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Article

Effect of Age, Sex, Stimulus Intensity, and Eccentricity on Saccadic Reaction Time in Eye Movement Perimetry

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Purpose: In eye movement perimetry (EMP), the extent of the visual field is tested by assessing the saccades using an eye tracker. The aim of the present study was to determine the effects of age and sex of the subjects, the eccentricity and intensity of the peripheral stimuli on saccadic reaction time (SRT), and the interaction between these parameters in healthy participants.

Methods: Healthy participants aged between 20 to 70 years underwent a complete ophthalmic examination and an EMP test. SRT was determined from detected peripheral stimuli of four intensity levels. A multilevel mixed-model analysis was used to verify the influence of subject and stimulus characteristics on SRT within the tested visual field.

Results: Ninety-five subjects (mean age 43.0 [15.0] years) were included. Age, stimulus intensity, and eccentricity had a statistically significant effect on SRT, not sex. SRTs were significantly faster with increasing stimulus intensity and decreasing eccentricity ($P < 0.001$). At the lowest stimulus intensity of 192 cd/m^2, a significant interaction was found between age and eccentricity.

Conclusions: The current study demonstrated significant SRT dependence across the visual field measured up to 27°, irrespective of sex. The presented SRT values may serve as a first normative guide for EMP.

Translational Relevance: This report of SRT interaction can aid in refining its use as a measure of visual field responsiveness.

Introduction

The sudden appearance of visual targets or any other features of interest in the peripheral visual field stimulates a cascade of events starting with a change in retinal activity. If not suppressed, this can eventually lead to ballistic eye movements known as saccadic eye movements (SEM).[1] Parasol cells, which are a subset of retinal ganglion cells (RGCs), provide input for this cascade of events.[2] Spatial information from the retina is subsequently encoded in a saccade generation network located in the cerebral cortex, thalamus, basal ganglia, cerebellum, superior colliculus (SC), and brainstem areas that maintain the spatial coding of the target with respect to the fovea.[3,4] This complex circuit then activates extra ocular motor neurons to break fixation of the current target of interest and to make adequate SEM to align the fovea with the new visual target of interest.[5]

Eye tracking technology offers several methods for the qualitative (i.e., visual inspection) and quantitative evaluation (i.e., calculate saccadic properties) of SEM. Important parameters are saccadic reaction time (SRT), saccade velocity, amplitude, and duration.[6] Various studies have reported alterations in SEM parameters in patients on psychotropic drugs and in various neurologic diseases, such as Parkin-

son's disease, Alzheimer's disease, as well as in optic nerve pathologies and glaucoma.[6–12] This change in ocular dynamics led to the use of saccadic parameters as a marker for evaluating the integrity of saccade-generating neural network and in diagnosis of neurodegenerative conditions.[6,7]

In previous studies, SEM parameters and the extent of saccade disruption were evaluated in patients with glaucomatous optic neuropathy. Kanjee et al.[6] evaluated glaucoma patients using a prosaccade step task, whereas Lamirel et al.[7] investigated patients with primary open-angle glaucoma (POAG) using static and kinetic targets. These studies reported significantly prolonged SRT and decreased eye movement precision in glaucoma patients. Smith et al.[8] and Asfaw et al.[9] found that the saccades and the spread of fixation during visual search processes were reduced in glaucoma patients when compared with their age-matched controls. Crabb et al.[10] observed characteristic eye movement patterns in glaucoma patients when viewing a driving scene in a hazard perception test (HPT). Their results showed that saccadic behavior was related to visual function and that patients with severe visual field defects showed fewer saccades per second than age-matched controls.

Investigators have also included SEM in visual field testing, so-called eye movement perimetry (EMP). During conventional visual field testing, such as in standard automated perimetry (SAP), a steady fixation throughout the course of testing is required. Especially the necessity to suppress reflexive eye movements compromises the test reliability.[11,12] Kim et al.[11] proposed an EMP system for visual field plotting based on eye movements as an alternative for SAP by presenting stimuli of various intensity levels (minimum of 15 dB). The visual field was reported on the basis of the minimum stimulus intensity seen (in dB). When compared between EMP and SAP, they reported less than 4 dB of sensitivity threshold difference in 92.8% of healthy subjects and 81.1% of glaucoma subjects.[11] The eye movements, however, were observed by the investigator using a video-based eye tracker and a decision algorithm classified each response as seen or not seen. Murray et al.[12] included remote eye tracking technology to quantify visual fields on the basis of primary eye movement responses toward the peripheral stimuli named 'saccadic vector optokinetic perimetry' (SVOP) in both children and adults. They reported good agreement in discriminating normal eyes (adults: 99.2%, children: 99.1%) and eyes with glaucomatous visual field defects (adults 89.8%) when compared between the SVOP 41 test points and the C-40 screening test of Humphrey Field Analyser (HFA).[12] The EMP and SVOP were reported to be consistent in discriminating between normal and glaucoma when compared with the SAP. It showed the potential for assessing the extent of the visual field, even though it was only based on binary responses from the subjects (i.e., seen or unseen).[11,12] Previous investigations conducted by the current study group attempted to quantify some of the SEM characteristics obtained from a similar remote eye-tracking EMP system. A decision algorithm to classify an eye movement response as seen or unseen was included along with determining SRT for each seen point. This was denoted as a quantitative measure of visual field responsiveness.[13–16] A significant delay in SRT was found in mild, moderate, and severe glaucoma patients when compared with their age-matched controls,[13] indicating the potential importance of altered SEM values in glaucoma.

Several studies have examined the effects of factors, such as stimulus eccentricity, contrast, luminance, size, and age on SEM in isolation. Munoz et al.[17] reported age-related changes in performance of healthy human subjects during pro- and antisaccade task by projecting eccentric targets at 20° to either side of the fixation. They described the presence of delayed SRT and longer saccade duration in elderly subjects (60–79 years of age) in comparison to the younger age groups.[17] However, the effect of eccentricity and contrast was not explored. In another study, Pel et al.[14] investigated the repeatability and variability of SRT at locations that covered 60° horizontal and 40° vertical visual field. They reported good repeatability across three measurement series (on average the differences were within 100 ms) and significantly delayed SRT with lower stimulus contrast and increasing stimulus eccentricity, but the subject's age was not included as a factor in the mixed linear analysis.[14] Although the dependency of SRT on several factors, such as the age of the subject, stimulus intensities, and locations, are well documented in the literature, their interactions (including sex) and combined effect on SRT obtained at locations in a visual field test have not been reported. To use SRT as a functional marker in visual field testing, it is essential to address its variability in healthy subjects. Therefore, the current study aims to assess the interaction of age, sex, intensity, and eccentricity on SRT in healthy subjects using a mixed-model statistical analysis. The obtained data may serve as a first normative guide for EMP.

Materials and Methods

Participants

A total of 107 healthy adult subjects aged between 20 to 70 years were enrolled from the outpatient clinic of Sankara Nethralaya, a tertiary eye care hospital in India. Each subject underwent a complete ophthalmic examination and subjects with spherical ametropia greater than ±5.00 Dsph and cylindrical ametropia of more than −2.00 Dsph, best-corrected visual acuity less than 20/40, 0.8 M, ophthalmic conditions (e.g., oculomotor nerve palsy, corneal opacity, and ptosis), which might affect the eye tracking, intraocular pressure more than 21 mm Hg, any sign of retinal nerve fiber layer changes or any abnormality on optic nerve head, any history of ocular surgery, or any retinal pathology were excluded. Only the eligible subjects were informed about the test and asked to participate. Twelve participants were excluded after recruitment due to eye tracking issues. Written informed consent was obtained prior to the clinical examination. The participant in Figure 1 provided informed consent to use the photograph for publication. Each subject underwent a visual field testing in HFA (HFA model 750; Carl Zeiss Meditec, Dublin) and subjects with reliable normal visual field were included. Reliability of the visual field test was assessed as per the recommendation of STATPAC algorithm by Anderson et al.[18] The study was approved by institutional review board and Ethics Committee of Vision Research Foundation, Chennai, India. The study adhered to the Declaration of Helsinki for research involving human subjects.

Instrument Description and Procedure

Eye Movement Perimeter (EMP)

The customized EMP testing setup comprised a laptop and a 17 in thin film transistor (TFT) display of screen resolution 1280 × 1024 pixels with an inbuilt eye-tracking device with a refresh rate of 120 Hz (accuracy 0.5°; Tobii 120, Tobii, Sweden). The display unit was placed at a distance of 55 cm, allowing a visual angle toward the monitor of 34° × 23° (1280 × 1024 pixels), from the subjects (Fig. 1). A chin rest was provided to maintain a constant distance and minimize the head movement during the test. No refractive correction was provided while performing the test. The test was performed under monocular viewing conditions by covering the left eye with a black polymethyl methacrylate plate (PMMA; see also Fig. 1 showing this lens holder including the PMMA glass). This plate permitted the passage of infrared light allowing the eye tracker to track both eyes for stable gaze tracking. Only the data of the right eye was used to prevent miscalculation of gaze positions due to any misalignment of the nontested eye. The tests were performed in a clinical testing room. The background luminance was kept constant and no talking was allowed during the test to avoid any distraction. The testing protocol began with an inbuilt nine-point calibration procedure to obtain good gaze accuracy. A red circular target was presented to align the subject's gaze with the calibration dots. The calibration procedure was repeated for locations that had insufficient sample points. In the main test, a central fixation stimulus was displayed at the center of the screen.[13,15] The EMP visual field grid included all the 54 locations tested on the 24-2 SITA standard of HFA. The projected stimuli resembled the Goldmann size III stimuli and were point-wise projected at four different stimulus intensities against a background illumination of 152 cd/m^2. The following stimulus intensities were used: 192, 214, 249, and 276 cd/m^2. A total of 216 stimuli were presented and the total duration per exam was on average 12 minutes, including subject positioning, instruction, calibration, and an 11-minute test duration. The central target was not only projected into the central position on the screen but also in different eccentric positions to expand the tested visual field up to a visual angle of maximally 27° horizontally and 21° vertically.

Stimuli were presented on the screen using an overlap paradigm (i.e., the central stimulus remained lit when a peripheral stimulus appeared). Subjects were asked to fixate the central stimulus. A central stimulus fixation of at least 0.2 seconds was followed by a random foretime between 1 and 2 seconds to prevent the predictability of presenting the next peripheral stimulus. Next, a peripheral stimulus was presented for a fixed duration of 1.2 seconds. Subjects were instructed to look at each of the visual stimuli detected in the periphery and then fixate again on the central fixation stimulus.

EMP Data Analysis

All 216 gaze data points of each subject were analyzed using the customized software developed in MATLAB version 7.11 (MathWorks, Natick, MA). A previously published decision algorithm was used for automated offline processing of the data.[13–16] For all trials, a post hoc check was done at the start of

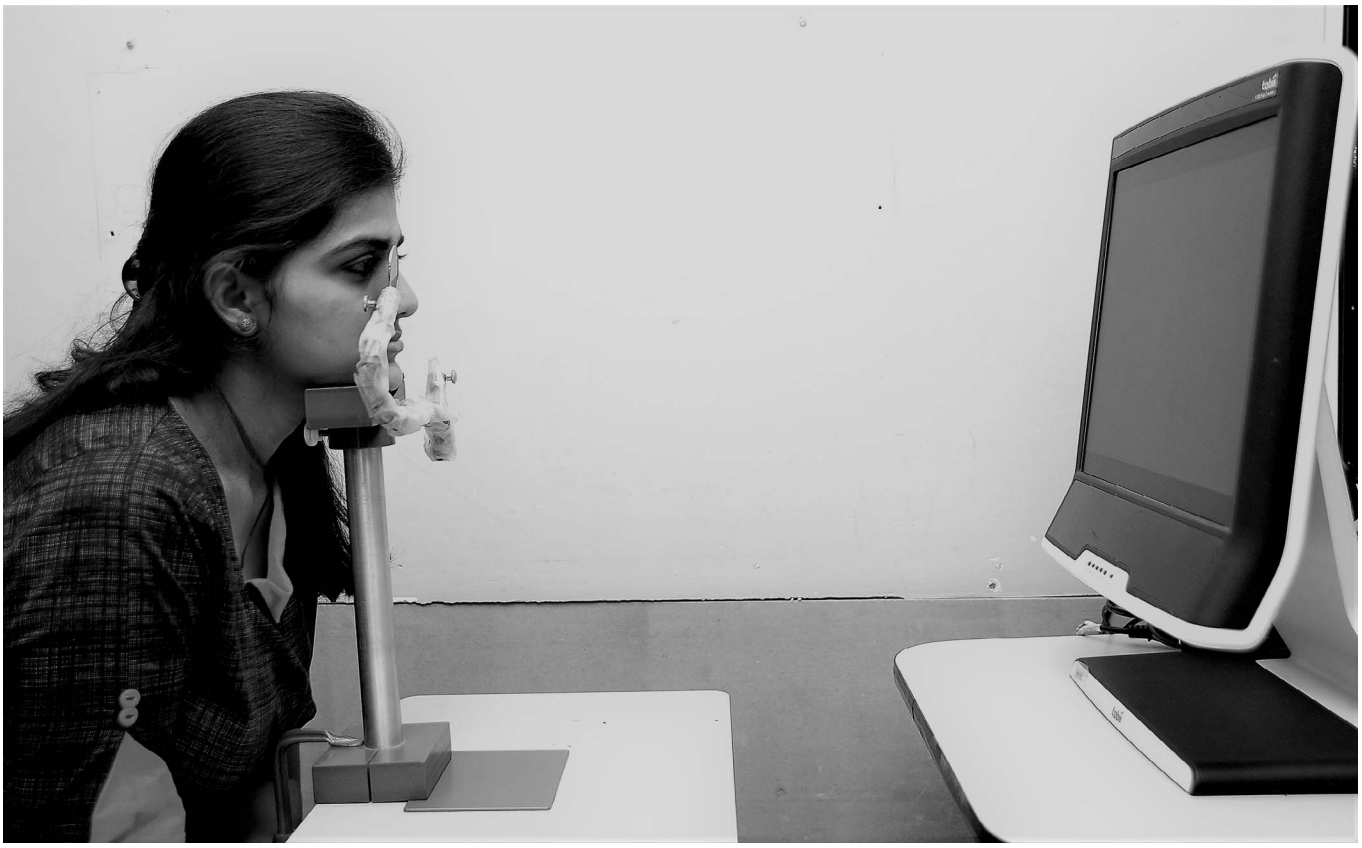

Figure 1. EMP test set up comprising of a 17-in TFT monitor with an inbuilt infrared-based eye tracking camera at the *bottom panel*. The chin rest placed at a distance of 55 cm was used for each measurement including a PMMA blocker holder positioned in a standard lens holder.

each trial to confirm a correct central stimulus fixation and to ensure that the correct location of the visual field was tested. Next, the gaze path from the central stimulus to the peripheral stimulus was visually inspected. Events were labelled as 'seen' when a SEM was initiated toward the presented visual target and covered more than 50% of the total central to peripheral stimulus distance. An event was classified as 'unseen' as follows when: (1) during the presentation of the peripheral target, no eye movements were made toward the target, (2) the first saccade was not in the direction of the target, and (3) the angular disparity between the direction of the primary SEM and the peripheral stimulus location was larger than 45°, indicating searching behavior. An event where no eye movement data were available due to blinking or pupil detection failure was labelled as 'invalid' and was excluded from the analysis. For each 'seen' target the SRT was calculated as the time difference between stimulus presentation and the onset of the SEM in the direction of the target (Fig. 2).[13–16] Calculation of SRT was done based on the gaze velocity criterion by calculating the reaction time at which the eye velocity crossed 50°/sec.[14,15] Special notice was given to the near central stimuli. Here, the eye velocity not always exceeded this limit.

Statistical Analysis

To assess the influence of age on SRT the subjects were divided into the following five age groups: 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 years and above. All four stimulus intensities (192, 214, 249, 276 cd/m^2) used in the testing algorithm were considered for analyzing their influence on SRT.

To assess SRT dependence on stimulus eccentricity four distinct eccentricities were determined by considering equidistance from the central fixation location which was termed as eccentricity 1 (4°), 2 (11°), 3 (16°), and 4 (22°) (Fig. 3). This approach was preferred over analyzing each location point wise, because it improved the statistical power of the test. The two most nasal test locations were combined and denoted as eccentricity 5 (27°). From eccentricity 3, one location corresponding to the blind spot region

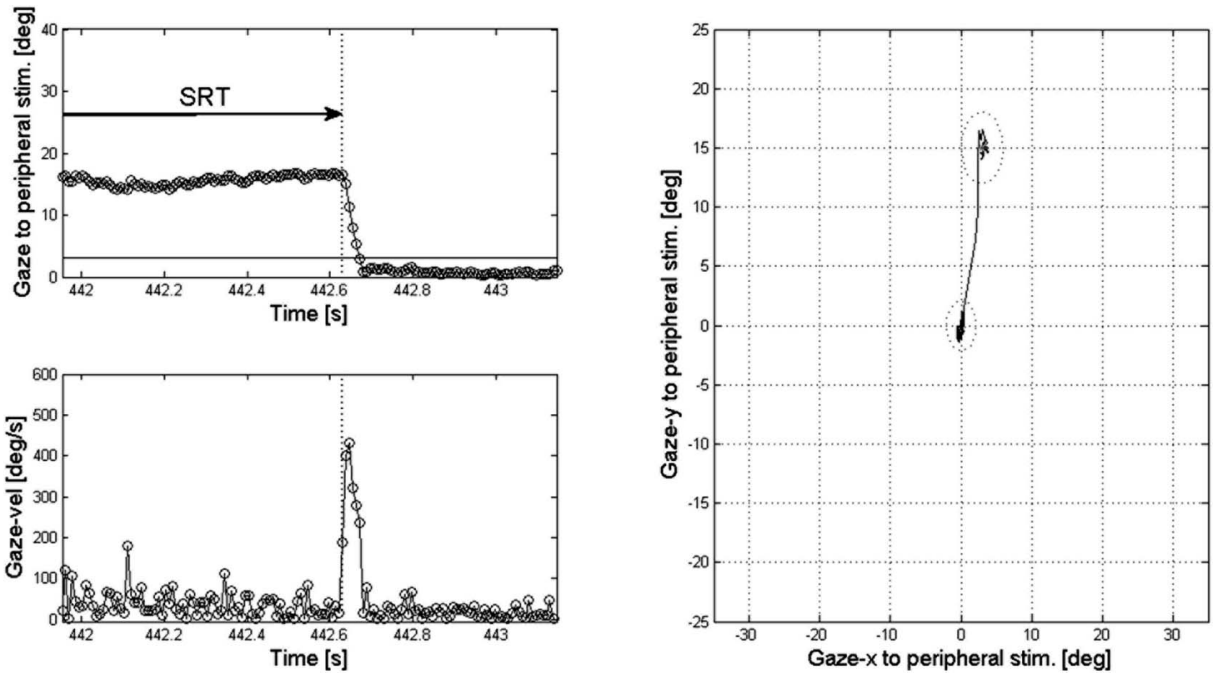

Figure 2. Illustration of an eye movement from the central fixation to a peripheral stimulus (*right panel*). The *top left panel* shows the relative gaze position with respect to the stimulus location and the *left bottom panel* shows the gaze velocity.

was eliminated (Fig. 3). In addition, we also segregated the tested visual field into hemifields around the horizontal and vertical midline (superior and inferior as well as nasal and temporal) to assess visual area dependence of SRT behavior. Data obtained from the right eye were considered for the analysis. SRT values were denoted in milliseconds. Tests for normality were carried out for each quantitative variable. Type I error was kept at the 5% level.

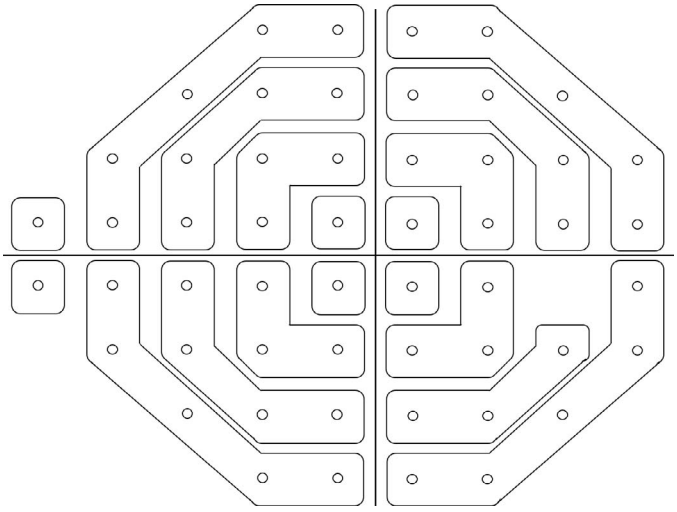

Figure 3. Illustration of stimulus grid (right eye) with distinctive eccentricities made by placing the concentric grid lines (not visible in the actual test) at different stimulus eccentricities. Stimulus locations were grouped by considering different sectors within each quadrant (i.e., 4 sectors per quadrant). Two nasal test locations were considered as eccentricity 5.

To determine the influence of the factors on the dependent variable SRT, a multilevel mixed model (generalized linear mixed model [GLMM]; SPSS, IBM, Armonk, NY) was used. GLMMs are an extension of linear mixed models to allow response variables from different distributions. The output of a GLMM is estimates of the mean SRT values and their corresponding confidence intervals. This method adjusts the SRTs for each factor, and as a result, only provides the estimate SRTs per factor. The individual factors included in the model were as follows: the age groups, sex, stimulus intensity levels, and stimulus eccentricity as categoric variables. The linear regression model allowed a levelled structure to look for SRT variability within each factor as follows: five age groups, two sex groups, four stimulus intensities, and four eccentricity-wise. Eccentricity 5 was not considered for the GLMM analysis as it consisted of only two test locations. The within factor levels were tested using pairwise contrast estimates as post hoc test. The interaction of different factors with SRT was added to the model using the following equation: gender × age group × stimulus intensity ×

Table 1. Demographics of the Study Population Subject Characteristics

Parameter	Value
Age range, y	20–70
Age, mean ± SD, y	43.0 ± 15.0
Age groups, age range (*n*)	20–29 (22)
	30–39 (18)
	40–49 (21)
	50–59 (17)
	≥60 (17)
Sex, *n* (%)	Male 50 (53)
	Female 45 (47)

eccentricity. The output reference categories were male, age group older than 60 years, stimulus intensity 276 cd/m^2 and eccentricity 4.

Results

A total of 95 healthy subjects were included in the study. The demographic details and the frequency of subjects in each age group are presented in Table 1.

Table 2 summarizes the total percentage of seen and unseen gaze data for each age group at the four stimulus intensities. The proportion of 'seen' was equally distributed between age groups at stimulus intensities 276 to 214 cd/m^2. However, for stimulus intensity 192 cd/m^2, the percentage of seen drops with approximately 15% to 25% in each age group. The percentage of invalid points remained low (<5%), and was consistent across all age groups.

A fixed-effect model with the dependent variable SRT and predictors as sex, age group, stimulus intensity, and eccentricity are presented in Table 3. Overall, a statistically significant effect ($P < 0.001$) was found for SRT with age, stimulus intensity, and stimulus eccentricity, not for sex ($P = 0.74$).

Next, a comprehensive overview of the model for the main effects of the factor levels (including age, stimulus intensity, and eccentricity) with SRT are presented in Table 4. Estimated mean SRTs with corresponding 95% confidence intervals are presented in Figures 4 to 6. SRTs were significantly faster with increasing stimulus intensity and decreasing eccentricity ($P < 0.001$).

The interaction of different factors on SRT is presented in Table 5. At the lowest stimulus intensity of 192 cd/m^2, a significant interaction was found between age and eccentricity. At eccentricity 4° and 22°, the oldest age group was significantly delayed compared with the younger subjects. At the intermediate eccentricities (11° and 16°), a significant difference was found between the different age groups, with the fastest SRTs assessed in 20- to 40-years-old subjects. Significant delays in SRT were also found at stimulus intensity 214 cd/m^2 at eccentricity 4° in the oldest age group.

Visual Response Map

To visualize the SRT behavior, the age-specific mean SRT values per sector within each of the five eccentricities were calculated for the four stimulus intensities, see Figure 7. For each sector, the average SRT value was calculated and plotted using a gray scale map as follows: SRT ranging from 130 to 1200 ms corresponded with red-green-blue values ranging from (230–25). In that way, the fastest SRT were plotted in light gray and the most delayed SRTs were dark gray. The blind spot was plotted in black (RGB: 0-0-0). These plots illustrate the delay in SRT with increasing age and decreasing stimulus intensity. Supplementary Figure S1 presents the age-specific mean SRT values within each eccentricity with respect to stimulus intensity.

Discussion

The current study systematically investigated the interaction of the subject's age, sex, stimulus intensity,

Table 2. The Total Eye Movement Responses (Percentage of Seen and Unseen Points) for All Age Groups in All Stimulus Intensities

	20–29 y		30–39 y		40–49 y		50–59 y		≥60 y	
Stimulus Intensity, cd/m^2	Seen	Unseen	Seen	Unseen	Seen	Unseen	Seen	Unseen	Seen	Unseen
192	69	31	67	33	63	37	50	50	46	54
214	83	17	81	19	80	20	75	25	71	29
249	75	25	74	26	72	28	68	32	73	27
276	83	17	79	21	80	20	76	24	78	22

Table 3. The Fixed-Effect[a] Model of the Individual Factors on Saccadic Reaction Time

Source	*F*	Numerator df	Denominator df	Significance
Intercept	17.99	80	12,412	<0.001
Sex	0.110	1	12,412	0.740
Age group	7.94	4	12,412	<0.001
Stimulus intensity	223.73	3	12,412	<0.001
Eccentricity	59.46	3	12,412	<0.001

[a] Dependent variable: SRT.

and eccentricity on SRT behavior using a remote eye tracker–based EMP system. All the factors except sex were found to have a statistically significant effect on the SRT. A significant interaction was found between the lowest intensity and age. Here, the delayed SRTs were found in the 60 years and above group at all tested eccentricities. These findings provide essential information needed for better understanding the natural behavior of SRT with aging.

Interacting Factors

A significant delay in SRT was found with increasing age, where approximately a 40% delay in response time was found in subjects above 60 years of age compared with the youngest age group (20–29 years). Irving et al.[19] reported the age dependency of horizontal saccade dynamics especially on SRT, accuracy, and peak velocity. Each parameter followed a distinct pattern of development and decline in relation to the complex network of brain structures accountable for the processing and generation of saccades. Saccades are found to be characterized by fast reaction times and high-peak velocities throughout the course of childhood and early adolescence, which stabilizes in the middle decades of life. Reaction time, peak velocity, and accuracy followed a significant decline with increasing age.[19] Munoz et al.,[17] Fischer et al.,[20] and Pratt et al.[21] evaluated the impact of age on SRT values. They demonstrated strong age-related effects on SRT and our study results were consistent with these previous findings. Kenward et al.[22] reported faster SRT (mean difference 28 ms) in

Table 4. The Results of the Multilevel Model of the Individual Factors and Their Levels

	SRT, ms		
Main Effect	Parameter Estimate	95%CI	*P* Value
Intercept	481	439–523	<0.001
Age, y			
20–29	−92	−144 to −39	<0.001
30–39	−94	−149 to −40	<0.001
40–49	−69	−122 to −16	0.01
50–59	−77	−135 to −20	0.008
≥60	Reference		
Stimulus intensity, cd/m^2			
192	141	109–174	<0.001
214	69	43–954	<0.001
249	17	−9 to 43	0.196
276	Reference		
Stimulus eccentricity			
Eccentricity 1 (4°)	−58	−106 to −11	0.016
Eccentricity 2 (11°)	−36	−69 to −3	0.034
Eccentricity 3 (16°)	−14	−44 to −17	0.387
Eccentricity 4 (22°)	Reference		

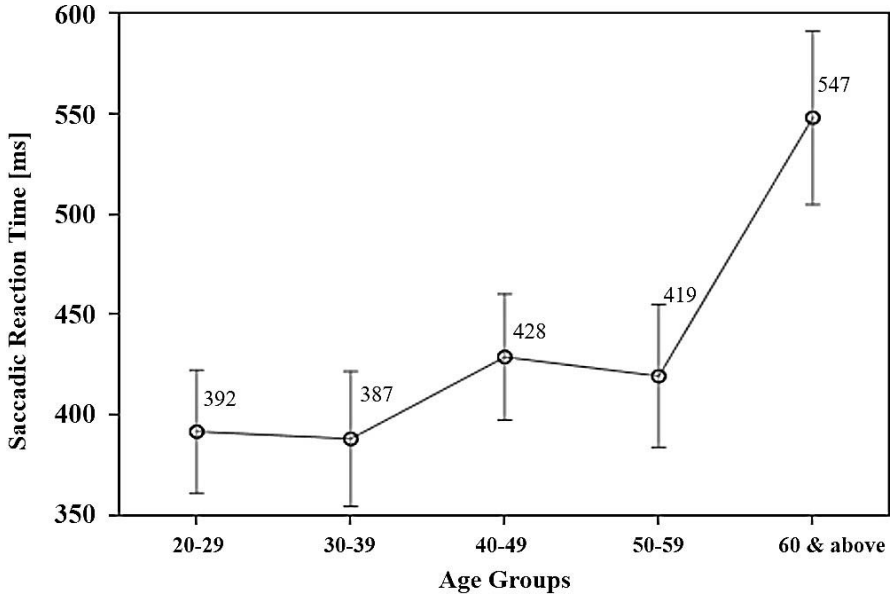

Figure 4. Estimated mean SRT and their 95% confidence intervals plotted as a function of age.

baby girls (between 9 and 15 months) compared with age-matched boys when stimuli were projected at 14.2°, whereas no such difference was found in adults. In the current study, we have also not found any significant difference in SRT between adult females and males in different age groups.

In addition, our results showed a delay in mean SRT (ranging from 394–503 ms) with decreasing stimulus intensity. A similar pattern was observed in previous studies.[14,23,24] Bell et al.[23] registered the commencement of neural activity in the intermediate layers of SC when saccades were generated in response to high- and low-intensity stimuli. They observed faster response onset for high-stimulus intensity in comparison with the lower- intensity stimuli. It was suggested that most of the age-related decline in visual functions cannot be credited to changes in the optical properties of the eye. Presumably, this decline is due to the alterations in quality of the neural networks of the central nervous system.[17,25]

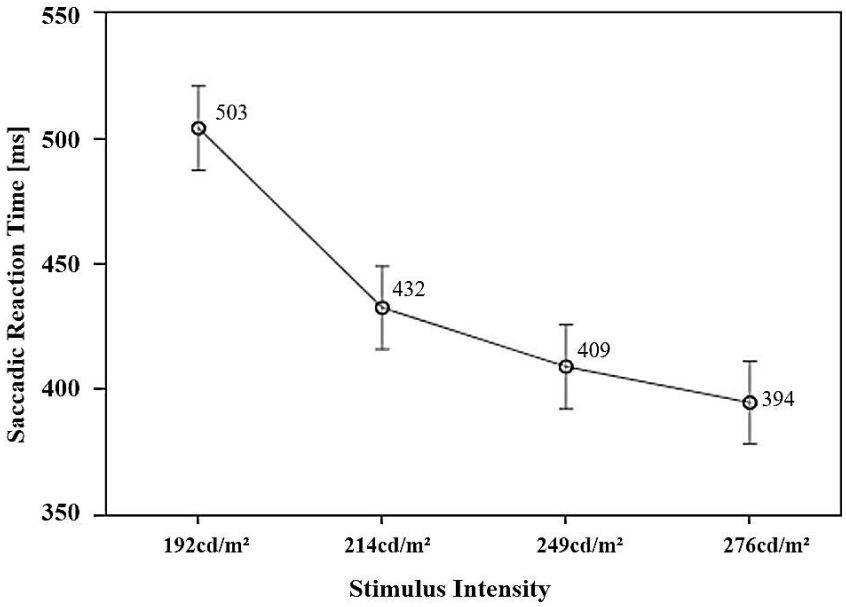

Figure 5. Estimated mean SRT and corresponding 95% confidence intervals plotted as a function of stimulus intensity.

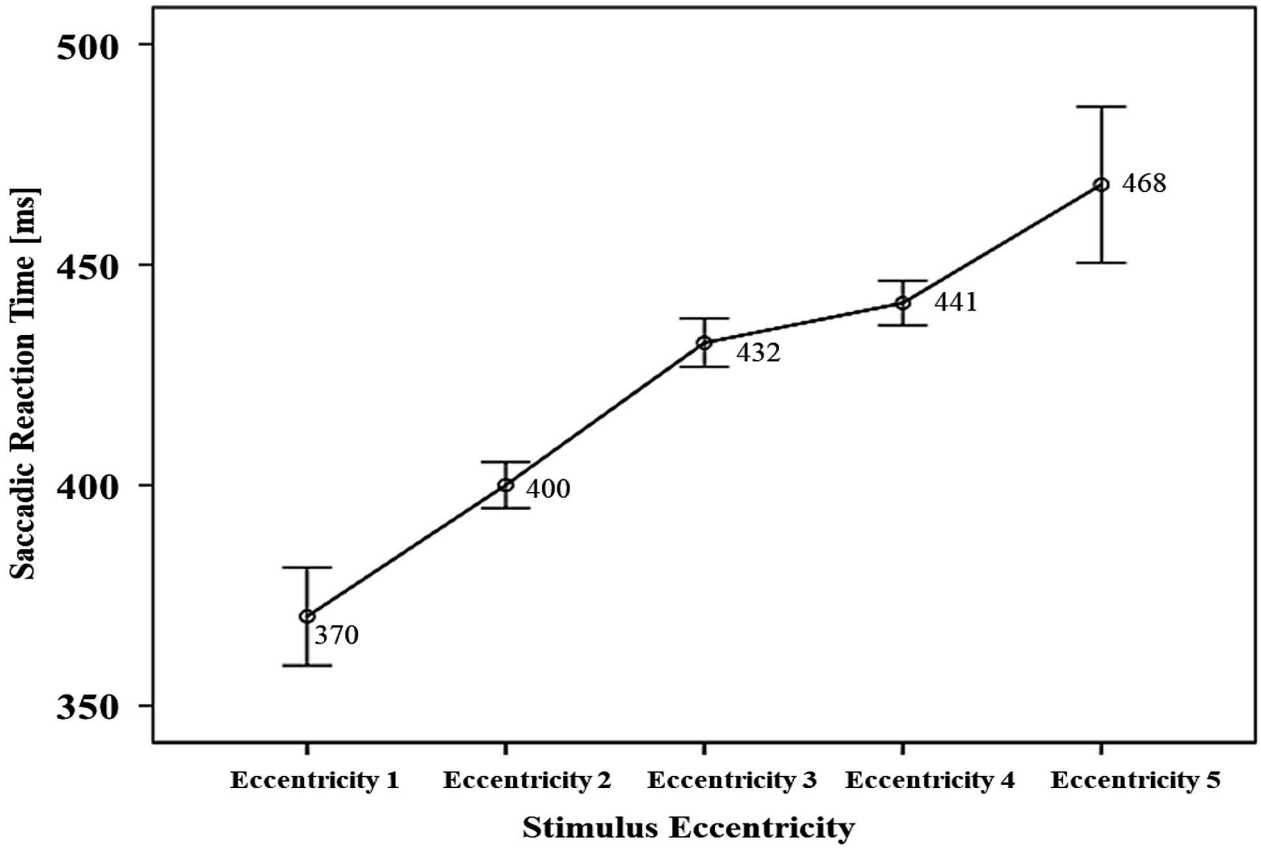

Figure 6. Estimated mean SRT and corresponding 95% confidence intervals plotted as a function of stimulus eccentricity.

It might include a decline in visual acuity, contrast sensitivity, binocular processing, and motion sensitivity. The delay found in SRT with respect to increasing age can also be attributed to the decline in visual abilities due to neurophysiologic changes during various stages of degeneration process that include gradual atrophy of the gray and white matter of the cerebral cortex.[26]

To investigate the SRT behavior with stimulus eccentricity, we created five eccentricities based on their distance from the center. We found SRT was dependent on stimulus eccentricity up to 27°. Hodgson investigated eye movements on a set of six subjects tested with a stimulus with and without location markers.[27] The eccentricities used were 3° and 9° on either side of the fixation along the horizontal axis. The target without location marker subtended 0.26° and those with location marker subtended 0.43° in diameter. He reported a delay in reaction time at 9° eccentricity when location markers were used. Our study confirmed this finding of SRT dependency on eccentricity[28,29]; yet other studies contradict the eccentricity effects on SRT.[30] Dafoe et al.[30] reported that SRT was independent of eccentricity; however, their eccentricity was limited to 8°. We found that the effect was stronger when the targets were presented in eccentricities 3, 4, and 5, which extended to 27° eccentricity (Fig 7). This effect could be attributed to the variation in photoreceptor stimulation with respect to retinal eccentricity.[31]

The differences in SRT between nasal and temporal hemifields were not significantly different as reported by Jóhannesson et al.[32] A comparison in SRT between superior and inferior visual field did reveal significantly faster SRT in the superior field (~24 ms). This might be the result of the anatomic asymmetry of the human retina, such as differences in cone and ganglion cell density.[33] The visual response maps introduced in the current study made the quantitative and qualitative visualization of SRT variability throughout the visual field visible. Based on the interactions, we conclude that at the lowest stimulus intensity of 192 cd/m^2 a significant interaction was found between age and eccentricity. Especially the SRT values in the oldest age group (≥60 years) showed significant delays. Such a general reduction in this age group is also found for the sensitivity thresholds in SAP. As a result, when

Table 5. Pairwise Contrast Estimates Between the Levels of Factors

Stimulus Intensity, cd/m^2	Eccentricity, Degrees	Age Groups, y		Contrast Estimate	SE	*t*	df	Adjusted Significance	95%CI Lower	95%CI Upper
192	4	≥60	20–29	133.86	43.98	3.04	12,412	0.02	47.64	220.07
			30–39	168.77	45.76	3.69	12,412	<0.001	79.07	258.48
			40–49	166.09	44.95	3.7	12,412	<0.001	77.98	254.2
			50–59	133.23	50.37	2.65	12412	0.008	34.49	231.97
	11	20–29	40–49	−62.65	27.52	−2.27	12,412	0.02	−116.5	−8.71
			50–59	−91.79	29.66	−3.09	12,412	0.002	−149.93	−33.65
		30–39	40–49	−78.87	29.11	−2.71	12,412	0.007	−135.93	−21.81
			50–59	−108.01	31.32	−3.45	12,412	0.001	−169.4	−46.61
		≥60	20–29	198.18	29.94	6.62	12,412	<0.001	139.49	256.87
			30–39	214.4	31.41	6.83	12,412	<0.001	152.83	275.96
			40–49	135.53	30.54	4.44	12,412	<0.001	75.66	195.39
			50–59	106.39	32.61	3.26	12,412	<0.001	42.47	170.31
	16	20–29	40–49	−55.99	27.65	−2.03	12,412	0.043	−110.19	−1.8
			50–59	−79.19	30.34	−2.61	12,412	0.009	−138.66	−19.71
		≥60	20–29	207.04	30.7	6.74	12,412	<0.001	146.86	267.23
			30–39	187.13	31.53	5.94	12,412	<0.001	125.33	248.92
			40–49	151.05	31.08	4.86	12,412	<0.001	90.13	211.96
			50–59	127.86	33.63	3.8	12,412	<0.001	61.93	193.77
	22	≥60	20–29	120.56	29.06	4.15	12,412	<0.001	63.6	177.52
			30–39	121.82	29.89	4.08	12,412	<0.001	63.23	180.41
			40–49	97.44	29.29	3.33	12,412	0.01	40.04	154.85
			50–59	129.26	32.36	3.99	12,412	<0.001	65.82	192.69
214	4	≥60	20–29	90.19	36.24	2.49	12,412	0.013	19.15	161.23
			30–39	119.71	38.44	3.11	12,412	0.002	44.36	195.05
			40–49	88.3	37.55	2.35	12,412	0.019	14.69	161.91

interpreting SRT values, it is important to take the normative values as a reference to correctly distinguish abnormal from normal SEM behavior.

Stimulus Conditions

An important question is, whether there are systematic differences between the SRT values reported in the present study and the wide range of SRT values that have been reported in literature.[2,14,16,31] In general, the SRT values seem to mostly depend on stimulus intensity and stimulus eccentricity. Warren et al.[31] reported similar SRT values between 400 and 500 ms in healthy subjects of 18 to 30 and 60 years and older. Their stimuli with an intensity of 250 cd/m^2 were projected on a comparable background intensity (150 cd/m^2) and eccentricity. In the present study, stimuli with higher intensity (e.g., 276 cd/m^2) indeed triggered slightly faster SRT values, whereas the stimuli with the lowest intensity of 192 cd/m^2 resulted in SRT values up to 700 ms in subjects of comparable age. In one of our previous EMP studies to test the effect of cataract on SRT, we were able to project peripheral stimuli with much higher intensities of 210, 300, 385, 475 cd/m^2 at a background luminance of 160 cd/m^2 due to a better-quality monitor.[16] Indeed, on average faster SRT values (∼380 ms; ∼16° eccentricity; age group ≥60 years) were found compared with the present study (∼550 ms; ∼16° eccentricity; age group ≥60 years).

The above comparisons seem to suggest that stimulus intensity dictates SRT. However, we cannot rule out the influence of background luminance on SRT. Darien et al.[2] measured SRT by conducting a test that used a white background, a black fixation target, and red peripheral targets. Instead of SRT dependence, they reported SRT values (mean SRT ∼250 ms) to be invariant with respect to eccentricity (10°, 15°, 20°, 24°, 28°) when stationary red targets

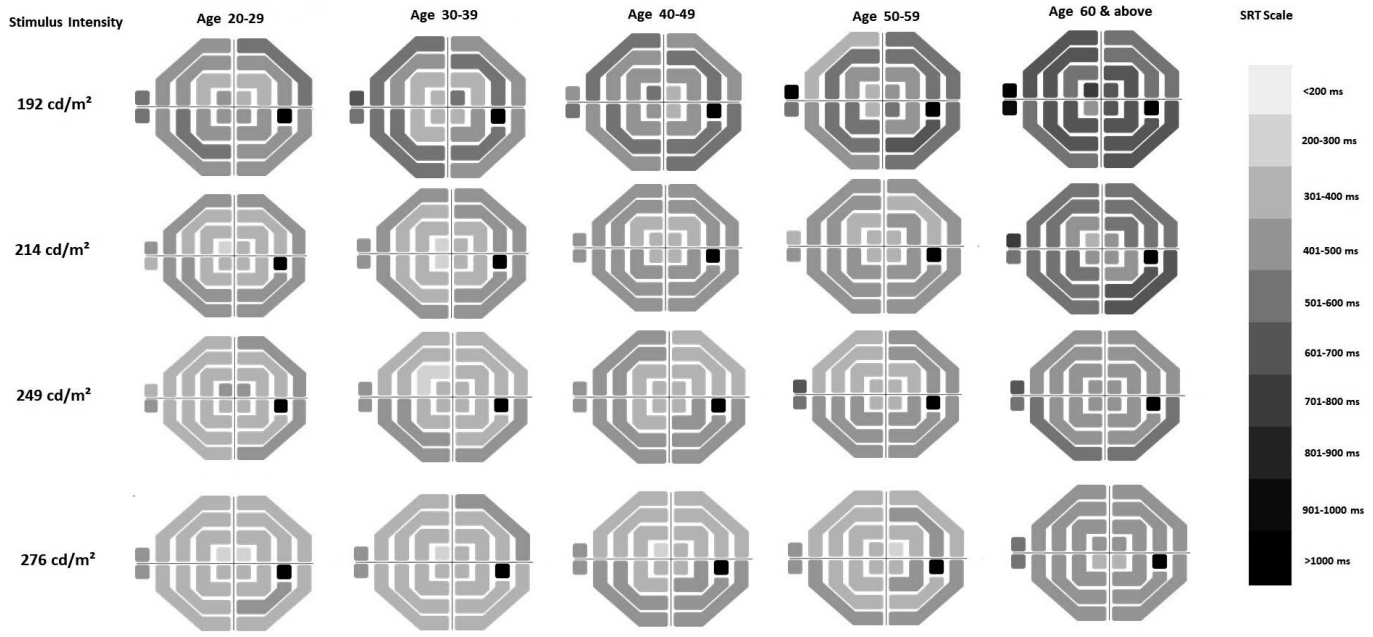

Figure 7. Illustration of visual response maps (*right eye*) created using mean SRT for each sector in the tested visual field for all age groups at four stimulus intensities. The SRT scale shows the gray scale corresponding to the SRT range.

were presented along the horizontal meridian at 10° to 30°.[2] Their results might be explained by the bleaching desensitization of the photoreceptors when exposed to a very bright background. This might reduce visual field responsiveness at the retinal level.[34] When stimuli were plotted on a black background, however, much faster SRT values were reported, not only in adults (~200–250 ms >10 years of age) but also in children (~180 ms).[35–37] We think that the influence of the background luminance could be very delicate. This might be best illustrated by a previous study also conducted within our group, where we kept background luminance lower (~140 cd/m^2) than we did in this study. We found slightly faster SRT values even when the intensities of the plotted stimuli were lower than the stimuli used in the present study (~190 cd/m^2) in subjects between 20 and 30 years of age. The variability in SRT was equally small.[14]

Finally, the test paradigm can also have an influence on SRT values. A gap paradigm may trigger eye movement responses.[38] In a gap paradigm, the fixation target disappears on the appearance of the peripheral stimulus and may trigger (1) the initiation of express saccades characterized by faster SRT (~100 ms), or (2) searching of the fixation target when the peripheral target is plotted in an affected part of the visual field. To prevent searching behavior during the test, we used an overlap paradigm in which the fixation target was kept illuminated while a new stimulus appeared in the periphery. This approach also resembles testing the visual field using SAP technique.

Study Limitations

The current study has some limitations to be addressed. Twelve of 107 participants had failure in eye tracking during the calibration procedure because of an error in pupil detection. From the 12 dropouts, eight were 60 years and above, one from the group 20 to 29, one from the group 40 to 49, and 2 from the group 50 to 59 years. Enrolling healthy subjects with age 60 years and above from a population (southern India) is challenging giving the high rate of unoperated cataract (53%) patients, especially when meeting the stringent inclusion criteria set for age-related changes in the optical media and ocular surface.[39] Despite these stringent criteria, some of the patients that met the cataract criteria could have had reduced contrast acuity due to other media opacity, such as (invisible) corneal and vitreous changes. Previously, we have shown that the eye tracker has good gaze tracking performance even in patients with cataract up to Lens Opacity Classification System III (LOCS III), grade 4.[16] In addition, prior to be enrolled in this study, the subjects first underwent an HFA measurement. Even here, we had similar number of dropouts, 13 healthy subjects (4 from the group 20–29, 2 from 50–29, and 7 from the group ≥60 years) were unable

to produce reliable HVF test results. Hence, these subjects were not selected for this study.

Table 2 described the pattern of eye movement responses (proportion seen/unseen) obtained from the subjects where the percentage of seen responses was found to decline with increasing age and decreasing stimulus intensity. In the elderly age group (≥60 years) the percentage of unseen responses was much lower for stimuli intensities, such as 276, 249, and 214 cd/m^2 when compared with 192 cd/m^2. This confirmed that the subjects did understand the task, and their reaction times, even to these low-intensity stimuli, were well within the 1200-ms projection time.

Even though the selected stimulus intensities are well within the visible range, yet the poor performance for the stimulus intensity 192 cd/m^2 was alarming. On further inspection of the data, it was found that the maximum percentage of unseen responses were most obtained at eccentricity 5 (27°) followed by eccentricity 1 (4°). Eccentricity 5 is the extreme periphery and it involved 2 testing locations which were excluded from the GLMM analysis. For eccentricity 1, the central four locations, unseen responses were highest for the lowest stimulus intensity of 192 cd/m^2 for the age group 60 and above. Maybe these stimuli were perceived even without making an eye movement or the eye movements were so small in amplitude, that neither the software nor visual inspection identified these saccades. This limits the application of EMP in testing for central visual field losses, as done, for example, in the HFA 10-2 protocol. The aim of the present study was to explore SRT as an outcome measure for plotting the visual field. It gave us the insight to modify the testing strategy by reducing testing points and stimulus intensities. As it is evident that the reliable response percentage is minimal with the lowest stimulus intensity (192 cd/m^2), inclusion of the same might not add any clinical value.

Clinical Application

Eye tracking technology has been recently used in several studies as a new method to eliminate drawbacks of traditional visual field plotting techniques, such as the requirement to maintain steady fixation while suppressing a reflexive eye movement or pressing a button on perceiving a stimulus.[11,12,40] Mc Trusty et al.[41] reported that a visual field test in combination with eye movements was preferred by subjects over conventional methods, especially with respect to the testing procedure as well as ergonomics. Even though EMP requires a central target fixation, subjects are encouraged to make eye movements toward detected stimuli. It thus incorporates the natural oculomotor response to new visual features and at the same time it avoids the continuous and conscious decision whether to press a button or not. Natural reflexive eye movements were used to quantify visual field isopters in infants and patients with special needs,[42] showing the potential of plotting visual fields on the basis of eye movements. The further development of EMP may hopefully result in a reliable tool for implementation in the community, especially in rural parts of countries like India to screen the visual field status of many people in order to detect the high percentage of visual impairment due to glaucoma.[43,44] In a previous published study, we have introduced an EMP screening grid.[15] This grid consisted of 26 locations that resulted in an average test duration of 2 minutes (test points at 214 and 276 cd/m^2). These data presented in this study may be a good normative guide for implementing EMP as a screening tool.

Conclusion

The current study provides the age-specific SRT characteristics in healthy subjects. Within the tested visual field, the interaction of age, sex, stimulus intensity, and eccentricity on SRT provided insight in age-dependent SEM behavior. The analysis of SRT interaction can help in refining its use as an index for plotting visual field responsiveness in patients with glaucoma and other neurologic disorders.

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