background: Studies on letter perception have shown that glaucoma exacerbates difficulties to detect a target within flankers (crowding) in parafoveal vision. A target can be missed because it is not seen or because attention was not focused at that location. This prospective study evaluates the contribution of spatial pre-cueing on target detection.

Method: 15 patients and 15 age-matched controls were presented with letters displayed for 200ms. Participants were asked to identify the orientation of the target letter T in two conditions: an isolated letter (uncrowded condition) and a letter with two flankers (crowded condition). The spacing between target and flankers was manipulated. The stimuli were randomly displayed at the fovea and at the parafovea at 5° left or right of fixation. A spatial cue preceded the stimuli in 50% of the trials. When present, the cue always signaled the correct location of the target.

46 **Results:** Pre-cueing the spatial location of the target significantly improved performance for 47 both foveal and parafoveal presentations in patients but not in controls who were at ceiling 48 level. Unlike controls, patients exhibited an effect of crowding at the fovea with a higher 49 accuracy for the isolated target than for the target flanked by two letters with no spacing 50 between the elements.

51 Conclusion: Higher susceptibility to central crowding supports data showing abnormal foveal 52 vision in glaucoma. Exogenous orienting of attention facilitates perception in parts of the 53 visual field with reduced sensitivity.

- 54
- 55
- 56 Keywords: glaucoma, spatial attention, crowding

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58 INTRODUCTION

Glaucoma is an ocular pathology characterized by progressive retinal ganglion cell 59 loss associated with visual field defect. The classical view of vision deficit in glaucoma is a 60 visual field defect that is initially restricted to the periphery with minimal impact on central 61 vision. However, studies using optical coherence tomography (OCT) have reported 62 abnormalities in the macula, the central part of the visual field, at all stages of the disease.¹ 63 Furthermore, evidence from experimental studies shows that some patients with glaucoma 64 exhibit deficits in central vision-dependent activities such as reading and face recognition.²⁻⁹ 65 Slower reading and deficits in face recognition have been accounted for by impaired eye 66 movements and/or reduced contrast sensitivity. ^{4, 6, 7, 10} Other explanations have emerged more 67 recently. It has been suggested that reading difficulties in glaucoma might result from an 68 increase in receptive field size, which may in turn exacerbate a crowding effect in parafoveal 69 vision.³ Visual crowding refers to the deterioration of performance when the feature to be 70 recognized (letter, object...) is near other stimuli.¹¹ In line with this account. Shamsi et al.¹² 71 reported that the critical spacing between target and flanker letters to escape crowding was 72 73 larger in patients with glaucoma than in normally sighted age-matched controls in parafoveal vision. However, higher susceptibility to crowding in glaucoma does not seem to be limited to 74 parafoveal vision. Stievenard et al.¹³ investigated susceptibility to crowding in foveal vision 75 in glaucoma with faces as stimuli. They showed that patients were better at recognizing a 76 facial feature (the mouth) in isolation (uncrowded condition) than within the context of a face 77 (crowded condition), whilst age-matched controls exhibited a better performance in the 78 "mouth within a face" condition. 79

In addition to reduced contrast sensitivity, and possibly a higher susceptibility to central 80 crowding, Phu et al.¹⁴ demonstrated that another factor can modulate performance in 81 glaucoma. They investigated the extent to which minimized spatial uncertainty, through 82 attentional cueing, affects contrast sensitivity. In their study, contrast sensitivity was 83 measured at two different eccentricities $(9.5^{\circ} \text{ and } 17.5^{\circ})$ and with two sizes of spotlights: 84 Goldmann sizes III (0.43° in diameter) and V (1.72° in diameter). In each trial, the number 85 86 and location of the stimuli was verbally cued to the participants. The results showed that reducing uncertainty through verbal cueing improved sensitivity at locations with severe 87 88 visual field defects. Phu et al. used endogenous cueing in which attention is voluntary oriented to certain regions of the visual field through verbal instructions. A transient 89 90 exogenous spatial cueing was used in the present study. Exogenous attention is more

automatic than endogenous attention. It reflects situations in which attention is automatically 91 captured by a change in color, luminance or motion in the visual field. Studies in young 92 individuals have demonstrated that spatial pre-cueing, via an exogenous transient cue, 93 enhances spatial resolution at the attended location.¹⁵⁻¹⁶ For instance, Yeshurun and Rashal¹⁷ 94 found that the critical spacing between letters to escape crowding was shorter when attention 95 was oriented towards the spatial location of the letters via a pre-cue. The purpose of the 96 present study was to determine whether transient spatial pre-cueing enhances perceptual 97 performance in patients with glaucoma, and especially, whether target detection in a crowded 98 99 condition is facilitated when a cue indicates the spatial location of the stimulus.

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101 METHOD

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103 **Participants**

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Fifteen patients with a visual field defect due to primary open-angle glaucoma 105 106 participated, ranging from 40 to 81 years of age (mean age 64.6 years). Each patient underwent a complete ophthalmological examination including a visual field evaluation just 107 before the experiment. As central vision was tested, visual field sensitivity (expressed as the 108 Mean Deviation) was measured with a central 10-2 strategy on the Humphrey Field Analyzer 109 SITA Standard (HFA II, Carl Zeiss Medical, CA, USA). The visual fields were classified 110 according to HPA classification. ¹⁸ Visual acuity and contrast sensitivity were measured using 111 the Freiburg Vision Test. 112

Fifteen age-matched controls ranging from 53 to 78 years of age (mean age: 64.5 113 years) were recruited among the patients' relatives and the staff of the department of 114 115 ophthalmology. Inclusion criteria for both patients and controls were the following: no history of neurological and/or psychiatric disease, no ocular disease other than glaucoma for patients, 116 and no family history of glaucoma for controls. Cataract was an exclusion criterion. Age-117 matched controls received an ophthalmological examination prior to inclusion to rule out any 118 sign of glaucoma. All controls had a normal intra-ocular pression, no anomaly of the optic 119 nerve at the fundus examination, a normal visual field and a normal OCT. All participants 120 were asked to come with their usual optical correction. Patients and controls were tested 121 monocularly. Controls were tested on their preferred eye. For patients with bilateral 122 glaucoma, the tested eye was the one that met the inclusion criteria: a significant deficit in the 123

mean deviation on the 10-2 visual field test and an acuity equal to or better than 0.1 logMar. If
both eyes were impaired at the 10-2, the better eye was chosen.

The study was approved by the ethics committee for behavioral sciences of the University of Lille. In accordance with the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants.

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130 Stimuli and apparatus

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The stimuli were uppercase letters, in Arial font, presented on a 15-inch DELL computer screen. The target was the letter T, either oriented upright or inverted. The flankers were the letter H positioned left and right of the target. The angular size of the letters was 0.4° in height and 0.3° in width, at a viewing distance of 57 cm with the head fixed by a chin rest. The stimuli were displayed in black (2.8 cd/m2) on a light gray (113 cd/m2) background. Based on Yeshurun and Rashal study ¹⁷ a high contrast large cue was used : a yellow line segment (200 cd/m2) covering 0.5° of visual angle and appearing 0.5° above the stimuli.

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140 **Procedure**

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The participants were tested in a dimply illuminated room with light coming from the edges 142 of venetian blind of the window. The lighting of the room was measured at 60 Lux 143 (Lightmeter Multimetrix LM76, Chauvin Arnoux, France). Each trial started with a black 144 central fixation cross (0.5°) displayed for 500ms. After a 500 ms blank gap, a yellow line 145 segment cue was displayed for 50 ms randomly in 50% of the trials. When present, the cue 146 always indicated the correct target location. The stimuli were displayed for 200 ms randomly 147 at three possible spatial locations (central 0°, at 5° left, at 5° right of fixation center to center) 148 149 immediately after the cue. The paradigm is illustrated in Figure 1. There was no control of fixation as the fixation cross disappeared for 500ms before the presentation of the stimulus to 150 151 avoid forward masking of a central stimulus by the fixation cross. The fixation cross also disappeared for 500ms before the presentation of parafoveal stimuli to avoid the fixation 152 153 marker serving as a cue that the stimulus would appear in the parafoveal field.

154 Crowding was assessed by manipulating the spacing between target and flankers and 155 by comparing performance between the crowded conditions and a baseline uncrowded 156 condition (an isolated T). In the crowded conditions, the target letter T was flanked by 2 Hs. 157 There were three spacings between target and flankers at 5° eccentricity. According to 158 Bouma's law, the critical spacing for identification of small letters is roughly half the 159 eccentricity. ¹¹ The three chosen spacings were 2° (below the critical spacing), 2.5° and 3° 160 edge-to-edge. For central stimuli, the spacings between target and flankers were 0 (no 161 spacing) and 0.3° (corresponding to the width of a capital letter).

The target letter T, either isolated or flanked, was randomly presented upright in 50% of the trials and inverted in the other 50%. Participants were asked to decide whether the letter T was upright or inverted regardless of the presence of flankers. The response was given using the arrow keys of the computer's keyboard (pointing top for upright and bottom for inverted). The inter-trial interval was set at 1500ms after response.

167 The spacing conditions (three at 5° left, 3 at 5° right of fixation and two for central stimuli + the isolated target), the cue (present/absent), the spatial locations of the stimuli and 168 the orientation of the T were randomly presented. The experimental session was composed of 169 440 trials determined by 120 central trials (isolated T and 2 spacing conditions X 2 cueing 170 171 conditions X 20 repetitions) and 320 parafoveal trials (isolated T and 3 spacing conditions X 2 cueing conditions X 2 spatial locations X 20 repetitions). The 20 repetitions were 10 upright 172 Ts and 10 inverted Ts. A pause was proposed after 110, 220 and 330 trials. Participants 173 resumed the experiment by pressing the space bar of the keyboard. The adaptation to the 174 ambient luminance varied between 5-7 minutes. It was followed by a training session of 20 175 trials to familiarize the participants with the exposure time of the letters, the experimental 176 session lasted 20-25 minutes depending on the response time and pauses of participants. 177

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[Figure 1 about here]

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181 STATISTICAL ANALYSIS

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As the number of spacing conditions was different for parafoveal and central presentations, separate ANOVAs were performed. As the percentage of correct responses is not linear accuracy was converted to a Z-score for each group. Analyses were carried out using Systat 8 software (Systat Software, Inc. San Jose, California). Although the upright T was detected more accurately than the inverted T the orientation of the T was not included as factor in the analysis since the advantage for the upright T was observed in both groups. Due to large inter-individual variability (500 to 3000 ms) response times were not analysed. The 190 group was the between-subject factor. The spatial location of the stimuli, the presence of the 191 cue and the spacing between target and flankers were the within-subject factors. The relations 192 between clinical data (contrast sensitivity, visual field defect), age and amplitude of crowding 193 were assessed in the patient group using a Spearman correlation analysis. The relations 194 between clinical data and the benefit induced by spatial cueing, computed as accuracy for the 195 cued condition minus accuracy for the uncued condition were also tested.

196

197 **RESULTS**

The 10-2 visual fields of patients are displayed in Figure. The characteristics of the two populations are summarized in Table 1. Patients and age-matched controls did not differ significantly in age (T(28) = 0.019, p = 0.98) but contrast sensitivity was significantly lower in patients than in controls (1.63 vs. 1.78; T(28) = 2.25, p = .032).

202

[Figure 2 and Table 1 about here]

203 Central presentation

On average, accuracy was higher in controls than in patients (by 13.5% F(1, 28) = 12.12, p = .002).

206 Spatial attention

The effect of pre-cueing was not statistically significant (F(1, 28) = 0.7, p= 0.41) but group interacted significantly with cueing (F(1, 28) = 4.4, p = .05). As can be seen in Figure 3A, the benefit of pre-cueing resulted from the patient's group (F(1, 14) = 9.7, p = .008) and more specifically for the isolated T (T(14) = 2.75, <.016) and for the large spacing (0.3°: T(14) = 4.11, p<.006). The effect of cueing was not significant in the control group (F(1, 14) = 1.85, p = 0.19).

213 Crowding

There was no main effect of crowding (F (2, 56) = 1.56, p = 0.21) but crowding interacted significantly with group (F(2, 56) = 6.48, p = .003). The effect of crowding mainly resulted from the patient's group (F(2, 28) = 11.58, p = .001). In patients, accuracy was higher in the uncrowded condition (isolated T) than in both crowded conditions (spacing 0.3° : T(14) = 2.42, p = .02 and no spacing: T(14) = 4.01, p = .001). There was no significant effect of crowding in age-matched controls (F(1, 14) = 3.06, p = .063). The effect of crowding was found in both cued and uncued conditions in patients (see Figure 3A). There was nosignificant interaction between cueing and crowding.

The magnitude of crowding in each participant is presented in Figure 4 and averaged over cue and no cue. Figure 4 shows that 12/15 patients exhibited a better performance with the isolated T than in the crowded conditions. P2 was at ceiling level in both crowded and uncrowded conditions and P11 and P15 did not exhibit an advantage in the uncrowded condition.

227

[Figures 3A and 3B about here]

228

229 **Parafoveal presentation**

No significant main effect of spatial location of the target was observed (left 88.8% vs. right: 84.8% F(1, 28) = 1.33, p = 0.25), nor was there any significant interaction involving this variable. Results are presented in Figure 3B, averaged over spatial location. On average, accuracy was higher in controls than in patients (93.6% vs. 80.1% F(1, 28) = 11.09, p = .002).

234 Spatial attention

The main effect of cueing was not significant (F(1, 28) <1) and cueing did not interact significantly with group (F(2, 28) = 1.52, p = 0.22). However, Figure 3B shows that cueing improved performance in patients (T(14) = 8.89, p<.010). The benefit of cueing was significant for the small spacing (2°: T (14) = 2.84, p<0.13) and the large spacing (3°: T(14= 2.17, p<.047 but not for the intermediate spacing 2.5° (T(14) = 1.5, p = 0.16). There was also a significant benefit of cueing for controls only at the larger spacing (3°: T(14) = 2.5, p<.023).

On average the benefit of parafoveal cueing was larger (cueing advantage: 9.68%) in patients with a visual field defect at a severe stage (MD: -18 to -23) than in patients with a visual field defect at an early or moderate stage (MD: -2 to -12) (cueing advantage 5.79%) according to the HPA classification. ¹⁸ The difference in cueing benefit for the two subgroups (moderate/severe visual field defect) was significant (F(1, 13) = 5.66, p<.033).

246 *Crowding*

No main effect of spacing was observed (F(3, 84) = 0.32, p< 0.81). Although performance was better with the isolated T than in the crowded conditions in the patients'

- group (see Figure 3B), no significant effect of spacing was observed in this group (F (3, 42) =
- 250 0.99, p = 0.40) or in the control group (F (3, 42) = 0.69, p = 0.46). There was no significant 251 interaction between cueing and spacing between elements.
- 252

[Figure 4]

253 Correlations

In the patient group the relations between the magnitude of crowding (defined as the 254 percentage of correct responses with the isolated T minus the percentage of correct responses 255 with the crowded T in the no spacing condition for central presentation) and age, contrast 256 sensitivity, acuity and mean deviation were tested. No significant correlations were observed 257 between the magnitude of crowding and age (R = .161, p = .564), visual acuity (R = .247, p =258 .374), contrast sensitivity (R = -.250, p = .368) and mean deviation (R = .0614, p = .828). No 259 significant correlation was found in central presentations between the benefit of cueing and 260 contrast sensitivity (R = .220, p = .429), visual acuity (R = .0362, p = .898) and mean 261 deviation (R = .802, p = .776), or in parafoveal presentations between the benefit of cueing 262 263 and contrast sensitivity (R = .182, p = .517), visual acuity (R = .189, p = .498) and mean deviation (R = .066, p = .814). 264

265 **DISCUSSION**

266 As spatial attention is one of the most important mechanisms for selecting relevant information and reacting automatically to salient peripheral signals it is important to 267 investigate how it modulates perception in people with visual field defect. Numerous 268 psychophysical studies on young and older healthy individuals have shown that directing 269 270 attention to a spatial location, via a peripheral pre-cue, improves perceptual performance in terms of accuracy, response times, contrast sensitivity and discriminability at that location.¹⁵⁻ 271 ¹⁷ Attention exogenously captured by a salient signal affects early stages of processing by 272 reducing external noise and boosting the gain of the neuronal responses to visual stimuli. ¹⁹⁻²⁰ 273 In the present study, visual pre-cuing improved spatial resolution and facilitated target 274 discrimination in glaucomatous patients in both foveal and parafoveal vision. Pre-cueing did 275 276 not affect the performance of age-matched controls whose performance was at ceiling level for both foveal and parafoveal presentations suggesting that the task was too easy for 277 278 normally sighted participants. A significant benefit of cueing was observed at the largest spacing in parafoveal vision in controls likely because increasing spacing increased 279

eccentricity. Consistent with Phu et al. ¹⁴ the benefit of cueing in parafoveal vision was greater in patients with a severe visual field defect than in patients at an early or moderate stage according to the HPA classification. Patients with cortical blindness are also known to benefit from spatial attention in their blind hemifield. For instance, with a predictive central cue Pedersini et al. ²¹ found significantly faster reaction times in valid trials (i.e., when the cue indicates the correct location of the target) in the sighted hemifield but also in the blind hemifield of patients with cortical blindness, despite a lack of awareness in this region.

In foveal presentations, the proximity of flankers deteriorated performance compared 287 288 to the isolated target and to target and flankers with a larger spacing. This crowding effect was observed in patients only. The lack of effect of crowding in central vision was expected in 289 controls, as sensitivity to visual crowding is usually observed in regions with lower spatial 290 resolution (i.e., in peripheral vision) in normally sighted individuals ¹² whilst little crowding is 291 reported in normal central/parafoveal vision.²²⁻²³ The crowding effect in foveal vision in 292 patients is consistent with previous results with faces as stimuli. ¹³ It is also consistent with 293 Kwon et al.³ Although they did not test the effect of crowding directly as they did not 294 manipulate the spacing between letters and there was no uncrowded condition, they found that 295 296 accuracy in reporting letters in central vision was lower in glaucoma patients than in controls. Shamsy et al. ¹² reported that glaucomatous damage is associated with increased crowding in 297 the parafoveal region (4°) relative to age-similar normal controls. No effect of crowding was 298 observed in parafoveal presentations in the present study although the tendency was present in 299 patients with a better performance for the isolated T (see Figure 3B). The better eye of 300 patients was tested in the present study whilst Shamsy et al. ¹² observed significantly larger 301 crowding in the eye with more severe glaucomatous damage compared with the better eye. 302

Although the differences were not statistically significant due to high inter-individual variability in patients, accuracy tended to be higher with the isolated T and with the large target-to-flanker distance than with the smaller target-to-flanker distances in the cueing condition in the parafoveal visual field. This result is consistent with Yeshurun and Rashal ¹⁷ who showed that transient attentional cueing reduces the effect of crowding.

No significant correlation between the magnitude of the crowding effect and clinical variables (contrast sensitivity and visual field defect) was observed likely because contrast sensitivity and visual field are measured at contrast threshold whilst the letters were highly above contrast threshold. However, contrast sensitivity of the tested eye was significantly lower in patients than in controls. Lower sensitivity in central vision might have modified the appearance of the crowded stimuli in patients, making the target difficult to discriminate. Indeed, when the flankers are too close to the target, the target remains visible, but its features
are confused with those of the flankers and observers perceive scrambled shapes. ²⁴⁻²⁵

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317 **Limitations**: There are several limitations to this research. First, studies investigating crowding usually measure a critical target-to-flanker spacing using a threshold technique. 318 Accuracy was measured with a limited number of target-to-flanker spacing conditions. 319 Second, owing to random presentations in three different spatial locations, central fixation 320 could not be measured because the fixation cross would have masked the foveal stimuli. A 321 322 blocked presentation of foveal and parafoveal stimuli with a control of fixation for peripheral presentation might have resulted in parafoveal crowding in patients. Third, the better eye was 323 tested in glaucomatous patients. Testing the worse eye, like Shamsy et al ¹² might have 324 resulted in parafoveal crowding in patients. Fourth, as saccade latencies are shorter in 325 normally sighted observers than in glaucoma²⁶⁻²⁷ the cue and the 200 ms duration of the 326 stimuli might have triggered a saccade in parafoveal vision and placed the stimulus in foveal 327 328 vision thus explaining the high accuracy in foveal and parafoveal presentations for normally sighted people. Finally, the patient group was heterogeneous in terms of visual field defect. 329

Conclusion: Reducing spatial uncertainty through exogenous visual cueing improved 330 performance in both foveal and parafoveal vision in glaucoma patients, without reducing 331 reliably the effect of central crowding. Cavanaugh et al ²⁸ showed that endogenous orienting 332 of spatial attention during training can accelerate restoration of discrimination performance at 333 two blind field locations in cortically blind patients. They suggested that damage to the visual 334 system may limit visual resources available for deployment of attention across the visual field 335 rendering the limited information processed noisy. By directing resources toward a single 336 location through spatial cueing, these limitations can be partially overcome and people may 337 thus benefit from training. Glaucoma is different from cortical blindness but evidence from 338 neuroimaging studies show that glaucomatous damage also induces anatomical and functional 339 cortical changes with a significant decrease of grey matter density in visual areas.²⁹⁻³⁰ 340

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432	FIGURE LEGENDS
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435	Fig.1. Schematic illustration and timing of the experimental paradigm for central and
436	parafoveal presentations with pre-cueing. The 50 ms cue was immediately followed by the
437	stimulus. When no cue was present, 50 ms were added to the 500 ms gap between fixation
438	and stimulus.
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440	Fig. 2. The 10-2 visual field of tested eye for each patient ordered as a function of the severity
441	of the visual field defect.
442	
443	Fig.3. Z-scores as a function of spacing conditions and cueing conditions in foveal vision (A)
444	and in parafoveal vision (B) in patients with glaucoma and healthy controls. Error bars
445	indicate the standard errors. Color dots correspond to individual observations.
446	
447	Fig.4. Z-scores averaged over cue/no cue for each crowding condition (isolated T, no spacing
448	HTH, spacing 0.3° H T H) in each of the 15 patients and the 15 controls for foveal
449	presentations.

Table 1. Clinical and demographic data for patients and controls. The patients are ordered as a function of the Mean Deviation (MD) of the visual field. MD is a statistical index used to determine the average difference in visual field sensitivity compared to the mean sensitivity of a normally sighted observer of the same age. Acuity is expressed in Logmar. CS = contrast sensitivity, RE = Right eye LE = Left eye.

Glaucoma	Age	Gender	CS	Acuity	MD	Tested eye
1	66	М	1.96	0.0	-2.15	RE
2	75	м	1.49	0.0	-3.23	LE
3	79	М	1.71	0.0	-4.53	LE
4	71	F	1.67	0.0	-4.85	LE
5	71	Μ	1.56	0.1	-5.46	LE
6	64	F	1.59	0.0	-6.13	LE
7	40	F	1.81	0.0	-6.16	RE
8	67	F	1.63	0.1	-8	RE
9	70	F	1.24	0.0	-8.88	RE
10	47	F	1.9	0.1	-11.34	RE
11	60	F	1.99	0.0	-12	RE
12	63	F	1.33	0.1	-18.43	RE
13	81	М	1.46	0.0	-18.51	RE
14	68	F	1.74	0.1	-22.8	LE
15	47	F	1.41	0.1	-23.8	LE
Controls	Age	Gender	CS	Aculty	Tested eye	
1	67	М	1.77	0.0	LE	
2	64	F	1.83	0.0	RE	
3	75	Μ	1.69	0.0	LE	
4	60	F	1.86	0.0	RE	
5	58	F	1.83	0.0	RE	
6	61	F	1.58	0.0	RE	
7	69	F	1.85	0.0	LE	
8	53	M	1.94	0.0	RE	
9	60	F	1.99	0.0	LE	
10	75	М	1.64	0.0	RE	
11	60	Μ	1.89	0.0	RE	
12	67	Μ	1.88	0.0	RE	
13	78	Μ	1.75	0.1	RE	
14	60	F	1.84	0.0	LE	
15	61	F	1.47	0.0	LE	

458 Figure 1





465 Figure 2







