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Disrupted Eye Movements in Preperimetric Primary Open-Angle Glaucoma

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Purpose. Primary open-angle glaucoma (POAG) can be associated with abnormal ocular motor behavior, possibly as a compensatory strategy following visual field loss. The aim of this study was to explore the characteristics of saccadic eye movements in patients with early-stage POAG without any detectable glaucomatous visual field loss (i.e., preperimetric POAG).

Methods. Binocular eye movements were explored in 16 patients with bilateral preperimetric POAG and 16 age-matched healthy controls in a cross-sectional, observational study. Visually guided horizontal prosaccades (5°, 10°, 15°, and 20° amplitude) and antisaccades (12° amplitude) were measured using infrared oculography. The latency, average and peak velocities, amplitude and gain of prosaccades as well as the percentage of errors in the antisaccades task were compared between groups.

Results. POAG patients exhibited a reduced average velocity of saccades compared to controls across all amplitudes of peripheral visual target presentation ($P = 0.03$). Saccades performed by POAG patients were hypometric, and with reduced amplitude ($P = 0.007$) and gain ($P = 0.01$) compared to controls. On average, POAG patients displayed more antisaccade errors (40.6%), as compared to controls (23.4%; $P = 0.04$).

Conclusions. Here, we show that patients with POAG without detectable glaucomatous visual field loss exhibit altered saccadic eye movements. These abnormalities may indicate disordered cortical and subcortical saccadic regulation, either on the basis of subthreshold visual impairment, or as a result of wider disease-associated neurodegeneration. Additional studies, controlling for glaucoma medications, are required to delineate the neural basis of eye movement abnormalities associated with POAG.

Keywords: primary open-angle glaucoma, preperimetric, eye movements, prosaccades, antisaccades, infrared oculography

Primary open-angle glaucoma (POAG) is a multifactorial progressive optic neuropathy that leads to an irreversible, yet gradual, visual field loss. It is characterized by axonal degeneration affecting the afferent visual pathways, from the retinal ganglion cells (RGCs) to the lateral geniculate nucleus (LGN) and visual cortex.[1–9] In addition to the visual system involvement, recent brain functional connectivity studies have suggested that various nonvisual cerebral areas could also be affected in glaucoma, as part of a more global neurodegeneration.[10,11] These affected regions include cortical and subcortical areas involved in the control of ocular motor behavior.[12–17]

Published reports on eye movements in glaucoma have already suggested that eye movements and visual exploratory behavior are altered in the disease. While some studies have shown that POAG patients with visual field defects perform more saccades compared to healthy controls when viewing a traffic video displayed on a computer screen or performing familiar and unfamiliar tasks,[18,19] others reported that POAG patients with visual field defects perform less saccades than

controls when viewing computer displayed photographs of everyday scenes.[20] In addition to protocol differences, discrepancies between these studies could arise from dissimilarities in visual field loss/sensitivity between patients,[21] as well as unpredictable adaptive oculomotor behaviors to compensate for visual field loss.[22–24] Compensatory oculomotor behavior, however, may not be the sole mechanism contributing to aberrant eye movements in POAG, as excessive saccades have also been reported when visual targets were displayed into unaffected visual field areas in POAG patients.[25] Furthermore, preliminary findings by Lamirel and colleagues,[25] suggest that saccadic eye movements can be altered at very early stages of POAG, with no detectable visual field deficit.

In an attempt to reduce the contribution of visual field loss as a potential confounding factor in the evaluation of ocular motor behavior in glaucoma, here we study saccadic eye movement abnormalities in patients with POAG, in whom structural damages (i.e., neuronal loss detectable via optical coherence tomography) were not associated with detectable functional deterioration in the visual fields. These patients are often referred to in the literature as preperimetric glaucoma patients.[26]

Materials and Methods

Participants

Sixteen patients diagnosed with bilateral preperimetric POAG and 16 age-matched healthy controls were included in this cross-sectional observational study. Patients and controls underwent a comprehensive ophthalmic examination that comprised slit-lamp examination (Model 900 BQ, Haag-Streit, Bern, Switzerland), best-corrected visual acuity (BCVA; logMAR chart), automated refraction (Canon RK 5 Auto Ref-Keratometer; Canon, Tochigiken, Japan), intraocular pressure (IOP) measurement (Goldmann applanation tonometer, Haag-Streit), gonioscopy (Sussman four mirror lens, Ocular Instruments, Bellevue, WA, USA), and baseline peripapillary retinal nerve fiber layer (RNFL) thickness via high definition optical coherence tomography (HD-OCT; Cirrus version 6.0, Carl Zeiss Meditec, Dublin, CA, USA). OCT results were validated only if the recorded signal strength had a value of 6 or better. The visual fields of all participants were assessed on two separate visits, at least 6 months apart, using the Humphrey visual field analyzer II (Carl Zeiss Meditec) with the Swedish Interactive Thresholding Algorithm (SITA fast 24-2 strategy [stimulus size III]). Repeated testing was performed if the rates of false-positive or false-negative responses were greater than 30%, or if the fixation loss rate was greater than 20%. Participants who did not achieve these levels of performance on repeat testing were excluded from the study. Details of antiglaucoma treatments were also recorded, when applicable. Preperimetric POAG patients were defined as having a glaucomatous optic neuropathy in the absence of any other causes of secondary glaucoma, based on abnormal optic disc cupping (vertical cup-disc ratio>0.7) and/or neuroretinal rim notching, with thinning of the RNFL on HD-OCT, and visual field results, of each eye, that do not meet the minimum criteria for diagnosing acquired glaucomatous damage based on Hodapp-Parish-Anderson's (H-P-A) criteria.[27] In addition, these patients were diagnosed with an IOP higher than 21 mm Hg and open angles on gonioscopy. Patients and controls were excluded if they had any associated ophthalmic conditions (e.g., cataracts, myopia worse than −6 D, retinopathies, potential alternative causes of optic neuropathy, and ocular motor disorders), as well as psychiatric conditions or neurologic disorders, including cognitive impairment or dementia. POAG patients were on glaucoma medications (e.g., brimonidine, prostaglandin analog, dorzolamide, and timolol). Patients on psychotropics or other medications that could affect alertness were also excluded. Informed consent was obtained from the participants after explanation of the nature and possible consequences of the study. The study adhered to the tenets of the Declaration of Helsinki; the study protocol was approved by the local Institutional Review Board of the University Hospital of Angers, France.

Experimental Setting and Eye Movement Recordings

Each participant was seated on a chair in a dark room with the head stabilized by a chinrest. Binocular eye movements were recorded using the Eyebrain T2 Tracker (SuriCog, Paris, France), a CE-marked medical eye-tracking device. The recording frequency of the system was set to 300 Hz and its precision was 0.25° to 0.5° in controlled conditions. Participants underwent binocular eye movement recordings while performing ocular motor paradigms presented on a 22-inch computer screen (resolution 1920 × 1080; refresh rate 60 Hz), at 15° of visual angle. Calibration of the system was performed at the beginning of each block. During the calibration procedure, participants were instructed to fixate various targets (0.5° in diameter) displayed successively at 13 positions mapping the screen. Each point had to be fixated for 250 ms for validation. A polynomial function integrating five parameters was used to fit the calibration data and to determine the visual angles. After manual validation of the calibration procedure, each subject underwent two ocular motor paradigms.

Prosaccades Paradigm

In this paradigm participants were instructed to fixate a central circular fixation point of 0.5° in diameter for a pseudo-random delay of 2000 to 3500 ms. Subsequently, the fixation point disappeared making way after a 200-ms gap to a peripheral visual stimulus. The peripheral stimulus consisted of a 0.5° red filled square presented at 5°, 10°, 15°, or 20° of horizontal eccentricity. Stimuli were randomly presented to the left or right of the fixation point for 1000 ms. Participants were instructed to look toward the stimulus as quickly and accurately after its presentation. Subsequently, the central fixation target reappeared, signaling central refixation and the beginning of the next trial. Each participant performed two blocks of trials, separated by 2 minutes of rest. Each block included presentation of 48 peripheral targets, 24 on each side of the fixation target. This gap paradigm is designed to elicit saccades with short latencies (80 to 130 ms) also coined as "Express Saccades" (ES) compared to regular saccades, which have latencies between 150 and 200 ms.[28]

Antisaccades Paradigm

Antisaccades were explored using a classical gap paradigm.[29] During the antisaccade task, participants were instructed to fixate on a central target displayed for a pseudo-random time of 2000 to 3500 ms. Subsequent to the disappearance of the central point (gap interval of 200 ms), a peripheral visual target consisting of a 0.5° red filled square was presented at 12° of horizontal eccentricity for 1000 ms. Participants were instructed to perform a saccade to the mirror location (same amplitude, opposite direction) of the visual target as quickly and accurately as possible.[30] Thus, when the visual target appeared on the right side, the subject had to perform a saccade to the left, aiming at a diametrically opposed, imaginary visual target. Subsequently to the disappearance of

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the peripheral visual stimulus, the central fixation target reappeared signaling the start of the next trial. An initial training block was performed to ensure that the instructions were well understood. This paradigm involves two distinct, successive processes: (1) inhibition of the "reflexive," unwanted prosaccade toward the peripheral target, followed by (2) execution of a voluntary, endogenous saccade in the opposite direction. This task tests the integrity of the "decision-making" cortical networks, and is regularly used in neurology to quantify the effects of age and neurodegenerative diseases.[31,32] Each participant performed two blocks of 12 randomly distributed horizontal antisaccades; each block was separated by 2 minutes of rest.

Data Analysis

The algorithm used to detect saccades was adapted from Nyström and Holmqvist.[33] Eye movements analysis was performed using the MeyeAnalysis software (SuriCog), allowing extraction of the saccades' parameters from the acquired data. This software automatically detects the onset and offset of each saccade from both eyes using a built-in saccade detection algorithm. The accuracy of automated saccade detection was verified by experienced investigators (CL and DM). The latency, average and peak velocities, amplitude, and consequently gain (i.e., ratio of the amplitude of the saccade and the position/amplitude of the peripheral visual target) of each saccade were examined monocularly in the eye with the least artifacts (i.e., blinks, pupil detection aberrations). In total, the right eye was used for saccade analyses in 28 participants (15 controls and 13 POAG). Saccades with latencies shorter than 50 ms or longer than 500 ms were excluded from the analysis. The percentage of ES correctly directed to the visible stimulus was also calculated. In the antisaccade task, we analyzed the percentage of antisaccade errors, as well as the latency and average velocity of each correct antisaccade. A correct antisaccade was defined as a saccade made in the opposite direction to the visible target, and an incorrect antisaccade was defined as a saccade made toward the target. Differences in demographics and comprehensive ophthalmologic examination of the eyes used in the saccade analyses were compared between groups using a Mann-Whitney *U*-test or a χ^2 test. The median of the absolute values of prosaccade parameters was calculated for each participant as a function of the eccentricity of the target cue and consequently compared using a 2-way repeated-measures analysis of variance (2-way RM-ANOVA) with position/amplitude of the visual target and condition (control, POAG) as factors. For those comparisons in which the omnibus test reached statistical significance, pairwise multiple comparison procedures were performed using the Holm-Sidak method. Percentages of ES were compared between groups using a χ^2 test. Comparison of incorrect antisaccade percentage, velocity, and latency was performed using either a Student's *t*-test or a Mann-Whitney *U*-test depending on the distribution of the data. Demographics and ophthalmologic examination results are represented as median (interquartile range [IQR]). Pro- and antisaccade parameters and data in figures are represented as mean (standard deviation [SD]). Statistical analyses and figures were performed using SigmaPlot v12.0 (Systat Software, Chicago, IL, USA).

Results

Sixteen patients (65.0 [12.8] years, six males) with bilateral preperimetric POAG and 16 age-matched healthy controls (65.5 [14.3] years, seven males) were included in this study. Patients and controls were not different in terms of BCVA, central corneal thickness, visual fields' mean deviation (HVF-MD), pattern standard deviation (HVF-PSD), visual field index (VFI), and IOP as POAG patients were on glaucoma medications. Compared to controls, patients with POAG had an overall reduced RNFL thickness (RNFL-T; $U = 59.5$, $P = 0.01$) particularly in the inferior ($U = 66.0$, $P = 0.02$) and superior ($U = 40.5$, $P = 0.001$) quadrants. A detailed description of the demographics and ophthalmic appraisals in all participants is provided in Table 1.

Table 1. Demographics and Ocular Characteristics of the POAG and Control Groups Using the Eyes Utilized in the Saccades Analyses

Demographics and Ocular Characteristics	Control	POAG	*P* Value
Age, y	65.5 (14.3)	65.0 (12.8)	0.93
Sex	7M, 9F	6M, 10F	0.72‡
BCVA, logMAR	0.0 (0.0)	0.0 (0.0)	0.40
HVF-MD, dB	−0.2 (2.3)	−0.7 (2.0)	0.83
HVF-PSD, dB	1.7 (0.8)	2.0 (0.8)	0.21
VFI, %	99.0 (2.0)	98.5 (3.0)	0.31
IOP, mm Hg	15.0 (5.5)	15.0 (2.0)	0.86
RNFL-T global, µm	89.0 (9.3)	80.5 (13.8)	0.01*
RNFL-T inf, µm	118.5 (25.3)	94.5 (33.3)	0.02*
RNFL-T sup, µm	115.0 (15.0)	94.0 (21.5)	0.001†
RNFL-T nas, µm	64.5 (11.5)	66.0 (10.3)	0.91
RNFL-T temp, µm	60.5 (6.5)	59.0 (12.3)	0.68

Data are represented as median (IQR) and compared using the Mann-Whitney *U*-test. dB, decibel; F, females; HVF, Humphrey visual field; M, males; MD, mean deviation; RNFL–T, retinal nerve fiber layer thickness; inf, inferior quadrant; sup, superior quadrant; nas, nasal quadrant; temp, temporal quadrant; PSD, pattern standard deviation.

* $P < 0.05$.

† $P < 0.01$.

‡ Statistics done using a χ^2 test.

Prosaccades

A total of 1337 prosaccades were analyzed in the POAG group and 1402 in the healthy control group (Table 2). There was an effect of visual target position (amplitude) on saccade latency in both groups, with 15° and 20° saccades having longer latencies compared to 5° and 10° saccades ($F[3, 30] = 20.19$, $P < 0.001$). Although the latency profile of POAG patients was skewed toward faster saccades and a higher percentage of ES (18.6%) compared to controls (15%; $\chi^2 = 6.25$, $P = 0.012$; Fig. 1A), when the data were analyzed per subject (Fig. 1B), the latency of prosaccades was not different between POAG patients and controls ($F[1, 30] = 1.11$, $P = 0.30$). The average velocity of saccades increased as a function of amplitude in both groups ($F[3, 30] = 298.27$, $P < 0.001$). Average velocity of prosaccades was reduced by 35.3°/s on average across different amplitudes in POAG patients compared to controls ($F[1, 30] = 5.39$, $P = 0.03$; Fig. 2). This reduction in average velocity was independent of the amplitude of the saccade ($F[3, 30] = 1.43$, $P = 0.24$). There was no difference between groups in peak saccade velocity ($F[1, 30] = 3.75$, $P = 0.06$). The amplitudes of the saccades were reduced in POAG patients compared to controls ($F[1, 30] = 8.31$, $P = 0.007$) at 10°, 15°, and 20° (Fig. 3A). Consequently, saccade gain was reduced in patients compared to controls ($F[1, 30] = 7.55$, $P = 0.01$; Fig. 3B). Saccades performed by POAG patients were hypometric (gain <1) when the peripheral visual targets were presented at 10°, 15°, and 20°, whereas the saccades performed by controls were hypermetric (gain >1) at visual target amplitudes of 5°, 10°, and 15°. Controls performed 18% more hypermetric saccades (at least 10% off target) compared to POAG (Figs. 3A, 3B).

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TABLE 2. Details of Prosaccades Results in Controls and POAG Patients

Visual Target Position, °	Controls				POAG				*P* Value		
	5	10	15	20	5	10	15	20	Group	Target Amplitude	Interaction
Latency, ms	168.8 (24.8)	158.2 (25.2)	174.8 (31.8)	176.7 (34.0)	157.9 (19.7)	151.3 (23.1)	168.4 (21.1)	165.5 (18.8)	0.3	<0.001	0.66
Average velocity, °/s	171.5 (35.6)	245.3 (48.8)	280.8 (62.5)	305.9 (63.8)	146.8 (21.8)	209.2 (39.9)	243.2 (36.2)	263.3 (41.3)	0.03	<0.001	0.24
Peak velocity, °/s	313.6 (68.1)	428.8 (94.9)	494.1 (111.7)	528.9 (120.8)	274.0 (46.5)	376.1 (71.7)	440.8 (57.6)	460.4 (62.7)	0.06	<0.001	0.38
Amplitude, °	6.1 (1.3)	11.1 (2.4)	15.9 (3.3)	19.9 (3.8)	5.2 (0.6)	9.5 (1.3)	13.3 (1.5)	16.7 (1.9)	0.007	<0.001	<0.001
Gain	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	1.0 (0.1)	0.9 (0.1)	0.9 (0.1)	0.8 (0.1)	0.01	<0.001	0.98

Prosaccade parameters (i.e., latency, average velocity, peak velocity, amplitude, and gain) were compared using a 2-way RM-ANOVA with group and visual target position/amplitude as factors. Data are represented as average (SD).

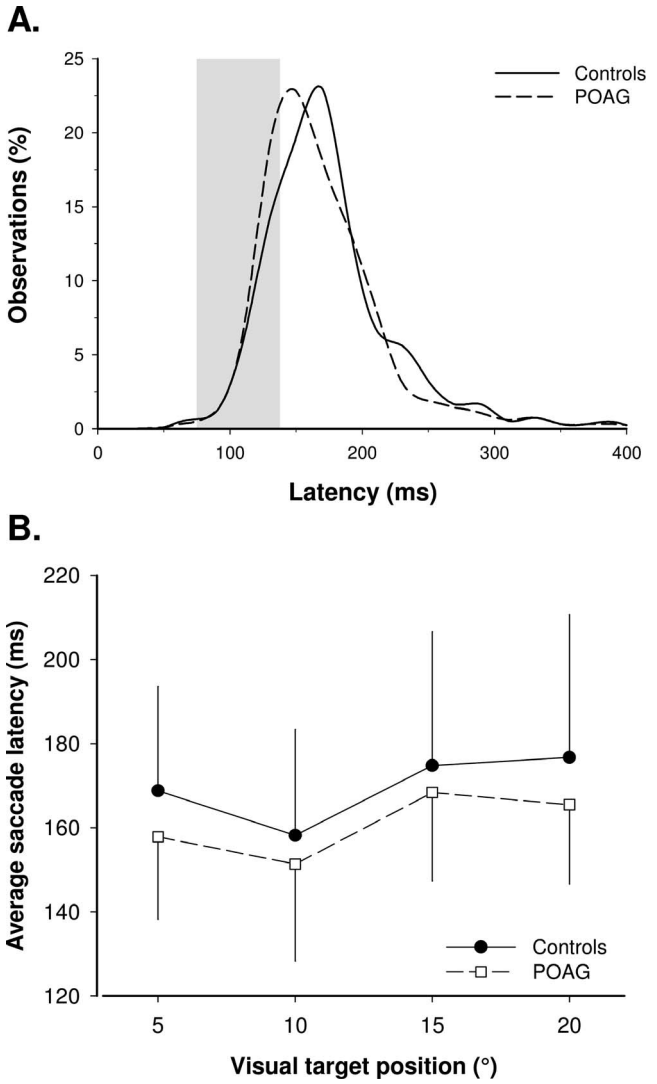

FIGURE 1. Distribution and differences in saccade latencies between controls and POAG patients. (**A**) Distribution of prosaccade latencies in both groups. Overall preperimetric POAG patients displayed a higher percentage of ES (18.6%; observation percentage within the *gray area*) compared to the control group (15%; $\chi^2 = 6.25$, $P = 0.01$). When data were analyzed per individual (**B**), the latency of prosaccades was not different between the POAG and controls ($F[1, 30] = 1.11$, $P = 0.30$).

Antisaccades

A total of 384 antisaccades trials were analyzed, including 192 trials in the POAG group and 192 trials in the control group. On average, 40.6% of the antisaccade trials performed by the POAG group were erroneous. This percentage of antisaccade errors in the POAG group was significantly increased by 17.2% compared to controls (23.4%; $t = 2.05$, $P = 0.04$; Fig. 4). There was no difference between groups in the latency and average velocity of correct ($t = 0.14$, $P = 0.89$; $U = 115$, $P = 0.86$, respectively) and the latency of incorrect antisaccades ($U = 110.5$, $P = 0.9$).

DISCUSSION

This study demonstrates that patients with early-stage POAG, with no detectable glaucomatous visual field loss on standard automated white-on-white perimetry, display abnormal pat-

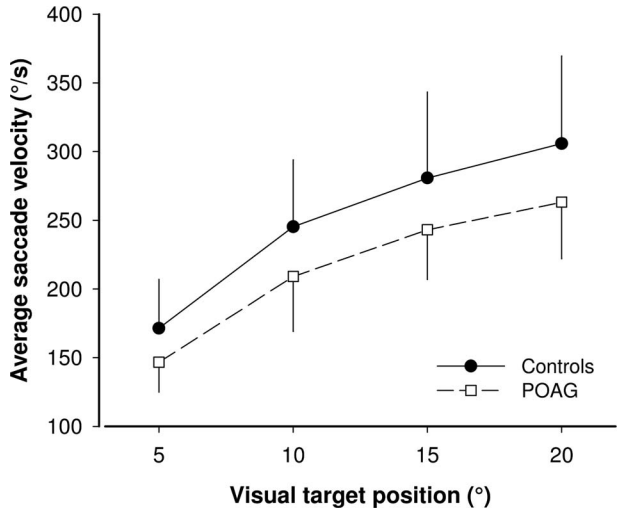

FIGURE 2. Average velocity of prosaccades in controls and POAG patients. The increase in the amplitude of the visual target was associated with an increase in the velocity of the saccades in both groups ($F[3, 30] = 298.27$, $P < 0.001$). POAG patients displayed slower saccades compared to controls ($F[1, 30] = 5.39$, $P = 0.03$). The reduction in saccadic velocity was not dependent of the amplitude of the saccades ($F[3, 30] = 1.43$, $P = 0.24$).

terns of saccadic eye movements compared to age-matched controls. Preperimetric POAG patients performed slower and hypometric saccades compared to controls during the prosaccade task. In the antisaccade paradigm, POAG patients also exhibited an inability to suppress unwanted reflexive saccades to peripheral cues, committing significantly more errors than controls. Taken together, our findings suggest that visual field loss is not the sole contributor to disrupted ocular motor behavior in early POAG. These disruptions could originate from a decreased ocular motor inhibition and altered neuronal signaling.

The network involved in reflexive prosaccade generation includes cortical (primary visual, extrastriate, and parietal cortices, and frontal and supplementary eye fields) and subcortical structures (striatum, thalamus, superior colliculi [SC], and cerebellar vermis).[12] Dysfunction in any of these structures could lead to faulty eye movements.[12,13] In our paradigm, POAG patients exhibited a reduction in the velocity and amplitude of saccades compared to age-matched controls. Amongst possible brain regions responsible for such defects in POAG, the SC stand out as the most conspicuous. In fact, the SC have been implicated in the amplitude and velocity of impending saccades,[34,35] and are targets of almost 10% of the RGC axons in primates, and the primary targets of RGC axons in rodents.[36] Electrophysiological and structural changes occur within the SC in a rodent model of glaucoma.[37,38] Slowed saccades could also arise from a reduced activation of burst neurons or inhibitory omnipause neurons in the pontine reticular formation. This structure has a predominant role in fixation, and the generation and velocity of saccades, and receives a main input from the SC.

The extent of reduction in saccade velocity observed in preperimetric POAG patients is comparable to that observed under intoxication[39–41] or sedation.[42] In fact, the 14.1% reduction in average velocity denoted in POAG patients here is even more prominent than that observed with 0.06% to 0.12% blood alcohol level (9%).[39] This suggests that visual field loss might not be the sole rationale for increased driving lapses and motor vehicle accidents in glaucoma patients.[43,44] Further investigations in simulated driving situations are essential to elucidate ocular movement and driving strategies in early-stage glaucoma. It is worth mentioning that, given the established relationship between saccade velocity and amplitude,[45] saccade hypermetria in controls could be a factor in the increased average velocity observed in that group. Saccade hypermetria in healthy participants is dependent upon the experimental paradigm and research settings,[46] and has previously been to associated with a top-down/predictive component in self-paced saccades.[47,48] Whether POAG pa-

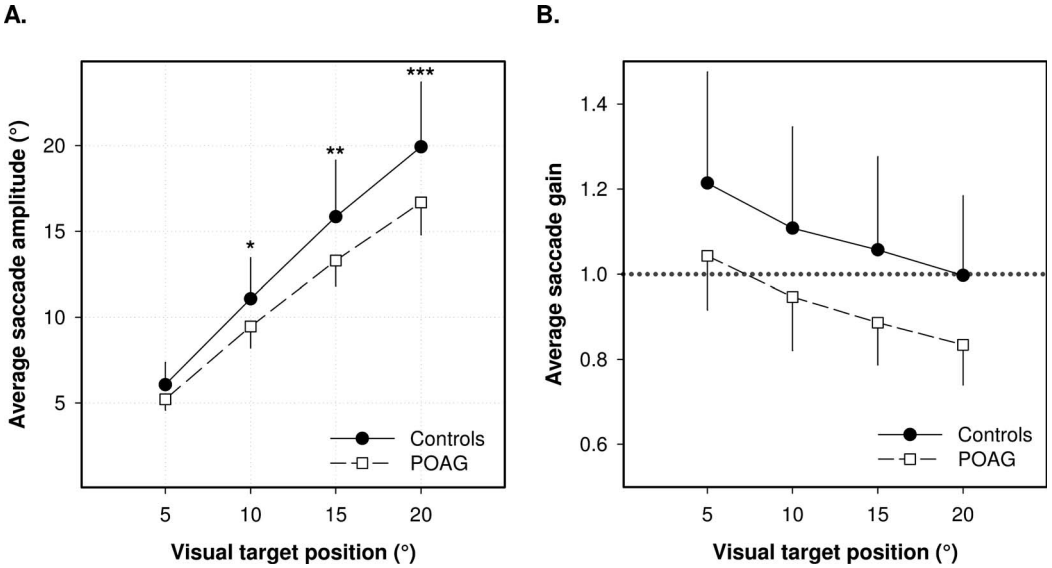

FIGURE 3. Amplitude and gain of prosaccades in controls and POAG patients. (**A**) The amplitudes of saccades performed by POAG patients were significantly reduced compared to controls when the target was presented at 10°, 15°, and 20° of eccentricity ($F[1, 30] = 8.31$, $P = 0.007$). Consequently, saccade gain (**B**) was reduced in POAG patients compared to controls ($F[1, 30] = 7.55$, $P = 0.01$). The difference in gain between groups was independent of the amplitude of the visual target ($F[3, 30] = 0.06$, $P = 0.98$). On average, POAG patients performed hypometric saccades when the visual target was presented at 10°, 15°, and 20° from the central fixation point, whereas controls performed hypermetric saccades when the visual target was presented at 5°, 10°, and 15° of eccentricity.

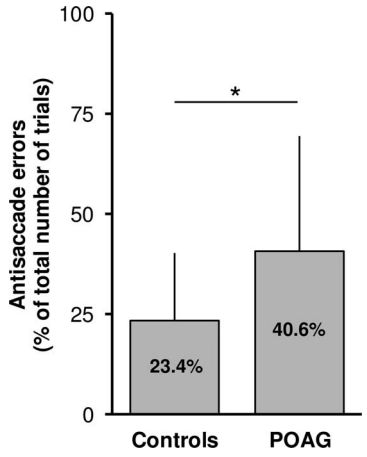

FIGURE 4. Antisaccade errors in controls and POAG patients. (**A**) On average, 40.6% of the antisaccade trials performed by the POAG group were erroneous. This percentage of antisaccade errors was significantly increased by 17.2% compared to controls (23.4%; $t = 2.05$, $P = 0.04$).

tients show reduced predictive pacing urge in the prosaccade paradigm remains to be clarified.

In addition to engaging similar brain regions to prosaccades, a correct antisaccade involves neural activity changes in regions such as the prefrontal and cingulate cortices, and requires inhibition of a reflexive, unwanted saccade toward the cue, prior to execution of an appropriate endogenous saccade in the opposite direction.[15,49] The antisaccade paradigm is widely used to test cortical networks involved in this "decision-making" process, which is abnormal in neurodegenerative disorders,[50] in multiple sclerosis,[51] in psychiatric diseases, and with aging.[30] Here we show that preperimetric POAG is associated with an increased number of unwanted reflexive saccades. Among the various putative causal explanations, we formulate the hypothesis that POAG may be associated with a dysfunctional cerebral inhibition, leading to disrupted control of reflexive eye movements. In POAG, structural changes have been found in the LGN and in the primary visual areas, presumably as a result of secondary anterograde trans-synaptic degeneration.[3] Recent multimodal, cerebral MRI and diffusion tensor imaging studies have shown diffuse structural and functional changes in the brains of patients with different stages of glaucoma.[10,11] These changes affected visual and nonvisual structures in the brain. Beyond atrophy of the visual cortex, these studies disclosed atrophy of scattered, distant gray matter regions such as the frontoparietal cortex, hippocampi, and cerebellar cortex, and decreased functional connectivity in visual, working memory and dorsal attention networks. The same study in glaucoma disclosed altered integrity of the superior longitudinal fascicle, resulting in decreased fractional anisotropy.[11] This fascicle is involved in providing information regarding perception of visual space to the prefrontal cortex, which in turn is responsible for the planning phase of an antisaccade.[52] Furthermore, the white matter of the precuneus showed abnormalities even in early-stage POAG.[11] This parietal brain structure has major subcortical connections in brainstem structures with strong oculomotor characteristics, such as the pretectal area, the SC, and the nucleus reticularis tegmenti pontis.[53–55]

Given the developmental, physiological, and anatomical features that the retina shares with the brain,[56] it is not surprising that functional changes affecting the retina could also translate into cerebral dysfunctions and vice versa. In line with this, evidence of a close link between glaucoma and various neurodegenerative diseases have been reported in a number of recent experimental studies,[57–59] and the prevalence of glaucoma seems to be higher in Alzheimer's disease patients than in the normal population.[60] Furthermore, a thinning of the RGC axons has also been observed in a number of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases.[22,61] The reduced saccadic velocity and increased antisaccade errors associated to a deficit in reflexive saccade suppression we report in POAG patients, also represent hallmarks of neurodegenerative diseases like Parkinson's and Alzheimer's diseases, progressive supranuclear palsy, or even Huntington's disease.[62–64] Such coherence in early eye movement symptoms between early POAG and neurodegenerative diseases, although inconclusive, deserves further attention to elucidate mechanisms associating glaucoma and neurodegenerative diseases. The understanding of such common pathophysiological pathways could provide valuable targets for novel therapeutics.

Besides the aforementioned plausible liaisons between altered saccadic eye movements and cerebral aberrations occurring in POAG, we cannot exclude a potential repercussion of undiagnosed visual processing abnormalities observed in early glaucoma[65–68] (i.e., chromatic aberrations and reduction in contrast sensitivity) on the saccadic eye movements of preperimetric POAG patients included in this study. The extent of impact of such inferences on different saccadic parameters remains to be elucidated in preperimetric POAG.

Irrespective of the physiological origins of altered saccadic eye movements in POAG, early detection remains essential to slow the progression of the disease. As the cost of treating glaucoma increases by 46% after the occurrence of vision loss,[69] delaying disease-related vision loss in POAG is not solely critical to maintain patients' quality of life but also to reduce associated health-economic burdens. Screening for early-stage POAG using saccadic eye movements can potentially complement ongoing endeavors for a timely detection of this debilitating disease. Such approaches have previously been investigated in more advanced stages of glaucoma.[70]

This study has a few limitations that should be reported. First, even though the SITA Fast algorithm is an accepted screening strategy for patients who are unable to maintain long-term attention, it may be less sensitive than SITA Standard, and could therefore underestimate visual field loss. Here, POAG patients underwent two HVF tests on two separate occasions prior to their inclusion in the study. Only patients whose visual field did not meet the minimum H-P-A criteria for acquired glaucomatous visual fields damage were included. Even though these criteria are known to be strict and could suggest a significant deterioration where there is none,[26] we cannot exclude that some of our POAG participants could have had very early, subthreshold, visual field loss. Second, this observational study has a limited number of participants and unlike other studies, does not provide information on eye movements in real-life situations.[18,70] When assessed in more realistic settings (e.g., the head not stabilized by a chinrest), parameters such as head movements, for example, could reveal peculiar strategies adopted by preperimetric POAG patients to compensate for impaired ocular motility even for minimal gaze shifts. Nevertheless, using gold standard paradigms specifically designed for the fine quantification of saccades in controlled conditions, we have reduced interindividual variability and yielded significant findings with a limited number of participants. Third, we cannot exclude a possible effect of glaucoma medication on saccades. To our knowledge, however, there are no reports on medication (e.g., prostaglandin analogs, α agonists, β blockers) and eye movement in glaucoma. Further investigations on a larger population of POAG patients are required to clarify this matter. Finally, since we did not compare the cognitive capabilities of our age-matched partic-

ipants, we acknowledge that possible age-related infraclinical cognitive impairments could contribute to the variability in saccadic parameters observed in controls and POAG groups.

In conclusion, this study provides new insight on saccadic eye movement changes in POAG with no detectable visual field loss on standard automated perimetry. These abnormal eye movements may occur as a result of altered neural signaling and disrupted inhibition of unwanted reflexive saccades, and might provide a new window into understanding the pathophysiology of glaucoma. Additional studies are needed to delineate the real-life consequences and neural basis of eye movements abnormalities associated with this irreversible ocular disease even at its earliest stages.

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