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ABSTRACT

Purpose: The article aims to assess the impact of Leber Hereditary Optic Neuropathy (LHON) on visual function in realistic tests of face recognition and execution of natural actions in a prospective pilot study.

Method: Twelve participants with LHON with central scotoma ranging from 5° to 20° and 12 unaffected age-matched controls took part in the experiment. In the face recognition test, participants were asked to recognize the gender and the facial expression of colored photographs of faces increasing dynamically in size to simulate approaching faces. In the natural action test, they were asked to manipulate real objects. The task was to put butter and jam on bread and to pour water in a glass while their eye movements were recorded.

Results: Although most patients were able to recognize the faces' gender at a size corresponding to a one-meter viewing distance, recognition of facial expressions was severely impaired. Patients were on average 40 seconds slower than controls in executing the natural action task. A dynamic strategy to sample information needed for the execution of the task appeared in the longer scanpath and in the higher frequency of saccades and fixations in patients than in controls.

Conclusion: As a function that relies on central vision, face perception is strongly impaired in patients with LHON. Although the selection and manipulation of real objects to execute a natural action task are slowed down, they can be performed efficiently using the peripheral vision.

Leber Hereditary Optic Neuropathy (LHON, OMIM#535000) is a rare (~ 1:50,000) [1–4] maternally inherited mitochondrial disease characterized by acute bilateral loss of central vision resulting from focal degeneration of the macular retinal ganglion cells and their axons forming the papillomacular bundle. [5] It is associated with severe reduction in visual acuity and dense scotoma in the central visual field. [6] Severity of visual loss and recovery are influenced by the underlying mtDNA pathogenic variant: m.11778G>A (OMIM*516003.0001) is the most frequently associated with the poorest visual recovery, while m.3460G>A (OMIM*516000.0001) and m.14484T>C (OMIM*516006.0001) are each responsible for approximately 15% of LHON cases and associated with a less severe disease course. [7]

The central visual field defect impacts the quality of life (QoL) as many visual functions require central vision (reading, cooking, manipulating objects, visual search, face recognition). Most of the limited data available on the effect of LHON on these functions come from QoL questionnaires (e.g., the VF-14). [8-9]

To our knowledge, no study has documented the impact of LHON on face recognition in realistic tests. However, it is essential to social interactions and daily life activities. Faces contain information for the recognition of identity, emotions, intentions, age, gender and attractiveness. [10] When face perception fails as a result of neurological (e.g., prosopagnosia) or ocular (e.g., macular degeneration) impairment, it may have significant psycho-social consequences and lead to anxiety in social situations and social withdrawal. [11-14] Face recognition difficulties have been well documented in patients with age-related macular degeneration, in whom discriminating faces from non-faces is slowed down [15-16] while more complex tasks such as recognition of facial expressions or identification are markedly impaired. [17-18] Similarly, little is known about the impact of central visual field loss on the execution of natural actions. Boucart et al. [19] examined the oculomotor behavior of patients with macular degeneration while they accomplished a natural action: a sandwich-making task. They were only 30 seconds slower (mean 3.01 min ranging from 2.01–4.22 min) than normally sighted age-matched controls and exhibited longer gaze durations only with irrelevant objects. There was no difference in gaze duration with relevant objects between the two groups.

Previous visual exploration studies conducted in people with central visual field loss resulting from macular degeneration, have used reaching/grasping tasks with static images of faces and objects [18, 20-21] or an isolated object. [22-23] However, in real-life situations, faces are searched and objects are grasped in clustered environments and they vary in both distance and size. We assessed the impact of central visual field loss using realistic tests in patients with

LHON and normally sighted age-matched individuals. Face recognition was evaluated with a dynamic technique in which a photograph of a face was initially displayed at a size corresponding to a viewing distance of 20 m, then automatically increased in size to simulate the face approaching. For each face, a threshold equivalent viewing distance (i.e., the distance at which a real face would have the same angle as the projected face) was measured for recognition of gender and recognition of facial expression. Natural action was assessed in a task involving the manipulation of real objects likely to be used every day for breakfast. We expected patients to be more impaired in the face recognition task than in the natural action one, as intact peripheral vision may be used to select relevant objects and guide movements in the latter.

MATERIALS AND METHODS

Participants

Twenty-one patients accepted to participate. Nine were excluded owing to poor best-corrected visual acuity (<1/40). Twelve patients (nine males) at a chronic stage of LHON were included, ranging from 19 to 53 in age (mean : 33.6 years). They were recruited in the department of Visual Explorations and Neuro-Ophthalmology of the Lille University Hospital. The criteria for exclusion were a LHON "plus" with neurological disorders and the presence of concomitant confounding ophthalmic pathologies such as glaucoma, cataract and all types of retinopathy leading to macular involvement. The mean duration of the pathology was 7.6 years. The mtDNA pathogenic variants are reported in Table 1 for each patient. Binocular best-corrected visual acuity (BCVA) was measured with the ETDRS chart. All patients showed a deficit in the 10° central visual field measured with the automated perimeter (Métrovision MonCVOne, Metrovision (Perenchies, France: https://metrovision.fr/perimeters-us.html), as presented in Table 1 (expressed as Mean Deviation : MD). Twelve normally sighted unaffected controls (six males) accepted to participate, ranging from 23 to 50 in age (mean : 33.7 years). To be included, their BCVA had to be above 0.1 logMAR. Group characteristics are summarized in Table 1. All the tests were performed in accordance with the declaration of Helsinki and approved by the committee of behavioral sciences of the University of Lille. Written informed consent was obtained from all participants.

Table 1. Characteristics of participants. Binoc : binocular VA: visual acuity (logMar), MD: mean deviation, RE : right eye, LE : left eye, Cent VFD: central visual field defect, Evol: duration of disease evolution in years. V4e, III4e refer to kinetic perimetry target size and intensity used for scotoma size measurements.

	Age	Gender	Binoc VA	MD RE	MD LE	Cent VFD	Evol.	Mutation	scotoma size
P1	24	M	0.7	12.6	15.3	yes	2	ND6 (14484)	10° V4e
P2	39	M	1.5	19.7	18.1	yes	17	ND4 (11778)	20° V4e
P3	19	F	1.3	14.8	14.8	yes	6	ND4 (11778)	15° III4e
P4	19	M	1.2	20.4	17.2	yes	5	ND4 (11778)	10° III4e
P5	53	M	1.6	NT	NT	yes	8	ND4 (11778)	20° III4e
P6	45	M	1.0	4.9	13.2	yes	8	ND4 (1019)	5° V4
P7	47	F	0.7	14.8	17.8	yes	3	ND4 (11778)	10° V4e
P8	36	M	0.2	21.7	23.0	yes	20	ND4 (11778)	10° III4e
P9	44	M	0.4	6.9	6.1	yes	6	ND1 (3460)	5° III4e
P10	24	M	1.0	6.2	5.8	yes	4	ND6 (14484)	10° V4e
P11	25	M	1.3	12.5	13.6	yes	8	ND4 (11778)	20° III4e
P12	29	F	0.7	7.3	11.3	yes	4	ND4 (11778)	10° V4e
	Age	**Gender**	**Binoc VA**						
C1	24	M	0.0						
C2	35	M	0.0						
C3	50	M	0.0						
C4	32	M	0.0						
C5	23	F	0.0						
C6	23	F	0.0						
C7	46	F	0.0						
C9	29	F	0.0						
C9	27	F	0.0						
C10	41	M	0.0						
C11	30	F	0.0						
C12	45	M	0.0						

Face recognition

Stimuli: The stimuli were colored photographs of male and female faces selected from the NimStim sorted emotions database. [24] Each face was presented on a black background screen but separated from it by a white rectangle so that the hair was visible. Three facial expressions were selected: angry, happy and neutral. Each of the three facial expressions was presented

five times with different male faces and five times with different female faces for a total of 30 faces.

Procedure: Participants were seated at a viewing distance of 2 m from a 30-inch DELL screen. Stimuli were presented in photopic conditions with light coming from the ceiling. Prior to the experiment, participants were shown an example of the three facial expressions on paper print. During each trial, a central white fixation cross (5°) was displayed for 1 sec on a black background. Five hundred ms later, it was followed by a face covering 0.36° x 0.5° simulating the angular size of an average face viewed at a distance of 20 m. The angular size increased automatically in 5-cm steps, mimicking the face moving progressively closer. Participants were asked to stop the progression (i.e., the increase in size) with a key press on a joystick as soon as they were able to identify the gender of the face. The experimenter recorded the answer (M/F) on the computer. At that moment, the participant was asked if he/she was able to categorize the facial expression. If not, he/she resumed the size increase by a key press and stopped it similarly when he/she recognized the facial expression (angry, happy or neutral). The experimenter entered the answer (A/H/N) on the computer, which recorded the equivalent viewing distance (EVD) for the categorization of gender, facial expression and the accuracy of the two responses. If the patient was unable to recognize the gender and/or the facial expression at the end of the display (i.e., the largest size of the face) then a "no response" was recorded and the experimenter pressed the space bar to start a new trial.

Natural action

Stimuli:

A scene layout included task-relevant objects, required to make a butter and jam sandwich and to pour a glass of liquid, as well as task-irrelevant objects, some being visually similar to the relevant ones to induce errors. All objects were laid out on a table within reach (see Figure 1) and located within an area covering 60° of the visual angle.

Equipment:

Eye movements were recorded binocularly with a remote Senso Motoric Instruments Eye Tracking Glasses 2.0 (SMI—ETG 2.0, Germany). The eye-tracker had a sampling rate of 60 Hz with automatic parallax compensation. The resolution of the front camera was 1280×960 pixels. Calibration was performed with the one-point automated method developed by SMI. Data management and analysis were processed with the SMI BeGaze™ analysis software version 3.7.

Procedure:

The participants were seated at the work surface, with all items within reach. They were asked to open the bread bag, to take a slice, to put butter and jelly on the bread using the knife and to pour water in the glass. Before the task, the layout was occluded by a white board showing a calibration dot, enabling the participants to be calibrated on the plane of the working surface. They had to fixate the dot while their eye positions were recorded by the eye tracker. Once the calibration was completed, the white board was removed and they could start the task. They were told that the layout contained irrelevant objects and asked to ignore them.

Statistical analyses

Statistical analyses were conducted with the Systat software 8 (Systat Software, Inc. San Jose California). In the face recognition task, the variables measured were the EVD in meters and the accuracy of responses for categorization of gender and facial expression. In the natural action task, the variables measured were the duration of the pre-task (i.e., exploration before the first reaching movement) and the duration of the task itself (the working phase). Regarding eye movements, we measured the scanpath, the amplitude and frequency of saccades, and the frequency and duration of fixations on both relevant and irrelevant objects.

Fig.1. Scene layout used. Task-relevant objects: bread, butter, jelly, knife, plate, glass, and water bottle. Irrelevant objects: toothbrush, tool, yogurt, scotch tape, and stapler.

RESULTS

Face recognition

Individual data are presented in Table 2. Normally sighted participants recognized the gender of the faces at an angular size corresponding to a distance of 18.35 m for male faces and 18.14 m for female faces. The mean number of errors was 2/30 faces. All 12 patients were able to recognize the gender of the faces at an average angular size corresponding to a distance of 1.9 m for male faces and 1.73 m for female faces. The mean number of errors was 4.33/30 faces.

Facial expressions were recognized at a shorter distance (i.e., at a larger angular size) than gender in normally sighed controls (happy: 16.57 m, angry: 15.49 m, neutral: 15.47 m). Accuracy was high with a mean number of errors of 0.75/30. Only 7/12 patients were able to recognize facial expressions with an accuracy above or equal to chance (33%). Happy and neutral faces were recognized at a mean distance of 1.16 m and angry faces at a distance of 1.03 m. The mean number of errors was 7.83/30 with a large disparity between patients and no responses were observed in many trials in patients 2, 3 and 5 (see Table 2).

Table 2: Individual data for patients with LHON and controls. EVD: equivalent viewing distance (m). M: male faces, F: female faces.

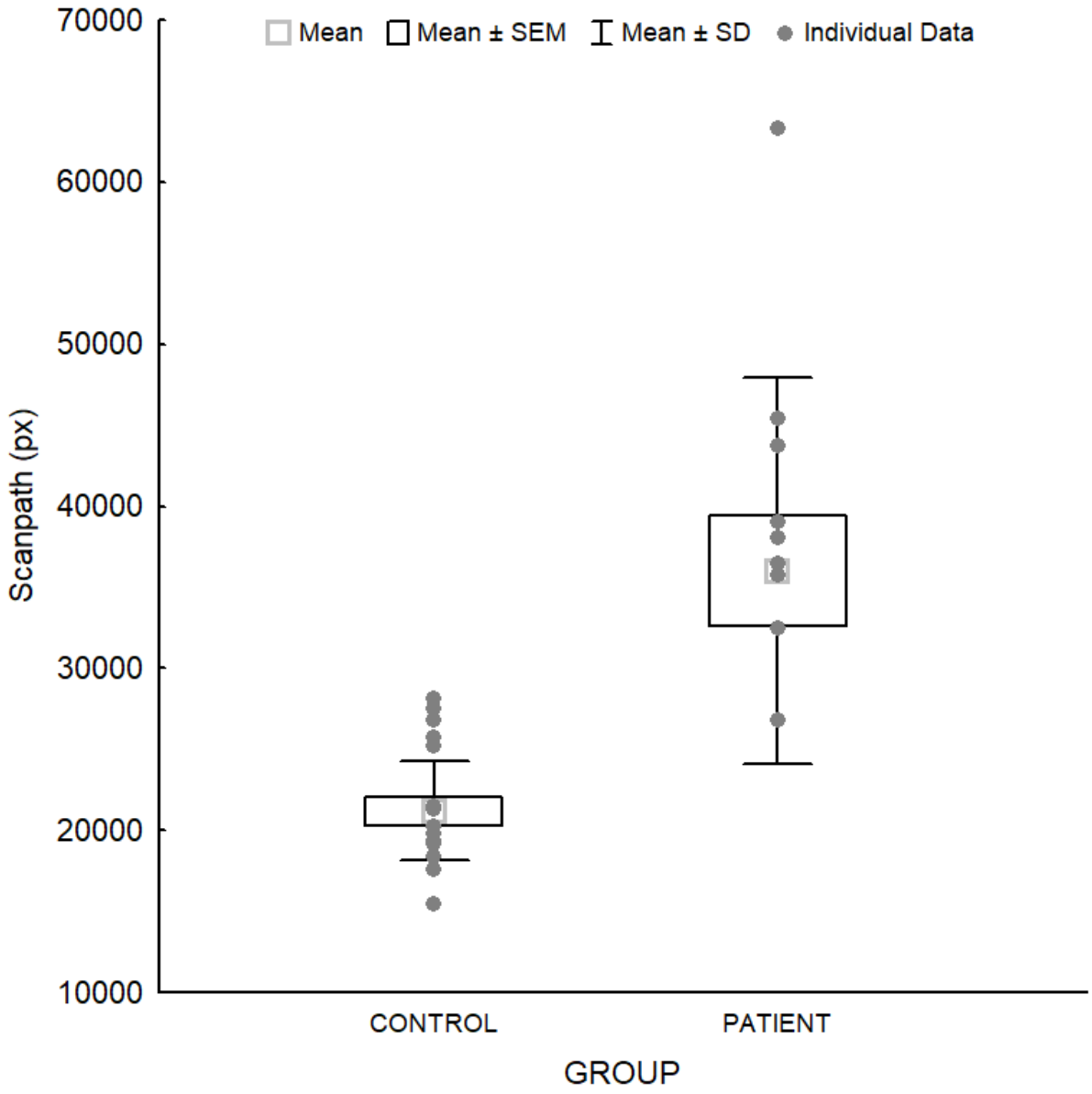
PATIENTS	EVD M faces	EVD F faces	Nb errors	EVD Angry	EVD Happy	EVD Neutral	nb errors	no response
1	1.8	1.74	3	1.00	1.12	1.08	0	0
2	1.00	1.00	4	1.00	1.00	1.00	2	28
3	1.00	1.00	4	1.00	1.00	1.00	7	12
4	1.00	1.00	4	1.00	1.00	1.00	10	0
5	1.00	1.00	11	1.00	1.00	1.00	19	11
6	1.11	1.00	1	1.00	1.00	1.00	5	0
7	1.07	1.00	2	1.00	1.00	1.00	8	0
8	6.18	6.71	3	1.39	2.83	2.91	2	0
9	4.86	2.57	5	1.00	1.01	1.00	4	0
10	1.03	1.09	8	1.00	1.00	1.00	15	0
11	1.02	1.00	5	1.00	1.00	1.00	14	0
12	1.81	1.67	2	1.00	1.00	1.03	8	0

CONTROLS	EVD M faces	EVD F faces	Nb errors	EVD Angry	EVD Happy	EVD Neutral	nb errors	no response
1	19.24	19.3	2	13.52	15.64	15.96	3	0
2	18.57	18.71	0	15.36	16.36	15.00	0	0
3	18.66	17.83	2	15.61	15.59	15.32	0	0
4	16.09	17.48	0	13.27	14.03	12.99	1	0
5	18.58	17.84	4	13.96	15.24	14.35	1	0
6	18.74	18.37	2	16.51	17.37	13.36	1	0
7	19.05	18.94	2	18.19	18.16	17.49	0	0
8	16.28	15.16	2	13.17	14.39	14.56	3	0
9	18.76	18.71	5	17.42	18.11	17.41	0	0
10	19.41	17.78	2	14.46	17.93	14.78	0	0
11	18.26	18.73	0	17.6	17.91	17.9	0	0
12	18.66	18.89	3	16.9	18.16	16.63	0	0

Natural action:

The mean duration of the pre-task was significantly longer in patients than in controls (15.2 sec vs. 9.6 sec $t(22) = 2.52$, $p<.019$). Patients were on average slower than controls in total duration (including the pre-task and the working phase): 109.5 sec [ranging from 70 to 170 sec] vs. 69.3 sec [ranging from 54 to 85 sec] ($t(22) = 4.6$, $p<.001$).

The scanpath was greater in patients than in controls (36022 pixels vs. 21210 pixels, $t(22) = 4.17$, $p<.001$, see Figure 2).



226

227 **Fig. 2**. Mean scanpath (in px) in controls and LHON patients. Individual data are represented
228 in grey circles and means in grey squares. Box plots indicate standard error of mean (SEM)
229 and error bars indicate standard deviation (SD).

230

231 Although the amplitude of saccades did not vary significantly between groups (5.9° vs. 5.3°,
232 $t(22) = 0.7$, $p = 0.47$), their frequency was higher in patients than in controls (2.96 vs. 2.53,
233 $t(22) = 2.27$, $p<.033$; see Figure 3).

234

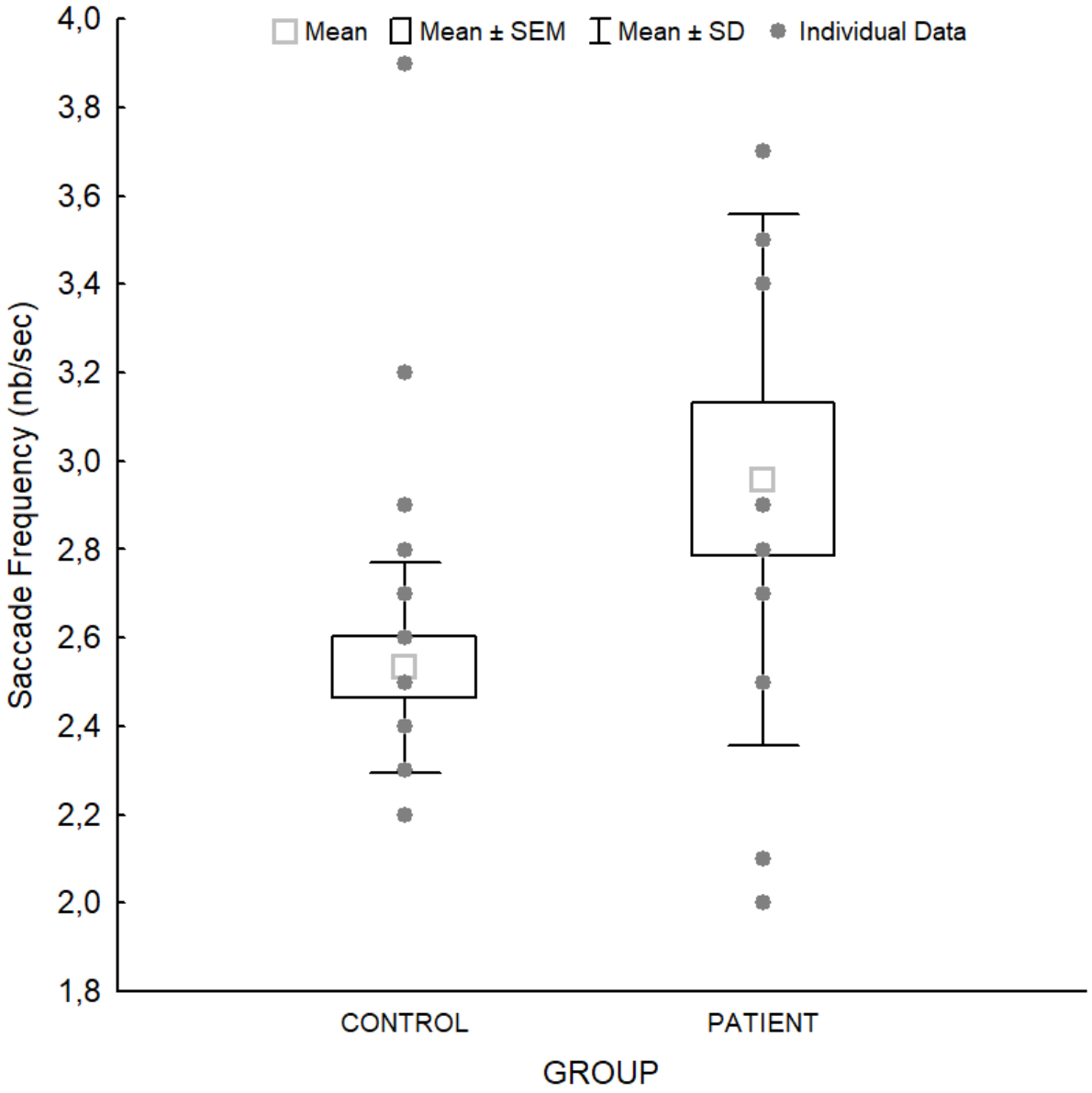


Fig. 3. Mean saccade frequency (nb/sec) in controls and LHON patients. Individual data are represented in grey circles and means in grey squares. Box plots indicate standard error of mean (SEM) and error bars indicate standard deviation (SD).

On average, the frequency of fixations was higher in patients than in controls ($t(22) = 2.23$, $p<.036$; Figure 4). Although the duration of fixations was significantly longer on relevant objects than on irrelevant ones in controls (relevant : 255 ms vs. irrelevant 189 ms, $t(11) = 3.9$, $p<.002$), the difference was not significant in patients (relevant : 216 ms vs. irrelevant 193 ms, $t(11) = 1.98$, $p = 0.072$). The interaction between groups and duration of fixations on relevant/irrelevant objects was marginally significant ($F(1, 22) = 4.25$, $p<0.051$).

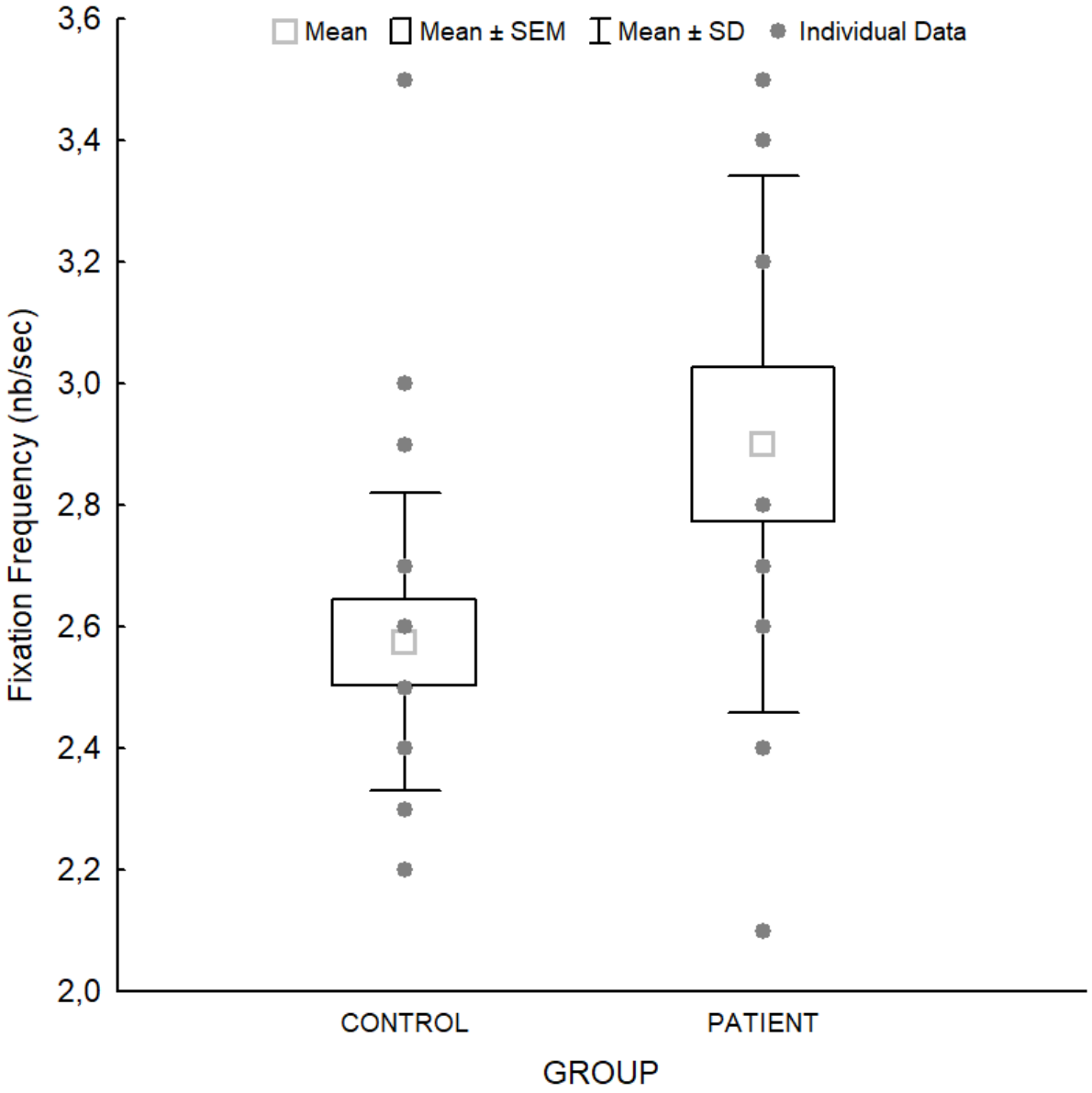


Fig. 4. Mean frequency of fixations (nb/sec) in controls and LHON patients. Individual data appear in grey circles and means in grey square. Box plots indicate standard error of mean (SEM) and error bars indicate standard deviation (SD).

DISCUSSION

Ocular pathologies leading to a loss of central vision and visual acuity have a significant impact on patients' QoL as reported in questionnaires. Although it is important to assess these difficulties, questionnaires are subjective measures. Except for a prospective pilot study to assess reading speed [25], the present study is the first to measure task-based

performance in two active vision tasks (face recognition and natural action) in realistic conditions with the simulation of an approaching face and the handling of real objects to execute a succession of actions.

Overall, our results show that patients with LHON were impaired in the face recognition task. Although most of them were able to recognize the gender of faces at a size corresponding to a one-meter viewing distance, only five patients (including P8 and P9, the two patients with a better binocular visual acuity) were able to recognize the gender at a greater equivalent viewing distance. While recognition of gender can be based on coarse information conveyed by low spatial frequencies, [26] recognition of facial expressions requires a finer perception of facial features (e.g., a frown for angry, a smile for happy). Gender was recognized at a greater distance than facial expressions by both controls and patients with a better binocular visual acuity. Studies on normally sighted young individuals have shown that the happy expression is dependent on low spatial frequencies [27] while other expressions such as anger, fear and sadness require higher spatial frequencies and a closer distance to be recognized. [28] In line with these studies, happy faces were recognized at a greater distance (i.e., a smaller size) than the angry and neutral faces were in controls and in P8 with the BCVA. The equivalent viewing distances observed for both gender and facial expressions in our experiment replicate those found in a previous study [29] in normally sighted young and older participants. The present results are consistent with the declarations of patients with LHON in questionnaires. Around 45% of them report major difficulties in recognizing faces. [25] This study suggests that these difficulties are probably underestimated, as the recognition of three facial expressions was severely impaired. Studies on ocular pathologies affecting the macular region have documented issues in the recognition of faces and facial expressions [18, 30-31], and while age-related macular degeneration is a progressive disease in which patients have time to adapt and develop cognitive strategies to compensate for vision loss, LHON is associated with rapid central vision loss. Taylor et al. [32] observed that people with dry macular degeneration do not suffer from problems with face recognition until the disease is in its advanced stage.

In everyday tasks, gaze is used actively to gather information for the control of actions. Eye movements reflect an overt manifestation of the momentary deployment of spatial attention in a scene. [33] Loss of central vision changes an individual's capacity to gather relevant visual information. With central visual field loss, visually guided actions must be mediated by peripheral vision in which spatial resolution is lower than in central vision. In the

natural action task used here, real objects were scattered over an area covering 60°. Patients were significantly slower than controls in the pre-task, before the first reaching movement. As the pre-task is used to identify and remember the spatial location of relevant objects, this result indicates that the peripheral vision is less efficient than the central vision to discriminate relevant from irrelevant objects. Patients were on average 35 sec slower than controls in the working phase (making a sandwich and pouring water in a glass). Similar durations were reported in a previous study on patients with age-related macular degeneration, who were 30 sec slower than age-matched normally sighted controls. [19] In this experiment, the working phase was longer in patients with LHON than in controls partly because some of them used tactile information to recognize the objects or grasped them to bring them closer to their faces before executing the action. Although patients were slower than controls, they managed to accomplish the task without mistakes. The longer scanpath and higher frequency of saccades and fixations in patients than in controls likely reflect a dynamic strategy to sample information that is needed for the execution of the task. The greater number of saccades may also reflect gaze instability and the need to use peripheral vision and one or several preferred retinal locations (PRLs) to compensate for the deficit. PRLs were not measured in this study. Although patients with LHON were slower than normally sighted individuals in accomplishing natural actions, they reported being able to perform daily life activities efficiently in spite of their scotoma and low visual acuity. Our results are in line with data from questionnaires indicating that cooking-related activities are the least impacted by the pathology with only 11.8% of patients reporting major difficulties and 21.3% reporting moderate ones, compared to 85% for reading. [8-9]

Limitations

The major limitation of this study is its small number of patients. However, LHON is a rare disease affecting about 1/50,000 persons in European countries. Nine patients were excluded owing to poor BCVA (< 1/40). Individuals with central visual field loss often use one or several PRLs depending on the task. [34] However, we did not measure them. In a single case study on a patient with Stargardt disease (a pathology causing bilateral central scotoma), Sullivan et al. [35] showed that a well-defined preferred retinal locus (PRL) is not necessary to perform natural action tasks adequately.

Conclusion

While limited in scope owing to its small sample, this study provides interesting insights into understanding active vision in patients with LHON. It shows that patients with dense bilateral central scotoma are able to accomplish a daily life natural action using their peripheral vision. However, they are strongly impaired in face recognition, which relies on central vision. [36]

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