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Effect of nystagmus on VEP-based objective visual acuity estimates

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In order to determine the effect of nystagmus on objective visual acuity (VA) estimates, we compared subjective (VA_{psych}) and objective (VEP, VA_{VEP}) VA estimates in participants with nystagmus. For this purpose, 20 participants with nystagmus (NY) caused by idiopathic infantile nystagmus, albinism, achiasma or acquired nystagmus were recruited in this study. Estimates of BCVA (best corrected visual acuity) were determined psychophysically (VA_{psych}; FrACT, Freiburg visual acuity test) and electrophysiologically (VA_{VEP}; EP2000) according to ISCEV (International Society of Clinical Electrophysiology of Vision) guidelines. For each participant the eye with the stronger fixation instability [Nidek microperimeter (MP-1), Nidek Instruments] was included for further analysis. VA_{psych} vs VA_{VEP} were compared via paired t-tests and the correlation of the difference between VA_{psych} and VA_{VEP} (ΔVA) vs the degree of fixation instability was tested with Pearson correlation (r). We found VA_{VEP} to be better than VA_{psych} [by 0.12 Logarithm of the Minimum Angle of Resolution (logMAR); mean ± standard error (SE) of VA_{VEP} vs VA_{psych}: 0.176 ± 0.06 vs. 0.299 ± 0.06, P = 0.017] and ΔVA to be correlated linearly with the degree of fixation instability ($r^2 = 0.21$, $p = 0.048$). In conclusion, on average we report a small VA overestimation, around 1 line, for VA_{VEP} compared to VA_{psych} in NY. This overestimation depended on the magnitude of the fixation instability. As a rule of thumb, a reduction of the fixation probability in the central 4° from 100 to 50% leads on average to a VA_{VEP} overestimation of around 0.25 logMAR, i.e. 2.5 lines.

Keywords VEP, Nystagmus, Visual acuity, Microperimetry

Subjective visual acuity testing is a ubiquitous routine tool for everyday clinical practice in ophthalmology and often the first step to check the integrity of retinal function and subsequent structures of the visual system. Critically, this measure of visual acuity (VA_{psych}) is challenged by the subjective nature of the responses, depends on the compliance of the participants, and is hence vulnerable e.g. to malingering[1]. This creates a need for an objective measure of visual acuity, which might be met by visual evoked potential (VEP) based visual acuity estimates (VA_{VEP}). In fact, previous research in this field has demonstrated the value of this approach[2]. However, limits to the applicability of VA_{VEP} naturally are expected for certain conditions, which might be particularly prone to systematic VA misestimations. The identification of such conditions is instrumental to avoid the misinterpretation of a patient's VA_{VEP} results. Within this context, it is uncertain whether VEP-acuity estimations maintain their validity in the presence of nystagmus.

As a matter of course, VEP-recordings depend on the capacity of a visual stimulus to drive responses in the visual cortex. One critical parameter is the spatial frequency of the stimulus, as only stimuli that can be resolved will generate responses. It is this dependence of the VEP on spatial frequency of the visual stimulus that is exploited for the estimation of the resolution limit in acuity-VEP paradigms. Specifically, these paradigms target the detection of the spatial frequency limit beyond which stimuli fail to elicit a response[2]. Another critical parameter for VEP recordings is the stimulation mode. This includes the distinction of pattern-reversal vs pattern-pulse stimulation, which is of particular importance when targeting populations with nystagmus. Notably, nystagmus reduces pattern-reversal VEPs, while VEPs to pattern-pulse stimulation are relatively spared[3,4]. Acuity-VEP paradigms are often based on pattern-pulse stimulation[2]. As a consequence, responses from participants with nystagmus are expected to be only little affected, preserving the validity of VEP-acuity estimates in nystagmus, or might even be overestimated. In fact, some reports do suggest the potential of an overestimation of VEP-acuity for nystagmus[5–7]. A systematic assessment of this issue with a contemporary approach to determine VEP-acuity is at

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present missing. At the same time, however, as nystagmus is a common feature in patients with low vision, it is of critical importance for clinical applications, whether the validity of VA_{VEP} measures is confounded by nystagmus.

We aimed to investigate the validity of VA_{VEP} in the presence of nystagmus by employing a VEP paradigm that is based on patten-pulse stimulation[8]. Specifically, we compared VA_{psych} and VA_{VEP} estimations in a cohort of patients (NY) with nystagmus due to different etiologies. To accurately determine the effect of eye motion on VA_{VEP} misestimation, fundus imaging was employed to quantify fixation instabilities. We hypothesized that VA_{VEP} might be overestimated compared to VA_{psych} in NY particularly, if fixation instabilities are pronounced.

Methods

This prospective observational study was conducted at the ophthalmic department of the Otto-von-Guericke University (OVGU), Magdeburg, Germany.

Participants

Participants were included after an ophthalmological examination: 20 participants with nystagmus (NY; 9 females; age (mean, range across all participants): 38, 20 − 64y) due to the idiopathic infantile nystagmus syndrome (n = 10), albinism (n = 6), achiasma (n = 1), or acquired nystagmus (n = 3), as detailed in Table 1. Optic nerve misrouting in albinism[9,10] and achiasma[11,12] was confirmed via the misrouting VEP[13,14], a VEP method detailed further in previous publications[9,15,16]. To study the effect of nystagmus on measures of VA, only the individual's eye with stronger fixation instability determined by microperimetry test (see below) was included in the analysis. Exclusion criteria were epilepsy, dizziness, neurological diseases unrelated to nystagmus and any eye diseases affecting visual function, e.g., diabetic retinopathy.

Microperimetry—Fixation stability

Fixation stability of participants within 2° and 4° was quantified by tracking fundus-motion at 25 Hz with a fundus-controlled microperimeter (MP-1 microperimeter, Nidek, Padua, Italy), for an epoch of 30 s, where participants were asked to fixate a central target. Eyes with stronger fixation instability, using fixation proportion within the central ± 2°, were selected for the analysis. See Table 1 for characteristics, including fixation instability and BCVA, of each participant's selected eye.

ID	Group	Sex	Age [years]	Nystagmus type	Stereopsis*	VEP	BCVA [logMAR]	Eye†	Fixation ± 2° [%]
BJA815	INS	m	21	J/H	Yes	–	0.12	OS	91
MFY773	INS	f	24	J/H	No	–	0.24	OS	83
ENH995	INS	f	21	J/H	No	–	0.54	OD	42
XAY182	INS	f	42	J/H	No	-	0.41	OD	86
SXB794	INS	f	60	J/H	No	-	-0.03	OD	99
JDG458	INS	m	29	P/H	No	-	0.32	OS	37
WQE170	INS	m	23	P/H	Yes	-	0.06	OD	n/a
SUQ660	INS	m	34	J/H	Yes	-	-0.15	OD	99
PEP763	INS	f	56	J/H	No	-	0.32	OS	99
DKX711	INS	m	51	J/H	Yes	-	0.28	OS	74
TGY248	AN	f	30	J/V	Yes	-	-0.08	OD	96
TIO945	AN	m	38	J/H	Yes	-	0.05	OD	98
UFX538	AN	f	42	J/H	Yes	-	-0.07	OD	99
PYV946	AL	f	23	J/H	No	+	0.47	OD	74
JTE807	AL	m	51	J/H	No	+	0.73	OS	91
GRV905	AL	m	63	J/H	No	+	0.69	OS	99
PNJ290	AL	m	64	J/H	No	+	0.69	OS	86
SLP201	AL	f	20	J/H	No	+	0.61	OS	36
SDN948	ACH	m	22	J/H	No	+	0.27	OS	88
XZE409	AL	m	40	J/H	No	+	0.57	OD	43

Table 1. Overview of participants' including characteristics of each participant's selected eye, on the basis of stronger fixation instability. BCVA [logMAR]: best corrected visual acuity; VEP: misrouting visual evoked potential; "+"/ "–" indicates presence/absence of optic nerve misrouting (negative/positive correlation coefficient between both eyes' inter-hemispherical activation difference); INS: idiopathic infantile syndrome (excluding albinism); AN: acquired nystagmus (causes: Arnold-Chiari Syndrome, pons bleeding, hydrocephalus shunt surgery); AL: albinism; ACH: achiasma; Nystagmus type: J: jerk, P: pendular, H: horizontal, V: vertical; f: female; m: male; n/a: not available. *Stereopsis test using Lang test. †Eye with stronger fixation instability.

Subjective VA estimation

Estimates of best corrected visual acuity (BCVA) for each eye were determined psychophysically (VA_{psych}) using the "Freiburg Visual Acuity and Contrast Test" [FrACT; VA_{psych},[17]] applying Landolt Cs at a viewing distance of 114 cm (as for the VA_{VEP} estimation). Every measurement was performed twice to reassure the validity of the measurements.

Objective VA estimation

Objective VEP-acuity testing (VA_{VEP}) was estimated according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards[18] and followed the procedure described previously[8]. Briefly, steady state (ss)-VEPs were recorded using pattern-pulse stimulation at 7.5 Hz as detailed in Table 2. The ssVEPs were Fourier analyzed. For each spatial frequency (SF [cpd] = $1/\sqrt{2} \times$ check size) the response magnitude at the stimulation frequency (7.5 Hz) and a noise estimate, the average of the response of the two neighboring frequencies (6.5 and 8.5 Hz) were obtained to determine the 'true', i.e. noise-corrected, amplitude $A^*(SF)$[19–21] and the significance-level of the response $p(SF)$[21]. A stepwise heuristic algorithm[8] was applied to calculate the upper SP where the log amplitude response extrapolated to zero, i.e., SF_0. SF_0 was converted to VEP acuity [decimal $VA_{VEP} = SF_0/17.6$ cpd, which corresponds to logMAR $VA_{VEP} = \log(SF_0/17.6 \text{ cpd})$]. For all participants tested, the heuristic algorithm produced an estimated VA_{VEP} (100% testability).

Analysis and statistics

Only one eye of each participant was included, namely the eye with the stronger fixation instability. As the data passed the Shapiro Wilk test for normality, parametric statistical testing was applied. The VA_{psych} vs VA_{VEP} estimates were compared using a paired t-test. Pearson correlation (r) was applied to test whether the difference between VA_{psych} and VA_{VEP} (ΔVA) correlated with the degree of fixation loss within 4° determined by Pearson correlation (r).

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committee of Faculty of medicine, Otto-von-Guericke University, Magdeburg (153/18).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Results

For a qualitative overview of the VEP-recordings obtained, VEP traces for a representative participant with nystagmus (NY) and a healthy control (HC) are juxtaposed in Fig. 1A together with the acuity estimation (Fig. 1B) according to the heuristic algorithm published previously[8]. The group's data (20 participants with nystagmus, for each individual's eye with stronger fixation instability) are depicted in Fig. 2 (cyan symbols). For comparison, results previously reported for participants without nystagmus by Bach et al. 2008 and Hoffmann et al. 2017 are

	VEP-based VA
Recording Device	EP 2000 Evoked potentials system [22]
Monitor	Monochrome CRT monitor (MDG403, Philips; P45 phosphor; 75 Hz)
Stimulus	Checkerboard
Ambient light	Dimly lit room
Mean luminance	50 cd/m^2; 40% contrast
Size of stimulus	For BCVA < 0.3 [logMAR]: Six logarithmically equidistant steps from 0.048° to 0.385° For BCVA values > 0.3 [logMAR]: A different sequence of check sizes was utilized: **0.09—0.8°**
Stimulation	steady-state brief onset pattern stimulation (7.5-Hz, 40 ms on, 93 ms off)
Electrode placement	Laplace montage [23]: Gold-cup electrodes at Oz, LO and RO, referenced to FPz (according to the international 10–20 System)
Recording setting	Signals amplified 100 K times the VEP signals & band pass filtered them (0.3, 70 Hz)
Artefact rejection	± 90 µV threshold
Eye	Monocular recording
Viewing distance	114 cm
Repetitions	A-B-B-A*
Fixation control	Random digits from 0–9 in the center of the screen & verbal feedback by participants
Processing	Responses digitally filter with low-pass cutoff of 40 Hz
Reporting	Decimal VEP-based BCVA [8]

Table 2. Overview of electrophysiological recording parameters. Amplifier: Grass Model 15, Astro-Med Inc., West Warwick, RI, USA. For further calculation of Correlation coefficient, [see[15] and text]. See further info of VA-VEP estimations[8]. *Repetitions trials were averaged.

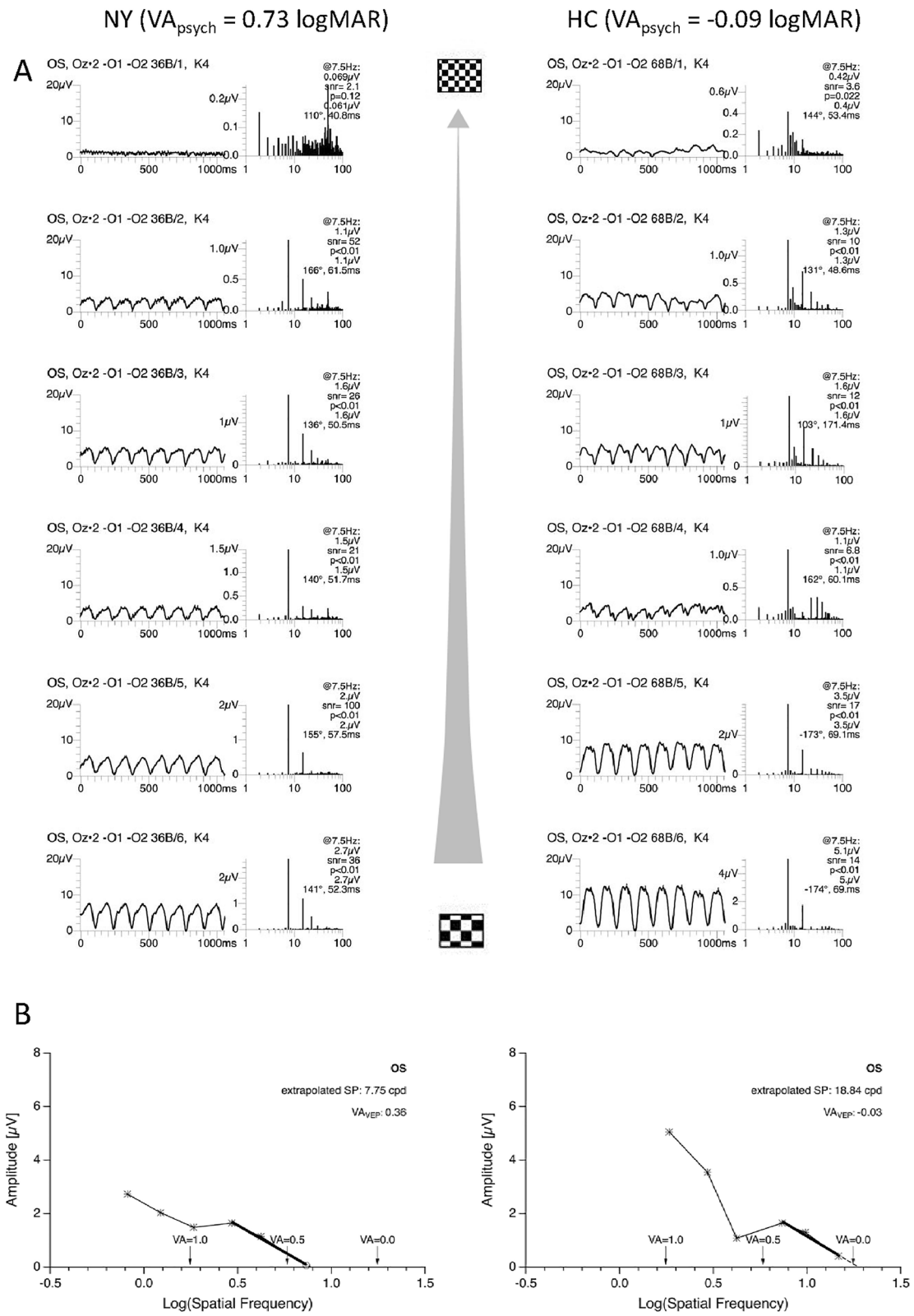

Figure 1. VEP data from two examples. Visual evoked potential visual acuity (VA_{VEP}) and subjective VA (VEP_{psych}) are given for two individuals, i.e., a healthy control (HC) and a participant with nystagmus (NY). A) VEP-results underlying the estimation of VA_{VEP}. For each participant, NY (JTE807) and a HC (OEX914), two panels are given. The left panel depicts the raw VEP traces for the different check sizes ranging from 0.046° to 0.370° . The right panel depicts the power spectrum and the respective significance of the response's amplitude at 7.5 Hz, i.e., the stimulation frequency, which enter the spatial frequency tuning curve. B) Spatial frequency tuning curve and VA_{VEP} estimate for NY and HC. VA_{VEP} is derived from the extrapolated spatial frequency (SF) limit determined from the regression line (strong black line) according to Bach et al.[8], as detailed in Methods. Significant responses are denoted with an asterix, non-significant with open symbols. For NY VA_{psych} and VA_{VEP} (0.73 vs 0.36) match less closely than for HC (− 0.09 vs − 0.03).

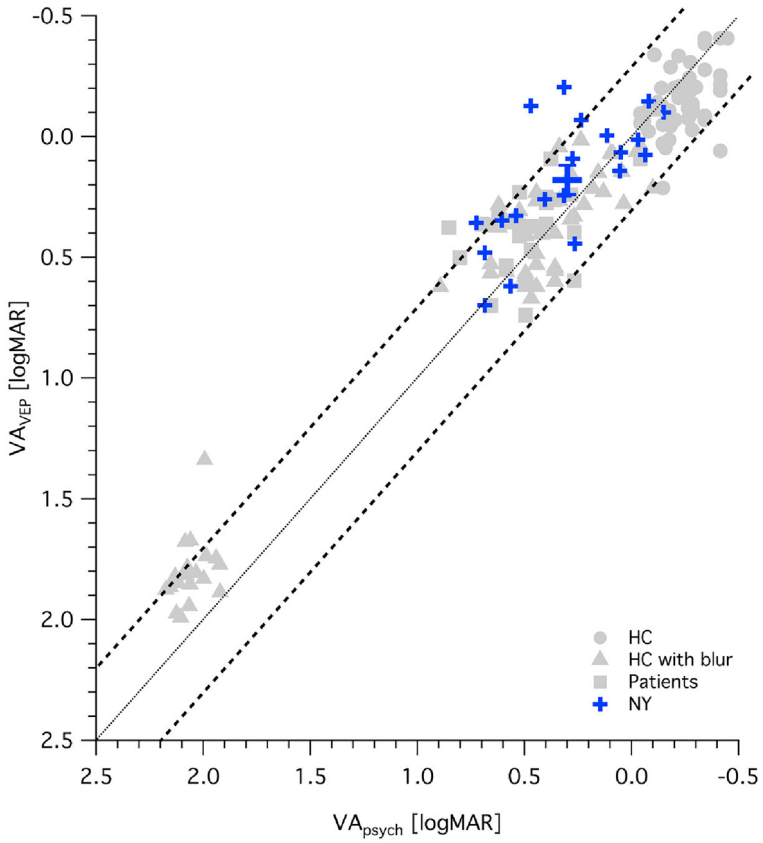

Figure 2. Objective vs subjective visual acuity. Participants with nystagmus [large symbol: mean ± SEM for VA_{VEP}] are given in comparison to previously published data from participants without nystagmus[8,24]). For our nystagmus cohort, 4 out of 20 eyes fell above the 95% CI established in Bach et al. 2008, indicating an acuity overestimation.

added (gray symbols). Overall, there was a significant overestimation of VA_{VEP} vs VA_{psych} for nystagmus by on average − 0.12 logMAR (mean ± SE of VA_{VEP} vs VA_{psych}: 0.18 ± 0.06 vs 0.30 ± 0.06, $p = 0.017$). Still, 16 (80%) of the 20 eyes were within the 95% confidence interval determined in Bach et al. 2008 for participants without nystagmus.

To test whether the VA_{VEP} overestimation in nystagmus was associated with nystagmus severity, we employed a measure of fixation instability (fixation proportion within the central ± 2°) as a surrogate measure of nystagmus severity. We tested the correlation of the acuity differences ($\Delta VA = VA_{VEP} - VA_{psych}$) with fixation instability. In fact, there was a weak, albeit significant correlation between fixation instability and the Δ VA ($r^2 = 0.21$, $p = 0.048$; Fig. 3). Consequently, 21% of the variance in the data can be attributed to the strength of the participants' fixation instability.

Discussion

We tested whether nystagmus affects the relationship of VA_{VEP} and VA_{psych}. In our cohort of 20 eyes, we report an overestimation of visual acuity, i.e., better VA, for nystagmus by around 1 line, i.e., 0.12 logMAR. The difference between VA_{VEP} and VA_{psych} correlated significantly with the degree of fixation loss, indicating that the VA_{VEP} estimates were particularly affected by higher degree of nystagmus.

VA_{VEP} offer a complementary or alternative option to assess VA, in cases where VA_{psych} appears questionable. However, as recently reported[2], consistency between VA_{VEP} and VA_{psych} is dependent on the etiology of visual dysfunction and acuity loss. Comparable VA_{VEP} and VA_{psych} reductions were reported in media opacities or retinal pathologies, while a VA_{VEP} and VA_{psych} mismatch is more likely in optic nerve, neurological diseases or amblyopia. For patients, where the stimulation is subject to retinal image slip, due to nystagmus, the matter was still unresolved. For our cohort we demonstrate the effect to be minor on average, i.e. an overestimation of around 1 line, but that stronger effects are more likely for higher degree of nystagmus-related fixation loss. Previous research on NY as a separate disease entity was up to now limited as reflected by a few studies from the 80-ies and 90-ies: In a small number of NY patients (n = 5) VA_{VEP} was reported to be poorer than VA_{psych} by 0.15 logMAR[5]. In a cohort of 14 NY children, Gottlob et al.[6] found slightly and non-significantly better estimates of VA_{VEP} (Sinusoidal sweep VEP, 0.48 log min arc) than VA_{psych} (recognition VA using Allen picture cards, 0.51 log min arc) and VA_{VEP} vs VA_{psych} not to be correlated. Westall et al.[7] also reported a non-significant trend of a VA_{VEP}

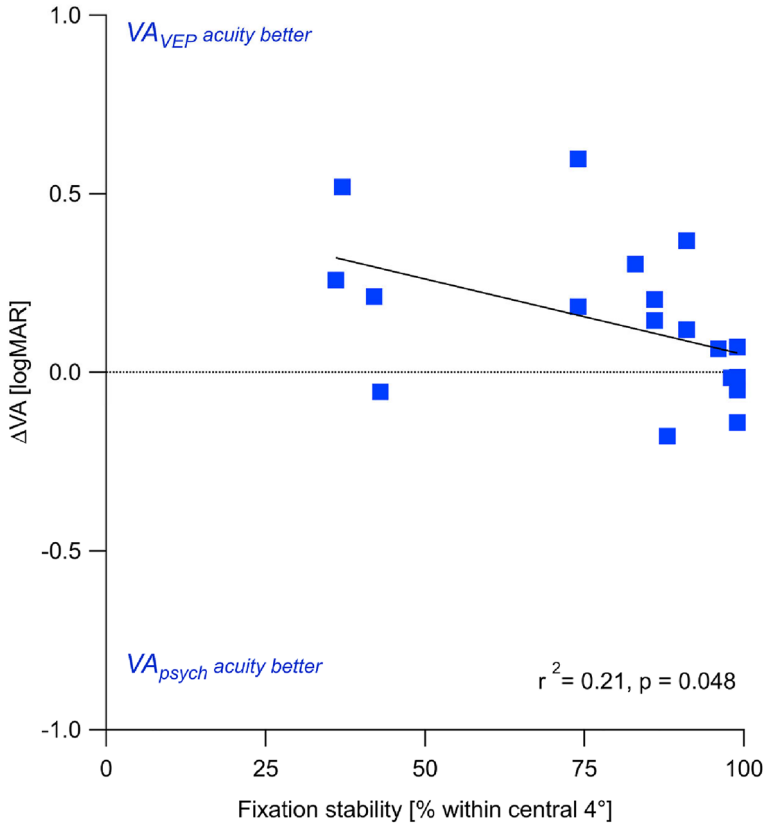

Figure 3. Correlation of VA_{VEP}–VA_{psych} differences (ΔVA) and fixation stability in NY. The significant correlation indicates that VA_{VEP} is overestimated for low fixation stability, i.e. more pronounced nystagmus. Fixation stability explains 21% of the variance.

overestimation by 0.09 logMAR compared to acuity-card VA in a group of NY children. Different stimulation paradigms, sample size, and study design of these earlier studies, might account for the discrepant findings between studies.

Practical considerations, limitations and outlook

In this study, we assessed the VEP-based VA estimation in comparison to subjective VA measures in an important disease cohort, nystagmus. We highlighted the importance of taking fixation stability in consideration when evaluating VA_{VEP} in nystagmus, as 21% of the variance in the data can be attributed to fixation instability. As a rule of thumb, a reduction of the fixation probability in the central 4° from 100 to 50% leads on average to a VA_{VEP} overestimation of around 0.25 logMAR, i.e. 2.5 lines.

At present, the mechanisms that might mediate this overestimation of VA_{VEP} compared to VA_{psych} are unclear. They might be associated with different stimulation schemes used for the VA estimation, as pulsed patterns are used for VA_{VEP} as opposed to continuous stimulation for VA_{psych}. As an alternative to a methodological cause, there might be a physiological cause. E.g., an association of nystagmus with other pathophysiologies that might lead to VA overestimation, e.g. amblyopia[25]. Further research is needed to address this issue. Additional insights into the underlying mechanisms might be uncovered in studies that employ fixation-monitoring via eye-tracking during the VEP recordings for a quantitative account of the fixation instabilities and ultimately correct for eye-movements that during VEP recording. Moreover, investigations that specifically address the dependence of VA_{VEP} -overestimation in nystagmus on etiology, ocular co-morbidity and type and strength of nystagmus might be of promise to specify the clinical implications of the influence of nystagmus on VEP-acuity.

Conclusion

This study reported a slight but significant overestimation of VA_{VEP} compared to VA_{psych} in the presence of nystagmus. The differences between objective and subjective VA estimates depended on the magnitude of fixation loss, i.e., higher magnitude of instability leads to higher differences between objective and subjective VA measures. This dependence needs to be taken into account when evaluating VA_{VEP} estimates in nystagmus, specifically when fixation instabilities are pronounced.

Data availability

Data are available upon request. Please contact the corresponding author, MBH, for data requests.

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Author contributions

EVQ, MBH, KA-N: Study concept and design. EVQ, JK, FK: Investigation. EVQ, MBH, KA-N: Data analysis. EVQ, MBH, KA-N: Original manuscript draft. All authors: comments on results, revision and approval of the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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