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Title: Effect of Cognitive Demand on Functional Visual Field Performance in Senior Drivers with Glaucoma

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- 10 Keywords: glaucoma, cognition, psychomotor, elderly, driving
- 11 Word count of the manuscript: 3848.
- 12 Abstract
- 13 **Purpose**: To investigate the effect of cognitive demand on functional visual field performance in drivers with glaucoma. **Method**:
- 14 This study included 20 drivers with open-angle glaucoma and 13 age- and sex-matched controls. Visual field performance was
- evaluated under different degrees of cognitive demand: a static visual field condition (C1), dynamic visual field condition (C2), and
- 16 dynamic visual field condition with active driving (C3) using an interactive, desktop driving simulator. The number of correct
- 17 responses (accuracy) and response times on the visual field task were compared between groups and between conditions using
- 18 Kruskal-Wallis tests. General linear models were employed to compare cognitive workload, recorded in real-time through
- 19 pupillometry, between groups and conditions. **Results**: Adding cognitive demand (C2 and C3) to the static visual field test (C1)
- adversely affected accuracy and response times, in both groups (p < 0.05). However, drivers with glaucoma performed worse than did
- control drivers when the static condition changed to a dynamic condition (C2 vs C1 accuracy; glaucoma: median difference (Q1-Q3) 3
- (2-6.50) vs controls: 2 (0.50-2.50); p = 0.05) and to a dynamic condition with active driving (C3 vs C1 accuracy; glaucoma: 2 (2-6) vs
- controls: 1 (0.50-2); p = 0.02). Overall, drivers with glaucoma exhibited greater cognitive workload than controls (p = 0.02).
- 24 **Conclusions**: Cognitive demand disproportionately affects functional visual field performance in drivers with glaucoma. Our results
- ²⁵ may inform the development of a performance-based visual field test for drivers with glaucoma.

26 **1. Introduction**

Glaucoma is a progressive optic neuropathy characterized by slow degeneration of retinal ganglion cells and their axons resulting in irreversible loss of peripheral field of vision.(1, 2) More than 70 million people worldwide are estimated to be affected by glaucoma with approximately 10% being bilaterally blind.(3) The usual process of the disease diagnosis includes assessment of damage to the optic disc and retinal nerve fiber layer, and clinical evaluation of the physiological visual field.(1, 4, 5)

The Humphrey visual field analyzer (HVF) is the most common used method of detecting physiological visual field in 31 individuals with glaucoma.(6-10) The physiological visual field assessed using the HVF comprises the detection of static stimuli 32 presented one at a time in the periphery. However, there is increasing evidence that physiological visual field defects do not reflect 33 performance in daily-life activities such as driving.(11-14) Driving requires an individual to respond appropriately to many static and 34 dynamic visual stimuli in cluttered environments. Outcomes on the HFV test are only moderately predictive on driving safety 35 outcomes in glaucoma (15, 16) which may be attributed to the fact that safe diving not only requires intact physiological visual field, 36 but also depends on the attentional capacity of the driver and the cognitive demand of the task.(17-19) These three factors define the 37 individual's functional visual field. 38

Since the HVF test lacks the face validity to determine functional visual field performance while driving, the Useful Field of 39 View (UFOV®) test was developed to evaluate the impact of cognitive demand on functional visual field performance.(20) The size 40 of the functional visual field is narrowed when a subject attempts to accurately detect a centrally presented stimulus while paying 41 attention to another stimulus that is simultaneously presented in the periphery without (divided attention) and with (selective attention) 42 additional distracters.(21, 22) The functional field of view of the UFOV® test is determined by the performance in speed of 43 processing, divided attention, and selective attention. The UFOV® test shows to be more sensitive in predicting the motor vehicle 44 crashes of older drivers and also of drivers with glaucoma compared with the HFV test.(15, 16) Yet, the UFOV® test only evaluates 45 30 degrees of horizontal field of view and does not account for the visual flow and the psychomotor activity of steering and pedal 46 operation that is typical of driving. 47

The shrinkage of the functional visual field is postulated to result from an increase in cognitive demand of the task. This increased cognitive demand imposes a greater strain on the available cognitive resources, resulting in a greater cognitive workload exhibited by the subject to continue performing the task.(23). Psychophysiological studies have identified several neurophysiological measures that can accurately assess the amount of cognitive workload needed to execute a task in real-time.(24) Task-evoked pupillary response (TEPR) accurately reflects cognitive workload through inhibition of the parasympathetic nucleus of Edinger Westphal, resulting in pupil dilation.(25, 26)

Recently, studies have investigated the use of TEPR as a measure of cognitive status in individuals at risk of cognitive impairment. (27, 28) Ranchet et al demonstrated that cognitive workload extracted from TEPR was greater in individuals with Parkinson's disease at risk for cognitive impairment when compared to age-matched control participants in a simple speed of

57 processing task.(29) The loss of peripheral field of view in glaucoma may impose a greater cognitive workload, especially under

heavy cognitive demand. This increased cognitive workload may reflect a compensatory mechanism for the loss of peripheral visual

field. Although the link between glaucoma and cognitive impairment remains elusive, some studies have shown a significant association between scores on a general screen of cognitive functions and visual field loss in glaucoma.(30-33) In addition,

neurodegenerative lesions have been detected in the intracranial optic nerve, lateral geniculate nucleus, and visual cortex, suggesting

that glaucoma could be grouped with Alzheimer's and Parkinson's diseases as a neurodegenerative condition. (34, 35) In support of

this hypothesis, individuals with glaucoma are expected to exhibit greater cognitive workload compared to controls, especially under

64 strenuous cognitive demand.

Therefore, the aim of this study was to investigate the effect of an increase in cognitive demand on the functional visual field of individuals with glaucoma while driving in a dynamic and cluttered environment. We hypothesized that 1) an increase in cognitive demand while driving in a dynamic and cluttered environment significantly alters the functional visual field of individuals with glaucoma and healthy controls, 2) functional visual field is affected more in individuals with glaucoma than in healthy controls and 3) cognitive demand disproportionately worsens the functional visual field in individuals with glaucoma than in healthy controls.

70 2. Materials and methods

2.1 Participants and recruitment. Twenty participants with open-angle glaucoma were recruited from the Department of Ophthalmology at Augusta University, Augusta, GA. Eligibility criteria included: (1) diagnosis of open-angle glaucoma exemplified by optic nerve damage and visual field loss; (2) a valid driver's license; (3) drove at least 500 miles one year prior to testing; and (4) devoid of other visual, neurological, internal or psychiatric conditions that might interfere with driving. Thirteen age- and sexmet the dispersive least the part the same acident planet, and the part of the part

matched controls who met the same criteria but without glaucoma were recruited through word-of-mouth and flyers.

76 **2.2 Protocol.** Participants were consented and evaluated on the same day. This protocol was approved by Augusta University

⁷⁷ Institution's Review Board. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Demographic

and driving data such as age, education, driving experience, and annual mileage were collected. The Trail Making Test A and B (TMT

A & B) (36-39) and Montreal Cognitive Assessment (MOCA) (40) were administered. TMT A is a paper-and-pencil test of

80 information processing and visuomotor tracking in which participants were required to connect 25 circles in an increasing order (1, 2,

3, 4 etc.). TMT B, which additionally tested shifting of attention, required participants to connect 25 circles containing either numbers

of letters in alternating order (1, A, 2, B etc.). (36-39) The time to complete each test and the number of errors was recorded. MOCA

is a comprehensive assessment of cognitive functions that was scored on an ordinal scale ranging from 0 to 30.(40)

2.3 Vision tests. The vision screening apparatus from Keystone view (Visionary Software version 2.0.14) was used as a general
 screen for binocular visual acuity (on /20) and horizontal field of view (in degrees). The Humphrey Visual Field Analyzer (Humphrey

Instrument, Dublin, USA) SITA Fast 24-2 was used for monocular visual field testing and had been established previously with 86

standardized protocols and test-retest reliability.(41) Mean deviation (MD) corrected absolute values and pattern standard deviation 87 (PSD) were used as outcome measures. 88

2.4 Driving simulator and conditions. A low fidelity (desktop model) driving simulator with images generated using the STISIM 89 Drive software (STI Inc., Hawthorne, CA) and displayed on three 22-inch DELL® computer screens was used to measure binocular 90 functional visual field (Figure 1). The three screens provided a horizontal field of view of 100° and a vertical field of view of 20°. 91 Participants drove through all simulated scenarios using a Logitech[®] steering wheel and pedals that were connected to the simulator 92 system. Each condition followed the same protocol. After standardized auditory and written instructions, participants completed a 93 practice trial of 45 seconds, followed by the actual evaluation of 13 minutes. The ambient luminance in the darkened room was on 94 average 0.40 cd/m². The display luminance of condition 1 was on average 21.64 cd/m², and 24.56 cd/m² for conditions 2 and 3. 95

Simulator Test Condition 1 (figure 2A) involved static visual field testing on a black background. Participants were to focus on a 96 central fixation point (White Square, RGB 255/255/255) at eye height in the middle of a black screen (RGB 0/0/0). Participants were instructed to press a button on the steering wheel with their right thumb as soon as they localized a red square (RGB 255/0/0) that appeared in the periphery of the black screen. The size and dimensions of the squares (2.0 cm x 2.0 cm) were carefully determined after review of the literature. (42) The red square appeared at different degrees of eccentricity (5° -100° of horizontal angle and 5° -20° of vertical angle, each in 5° increments) on 8 line coordinates at various degrees of radial angles (0°-337.5° in 22.5° increments). Horizontal and vertical angles were defined as the angle between the line perpendicular to the screen through the origin of gaze and the line through the center of the symbol and the origin of gaze. Overall, 114 symbols were presented at random time intervals

(between 0.5 seconds and 2 seconds) and at an unpredictable amplitude (Figure 3). 104

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Simulator Test Condition 2 (figure 2B) involved a dynamic visual field task with no active driving to evaluate the effect of optic flow 105 on functional visual field. Like condition 1, participants were requested to press the thumb button as soon as they localized the 106 peripheral target. However, the background was changed to a dynamic driving scene with an automatic pilot of 45mph. A white lead 107 vehicle with the same dimensions as the central white square in condition 1 was used as fixation point. 108

Simulator Test Condition 3 (figure 2C) involved the same dynamic visual field task but with the participant actively driving to 109 evaluate the additional impact of psychomotor activity on functional visual field. In this condition, the participant was requested to 110 drive the car on a straight road at a constant speed of 45 mph. The participant focused on a lead car and there were auditory speed 111 warnings if the driver drove at 5mph above or below the stipulated speed. In addition to focusing on the lead car, the participant 112 pressed the thumb button whenever a red square appeared on the screen. 113

Computer-generated measures of number of correct responses (accuracy) and the response time to the peripheral target in all three 114 conditions were the primary outcome measures. Automatically generated driving data from condition 3 such as time spent and 115

distance driven over the speed limit, time spent and distance driven over the center lane, mean lateral position and speed, and standard deviation of lateral position and velocity were used as secondary outcome measures at 60 Hz.

2.5 Useful field of view test (UFOV®). The UFOV® is a binocular functional visual field test involving three subtests that increased in cognitive demand with each subsequent subtest. In the speed of processing subtest, the participant had to identify a target presented in the central vision. In the divided attention subtest, the participant had to identify the target presented in the central vision along with a concurrent peripheral target localization task. In the selective attention subtest, the participant performed similar tasks as in divided attention subtest. However, the target displayed in the periphery was embedded in distracters. All subtests were measured in milliseconds. More detailed description of the UFOV® test has been reported elsewhere.(15, 16)

2.6 Fixation stability and cognitive workload. The FOVIO eve tracker (Seeing Machines Inc., Canberra, Australia) was used to 124 confirm fixation of the central point when peripheral targets were presented to ensure reliability of visual field testing. The percentage 125 gaze time on the central fixation target across three conditions was used as an outcome variable. The cognitive workload, i.e., the 126 amount of mental effort indexed through TEPR, was also recorded at 60 Hz by analyzing the changes in raw pupil size of the left eye, 127 while adjusting for individual differences in pupil size, lighting and accommodation.(43) Although TEPR is sensitive to cognitive 128 workload and task difficulty in working memory, it is not accurate to detect complexity of sentences in older adults.(44) Calibration of 129 pupils takes about two minutes. TEPR has been found to correlate well with other indices of neural activity, such as electro-130 encephalogram and functional magnetic resonance imaging. (29) The TEPR scores were transformed into a continuous scale of 131 cognitive workload. This Index of Cognitive Activity (ICA) ranges from 0 to 1, with greater values indicating more cognitive 132 workload. The resulting ICA scores are thought not to be subject to practice effects, education, race, and sex.(45) 133

2.7 Data analysis. Data were checked for normal distribution using the Kolmogorov-Smirnov statistic. Results from the normality 134 testing enabled us to use non-parametric analyses for all hypotheses. Friedman analysis and post-hoc pairwise comparisons using the 135 Wilcoxon Signed Rank Test were conducted for hypothesis 1. The Wilcoxon Rank Sum test was conducted for hypothesis 2 and 3 and 136 to examine between group differences in demographics, UFOV metrics and driving simulator measures. Since the ICA data was 137 normally distributed, general linear models were used to verify the main effects of group (glaucoma vs healthy controls) and condition 138 (1, 2, and 3), and the interaction effect of group by condition, on cognitive workload. Post-hoc pairwise comparison was employed to 139 investigate differences in main and interaction effects. Chi-square analysis was performed to determine the effect of cognitive demand 140 on the eccentricity of missed responses across the three conditions for both groups. All analyses were conducted with SPSS version 141

142 23. P values of less than 0.05 were considered significant.

143 **3. Results**

3.1 Comparison of demographic, clinical, and visual characteristics. Sixteen participants had bilateral open-angle glaucoma and
 four had unilateral open-angle glaucoma. The differences between the glaucoma and healthy control groups in demographics, clinical

and visual field measures are presented in Table 1. Both groups differed significantly in TMT B, mean deviation and pattern standard
 deviation of left eye and mean deviation of right eye derived from HVF.

3.2 Effect of cognitive demand on functional visual field. Within group comparisons showed a significant effect of cognitive 148 demand on functional visual field performance in both groups (Table 2). Post-hoc comparisons showed that both groups responded 149 less accurately and slower in conditions 2 and 3 compared to condition 1 (p<0.05). Between groups comparisons did not reveal 150 significant differences in the performance on the static visual task (condition 1, Table 2, Supplementary Figures 1A and 1B). 151 However, the glaucoma group responded less accurately and slower in the dynamic visual field task without active driving (condition 152 2) and with active driving (condition 3) compared with healthy controls (p < 0.05) (Table 2, Supplementary Figures 1A and 1B). 153 Pairwise comparisons showed that adding visual flow to the visual field test without (C2 - C1) or with active driving (C3 - C1)154 affected accuracy on the functional visual field worse in the glaucoma group than in healthy controls (Table 2). No such effects were 155 observed on response time. 156 No differences in percentage gaze time on the central fixation were found between both groups, indicating that both groups 157 spent an equal amount of time looking at the central target (p > 0.05, data not shown). Finally, with increased cognitive demand, 158

drivers with glaucoma missed more responses at greater angles of eccentricity ($\chi^2 = 32.11$, p < 0.05, Supplementary Table 1). No such effect was seen in healthy controls.

- **3.3 Cognitive workload.** General linear models further revealed a significant effect of glaucoma (F = 5.45; p = 0.02) on the cognitive workload, as indexed by increased ICA (Figure 4). Overall, individuals with glaucoma exhibited greater cognitive workload across all 3 conditions compared to controls (condition 1: ICA glaucoma mean (SD), 0.37 (0.13); controls, 0.35 (0.19); condition 2: ICA glaucoma, 0.36 (0.11); ICA controls, 0.29 (0.17); condition 3: ICA glaucoma, 0.41 (0.11); ICA controls 0.28 (0.16) Within group analyses revealed no significant differences in the cognitive workload (F = 0.38; p = 0.68). Likewise, the interaction effect of group by
- 166 condition was not significant (F = 1.03; p = 0.36).

167**3.4 UFOV tasks**. A similar pattern of effect of cognitive demand was observed for the UFOV. Within group analyses revealed that168both groups showed slower speed of processing as the tasks became more difficult (p < 0.05, Supplementary Table 2). Between group169differences in UFOV metrics demonstrated that the glaucoma group was significantly slower while performing the divided and170selective attention tasks than the healthy controls (p < 0.05, Supplementary Table 2). The addition of a car symbol in a non-cluttered171(divided attention) and cluttered (selective attention) periphery disproportionally worsened speed of processing in the glaucoma group172compared to the control group (pairwise comparisons (p < 0.05, Supplementary Table 2).

3.5 Comparison of driving simulator characteristics. Analyzing the driving simulator performance (condition 3) of both groups revealed that the glaucoma group was significantly different from the control group in time spent (p = 0.05) and distance (p < 0.05)

driven over the lane (Table 3). However, no significant differences were observed between these groups in other driving simulator
 measures.

4. Discussion

This study is one of the very few studies to investigate the effects of cognitive demand on the functional visual field of drivers 178 with glaucoma in comparison to healthy controls. Our findings support our hypotheses that an increase in cognitive demand reduced 179 the functional visual field performance both in drivers with glaucoma as well as healthy controls. However, drivers with glaucoma 180 performed worse on the visual field task, especially when dynamic visual flow was added. Furthermore, the study findings 181 demonstrated that an increase in cognitive demand disproportionately worsened the functional visual field performance of drivers with 182 glaucoma compared with healthy controls. Our results therefore suggest that visual field testing for activities that require timely 183 detection of stimuli in a highly dynamic and rapidly changing environment such as driving should consider the participants' 184 physiological visual field, their cognitive capacity, and the cognitive demand of the task to fully appreciate the impact of any visual 185 field loss performance. 186

Drivers with glaucoma differed significantly from healthy controls in the functional visual field while reacting to an increase in 187 cognitive demand in a driving simulator. Although the addition of visual flow affected the functional field of view similarly in both 188 groups, participants with glaucoma performed disproportionally worse when the psychomotor component of operating the steering 189 wheels and pedals was added. The allocation of cognitive resources to focusing on the central target, concentrating on identifying the 190 peripheral target in a cluttered environment, while maintaining control over the vehicle, resulted in disproportionately greater 191 cognitive workload in drivers with glaucoma. As a result, drivers with glaucoma identified fewer symbols than controls in the 192 functional visual field tests compared to their baseline performance on the static visual field test. In particular, the symbols in the 193 periphery became more difficult to detect with increased cognitive demand. Our findings support the results of Prado Vega et al that 194 also showed drivers with glaucoma to detect fewer peripheral stimuli.(46) 195

The relationship between increased cognitive demand of the task and reduction in functional visual field has been studied previously using the UFOV® test.(16, 47, 48) In those studies, the divided attention subtest of the UFOV® showed to correlate best with motor vehicle crashes in drivers with glaucoma.(16, 47, 48) Tatham et al observed that individuals with glaucoma who had a history of motor vehicle collisions (MVC) reported reduced divided attention metrics of the UFOV® test than those drivers with no MVC history, suggesting that increased cognitive demand shrunk the functional visual field, and in turn, impacted driving safety.(16) Our study confirms that drivers with glaucoma perform worse on the UFOV®, but only in the dual task conditions of divided attention and selective attention.

The increase in cognitive demand did not only affect their performance on the visual field test, drivers with glaucoma also exhibited poorer performance in vehicle control. Participants with glaucoma drove closer to the center lane and crossed the center lane for a longer distance than did controls. Previous studies showed that driving performance of participants with glaucoma was

significantly reduced with higher number of collisions than the age matched controls on a driving simulator.(49) This was in spite of

the fact that tasks used in one particular study were neither cognitively demanding nor did they evaluate visual field tasks in a

functional setting.(49) Participants in that study were asked to follow simple traffic signals or stop signs, obstacle avoidance in terms of vehicles or children rushing out from the sides. By contrast, Prado Vega et al did not find significant differences between groups in

of vehicles or children rushing out from the sides. By contrast, Prado Vega et al did not find significant differences between groups in the performance of primary tasks such as lane keeping and obstacle avoidance. (46) Yet, drivers with glaucoma in their study exhibited

the performance of primary tasks such as lane keeping and obstacle avoidance. (46) Yet, drivers with glat increased steering activity, suggesting more difficulty performing the driving task. (46)

In addition to decrements in performance on the visual field tasks and the driving tasks, participants with glaucoma also 212 showed increased cognitive workload across all three conditions. This finding suggests that drivers with glaucoma had to concentrate 213 harder to detect the visual field symbols in all three conditions. Our Index of Cognitive Activity was based on TEPR, a real-time 214 physiological measure of mental effort. To our knowledge, this is the first time that a neurophysiological measure of cognitive 215 workload was used to determine mental effort during functional visual field tasks in glaucoma. Prado-Vega et al. found no significant 216 differences in self-reported cognitive workload between drivers with glaucoma and controls in four simulator conditions.(46) 217 However, self-report ratings depend on the perception of the individuals, whereas the Index of Cognitive Activity is thought to be a 218 reliable, objective estimate of cognitive workload.(45) Whereas Prado-Vega et al. found a significant effect of cognitive demand on 219 subjective cognitive workload, our study did not show a linear relationship between cognitive demand and cognitive workload. 220 Psychophysiological studies have demonstrated that cognitive workload increases as a function of cognitive demand, until a tipping 221 point is reached where the task becomes too difficult to complete.(25) The decrements in accuracy and response time with increased 222 cognitive demand may have resulted in cognitive overload. As a result, no within group effects on cognitive workload were observed 223 in our study. Further research is warranted to confirm the usefulness of pupillometry as an objective, real-time measure of cognitive 224 workload in glaucoma. 225

The results of the study should be considered preliminary. We found that the functional visual field of the participant with glaucoma with slight to moderate visual impairment was altered when driving in a highly-cluttered environment such as driving. However, care should be taken when generalizing these findings to a larger patient population since our sample size was small. Future studies should include a larger sample of drivers with glaucoma with various severity of visual impairment to confirm our findings. Such studies should also aim at generalizing the driving simulator findings to real-life on-road driving ability because our dynamic driving simulator task only included a car following task.

5. Conclusions

233 Cognitive demand, especially in a functional context such as driving, significantly reduced the functional field of view of individuals

with glaucoma. The disproportionate impact of cognitive demand on functional visual field in glaucoma was more evident when

cluttered visual flow was added than when a psychomotor activity was added to the visual field task. Our findings suggest that visual

field testing to determine eligibility for driving resumption in glaucoma need to be conducted in a cluttered, driving-related setting to

²³⁷ fully appreciate the cognitive demands of real-world driving.

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243 References:

Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet (London, England) (2004) 363(9422):1711-20.
 Epub 2004/05/26. doi: 10.1016/s0140-6736(04)16257-0. PubMed PMID: 15158634.

Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. Jama (2014)
 311(18):1901-11. Epub 2014/05/16. doi: 10.1001/jama.2014.3192. PubMed PMID: 24825645; PubMed Central PMCID: PMCPmc4523637.

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. The British
 journal of ophthalmology (2006) 90(3):262-7. Epub 2006/02/21. doi: 10.1136/bjo.2005.081224. PubMed PMID:
 16488940; PubMed Central PMCID: PMCPmc1856963.

Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma. II. The site of
 injury and susceptibility to damage. Archives of ophthalmology (Chicago, Ill : 1960) (1981) 99(4):635-49.
 Epub 1981/04/01. PubMed PMID: 6164357.

5. Harwerth RS, Wheat JL, Fredette MJ, Anderson DR. Linking structure and function in glaucoma. *Progress in retinal and eye research* (2010) **29**(4):249-71. Epub 2010/03/17. doi: 10.1016/j.preteyeres.2010.02.001.
PubMed PMID: 20226873; PubMed Central PMCID: PMCPmc2878911.

6. Beck RW, Bergstrom TJ, Lichter PR. A clinical comparison of visual field testing with a new automated perimeter, the Humphrey Field Analyzer, and the Goldmann perimeter. *Ophthalmology* (1985) **92**(1):77-82. Epub 1985/01/01. PubMed PMID: 3974997.

Agarwal HC, Gulati V, Sihota R. Visual field assessment in glaucoma: comparative evaluation of manual
kinetic Goldmann perimetry and automated static perimetry. *Indian journal of ophthalmology* (2000) **48**(4):301-6. Epub 2001/05/09. PubMed PMID: 11340889.

8. Ballon BJ, Echelman DA, Shields MB, Ollie AR. Peripheral visual field testing in glaucoma by automated
kinetic perimetry with the Humphrey Field Analyzer. Archives of ophthalmology (Chicago, Ill : 1960) (1992)
110(12):1730-2. Epub 1992/12/01. PubMed PMID: 1463413.

9. Mills RP, Hopp RH, Drance SM. Comparison of quantitative testing with the Octopus, Humphrey, and
 Tubingen perimeters. American journal of ophthalmology (1986) 102(4):496-504. Epub 1986/10/15. PubMed PMID:
 3766667.

Talbot R, Goldberg I, Kelly P. Evaluating the accuracy of the visual field index for the Humphrey
Visual Field Analyzer in patients with mild to moderate glaucoma. *American journal of ophthalmology* (2013) **156**(6):1272-6. Epub 2013/10/01. doi: 10.1016/j.ajo.2013.07.025. PubMed PMID: 24075425.

11. Wood JM, Troutbeck R. Elderly drivers and simulated visual impairment. Optometry and vision science : official publication of the American Academy of Optometry (1995) 72(2):115-24. Epub 1995/02/01. PubMed PMID: 7753525.

276 12. Hills B, Burg A. A reanalysis of California driver vision data: general findings. (1977). 277 13. Henderson RL, Burg A. Vision and audition in driving: System Development Corporation (1974). 278 14. Shinar D. Driver visual limitations diagnosis and treatment. (1977). 279 15. Ball K, Owsley C, Sloane ME, Roenker DL, Bruni JR. Visual attention problems as a predictor of vehicle 280 crashes in older drivers. Investigative ophthalmology & visual science (1993) **34**(11):3110-23. Epub 281 1993/10/01. PubMed PMID: 8407219. 282 16. Tatham AJ, Boer ER, Gracitelli CP, Rosen PN, Medeiros FA. Relationship Between Motor Vehicle 283 Collisions and Results of Perimetry, Useful Field of View, and Driving Simulation in Drivers With Glaucoma. 284 Translational vision science & technology (2015) **4**(3):5. Epub 2015/06/06. doi: 10.1167/tvst.4.3.5. PubMed 285 PMID: 26046007; PubMed Central PMCID: PMCPmc4451501. 286 Owsley C, Ball K, McGwin G, Jr., Sloane ME, Roenker DL, White MF, et al. Visual processing impairment 17. 287 and risk of motor vehicle crash among older adults. Jama (1998) 279(14):1083-8. Epub 1998/04/18. PubMed 288 PMID: 9546567. 289 18. Rubin GS, Ng ES, Bandeen-Roche K, Keyl PM, Freeman EE, West SK. A prospective, population-based study 290 of the role of visual impairment in motor vehicle crashes among older drivers: the SEE study. *Investigative* ophthalmology & visual science (2007) **48**(4):1483-91. Epub 2007/03/29. doi: 10.1167/iovs.06-0474. PubMed 291 292 PMID: 17389475. 293 Owsley C, McGwin G, Jr. Vision and driving. *Vision research* (2010) **50**(23):2348-61. Epub 2010/06/29. 19. doi: 10.1016/j.visres.2010.05.021. PubMed PMID: 20580907; PubMed Central PMCID: PMCPmc2975746. 294 295 Ball KK, Roenker DL, Bruni JR. Developmental changes in attention and visual search throughout 20. 296 adulthood. Advances in psychology (1990) 69:489-508. 297 Parasuraman R, Nestor PG. Attention and driving skills in aging and Alzheimer's disease. Human factors 21. 298 (1991) **33**(5):539-57. Epub 1991/10/01. PubMed PMID: 1769674. 299 Plude DJ, Hover W. Attention and performance: Identifying and localizing age deficits. Aging and human 22. 300 performance (1985):47-99. 301 Kahneman D. Attention and Effort. Englewood, NJ: Prentice Hall (1973). 23. 302 Ranchet M, Morgan JC, Akinwuntan AE, Devos H. Cognitive workload across the spectrum of cognitive 24. impairments: A systematic review of physiological measures. Neuroscience and biobehavioral reviews (2017). 303 304 doi: 10.1016/j.neubiorev.2017.07.001. PubMed PMID: 28711663. 305 25. Beatty J. Task-evoked pupillary responses, processing load, and the structure of processing resources. 306 Psychol Bull (1982) 91(2):276-92. Epub 1982/03/01. PubMed PMID: 7071262. 307 26. Eckstein MK, Guerra-Carrillo B, Miller Singley AT, Bunge SA. Beyond eye gaze: What else can 308 eyetracking reveal about cognition and cognitive development? Developmental cognitive neuroscience (2017) 309 **25**:69-91. Epub 2016/12/03. doi: 10.1016/j.dcn.2016.11.001. PubMed PMID: 27908561. 310 Wang CA, McInnis H, Brien DC, Pari G, Munoz DP. Disruption of pupil size modulation correlates with 27. 311 voluntary motor preparation deficits in Parkinson's disease. Neuropsychologia (2016) 80:176-84. Epub 312 2015/12/04. doi: 10.1016/j.neuropsychologia.2015.11.019. PubMed PMID: 26631540. 313 28. Orlosky J, Itoh Y, Ranchet M, Kiyokawa K, Morgan J, Devos H. Emulation of Physician Tasks in Eyetracked Virtual Reality for Remote Diagnosis of Neurodegenerative Disease. IEEE Transactions on 314 315 Visualization and Computer Graphics (2017) **23**(4):1302-11. 316 29. Ranchet M, Orlosky J, Morgan J, Qadir S, Akinwuntan AE, Devos H. Pupillary response to cognitive

317 workload during saccadic tasks in Parkinson's disease. Behavioural brain research (2017) 327:162-6.

30. Diniz-Filho A, Delano-Wood L, Daga FB, Cronemberger S, Medeiros FA. Association Between Neurocognitive
Decline and Visual Field Variability in Glaucoma. *JAMA ophthalmology* (2017) 135(7):734-9. Epub 2017/05/19.
doi: 10.1001/jamaophthalmol.2017.1279. PubMed PMID: 28520873.

- 31. Harrabi H, Kergoat MJ, Rousseau J, Boisjoly H, Schmaltz H, Moghadaszadeh S, et al. Age-related eye 32. disease and cognitive function. *Investigative ophthalmology & visual science* (2015) **56**(2):1217-21. Epub 323 2015/02/05. doi: 10.1167/iovs.14-15370. PubMed PMID: 25650424.
- 324 32. Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease and glaucoma: is there a causal relationship?
 325 The British journal of ophthalmology (2009) 93(12):1557-9. Epub 2009/03/17. doi: 10.1136/bjo.2008.148064.
 326 PubMed PMID: 19286688.
- 32. Bulut M, Yaman A, Erol MK, Kurtulus F, Toslak D, Coban DT, et al. Cognitive performance of primary
 328 open-angle glaucoma and normal-tension glaucoma patients. Arquivos brasileiros de oftalmologia (2016)
 329 79(2):100-4. Epub 2016/05/26. doi: 10.5935/0004-2749.20160030. PubMed PMID: 27224073.
- 34. Gupta N, Ang LC, Noel de Tilly L, Bidaisee L, Yucel YH. Human glaucoma and neural degeneration in 331 intracranial optic nerve, lateral geniculate nucleus, and visual cortex. *The British journal of* 332 *ophthalmology* (2006) **90**(6):674-8. Epub 2006/02/09. doi: 10.1136/bjo.2005.086769. PubMed PMID: 16464969; 333 PubMed Central PMCID: PMCPMC1860237.
- 334 35. Gupta N, Ly T, Zhang Q, Kaufman PL, Weinreb RN, Yucel YH. Chronic ocular hypertension induces dendrite
 pathology in the lateral geniculate nucleus of the brain. *Experimental eye research* (2007) 84(1):176-84.
 336 Epub 2006/11/11. doi: 10.1016/j.exer.2006.09.013. PubMed PMID: 17094963.
- 337 36. Reitan RM. The relation of the trail making test to organic brain damage. *Journal of consulting* 338 psychology (1955) **19**(5):393-4. Epub 1955/10/01. PubMed PMID: 13263471.
- 339 37. Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, Rodriguez-Sanchez JM, Rios-Lago M, Tirapu J, et al. 340 Construct validity of the Trail Making Test: role of task-switching, working memory,
- inhibition/interference control, and visuomotor abilities. Journal of the International Neuropsychological
 Society : JINS (2009) 15(3):438-50. Epub 2009/05/01. doi: 10.1017/s1355617709090626. PubMed PMID: 19402930.
 Kelty-Stephen DG, Stirling LA, Lipsitz LA. Multifractal temporal correlations in circle-tracing
- behaviors are associated with the executive function of rule-switching assessed by the Trail Making Test. *Psychological assessment* (2016) **28**(2):171-80. Epub 2015/06/09. doi: 10.1037/pas0000177. PubMed PMID: 26053002.
- 347 39. Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a 348 set-switching paradigm. *Journal of clinical and experimental neuropsychology* (2000) **22**(4):518-28. Epub 349 2000/08/03. doi: 10.1076/1380-3395(200008)22:4;1-0;ft518. PubMed PMID: 10923061.
- 40. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal
 Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* (2005) 53(4):695-9. Epub 2005/04/09. doi: 10.1111/j.1532-5415.2005.53221.x. PubMed PMID:
 15817019.
- 41. Investigators AGIS. Advanced Glaucoma Intervention Study: 2. Visual field test scoring and reliability. *Ophthalmology* (1994) **101**(8):1445-55.
- 356 42. Bentley SA, LeBlanc RP, Nicolela MT, Chauhan BC. Validity, reliability, and repeatability of the 357 useful field of view test in persons with normal vision and patients with glaucoma. *Investigative*

ophthalmology & visual science (2012) 53(11):6763-9. Epub 2012/09/08. doi: 10.1167/iovs.12-9718. PubMed 358 359 PMID: 22956614. 360 43. Marshall SP. Method and apparatus for eye tracking and monitoring pupil dilation to evaluate cognitive 361 activity. Google Patents (2000). Piquado T, Isaacowitz D, Wingfield A. Pupillometry as a measure of cognitive effort in younger and 362 44. older adults. *Psychophysiology* (2010) **47**(3):560-9. 363 364 45. Marshall SP. Identifying cognitive state from eve metrics. Aviation, space, and environmental medicine 365 (2007) **78**(5):B165-B75. 366 46. Prado Vega R, van Leeuwen PM, Rendon Velez E, Lemij HG, de Winter JC. Obstacle avoidance, visual 367 detection performance, and eye-scanning behavior of glaucoma patients in a driving simulator: a preliminary 368 study. Plos one (2013) 8(10):e77294. Epub 2013/10/23. doi: 10.1371/journal.pone.0077294. PubMed PMID: 369 24146975; PubMed Central PMCID: PMCPmc3797776. 370 Lee SS, Black AA, Wood JM. Effect of glaucoma on eve movement patterns and laboratory-based hazard 47. 371 detection ability. PLoS One (2017) 12(6):e0178876. Epub 2017/06/02. doi: 10.1371/journal.pone.0178876. 372 PubMed PMID: 28570621; PubMed Central PMCID: PMCPMC5453592. Gracitelli CP, Tatham AJ, Boer ER, Abe RY, Diniz-Filho A, Rosen PN, et al. Predicting Risk of Motor 373 48. 374 Vehicle Collisions in Patients with Glaucoma: A Longitudinal Study. *PloS one* (2015) **10**(10):e0138288. Epub 375 2015/10/02. doi: 10.1371/journal.pone.0138288. PubMed PMID: 26426342; PubMed Central PMCID: PMCPmc4591330. 376 49. Kunimatsu-Sanuki S, Iwase A, Araie M, Aoki Y, Hara T, Nakazawa T, et al. An assessment of driving 377 fitness in patients with visual impairment to understand the elevated risk of motor vehicle accidents. BMJ 378 open (2015) 5(2):e006379. Epub 2015/03/01. doi: 10.1136/bmjopen-2014-006379. PubMed PMID: 25724982; PubMed

379 Central PMCID: PMCPmc4346674.

380 Tables

Table 1. Demographics, clinical and visual measures between the Glaucoma (n = 20) and healthy control group (n = 13).

Variable	Glauc	coma	Cor	ntrols	W value*	p value	
	Median	Q1 - Q3	Median	Q1 - Q3			
Demographics							
Age (years)	62.50	59 - 71	57	53 - 70	178	0.11	
Education (years)	13.50	12 - 16	12	12 - 14	197.50	0.39	
Driving experience (years)	46.50	40.50 - 51.50	42	37 - 54	205.50	0.58	
Annual mileage (miles/year)	12000	5500 - 15500	12500	8000 - 18200	232	0.70	

Clinical measures

TMT A (seconds)	36	28.50 - 48.50	29.50	26.50 - 40.57	156.50	0.11
TMT B (seconds)	124.50	81.50 - 190.50	72	57.50 - 96.00	145.50	0.04**
MOCA (0 -30)	26.50	24.50 - 29.00	27.50	27.00 - 28.50	216.50	0.47
Visual measures						
Visual acuity (0/20 - 20/20)	30	20 - 40	25	20 - 30	137	0.28
Total visual field (0°- 170°)	170	155 - 170	170	170 -170	183	0.19
Humphrey left MD	5.04	1.45 - 13.24	-0.90	0.53 - 2.17	252	0.006**
Humphrey left PSD	2.84	2.00 - 9.20	1.51	1.32 - 2.30	116	0.003**
Humphrey right MD	2.90	1.20-10.72	-0.61	0.08 - 2.51	258	0.02**
Humphrey right PSD	1.93	1.60 - 8.63	1.90	1.51 - 2.34	173.50	0.35

* indicate Wilcoxon Rank sum test; ** indicate p value < 0.05; MOCA, Montreal Cognitive Assessment; TMT A and TMT B, Trail making test A and B; MD,

383 Mean Deviation; PSD, Pattern Standard Deviation.

Table 2. Functional visual field performance of the Glaucoma (n = 20) and healthy control group (n = 13).

	Condition 1 (C1)	Condition 2 (C2)	Condition 3 (C3)	Within group p-value ‡	Pairwise c	omparisons ^{\$}	
Correct responses							
Glaucoma^	114 (113 - 114)	111 (106 - 112)	111.50 (104 - 112)	0.001*	C2 - C1*	C3 - C1*	C3 - C2
Controls^	114 (114 - 114)	112 (111 - 114)	113 (112 - 114)	0.02*	C2 - C1*	C3 - C1*	C3 - C2
Between group p-value §	0.20	0.01*	0.01*		0.05	0.02*	0.047*
Response time (s)							
Glaucoma^	0.52 (0.49 - 0.60)	0.63 (0.56 - 0.82)	0.76 (0.64 - 0.95)	0.001*	C2 - C1*	C3 - C1*	C3 - C2*

Controls^	0.47 (0.43 - 0.52)	0.58 (0.52 - 0.60)	0.64 (0.57 - 0.73)	0.001*	C2 - C1*	C3 - C1*	C3 - C2*
Between group p-value §	0.08	0.01*	0.04*		0.17	0.34	0.73

³⁸⁵ ^ indicate values in median (Q1 – Q3); *indicate p value < 0.05; Response time in seconds; § indicate p-value from Wilcoxon rank sum test; ‡ indicate p-value

386 from Friedman Test; ^{\$} Wilcoxon signed rank test

387	Table 3. Driving	simulator	performance	e of the	Glaucoma	n = 20) and health	v control	group	(n = 13)) during	g condition	3
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	G	laucoma	C	ontrols	W value*	p value
	Median	Q1 - Q3	Median	Q1 - Q3		
Time spent over the speed limit (seconds)	48.4	31.0 - 59.4	52.5	35.3 - 61.0	285	0.68
Distance drove over the speed limit (feet)	51.3	61.0 - 33.7	54	36.9 - 62.6	287	0.75
Time spent over the center lane (seconds)	4.2	3.1 - 6.5	1.1	0.6 - 3.5	125	0.05**
Distance drove over the center lane (feet)	4.6	3.2 - 7.4	1.1	0.6 - 3.5	114	0.01**
Mean lateral position (feet)	5.3	4.6 - 5.8	5.9	5.0 - 6.2	266	0.22
Mean speed (miles/hour)	44.9	44.4 - 45.1	44.9	44.5 - 45.1	281	0.56
Standard deviation lateral position (feet)	1.2	0.8 - 1.3	0.9	0.8 - 1.4	163	0.75
Standard deviation velocity (miles/hour)	1.3	1.1 - 1.9	1.3	1.1 - 1.4	155	0.50

388 * indicate Wilcoxon Rank sum test; ** indicate p value ≤ 0.05

389 Figure legends

390 Figure 1: Low-fidelity driving simulator (©STISIM drive)

Figure 2: Three different visual field conditions used in the study

Figure 3: Visual field targets expanding 100° of horizontal field of view and 20° of vertical field of view

Figure 4: Mean and standard deviations for cognitive workload between the Glaucoma (n = 20) and healthy control group (n = 13)

across three conditions; between group effect p = 0.02