

Detecting glaucomatous damage: evaluation with contrast independent tasks

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Several studies have indicated that contrast-dependent tasks, such as detecting threshold stimuli, may be more effective in discriminating glaucoma from normal groups if external noise is added to the stimulus. We sought to determine if the same were true for contrast-independent tasks. Subjects were 15 patients with glaucoma and a group of 20 normals with the same mean age. We employed two contrast-independent tasks, orientation defined texture and dot numerosity discrimination. The stimulus was presented on a computer controlled video monitor. One side of the display contained a standard and the other contained a non-standard target. For each task, noise was added by perturbing the main feature of the display, dot number or line orientation, by a Gaussian distribution truncated at 2 standard deviation units. There were four noise levels for each task. Subjects viewed the stimulus display and made a spatial two-alternative forced choice judgment. Subjects judged the side of the orientation texture which contained a sub-region with a different angle and the side of the dot figures which had the larger number of dots. Glaucoma patients performed more poorly than normals in discriminating the orientation texture ($p < 0.05$) and in judging dot numerosity ($p < 0.05$). This was true even in the absence of added external noise. Adding external noise did not increase the differences between glaucoma patients and normals. Unlike contrast-dependent tasks in which the differences between normal and glaucoma patients are increased when external noise is added, contrast-independent tasks show maximal differentiation between the two groups without added noise. Tasks such as texture discrimination and dot numerosity may be useful in detecting glaucoma.

1. Introduction

Open angle glaucoma (OAG) is the second leading cause of blindness in the industrialized world [1]. In the United States, OAG is estimated to affect about 1.86% in adults aged more than 40 years and affects about 2.25 million Americans [2].

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African Americans have almost 3 times the age-adjusted prevalence of OAG than European Americans.

OAG is a multi-factorial optic neuropathy characterized by progressive damage to the optic nerve head with visual field (VF) loss. Many, but not all, patients with OAG have elevated intraocular pressure (IOP), the primary risk factor of the disease [3]. VF loss and increased disc cupping are presumed to result from ganglion cell death secondary to elevated IOP [4]. The degenerated optic nerve (ON) fibres are distributed throughout the ON, indicating that ganglion cell damage is not limited to one area or type [5–7]. Early treatment may be essential for preventing irreversible loss of visual function; therefore development of sensitive tests for early detection of OAG could be a major step in blindness prevention [1, 8–11].

Efforts at early detection of OAG using the VF and IOP have proved disappointing. By the time glaucomatous VF deficits are clinically detectable about 20% of the ON fibres in the affected region have degenerated [12]. Patients with increased IOP develop glaucoma at $\leq 1\%$ per year [13]. Consequently, IOP, while a major risk factor, is not very predictive of who will develop glaucoma.

Because of the potential benefits from early detection, several strategies have been applied to develop OAG screening tests. However, the inherent population variability of normal function suggests that there are limits to the likely success of any screening technology. Let us consider this issue of variability from the perspective of anatomical variability. The number of ON fibres in normals has a standard deviation of about 20% of the mean [14, 15]; therefore, if one assumes that on average the number of ON fibres in the optic nerves of patients who develop glaucoma is the same as in those who do not develop glaucoma, the number of fibres of an individual ON must be reduced at least 40% before an individual nerve could be identified as abnormal with 95% confidence (see [15–18]). The underlying anatomical and physiological variability of the eye and visual system limits the precision of tests of structure or function.

Several general strategies are possible to develop functional tests of glaucoma detection. One strategy is to develop tests which increase the mean difference between normals and OAG suspects with OAG and/or reduce the groups' response variability. One may decrease the variability of normal subjects by using tasks to which they are very sensitive, for example, large target or full field flicker [19]. Alternatively, one may increase the difference in group means by increasing the demands on the visual system, so that the slight differences in performance between normals and patients with glaucoma are magnified [20, 21].

Consideration of the underlying pathology might provide clues for creating sensitive glaucoma screening tests. Data indicate a greater loss of large diameter retinal ganglion cells in glaucomatous eyes [5–7]. Some authors have interpreted this to suggest that glaucoma produces a loss in functions subserved by the magnocellular pathways (e.g. [22]). Early diagnosis would then best be accomplished by testing functions mediated primarily by the magnocellular pathway such as flicker, motion detection or frequency doubling [23–26]. However, there is also evidence of poor colour vision in glaucoma patients [27]. Specifically, there is a marked deficit in the ability to detect blue objects on a yellow background [28].

Since colour vision is a function mediated by the parvocellular and koniocellular systems [29, 30], the effects of glaucoma cannot be assumed to be specific to a single pathway.

An alternate hypothesis is that glaucoma affects a broad range of retinal cells, especially in its early stages [5–7]. The functions of sparsely distributed cells may be more easily affected because of their smaller number under relatively standard testing conditions [23, 24].

We have proposed a strategy of testing for glaucoma based on stressing the visual system by adding noise to visual stimuli and demonstrated that in many situations visual tasks which artificially stress the visual system may be more effective in identifying neural damage from glaucoma [20]. The stimuli in our previous experiments were contrast dependent, the noise was luminance noise and the threshold we determined was contrast. The present experiments are similar to our earlier experiments conceptually. However, the stimuli are contrast independent and the noise is second-order noise.

1.1 Contrast dependent and contrast independent tasks

Different tasks appear to be limited by different noise sources; observers perform some visual tasks using internal measurements made at or near the light transduction stage of visual processing and other tasks using cortical measurements (e.g. [31–33]). In the first type of task, such as contrast detection, departure from the ideal observer is due primarily to a peripheral, equivalent noise source [34]. Performance on the second type of task is contrast independent once the targets reach 2–3 times threshold. Examples of such tasks include discrimination of spatial frequency, temporal frequency and orientation [32], direction of motion [35], letters [36, 37], sampled waveforms [38] and spatial intervals [31]. Contrast-independent tasks appear to differ fundamentally from contrast-dependent tasks such as contrast detection; they appear to be limited by a second, central noise source (e.g. [32, 39]).

Our stimuli consisted of dots or short line segments composed of high-contrast dots. Neural efficiency measured by performance on tasks such as dot numerosity approach theoretically perfect levels [40, 41]. One advantage of displays composed of small discrete elements, such as dots or line segments, is that when each individual stimulus element is clearly visible, it can be assumed that the discrimination task is testing neural mechanisms ‘beyond the point of light transduction’ [42, 43]. Using suprathreshold dots should make optics and photon noise minimal factors.

2. Methods

2.1 Subjects

The experiments were part of an exploratory series conducted under contract from the US Air Force. The intent was that the experiments should be applicable to the evaluation of USAF personnel. Therefore, subject age had to be within the accepted ages for USAF pilots (21–55 years), visual acuity had to be 20/20 or better, and visual field defects could not impinge on the central 20 degrees.

Subjects were 20 normals (mean age = 39 years) and 15 patients with glaucoma (mean age = 40.2 years). The 1.2-year difference in mean ages was not statistically significant ($p > 0.10$). The eye with the better visual function, i.e. better acuity or if acuity were equal with less field damage, was tested. All patients had visual acuity of 20/20 or better at the viewing distance of 1 m in the tested eye. No patients had other visual diseases or systemic diseases which might have visual complications. Table 1 presents the clinical information on the 15 glaucoma patients.

2.2 Stimulus conditions

The stimuli were presented on a RGB monitor. The field size was 15×11.4 arc deg at a viewing distance of 100 cm. The screen illuminance was 21 lux. Stimuli were presented for 666.67 ms (40 of 60 frames). Stimuli were black on a grey background. In the centre of the screen was a red outline circle subtending 0.17 arc deg to aid fixation.

2.3 Procedures

2.3.1 Thresholds. Thresholds were measured on two tasks, discrimination of (1) dot number and (2) orientation differences in two line textures. To create noise, a Gaussian distribution truncated at two standard deviations perturbed the number of dots or line orientations. Noise level was defined as the standard deviation of the distribution. Each task had a total of 4 noise levels in its stimulus sequence. Thresholds were determined using a 2 spatial alternative forced choice method in conjunction with a staircase with a 2 down, 1 up staircase rule. Auditory feedback was provided regarding correctness of performance. Prior to the beginning of each task, the subject was given an opportunity to practice the task in the no added noise condition. The choice of which task to present first was alternated pseudo randomly so approximately half of the subjects in each group began their testing with each task. The sequence of testing within tasks was fixed. It began with the no added noise condition progressed through the lower noise levels to the highest added noise condition.

2.3.2 Orientation texture discrimination. The stimulus area consisted of a set of 144 lines (12 columns \times 12 rows) with a subset of 24 lines (3 columns \times 8 rows) which were of a different orientation than the surrounding lines. The stimulus field containing the lines was square and subtended 10.29 arc deg on each side. Individual lines subtended 0.859 arc deg in length and 0.048 arc deg in width. The target area was located 1.146 arc deg to the left or right of fixation and subtended 2.6×6.9 arc deg. The standard line orientation was 45° . Trials began with an orientation difference of -20° (i.e. the target region had an orientation of 25°). The difference changed in steps of one degree. The standard deviations of the orientations within the background and target regions, i.e. the four noise levels,

Table 1. Clinical features of patients in the glaucoma group.

Group#	Age	Diagnosis	OD				OS				Treatment
			IOP at test	Highest IOP	Visual defect field	Optic nerve	IOP at test	Highest IOP	Visual defect field	Optic nerve	
1	39	OAG	24	27	Superior scotoma	0.2	22	27	Superior bjerrum	0.3	None at time of test planned to start on timoptic
2	39	Pigmentary dispersion glaucoma	15	27	Nasal step	0.3	15	27	Normal	0.3	Propine betagan
3	32	OAG	14	45	Superior arcuate	0.8	15	24	Superior bjerrum	0.5	Tim & betoptic
4	48	Low tension glaucoma	12	16	Nasal step	0.8	12	18	Arcuate	0.8	Betoptic 0.5
7	48	OAG	17	27	Nasal step	0.6	18	24	Normal	0.5	Tyroptic xe
5	50	OAG	20	43	Arcuate	0.65	20	25	Superior/inferior bjerrum	0.5	Betagan
6	45	OAG	19	23	Nasal step	0.6	20	26	Superior arcuate	0.6	Betoptic 0.5
8	32	OAG	24	30	Scotoma Scotoma	0.45	25	30	Step Step	0.4	Timoptic XE
9	32	OAG	18	32	Nasal step	0.3	19	28	Normal	0.1	Betiopidine
10	48	OAG	18	21	Enlarged blind spot	0.3	18	21	Enlarged blind spot	0.4	None at time of test planned to start on timoptic
11	38	Pigmentary dispersion glaucoma	12	-	-	0.85	13	-	-	0.7	Pilocarpine
12	48	Steroid dependent glaucoma	29	33	Superior field	0.3	31	33	Superior field	0.3	Pilocarpine
13	21	Narrow angle	22	33	Superior field	0.6	21	31	Normal	0.6	Occupress
14	35	Surgery right eye; Only OS tested	16	33	Superior scotoma	0.7	21	23	Nasal step	0.5 0.5 0.5	None at time of test; planned to start on timoptic
15	48	OAG	24	28	Superior field	0.7	24	29	Normal	0.5	Timoptic, propine

were 0°, 10°, 15° and 20°. The individual orientations of lines were determined independently.

2.3.3 Dot numerosity discrimination. The target areas consisted of two rectangles each outlined with a red line. Each rectangle subtended 2.6 × 6.9 arc deg and was

located 0.17 arcdeg on each side of the fixation circle. Within the rectangle there were dots which subtended about 0.05 arcdeg. The standard number of dots was 100. The beginning difference in dot number was 40. The difference changed with a step size of one dot. The number of dots in the two rectangles was perturbed independently with noise levels (i.e. standard deviations) of 0, 5, 10 and 15 dots. The sampling from the noise distribution was independent for the two regions.

2.3.4 Data analysis. The effects of glaucoma on numerosity and orientation defined texture were evaluated using an analysis of variance (ANOVA) for repeated measures for each test separately (2×4 ANOVA). Statistically significant ANOVAs were followed up with *t*-tests to compare the differences in means of normal and glaucoma patients at each noise level. Because differences in the numerical values between the two tests made it difficult to compare them directly, we also compared the two tests using the area under the receiver operating curve (ROC). ROC area is a non-parametric method of comparing tests.

3. Results

3.1 Orientation texture discrimination

The effects of noise on orientation texture discrimination are presented in figure 1. In general, as noise level increased the thresholds increased. However, there was no great change in threshold differences between the two groups as noise level increased.

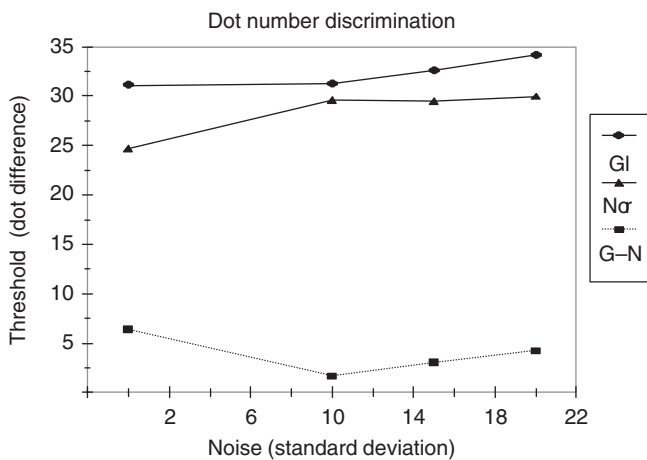


Figure 1. Discrimination of dot number. The Y axis indicates the threshold in number of dots which differed between the standard and the non-standard regions. The X axis indicates the standard deviation of the Gaussian noise which perturbed the number of dots in the two regions. The legend indicates GI for glaucoma group, Nor for the normal group and G-N for the difference between the glaucoma and normal groups. The greatest difference between glaucoma and normal patients was under the no noise level condition.

The ANOVA to examine the effects of noise on orientation texture discrimination indicated two statistically significant main effects, one for group ($F = 14.66$; $df = 1, 33$; $p = 0.000 546$) and one for noise level ($F = 19.99$; $df = 3, 99$; $p < 0.000 0005$) with no significant interaction effect between noise level and patient group ($p > 0.10$). Neither the absolute size of the difference nor its statistical significance increased with increasing noise level. Under the no noise condition the difference between glaucoma and normal patients is highly significant (5.7 arc deg, $p = 0.006$). As external noise was added the difference between the two groups declined. At noise levels of 5 and 10 arc deg, the differences between the two groups were 4.7 ($p = 0.007$) and 3.3 ($p = 0.05$) deg respectively). However, the difference at a noise level of 15 arc deg (2.31 deg) was not significant.

3.2 Dot numerosity discrimination

The effects of noise on orientation texture discrimination are presented in figure 2. In general, as noise level increased the thresholds increased. However, there was no great change in threshold differences between the two groups as noise level increased.

The ANOVA to examine the effects of noise on orientation texture discrimination indicated two statistically significant main effects, one for group ($F = 13.91$; $df = 1, 33$; $p = 0.000 743$) and one for noise level ($F = 19.54$; $df = 3, 99$; $p < 0.000 0005$) with no significant interaction effect between noise level and patient group ($p > 0.10$). Students *t*-tests indicated that the differences between normal subjects and the patients with glaucoma were statistically significant without

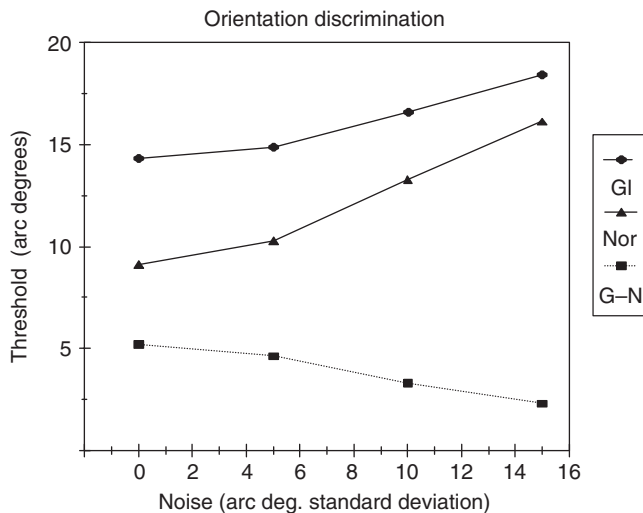


Figure 2. Discrimination of orientation differences between two textures. The Y axis indicates the threshold in degrees of arc. The X axis indicates the standard deviation of the Gaussian noise which perturbed the orientation of individual line elements in the texture. The legend indicates Gl for glaucoma group, Nor for the normal group and G-N for the difference between the glaucoma and normal groups. The greatest difference between glaucoma and normal patients was under the no noise level condition.

noise (noise level = 0; difference = 6.4; $p = 0.005$). At higher noise levels the thresholds of both groups increased but the difference between the groups did not (noise level = 10, difference = 1.7, $p = 0.39$; noise level = 15, difference = 3.1, $p = 0.111$; noise level = 20, difference = 4.26, $p = 0.01$).

3.3 ROC comparisons

In general both orientation texture discrimination and dot numerosity discrimination had statistically significant ROC areas (orientation: from no noise: $A = 0.77$; $p = 0.0005$ to noise = 15: $A = 0.69$; $p = 0.02$; dot: from no noise: $A = 0.77$; $p = 0.0005$ to noise = 10; $A = 0.550$; $p = 0.3088$). Comparing the optimum, no noise condition of each task failed to show a statistically significant difference between the two tasks in discriminating between the two groups ($p > 0.01$).

4. Discussion

Both dot numerosity and orientation discrimination are impaired in patients with glaucoma who have normal visual acuity with no central visual field changes. This difference is present with or without noise perturbation. We will discuss the results first in the context the special aspects of the stimuli, second we will consider noise and signal detection models of human visual performance which may suggest confounds, and last we will consider clinical applicability.

4.1 Signal detection models and noise

Because our glaucoma patients did not have advanced glaucoma, we did not expect to observe statistically significant differences between normal and glaucoma groups in numerosity and orientation texture discrimination; however, we did. We expected to find that differences between normal and glaucoma groups would increase as second-order noise was added. They did not. The results appear inconsistent with the implications of ideal observer models as we originally conceptualized them. However, there are two possibilities within the model that might explain the failure to observe the expected results. They are observer uncertainty and internal noise.

4.1.1 Uncertainty. Uncertainty about the task or stimulus can account for a large portion of human threshold performance [44]. Uncertainty enters into the ideal observer model presented earlier as another multiplicative factor that has the opposite effect of efficiency (see [45]). In other words, uncertainty can mimic the effects of reduced efficiency and reduced uncertainty can mimic improved efficiency [44]. We were aware of the potential confounding effects of uncertainty; therefore, we attempted to minimize the differential effects of uncertainty on our results by training subjects prior to testing them. However, if we were unsuccessful in the attempt, as the patients gained experience in the task their uncertainty about the task

might have been reduced. If glaucoma patients started out with greater uncertainty, differences between the groups could even be reduced as noise levels increased.

If decreased uncertainty accounted for the failure of noise to increase separation between the groups on dot numerosity and texture discrimination, one might expect uncertainty to have had a similar effect in our earlier studies employing contrast-dependent tasks masked by luminance noise [20] in which noise was effective in elevating thresholds. Procedural differences in testing may be important if changes in uncertainty account for our data. One procedural difference between the earlier studies with contrast-dependent tasks and those with contrast-independent tasks was that subjects received feedback as to the correctness of their responses in the contrast-independent tasks while they did not in the contrast-dependent tasks. Therefore, over time subjects were more likely to learn the task and a strategy for improving their performance (i.e. their uncertainty would be reduced). A second procedural difference is the degree of training given patients at different noise levels in the current experiments compared to the previous experiments. Patients in the contrast-dependent tasks were given brief training at each noise level. In the discrete tasks, patients were trained extensively in the no noise condition, but no further training was provided.

4.1.2 High internal noise. A second possible explanation other than uncertainty may be high internal noise. An important aspect of the model presented is internal noise [34, 46]. If the internal noise is high relative to the external noise levels used, accurate estimates of efficiency and internal noise may not be possible using the strategy employed in these experiments. If the internal noise on these tasks were high then it might not be possible to increase separation with added noise. There is little evidence from other studies that internal noise is high relative to the noise levels we have used. In fact, we have argued that the internal noise should be less for these tasks because the stimuli are suprathreshold.

We did estimate internal noise for our conditions. For dot numerosity the means ranged from about 25 to 35 dots and for orientation the means ranged from about 10 to 20°. Therefore we cannot exclude the possibility that with higher noise levels we would not have found an effect of noise consistent with original hypothesis that increased noise would improve the separation between the groups.

In summary, we cannot exclude possible confounds which may account for the failure to observe increased differences between normal subjects and patients with glaucoma as noise increased resulted. These potential confounds were procedures which alter the level of uncertainty and a choice of noise levels which was not sufficiently higher than the subjects' internal noise.

4.2 Contrast-independent tasks

Even in the absence of external noise, there were statistically significant differences between the normal subjects and those with glaucoma. This is quite different from what we observed in contrast-dependent tasks [20] and, probably, reflects the special characteristics of contrast-independent tasks and the specific contrast independent tasks we employed.

Glaucoma is defined by ganglion cell death as evidenced by optic disc changes and visual field deficits. Until recently the implications of the loss of ganglion cells for more central functions has been largely ignored. However, recent evidence indicates that alterations in the numbers of neural cells and their activity levels occur at all levels of the visual system. Photoreceptors are lost in a patchy fashion [47]. Ganglion cells have altered dendritic fields [48, 49] as well as reduced numbers and activity. These reduced inputs lead to changes in the numbers and activity of active relay neurons in the lateral geniculate nucleus [49, 50] that culminate in altered properties of cortical neurons [51–55]. Even brief elevation of intraocular pressure disrupts orientation tuning in feline cortex [55]. Moreover, in at least one primate model of glaucoma, metabolic changes can be observed in the visual cortex prior to observation of changes in the retina or optic nerve [56].

Contrast-independent tasks, such as orientation defined texture and dot numerosity discrimination, appear to be limited by more central, cortical level processes while contrast-dependent tasks, such as contrast sensitivity, appear to be limited by earlier neural processes [31–33, 39]. Our use of stimuli with small discrete elements are thought to tap cortical processes which are at higher levels than those at which functions such as contrast sensitivity or colour vision are determined [44, 45]. This is almost certainly true of orientation texture discrimination. Orientation tuning of cortical cells is contrast independent and there is no substantial orientation tuning before the visual cortex [57].

One way to conceptualize texture and dot numerosity discrimination is to presume that they rely on cortical processes which sum over a number of lower level receptive fields, i.e. at the level of the cortical layer 4c, the lateral geniculate, the ganglion cells and ultimately the photoreceptors. If lower level neural cells are either absent or not functioning optimally, these cortical processes cannot combine their inputs as effectively and thresholds for cortically-dependent tasks are impaired.

In both of our tasks, patients must integrate information across small regions of the visual field to perform the tasks. Small regions of impaired vision or a generalized impairment across the central visual field could impair patients' ability to perform these tasks. This type of explanation is clearly plausible in the case of orientation texture discrimination as oriented cortical receptive fields are presumed to derive their orientation tuning by combining inputs from a number of lower level receptive fields with more circular receptive fields [57]. If the lower level cells which provide input to the orientation selective cells are absent or function less well, orientation tuning will be reduced and orientation defined texture discrimination will be decreased. This would be true even in the absence of external noise.

If the rationale presented above were correct, one would expect that the internal noise of observers with glaucoma on these tasks would be elevated with little or no change in efficiency relative to the normal observers. This would have precisely the effect that we have observed. Differences between the two groups would be present without noise and adding external noise would have minimal or no effect. We tested these internal noise and efficiency predictions. Although the internal noise of patients was greater than that of normal subjects, the difference was not statistically

significant given our sample size. There were no statistically significant differences in efficiency either.

4.3 Clinical relevance

The ability of dot numerosity and orientation defined texture discrimination to differentiate patients with glaucoma from normal subjects in the absence of noise when more standard tests such as contrast sensitivity fail to do so (see [20]) indicates that the tasks may be useful in glaucoma detection. However, the results may suggest a more broadly based change in the approach to glaucoma detection. Most tests of glaucoma are directed toward detecting a specific ganglion cell function, often a ganglion cell function that can be related to a specific ganglion cell type. Fewer tests have been developed which specifically target cortical functions that rely on ganglion cell integrity. Other than our own study, we have been able to identify only two groups of studies involving humans that targeted the effects of glaucoma on cortical functioning, studies of the effects of glaucoma on stereopsis [58–60] and on vernier acuity [61, 62]. The earliest rationale for investigating stereopsis in glaucoma patients was that stereopsis was presumed to be subserved by the magnocellular system, therefore the cortical function reflected relative loss of a specific neural pathway [57].

We performed *post hoc* comparisons of the area under the ROC curves of the texture discrimination and dot numerosity tasks in this experiment with the best tasks from our prior experiment [20]. There was not a statistically significant difference; however, the areas for texture and dot numerosity discrimination were actually greater.

5. Conclusion

The data indicate that cortical tasks, e.g. texture discrimination and dot numerosity discrimination, are at least as good and may be better at detecting glaucoma than lower level tasks such as contrast detection even when these are optimized by adding external noise. Therefore, we suggest that there may be an advantage in targeting glaucoma tests specifically toward higher order cortical perceptual functions. Whether they are more effective than more traditional functional tests is an empirical question and ultimately depends on whether the lower level deficits are magnified as they progress up the visual pathway or whether there are compensatory neural mechanisms which delay their impact on cortical systems until later stages of the disease with more extensive neural damage.

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