

# Saccadic movements assessment in eccentric fixation: A study in patients with Stargardt disease

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## Abstract

**Purpose:** To investigate saccadic movements in subjects with eccentric fixation due to a deep central scotoma in Stargardt disease (STGD).

**Methods:** We studied 10 patients with STGD and 10 healthy subjects (control group). Saccadic movements of all the 20 subjects were assessed by using the eye tracker technique Tobii Glasses Pro 2. Standard measurements of reading ability (MNREAD charts), visual acuity (ETDRS charts), contrast sensitivity (Pelli-Robson charts), reading contrast threshold and speed (REX charts), retinal sensitivity and stability and localization of the fixation (MPI fundus perimetry) were obtained in all subjects.

**Results:** The saccadic movements time was significantly slower in STGD than in healthy subjects ( $699 \pm 193$  ms vs  $299 \pm 40$  ms,  $p < 0.001$ ). When STGD patients moved fixation to the target localized in retinal scotomatous areas, the movement was significantly slower compared to non scotomatous areas in the retina ( $1103 \pm 798$  ms vs  $524 \pm 187$  ms,  $p = 0.039$ ). There was a trend toward a correlation between slow saccadic movements in STGD subjects and the reading performance indices, although statistical significance was not achieved.

**Conclusion:** Ocular saccades guided by eccentric fixation in STGD patients are significantly slower than in the control group, especially when the target corresponds to retinal areas with a deep scotoma. These results can explain the worse reading performance in STGD subjects, in particular when a non-viewing area on the right part of the text is present.

## Keywords

Macular and RPE dystrophies, retina, ocular motility disorders, pediatric ophthalmology, retinal pathology/research, genetic disease/congenital abnormalities, neuro-ophthalmic disease

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## Introduction

Stargardt's disease (STGD) is the most frequent inherited macular dystrophy. Its prevalence in the population is 1:8000/1:10,000.<sup>1,2</sup> STGD shows a progressive atrophy of the central retina caused by toxic metabolites accumulation, such as lipofuscins, in the retinal pigment epithelium (RPE).<sup>3–5</sup>

Therefore, these eyes frequently develop a deep scotoma in the central visual field and, consequently, the fixation migrates from foveal to eccentric. This eccentric fixation area is called “Preferential Retinal Locus” (PRL) and it is characterized by various degrees of instability.<sup>6–11</sup>

The performance of the PRL in terms of visual acuity, reading speed and contrast sensibility is reduced, sometimes significantly, compared to that of the natural fovea.<sup>12–15</sup> The

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PRL ability to correctly manage the ocular saccades has never been investigated in these patients, despite the fact that a correct execution of the ocular saccadic movement is the basis of a good reading ability and speed.<sup>16–20</sup>

This study aims to analyze the speed and accuracy of saccadic movements in patients with a deep central scotoma and an eccentric fixation due to STGD, evaluating a possible correlation with fixation stability, PRL position, and reading speed and accuracy.

## Methods

### Patient selection

We consecutively enrolled 10 low vision patients affected by STGD (Group 1) and compared their data with 10 age-matched healthy subjects (Group 2). STGD patients were selected from those referred to Careggi Hospital in Florence for low vision rehabilitation. Inclusion criteria for Group 1 subjects were: visual acuity between 0.3 logMAR and 1.0 logMAR, absence of important refractive errors, no clinical or visual changes during the previous 6 months. Exclusion criteria were the presence of maculopathy due to causes different from STDG, strabismus or nystagmus, high photophobia, education lower than grade 3, informed consent not obtained.

### Eye tracker testing

To record relative eye movements with a high spatial and temporal resolution, we used a head-mounted mobile eye-tracker system, the Tobii pro-glasses 2. It tracks movements of both eyes and uses an additional scene camera to track the external world. This system has a gaze sampling frequency of 50 Hz, a gyroscope and an accelerometer that allows to check not only eye movements but also head movements. The scene camera recording angle is 82° horizontal and 52° vertical.

Obtaining a reliable calibration of the system is the main problem when Stargardt patients are recorded. “Pro Glasses 2 must be calibrated individually for each participant to be able to collect accurate eye tracking data. During the calibration process, the participant must be wearing the Head Unit while focusing on the center of the calibration target.”<sup>21</sup> The calibration target is printed on a supplied calibration card which should be held flat at a distance like the distance of the display used for presenting the stimuli. The experimenter should “ask the participant to look at and focus on the center of the calibration target”<sup>21</sup> and should “keep the calibration card completely, still during the calibration process.”<sup>21</sup> With some patients, it was necessary to repeat the calibration procedure, due to unstable eccentric fixation. Nevertheless, in all enrolled patients a correct calibration of the instrument was obtained.

We wrote our experimental stimuli in Matlab, using the Psychophysics Toolbox extensions.<sup>22–24</sup> The stimuli were displayed on a monitor of 29.5 × 17 cm (14 inch) with a

resolution of 1980 × 1024. The stimuli consisted in a spot of 1° angular size which started in the center of the screen and, after a random time spanning from 0.2 to 1 s, could appear in one of four different positions. The eye tracker Tobii Glasses Pro 2 was used to record saccadic movements and fixation thanks to the front camera of the instrument. Obtained data were integrated with a video of the subject during the test performance.

The stimulus consisted of a yellow circle, in a sharp chromatic contrast with respect to the blue background, which appeared suddenly and intermittently. Its duration was 3 s and it was characterized by a random distribution to the four cardinal points of the screen (high, down, right, and left), to allow four appearances per side. After the appearances of the targets, the patient had to bring his fixation to a resting position, represented by a cross placed in the center of the screen which disappeared and reappeared variably from 3 to 7 s.

Therefore, the patient task was to fixate the cross, moving on the target at its appearance and maintaining the fixation, whereas the subject had to return to the cross when the target disappeared. The size of the fixation cross was 2.5°, the size of the yellow circle was 2.2° and the distance between the two was 7°.

The eye tracker testing was recorded for each patient, both in binocular vision and in monocular vision using the preferred eye for near tasks and reading. A chin guard was used to avoid head movements. It was possible to assess the time taken to reach a given target.

The Tobii pro-glasses 2 has been used in the field of behavioral study of gaze direction in eye diseases in a previous work on tubular vision.<sup>25</sup>

### Psychophysical testing

In order to collect psychophysical data, we used methods that we validated in two previous studies,<sup>26,27</sup> we used methods from the first study to collect Visual Acuity (VA) and Contrast Sensitivity (CS) data and from the second for microperimetry. Psychophysical tests were conducted in binocular vision to be compared with binocular eye tracker testing and were all obtained once for each patient. ETDRS charts at 2 m were used to measure Visual Acuity, recorded as LogMAR.<sup>28</sup> Pelli-Robson charts at 1 m were used to measure Contrast Sensitivity, recorded as log10 contrast sensitivity.<sup>29</sup> The Italian version of the MNREAD charts at 20 cm was used to obtain maximum reading speed (RS) (log10 words/min) and reading acuity (RA), both recorded as LogMAR.<sup>30,31</sup> The REX test<sup>32</sup> at a distance of 20 cm allowed us to study Reading speed at variable levels of text contrast. We recorded as log10 Reading contrast sensitivity the text contrast at which reading became impossible was recorded as log10 Reading Contrast Sensitivity.<sup>26</sup> A near addition of +5 D was adopted in reading tests. To avoid

**Table 1.** Average saccadic movements time in STGD and Healthy subjects.

	STGD	Healthy	p-value
Binocular outward time (1)	699 (193)	299 (40)	<0.001
Monocular outward time (2)	678 (116)	290 (29)	0.012
Monocular outward time (non scotomatous area STGD) (3)	524 (187)	290 (29)	0.009
Monocular inward time (4)	493 (152)*	369 (100)	0.054

1. Binocular outward time: all-time average used to move the eyes from the central cross to the target in binocular vision.

2. Monocular outward time: all-time average used to move the eye from the central cross to the target in monocular vision (better eye).

3. Monocular outward time (non scotomatous area STGD): average time used to move the eye from the central cross to retinal areas free from a deep scotoma in monocular vision (better eye, only STGD patients).

4. Monocular inward time: average time used to move back the eye from the peripheral target to the central cross in monocular vision (better eye).

\*Only eight patients (two patients weren't able to move fixation back to the central cross).

the learning effect each measurement was performed only once. When a psychophysical test was repeated, to test mono and binocular vision, different tables were used.

### MPI microperimetric testing

The MP-1 Microperimeter (Nidek Technologies Inc., Padova, Italy) was used to study the location and stability of the fixation and the macular sensitivity.<sup>32</sup> Data were obtained in monocular vision as allowed by the instrument to be compared with monocular eye tracker testing. Only the eye with better Visual Acuity (VA) was considered for each patient. In case the patient had similar VA in both eyes, the preferred eye for reading and for other near tasks was considered. To study the Preferred Retinal Locus (PRL), the patient was requested to fixate a target for 30 s (red cross, 2° in diameter). The non-tested eye was occluded. Fundus perimetry was used to study retinal sensitivity around the PRL. We adopted a 20° 10 dB program, a 4–2 threshold strategy, a Goldmann III white stimulus of 200 ms on a 1.27 cd/m<sup>2</sup> background.<sup>27</sup>

The fixation stability was previously defined either in terms of the percentage of fixation points that fall within 4° diameter circle during the visual field test, or in terms of bivariate contour ellipse areas (BCEA).<sup>33</sup>

PRL was referenced to the fovea and the distance was measured in degrees according to methods described in other studies.<sup>34–37</sup>

### Statistical methods

Mean values of saccadic times were compared between healthy and Stargardt patients using a two-sample *t*-test, with equal or unequal variance as appropriate. A paired *t*-test was used to compare saccadic times in scotomatous versus non-scotomatous directions in Stargardt patients. The correlation pattern among saccadic times and psychophysical variables was analyzed using Spearman correlation. Statistical significance was considered for *p*-value <0.05. Analyses were conducted using Stata 16.1 software (StataCorp, College Station, TX).

### Results

The mean age of the enrolled STGD patients was 37 ± 6.5 years while for healthy patients it was 35 ± 9.2 years. The mean VA in STGD patients was 0.5 ± 0.3 LogMAR while all healthy subjects had 0.0 LogMAR or better VA. On MP1 examination all subjects affected by Stargardt disease showed a deep scotoma located inside the vascular arches with an eccentric fixation characterized by various degrees of instability. On the contrary healthy subjects showed a stable central fixation without scotomas in the central retinal area.

### Comparison of binocular and monocular saccadic movements timing in STGD and healthy subjects

We compared saccadic movements timing in binocular vision between healthy and STGD subjects (Table 1). Group 1 had significantly slower movements than healthy control, as they reached the goal in 699 ± 193 ms and group 2 in 299 ± 40 ms (*p* < 0.001).

Results were similar in monocular vision when the better eye was studied, since group 1 reached the goal in 678 ± 116 ms and group 2 in 290 ± 29 ms (*p* < 0.05). This difference was confirmed considering the only saccadic movements directed to healthy areas in the retina in STGD patients in order to eliminate scotoma disturbance in the eye tracker test (*p* < 0.01).

### Comparison between monocular saccadic movements timing when directed to scotomatous areas or to not scotomatous areas in the retina in STGD patients

We compared eye tracker test timing in different directions, in order to study the effect of scotoma on eye movements in group 1 in a more accurate way. The time needed to move the eye from the central cross to the target, when directed to the central deep scotoma in the retina, was compared with the time employed when the eye moved to

**Table 2.** Correlation between saccadic movements timing and other studied psychophysical tests.

	REX reading speed (log)	Pelli robson and R.Ex. logCS	MNREAD maximum reading speed (log)	Reading accessibility index <sup>6</sup>	ETDRS visual acuity	Fixation stability (4°)	BCEA	Eccentricity
Monocular Outward time (all direction) (1)	0.24	-0.41	-0.22	-0.57	0.41	-0.19	0.14	0.08
Monocular Outward time (scotomatous area) (2)	0.19	-0.59	-0.33	-0.38	0.39	-0.31	-0.38	-0.02
Monocular Outward time (non scotomatous area) (3)	0.31	-0.32	-0.22	-0.55	0.23	-0.36	0.29	-0.06
Monocular Inward time (4)	0.31	-0.41	-0.33	-0.74*	0.23	-0.47	0.43	0.13
Binocular Outward time (all directions) (5)	0.30	-0.12	0.08	-0.40	0.25	-0.02	0.02	0.04
Binocular Inward saccadic time (6)	0.61	-0.354	0.47	-0.85*	0.08	-0.03	0.08	-0.02

1. Monocular Outward time (all directions): all-time average used to move the eye from the central cross to the target in monocular vision (better eye).

2. Monocular Outward time (scotomatous area): average time used to move the eye from the central cross to retinal areas presenting a deep scotoma in monocular vision (better eye, only STGD patients).

3. Monocular Outward time (non scotomatous area): average time used to move the eye from the central cross to retinal areas free from a deep scotoma in monocular vision (better eye, only STGD patients).

4. Monocular Inward time: average time used to move back the eye from the peripheral target to the central cross in monocular vision (better eye).

5. Binocular Outward time (all directions): all-time average used to move the eyes from the central cross to the target in binocular vision.

\*Only eight patients (two patients weren't able to move fixation back to the central cross).

other healthy retinal areas (i.e. without a deep scotoma). Saccadic movements to deep retinal scotoma were significantly slower ( $1103 \pm 798$  ms vs  $524 \pm 187$  ms,  $p < 0.05$ ).

### Secondary analyses: Correlation between saccadic movements timing and other studied psychological tests

Table 2 shows the correlation between all recorded psychophysical testing and saccadic movements either toward the targets in the four principal directions or inward to the central cross. There was a trend toward a correlation between slow saccadic movements in STGD subjects and the reading performance indices or logCS, but statistical significance was not achieved. This may be due to the small number of enrolled patients.

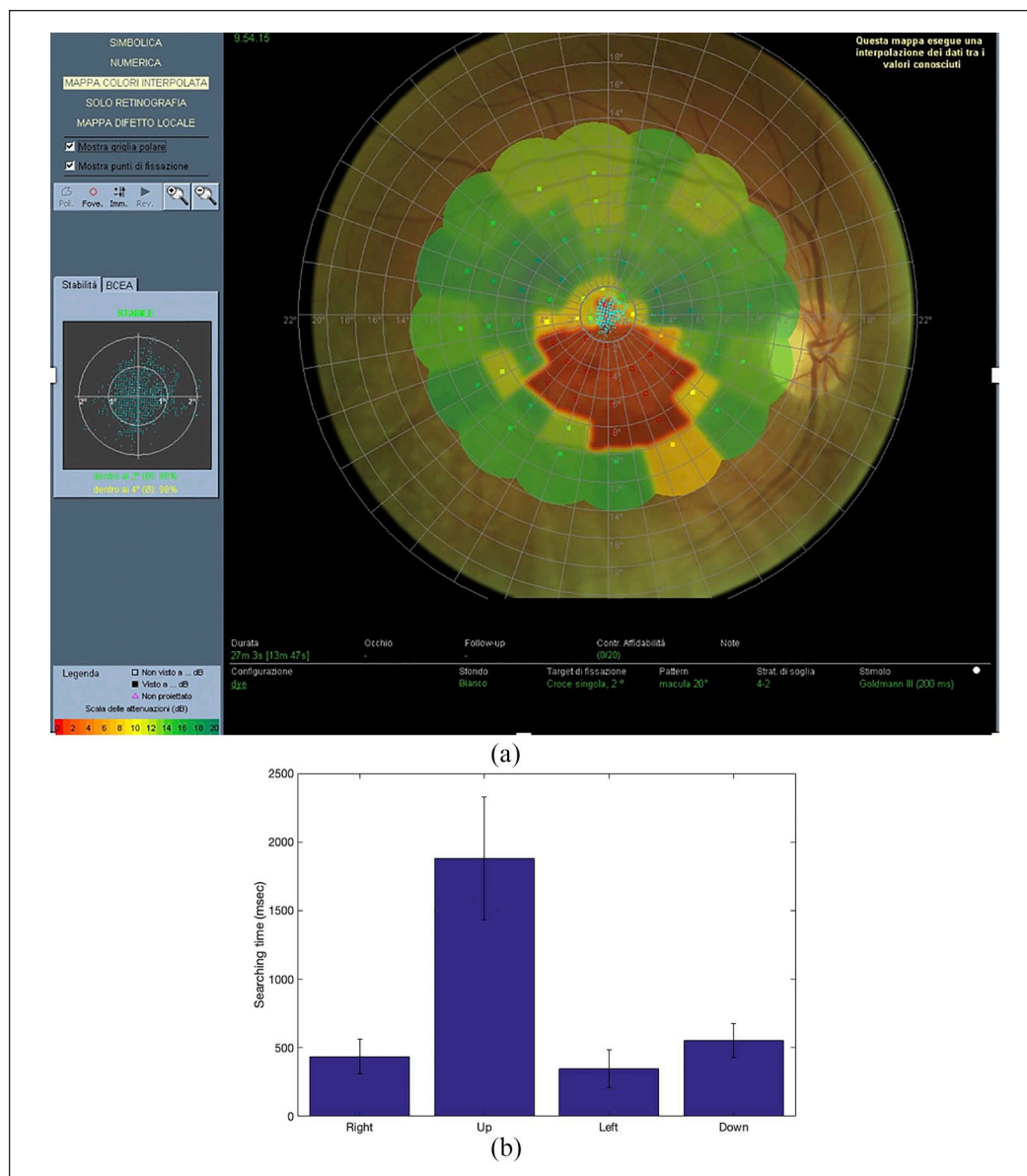
### Case report

We report the case of a STGD patient aged 43 years. VA in his better eye was 0.8 LogMAR. Figure 1(a) shows fundus perimetry in the right eye. It is possible to note that a large deep central scotoma was present under the PRL so that the upward movement was disturbed. Figure 1(b) shows the timing of his saccades in the four studied directions. The upward movement was much slower than the other ones (1480 ms upward vs a mean of 512 ms in the other directions).

### Discussion

Our results show that binocular saccadic movements are slower when guided by an eccentric fixation in patients with a deep macular scotoma due to STGD. Previous

studies demonstrated that reading ability and speed are worse in patients with central deep scotoma and loss of foveal fixation than in healthy subjects.<sup>6,14,22,36,38-46</sup> In binocular testing, the highest correlation (though statistical significance was not achieved) was obtained between saccade duration and contrast sensitivity (LogCS: Pelli Robson, REX test). This result, if confirmed in a larger sample of patients, would suggest that a lower saccade speed could be due to decreased retinal contrast sensitivity in the PRL area. Moreover, reading performance (reading accessibility index<sup>47</sup>) shows a trend toward a positive correlation with saccade speed. We hypothesize that a reduced reading ability in these patients may be partly due to a decreased speed of ocular movements. Monocular results with fundus perimetry confirmed that saccadic movements in STGD patients are slower than in healthy controls, even if we exclude disturbance by deep scotoma position with respect to the PRL. In fact, saccadic movements of patients with eccentric fixation are slower than the ones performed by subjects with a foveal fixation even when they are directed to retinal areas free from deep scotoma. Moreover, in STGD subjects saccadic movements are much more difficult and slow when directed to a retinal area with deep scotoma. In our previous study we demonstrated that the presence of a deep scotoma right to fixation on the reading text is correlated with the worse reading speed when compared with other scotoma positions.<sup>22</sup> Based on the results of this study we can hypothesize that the slower reading speed of patients with eccentric fixation is at least partly due to the slowing down of saccadic movements. The worse performance when a deep scotoma is present on the right of the text, may be due to the increased duration of the ocular



**Figure 1.** (a) Fundus perimetry and saccadic movements timing in a STGD patient. (b) Correlation between a slow eye saccade upward and a deep scotoma under PRL fixation in the considered STGD patient.

movement to reach a target on the side of non-functioning retina.<sup>48</sup> We suggest that a deep scotoma hiding the target that must be reached by the saccadic movement slows the programming of the saccade and that this slowdown is added to that due to the eccentric fixation which, as mentioned, seems related to a reduced contrast sensitivity in the PRL. The cross-sectional design of this study, together with the limited case number, does not allow us to reach a final opinion about the main cause of the increased duration of ocular saccades in STGD patients with eccentric fixation.

Further studies with a greater number of cases will be necessary to investigate the causes of the slowing down of the ocular saccades guided by eccentric fixation in STGD

patients and to better understand the relation between saccades speed and reading ability.

For this purpose we plan to modify the test so that it will require the execution of ocular movements which simulate those recorded during reading in terms of both width and direction. To achieve this goal, we plan to study a larger sample of patients with central scotoma and eccentric fixation. Therefore the software could be used to train reading ability together with biofeedback-based PRL stabilization in low vision patients.

#### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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