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ORIGINAL ARTICLE

Neonatal Assessment Visual European Grid accuracy in detecting infants born preterm at risk of neurological impairment

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Abstract

Aim: To analyse the factorial structure of the Neonatal Assessment Visual European Grid (NAVEG), its diagnostic accuracy, the discriminative capacity of its individual items, and total score in detecting infants born preterm with neurological and/or brain ultrasound anomalies.

Method: A total of 109 infants born preterm and 79 born at term underwent a visual function assessment using the NAVEG, a neurological examination based on the Amiel-Tison Neurological Assessment (ATNAT), and, for infants born preterm, brain ultrasound imaging. Exploratory factor analysis, diagnostic accuracy, discriminative capacity, and differences in NAVEG scores among infants born preterm and at term were calculated.

Results: The exploratory factor analysis revealed that 16 out of the 17 items in NAVEG accounted for 61% of the variance in a one-factor solution model. Receiver operating characteristic curves demonstrated the discriminative capacity of NAVEG in detecting neurological signs for a total score of 3 or higher. Good levels of sensitivity and specificity were observed in infants born preterm, with ATNAT scores as reference (sensitivity 93.02%; specificity 78.79%) or in combination with brain ultrasound results (sensitivity 84.89%; specificity 83.93%). The most discriminative NAVEG items in detecting the presence of neurological signs in infants born preterm were oculomotor functions and visual field. Significant differences were found in the visual profiles of infants born preterm with neurological signs and/or brain ultrasound anomalies compared with those without these anomalies, and with infants born at term.

Interpretation: NAVEG could be a useful screening tool in infants born preterm to evaluate visual dysfunctions and to detect those with neurological signs and/or brain ultrasound anomalies.

KEYWORDS
brain injury, diagnostic accuracy, prematurity, psychometric property, vision disorder

Abbreviations: ATNAT, Amiel-Tison Neurological Assessment; AUC, area under the curve; NAVEG, Neonatal Assessment Visual European Grid; NICU, neonatal intensive care unit; OCC, overall correct classification index; ROC, receiver operating characteristic.

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Visual function and daily experiences shape the development of many pathways of the central nervous system from the first days of life.[1,2] Early identification of signs of visual impairment may alert clinicians to underlying neurological or brain anomalies.[3] Visual functions can be assessed from the first days of life, and methods have been developed for their evaluation in infants.[3–8] Among the available assessment tools, behavioural and electrophysiological techniques are included.[5,7,9–12] Particular attention has been given to the assessment of visual functions in infants born preterm,[3,8,13,14] who are at high risk of visual and neurological outcomes.[15–18] However, only a few of these tools provide a comprehensive screening of all aspects of visual function, and they often lack normative data related to specific clinical populations.

The Neonatal Assessment Visual European Grid (NAVEG) has been designed and previously described as a fast, reproducible, easy-to-administer, and non-invasive screening tool for the assessment of visual functions in infants within the first hours of life.[3] The NAVEG tool can distinguish infants with and without signs of neurological impairment, as confirmed by neurological examination and brain ultrasound imaging (Table 1).[3] However, the sensitivity and specificity of this screening tool, critical variables for establishing evidence of construct validity of the assessment, have not yet been reported.

In this study, the psychometric properties of the NAVEG assessment tool were analysed, encompassing the estimation of the factorial structure of the test and its sensitivity and specificity in identifying early visual problems associated with neurological/brain impairment in infants born preterm. The study also investigated its capacity to differentiate between infants born preterm with neurological signs and/or brain ultrasound anomalies and infants born preterm without such anomalies and from infants born at term, on the basis of their visual profiles.

Specifically, the aims of the present study were as follows. (1) To perform an exploratory factor analysis on the NAVEG assessment to identify its factorial structure in infants born preterm. (2) To assess the diagnostic accuracy (sensitivity and specificity) of the NAVEG in relation to the presence of neurological signs detected by neurological examination and brain anomalies detected by brain ultrasound in infants born preterm. (3) To define which items of the NAVEG can be indicators for the presence of neurological signs and/or ultrasound brain anomalies in infants born preterm. (4) Finally, to assess the discriminative capacity of the NAVEG in identifying infants born preterm with neurological signs and/or ultrasound anomalies from those without such anomalies and from infants born at term, on the basis of their visual profiles.

What this paper adds

- Neonatal Assessment Visual European Grid (NAVEG) shows good sensitivity and specificity in identifying at-risk infants born preterm.
- A NAVEG total score of 3 or more is the most valid cut-off both in infants born preterm and at term.
- Oculomotor functions and visual field most accurately predict the presence of neurological signs and/or brain ultrasound anomalies.

METHOD

Participants

A total of 111 infants born preterm with a gestational age as the time elapsed between the first day of the last menstrual period and the day of birth of not more than 34 weeks and 80 typically developing infants born at term (38–42 weeks gestational age) were recruited for this study.

Infants born preterm

The 111 infants born preterm (55 females, 49%) were consecutively recruited in the neonatal intensive care unit (NICU) at ASST Spedali Civili Hospital, Brescia, Italy, from February 2017 to February 2018. Inclusion criteria were gestational age not more than 34 weeks and admitted in the local NICU. Exclusion criteria included the presence of severe congenital diseases, chromosomal abnormalities, severe infectious diseases, and evidence of severe (stage 3) retinopathy of prematurity. Mean gestational age ranged from 23 to 33 weeks (mean [SD] 30.80 weeks [1.99 weeks]; median 31.00 weeks; interquartile range 2 weeks) and weight ranged from 450 g to 2430 g (mean [SD] 1526.33 g [464.21 g]; median 1518.00 g; interquartile range 754 g).

Infants born at term

The 80 infants born at term (40 females, 50%) had been previously recruited from the Neonatal Unit at ASST Spedali Civili Hospital, Brescia, Italy, from 2011 and 2014 for a previous study[3] and were selected according to the optimality criteria.[19,20] Inclusion criteria were gestational age between 38 weeks and 42 weeks (mean [SD] 39.29 weeks [0.989 weeks]; median 39.29 weeks; interquartile range 1 week) and conditions of clinical optimality, particularly with normal findings on neonatal/neurological clinical evaluation. Newborn infants with significant perinatal complications (neurological/cardiopulmonary/gastroenteric), congenital anomalies or known genetic syndromes, history of severe neonatal infections (e.g. sepsis, meningitis, TORCH [toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex] infections), and admission to NICU were excluded.

Two infants born preterm and one infant born at term did not complete the assessment protocol. Thus, a total of 109 infants born preterm and 79 born at term completed the evaluation.

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TABLE 1 NAVEG: previous findings.

Study	Rossi et al.[3]
Aims	• To assess visual function using NAVEG in a large cohort of newborn infants. • To perform an exploratory analysis of the features of the testing battery. • To evaluate NAVEG's discriminating capability in the detection of infants with neurological impairment and brain damage.
Participants	160 newborn infants (80 at term and 80 preterm) from the Department of Neonatology and neonatal intensive care unit of the ASST Spedali Civili Hospital in Brescia, Italy.
Procedures	All infants underwent the following: • NAVEG • Neurological examination (ATNAT[21]) 81 newborn infants (80 infants born preterm and 1 at term) underwent brain ultrasound scans. NAVEG Three sections: • Ocular visual component: fundus oculi, photomotor reflex. • Oculomotor visual component: fixation, smooth pursuit, saccadic movements evaluated with three targets (bull's eye, high-contrast face figure, human face). • Perceptual visual component: contrast sensitivity (Hiding Heidi Low Contrast Face Test), visual acuity (Teller Acuity Cards), visual field.
Measures	Descriptive statistics, univariate test, and MCA were used to investigate the structure of NAVEG.
Results	• Univariate tests were applied to NAVEG items to explore associations between the presence of brain lesions or neurological examination and were all statistically significant. • MCA was able to explain 82.6% of the total variability in two dimensions. The coordinate plot revealed two alternative average profiles. In the first, NAVEG items were typically not impaired, while the second was characterized by moderate or severe impairment. The presence of a brain lesion, added as a supplementary, fitted perfectly in the 'impaired profile'. • Results were also confirmed when computing the MCA solution excluding infants born at term. • The MCA results were also confirmed when the item scores were dichotomized.
Conclusions	• The NAVEG is fast, easy, and non-invasive assessment tool revealing meaningful information on visual function since birth. • NAVEG can be performed in infants born at term and preterm. • MCA showed that NAVEG can discriminate the profile of newborn infants with respect to neurological status, considering brain ultrasound scan and neurological examinations as variables. • NAVEG can record information for research purposes and it is useful also in daily clinical practice.

Abbreviations: ATNAT, Amiel-Tison Neurological Assessment; MCA, multiple correspondence analysis; NAVEG, Neonatal Assessment Visual European Grid.

Procedures

This study was approved by the Ethics Committee of ASST Spedali Civili of Brescia (protocol number NP 3042). All study procedures were conducted in accordance with relevant guidelines and regulations. Written informed consent was obtained from the parents or legal guardians of the recruited infants born preterm and at term.

All infants born preterm and infants born at term underwent the evaluation protocol, which included NAVEG (for a detailed description of the protocol, see Rossi et al.[3]) and the Amiel-Tison Neurological Assessment (ATNAT) neurological examination[21] (see below for more details). Infants born preterm also underwent a brain ultrasound scan according to institutional protocol.[22,23]

All tests were administered and evaluated according to the standardized procedures described by the original authors of each test and, for statistical reasons, the results were dichotomized. Specifically, optimal responses to NAVEG and ATNAT and normal brain ultrasound were coded as 0 while all the other responses/results (mild or severely impaired) were coded as 1.

The NAVEG was administered by a child neuropsychiatrist, blinded to the ATNAT/brain ultrasound results for the infants born preterm and the ATNAT results for those born at term. NAVEG was conducted in the outpatient clinics of the Child Neuropsychiatry Unit at ASST Spedali Civili di Brescia for the infants born preterm, and in a dedicated clinic within the neonatal unit of the same hospital for the infants born at term.

All enrolled infants born preterm and at term underwent the NAVEG visual assessment: between 38 to 42 weeks corrected age for the infants born preterm and gestational age for those born at term. NAVEG was administered between meals, and under optimal conditions (III–IV behavioural state[24]).

Qualitative items from the original NAVEG score were dichotomized as follows: all values between 1 and 2 were converted to a score of 1 and all values labelled '0' remained unchanged.

Grating visual acuity (evaluated by Teller Acuity Cards[25]) was coded according to the method of Brown and Yamamoto.[26] As previously stated, for statistical reasons, values of cycles/degree greater than or equal to 0.69 were coded as 0 while values equal to or less than 0.69 cycles/degree were coded as 1.

Contrast sensitivity evaluated with the Hiding Heidi Test[27] was coded according to the method of Leat and Wegmann.[28] Contrast thresholds equal to or less than 1.25% were scored as 0 and for remaining values the score was 1.

On the basis of ATNAT results (see Table S1), infants born preterm were classified into two groups: ATNAT+ and ATNAT–. ATNAT+ was defined by the presence of at least

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three neurological signs while ATNAT– was defined by absence of neurological signs or by the presence of minor signs (one or two).

Brain ultrasound was performed on all the infants born preterm during hospitalization in the NICU, according to institutional protocol.[13,22,23] On the basis of brain ultrasound results (Table S1), infants born preterm were also classified in two groups: brain ultrasound+ and brain ultrasound–. Brain ultrasound+ was defined by the presence of one or more brain ultrasound anomalies (for example non-transient hyperechogenicity lasting more than 7 days, germinal and intraventricular haemorrhage, periventricular leukomalacia, parenchymal injury, etc.). Brain ultrasound– was defined by the absence of brain anomalies detected by brain ultrasound. In accordance with the protocol in use at the NICU of ASST Spedali Civili di Brescia, no brain ultrasound examination was performed in the typically developing infants born at term.

In addition, the infants born preterm were further grouped according to both ATNAT and brain ultrasound results: the ATNAT–/brain ultrasound– group and the ATNAT+ and/or brain ultrasound+ group (Table S1).

Statistical analysis

Frequencies of NAVEG item scores in preterm and term infants

For each NAVEG item, the percentage of individuals with a score of 0 and a score of 1 in each group was computed.

Exploratory factor analysis of NAVEG in infants born preterm

A series of exploratory item factor analyses (JASP 0.19.3.0 statistical analysis software[29]) was used as an item analysis method to arrive at the final version of the NAVEG, comprising the 17 items with the highest validity. Each subsequent factor analysis of the items arrived at a satisfactory solution to reduce the number of items at each step. The process converged and was stopped once the analysis did not suggest that removing any more items would result in an interpretable factor solution. For each subsequent exploratory factor analysis, statistical assumptions were verified (Kaiser–Meyer–Olkin measure of sampling adequacy and Bartlett's test of sphericity), and a tetrachoric matrix correlation of the 2-point responses from the 109 newborn infants on an increasingly lower number of NAVEG items was obtained. The exploratory factor analysis was run with the weighted least squares estimator as a factor extraction technique, followed by an Oblimin factor rotation. On the basis of the parallel analysis and screen test, several factor solutions were investigated, and items with a factor loading of at least 0.320 on only one factor and adequate estimated residual variance were selected. On the basis of the interpretability of the pattern of the item factor loadings, the best solution was selected.[30] Finally, point-biserial item-total score correlation was computed, and, as a measure of reliability, the ordinal coefficients alpha for response scales proposed by Zumbo et al. was used.[31]

Diagnostic accuracy of NAVEG total score in infants born preterm

The diagnostic accuracies of the selected factorial solution NAVEG total score for possible cut-offs derived with receiver operating characteristic (ROC) curve coordinates were evaluated with the ATNAT score, brain ultrasound results, or both (i.e. defined as positive if at least one criterion was present) as the reference criteria. Diagnostic accuracy in discriminating participants with and without detected neurological signs and/or brain ultrasound anomalies was then estimated using two statistical methods.

First, sensitivity, specificity, overall correct classification index (OCC), rate of false positives and false negatives, positive likelihood ratio, and negative likelihood ratio were all computed. Test sensitivity was computed as the proportion of infants born preterm with neurological signs detected by ATNAT, neuroimaging anomalies detected by brain ultrasound, or both, who were also correctly identified by NAVEG as 'positive' (i.e. with a NAVEG score equal to or greater than the cut-off).

Test specificity was calculated as the proportion of individuals without neurological signs, without brain ultrasound anomalies, or without both conditions, who were also correctly identified by NAVEG as 'negative' (i.e. with a NAVEG score lower than the cut-off). Given that NAVEG is designed as a screening tool, to increase the chance of identifying infants born preterm with potential brain anomalies, sensitivity was considered more informative than specificity in this context. The OCC was computed as the overall proportion of infants born preterm with or without neurological signs or brain ultrasound anomalies correctly identified by NAVEG. Positive likelihood ratio (LR+) was equal to the odds that an infant born preterm with neurological signs or brain ultrasound anomalies, or at least one condition, was correctly detected by NAVEG. Negative likelihood ratio (LR–) was equal to the odds that an individual without neurological signs or brain ultrasound anomalies or without both conditions was erroneously classified with positive conditions. Sensitivity, specificity, and OCC are considered statistically significant if their confidence intervals (CI) do not include the value of 0.50 (i.e. the classification made by the test scores is more accurate than a random classification). While higher values are generally preferred, a sensitivity of at least 0.70 and specificity of least 0.80 represent the minimum standard for accuracy for screening tests.[32] Conversely, lower rates of false positives and false negatives are preferred. LR + and LR– are statistically significant if their confidence intervals do not include the value of 1. As a rule of thumb, the following values are recommended[33] for their clinical significance: LR+ > 1

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or LR− < 1 = fail; LR+ > 2 or LR− < 0.5 = poor; LR+ > 5 or LR− < 0.2 = good; and LR+ > 10 or LR− < 0.1 = excellent.

The capacity of the NAVEG score to discriminate participants with and without neurological signs and/or brain ultrasound anomalies was also estimated using an ROC analysis. The ROC is computed by plotting the true positive rate (sensitivity) against the false positive rate (1, true negatives or 1, specificity) for different possible cut points on NAVEG.[34–36] The area under the curve (AUC) is equal to the probability of a test giving a correct classification (i.e. correctly identifying individuals with and without neurological signs and/or brain ultrasound anomalies). In other words, given the selected factorial solution of the NAVEG total score, the AUC reflects the probability that a randomly selected person from the group of individuals with neurological signs or brain ultrasound anomalies, or at least one of these conditions, will have a NAVEG total score below the NAVEG total score of a randomly selected person from the group of individuals without neurological signs or brain ultrasound anomalies or without both conditions. AUC values range from 0 to 1 and are statistically significant if their confidence intervals do not include the value of 0.5. The following values were used to interpret AUC: 0.5 to 0.6 = fail; 0.6 to 0.7 = poor; 0.7 to 0.8 = fair; 0.8 to 0.9 = good; and 0.9 to 1.0 = excellent.

Discriminative capacity of each NAVEG item to identify the risk of neurological impairment in infants born preterm

The diagnostic accuracy of each NAVEG item in discriminating between participants with and without detectable neurological signs or brain ultrasound anomalies was investigated by computing the agreement between performance on the item (0 = typical, 1 = impaired) and ATNAT examination score or brain ultrasound scanning result with a χ^2 test. Cohen's index of effect size was interpreted as follows: $w < 0.10$ = negligible; $0.10 \leq w < 0.30$ = small; $0.30 \leq w < 0.50$ = moderate; and $w \geq 0.50$ = large.

Descriptive of NAVEG total score in infants born at term

Centiles corresponding to each NAVEG total score obtained from infants born at term were computed as well as mean and standard deviations of visual acuity expressed in cycles/degree and of contrast sensitivity expressed in five levels.

Discriminative capacity of the NAVEG total score in discriminating infants born at term from infants born preterm

We investigated the discriminative capacity of the NAVEG total score in distinguishing infants born preterm with neurological signs from those without, as well as infants born preterm from infants born at term by verifying whether there were statistically significant differences between the scores obtained by the three groups, followed by post hoc comparisons. Because the distribution of the NAVEG total score was not normal, a Kruskal–Wallis test was used, followed by Dunn's post hoc comparisons. We computed rank ε^2 as an index of the effect size for the Kruskal–Wallis test and interpreted it as follows: $\varepsilon^2 < 0.01$ = negligible; $0.01 \leq \varepsilon^2 < 0.04$ = small; $0.04 \leq \varepsilon^2 < 0.16$ = moderate; $0.16 \leq \varepsilon^2 < 0.36$ = relatively large; $0.36 \leq \varepsilon^2 < 0.64$ = large; and $0.64 \leq \varepsilon^2 < 1.00$ = very large. We also computed rank biserial correlation as an index of the effect size for the Dunn's post hoc comparisons and interpreted as small, rank biserial correlation <0.10, moderate 0.10 ≤ rank biserial correlation <0.30, or large ≥0.30. All analyses were conducted in SPSS Statistics 25 (IBM Corp., Armonk, NY, USA), unless otherwise specified. For inferential testing, a significance threshold of 5% was used.

RESULTS

Frequencies of NAVEG item scores in preterm and term infants

Score frequencies (0/1) for each of the 17 NAVEG items obtained from both preterm and full-term groups are reported in Table 2.

In infants born preterm, the NAVEG items with the highest percentage of scores equal to 1 were as follows: contrast sensitivity, vertical smooth pursuit – down, and visual field of view – down. Conversely, the three items with the highest percentage of scores equal to 0 were fixation face figure, fixation – bull's eye, and visual field – left.

In infants born at term, the NAVEG items with the highest percentage of scores equal to 1 were contrast sensitivity, visual field of view – down, and vertical smooth pursuit – both up and down. The remaining items exhibited a score rate of less than 10%.

Exploratory factor analysis of NAVEG in infants born preterm

On the basis of the criteria previously described, the first exploratory factor analysis was run with the responses of the 109 infants born preterm for all 17 NAVEG items. Three- to one-factor solutions were investigated, and the best solution was selected. This was a one-factor solution (Kaiser–Meyer–Olkin = 0.74, Bartlett's test $\chi^2_{136} = 14524.04$; $p < 0.001$) that explained 59% of variance. All items showed a factor loading greater than 0.32 except for item 12 (contrast sensitivity). Consequently, a second exploratory factor analysis was run with the responses for 16 NAVEG items (all except item 12). Three- to one-factor solutions were investigated, and the best solution was selected. This was a one-factor solution

TABLE 2 Frequencies of scores for the NAVEG items in the infants born preterm and at term.

NAVEG items	Score: 0 = typical; 1 = impaired perfomance	Infants born preterm, *n* (%)	Infants born at term, *n* (%)
1. Pupillary reflex	0	74 (68)	78 (99)
	1	35 (32)	1 (1)
2. Ocular fundus examination	0	90 (83)	/
	1	19 (17)	/
3. Fixation – bull's eye	0	102 (94)	77 (97)
	1	7 (6)	2 (3)
4. Fixation – face figure	0	104 (95)	75 (95)
	1	5 (5)	4 (5)
5. Fixation – human face	0	65 (60)	77 (97)
	1	44 (40)	2 (3)
6. Horizontal smooth pursuit – left	0	85 (78)	74 (94)
	1	24 (22)	5 (6)
7. Horizontal smooth pursuit – right	0	88 (81)	75 (95)
	1	21 (19)	4 (5)
8. Vertical smooth pursuit – down	0	60 (55)	70 (89)
	1	49 (45)	9 (11)
9. Vertical smooth pursuit – up	0	80 (73)	70 (89)
	1	29 (26)	9 (11)
10. Attraction saccadic movements from right	0	83 (76)	78 (99)
	1	26 (24)	1 (1)
11. Attraction saccadic movements from left	0	82 (75)	77 (97)
	1	27 (25)	2 (3)
12. Contrast sensitivity	0	6 (5)	4 (5)
	1	103 (95)	74 (95)
13. Visual acuity (grating visual acuity)	0	95 (87)	79 (100)
	1	14 (13)	0 (0)
14. Visual field of view – right	0	96 (88)	79 (100)
	1	13 (12)	0 (0)
15. Visual field of view – left	0	101 (93)	78 (99)
	1	8 (7)	1 (1)
16. Visual field of view – up	0	89 (82)	74 (94)
	1	20 (18)	5 (6)
17. Visual field of view – down	0	61 (56)	68 (86)
	1	48 (44)	11 (14)

Abbreviation: NAVEG, Neonatal Assessment Visual European Grid.

that explained 61% of the variance. Exploratory factor analysis statistical assumptions were confirmed: Kaiser–Meyer–Olkin = 0.72, Bartlett's test $\chi^2_{(120)} = 12510.06$; $p < 0.001$. The factor solution can be considered satisfactory as it exceeds the 50% threshold suggested by Streiner[37] and falls within the 50% to 60% range commonly accepted in the social sciences according to Williams et al.[38] Furthermore, the 61% variance is notably greater than the average of 52.03% reported by Henson and Roberts[39] in their review of published psychological research. Table 3 shows factor loading, estimated residual variance, and the item-total score point-biserial correlation for each item. Item factor loadings ranged from 0.53 to 0.91 (mean = 0.77, median = 0.82), estimated residual variance ranged from 0.18 to 0.72 (mean = 0.39, median = 0.32), and item-total score point-biserial correlation ranged from 0.41 to 0.79 (mean = 0.64, median = 0.66). Ordinal alpha reliability was equal to 0.96, indicating a good internal consistency. Sample size adequacy was evaluated a posteriori according to the guidelines provided by Mundfrom et al.[40] For a one-factor model with at least eight variables and widely distributed communalities (0.20–0.80), a sample size of 130 or more is classified as excellent, whereas a sample size of 60 or more

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TABLE 3 Exploratory factor analysis of NAVEG in infants born preterm: item factor loadings, estimated residual variance, and item-total score point-biserial correlation.

Item	Factor loading	Estimated residual variance	Item-total score point-biserial correlation
10. Attraction saccadic movements – from left	0.91	0.18	0.76
16. Visual field – down	0.89	0.20	0.79
15. Visual field – up	0.87	0.24	0.66
7. Vertical smooth pursuit – down	0.85	0.28	0.74
12 Visual acuity (grating visual acuity)	0.85	0.28	0.73
4. Fixation – human face	0.84	0.30	0.55
9. Attraction saccadic movements – from right	0.83	0.30	0.75
8. Vertical smooth pursuit – up	0.83	0.30	0.77
14. Visual field – left	0.82	0.33	0.66
5. Horizontal smooth pursuit – left	0.77	0.41	0.66
6. Horizontal smooth pursuit – right	0.74	0.45	0.63
17. Ocular fundus examination	0.74	0.46	0.66
1. Pupillary light reflex	0.72	0.48	0.63
3. Fixation – face figure	0.63	0.61	0.41
2. Fixation – bull's eye	0.57	0.67	0.45
13. Visual field – right	0.53	0.72	0.42

Abbreviation: NAVEG, Neonatal Assessment Visual European Grid.

is classified as good. Given that the present analysis included 17 variables and 109 participants, the sample size may be considered adequate.

Diagnostic accuracy of NAVEG total score in infants born preterm

Sensitivity and specificity of the NAVEG total score

On the basis of the coordinates of the resulting ROC analysis, we derived possible cut-off scores of the NAVEG total score for the selected 16 item factorial solution. These cut-offs were equal to scores 2 and 3. False negatives (i.e. newborn infants belonging to ATNAT+/brain ultrasound+ who obtained fewer than 2 or 3 scores at NAVEG) and false positives (i.e. newborn infants belonging to ATNAT–/brain ultrasound– who obtained a scores equal or greater than 2 or 3 at NAVEG), sensitivity, specificity, and OCC are reported in Table 4.

When the reference was the ATNAT score, a NAVEG score equal or greater than 2 detected the presence of impairment with high sensitivity (100%) and good specificity (72.73%), with an OCC of 83.49%. A NAVEG score of at least 3 still showed high sensitivity (93.02%) and better specificity (78.79%); OCC was 84.40%.

Using brain ultrasound scores as reference, a NAVEG score equal or greater than 2 detected the presence of brain ultrasound anomalies with a good sensitivity (82.14%), but low specificity (53.09%); OCC was 60.55%. A NAVEG score of at least 3 was more accurate in identifying newborn infants with brain ultrasound brain anomalies, and sensitivity and specificity were 82.14% and 61.73% respectively; OCC was 66.97%.

Finally, using both brain ultrasound and ATNAT scores combined as reference, a NAVEG score equal or greater than 2 detected the presence of neurological signs and/or brain ultrasound anomalies with a good sensitivity (90.57%) and a good specificity (76.79%); OCC was 83.49%. A NAVEG score of at least 3 was even more accurate in identifying newborn infants with neurological signs and/or brain ultrasound anomalies with a good sensitivity (84.89%) and higher specificity (83.93%), while OCC was 84.40%.

ROC curves

The ROC curves and corresponding AUCs are presented in Figure 1. For all evaluated comparisons (NAVEG vs ATNAT, NAVEG vs brain ultrasound, and NAVEG vs ATNAT and/or brain ultrasound), the confidence intervals of the AUCs were all consistently above the 0.5 threshold. This indicates that the NAVEG performed significantly better than a random classification in distinguishing newborn infants with neurological signs detected by ATNAT ($p < 0.001$), brain ultrasound anomalies ($p = 0.003$), or both combined ($p < 0.001$). Clinical relevance was assessed through the interpretation of AUC confidence intervals. The NAVEG demonstrated excellent discriminative capacity for detecting neurological signs (AUC CI all above 0.954; 95% CI 0.920–0.987), but poor performance for identifying brain ultrasound anomalies (AUC CI centred

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TABLE 4 Diagnostic accuracy of NAVEG total score in infants born preterm: sensitivity and specificity of the NAVEG total score equal to 2 and 3 in discriminating infants born preterm classified on the basis of ATNAT and/or brain ultrasound.

Cut-off score	False negative (95% CI)	False positive (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	OCC (95% CI)	LR+	LR−
Reference: ATNAT							
NAVEG score ≥2	0% (0–0)	27.27% (13.95–40.58)	100% (100–100)	72.73% (61.98–83.47)	83.49% (76.52–90.46)	3.67 (2.63–6.05)	0 (0–0)
NAVEG score ≥3	6.98% (0.8–13.12)	21.21% (8.99–33.43)	93.02% (85.40–100)	78.79% (68.92–88.65)	84.40% (77.59–91.21)	4.39 (2.75–8.81)	0.09 (0–0.21)
Reference: brain ultrasound							
NAVEG score ≥2	17.86% (9.52–26.20)	46.91% (28.42–65.39)	82.14% (67.95–96.32)	53.09% (42.22–63.96)	60.55% (51.37–69.72)	1.75 (1.18–2.67)	0.34 (0.06–0.76)
NAVEG score ≥3	17.86% (9.51–26.20)	38.27% (202.26–56.27)	82.14% (67.95–96.32)	61.73% (51.14–72.31)	66.97% (58.14–75.79)	2.15 (1.39–3.48)	0.29 (0.05–0.63)
Reference: ATNAT and/or + brain ultrasound+							
NAVEG score ≥2	9.43% (1.56–17.30)	23.21% (12.15–34.27)	90.57% (82.70–98.43)	76.79% (65.73–87.85)	83.49% (76.52–90.46)	3.90 (2.41–8.10)	0.12 (0.02–0.26)
NAVEG score ≥3	15.09% (5.71–24.46)	16.07% (6.18–25.96)	84.91% (75.27–94.54)	83.93% (74.31–93.55)	84.40% (77.56–91.21)	5.28 (2.93–14.65)	0.18 (0.06–0.33)

Abbreviations: ATNAT, Amiel-Tison Neurological Assessment; CI, confidence intervals; LR+, LR−, positive, negative likelihood ratio; NAVEG, Neonatal Assessment Visual European Grid; OCC, overall correct classification index.

around 0.687; 95% CI 0.581–0.794). When considering both neurological and brain ultrasound indicators combined (ATNAT and/or brain ultrasound), NAVEG again showed excellent discriminative ability (AUC CI all above 0.900; 95% CI 0.840–0.959).

Discriminative capacity of each NAVEG item to identify the risk of neurological impairment in infants born preterm

As shown in Table 5, the individual items of the NAVEG that seem to have the greatest discriminative ability (based on the index of agreement between the NAVEG score and ATNAT results) are as follows: fixation human face ($w = 0.54$), smooth pursuit to the left ($w = 0.54$) and to the right ($w = 0.58$), smooth pursuit down ($w = 0.61$), attraction saccadic movements to right ($w = 0.63$) and to the left ($w = 0.52$), and visual field down ($w = 0.55$).

When considering the agreement of the NAVEG score and the brain ultrasound results, none of the NAVEG items showed a large discriminative ability (w values less than 0.50).

NAVEG total score centiles and descriptive in infants born at term

Centiles corresponding to each NAVEG total score obtained from infants born at term are described in Table 6. Means and standard deviations of visual acuity expressed in cycles/degree were equal to 1.13 (0.44) ($n = 74$) and of contrast sensitivity expressed in five levels (see Hyvärinen et al.[41] for level values) were equal to 0.69 (SD 0.38; $n = 77$).

Capacity of NAVEG total score in discriminating preterm from infants born at term

NAVEG total scores were compared among infants born preterm with risk of neurological impairment (with ATNAT signs and/or brain ultrasound anomalies) from those without neurological risk, as well as infants born preterm from typically developing infants born at term (see Table 7). The results indicate that infants born preterm belonging to the ATNAT+ group showed a significantly higher mean total score compared both with infants born at term and with infants born preterm belonging to the ATNAT− group, with large effect sizes. Infants born at term and infants born preterm belonging to the ATNAT− group showed similar total NAVEG scores, with a very low mean number of observed signs. Total NAVEG scores were also analysed between infants born at term and those belonging to the brain ultrasound+ or brain ultrasound− groups. In this case, significant differences were observed between all three groups, but the effect size of the differences was significant only between

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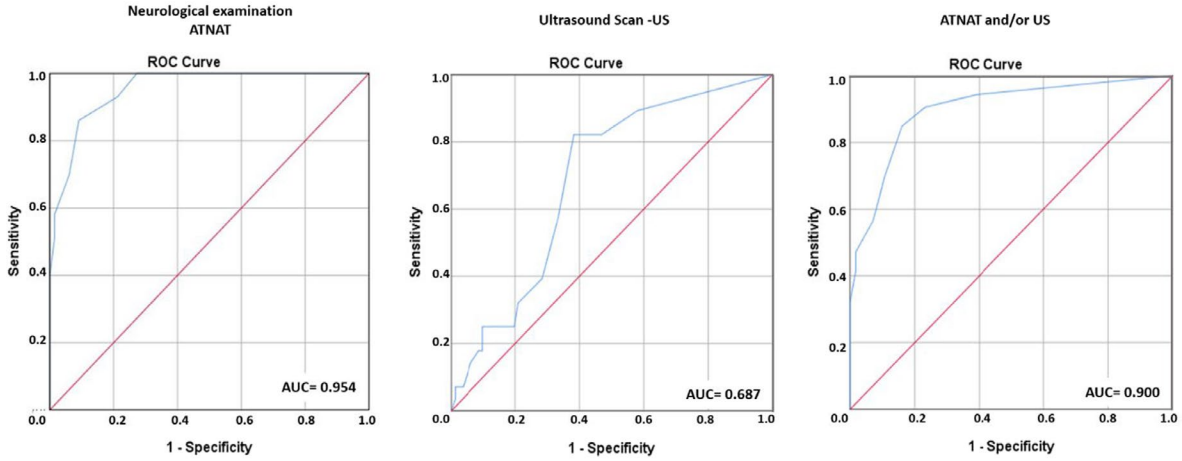


FIGURE 1 Diagnostic accuracy of NAVEG total score in infants born preterm classified on the basis of ATNAT, brain ultrasound, or both: ROC curves. Abbreviations: AUC, area under the curve; ATNAT, Amiel-Tison Neurological Assessment; NAVEG, Neonatal Assessment Visual European Grid; ROC, receiver operating characteristic.

TABLE 5 Discriminative capacity of each NAVEG item to identify risk of neurological impairment in infants born preterm.

	ATNAT		Brain ultrasound	
NAVEG items	χ^2, p	**Cohen's *w***	χ^2, p	**Cohen's *w***
1. Pupillary reflex	24.09, <0.001	0.47	1.39, 0.238	0.11
2. Ocular fund examination	13.09, <0.001	0.35	2.30, 0.129	0.14
3. Fixation – b	8.93, 0.003	0.28	0.39, 0.532	0.06
4. Fixation – face figure	5.61, 0.018	0.23	0.05, 0.823	0.02
5. Fixation – human face	31.91, <0.001	0.54	3.52, 0.061	0.18
6. Horizontal smooth pursuit – left	32.38, <0.001	0.54	3.11, 0.078	0.17
7. Horizontal smooth pursuit – right	36.85, <0.001	0.58	0.38, 0.538	0.06
8. Vertical smooth pursuit – down	40.58, <0.001	0.61	9.28, 0.002	0.29
9. Vertical smooth pursuit – up	24.06, <0.001	0.47	1.03, 0.310	0.10
10. Attraction saccadic movements from right	42.90, <0.001	0.63	3.86, 0.049	0.19
11. Attraction saccadic movements from left	28.95, <0.001	0.52	3.28, 0.070	0.17
12. Contrast sensitivity	0.55, 0.458	0.07	1.00, 0.317	0.10
13. Visual acuity (grating visual acuity)	3.04, 0.081	0.17	1.56, 0.212	0.12
14. Visual field of view – right	14.88, <0.001	0.37	0.62, 0.431	0.07
15. Visual field of view – left	10.66, 0.001	0.31	1.47, 0.225	0.12
16. Visual field of view – up	23.68, <0.001	0.47	0, 1.000	0
17. Visual field of view – down	33.06, <0.001	0.55	3.39, 0.066	0.18

Abbreviations: ATNAT, Amiel-Tison Neurological Assessment; NAVEG, Neonatal Assessment Visual European Grid.

TABLE 6 Centiles corresponding to the NAVEG total score obtained by the infants born at term.

NAVEG total scores	Centiles
0	33
1	71
2	85
3	95
4	98

Abbreviation: NAVEG, Neonatal Assessment Visual European Grid.

infants born preterm belonging to the brain ultrasound+ group and the infants born at term, while it was moderate in the other two comparisons.

Finally, a comparison was conducted between infants born at term, infants born preterm without any neurological signs or neuroimaging abnormalities (ATNAT–brain ultrasound–), and infants born preterm with neurological impairment and/or abnormal brain ultrasound findings (ATNAT+ and/or brain ultrasound+). This analysis confirmed that infants born at term and newborn infants belonging to ATNAT–/brain ultrasound– group had similarly low total

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TABLE 7 Capacity of NAVEG total score in discriminating infants born at term from infants born preterm.

Reference	Infants born preterm classified as positive (group 1)		Infants born preterm classified as negative (group 2)	Term-born infants (group 3)	Kruskal–Wallis test	Dunn's post hoc comparisons		
	Mean (SD)		Mean (SD)	Mean (SD)	Statistic (rank ε^2)	Group 1 vs group 2 z (rank biserial correlation)	Group 1 vs group 3 z (rank biserial correlation)	Group 2 vs group 3 z (rank biserial correlation)
ATNAT	$n = 43$		$n = 66$	$n = 79$				
	7.35 (3.84)		1.11 (1.64)	0.71 (1.12)	98.40 (0.53), $p < 0.001$	8.25 (0.91), $p < 0.001$	9.46 (0.96), $p < 0.001$	1.05 (0.11), $p = 0.881$
Brain ultrasound	$n = 28$		$n = 81$	$n = 79$				
	5.25 (4.25)		2.99 (3.90)	0.71 (1.12)	41.58 (0.22), $p < 0.001$	3.36 (0.37), $p = 0.002$	6.19 (0.78), $p < 0.001$	3.94 (0.33), $p < 0.001$
ATNAT+ and/or brain ultrasound+	$n = 53$		$n = 56$	$n = 79$				
	6.28 (4.153)		1.00 (1.66)	0.71 (1.12)	88.81 (0.47), $p < 0.001$	7.65 (0.80), $p < 0.001$	8.82 (0.86), $p < 0.001$	0.57 (0.05), $p = 1.000$

Abbreviations: ATNAT, Amiel-Tison Neurological Assessment; NAVEG, Neonatal Assessment Visual European Grid; SD, standard deviation.

NAVEG scores, with a minimal mean number of signs. On the contrary, the ATNAT+ and/or brain ultrasound+ groups showed a significantly higher mean total score, compared with both infants born at term and the ATNAT–/brain ultrasound– group, with large effect sizes.

DISCUSSION

Significant changes in the spectrum of preterm birth-related outcomes characterize the evolving clinical and epidemiological landscape of preterm birth.[16,42,43] For example, an increased rate of visual deficits,[15,17,44] such as cerebral visual impairment,[45–47] is often reported and is associated with other neurodevelopmental outcomes of preterm birth, such as cerebral palsy.

There is an increasing need to implement short- and long-term screening tools for this clinical population, also taking into consideration the assessment of visual functions as a possible indicator of risk for brain injury. According to current guidelines,[48] only the ocular aspects of visual function are usually evaluated (e.g. ocular history, external inspection of the eyelids and eyes, red reflex, and pupil examination). The policy statement of the American Academy of Pediatrics emphasizes the importance of referral to a specialist ophthalmologist for the detection of retinopathy of prematurity.[49] It also highlights the importance of evaluating fixation and tracking abilities, as well as visual acuity. However, it does not provide specific recommendations about the timing of these assessments or the screening tools to be used.

Critically low visual acuity or contrast sensitivity values signal the need for prompt ophthalmological referral to assess the necessity of refractive correction, especially in the absence of overt retinal or anterior visual pathway pathologies. These functions improve significantly during the first years of life, serving as key indicators of the plasticity and maturation of the visual system, and their assessment is valuable not only for immediate clinical screening but also from a longitudinal perspective.

There is limited evidence about the validity of visual screening tools that could alert clinicians not only to the possible risk of visual impairment but also to associated concomitant neurological problems.[50]

In response to the existing knowledge gap, and as a continuation of our previous work,[3] this study analysed the factorial structure of NAVEG. It provides evidence about the diagnostic accuracy and discriminative capacity of its items in detecting neurological signs and/or ultrasound brain anomalies. The study also presents data on the discriminative capacity of NAVEG in distinguishing between infants born preterm at risk of neurological impairment and those without such risk, as well as in comparison with typically developing infants born at term.

Exploratory factor analysis showed that almost all the variables in NAVEG share a common structure for assessing visual function. Contrast sensitivity was excluded from the analysis because it did not show high factor

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loading and therefore did not contribute to the shared factor structure.

Infants born preterm in our sample exhibited contrast sensitivity thresholds that were significantly greater than those reported by Leat and Wegmann.[28] In most cases, they could only detect 100% contrast. However, through the dichotomization procedure based on the available reference data, this difference in values within our infants born preterm was amplified, with almost all values falling within the pathological range. Even the infants born at term exhibited very high contrast sensitivity thresholds compared with the reference sample. Once dichotomized, this indicated the presence of the disorder in approximately 70% of the participants. In the future, it would be desirable to update the reference data with contrast sensitivity values, possibly by comparing them with other assessment approaches currently available for newborn infants.[13]

Our analysis showed that a NAVEG total score of 3 or more (at least three items with a score of 1) yielded good sensitivity and specificity thresholds within the infants born preterm, when considering ATNAT scores and/or brain ultrasound scores (sensitivity 93.02%, specificity 78.79%) or ATNAT scores in combination with brain ultrasound (sensitivity 84.89%, specificity 83.93%). In the absence of validated tests that use visual function as an indicator of risk not only for visual impairment but also for neurological damage, we combined the NAVEG with the ATNAT neurological examination and brain ultrasound, which represents the criterion standard for detecting infants at risk of neurological or brain anomalies. Furthermore, the use of criterion standards based on neurological and brain ultrasound parameters is justified because they are widely recognized assessment measures[50] internationally accepted across NICU centres. Further research is needed to evaluate whether NAVEG has predictive validity, with respect to visual function outcomes, particularly for the presence of cerebral visual impairment, and for other neurodevelopmental outcomes.

This study showed that, among all the visual function parameters assessed through NAVEG, oculomotor function, and visual field were the most significant. Specifically, visual fixation (the ability to stabilize an image on the fovea), smooth pursuit (the ability to track a moving target), and reactive saccades (rapid, conjugate eye movements used to quickly shift fixation) are among the variables with the greatest discriminative power in detecting presence of neurological signs in infants born preterm.

Our findings are consistent with a recent study by Jonsson et al.,[51] who investigated gaze behaviour in infants with early-onset epilepsy using eye-tracking technology. Notably, the authors found that neurologically typical infants exhibited more stable fixation and were more likely to shift their gaze than neurologically atypical infants.[51] This is not surprising, given that eye movements are controlled by multiple circuits involving cortical and subcortical regions that are also engaged in various neurological and behavioural functions, such as motor, cognitive, and attention processes.[52–54] Indeed, oculomotor anomalies have been observed in patients with a variety of central nervous system conditions, such as cerebral palsy,[47] movement disorders,[55] rare neurological diseases,[56,57] as well as neurodevelopmental disorders.[47,52,53] Oculomotor functions also remain relatively robust even in the presence of moderate refractive error. Their relative independence from optical factors makes them more reliable indicators of underlying neurological visual function in infancy, particularly in heterogeneous clinical populations where refractive status is variable and often uncorrected. Moreover, consistent with our results, previous data show that early evaluations of fixation, smooth pursuit, and attractive saccades are highly predictive of cognitive outcomes at 12 months of age.[58]

This study also demonstrated that an inferior visual field restriction has high discriminatory power in detecting neurological impairment in infants born preterm.[59] Such deficits have been linked to damage to the superior portion of the optic radiations,[60] a pathway that can be affected, along with other white matter regions, in children born preterm. Owing to the anatomical proximity of the optic radiations and the corticospinal tract, both of which can be affected in infants born preterm,[61] abnormalities in motor function that can be identified through ATNAT examination may also be associated with visual impairments. This association is supported by literature highlighting the strong relationship between neurological and visual impairment in the context of preterm birth.[62]

In our study, neither the oculomotor nor the visual field items demonstrated sufficient discriminatory power to identify brain lesions detected by ultrasound in the sample of infants born preterm. This may be explained by the fact that ultrasound scans often fail to visualize critical structures along the visual pathway, such as the superior colliculus,[63] and lack the resolution required to observe fine structural abnormalities. Additionally, there is growing evidence that a correlation between neurovisual assessments (including visual field function), and conventional neuroimaging findings is not always apparent, probably because of the difficulty of detecting white matter damage within the visual pathways.[64,65]

Finally, significant differences in NAVEG scores were observed between infants born preterm with ATNAT+ and infants born preterm with ATNAT–, as well as between infants born preterm with ATNAT+ and typically developing infants born at term, supporting the discriminative capacity of NAVEG. Specifically, infants born preterm without neurological impairment signs or brain-ultrasound-detected anomalies demonstrate NAVEG performance similar to infants born at term, and significantly better than newborn infants with ATNAT and/or ultrasound abnormalities. Our data are consistent with previous studies that have shown low-risk infants born preterm without major brain lesions have visual skills within the normal range, such as the ability to fixate and follow a black-and-white target and discriminate black-and-white stripes of increasing spatial frequency and contrast sensitivity, when evaluated at term-equivalent

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age.[66,67] In contrast, infants born preterm with major abnormalities on cranial brain ultrasound scans were more likely to have a visual impairment.[11,47] These findings further support the usefulness of the NAVEG tool in assessing visual abilities in newborn infants and for the early identification of those at risk of neurological impairment. Further research should be conducted to assess the capacity of NAVEG to predict cerebral visual impairment specifically.

This study has several limitations that need to be considered. First, in this study we considered two different populations, at term and preterm, that had been recruited in different time spans. We know that could be considered a limitation, but the standard care protocols for typically developing infants born at term at our institution remained unchanged during the period between the first and second study. Furthermore, all participants were recruited from the same hospital and geographical area, and the inclusion criteria were identical across both studies. The clinical team that performed the neonatal evaluations during 2012 to 2014 overlapped with the current team and the examiners adopted the same standardized approach. Supervision among team members was consistent across both study periods. To date, only evidence of concurrent validity has been investigated for the NAVEG assessment. Consequently, the NAVEG score derived from the assessment cannot currently be considered a predictive measure of potential visual outcomes related to preterm birth. Nevertheless, it can be obtained quickly and is useful for clinicians in identifying neonates who may require closer neurological and neuroimaging evaluation as well as visual assessment. Additionally, dichotomizing NAVEG scores to facilitate clinical interpretation may result in the loss of potentially relevant clinical information. Nevertheless, the assessment allows for the inclusion of qualitative clinical observations, which, while not factored into the overall score, could be valuable for longitudinal follow-up. However, as a screening tool, it possesses certain advantages such as accessibility, ease of use (and not requiring sophisticated instrumentation), and rapidity of administration. Specifically, it can be administered in approximately 10 minutes, is neither language-dependent nor reliant on direct responses from newborn infants, and its procedures can be easily replicated by other practitioners across different clinical settings.

In conclusion, despite current methodological limitations, this rapid and easily administered screening grid has proved effective in assessing the visual profile of newborn infants and identifying neurological signs, whether isolated or associated with brain ultrasound anomalies. Further implementation may facilitate the early identification of those visual impairments, whose signs and symptoms often emerge later in infancy or childhood, such as cerebral visual impairment. It may also facilitate the early identification of neurodevelopmental disorders, which are increasingly recognized among the still underexplored outcomes of preterm birth.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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SUPPORTING INFORMATION

The following additional material may be found online:
Table S1. Clinical features according to ATNAT and ULTRASOUND.

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