


Effects of Multimodal and Unimodal Physical Training Interventions on Visual Function in Glaucoma and Elderly Controls – A Pilot Study

Cynthia Moffack Djuloun¹, Khaldoon O Al-Nosairy¹, Rosalie Beyer¹, Constantin W Freitag², Francie H Stolle¹, Martin Behrens^{3,4}, Tom Behrendt², Gokulraj T Prabhakaran¹, Hagen Thieme¹, Lutz Schega^{2,*}, Michael B Hoffmann ^{1,5,*}

¹Ophthalmic Department, University Hospital, Magdeburg, Germany; ²Department of Sport Science, Institute III, Otto von Guericke University, Magdeburg, Germany; ³University of Applied Sciences for Sport and Management, Potsdam, Germany; ⁴Department of Orthopedics, Rostock University Medical Center, Rostock, Germany; ⁵Center for Behavioral Brain Research, Magdeburg, Germany

*These authors contributed equally to this work

Correspondence: Michael B Hoffmann, Ophthalmic Department, University Hospital, Magdeburg, Germany, Tel +49 391 67 13585, Fax +49 391 67 13570, Email michael.hoffmann@med.ovgu.de

Purpose: This study aimed to investigate the effects of a 12-week multimodal motor-cognitive and resistance training (MMI) compared to a unimodal resistance training intervention (UMI) on static and dynamic visual function in glaucoma (GLA) patients and healthy controls (HC).

Methods: Fifteen GLA and 24 age-matched HC participated in this randomized, controlled longitudinal pilot study. Visual function was assessed using clinical parameters and on a treadmill (TM) while standing (static, S_0) as well as during walking at 3.5 km/h ($S_{3.5}$) and a self-preferred speed (S_{Self}). The following outcomes were measured pre and post 12-weeks of intervention (MMI or UMI): (a) standard clinical measures and (b) TM-related measures, i.e.: 1) best-corrected visual acuity without (VA_S) and with crowding (VA_C); 2) visual field sensitivity (VF); and 3) contrast sensitivity (CS). A 4-factorial repeated-measures ANOVA (SPEED [S_0 ; $S_{3.5}$; S_{Self}] × TIME [pre; post] × INTERVENTION [UMI; MMI] × GROUP [GLA; HC]) was applied to determine significant interaction effects ($p \leq 0.05$) and the effect size partial-eta-squared was calculated.

Results: Post-interventional improvement of visual function was absent or minor. Only the main effect of TIME (visual acuity; $p = 0.024$) and a TIME × INTERVENTION interaction (foveal sensitivity; $p = 0.039$) were found for standard clinical measures. For S_0 vs. $S_{3.5}$ small effects appeared in post-hoc comparisons, but TIME and TIME × SPEED just failed to reach significance for CS ($p = 0.059$) and VA_S ($p = 0.052$), respectively. No GROUP interactions were observed.

Conclusion: While trends were evident in this pilot study, the effect of the 12-week interventions on visual function was non-significant and, especially for TM-walking, largely independent of group and intervention type. In future studies, a greater sample size, with more advanced GLA cases, should be included to probe for significant visual function differences between groups and intervention types.

Keywords: dynamic visual function, glaucoma, multimodal training, cognitive training, mobility

Introduction

Glaucoma (GLA), a progressive optic neuropathy, is a leading global cause of irreversible blindness.¹ Current estimates expect an increase of affected individuals from 76 million to 112 million by 2040.¹ GLA damage impedes activities important for daily living not exclusively in the visual domain, but also with respect to mobility, e.g., via an increased incidence of falling during walking.² Consequently, GLA has an impact at the individual level due to quality of life reduction^{3,4} and at the societal level due to health-care cost increase.^{5,6} However, these conventional measures often overlook broader aspects of functional impairment in GLA patients, particularly those related to motor and cognitive

abilities.⁷ A growing body of evidence suggests that GLA shares morpho-functional changes in the eye and brain similar to those seen in neurodegenerative disorders such as Alzheimer's disease and that there might be an association with cognitive impairment.⁸

It has been shown that resistance training mitigated the risk of falls in elderly^{9,10} and might also increase cognitive performance.¹¹ Recent reports¹² also indicate that the combination of motor and cognitive exercise has beneficial effects on motor and/or cognitive function in patients with neurodegenerative diseases, e.g., Alzheimer's disease^{8,13,14} and in healthy participants with cognitive decline.¹⁵ Moreover, this interventional approach might reduce the risk of falls.^{9,10} Due to the fact that GLA might be associated with cognitive dysfunction,⁸ combining motor-cognitive exercises¹² with resistance training in GLA management might be of promise to improve mobility and cognitive function eventually translating in an increased quality of life. This prompts the question of whether a combination of motor-cognitive and resistance training (i.e., multimodal intervention [MMI]) improves motor-cognitive function more than resistance training alone (i.e., unimodal intervention [UMI]) in GLA patients, which has, to our knowledge, not been addressed so far.

The present study reflects on a subset of data from a larger randomized controlled trial examining the effects of two physical training interventions (MMI and UMI) on several primary and secondary outcomes (German Clinical Trial Register, ID: DRKS00022519, 05.08.2020, <https://drks.de/search/de/trial/DRKS00022519>). The primary endpoints include gait kinematics and functional brain connectivity addressed in separate works.²

In the present pilot study, visual function, as a secondary endpoint, is addressed. Specifically, we investigated the influence of a 12-week MMI and UMI on visual function during treadmill (TM) walking in GLA patients and healthy elderly controls. The baseline findings, which were collected 2–3 weeks prior to intervention and previously published,¹⁶ indicated that TM walking, compared to standing, showed reduced visual function similarly in both GLA patients and elderly controls (i.e., a visual acuity loss by more than 0.02 logMAR and visual field sensitivity by 1.0 dB visual field mean deviation). Consequently, it is of interest whether MMI or UMI can improve visual function and thus ultimately, reduce the risk of falls. While these interventions may not restore lost retinal ganglion cells, they may facilitate better gait control and hence visual information processing during locomotion, attentional control, and overall adaptation to visual impairment, potentially leading to improve functional vision and quality of life. The underlying rationale being that movement interventions improve gait control and stability and in turn benefit visual tasks that are affected during walking.¹⁷ We hypothesized that visual function will be improved after the interventions in GLA, especially following MMI, as this intervention specifically targets visuo-cognition compared to UMI.

Methods

Study Design

To investigate the effect of MMI and UMI, a two-arm randomized controlled prospective longitudinal study was conducted from August 2020 to December 2022. Patients with glaucoma (GLA) and age-matched healthy control (HC) subjects were recruited and randomly assigned to either MMI or UMI using counterbalanced randomization and allocation ratio of 1:1 (Figure 1).

The experimental protocol was approved by the Ethics Committee of the Otto-von-Guericke University of Magdeburg in Germany (registration number: 32/18) and all procedures were in line with the Declaration of Helsinki on experiments on human beings. All visual-function related measurements were taken in the Department of Ophthalmology and at the Otto-von-Guericke University Magdeburg, Germany. The interventions were performed in the Department of Sport Science at the Otto-von-Guericke University Magdeburg, Germany. Reporting was performed in accordance with the Consolidated Standards of Reporting Trials Statement (Consort) for randomized pilot trials.¹⁸ All participants gave written informed consent.

Participants

A total of 39 participants, including 15 GLA and 24 HC, were recruited in this study. For GLA, only two of the participants had an advanced stage, two had a mild stage and the rest had a pre-perimetric stage.

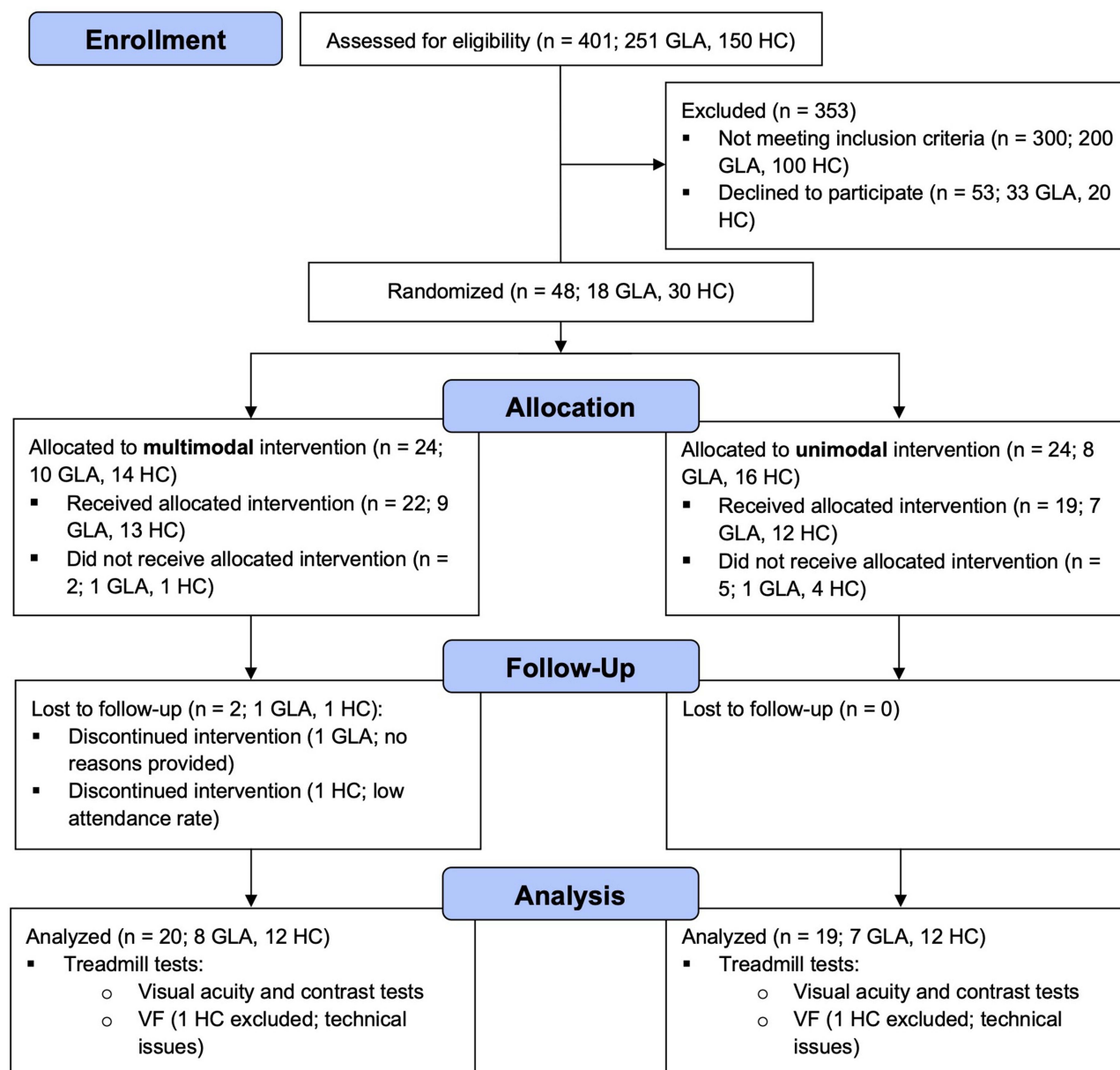


Figure 1 CONSORT flow chart for the recruitment process shows the number of participants and dropouts through the study phases. **Abbreviations:** GLA, glaucoma participants; HC, healthy participants.

Participants underwent complete ophthalmological examination, which is detailed elsewhere.¹⁹ Briefly, we assessed best corrected visual acuity, refractive correction for far (at 5 m) with early treatment diabetic retinopathy study charts (ETDRS), slit-lamp exam, intraocular pressure (IOP), fundus exam, and standard tests for visual field (VF) and retinal structure. GLA was defined according to the European Glaucoma Society Terminology and Guidelines for Glaucoma.²⁰ For GLA staging, we used the Hodapp-Parrish Anderson criteria. The following inclusion criteria were applied: 1) age \geq 60 years; 2) diagnosis of open-angle GLA; 3) patients are under intraocular pressure medications; 4) best corrected visual acuity (BCVA) \geq 0.8 decimal unless GLA-related in the GLA group; 5) normal visual function parameters unless GLA related; 6) no other conditions affecting visual function such as age-related macular degeneration or retinal detachment; 7) ability to walk at least 6 min without walking support; and 8) visual field defects classified according to the Hodapp-Parrish Anderson criteria²¹ in GLA with defects. Exclusion criteria were as follows: 1) neurological disorders; 2)

rheumatism; 3) cardiovascular disorders; 4) stroke; and 5) orthopedic diseases including arthrosis (grade II or higher), musculoskeletal impairment, tendinitis, tenosynovitis, myositis, prosthesis in the lower extremities, and joint replacements.

Interventions

The training (i.e., MMI and UMI) was conducted twice a week on non-consecutive days for 12 weeks resulting in a total of 24 sessions. Each session lasted 60 min and was supervised by experienced instructors.

The MMI was split into: 1) motor-cognitive training; 2) resistance training; and 3) cool-down (i.e., static stretching). Over the course of the intervention, the proportion of time spent on motor-cognitive and resistance training changed (see Table 1). The motor-cognitive exercises consisted of simultaneously performed motor, cognitive, and visual tasks based on the LifeKinetik program.²² These exercises were designed in such a way that it is almost impossible to perform them without making mistakes. If the exercises were performed correctly in 6 out of 10 attempts, the instructor continued with a more difficult exercise. As examples, two exercises are briefly explained below: 1) balls of different colors (e.g., yellow, green, red) are thrown in a circle, whereby a corresponding name must be said for each color (e.g., yellow = persons own name, green = name of the person to whom the ball is to be thrown; and 2) participants line up next to each other and after an announcement (e.g., left, right, front, back) they walked in the corresponding direction (line of vision remained the same, i.e., no returns), whereby a corresponding name for each direction were varied (e.g., right = “1”, left = “2”, front = “3”, back = “4”).

The UMI consisted of: 1) 10-min standardized warm-up (i.e., 5 min fast walking and dynamic stretching); 2) 40-min resistance exercises; and 3) 10-min cool-down (i.e., static stretching). The resistance training included multiple-set (2×7 repetitions, 30 s rest between sets, time under tension: 2 s concentric and eccentric) circuit training using free weights and weight machines (e.g., dumbbell seated front raise and seated leg press) (Table 2). External training load was adjusted by increasing the weight and controlled via individuals' rating of perceived exertion (RPE) using the Borg CR 10 Scale (i.e., RPE = 3–4 (moderate to somewhat severe)).

Resistance training was carried out in the same way as the MMI, although the number of exercises and its duration varied (see Tables 1 and 2). All exercises were performed while sitting because exercising in a supine or other positions affects the intraocular pressure.^{23,24} Both interventions ended with a 10-min cool-down consisting of static stretching for the major muscle groups (e.g., standing side stretch, standing forward fold, overhead triceps stretch).

Outcome Parameters

At the start of this study, participants' demographic and anthropometric data as well as their physical activity level, and visual function were recorded. Standard ophthalmology tests included: i) standard automated perimetry (SAP) for visual field estimation with 24–2 SITA-Fast test (Humphrey Field Analyzer, Carl Zeiss Meditec AG, Jena, Germany) and ii) optical coherence tomography (OCT) of macula and disc using a spectral-domain OCT device with a Glaucoma Module Premium Edition (Heidelberg Spectralis[®], Heidelberg Engineering, Heidelberg, Germany). Of note, single- and dual-task gait performance (i.e., stride length, gait velocity) as well as gaze behavior (i.e., saccade duration, fixation duration) were also assessed at the beginning of the study.^{2,19} Effects of the interventions were scrutinized for: (A) the standard clinical tests including BCVA, VF parameters, e.g., foveal sensitivity and VF MD; and for (B) TM walking testing. For TM

Table 1 Multimodal Training Schedule

Training components	Course of intervention		
	Week 1–4	Week 5–8	Week 9–12
Motor-cognitive training	10 min	20 min	30 min
Resistance training	40 min	30 min	20 min
Cool down	10 min	10 min	10 min

Table 2 Resistance Exercises

Week	UMI	MMI
Weeks 1–4	<ul style="list-style-type: none"> • Seated leg press • Lever pulldown • Lever seated twist • Lever chest press • Cable curl • Lever back extension • Cable pushdown • Cable upright row • Seated leg curl 	<ul style="list-style-type: none"> • Seated leg press • Lever pulldown • Lever seated twist • Lever chest press • Cable curl • Lever back extension • Cable pushdown • Cable upright row • Seated leg curl
Weeks 5–8	<ul style="list-style-type: none"> • Seated leg press • Cable straight back seated row • Lever seated twist • Lever chest press • Cable curl • Lever back extension • Cable pushdown • Cable upright row • Lever leg extension 	<ul style="list-style-type: none"> • Seated leg press • Cable straight back seated row • Lever seated twist • Lever pec deck fly • Cable upright row • Cable curl
Weeks 9–12	<ul style="list-style-type: none"> • Seated leg press • Cable straight back seated row • Lever chest press • Lever seated twist • Reverse cable curl • Dumbbell seated front raise • Seated leg curl • Lever back extension • Cable pushdown 	<ul style="list-style-type: none"> • Seated leg press • Dumbbell seated front raise • Reverse cable curl • Lever chest press • Lever seated twist

walking testing, four visual function tests were performed binocularly [BCVA without crowding (VA_s), BCVA with crowding (VA_c), contrast sensitivity (CS) and binocular visual field (Bin-VF)] as detailed below. Further, heart rate was also measured during these measurements and averaged for each speed condition.

Heart rate was monitored with a wireless transmitter belt (POLAR Heart Rate Sensor H9) wrapped around the lower part of the chest coupled with the h/p/cosmos[®] TM setup (h/p/cosmos sports and medical gmbh, Germany). For each Speed condition, the median heart rate was calculated. In case of technical malfunctions with the heart rate transmitter, we used the heart rate value at the end of each session.

Visual Function During TM Walking

Visual function was tested at 5 m and to account for variable viewing distance during TM walking as a confound factor, visual functions were corrected using a distance sensor (Vivior[®] sensor) as detailed in Beyer et al.¹⁶

TM Walking Testing Procedure

Visual functions were tested for 3 speed conditions in a fixed order: 1) static (S_0), 2) TM speed of 3.5 km/h ($S_{3.5}$) and 3) a self-preferred TM speed (S_{Self}).

Visual Function Testing Procedure

For each speed condition, three binocular visual tests were performed respectively using Freiburg Vision Test (FrACT[®])²⁵ in a dimly-lit room at 5-m distance and repeated twice in the following order: 1) VA_s , 2) VA_c and 3) CS.

This was followed by one Bin-VF test using Ocusweep (Ocusweep[®], Ocuspecto Ltd, Turku, Finland) in an ambient room light. Total experiments duration was about 75 min.

- 1) VA_s: An 8-alternative-forced choice (AFC) single Landolt ring was presented to estimate VA and reported as a logarithmized minimal angle of resolution (logMAR).
- 2) VA_c: The same applies to VA_s but with using a single optotype surrounded by a circle (“©”).
- 3) CS: An 8-alternative-forced choice (AFC) optotype with varying contrasts was used to determine the weber contrast (logCS).
- 4) Bin-VF: A square stimulus comprised of 9 LEDs (5.2 mm × 5.2 mm) was presented at near distance (~40 cm) without proximity sensor to estimate the mean deviation of VF sensitivity (MD). Ocusweep[®] allowed for VF testing while TM walking since it requires no fixed head or chin rest. The device adjusts to ambient light levels using light sensors. The outcome measure was the binocular VF mean deviation (Bin-VF-MD).

All visual functions were performed using BCVA except for Bin-VF where near refractive correction is not mandatory as long as the VA < 0.1 logMAR.

Statistical Analysis

After testing for normal distribution (Shapiro–Wilk test) and for assumptions for repeated measures analysis of variance (RM-ANOVA), data were analyzed and presented accordingly. Data were reported as mean ± standard deviation (SD) for normally distributed data and as median and range for non-normally distributed data. The analyses of standard clinical test outcomes were performed employing a 3-way RM-ANOVA with the factors TIME (pre and post), INTERVENTION type (MMI and UMI), and GROUP (GLA and HC). In addition, data of the specific visual tests performed during the different TM walking conditions were analyzed using a 4-way RM-ANOVA with the factors: TIME, INTERVENTION, GROUP, as well as SPEED (S₀, S_{3.5} and S_{Self}). If a violation of sphericity was detected, the Greenhouse-Geisser correction was applied. In case of significant interactions or main effects, post-hoc tests with Sidak-correction were performed. The effect size partial eta-squared (η^2_p) was calculated and interpreted as small (0.01–0.05), medium (0.06–0.13), and large effect (≥ 0.14) according to Cohen (1988).²⁶ Effects were classified as significant if $p \leq 0.05$ and relevant, if at least a medium effect size was observed. Data analysis was conducted in R²⁷ and SPSS (Statistical Package for the Social Sciences; IBM, Armonk, NY, USA). For IOP and heart rate data across factors, linear mixed model was used, since data was missing for few participants.

Results

Participants (18 GLA and 30 HC) were randomly assigned to either MMI (GLA: n = 8, HC: n = 12) or UMI group (GLA: n = 7; HC: n = 12). There was no age difference between groups ($p = 0.276$, Table 3). Three GLA and 6 HC had dropped out during the intervention period due to personal reasons. Baseline and demographic characteristics of the included participants are given in Table 3.

We next detailed the effects of the 12-week intervention on A) standard clinical tests and B) the TM based visual functional tests.

Effect of the Interventions on Standard Clinical Tests

Main effects: We observed a significant TIME effect with regard to ETDRS BCVA ($p = 0.024$, $\eta^2_p = 0.15$), i.e., an improvement by 0.03 logMAR after the 12-week interventions. Interaction effects: There was a significant TIME × INTERVENTION interaction effect for the VF parameter “foveal sensitivity” ($p = 0.039$, $\eta^2_p = 0.12$). Post-hoc tests indicated an improvement of foveal mean sensitivities only for UMI, by 1.07 dB compared to the pre-intervention foveal sensitivities (35.2 dB), $p = 0.024$ (Table 4A). (Table 4A).

For IOP measurements, there were neither significant main nor interaction effects of different factors. However, there was a trend of lower IOP measurements before training, 15.2 mmHg compared to post-training 16.2 mmHg, $p > 0.054$. For effects on heart rate, GLA had lower heart rates, 92.9 beats per minute (BPM), compared to HC, 95.2 BPM, $p = 0.007$.

Table 3 Patients' Demographic and Clinical Results Before and After the 12-Week Interventions

			HC (n = 24)	GLA (n = 15)	p-value
			Mean ± SD (Median, Range)		
Age [years]			71.6 ± 1.1	69.8 ± 1.1	0.276
Sex		m f	11.0 13.0	8.0 7.0	0.450
SAP foveal sensitivity [dB] [#]	OS	Pre	(36.0, 8.0)	(34.5, 12.0)	0.101
	OS	Post	(35.4, 7.0)	(35.3, 7.0)	0.953
	OD	Pre	(36.1, 8.0)	(36.1, 15.0)	0.723
	OD	Post	(36.9, 16.0)	(36.6, 6.0)	0.953
SAP-MD [dB] [#]	OS	Pre	(0.1, 5.9)	(-1.0, 22.0)	0.054
	OS	Post	(0.0, 2.9)	(-1.0, 21.2)	0.016
	OD	Pre	(0.3, 5.1)	(-0.0, 14.0)	0.103
	OD	Post	(0.2, 3.4)	(-0.4, 14.2)	0.028
BCVA [logMAR] [#]	OS	Pre	(-0.1, 0.2)	(-0.2, 0.5)	0.224
	OS	Post	(-0.1, 0.2)	(-0.0, 0.3)	0.092
	OD	Pre	(-0.1, 0.3)	(0.0, 0.3)	0.038
	OD	Post	(-0.1, 0.2)	(-0.1, 0.4)	0.290
VA _s [logMAR]	Bin	Pre	0.0 ± 0.1	0.0 ± 0.1	0.214
		Post	0.0 ± 0.2	0.0 ± 0.1	0.076
VA _c [logMAR]	Bin	Pre	0.1 ± 0.1	0.1 ± 0.1	0.320
		Post	0.1 ± 0.0	0.0 ± 0.1	0.043
CS [logCS]	Bin	Pre	1.7 ± 0.1	1.6 ± 0.2	0.765
		Post	1.7 ± 0.2	1.7 ± 0.2	0.800
VF [dB] [#]	Bin	Pre	(0.8, 3.3)	(-0.4, 9.6)	0.006
		Post	(0.6, 3.2)	(-0.4, 7.6)	0.005

Notes: [#]Mann-Whitney Test. Significant p-values are given in bold. Mean and SD for normative data distribution and (median, range) are given for non-normal data distribution.

Abbreviations: SEM, standard error of the mean; SAP, standard automated perimetry; BCVA, best corrected visual acuity using ETDRS charts; VA_s, best corrected visual acuity without crowding (VA_s) and with crowding (VA_c); CS, contrast sensitivity; VF-MD, mean deviation of visual field; OD, right eye; OS, left eye; bin, binocular.

Effects of the Interventions on TM Walking Visual Function

TM Walking SPEED Effects (S₀ vs. S_{3.5} and S_{Self})

Some of the results of the pre-intervention data set have previously been reported by Beyer et al.¹⁶ Of note, the present study analyzed data of a smaller sample due to dropouts during the intervention period (GLA: 3, HC: 6). Main effects (significant effects detailed in Table 4B): For VA_s, the mean BCVA static (mean ± SD: -0.015 ± 0.11 logMAR) was better than dynamic readings (mean ΔS₀-S_{3.5} [ΔS₀-S_{Self}] ± SD: -0.03 ± 0.04, *p* = 0.001, see Figure 2A). Participants also had better VA_c at S₀ (0.031 ± 0.09 logMAR) than S_{3.5} [S_{Self}] (mean S₀-S_{3.5} [S₀-S_{3.5}] difference ± SD: -0.02 ± 0.05, *p* = 0.100 [-0.043 ± 0.061, *p* < 0.001]). For CS there was no effect of speed (comparable CS across different speeds with an average of 1.65 ± 0.16 logCS, see Figure 2B). Bin-VF were reduced during dynamic compared to static viewing (S₀: 0.12 ± 0.183 dB) by a mean deviation loss of -0.9 ± 0.44 dB during both S_{3.5} and S_{Self}, *p* < 0.001, see Figure 2C).

Table 4 Overview of Statistical Outcomes of the RM-ANOVAs of Only Significant Effects of SPEED, TIME, and INTERVENTION Type on Visual Function Parameters for the Study GROUPs

Effect	F	p-value	Partial Eta-Squared
(A) Clinical parameters			
ETDRS BCVA			
TIME	1, 33 = 5.6	0.024	0.15
Foveal sensitivity [dB]			
TIME × INTERVENTION type	1, 34 = 4.6	0.039	0.12
(B) Dynamic visual function			
VA_s [logMAR]			
SPEED	2, 70 = 19.0	< 0.001	0.35
TIME × SPEED	2, 70 = 3.1	0.052	0.08
VA_c [logMAR]			
SPEED	2, 70 = 9.1	< 0.001	0.21
CS [logCS]			
TIME	1, 35 = 3.8	0.059	0.10
Bin-VF mean deviations [dB]			
SPEED	2, 66 = 124.9	< 0.001	0.79
GROUP	1, 33 = 6.49	0.016	0.16
TIME × GROUP	1, 33 = 3.6	0.066	0.10
INTERVENTION type × TIME × SPEED	2, 66 = 2.34	0.105	0.07

Notes: F: F-value of repeated measures ANOVA. For abbreviations, see Table 3. As shown in methods we used either $p < 0.05$ or effect size of 0.06 as a cutoff for any significance. For further details, refer to results.

Time Effects

Overall, visual function did not differ significantly after the 12-week intervention. Main effects: We observed a non-significant small trend of CS improvement after intervention (by 0.04 ± 0.1 logCS, $p = 0.059$, $\eta_p^2 = 0.10$). Interaction effects: For VAs, there was a non-significant trend of TIME × SPEED interaction effect, $p = 0.052$, $\eta_p^2 = 0.08$.

Intervention Effects (MMI vs. UMI)

The intervention effects were not differentially affected by the two intervention types (MMI or UMI). Main interaction effects: There were no significant effects.

GROUP Effects (GLA vs. HC)

Only for Bin-VF, VF mean deviations were reduced for GLA, as expected from the pathology, -1.20 ± 2.4 dB than HC, 0.25 ± 0.91 dB, $p = 0.016$. Interaction effects: None detected.

Discussion

The present study investigated the effect of MMI and UMI on visual function: 1) tested with clinical parameters; and 2) during TM walking at different speeds. While trends were evident, the effect of the 12-week interventions on visual function were small and largely independent of group and intervention type.

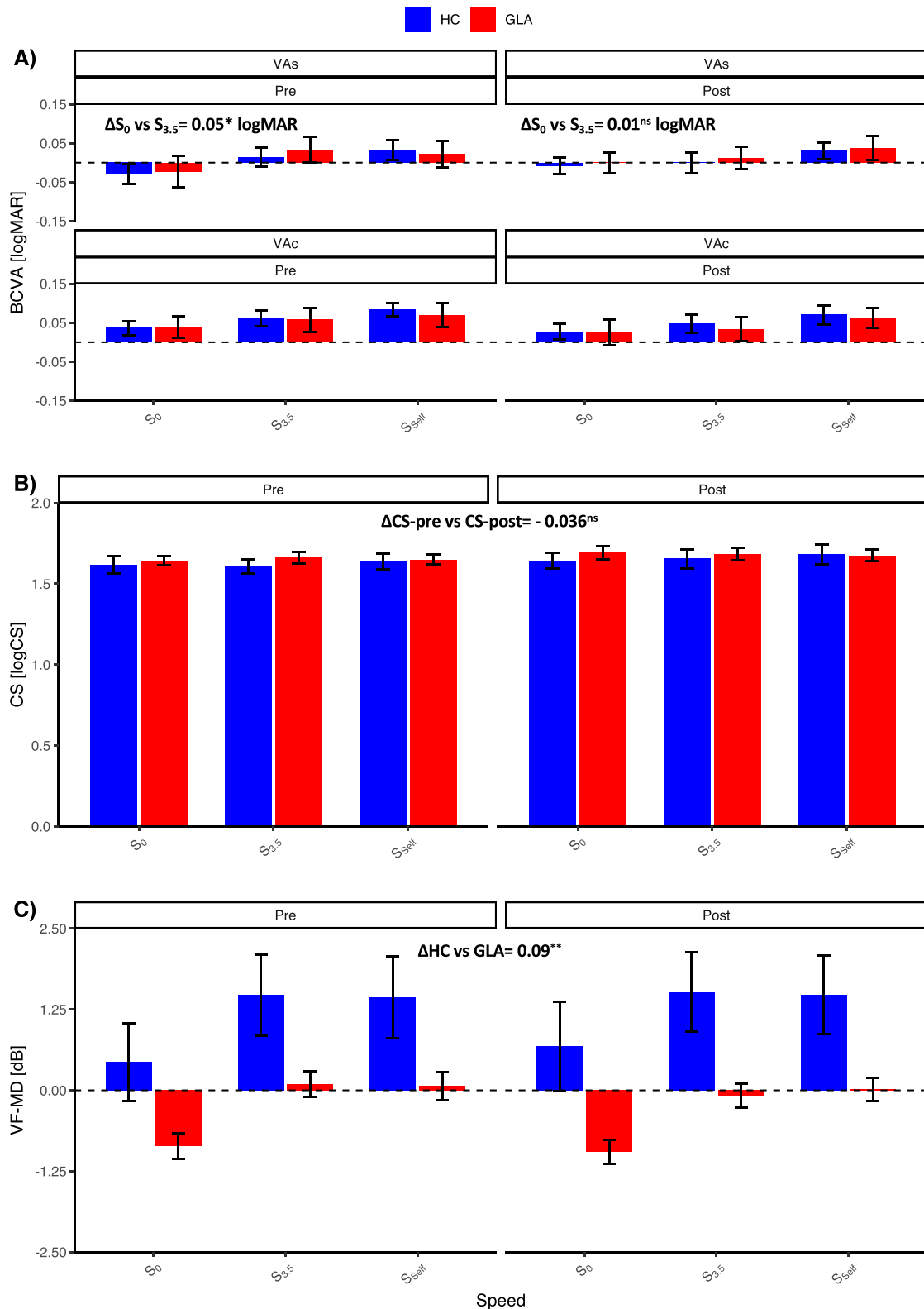


Figure 2 RM-ANOVA analysis of visual performance before (pre) and after (post) the 12-week interventions TIME for the two intervention modalities (multimodal, MMI & unimodal, UMI) at 3 treadmill (TM) walking speeds. **(A)** Best-corrected visual acuity with (VAs, upper panel) and without (VAc, lower panel) crowding: For VAs, TIME \times SPEED interaction indicated that pre-interventional VA at a 3.5 km/h ($S_{3.5}$) was 0.05 logMAR worse than static (S_0) VA, $p < 0.05$. For VAc, there were no significant effects. **(B)** Contrast sensitivity (CS) effects: There is an effect of TIME based on partial eta squared cutoff in which participants had a 0.036 higher CS [logCS] than pre-intervention. No other main or interaction effects. **(C)** Binocular visual field mean deviations (VF-MD) in decibels (dB): There was only a group effect in which VF-MD was lower in glaucoma (GL) than HCs by 0.09 dB, $p < 0.01$. For statistics, see Table 4. Dotted line indicates zero-read-out. Intervention types' effects are pooled due to lack of significant differences. Ns: non-significant test result; * p value < 0.05 ; ** p value < 0.001 .

Intervention Effects on Visual Performance

The observed intervention effects were marginal and reached significance only for the standard clinical measures of BCVA and foveal luminance sensitivity. Although improvements in dynamic CS and VA were not statistically significant, enhanced visual function is generally associated with a better health-related quality of life.²⁸ Moreover, both BCVA and CS have been identified as strong predictors of a GLA patient's ability to perform activities of daily living.²⁹ The absence of strong effects is likely due to the early stage of GLA in most of the included patients. This demonstrates the robustness of visual outcomes at this stage and underscores the clinical relevance of monitoring progression for preventing future visual loss. We also demonstrated an improved foveal sensitivity of 1 dB following the intervention. However, since this change was not group specific, we regarded it as non-clinically significant. Accordingly, Lee et al, investigating more advanced GLA cases, reported a 10% improvement of glaucomatous VF following 1-week of moderate-vigorous physical exercise.³⁰ Even in healthy athletes, exercise, namely ocular-motor, has beneficial effects on dynamic visual acuity.³¹

Beyond visual function, combined cognitive and physical training also positively influenced balance, cerebral health and cognition in older adults.³¹ It has been also shown that patients with cerebral vascular disease benefited from dual task rehabilitation training to improve balance and gait as well as prevent falls.¹⁷ In the context of neurodegenerative disorders, the relationship between motor function and cognitive abilities is also established. It has been shown that dual task training improved gait performance in Parkinson's disease.³³ Moreover, aerobic and resistance training have been shown to improve brain structure and function in patients with mild cognitive impairment.³⁴ Thereby, the higher cognitive function seems independent of the intervention type,³² meaning that both physical and cognitive training have beneficial effects.

Several factors might explain the lack of relevant positive effects from our interventions on visual function readouts, including the early stage of disease progression in GLA patients and small sample size. Clinical endpoints to capture the consequences of motor-intervention on visual function in early-stage GLA might need to be re-considered. For example, BCVA might not be sensitive enough given that a 5-letter improvement compared to baseline is often considered the threshold for a minimal clinically important difference,³⁵ which was not reached in our study (3 letters). Such small changes of visual function might also reflect insensitivity due to small sample size. While our initial sample size calculation to detect medium sized effects ($f = 0.23$) resulted in a sample size of 39 participants, our post-hoc power analysis based on the current results suggests a sample of $n = 218$ for the applied intervention schemes. Further, the intervention effects in early GLA might be better captured by non-visual outcomes related to visuo-cognitive-motor skills, including kinematic measures during physical locomotion, rather than basic visual function. Finally, the intervention type applied might need adjustment. The lack of superiority of MMI might be explained by the relatively low dose of resistance training in the Life Kinetik[®] program²² compared to higher exercise volume³⁶ in UMI and/or insufficiently embedded intervention type to drive additive benefits in gait in GLA.²² Further, the effect of the Life Kinetik[®] program might not reflect on behavioral parameters, as determined in the present study, as its cognitive challenges might not translate into improvement of gait parameters, but rather act as secondary distractors. Other cognitively challenging interventions might be more effective in this respect. Hamacher et al³⁷ for example, employed a 6-month dancing program, which showed greater beneficial effects than a combined exercise intervention in elderly. In contrast to the Life Kinetik program,²² Hamacher et al³⁷ integrates cognitive challenges into the motor task rather than rendering them as secondary distractors. Consequently, gait improvement might benefit better from such an intervention program. This might also allow for the detection of such effects with a sample size considerable smaller than the one determined in the present study.

Limitations and Outlook

When interpreting the results of the present pilot study, several limitations must be considered. First, the sample size was small mainly due to the impact of the COVID-19 pandemic on recruitment and regular study/intervention participation, as reflected in the "pilot study" nature of our report. Second, most GLA patients were in the early stages of GLA, which may have resulted in the small magnitude of the observed effects of the interventions as one might have expected in the later stages. This is confirmed by our previous findings¹⁶ that healthy elderly and early GLA participants have

comparable visual function loss during TM walking. Hence, to realistically capture intervention impacts, in future studies more advanced GLA stages should be included where functional deficits are larger and might benefit from our training programs. Further, pointwise analysis of VF metrics in more advanced GLA stages might elucidate more evident intervention or time related changes. Finally, follow-up of the training intervention at the retinal structural and vascular levels might promise valuable insights.

Conclusion

In summary, while the intervention approach of the present study established a foundation for a novel movement-related intervention regime for GLA, the effect of the 12-week interventions specifically on visual function were small. Based on the data of the present study, future trials should recruit a larger sample size and participants with more severe GLA stages in order to identify the effects MMI und UMI on visual function to prevent GLA-induced loss of quality of life.

Data Sharing Statement

Data is available upon request to the corresponding author.

Ethical Approval

The study was approved by the Ethics Committee of the Otto-von-Guericke University of Magdeburg in Germany (registration number: 32/18) and all procedures were in line with the Declaration of Helsinki on experiments on human beings. A consent form was obtained from all participants.

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Disclosure

The authors report no conflicts of interest in this work.

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