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Visual acuity in the context of retinal neuroaxonal loss in people with epilepsy

Luisa Delazer [a], Joachim Havla [b], Soheyl Noachtar [a,c], Elisabeth Kaufmann [a,c,*]

[a] Epilepsy Center, Department of Neurology, LMU University Hospital, LMU Munich, Marchioninistr. 15, 81377, Munich, Germany
[b] Institute of Clinical Neuroimmunology, LMU University Hospital, LMU Munich Marchioninistrasse 15, 81377, Munich, Germany
[c] Department of Neurology, LMU University Hospital, LMU Munich, Marchioninistr. 15, 81377, Munich, Germany

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SUMMARY

Objective: Recent studies reported a significant retinal neuroaxonal loss in people with epilepsy (PWE). However, the impact of these structural alterations on visual function, i.e., visual acuity is yet unknown.
Methods: In this prospective cohort study, 70 PWE and 76 healthy controls (HC), all aged 18–55 years, underwent an assessment of visual acuity with 100 % high contrast (HCVA) and 2.5 % low contrast (LCVA) Sloan letter charts. Thickness of the global peripapillary retinal nerve fiber layer (G-pRNFL) and volume of the ganglion cell inner plexiform layer (GCIP) were assessed with spectral-domain optical coherence tomography (OCT). For the statistical analyses, the epilepsy group was subdivided into PWE with sodium channel blocking (SCB)-drug intake ($n = 52$) and PWE without SCB-drug intake ($n = 18$), since an effect of SCB-drugs on visual perception has been reported previously.
Results: The overall PWE cohort presented significantly lower structural retinal measures, i.e., G-pRNFL thickness (97.57 ± 9.06 μm) and GCIP volume (1.99 ± 0.13 mm^3) than HC (101.31 ± 8.28 μm, $p = .01$; 2.10 ± 0.15 mm^3, $p < .001$). Subgroup analyses revealed that PWE who were treated with SCB-drugs had a significantly reduced G-pRNFL thickness (96.61 ± 9.70 μm, $p = .01$) and GCIP volume (1.98 ± 0.14mm^3, $p < .001$) compared to HC, while PWE without SCB-drugs (100.36 ± 6.32 μm, 2.01 ± 0.13 mm^3) did not differ from HC or PWE with SCB-drugs. In visual acuity tests (HCVA and LCVA), the overall PWE cohort (52.28 ± 8.56; 31.71 ± 8.49) scored significantly lower than HC (56.57 ± 4.74, $p = .001$; 35.13 ± 5.50, $p = .04$). In subgroup analyses only PWE with SCB-drugs presented significantly lower HCVA (51.25 ± 9.35, $p = .003$) and LCVA (30.04 ± 8.93, $p = .03$) scores compared to HC, while visual acuity scores did not differ between PWE without SCB-drugs (55.25 ± 4.75, 36.53 ± 4.50) and HC. PWE with SCB-drugs had significantly lower LCVA scores than PWE without SCB-drugs ($p = .03$). Importantly, no association was found between visual acuity scores and structural parameters, neither in the overall sample, nor in any of the subgroups.
Significance: Retinal neuroaxonal loss in PWE was not associated with reduced visual acuity under high and low contrast. Instead, our findings reinforce SCB-drug intake as an important factor for reduced visual acuity under high and low contrast.

1. Introduction

Up to now, alterations in visual perception in people with epilepsy (PWE) have typically been attributed to the use of certain anti-seizure medications (ASM) [1,2]. Especially vigabatrin, a GABA-transaminase inhibitor, has been described to cause clinically relevant visual impairment including concentric visual field defects, reduced contrast sensitivity, and abnormal color perception [2]. Besides, commonly used classical sodium channel blocking (SCB) drugs have been associated with comprised visual function: valproic acid has been reported to cause visual acuity deficits, visual field defects [3], reduced color discrimination, and altered contrast sensitivity [4]. Further, carbamazepine was

Abbreviations: ASM, Anti-seizure medication; GCIP, Ganglion cell inner plexiform layer; G-pRNFL, Global peripapillary retinal nerve fiber layer; HC, Healthy control; HCVA, High contrast visual acuity; LCVA, low contrast visual acuity; OCT, optical coherence tomography; PWE, people with epilepsy; SCB, sodium channel blocking.

* Corresponding author at: Epilepsy Center, Dept. of Neurology, LMU Munich, Marchioninistr. 15, 81377, Munich, Germany
E-mail address: elisabeth.kaufmann@med.lmu.de (E. Kaufmann).

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associated with reduced color discrimination and altered contrast sensitivity [4], whereas oxcarbazepine and lamotrigine have been claimed to cause diplopia [2]. However, effects of new generation SCB-drugs, namely lamotrigine, lacosamide, and eslicabrazepine on visual perception have not been systematically investigated yet.

Additionally, recent studies reported a significant retinal neuroaxonal loss in PWE in various layers, i.e. the retinal nerve fiber layer (RNFL), ganglion cell inner plexiform layer (GCIP), inner nuclear layer and the total macula volume. Across several cross-sectional studies, differences between PWE and healthy controls (HC) were small but significant [5–8] and one longitudinal study reported group differences in a short-term interval of less than a year [9]. Whether the retinal neuroaxonal loss leads to deficits in visual function in PWE has not been investigated yet.

Against this background, this study aimed to assess whether the structural retinal changes are associated with reduced visual acuity under high and low contrast in an unselected cohort of PWE. To account for possible drug effects, PWE on SCB-drugs and PWE without SCB-drugs intake were compared to healthy controls (HC). In an additional explorative subgroup analysis, PWE treated with only new generation SCB were assessed.

2. Methods

2.1. Participants and recruitment

In this prospective single center study, an unselected cohort of PWE was consecutively recruited from the local tertiary epilepsy center from February 2021 to August 2021. All PWE have previously been diagnosed with epilepsy according to the criteria of the International League Against Epilepsy (ILAE) [10]. Hospital staff and acquaintances were recruited as HC. Note that all PWE and HC have been part of our previous publication [8]. PWE and HC had to be between 18 and 55 years of age, have sufficient German knowledge, and the physical ability to take part in the study examination. The upper age limit was set in order to reduce the risk of a confounding, yet undiagnosed ocular disorder. Individuals were excluded if they reported a refractive error of more than ±4.5 diopters mean sphere or more than 2.5 diopters cylinder, lesions in the central visual pathway, history of eye surgery or known ocular disease as listed in the OSCAR-IB consensus criteria [11], such as macular degeneration, glaucoma, or history of optic neuritis, as well as current or former vigabatrin or retigabine intake. Further exclusion criteria were focal to bilateral tonic clonic or generalized tonic clonic seizures (FBTCS, GTCS) within the last 48 h, pregnancy, diabetes mellitus, untreated arterial hypertension, current or former drug abuse, cognitive disability (as mentioned in medical records and/or IQ < 70 in neuropsychological testing), and neurological diseases other than epilepsy or migraine. In order to avoid a potential confound, the data acquisition was postponed if a patient had a change in anti-seizure medication (ASM) within the last 14 days.

In total, 108 PWE and 90 HC were initially enrolled. Nine PWE were excluded retrospectively due to a delayed identification of exclusion reasons (history of vigabatrine intake ($n = 1$), history of drug abuse ($n = 1$); history of subarachnoidal bleeding ($n = 2$), history of severe concussion and subdural hemorrhage, increased optic nerve sheath diameter ($n = 1$), LGI1 autoimmune encephalitis ($n = 1$), postsurgical visual field defects ($n = 2$)) or poor OCT scan quality (n = 1). Another 29 PWE and 14 HC were excluded due to a refraction error of more than ± 0.5 dioptres and unavailability of their glasses or contact lenses at the time of the examination.

This study was approved by the local ethics committee and all participants provided written informed consent before study participation.

2.2. Clinical and demographic parameters

Participants were interviewed on demographic and clinical data with possible impact on retinal layer measurements and visual functions, including sex, age, ethnicity, body mass index (BMI), arterial hypertension, current and prior ASM, and other medication. Moreover, years of education, and - for PWE - epilepsy type, etiology, disease duration, history of brain surgery, history of psychogenic non-epileptic seizures, seizure semiology and frequency, as well as use of implantable stimulation devices were registered.

For subgroup analyses, PWE were divided in two groups: 1) PWE treated with only non-SCB drugs and 2) PWE treated with at least one SCB-drug (lamotrigine, lacosamide, oxcarbazepine, eslicarbazepine, valproic acid) in mono- or polytherapy. The broad spectrum ASMs topiramate and zonisamide were not categorized as SCB-drugs, since their sodium-channel blocking effect is secondary. At time of recruitment, none of the participants were treated with phenytoin or carbamazepine and cenobamate has not been prescribed yet.

2.3. Optical coherence tomography

Thickness and volume of retinal layers were assessed by a Heidelberg Engineering spectral-domain optical coherence tomography (SD-OCT, SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany) with automatic real-time (ART) averaging. The APOSTEL version 2 recommendations were applied for performing and reporting of the scans [12]. All OCT examinations were conducted by the same investigator (LD) in a dark room without dilatation of the pupils. The global thickness of the pRNFL (G-pRNFL) was measured in a peripapillary scan with automatic eye-tracking (12°, 3.5 mm ring, $50 \leq$ ART ≤ 100). The volume of the ganglion cell and inner plexiform layer (GCIP) was analyzed in a cylinder scan of six millimeters diameter around the fovea (20° × 20°, 25 vertical B-scans, $20 \leq$ ART ≤ 49). The segmentation of all layers was performed semi-automatically using the Eye Explorer (version 1.9.10.0) with viewing module 6.3.4.0 (Heidelberg Engineering, Heidelberg, Germany).

For statistical analyses, the average thickness or volume of each layer of both eyes (right + left eye score/2) was used. Only OCT scans with sufficient quality (peripapillary scans: >20 and ART ≥90; macula scans; >20 and ART ≥40) were used for statistical analyses. Quality values (with a possible range from 0 to 100) were automatically determined during the OCT scan.

2.4. Visual acuity und high and low contrast

Monocular contrast vision was tested with 100 % high contrast (HCVA) and 2.5 % low-contrast (LCVA) Sloan letter charts, placed in a retro-illuminated light box at two meters distance. Monocular best-corrected acuities were obtained of both eyes. Both charts are constituted of 70 letters with five equally sized and spaced letters in each line. While the size and space between the letters decreases in equal logarithmic steps, the contrast level remains the same. The study participants had to cover one eye and read out loudly the letters starting in the upper most line. The test was terminated when less than four letters in a line were recognized correctly. The HCVA and LCVA scores were then obtained by summing up the number of correctly identified letters, respectively.

To control for a possible effect of low visus, HCVA and LCVA scores were corrected for Snellen visual equivalent. Visus was tested with a Snellen chart, placed at six meters distance from the participant. The last correctly identified line (1 error permitted in each line) corresponded to the Snellen visual acuity equivalent (percentage of 6/6 visus). For statistical analysis, an average score of both eyes (right + left eye score/2) was used.

2.5. Statistical analyses

Statistical analyses were processed using SPSS version 29.0 (IBM SPSS Statistics). For group comparison of demographic data, Chi-square

tests, independent *t*-tests and ANOVAs for categorial and continuous parametric data were used, respectively. Snellen equivalents were compared using a Kruskal-Wallis test, and group comparisons of retinal measures were performed with ANOVAs, followed by Bonferroni corrected post-hoc tests, respectively. For group comparisons of visual acuity scores (HCVA and LCVA), Snellen visus corrected ANCOVAs were applied, followed by Bonferroni corrected post-hoc tests in case of significant results. In a subgroup analysis, HCVA and LCVA scores of PWE treated only with new generation SCB-drugs (lamotrigine, lacosamide, eslicarbazepine) were compared to PWE treated without SCB-drugs via Man-Whitney U test.

Partial correlation analyses, were conducted between visual acuity scores (HCVA and LCVA) and retinal measures, corrected for Snellen visus. P-values <0.05 were considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics of the study cohort

The final study cohort encompassed 70 PWE (40 female, 32.07 ± 9.86 years of age) and 76 HC (44 female, 30.47 ± 8.1 y). Most PWE (52/70, 74.3 %) were treated with at least one SCB at the time of study participation (32 female, 32.89 ± 10.10 y), whereof 14 PWE received exclusively new generation SCB-therapy with lacosamide and/or lamotrigine and/or eslicarbazepine (11 female, 29.63 ± 7.94 y, median visus 0.73 [IQR 0.62–0.97]). The other 18 PWE received no SCB treatment (8 female, 29.70 ± 8.98 y). Demographic and clinical characteristics of the two epilepsy groups and HC are summarized in Table 1.

3.2. Retinal measures

PWE had a significantly reduced G-pRNFL thickness (97.57 ± 9.06 μm) and GCIP volume (1.99 ± .13 mm^3) compared to HC (101.31 ± 8.28 μm, $p = .01$; 2.10 ± 0.15 mm^3, $p < .001$). While PWE treated with SCB-drugs ($n = 52$) differed significantly in their G-pRNFL ($p = .01$) and GCIP ($p < .001$) measures from HCs ($n = 76$), no difference was found between PWE without SCB-drugs therapy ($n = 18$) and HC, nor between PWE with and without SCB-drugs therapy (Table 2).

3.3. Visual acuity scores

PWE presented significantly lower HCVA (52.28 ± 8.56) and LCVA (31.71 ± 8.49) scores than HC (HCVA: 56.57 ± 4.74, $p = .001$; LCVA: 35.13 ± 5.50, $p = .04$). Similarly, the subgroup of PWE with SCB-drugs showed significantly lower HCVA ($p = .003$) and LCVA ($p = .008$) scores compared to HC. Further, PWE with SCB-drugs ($p = .03$)) as well as PWE exclusively treated with the new generation SCB-drugs ($n = 14$, median 30.25 [23.50 – 37.50], $p = .02$) had significantly lower LCVA scores than PWE without SCB-drugs. Of note, the two subgroups (PWE on new SCB and without SCB-drugs) were comparable in age and Snellen visus. PWE without SCB-drugs did not differ in their visual acuity scores from HC. The results of the subgroup analyses are summarized in Table 2 as well as Fig. 1.

3.4. Associations of visual acuity retinal measures

No association was found between HCVA and LCVA scores and the parameters of retinal structural integrity (i.e., thickness/volume of the G-pRNFL, and the GCIP) - neither in the overall sample, nor in any of the subgroups (Table 3, Fig. 2).

4. Discussion

In the light of recent descriptions of a significant retinal neuroaxonal loss in PWE, we investigated whether these retinal structural changes are associated with reduced visual acuity under high and low contrast.

Table 1
Demographic and clinical characteristics of people with epilepsy (PWE) with SCB-drugs, PWE without SCB-drugs, and healthy controls (HC)
Statistical tests used: a) Chi square test, b) ANOVA, c) Kruskal -Wallis (followed by Bonferroni corrected post-hoc test), d: independent *t*-test
Abbreviations: ASM: antiseizure medication; SCB: sodium channel blocking drugs; TCS: tonic clonic seizure.

	PWE without SCB (n = 18)	PWE with SCB (n = 52)	HC (n = 76)	p-value	Post-hoc (Bonferroni corrected)
Sex (female/male) (n)	8/10	32/20	44/32	.45 [a]	
Age [years] (mean ± sd)	29.70 ± 8.98	32.89 ± 10.10	30.47 ± 8.07	.24 [b]	
Snellen visual acuity equivalent (median, IQR)	.83 (0.73 – 0.97)	.73 (0.62 – 0.83)	.83 (0.73 – 0.97)	.02 [c]	PWE with SCB < HC PWE with SCB < PWE without SCB
Epilepsy onset (n %)					
Generalized	6 (33.3 %)	7 (13.5 %)			
temporal	7 (38.9 %)	15 (28.8 %)			
frontal	1 (5.6 %)	8 (15.4 %)			
other (multifocal, undefined)	4 (22.2 %)	22 (42.3 %)			
Disease duration [years] (mean ±sd)	7.53 ± 9.71	13.59 ± 12.02		.06 [d]	
Number of seizures in the last year (mean ± sd)	26.53 ± 88.01	57.02 ± 94.95		.49 [d]	
Highest annual TCS count (mean ±sd)	7.06 ± 20.95	8.10 ± 14.85		.82 [d]	
Number of current ASM (mean ± sd)	.83 ± 0.38	2.21 ± 0.94		<0.001 [d]	
Lifetime number of ASM (mean ± sd)	1.61 ± 1.29	4.90 ± 3.21		<0.001 [d]	
PWE with exclusive SCB treatment (n %)	0 (0 %)	16 (30.8 %)			
PWE with prior SCB intake (n %)	6 (33.3 %)	52 (100 %)			
Current ASM intake (n):					
Brivaracetam	1	7			
Clobazam		3			
Clonazepam		1			
Eslicarbazepine		8			
Ethosuximid		1			
Lacosamide		17			
Lamotrigine		28			
Levetiracetam	12	21			
Oxcarbazepine		5			
Perampanel		8			
Phenobarbital		1			
Pregabalin		1			
Sultiam	1				
Topiramate	1	6			
Valproate		6			
Zonisamide		2			

Table 2
Visual acuity scores and retinal measures of people with epilepsy (PWE) with SCB-drugs, PWE without SCB-drugs and healthy controls (HC)
Statistical tests used: b) ANOVA, followed by Bonferroni corrected post-hoc tests, (effect size given: $\eta^{2)}$, e) ANCOVA, corrected for Snellen visus, followed by Bonferroni corrected post-hoc tests (effect size given: partial η^2)
Abbreviations: HCVA: High Contrast Vision Score (100 %); LCVA: Low Contrast Vision Score (2.5 %); G-pRNFL: Global Peripapillary Retinal Nerve Fibre Layer; GCIP: Ganglion Cell Inner Plexiform Layer.

	PWE without SCB (n = 18)	PWE with SCB (n = 52)	HC (n = 76)	p-value	F ($_{2143}$)	Significant post-hoc tests (Bonferroni corrected)	Effect-size
HCVA score (mean±sd)	55.25 ± 4.75	51.25 ± 9.35	56.57 ± 4.74	.004 [e]	5.78	PWE with SCB < HC	.08
LCVA score (mean±sd)	36.53 ± 4.50	30.04 ± 8.93	35.13 ± 5.50	.004 [e]	5.73	PWE with SCB < PWE without SCB; PWE with SCB < HC	.08
G-pRNFL [µm] (mean ±sd)	100.36 ± 6.32	96.61 ± 9.70	101.31 ± 8.28	.01[b]	4.70	PWE with SCB < HC	.06
GCIP [mm^3] (mean ± sd)	2.01 ± 0.13	1.98 ± 0.14	2.09 ± 0.15	<.001[b]	9.94	PWE with SCB < HC	.12

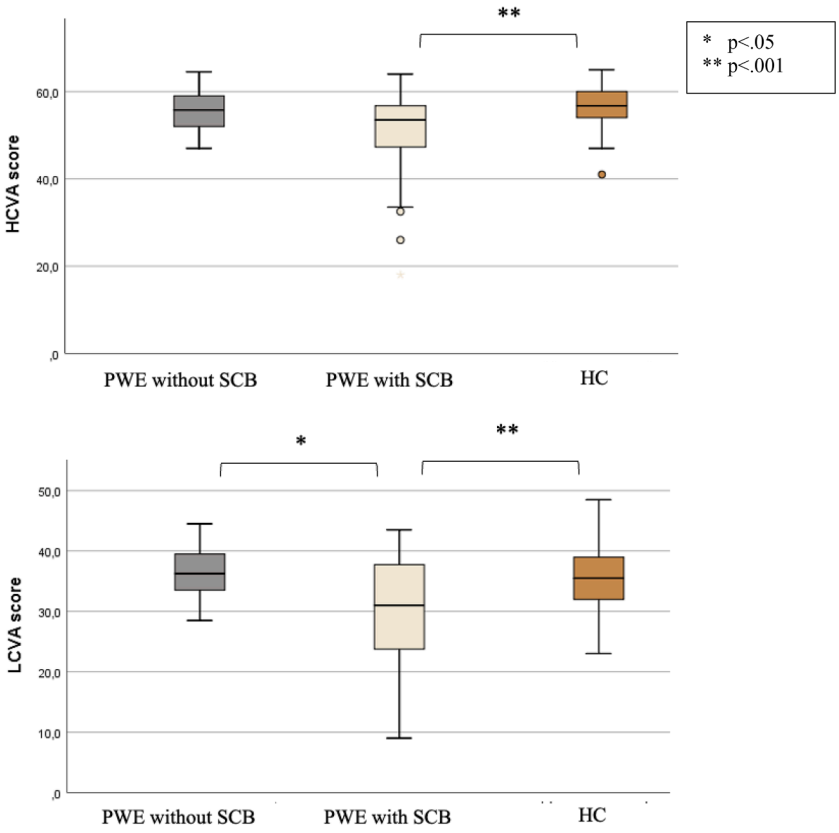

Fig. 1. High and low contrast vision (HCVA and LCVA) scores of people with epilepsy (PWE) with SCB-drugs, PWE without SCB-drugs and healthy controls (HC).

Table 3
Correlation analyses between visual acuity scores and retinal measures:
Statistical tests used: Partial correlation analyses, corrected for Snellen equivalent, Pearson correlation coefficients r given, all p-values >0.05.
Abbreviations: HCVA: High Contrast Vision Score (100 %); LCVA: Low Contrast Vision Score (2.5 %); G-pRNFL: Global Peripapillary Retinal Nerve Fiber Layer; GCIPL: Ganglion Cell Layer + Inner Plexiform Layer.

	PWE without SCB		PWE with SCB		HC		Overall sample	
	HCVA	LCVA	HCVA	LCVA	HCVA	LCVA	HCVA	LCVA
G-pRNFL [µm]	.27	-0.003	-0.03	-0.13	-0.19	-0.004	-0.14	-0.05
GCIPL [mm3]	-0.07	-0.36	.002	-0.24	-0.14	.04	.03	-0.03

Although our findings confirmed a significant retinal neuroaxonal loss and suggested reduced visual acuity in PWE compared to HC, no association was found between the structural and functional deficits. Of note, significant functional and structural ocular changes were found in the subgroup of PWE with SCB-drugs, but not in PWE without SCB-drugs. Our findings suggest that the reduced visual acuity in PWE might be more likely caused by the intake of certain ASM than the retinal neuroaxonal loss.

The retinal neuroaxonal loss in PWE was also previously reported and described to reflect the cerebral neuronal loss [7,13]. In our study,

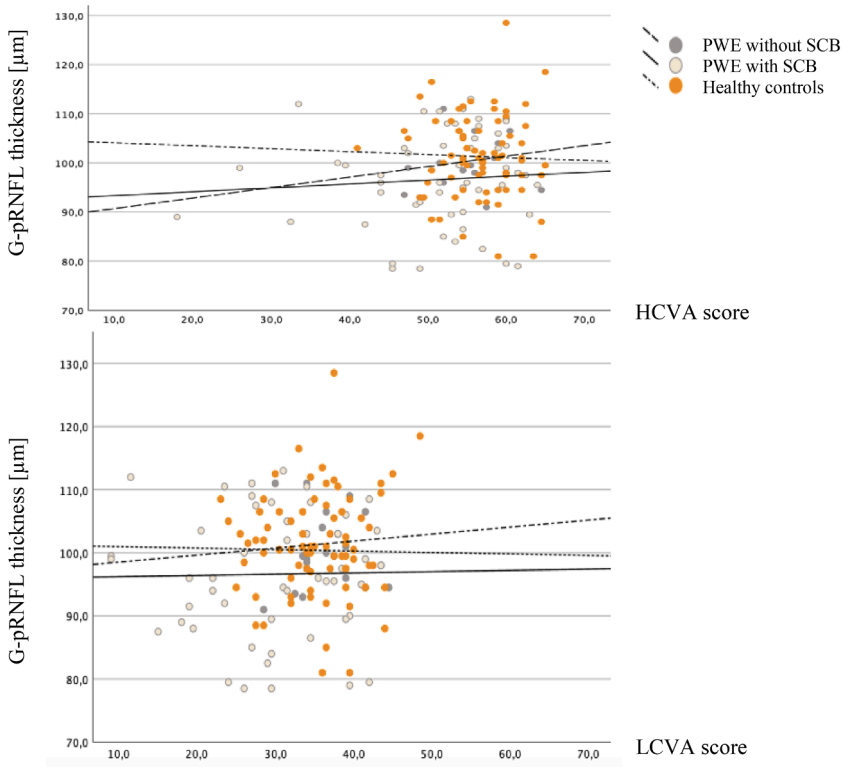

Fig. 2. Scatterplot of G-pRNFL thickness and HCVA and LCVA scores
Correlation coefficients are given in Table 3.

the SCB-subgroup revealed more extensive retinal alterations than the non-SCB-subgroup. This is most likely due to the significantly higher ASM load in the SCB-subgroup, as the number of current ASM is a known driver of the retinal neuroaxonal loss [8]. Besides, none of the other known drivers differed significantly between both groups, i.e., sex, the frequency of TCS, and disease duration [7,8]. However, the group comparison is limited by the small and different size of the two sub-groups. The underlying pathophysiology of the retinal neuroaxonal loss, though, remains widely unknown. The TCS associated head trauma, the periictal cerebral hypoperfusion and hypoxemia as well as ASM-associated effects have been discussed as potential mechanisms [7–9].

According to studies in people with optic neuritis and/or multiple sclerosis, a correlation between the retinal neuroaxonal loss and visual acuity would have been expected [14–17]. For example, a thinning of the G-pRNFL by 4 µm was reported to be associated with a decline of five letters in Sloan low contrast letter charts (LCVA) in people with multiple sclerosis [18]. However, these neuroimmunological disorders typically lead to a more extensive thinning of the retinal layers (e.g. G-pRNFL thinning in multiple sclerosis with and without optic neuritis by up to 20 µm or 7 µm) [19] than in PWE (G-pRNFL thinning by up to 4 µm), though their retinal measures also differed significantly from HC. Possibly, a certain threshold of retinal neuroaxonal loss needs to be crossed before it manifests clinically, i.e., with an impaired visual acuity. Our results suggest that the threshold for a clinically apparent retinal neuroaxonal loss was not exceeded in our study cohort. The SCB-subgroup revealed more extensive retinal alterations than the non-SCB-subgroup – possibly due to the significantly higher ASM load in this subgroup [8] – but still no association was found with the measures of visual acuity.

Since the structural retinal changes in PWE showed no association with visual acuity under high and low contrast in our study, other factors, such as adverse effects of SCB treatment seem more pressing. Indeed, an association between impaired contrast vision and monotherapy with the SCB drugs valproic acid, carbamazepine, and oxcarbazepine have been reported previously [4,20,21]. Contrast sensitivity was thereby inversely correlated with the serum carbamazepine levels [21]. Evidence on the impact of new generation SCB-drugs, and polytherapy, though, remains scarce [2,22,23]. In our study, most PWE in the SCB group (46/52, 88.5 %) received either lamotrigine and/or lacosamide and/or eslicarbazepine (exclusively or besides other ASM). Thus, it seems likely that also new generation SCBs-drugs affect visual perception. This hypothesis is supported by the observation that the 14 PWE receiving exclusively lamotrigine and/or lacosamide and/or eslicarbazepine scored significantly lower in LCVA than the 18 PWE without SCB-drugs. The mechanism of SCB altering visual function is not fully understood yet. SCB-drugs possibly negatively affect physiological signal transmission. Studies on sensory (SEP) and visual evoked potentials (VEP) in PWE showed longer latencies in patients treated with SCB compared to HC [24,25]. In detail, Tumay et al. reported a significantly increased P100 latency and a significantly decreased VEP amplitude in PWE treated with valproate and carbamazepine [24]. Importantly, these alterations were not apparent in PWE before but only after initiation of SCB treatment [25]. Possibly, SCB medication has a disruptive effect on the complex interplay of inhibition, disinhibition, and activation of retinal cells and central nervous pathway, mediating visual acuity under high and low contrast. For the above reasons we suggest that the observed reduced visual acuity scores are due to functional rather than structural changes.

4.1. *Limitations*

Since our study cohort represents a cross-section of PWE treated in an epilepsy outpatient setting, the variety of epilepsy types and drug regimens causes inhomogeneities and limits subgroup analyses. Further, most of the PWE were on polytherapy. While the use of more than one drug represents a standard procedure of disease management and thus reflects everyday practice, it prevents definite conclusions regarding the

effects of single drugs. Since polytherapy is sometimes inevitable in patient's care, future research should aim to define the effects of single drugs not only in monotherapy, but also in combination with other ASM. Serum drug levels could verify ASM intake and reflect the individual drug load but were not available in this study. Importantly, the participants had no detailed ophthalmologic assessment, which would have contributed to a fuller picture of visual perception. Further, assessment of contrast vision may be accomplished by more sophisticated methods covering the full range from high to low contrast. Finally, group sizes were small and thus do not allow for firm conclusions. Especially the subgroup of PWE without SCB treatment was small, since SCB drugs are very frequently prescribed in epilepsy care. Thus, subgroups analyses might have been underpowered.

Conclusion

In PWE, reduced visual acuity was not adequately explained by retinal neuroaxonal loss. Instead, SCB-drug intake seemed to be a driver of the functional deficits. Our findings might impact patient management and information, as reduced visual acuity was also observed in PWE treated with the commonly prescribed new generation SCB-drugs lacosamide, lamotrigine, and eslicarbazepine. However, larger group sizes, monotherapy studies, and more advanced ophthalmological diagnostic are needed for confirmation.

Author contributions

LD collected the data, conducted statistical analyses, drafted the manuscript and designed Figs. 1 and 2; JH advised the OCT acquisitions and analyses and critically revised the manuscript; SN advised the study design and critically revised the manuscript; EK was responsible for the study design, as well as manuscript drafting and revision.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Declaration of competing interest

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