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The Driving Simulator Visual Field in Glaucoma – A Novel Task to Test Available Field of View

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THE DRIVING SIMULATOR VISUAL FIELD IN GLAUCOMA – A NOVEL TASK TO TEST AVAILABLE FIELD OF VIEW

By

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ABSTRACT: Glaucoma causes peripheral vision loss and impaired driving performance. We developed a novel driving simulator visual field task (DSVF) in a panoramic driving simulator to map the available field of view under different perceptual task loads in naturalistic settings. Our hypothesis is that "available field of view" will decrease with increasing task load in both glaucoma subjects and controls. This is a cross-sectional study with 28 glaucoma subjects and 19 controls. DSVF (60° x 20° visual field at 2.5 m) was tested in a high-fidelity interactive driving simulator in 4 different scenarios: a) no distractions b) no driving condition with unrestricted head/eye movements c) driving d) driving with PASAT (Paced Auditory Serial Addition Test). Each test was repeated twice. The main outcome measure was a visual field index (DSVF-VFI). DSVF-VFI was compared to the Humphrey Visual field -HVF-VFI monocularly and binocularly to validate the test. The DSVF task was highly reproducible and comparable to HVF. An A-pillar scotoma appeared in all DSVF trials**.** In both glaucoma subjects and controls, the DSVF-VFI decreased with increasing task load. The DSVFI decreased significantly more in the glaucoma group as compared to the control group. We developed a predictive formula to predict available field of view while driving from clinic based HVF. Glaucoma subjects were impaired in completing multiple task demands, such as driving and DSVF- either because a) compensation for peripheral vision loss acts as a continuously present load on attention capacity b) glaucoma is associated with diminished cognitive capacity as compared to controls.

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LIST OF ABBREVIATIONS

DSVF	Driving Simulator Visual Field
PASAT	Paced Auditory Serial Addition Test
VFI	Visual Field Index
DSVF-VFI	Driving Simulator Visual Field - Visual Field Index
TMT-A	Trail Making Task -A
TMT-B	Trail Making Task -B
MVC	Motor vehicle crash
UFOV	Useful Field of View
SENSEI	Simulator for Ergonomics, Neuroscience, Safety Engineering and Innovation
OD	Right Eye
OS	Left Eye
OU	Both eyes
MoCA	The Montreal cognitive assessment
ICC	Intra class coefficient
NEI VFQ 25	National eye institute Visual field questionnaire

CHAPTER 1: INTRODUCTION

1a: Glaucoma:

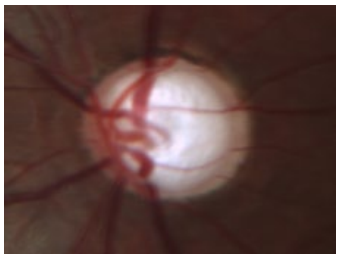


Figure 1: Glaucomatous "cupping" representing loss of optic nerve axons

Glaucoma is a chronic, progressive optic neuropathy with a characteristic acquired atrophy of the optic nerve (called cupping) and loss of retinal ganglion cells and their axons[1]. It is the leading global cause of irreversible blindness. It affects 2% of the population over 40 years of age in the USA[2] and has a strong racial predilection – affecting 22% of the Black and Latino population over the age of 80 years[3,4]. Glaucomatous visual field loss begins in the nasal and paracentral regions, then proceeds to arcuate field defects and concentric field constriction that respects the horizontal meridian. Patients with advanced disease show declines in visual acuity. Glaucoma is a silent disease, patients may not realize that they have lost peripheral vision because their brain "fills in" the area of vision loss[5]. More than half (56-75%) of glaucoma in the USA is undiagnosed[3,6]. Of all newly diagnosed glaucoma patients in Western countries, 50-75% already have moderate to advanced peripheral visual field loss at the time of diagnosis[7,8]. Patients with moderate to advanced field loss experience their vision loss as "blur" in the missing areas of their field of view[9].

Clinical perimetry is used to map a glaucoma patient's peripheral visual field, most commonly using Humphrey visual fields (HVF). HVF are routinely mapped monocularly with a fixation target under no-distraction conditions in clinic. The commonly used strategies use a threshold strategy to test the central 24- 30 degrees of visual field. The retinal loci tested straddle the horizontal and vertical meridians and are 3 degrees apart from each other. The output is in the form of several gray scales and global indices. The

visual field index (VFI) is an estimate of the amount of field of view the patient has. A 100% VFI indicates perfect peripheral vision. HVF are used in clinic to monitor progression, by looking at the pattern of the gray scale or by following the global indices (figure 2).

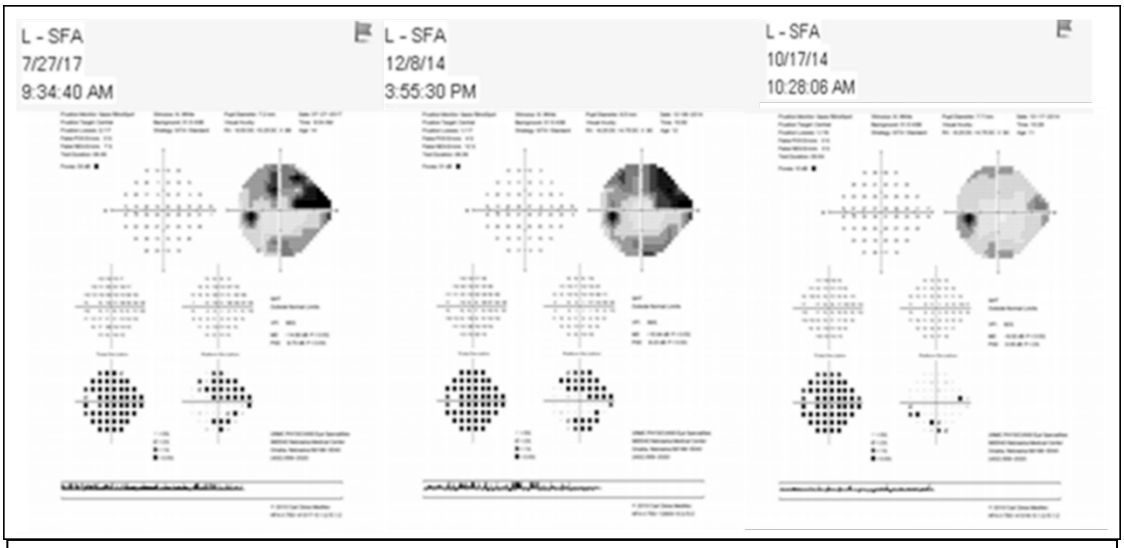


Figure 2: Humphrey visual field of left eye demonstrating worsening of field loss from October 2014 to December 2014 with some fluctuation/worsening noted on

1b: Driving and Glaucoma:

Subjects with glaucoma have a worse overall performance relative to age matched healthy subjects [10,11]. In an on-road driving study, 52% of glaucoma drivers received a "fail" driving rating as compared to 21% in the control group [11]. Surprisingly, the visual acuity, contrast sensitivity and visual fields were not statistically different between the glaucoma drivers who "passed" and "failed", the glaucoma drivers who received a failing score performed worse on measures of visual-spatial processing (TMT-A) and executive function (TMT-B). Glaucoma drivers commit a larger number of driving safety errors related to observation, lane position, and approach, and demonstrated poor performance during traffic light and give-way scenarios [10]

Increasing severity of glaucomatous vision loss increases the risk of at-fault and injurious motor vehicle crashes (MVC) . Glaucoma drivers in an MVC are more likely to have moderate to severe field defects in the worse eye [12]and glaucoma drivers with severe field defects are twice as likely to be involved in an at-fault collision as compared to those glaucoma drivers with mild-moderate field loss [13]. A study from Japan in glaucoma drivers found a 10 year prevalence of MVC of 0% in mild glaucoma, 4% in moderate and 25% in severe glaucomas compared to 3.5% MVC prevalence in the healthy control group [14].

Other studies have not found an association between glaucoma and MVCs [12,15]. In a large (n=3,168) multistate cohort study, a glaucoma diagnosis (37% of the cohort) was not found to be a risk factor for at-fault MVC [16].

This could be due to the a) variability in severity of disease- severe glaucoma affects driving far more than mild disease b) driving cessation or driving restrictions in the glaucoma population. A Baltimore study found that 42% of patients with bilateral glaucoma discontinued driving relative to 21% of patients with unilateral glaucoma and 15% of healthy controls [17]with the extent of visual field loss being the most predictive factor for driving cessation.

In our own work, we have found that drivers with glaucoma have worse vehicle control in a simulator based task as compared to controls without field loss[18]. In an on-road driving study, we found that glaucoma subjects make more driving errors, particularly in lane maintenance, and have trouble identifying road signs compared to controls. Significantly, we found that inferior field loss has greater influence on driving performance than superior field loss (unpublished data).

1c: Attention and Glaucoma and Driving:

Attention is a neural process that selectively and dynamically processes incoming and frequently competing sources of information often from multiple sensory sources. The central tenet of the load theory of attention (which forms much of the basis of the current work) is that sensory processing becomes "selective" when the limits of processing are reached. If a task imposes low attentional demands- remaining capacity is allocated to processing of task-irrelevant items. However, if the task imposes attentional demands beyond an individual's capacity, task-irrelevant items don't get processed and "get ignored" [19]. This "load" or demand can be perceptual load (through different sensory modalities) or executive control load. Both are very relevant to driving and glaucoma. Driving is a complex task that tests an individual's ability to interact, perceive and attend external stimuli (Figure 1) for timely response to on-road hazards and events.

The effect of perceptual load is illustrated by the phenomenon of "inattentional blindness"- illustrated by the famous "missed gorilla" experiment by Simon and Chabris [20]wherein people missed the gorilla in the room while doing a complex task. Load theory can be used to study the processing capacity differences between groups of people, such as those with peripheral vision loss from glaucoma and controls. This theory of "ignoring distractions" under high perceptual load is complicated by another determinant of attention- executive load (such as working memory processes). Prioritization of task-relevant processing is dependent on availability of executive control functions. Once these functions are loaded, the prioritization process gets impaired and distractors cannot be ignored easily again.

Attention and Driving: The information processing model (figure 3) below describes how drivers are engaged at every moment of driving. There are multiple modalities of stimuli that drivers perceive- auditory, visual and haptic. Each stimulus is interpreted and

the driver has to plan and execute an appropriate action such as pressing the brake pedal before a stop sign or changing lanes during a turn.

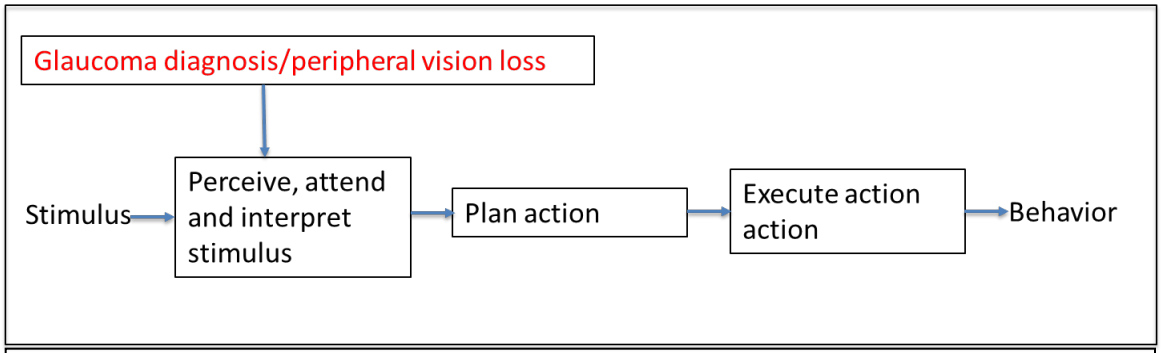


Figure 3: Information processing model for understanding driving error

Distraction and inattention are major contributors to motor vehicle crashes[21]. "Inattentional blindness" or "looked but fail to see" accounted for 18-23% of all crashes reported by Treat et al[22]. In a driving simulator study, distracted participants (using a cell phone) noted 50% fewer driving-safety relevant objects on the road as compared to participants not on a cell phone despite "looking" straight at the objects[23]. Multi-tasking or divided attention tasks demonstrate significant age-related declines. These declines were more pronounced when a motor response was required while multitasking[24]

Glaucoma occurs in older individuals. Despite excellent central vision, several studies have demonstrated that glaucoma subjects (even those with mild-moderate field loss) do worse on tasks of executive function and visual search such as the trail making test[11,25]. The ability to divide attention also significantly impacted reading speed in a cohort of glaucoma subjects[26]. Loughman et al[27] have shown preattentive visual search to be affected in early glaucoma when compared to suspects and normal subjects. Gangedulla et al[28] (in a desktop simulator in glaucoma and controls) and Park[29] (on a screen with 60 degrees of view in healthy young adults) found that increasing cognitive

task load significantly affected the functional visual field performance. Gangedulla found that drivers with glaucoma performed far worse than controls.

Useful field of view (UFOV) : The UFOV test was introduced by Ball and colleagues[30] . In its current commercial version administered on a desktop, it scores visual processing speed rather than field of view. Stimuli are presented centrally and peripherally at 10 degrees in 8 directions in various algorithms in a quick test of divided attention [31]. The UFOV has proven valuable for its ability to predict driving performance in older adults[32,33]. Glaucoma subjects do significantly worse than older adults on the UFOV test although it is unclear if this is due to their field loss or their visual processing ability[34].

1d: Gaps in literature:

Clinical perimetry (HVF) is used to map a glaucoma patient's peripheral visual field. HVF are routinely mapped monocularly with a fixation target under no-distraction conditions in clinic. However, in real world situations such as driving, there are demands on attention. Driving is a complex task that tests an individual's ability to interact, perceive and attend external stimuli (Figure 3) for timely response to on-road hazards and event. Distractions during driving such as the radio, conversations or texting all increase the attention task load and have been shown to affect driving performance[35,36]. Both standard clinical perimetry and the UFOV tests do not measure what part of the driving environment is visually "available" under realistic, ecologically valid settings.

There is a need for a task that can simultaneously a) map the "available field of view" - the field of view in in realistic driving condition under different task loads and b) be comparable directly to clinic based perimetry. Such a task would allow us to:

a) Study the processing capacity differences between different groups

b) Evaluate the effect of these processing capacity differences on driving performance

c) Evaluate which region of the field loss (such as superior, inferior, central) is most impacted by changing task loads

d) Evaluate the impact of different regions of field loss on driving specific tasks under different perceptual task load.

In response, we designed a novel driving simulator visual field (DSVF) test to map the “available field of view”.

1e: Hypothesis and Aims

Our hypothesis is that “available field of view” will decrease with increasing task load in both glaucoma subjects and controls. We hypothesize that the decrease will be greater in glaucoma subjects because part of their processing capacity is diverted towards functioning with sensory deprivation. We propose that DSVF results are of greater relevance to driving than standard clinical perimetry.

The aims of this current proposal are to:

1) Assess the validity and reproducibility of the DSVF test

2) Quantify the “available” field of view in subjects with glaucoma under differing driving task loads.

Our ultimate aim is to have clinicians look at a visual field and predict the driving tasks that would be most impacted by the field loss. This would allow targeted rehabilitation and improve driving safety in patients with peripheral vision loss.

CHAPTER 2: METHODS

This was a prospective study designed to study the available field of view with increasing task load in glaucoma patients. It was approved by the University of Nebraska Medical Center Institutional Review Board and followed the tenets of the Declaration of Helsinki.

2a: Subjects:

Glaucoma subjects and controls were recruited from the glaucoma clinic at the Truhlsen Eye Institute at the University of Nebraska Medical Center. We included subjects with best corrected visual acuity of at least 20/40 in the worse eye, with stable glaucoma (at least two reliable and reproducible HVF over 2 years). Visual fields were performed using the Humphrey field analyzer (Carl Zeiss Meditec Inc., Dublin CA) using the 24-2 or 30-2 Swedish Interactive Threshold Algorithm strategy as part of routine clinical care. The reliability and reproducibility of the visual fields was assessed by the treating glaucoma physician. Subjects in the glaucoma group had field defects commensurate with their diagnosis and those in the control group had normal visual fields with a normal glaucoma hemifield test and a clinical diagnosis of ocular hypertension or glaucoma suspect.

We excluded patients with (a) poor reliability indices on HVF (>20% false positives, false negatives or fixation losses) (b) non-glaucomatous causes of field loss (retinal disease, central nervous system disease or other optic neuropathies) and (c) previous diagnosis of a neurological disorder such as stroke, movement disorder or cognitive disorder in the electronic medical record d) medications with daytime sedating effects

2b: Tests:

The Driving Simulator visual field (DSVF) scenario was coded and implemented in SENSEI[37] (Simulator for Ergonomics, Neuroscience, Safety Engineering and Innovation), a DriveSafety RS-600 (Salt Lake City, UT), fully integrated, high

performance, high fidelity driving simulation system with an authentic automotive cab (based on a 2004 Ford Focus) and a 290˚out of the window display environment. The DSVF tests visual field 60˚horizontally and 20° vertically at a distance of 2.5 m. Forty grid locations placed 6˚apart were tested, straddling the horizontal and vertical meridian similar to HVF 30-2 strategy. Red supra-threshold stimulus images subtending a 0.5˚degree visual angle (similar to HFA stimulus size III) were presented randomly 4 times at each locus with a stimulus duration of 200 milliseconds, and a varying inter-stimulus interval from 1.2 to 1.7 seconds. Each locus was tested 4 times in a multisampling suprathreshold algorithm. Pass criterion was defined if the subject responded to more than 50% of the stimuli on that locus. This pass criterion was chosen for its sensitivity and specificity trade-off[38] .

VFI calculations were performed using Bengtsson and Heijl's technique[39] to calculate a DSVF-VFI for each DSVF using the same weights for the retinal loci that they use for HVF calculations. As previously described, VFI gives a percentage estimate of the "available" field of view (tested area with correct response in the stimulus detection task). The DSVF-VFI was our main outcome measure and was calculated under different task conditions and a grey scale was created for every DSVF.

Tasks: Subjects underwent the following tasks in the driving simulator in the same order with the task load increasing successively. Each task duration was approximately 4 minutes. All tasks were repeated twice to test for reproducibility.

(1) *Task 1:* This was a no-driving, no distraction task similar to the HVF. The DSVF was performed with a fixation target and grey background in the right eye (OD), left eye (OS) and both eyes (OU).

(2) *Task 2A:* DSVF in a naturalistic background with unrestricted eye and head movements in a no-driving condition. The naturalistic background introduces visual information that competes for access to visual attention resources.

(3) Task 2B: DSVF in a driving scenario with the participant driving on the simulator. The driving scene was a straight rural road without any other vehicles or turns and a speed limit of 55 miles per hour. The driving condition requires dividing attention resources across two primary task demands, driving and the DSVF task.

(4) Task 2C: A paced auditory serial addition test (PASAT) superimposed on the driving scenario and DSVF. PASAT was presented in a prerecorded standardized audio format. Single digits were presented serially every three seconds[40]. The participants had to add each new digit to the one immediately before it . A practice PASAT was done to familiarize the subjects with the test. This task dividing attention across multiple demands like auditory information, performing arithmetic, driving and DSVF task. PASAT task has been shown to simulate distraction and affect performance on frequency-doubling technology perimetry[41] and HVF sensitivity[42] and driving[43].

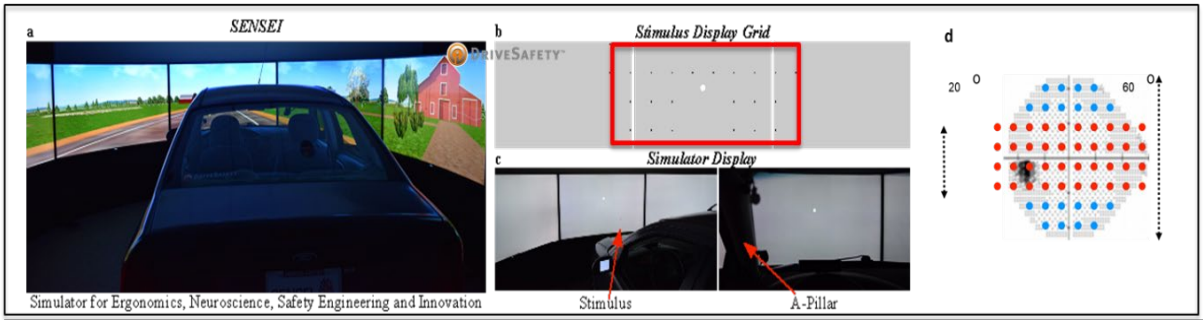


Figure 4: a) SENSEI (Simulator for Ergonomics, Neuroscience, Safety Engineering and Innovation) b) the stimulus grid used for the DSVF task c) red stimulus displayed and A pillar of the car d) red dots indicate the precise location of the field tested as compared to the retinal loci of a 24-2 HVF

The Montreal cognitive assessment (MoCA)[44], a cognitive screening tool, was done for all subjects at the beginning of the study. It is a reliable and valid tool that assesses 7 cognitive domains: visuospatial and executive functioning, object recognition, verbal memory, attention, verbal fluency, abstract reasoning, and orienting.[45] . The 25 question National eye institute Visual field questionnaire (NEI VFQ 25)[46] was completed in a self-administered format to assess vision related quality of life. The desktop based UFOV test was administered to assess visual processing speed.

2c: Analysis and statistics

Visual field index (VFI): VFI calculations estimate the unimpaired proportion of visual field, ranging between 0% (fully impaired) to 100% (fully intact). Monocular HVF-VFI values (labelled as HVF OD and HVF OS for right and left eyes) were directly acquired from the HVF performed in the clinic. Binocular (OU) integrated visual fields were derived from the right and left eye HVF for each subject using the binocular summation method described by Nelson-Quigg et al.[47] HVF VFI was calculated for the binocular integrated fields (labelled HVF OU*)* using Bengtsson and Heijl's technique.[39] The calculations have been described in detail previously[9] and are detailed in the appendix section.

Statistical analysis: All statistical analyses were performed using SAS/STAT software, Version 9.4, (SAS Institute Inc., Cary, NC, USA). Participant characteristics were compared between groups using t-tests and chi-square tests. Reproducibility of measurements for the glaucoma group was assessed using intraclass correlation coefficients (ICC). Control subjects were omitted from ICC calculations since the very small subject variability produced deceptively smaller ICCs. ICC values greater than 0.9 indicate high reproducibility. A logit transformation was applied to calculated visual field

values for data analysis and then back-transformed for reporting purposes. Generalized linear mixed models were used to analyze the transformed visual field data comparing the between subject effect, diagnosis (control/glaucoma); and the within subject effect, task, ordered by increasing levels of difficulty, adjusting for subject age. Correlation of multiple observations from each subject were accounted for with a random intercept model. A separate sub group analysis was done for subjects who completed all tasks upto task 2c. To include subjects with missing values, multiple imputation with appropriate analysis techniques were implemented, given the “missing at random” assumption seemed reasonable. A Logistic regression model with random effects was used to predict factors responsible for an inability to complete the PASAT task.

CHAPTER 3: RESULTS

We included 28 glaucoma subjects and 19 controls (table 1).The demographics, MoCA scores and the NEI-VFQ 25 scores are reported in table 1. Age and gender were significantly different in the glaucoma group as compared to the controls. The HVF-VFI is the control group ranged from 98-100% and in the glaucoma group ranged from 19-100% in the better eye and 16-99% in the worse eye.

Visual acuity was excellent in both groups with inclusion criteria being at least 20/40 in the worse eye. There was no significant difference in distribution of visual acuities between controls and glaucoma subjects. Twenty of forty seven subjects had 20/20 or better vision in both eyes, 35/47 subjects had 20/25 or better in the worse eye. Only 5 subjects (2 glaucoma, 3 controls) had 20/40 in the worse eye with only one subject with 20/40 in both eyes (glaucoma).

Patients were excluded if they were on any medications that caused daytime sedation. Medication lists were reviewed for all the participants. Seven subjects were on either PRN or night-time medications with potential sedating effects. One control and one glaucoma subject were on gabapentin at night, one glaucoma subject was using ambien at night, two control subjects were on tramadol PRN, one glaucoma subject was on alprazolam PRN, one control subject was on Seroquel.

Table 1: Characteristics of subjects:

	Glaucoma (n=28)	Control (n=19)	P value
Age (Mean ± SD)	70.82 ±10.95	61.16 ±13.20	0.01
Gender	12 women, 16 men	14 women, 5 men	0.037
Race	18 Caucasian (93%), 10 others	16 Caucasian (84%) 3 others	
MoCA (Mean ± SD)	25.29 ± 2.7 (range: 19 to 30)	25.89 ± 2.4 (range: 21 to 30)	0.4
NEI VFQ (Mean ± SD)	88.21 ± 6.8	90.8 ± 7.35	0.2

(SD: standard deviation, MoCA: montreal cognitive assessment, NEI VFQ: National Eye Institute Visual Function Questionnaire)

3a) Validating the new DSVF task:

3ai) Reproducibility: Reproducibility was tested by repeating each task twice. The DSVF task was highly reproducible. Intra class correlation (ICC) calculations for the 2 DSVF trials ranged from 0.91-0.97. In the glaucoma subject group, the mean difference in DSVF VFI between the two trials was 0.9-3.5% in task 1, 0.9 % in task 2A, 2.2 % in task 2B and 2.1% in task 2C. In the control group, the mean difference in VFI between the two trials of DSVF was 0.3-1% in task 1, 0.4% in task 2A and 0.9% in task 2B.

3aii) Comparison to clinic HVF: The DSVF gray scale in task 1 was subjectively very similar to the monocular and calculated binocular HVF (Figure 1) apart from the A-pillar scotoma (in green) which will be discussed in section 3b. In glaucoma subjects, the VFI calculations of the DSVF VFI for task 1 and HVF VFI corresponded extremely well (ICC of 0.8 for OD, OS and OU). ICC calculations were not meaningful for the control subjects due to lack of subject variability.

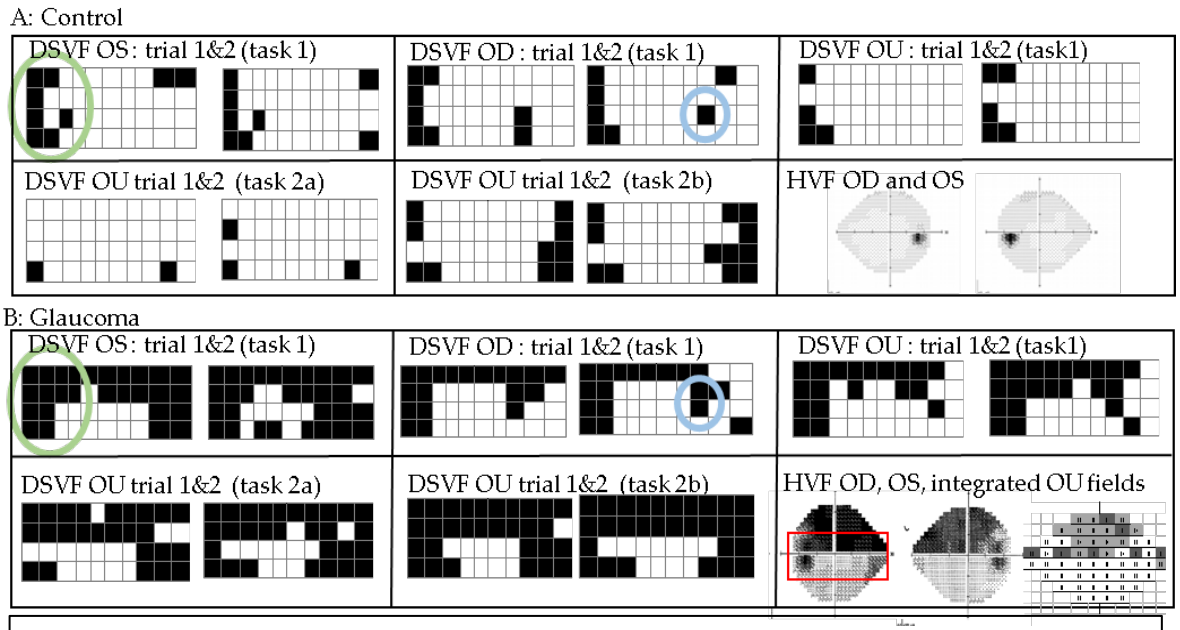


Figure 5 : Gray scales of DSVF outputs in controls (A) and glaucoma (B) in tasks 1, 2A and 2B. Each task was repeated twice (trial 1 and 2). Black represents a not-seen locus. Accurate positioning of blind spots (blue circle) is seen in monocular fields and A-pillar scotoma (green circle) is seen in all fields. HVF gray scales demonstrate similarity of gray scales in DSVF and HVF apart from the A-pillar scotoma (green). There is worse performance in the visual field task under increasing task load (task 2b). This is more pronounced in the glaucoma group.

3aiii) Blind spot mapping and eye tracking data: The blind spot was mapped accurately (15-21˚ location temporally) in 92/94 monocular DSVFs (Figure 1). Eye tracking data was

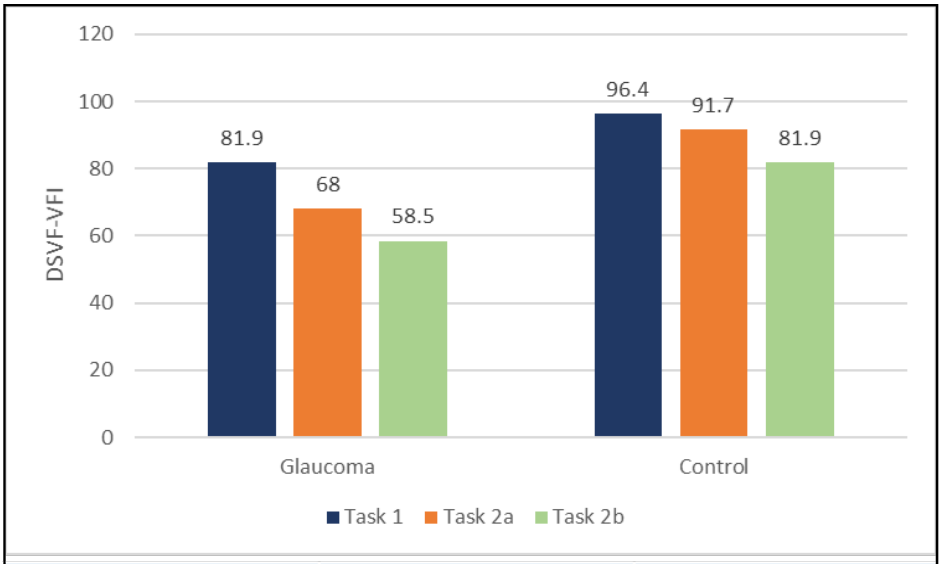
available for 13 DSVFs and showed excellent fixation throughout task 1 (average saccadic distance in the non-distraction task was 4.7 +/- 2.1˚)

3b) A-pillar scotoma: In all DSVF trials (Figure 1), a vertical scotoma in the left 21˚ - 27˚ location in the DSVF gray scale was noted corresponding to the vehicle's A-pillar. It was mathematically calculated in the control group as "HVF VFI – DSVF VFI", where the HVF-VFI is 100 by definition since the controls did not have any peripheral vision loss for both monocular and binocular DSVF . The A-pillar caused 10±12 % decrease in VFI OD, 9±3 % decrease in VFI OS and 4±3 % decrease in VFI OU.

3c) VFI change with different task loads: All subjects (47) completed task1 (one subject completed only one trial), 44 subjects completed task 2a (2 subjects completed only one trial), 41 subjects completed task 2b (1 subject completed only 1 trial) and 28 subjects completed task 2C (1 subject completed only 1 trial). 4 subjects had simulator adaptation syndrome and could not complete the tasks while the others did not wish to continue the experiment.

In both groups, glaucoma subjects and controls, the DSVF-VFI decreased with increasing task load ($p<0.001$). The subjects who completed all 3 tasks (n=28) were analyzed separately in a sub-group analysis and were found to have similar DSVF-VFI values as the complete data set (mean DSVF-VFI values in subjects for task 1, task 2a, task 2b, task 2c were 82%,68%,58% respectively and for controls were 96%, 92%, 82% and 62% respectively). Because of the significant drop-off, the PASAT task (task 2b) was not included in subsequent analysis.

The DSVFI decreased significantly more ($p<0.001$) in the glaucoma group from task 1 to task 2b (driving) (mean 22.5%+/-14.8) as compared to the control group (mean 14.5%+/-7.4)



Mean DSVF-VFI (95% CI)	Glaucoma (n=28)	Control (n=19)
Task 1 (no distraction, central fixation)	81% (72-88)	96.4% (85-97)
Task 2a (no fixation, naturalistic background)	68% (55-78)	91.7% (88-94)
Task 2b (driving)	58.5% (45-70)	81.9% (76-86)

Figure 6: DSVF-VFI values from glaucoma subjects and controls. There is decrease in DSVF-VFI with increasing task load in both glaucoma subjects and controls

Figure 7 has representative gray scales of the DSVF output from 2 control and 2 glaucoma subjects:

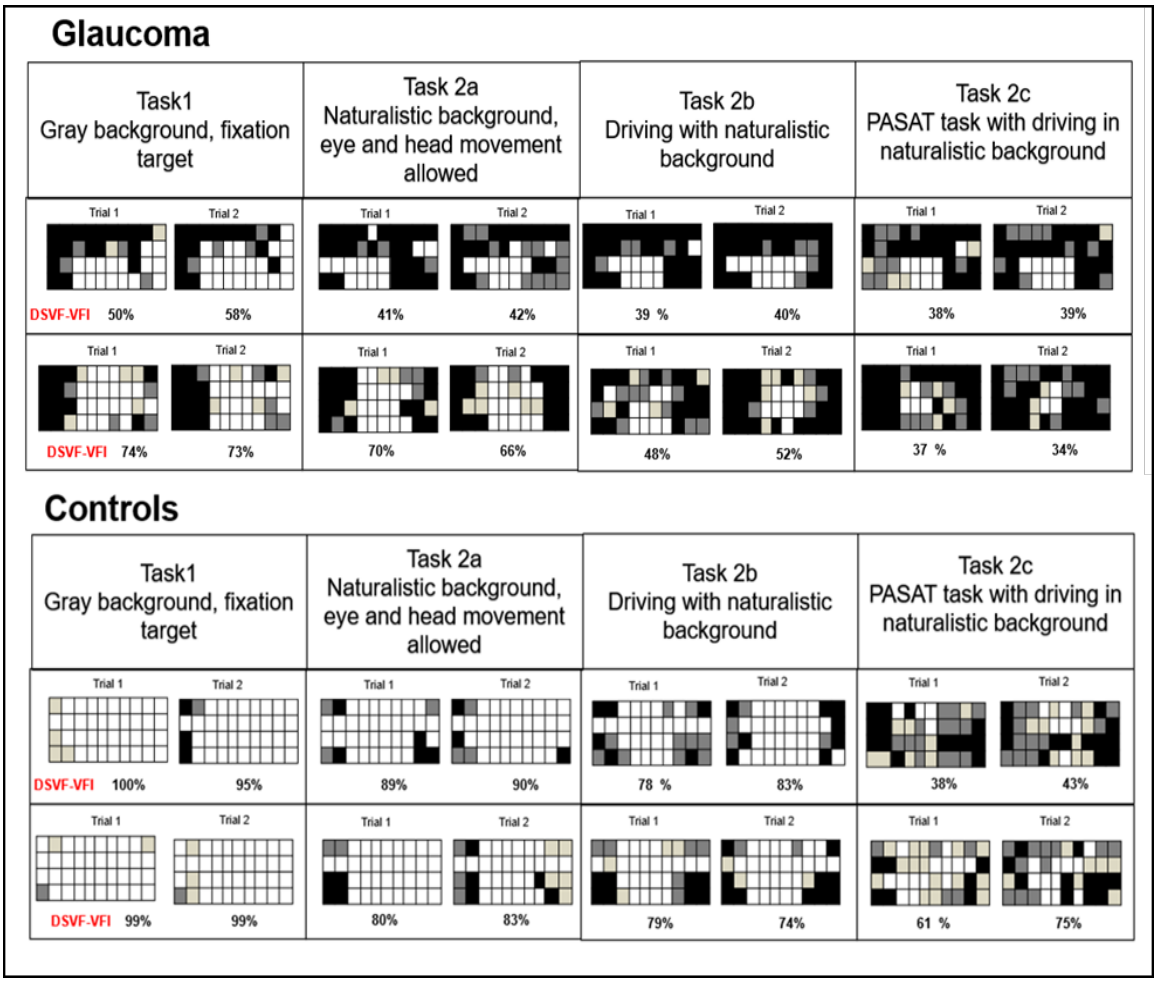
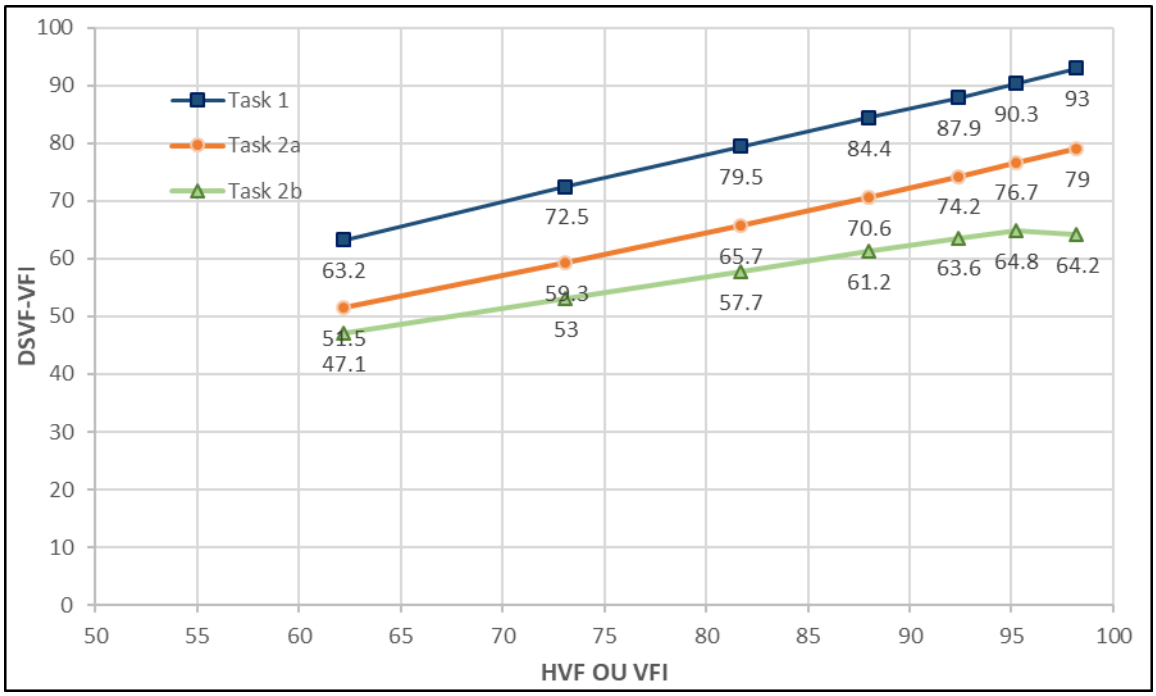


Figure 7: DSVF output demonstrating a progressive decrease in DSVF-VFI with increasing task load in 2 glaucoma subjects and 2 controls. Each horizontal line represents gray scales of DSVF of 1 subject. Each test was repeated twice.

3ci) Predictors for change in DSVF-VFI : When we evaluated the change in DSVF-VFI with HVF OU. age and MoCA as co variates, only the HVF OU was predictive of change in VFI (coeff : -0.99 , 95% CI -1.98 to -0.013, p=0.047). Age and MOCA were not significantly associated with change in DSVF-VFI. Age and HVF OU interaction was significant in this model (age related effect was more pronounced in suspect group than glaucoma group, difference between glaucoma group and suspect group is highest at

younger ages). When only glaucoma group studied, severity of glaucoma was not associated with delta DSVF-VFI. Other parameters studied (age, MoCA, VFI worse eye, VFI better eye ,VFI OU, VFQ, RNFLT) were also not associated with delta DSVF.

3cii) Predictive formula for change in DSVF under different task loads**.** A predictive formula was generated to calculate DSVF VFI using the methodology described above for 28 glaucoma subjects, keeping HVF OU values as an independent variable. Subjects in the control group had HVF OU values close to 100% with little variability so they weren't included in the predictive modeling. The predictive formula is displayed in Figure 3A for each task. These predictive formulas hold true for a VFI ranging from 60% to 99%.



Predictive formula to calculate DSVF VFI

$Y = 1 / (1 + EXP(-Y'))$

$X' = \log((1-x)/x)$ where x ranges from 60 to 99

Where X is the HVF-VFI and Y is the DSVF –VFI

To calculate Y'

Task 1

$Y' = 6.72+ + (99.61 * X') - (9.09 * X'^{2})$

Task 2A

$Y' = -29.78 + (99.6 * X') - (22.6 * X') - (9.09 * X'^{2})$

Task 2B

$Y' = -39.38 + (99.6 * X') - (38.7 * X') - (9.09 * X'^{2})$

Figure 8 : Graph of the predictive DSVF-VFI means at age 70. x axis is binocular calculated HVF OU (from clinic based visual fields) expressed as a fraction. y axis includes task1 (binocular static), task2A(binocular eye movement)and task 2B (Driving). The predicted DSVF-VFI during task 1 was calculated as 93 % (95%CI: 88-95) 80% (95%CI: 73-85) and 63% (95%CI: 52-73) for a subject with 99%, 82% and 62% HVF-OU VFI respectively (blue line with squares). The predicted DSVF-VFI in task 2a was calculated as 79% (95%CI: 68-87), 66% (95%CI: 57-73) and 52% (95%CI: 40-63) for a subject with 98%, 82% and 62% HVF-OU VFI respectively (orange line with circles). The predicted DSVF-VFI in task 2B was calculated as 64% (95%CI: 50-76), 58% (95%CI: 48-66) and 47% (95%CI: 35-59) for a subject with 98%, 82% and 62% HVF-OU VFI respectively (green line with triangles)

3d) Comparison to UFOV:

Due to logistic reasons, UFOV (desktop version) was performed in only 10 individuals (4 controls, 6 glaucoma subjects).

As expected, the DSVF-VFI (which is a measure of the degree of visual loss) correlated well with the UFOV measures of processing speed (r=0.44), divided attention (r= -0.85) and selective attention (r=-0.52).

The delta-DSVF-VFI (change in available field of view while driving) correlated well with the measure of selective attention (r= 0.66) and processing speed (r=-0.53) but not with the measure of divided attention (r= 0.17).

3e) Inability to complete PASAT (task 2c)

Subjects were allowed to discontinue the study at will. Out of the 41 subjects who completed task 2B, 13 could not complete task 2c (PASAT with driving task). A logistic regression modelling was performed to predict inability to complete task 2c with the predictor variables being gender, age, MoCA score, visual function score (VFQ) and HVF OU. A poor MoCA score was associated with increasing odds of inability to complete task2c. (odds ratio:0.51,95% CI 0.26- 0.9, p=0.019).

CHAPTER 4: DISCUSSION

Driving is a complex process involving visual recognition, visual attention, memory and motor coordination in a busy environment.[48] As the information processing model in figure 3 demonstrates, data from the visual system is a critical component of a driver's decision making response. We believe that a thorough understanding of all the intermediate steps in figure 3 is necessary to develop rehabilitative strategies that modify driving behavior in glaucoma. In this study, we focus on the effect of peripheral vision loss due to glaucoma on an individual's ability to perceive and attend a visual stimulus in a driving environment under different task loads.

4a: DSVF field task:

The DSVF task that we designed in our hi-fidelity driving simulator SENSEI fulfills our design aims to a) map the field of view in in realistic driving condition b) be comparable directly to clinic based perimetry c) allow comparisons of fields of view under different task loads d) study the processing capacity differences between different groups.

We validated and tested the DSVF task in controls and in patients with mild-severe glaucoma. The DSVF task is highly reproducible as shown by our results and past pilot data.[49] Accurate blind spot mapping and the similarity of the gray scales to HVF in task 1 (Figure 5) demonstrates the validity of the design. We have chosen to use visual field methodology used in the clinic (field of view, visual field index, field mapping etc) for the design (stimulus size, loci) and scoring of this stimulus detection task so as to allow a direct comparison with clinic perimetry to allow an extrapolation of our results to glaucoma patients.

<u>4ai) DSVF compared to currently available tasks:</u> The DSVF task fulfills our aims better than currently available technology.

It differs from the UFOV test by

a) Testing field of view across 60 degrees of horizontal field and 20 degrees of vertical field rather than the 10 degrees of view tested by the desktop version of UFOV

b) The DSVF output is a visual field index (estimate of available field of view) and a gray scale that gives a qualitative estimate of field of view. The DSVF task is customizable. We estimated the field of view under a no-driving condition, driving and driving with PASAT. The UFOV output is measures of processing speed with 2 attention tasks (selective attention, divided attention)

The delta DSVF output (DSVF –VFI in driving vs no distraction) was highly correlated with the selective attention UFOV score and UFOV visual processing speed in our subjects but not with the divided attention score. This could be because the central 10 degrees that the UFOV tests are preserved in most glaucoma patients. Presumably the divided attention task performance will be different when tested in areas of vision loss rather than areas of preserved vision. Glaucoma subjects do tend to have lower processing capacity as compared to controls, which may explain the correlation of our task with the UFOV selective attention scores. This will be discussed in subsequent sections (section 4c).

4b: A-pillar scotoma:

The DSVF task allows quantitative mapping of physical obstructions due to in-cab geometry such as the “A- pillar” . The A pillar scotoma, which has been previously studied using wide angled photographs[50], varies with the make of the car and has been identified as potential threat to safety while driving[51]. The A-pillar scotoma decreased field of view 9-10% monocularly and 4% binocularly in our experiment. This is of particular relevance to monocular patients and those with severe glaucoma. For example, a patient with a blind right eye and severe glaucoma in the left eye will lose an additional 9% of his tested visual field while driving due to the A-pillar scotoma.

4c: DSVF output under different task loads in glaucoma and controls:

The available field of view of a person is an interplay of the visual field, attentional capacity and the cognitive demand of the task being performed.[52] Visual search is our ability to process competing stimuli in parallel from a visual scene and direct attention to task related information.[53] Goal driven attentional shifts occur to enable us to allocate the attention to the most relevant part of the visual field in order to complete that action.[54]

Our DSVF task allows assessments of processing capacity in different groups- such as glaucoma subjects and controls – by comparing the available field of view in these groups under differing perceptual task loads. In the no-distraction task, DSVF-VFI was directly related to field of view (HVF) tested in clinic. As the task load increased, the available visual field (DSVF VFI) decreased in both groups (figure 6) as expected[19]. The increasing task loads used in our study in the form of a naturalistic background and driving resulted in diversion of the visual attention and consequent decrease in the functional visual field (DSVF-VFI).

We found that the decrease in DSVF-VFI while driving as compared to a no-distraction scenario was significantly larger in the glaucoma group than in controls (figure 6). This is similar to results in previous studies on a desktop simulator[28] and a large computer screen[27] that have demonstrated that visual search in glaucoma subjects is more sensitive to perceptual load as compared to controls. Our results suggest glaucoma patients may be impaired in completing multiple task demands, such as driving and visual field task. This could be due to 2 reasons:

a) Compensation for loss of vision represents a continuously present load on attention capacity: There is evidence that in adults with sensory loss, cognitive resources take on additional importance[55]. The presence of field loss can then be extrapolated to a perceptual load that the glaucoma patient has to process continuously while awake. Glaucoma subjects develop compensatory mechanisms while driving such as exploratory eye movements towards regions of field loss. [56,57]. Our own work (post-hoc analysis of driving simulator data from this study) shows that drivers with larger binocular visual field defects showed more restricted, spatially biased eye movements, and greater task load led to more spatially biased eye movements in drivers with larger binocular visual field defects[58]. When we looked at the driving performance in the simulator in this task (post-hoc analysis), we found that overall the driving performance was similar in both glaucoma subjects and controls apart from some parameters of steering control [48].

Glaucoma subjects may have lower processing capacity leftover after compensating for their vision loss and are a) unable to accommodate the increasing perceptual task load imposed by driving and b) miss visual stimuli in the periphery in the DSVF task.

b) Glaucoma patients have decreased cognitive capacity as compared to controls: Glaucoma is a chronic neurodegenerative illness of the optic nerve. Due to similar pathophysiology and age distribution, there has been considerable research on the link between glaucoma and other neurodegenerative diseases of aging[59]. There is a greater prevalence of glaucoma seen in Alzheimer's disease patients in epidemiological studies[60] and in smaller cohort studies of institutionalized Alzheimer's disease[61,62]. But the reverse has not held true- large epidemiological studies have not shown an increased incidence of Alzheimer's disease in glaucoma patients[63,64]. Subjects with glaucoma had similar MoCA scores as compared to controls in our work and in literature

[48,65]. Subjects with glaucoma do appear to have impaired visual processing ability[11] which may lead to worse outcomes on our visual search task.

Further work is needed to explore the relationship between a glaucoma diagnosis (rather than degree of vision loss) and processing capacity.

4d: Predicting driving field of view based on clinic based HVF

We developed a predictive formula (Figure 8) to estimate the "available" field of view of a glaucoma patient from their clinic based HVF tests. This predictive formula was derived only from the glaucoma group. When the predictive formula was applied to a HVF-VFI of 99% (almost normal HVF), the predicted DSVF values (93% DSVF-VFI for task 1 from figure 8) matched those of the control group in our experiment (96% DSVF-VFI for task 1 figure 6) which validates the formula. The change in DSVF VFI with increasing task load was consistent at higher HVF VFI values (80-99%) whereas the change seemed to be less at lower HVF VFI values (Figure 8) although statistically we found that the severity of field loss was not associated with the delta-DSVF-VFI. To the best of our knowledge, there are no studies in literature comparing the clinic HVF to available visual fields while driving. This predictive formula is novel in that it helps to transform clinic derived perimetry values to real life driving scenarios and gives a quantitative assessment of the driver's available field of view under different conditions. For example, a patient with a HVF-VFI of 80% (moderate glaucoma) will have a DSVF-VFI of 55%- which is severe field loss when extrapolated from figure 8. This is a useful patient education tool to give insight on the implications of visual field loss while driving.

4e: Limitations of the study

Forty percent of our subjects were unable to complete the PASAT portion of the study. PASAT is a neuropsychological test that involves a complex interplay of attentional resources, information processing speed and working memory[66] and has been shown to

correlate with MoCA scores in various neurological diseases[67] and general intelligence in healthy adults.[68,69] In our study, only the MoCA score was found to be predictive of the inability to complete this task. We found no significant association of age, gender and severity of field loss or diagnosis of glaucoma. Age and gender have been shown to affect PASAT performance[70] in the past. We did have a very narrow distribution of age in our subjects, which may explain our results. However, we did not measure the PASAT scores of our participants and the association between performance on PASAT task and the visual field task.

There could be concerns about the external validity of our study and translation of our results to on road driving scenarios, however, previous work has shown good correlation between simulator performance and on road driving.[71,72] Our predictive formulas are valid only for certain HVF VFI range (60-99). Therefore, caution should be exercised while generalizing these findings to the population. Also, future studies involving driving in everyday scenarios like driving through a busy road, different weather conditions and night time driving with various severity of glaucoma and a larger sample size are warranted.

Other limitations of the study include a small sample size and not measuring contrast sensitivity which has been shown to be an important predictor of driving performance. Our controls were very homogenous (in terms of age range and by definition in terms of field characteristics). This caused clustering at one end of the spectrum. We accounted for this by analyzing the glaucoma group separately in all cases.

4f: Conclusions:

The DSVF is a novel driving simulator task that allows us to map out the part of the driving environment that is “missed” under conditions of divided attention and to quantify the extent of this visual field change while driving under varying task loads. Subjects with

glaucoma have a larger decrease in the “available” field of view with increasing task load as compared to controls which is likely a function of their diagnosis, their constricted peripheral vision and reduced ability to efficiently distribute attention across competing task demands. Our results give us a better understanding of patient response to road hazards in an area of compromised visual field and could potentially lead to the development of vehicular alert systems when obstacles appear in areas of uncompensated field defects, similar to blind spot alert systems.

Future studies will focus on using the DSVF task to a) evaluate the effect of these between group processing capacity differences on driving performance b) evaluate which region of the field loss (such as superior, inferior, central) is most impacted by changing task loads c) evaluate the impact of different regions of field loss on driving specific tasks under different perceptual task loads.

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APPENDIX

An integrated binocular visual field was created using the participant's most recent right and left HVF, using the binocular summation method described by Nelson-Quigg et al.

(Nelson-Quigg JM, Cello K, Johnson CA. Predicting binocular visual field sensitivity from monocular visual field results. Invest Ophthalmol Vis Sci. 2000 Jul;41(8):2212–21.)

The following steps were followed:

1. Threshold values (TV) for all points in the right and left HVFs were converted from logarithmic decibel values to antilogarithmic values.

   Antilog value (S) = $10^{TV/10}$

2. The binocular sensitivity (S_B) was then calculated for each point using the quadratic summation equation

   $S_B = (S_R^2 + S_L^2)^{1/2}$,

   Where S_R represents the sensitivity (antilog threshold value) of a point in the right eye HVF and S_L represents the sensitivity of the corresponding point in the left eye HVF.

3. The S_B values for each point were converted back to their logarithmic decibel to obtain the threshold value for the binocular visual field.

   $S_B db = 10 \log_{10} (S_B)$

4. Binocular Total deviation plot calculation

   a. Expected threshold (e) values for each point in the right (e^{OD}) and left eye (e^{OS}) were calculated by subtracting the threshold value of each point from the total deviation (TD) plot value of each point

      e = TV – (TD)

   b. These were converted from logarithmic decibel values to antilog values.

      Antilog value = $10^{e/10}$

   c. The expected threshold values for the binocular fields were then calculated from the monocular expected threshold values using the same quadratic summation formula described above to calculate the S_B and were reconverted to their logarithmic decibel

      $$e^{OU} = \log \sqrt{(e^{OD})^2 + (e^{OS})^2}$$

   d. The expected threshold values of the binocular fields (e^{OU}) were converted back to log scale.

      e^{OU} db = **$10 \log_{10}$ (e^{OU})**

   e. The difference between the logarithmic threshold values (S_B dB) and the expected threshold (e^{OU} dB) was calculated to obtain the binocular total deviation (TD) plot.

      Binocular TD plot value = S_B dB - e^{OU}dB

5. Binocular VFI calculation

Binocular VFI was calculated using the method described by Bengtsson and Heijl.

(Bengtsson B, Heijl A. A visual field index for calculation of glaucoma rate of progression. Am J Ophthalmol. 2008 Feb;145(2):343–53)

a. Test points having a positive value on the total deviation plot were considered normal and were scored 100%.
b. Sensitivity for the remaining points was scored in percent as

   100- [(|total deviation|/ age-corrected normal threshold) * 100]

   where |total deviation| is the absolute value of the numerical total deviation value and the age corrected normal threshold is the ET value.

c. Bengtsson and Heijl's weighting procedure was applied to the test points to give a higher importance to central and paracentral points as compared to the peripheral points. For this purpose, the test point pattern was divided into five concentric rings of increasing eccentricity. The central four points were allotted a weight of 3.29, and with increasing eccentricity, the weights decreased from 1.29, 0.79, and 0.57 to 0.45 (as shown below).

			0.57	0.57	0.57	0.57			
		0.79	0.79	0.79	0.79	0.79	0.79		
	0.57	0.79	1.29	1.29	1.29	1.29	0.79	0.57	
0.45	0.57	0.79	1.29	3.29	3.29	1.29	0.79	0.57	0.45
0.45	0.57	0.79	1.29	3.29	3.29	1.29	0.79	0.57	0.45
	0.57	0.79	1.29	1.29	1.29	1.29	0.79	0.57	
		0.79	0.79	0.79	0.79	0.79	0.79		
			0.57	0.57	0.57	0.57			

d. The VFI was calculated as a mean of all these weighted points in percentage.