Infant Behavior and Development 49 (2017) 21–30

Contents lists available at ScienceDirect

Infant Behavior and Development

journal homepage: www.elsevier.com/locate/inbede

Full length article

Neonatal Assessment Visual European Grid (NAVEG): Unveiling neurological risk

Andrea Rossi[a,*], Marco Gnesi[b], Cristina Montomoli[b], Gaetano Chirico[c], Laura Malerba, MD[d], Lotfi B. Merabet[e], NAVEG Study Group[1], Elisa Fazzi[a,d]

[a] Child and Adolescent Neurology and Psychiatry Unit, Children Hospital, ASST Spedali Civili of Brescia, Italy
[b] Department of Public Health, Experimental and Forensic Medicine, Section of Biostatistics and Clinical Epidemiology, University of Pavia, Italy
[c] Department of Neonatology and Neonatal Intensive Care Unit, Children Hospital, ASST Spedali Civili of Brescia, Italy
[d] Department of Clinical and Experimental Sciences, University of Brescia, Italy
[e] The Laboratory for Visual Neuroplasticity, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Assessment
Preterm
Newborn
Visual function
Brain lesion

1. Introduction

The importance of visual function and its crucial role in early development are well established (Braddick & Atkinson, 2011; Fazzi, 2010; Fazzi et al., 2004; Matsuba & Jan, 2006). Previous experimental research (Fantz, 1963, 1965) has demonstrated that newborn infants have a significant level of perceptual functioning. For instance, they respond selectively to different environmental stimuli and are actively engaged in the acquisition of information through exploration of the environment. Albeit rudimentary, this exploratory behavior appears to be oriented and controlled. Assessments of visual function such as acuity are relatively easy to carry out in newborns (Brown & Yamamoto, 1986; Cavallini et al., 2002), and the importance of an early evaluation has been previously highlighted in a number of reports (Atkinson et al., 2008; Dubowitz, Dubowitz, Morante, & Verghote, 1980; Hyvärinen, Walthes, Jacob, Chaplin, & Leonhardt, 2014; Leonhardt, Forns, Calderón, Reinoso, & Gargallo, 2012; Mercuri, Baranello, Romeo, Cesarini, & Ricci, 2007; Ricci, Cesarini et al., 2008). More recently, the feasibility of testing early visual function has increased considerably, and

* Corresponding author at: Child and Adolescent Neurology and Psychiatry Unit, Children Hospital, ASST Spedali Civili of Brescia, Piazzale Spedali Civili, 1, 25123 Brescia, Italy.
E-mail address: and78rossi@gmail.com (A. Rossi).

[1] NAVEG Study Group: Alessandrini A, D'Adda N, Tansini F, Micheletti S, Galli J, Accorsi P, Martelli P, Gritti M, Mattei P (Child and Adolescent Neurology and Psychiatry Unit, Children Hospital, ASST Spedali Civili of Brescia, Italy; Department of Clinical and Experimental Sciences, University of Brescia, Italy); Bettelli S, Franzoni A, Nascimbeni G, Semeraro F, (Department of Medical and Surgical Specialties, Radiological Specialties and Public Health, Ophthalmology, University of Brescia, Italy); Gasparoni A (Department of Neonatology, Children Hospital, ASST Spedali Civili of Brescia, Italy); Ferrari F, Della Casa E. (Institute of Pediatrics and Neonatal Medicine and NICU of Modena University Hospital, Modena, Italy); Orcesi S (Unit of Child Neurology and Psychiatry, C. Mondino National Neurological Institute, Pavia, Italy); Stronati M (Neonatal Intensive Care Unit, IRCCS Foundation Policlinico San Matteo, Pavia, Italy); Lebrun F, Marcou V (Service de Médecine Néonatale de Port-Royal, Groupe hospitalier Cochin Saint-Vincent de Paul (AP-HP) et Faculté de Médecine Paris Descartes, Paris, France); Haumont D, Tackoen M (Centre Neonatal, C.H.U. Saint-Pierre, Bruxelles).

http://dx.doi.org/10.1016/j.infbeh.2017.06.002
Received 6 April 2017; Received in revised form 5 June 2017; Accepted 7 June 2017
Available online 05 July 2017

several authors have developed methods for the examination of visual function in neonates (Leonhardt et al., 2012; Ricci, Cesarini et al., 2008; Ricci, Romeo et al., 2008; Romeo et al., 2012). Again, current scientific evidence appears to support this view and calls attention to assessing visual function as an important "window" into the developmental trajectory of the brain (Hubel & Wiesel, 1979). Indeed, the assessment of visual function can be an indicator of a patient's neurological status and therefore, the identification of visual impairment can alert the clinician to the possibility of underlying neurological damage. Based on the extensive and multidisciplinary experience of our group with regards to the evaluation of visual function in infants and toddlers with visual impairment and brain lesions (Cavallini et al., 2002; Fazzi, Galli, & Micheletti, 2012 ; Fazzi et al., 2007; Lanzi et al., 1998), we have developed a visual screening and testing battery called "NAVEG" (Neonatal Assessment Visual European Grid) designed to investigate different aspects of visual function in newborn infants (Rossi et al., 2016). Taking into consideration the contribution of previous studies by our group (Cavallini et al., 2002) as well as others (Dubowitz et al., 1980), we propose a clinical testing battery which can be easily performed in full-term and preterm newborns and within the setting of the neonatal intensive care unit. The NAVEG testing battery (see Table 1) includes an ophthalmological/ocular visual component (OVC), a motor visual component (MVC) related to oculomotor functions, and a perceptual visual component (PVC) which explores perceptual functions related to retrogeniculate visual pathways (Rossi et al., 2016).

The aims of this study were the following. First, assessing visual function using NAVEG in a large cohort of newborn infants (both full-term and preterm). Second, use the results of this assessment to perform an exploratory analysis of the features of the testing battery. Finally, to evaluate NAVEG's discriminating capability in the detection of infants with neurological impairment and brain damage.

2. Methods and materials

2.1. Study sample

Newborns were recruited for this study between January, 2011 and December, 2014 from the department of neonatology and neonatal intensive care unit of the ASST Spedali Civili Hospital in Brescia, Italy. Inclusion criteria included infants aged at or below 34 weeks gestational age. Exclusion criteria included presence of severe hereditary disease or chromosomal abnormalities, and evidence of retinopathy of prematurity (ROP) greater than or equal to stage 2. The study was approved by the Ethical Board of the ASST Spedali Civili of Brescia and parents offered written informed consent prior to the enrollment of their child in the study.

The study sample consisted of 160 newborn infants (equally split between 80 full-term and 80 preterm). A description of their main characteristics at birth is detailed in Table 2.

2.2. Assessments

Each newborn underwent the NAVEG visual evaluation (administered by an experienced child neurologist) and a neonatal neurological examination following the Amiel-Tison neurologic assessment procedure (Amiel-Tison, 2002; Gosselin, Gahagan, & Amiel-Tison, 2005). This assessment evaluates cranial characteristics, alertness, behavior and spontaneous activity, passive tone in limbs and axis, active tone, and primary reflexes of the newborn. The complete procedure takes approximately 5 min and a simple 0, 1, 2 scoring system is used (0 = a typical result, within the normal range; 1 = a moderately abnormal result; 2 = a very abnormal result). Interobserver reliability of the Amiel-Tison assessment tool is very good, and when performed by a highly trained examiner, the results correlate with developmental performance at 2 years of corrected age (Simard, Lambert, Lachance, Audibert, & Gosselin, 2011). The assessment was performed 24–72 h after birth in full-term infants, and at approximate term age (38–42 weeks gestational age) in pre-term infants. In order to maximize the possibility of obtaining optimal results, visual evaluation was carried out under the conditions characterized as Prechtl's state III (Prechtl, 1974), that is, in a dimly lit room and between meals. The examiner was instructed not to talk during the presentation of visual targets. Individual tests were scored according to the following criteria: "0" for absence of any clinical sign of impairment; "1" for uncertain impairment or inconsistent signs (only items where this score was provided); "2" for clear evidence of impairment; "NA" for not assessable (e.g. due to inadequate behavioral state. This was considered as a missing value). As the scoring system is not quantitative, a computation of quotient or total score was deemed inappropriate. Ocular fundus ("Fundus Oculi") examination was performed by an experienced ophthalmologist only in preterm subjects (i.e. less than 32 weeks gestational age, in accordance to the local protocol of the neonatal intensive care unit).

Ultrasound (US) imaging was performed in all preterm and in full-term newborns with signs of neonatal distress according to local departmental protocol. The primary endpoint for the presence of a brain lesion (based on the US report) was determined as follows: abnormal ("US+") in presence of periventricular hemorrhage (according to the criteria of Volpe (2008)) or periventricular damage (according to criteria of De Vries, Eken, and Dubowitz, (1992)); normal ("US-") in the absence of the above-mentioned signs or when ultrasound imaging was not warranted. As a secondary endpoint, outcomes from the Amiel Tison neurological assessment (Amiel-Tison, 2002) were also considered. This was classified as normal ("AT-") when every individual item was coded "0", or abnormal ("AT+") when a score of 1 or 2 was assigned to some or most of the Amiel Tison's items.

2.3. Statistical analyses

Given the exploratory aims of this study and considering that NAVEG items are categorical variables, a Multiple Correspondence Analysis (MCA) was carried out to investigate the structure of NAVEG. This approach provides coordinate plots that can be

Table 1
Neonatal Assessment Visual European Grid (NAVEG) items and descriptive results in 160 newborns.

1. OPHTALMIC/OCULAR VISUAL COMPONENT (OVC)					
Pupillary Light Reflex		*0*	*Present*	140	(91.50%)
		1	*Slow*	13	(8.50%)
		2	*Absent*	0	(0.00%)
		NA		7	---
Red Reflex		*0*	*Present*	101	(100.00%)
		2	*Unequal refraction / white pupillary reflex*	0	(0.00%)
		NA		59	---
Eye Abnormalities	Ptosis	*0*	*Absent*	160	(100.00%)
		2	*Present*	0	(0.00%)
		NA		0	---
	Corneal opacities	*0*	*Absent*	160	(100.00%)
		2	*Present*	0	(0.00%)
		NA		0	---
	Iris coloboma microphtalmia/anophthalmia	*0*	*Absent*	160	(100.00%)
		2	*Present*	0	(0.00%)
		NA		0	---
	Other changes	*0*	*Absent*	158	(98.75%)
		2	*Present*	2	(1.25%)
		NA		0	---
Fundus Oculi *(only in preterms)*		*0*	*Normal*	51	(80.95%)
		2	*Abnormal*	12	(19.05%)
		NA		97	---

2. MOTOR VISUAL COMPONENT (MVC)					
Fixation	Bull's Eye 	*0*	*Present, stable and sustained (at least 3")*	136	(85.00%)
		1	*Difficult to obtain, short duration (<3") or alternating*	24	(15.00%)
		2	*Absent*	0	(0.00%)
		NA		0	---
	Face Figure 	*0*	*Present, stable and sustained (at least 3")*	127	(79.38%)
		1	*Difficult to obtain, short duration (<3") or alternating*	33	(20.63%)
		2	*Absent*	0	(0.00%)
		NA		0	---
	Human Face	*0*	*Present, stable and sustained (at least 3")*	132	(82.50%)
		1	*Difficult to obtain, short duration (<3") or alternating*	26	(16.25%)
		2	*Absent*	2	(1.25%)
		NA		0	---

(continued on next page)

Table 1 *(continued)*

Horizontal Smooth Pursuit 	Left	*0*	*Present and complete*	122	(76.25%)
		1	*Difficult to obtain, incomplete and/or asymmetrical*	38	(23.75%)
		2	*Absent*	0	(0.00%)
		NA		0	---
	Right	*0*	*Present and complete*	123	(76.88%)
		1	*Difficult to obtain, incomplete and/or asymmetrical*	37	(23.13%)
		2	*Absent*	0	(0.00%)
		NA		0	---
Vertical Smooth Pursuit 	Up	*0*	*Present and complete*	97	(61.01%)
		1	*Difficult to obtain, incomplete and/or asymmetrical*	62	(38.99%)
		2	*Absent*	0	(0.00%)
		NA		1	---
	Down	*0*	*Present and complete*	78	(49.06%)
		1	*Difficult to obtain, incomplete and/or asymmetrical*	72	(45.28%)
		2	*Absent*	9	(5.66%)
		NA		1	---
Saccadic Movements	From Right	*0*	*Present*	138	(86.25%)
		1	*Difficult to obtain, not fluid*	19	(11.88%)
		2	*Absent*	3	(1.88%)
		NA		0	---
	From Left	*0*	*Present*	133	(83.13%)
		1	*Difficult to obtain, incomplete and/or asymmetrical*	24	(15.00%)
		2	*Absent*	3	(1.88%)
		NA		0	---
Abnormal Eye Movements	Erratic Eye movements	*0*	*Absent*	160	(100.00%)
		2	*Present*	0	(0.00%)
		NA		0	---
	Sunset	*0*	*Absent*	160	(100.00%)
		2	*Present*	0	(0.00%)
		NA		0	---
	Nystagmus	*0*	*Absent*	158	(98.13%)
		2	*Present*	2	(1.88%)
		NA		0	---
	Paroxysmal ocular deviations	*0*	*Absent*	160	(100.00%)
		2	*Present*	0	(0.00%)
		NA		0	---
	Other (inconstant strabismus)	*0*	*Absent*	150	(93.75%)
		2	*Present*	10	(6.25%)
		NA		0	---

3. PERCEPTUAL VISUAL COMPONENT (PVC)					
Contrast Sensitivity 		*0*	*Very low contrast (10% card)*	6	(3.95%)
		1	*Low contrast (25% card)*	38	(25.00%)
		2	*High contrast (100% card)*	105	(69.08%)
		3	*Absent (none)*	3	(1.97%)
		NA		8	---
Visual Acuity 		*0*	*1.70 cy/deg card*	3	(1.96%)
		1	*1.10 cy/cm card*	14	(9.15%)
		2	*0.90 cy/cm card*	27	(17.65%)
		3	*0.60 cy/cm card*	47	(30.72%)
		4	*0.44 cy/cm card*	40	(26.14%)
		5	*0.30 cy/cm card*	12	(7.84%)
		6	*0.22 cy/cm card*	10	(6.54%)
		NA		7	---
Visual Field 	Right	*0*	*Typical (localization within 30° from midline)*	147	(93.63%)
		2	*Limited*	10	(6.37%)
		NA		3	---
	Left	*0*	*Typical (localization within 30° from midline)*	144	(92.31%)
		2	*Limited*	12	(7.69%)
		NA		4	---
	Up	*0*	*Typical (localization within 30° from midline)*	125	(79.62%)
		2	*Limited*	32	(20.38%)
		NA		3	---
	Down	*0*	*Typical (localization within 30° from midline)*	108	(68.79%)
		2	*Limited*	49	(31.21%)
		NA		3	---
Optokinetic Nystagmus 		*0*	*Typical (present, asymmetrical)*	69	(93.24%)
		2	*Absent*	5	(6.76%)
		NA		86	---

Table 2
Main characteristics at birth of the newborns included in the sample: descriptive statistics.

Characteristic	Preterms subgroup (n = 80)	Full-terms subgroup (n = 80)
Females[a]	30 (37.50%)	40 (50.63%)
Gestational Age at birth[b] (weeks)	30.7 (2.6), 24.0–34.3	39.4 (1.0), 37.0–41.5
Apgar 5'[c]	9 (2), 0–10	10 (1), 8–10
Weight at birth[b] (g)	1466 (518), 535–2500	3262 (399), 2690–4320
Length at birth[b] (cm)	40.5 (4.3), 30–47	50.5 (2.6), 35.5–55.0
Head circumference at birth[b] (cm)	8.4 (3.4), 20.0–41.0	34.5 (1.5), 31.5–38.0

[a] Statistics: n (% of the correspondent sex within subgroup).
[b] Statistics: mean (SD), min–max.
[c] Statistics: median (IQR), min–max.

graphically interpreted to help identify "average profiles" in order to highlight the latent structure of the data. In the coordinate plot, each point represents the average occurrence of a certain category for a given variable, with the dispersion of those points being the geometrical counterpart of the variability in the sample (i.e. associations in the occurrence of categories). The number of dimensions to be retained in MCA solutions were designed to explain at least 80% of the total (observed) variability (Abdi & Valentin, 2007; Greenacre & Blasius, 1994). Variables can be computed either as active (i.e. determining the MCA dimensions) or as supplementary (i.e. passively included in the MCA solution for reasons of interpretability). Computations can either include or exclude missing data. To be conservative, statistical analyses were initially performed by keeping only those subjects for whom all items were obtainable, and then repeated in a subsequent sensitivity analysis using missing values as allowed items. A secondary analysis included a dichotomization of all items. That is, items already having a binary structure were retained while items with a three-level structure were re-classified as "optimal" ("0": absence of impairment) versus "impaired" ("1" and "2": i.e. both borderline and clear evidence of impairment). Contrast Sensitivity was marked as "impaired" only if absent (otherwise scored as "optimal"), and visual acuity was considered as "impaired" at a level of 0.43cy/cm^2 or lower (otherwise scored as "optimal"). In hypothesis testing procedures, significance level (alpha) was set at 0.05. Statistical analyses were performed using Stata IC 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3. Results

A total of 81 newborns (80 preterm and 1 full-term) underwent ultrasound (US) imaging, of which 42 preterm subjects were identified with a lesion (US+; as defined above). A neurological examination was performed in all the subjects identifying an impairment (AT+) in 31 individuals (19.4%), all of which were pre-term infants. Twenty six (26) of these infants (83.9%) also had evidence of a brain lesion (US+). NAVEG was administered on all the infants at a mean gestational age of 39.1 (SD 1.8) weeks. Descriptive results are presented in Table 1. In some cases, a full evaluation was not possible, largely because of an inadequate behavioral state. The mean time of NAVEG assessment was 9 (SD 2) minutes. Nine of the NAVEG items ("red reflex", "ptosis", "corneal opacities", "micro/anophthalmia or iris coloboma", "erratic movements", "sunset", "paroxysmal deviations", "other ophthalmological abnormalities", "other visuomotor abnormalities") had no variability in the sample. "Optokinetic nystagmus" (OKN) proved to be rarely assessable (not testable in 86 subjects, 53.8%), and among the 74 newborns who had it assessed, it was normal in 69 individuals (93.2%). Consequently, these items were excluded and not considered for further analyses. Univariate tests were applied to the remaining items to explore associations between the presence of brain lesions or neurological examination. All these associations were statistically significant (Table 3). Therefore, the remaining items were considered potentially relevant for brain lesions for the purpose of the MCA. These were "pupillary light reflex", fixation of targets ("bull's eye", "Heidi", "human face"), smooth pursuits ("left", "right", "up", "down"), saccadic movements ("from left" and "from right"), "contrast sensitivity", "visual acuity", "visual field of view" ("left", "right", "up", "down"). A complete NAVEG profile for these items was obtained in 139 individuals. The MCA solution (shown in Fig. 1) was able to explain 82.6% of the total variability in two dimensions, with the first dimension (horizontal axis) alone representing more than 75% of the variability. 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 variable in order to address the interpretation of those profiles (see Methods), fit perfectly in the "impaired profile" while an absence of lesions was consistent with the "optimal profile". Profiles were mainly distinguished on the first dimension. Therefore, this was interpreted as the "brain lesion" component. These profiles were not altered by including missing values, which did not cluster with a clear pattern when they were computed in the MCA solution as a true category for the items. Thus, it was assumed that missing data were randomly recorded, independently from the presence of a brain lesion. Results were also confirmed when computing the MCA solution excluding full-term infants (Fig. 2), aiming to control for any possible confounding effect of gestational age at birth. Other observations are worth of note from the results reported in Fig. 1. For example, absent or severe impairments in saccadic eye movements (in both the right and left directions) and severely reduced contrast sensitivity appeared to be out of the above-mentioned "impaired" profile, although optimality lying in the "optimal" profile in both cases. However, frequencies of impairment were extremely low for these items, which potentially could affect their relative positions in the plot.

Finally, in an attempt to simplify NAVEG (and partly to also reduce the impact of the limitations reported above), outcomes from

Table 3
Associations with brain lesions and neurological examination (univariate test).

Item		Impairment[a] (by brain lesions)			Impairment[b] (by neurological assessment)		
		US-	US +	p-value[^]	AT-	AT +	p-value[^]
Pupillary light reflex		3 (2.65%)	10 (25.00%)	< 0.001	4 (3.31%)	9 (30.00%)	< 0.001
Target fixation	Bull's Eye	11 (9.32%)	13 (30.95%)	0.001	14 (11.02%)	10 (32.26%)	0.009
	Face Figure	15 (12.71%)	18 (42.86%)	< 0.001	19 (14.96%)	14 (45.16%)	< 0.001
	Human Face	10 (8.48%)	18 (42.86%)	< 0.001	12 (9.45%)	15 (48.39%)	< 0.001
Smooth Pursuit	To Left	14 (11.86%)	24 (57.14%)	< 0.001	18 (14.17%)	19 (61.29%)	< 0.001
	To Right	13 (11.02%)	24 (57.14%)	< 0.001	21 (16.54%)	16 (51.61%)	< 0.001
	To Up	37 (31.62%)	25 (59.52%)	0.001	43 (34.13%)	19 (61.29%)	0.006
	To Down	50 (42.74%)	31 (73.81%)	< 0.001	58 (46.03%)	22 (70.97%)	0.005
Saccadic Movements	From Left	13 (11.02%)	14 (33.33%)	0.003	15 (11.81%)	12 (38.71%)	0.001
	From Right	10 (8.27%)	12 (28.57%)	0.005	13 (10.24%)	9 (29.03%)	0.015
Contrast Sensitivity		1 (0.87%)	2 (5.41%)	0.007	0 (0.00%)	3 (10.34%)	0.002
Visual Acuity		9 (8.11%)	13 (30.95%)	< 0.001	11 (9.16%)	11 (35.48%)	0.001
Visual Field	Left	3 (2.59%)	9 (22.50%)	< 0.001	5 (4.03%)	7 (23.33%)	0.002
	Right	1 (0.86%)	9 (21.95%)	< 0.001	5 (4.00%)	5 (16.67%)	0.024
	Up	14 (12.07%)	18 (43.09%)	< 0.001	16 (12.80%)	15 (50.00%)	< 0.001
	Down	26 (22.41%)	23 (56.10%)	< 0.001	31 (24.80%)	17 (56.67%)	0.001
Ocular Fundus ("Fundus Oculi")		0 (0.00%)	12 (31.58%)	0.002	1 (2.94%)	11 (39.29%)	< 0.001

[a] Observed frequencies of moderate or severe impairment (Contrast Sensitivity: absent; Visual Acuity: card 0.43 cy/cm^2 or lower); percentages represent the portion of subjects with impairment for a given item within US + and US- groups.

[b] Observed frequencies of moderate or severe impairment (Contrast Sensitivity: absent; Visual Acuity: card 0.43 cy/cm^2 or lower); percentages represent the portion of subjects with impairment for a given item within AT + and AT- groups.

[^] Crude associations (items vs. endpoint) were tested by using Pearson's Chi-Square test or Fisher's exact test (as appropriate).

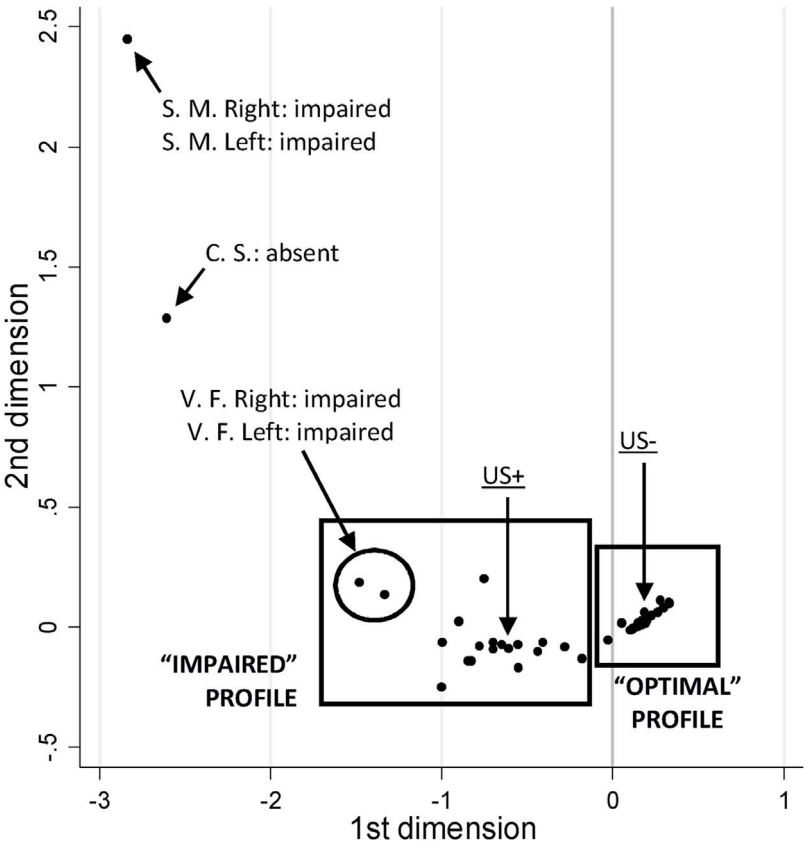

Fig. 1. Multiple Correspondence Analysis (original items).
Coordinates Plot: Multiple Correspondence Analysis of 16 NAVEG relevant items; supplementary variable: presence of brain lesions defined on the basis of ultrasound imaging ("US + " and "US-"). Normalization: principal coordinates. Explained variability: 1st dimension (horizontal) 76.35%; 2nd dimension (vertical) 6.29%; please note that axes scales are symmetric, i.e. not proportional to explained variability. Legend: "C. S." for Contrast Sensitivity; "S. M." for Saccadic Movements; "V. F." for Visual Field of view.

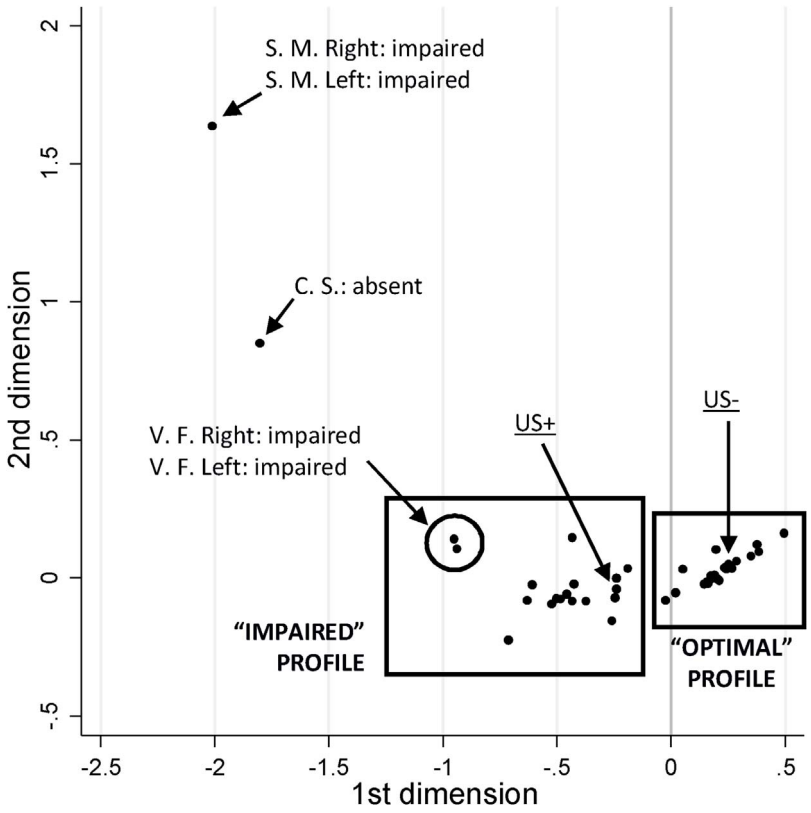

Fig. 2. Multiple Correspondence Analysis (original items), subgroup of preterm infants.
Coordinates Plot: Multiple Correspondence Analysis of 16 NAVEG relevant items; supplementary variable: presence of brain lesions defined on the basis of ultrasound imaging ("US+" and "US-"). Normalization: principal coordinates. Explained variability: 1st dimension (horizontal) 71.13%; 2nd dimension (vertical) 6.25%; please note that axes scales are symmetric, i.e. not proportional to explained variability. Legend: "C. S." for Contrast Sensitivity; "S. M." for Saccadic Movements; "V. F." for Visual Field of view.

the test items were all dichotomised and the MCA was re-run in a secondary analysis. This solution was able to explain approximately 86% of observed variability in its first dimension alone, reaching more than 90% in two dimensions. The interpretation of the first axis as the "brain lesion" component was again confirmed and the distinction of the two main profiles (see above) appeared to be further enhanced (Fig. 3). Only impairment in visual field of view ("left" and "right") and absence of contrast sensitivity remained distant from the "impaired profile". However, outcome items for visual field function were already binary, and observed frequencies for absence of contrast sensitivity were still very low. The three items for target fixation, as well as those for smooth pursuit, saccadic movements, and visual field, appeared to be grouped in the average profiles, so they were also considered together adopting the criteria that, for each group, one impaired item was sufficient to define impairment for the whole group. For example, smooth pursuit was considered impaired if at least one out of the four tested items ("left", "right", "up", "down") was impaired. The MCA was then repeated with these new grouped variables; pupillary light reflex (binary), visual acuity (binary), contrast sensitivity (binary) and evidence of brain lesions (supplementary variable). The MCA solution was further strengthened and explained variability rose up to 90.8% in one dimension and profiles were maintained, with impaired contrast sensitivity still quite distant from the "impaired" profile (Fig. 4). Despite being available in only 49% of the cases, results from the ocular fundus examination showed an apparent discriminating capability in bivariate testing (Table 3). This was confirmed by its introduction in a second stage that comprised again an MCA on the original items with or without missing values as a true category, dichotomised items, and grouped items. Finally, it was noted that in all the previously illustrated analyses, "impaired" and "optimal" profiles were also consistent with neurological examination results (abnormal or normal) as a supplementary variable in lieu of brain lesion status.

4. Discussion

The NAVEG testing battery was found to be a fast, easy, and non-invasive assessment tool revealing meaningful information regarding the early developmental stages of the visual system. The results obtained by the MCA suggest that NAVEG may be effective in discriminating the profile of newborns with respect to neurological status, allowing a clinician (or assessor) to carry out a rapid clinical evaluation that could help guide physicians to perform further examinations, or even record information for research purposes. It is important to note that the analysis was repeated considering only the subgroup of pre-terms. The MCA solution was consistent with the results generated by the total sample, suggesting the lesion profiling capability of NAVEG when administered

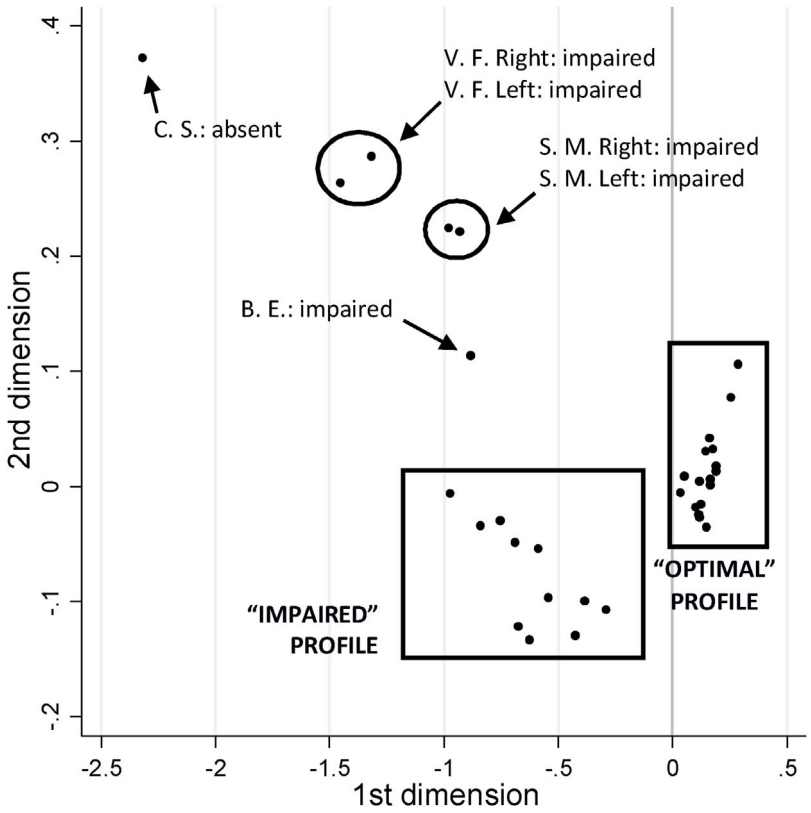

Fig. 3. Multiple Correspondence Analysis (dichotomized items).
Coordinates Plot: Multiple Correspondence Analysis of 16 NAVEG relevant items after dichotomization; supplementary variable: presence of brain lesions defined on the basis of ultrasound imaging ("US+" and "US-"). Normalization: principal coordinates. Explained variability: 1st dimension (horizontal) 86.45%; 2nd dimension (vertical) 3.66%; please note that axes scales are symmetric, i.e. not proportional to explained variability, and that 2nd dimension could be discarded (it is represented only for the sake of readability of the plot). Legend: "B. E." for Fixation – Bull's Eye; "C. S." for Contrast Sensitivity; "S. M." for Saccadic Movements; "V. F." for Visual Field of view.

approximately 40 weeks gestational age is not strongly influenced by the premature status of the infant. This result overcomes a possible limitation of the study. Specifically, item clustering (i.e. functional profiles of subjects) is not influenced by longer exposure to visual stimuli in preterm infants. The results of this preliminary study can certainly be a useful for further improving the usability of NAVEG. First of all, the assessment could be simplified by removing items that proved to have poor discriminating value, or were difficult to obtain from a testing standpoint. For instance, OKN represented a challenge to testing (i.e. using a large flexible board that may reduce the examiner's view), was assessable on only a small subset of subjects, and was normal in 69 on 74 subjects evaluated (93.2%). For these reasons, we decided to propose OKN evaluation only in subjects that showed an inadequate visual profile during the test performance. The retaining of ocular fundus examination should also be carefully considered. Despite its diagnostic value, it requires a relatively invasive procedure carried out by a specialized ophthalmologist, thus suggesting this might be worth omitting from the testing battery. Therefore, it is proposed that retained items should be pupillary light reflex, target fixations, smooth pursuits, saccadic movements, contrast sensitivity, visual acuity, and visual field of view. All the MCA solutions suggested accordingly the chance to adopt a binary structure for all these items. In those items that were not already dichotomous, both moderate and severe abnormalities were in the "impaired" profile, indicating that this subtle distinction could be unnecessary. Moreover, the MCA analysis with grouped items demonstrated a redundancy of several items. The refinements proposed above (i.e. removal of several items, dichotomisation of polytomous items and, potentially, grouped items) could make NAVEG even faster and easier to administer. Moreover, due to the nature of the testing items comprising NAVEG, there is no apparent need for cross-cultural validation.

Further studies will be needed to analyze the effect of development and brain lesions on profiles of visual function in order to provide proper validation of this potentially useful tool. Once validated, an attending neonatologist could have access to a rapid and easy-to-use tool, which may be potentially comparable to more complex existing and time consuming procedures. Finally, as this instrument has been designed to be used not only in the neonatal period, but also in infant age stages, NAVEG could also be useful in follow-up programs in "at risk" subjects such as pre-term infants.

5. Conclusion

The development of an assessment tool to evaluate visual function in newborns, focused on identifying those at higher risk of

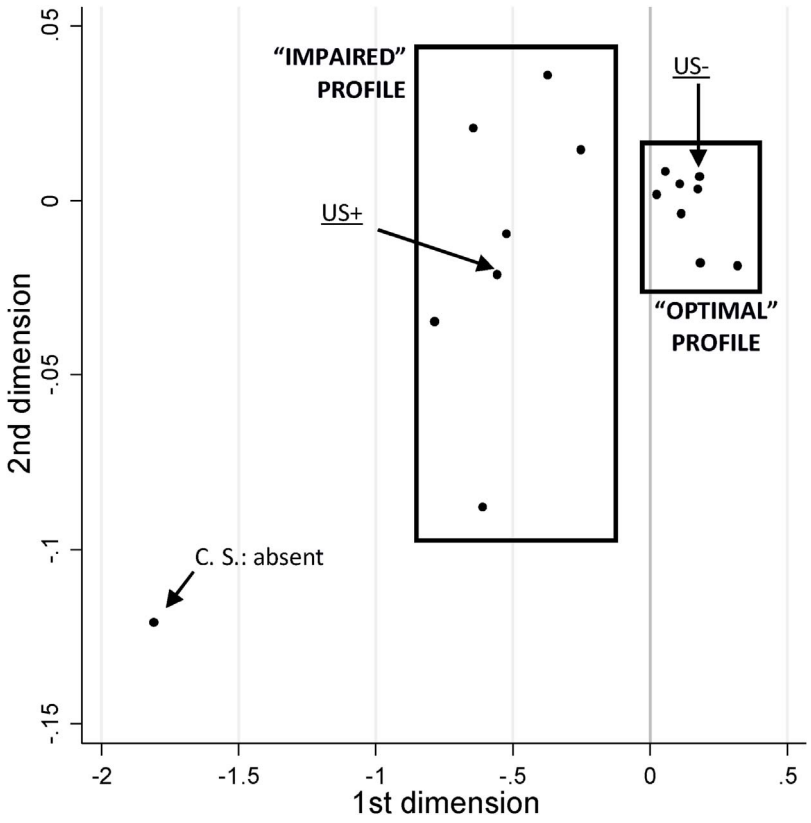

Fig. 4. Multiple Correspondence Analysis (grouped items).
Coordinates Plot: Multiple Correspondence Analysis of 7 grouped NAVEG items; supplementary variable: presence of brain lesions defined on the basis of ultrasound imaging ("US+" and "US-"). Normalization: principal coordinates. Explained variability: 1st dimension (horizontal) 90.77%; 2nd dimension (vertical) 0.40%; thus, the 2nd dimension is irrelevant (it is represented only for the sake of readability of the plot). Please note that the horizontal axis has 10× the scale of the vertical axis. Legend: "C. S." for Contrast Sensitivity.

neurological distress, is of utmost importance. Our assessment strategy proved to be sufficiently sensitive in discriminating subjects regarding the presence or absence of neurological impairment, defined on the basis of brain lesion assessment or neurological examination. Given the pilot and exploratory nature of this study, further research is necessary for a complete formal validation of NAVEG. Nevertheless, the results of the present study will be useful in the design of subsequent phases of our work and engage other centers in the process. Increasing attention to these issues could lead to the eventual development of a visual screening protocol suited for newborns in the neonatal and intensive care unit. It could also serve to integrate traditional ophthalmologic and neurologic evaluations. This is of particular importance given current evidence suggesting that the monitoring of visual function during the early stages of development may be helpful in following the maturation of the central nervous system and its potential reorganization as a result of brain damage (Atkinson et al., 2008). Early diagnosis of visual impairment is the key to early intervention aimed at minimizing the functional impact of disease through clinical care, visual habilitation, and mobility training (Rahi, Cumberland, Peckham, & British Childhood Visual Impairment Interest Group, 2010). The optimization of early intervention programs could improve the visual, neuromotor, and cognitive outcomes of all infants.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank Professor Claudine Amiel Tison for her continuous support of this project and for helpful suggestions regarding the preparation of this manuscript. We also thank the "Nati per vivere" association of Brescia, Italy for supporting this project. LBM is supported by the Research to Prevent Blindness/Lions Clubs International Foundation and National Institutes of Health (R01 EY019924-08).

References

Abdi, H., & Valentin, D. (2007). Multiple correspondence analysis. In N. Salkind (Ed.), *Encyclopedia of measurement and statistics* (pp. 2007–). Thousand Oaks, CA: Sage.

Amiel-Tison, C. (2002). Update of the Amiel-Tison neurologic assessment for the term neonate or at 40 weeks corrected age. *Pediatric Neurology*, *27*(3), 196–212.

Atkinson, J., Braddick, O., Anker, S., Nardini, M., Birtles, D., Rutherford, M. A., et al. (2008). Cortical vision, MRI and developmental outcome in preterm infants. *Archives of Disease in Childhood – Fetal and Neonatal Edition*, *93*(4), F292–F297.

Braddick, O., & Atkinson, J. (2011). Development of human visual function. *Vision Research*, *51*(13), 1588–1609.

Brown, A. M., & Yamamoto, M. (1986). Visual acuity in newborn and preterm infants measured with grating acuity cards. *American Journal of Ophthalmology*, *102*(2), 245–253.

Cavallini, A., Fazzi, E., Viviani, V., Astori, M. G., Zaverio, S., Bianchi, P. E., et al. (2002). Visual acuity in the first two years of life in healthy term newborns: An experience with the teller acuity cards. *Functional Neurology*, *17*(2), 87–92.

De Vries, L. S., Eken, P., & Dubowitz, L. M. (1992). The spectrum of leukomalacia using cranial ultrasound. *Behavioural Brain Research*, *49*(1), 1–6.

Dubowitz, L. M., Dubowitz, V., Morante, A., & Verghote, M. (1980). Visual function in the preterm and fullterm newborn infant. *Developmental Medicine & Child Neurology*, *22*(4), 465–475.

Fantz, R. L. (1963). Pattern vision in newborn infants. *Science*, *140*(3564), 296–297.

Fantz, R. L. (1965). Visual perception from birth as shown by pattern selectivity. *Annals of the New York Academy of Sciences*, *118*(21), 793–814.

Fazzi, E., Bova, S. M., Uggetti, C., Signorini, S. G., Bianchi, P. E., Maraucci, I., et al. (2004). Visual-perceptual impairment in children with periventricular leukomalacia. *Brain and Development*, *26*(8), 506–512.

Fazzi, E., Signorini, S. G., Bova, S. M., La Piana, R., Ondei, P., & Bertone, C. (2007). Spectrum of visual disorders in children with cerebral visual impairment. *Journal of Child Neurology*, *22*(3), 294–301.

Fazzi, E., Galli, J., & Micheletti, S. (2012). Visual impairment: A common sequel of preterm birth. *Neoreviews*, *13*(9), 542–550.

Fazzi, E. (2010). The effect of impaired vision on development. In G. Dutton, & M. Bax (Eds.), *Visual impairment in children due to damage to the brain: Clinics in developmental medicine* (pp. 162–173). London: Mac Keith Press.

Gosselin, J., Gahagan, S., & Amiel-Tison, C. (2005). The Amiel-Tison Neurological Assessment at Term: Conceptual and methodological continuity in the course of follow-up. *Mental Retardation and Developmental Disabilities Research Reviews*, *11*(1), 34–51.

Greenacre, M., & Blasius, J. (1994). *Correspondence analysis in the social sciences*. Academic Press.

Hubel, D. H., & Wiesel, T. N. (1979). Brain mechanisms of vision. *Scientific American*, *241*(3), 150–162.

Hyvärinen, L., Walthes, R., Jacob, N., Chaplin, K. N., & Leonhardt, M. (2014). Current understanding of what infants see. *Current Ophthalmology Reports*, *2*(4), 142–149.

Lanzi, G., Fazzi, E., Uggetti, C., Cavallini, A., Danova, S., Egitto, M. G., et al. (1998). Cerebral visual impairment in periventricular leukomalacia. *Neuropediatrics*, *29*(3), 145–150.

Leonhardt, M., Forns, M., Calderón, C., Reinoso, M., & Gargallo, E. (2012). Visual performance in preterm infants with brain injuries compared with low-risk preterm infants. *Early Human Development*, *88*(8), 669–675.

Matsuba, C. A., & Jan, J. E. (2006). Long-term outcome of children with cortical visual impairment. *Developmental Medicine & Child Neurology*, *48*(6), 508–512.

Mercuri, E., Baranello, G., Romeo, D. M., Cesarini, L., & Ricci, D. (2007). The development of vision. *Early Human Development*, *83*(12), 795–800.

Prechtl, H. F. (1974). The behavioural states of the newborn infant (a review). *Brain Research*, *76*, 185–212.

Rahi, J. S., Cumberland, P. M., Peckham, C. S., & British Childhood Visual Impairment Interest Group (2010). Improving detection of blindness in childhood: The british childhood vision impairment study. *Pediatrics*, *126*(4), 895–903.

Ricci, D., Cesarini, L., Groppo, M., De Carli, A., Gallini, F., Serrao, F., et al. (2008). Early assessment of visual function in full term newborns. *Early Human Development*, *84*(2), 107–113.

Ricci, D., Romeo, D. M., Serrao, F., Cesarini, L., Gallini, F., Cota, F., et al. (2008). Application of a neonatal assessment of visual function in a population of low risk full-term newborn. *Early Human Development*, *84*(4), 277–280.

Romeo, D. M., Ricci, D., Serrao, F., Gallini, F., Olivieri, G., Cota, F., et al. (2012). Visual function assessment in late preterm newborn. *Early Human Development*, *88*(5), 301–305.

Rossi, A., Gritti, M., Mattei, P., Semeraro, F., Chirico, G., Fazzi, E., et al. (2016). Visual profile in healthy fullterm newborns: Neonatal assessment visual european grid (NAVEG). In E. Fazzi, & P. E. Bianchi (Eds.), *Visual impairments and neurodevelopmental disorders: From diagnosis to rehabilitation* (pp. 133–141). Mariani Foundation Paediatric Neurology Series, John Libbey Eurotext.

Simard, M. N., Lambert, J., Lachance, C., Audibert, F., & Gosselin, J. (2011). Prediction of developmental performance in preterm infants at two years of corrected age: Contribution of the neurological assessment at term age. *Early Human Development*, *87*(December (12)), 799–804.

Volpe, J. J. (2008). Intracranial hemorrhage: Germinal matrix-intraventricular hemorrhage of the premature infant. In J. J. Volpe (Ed.), *Neurology of the newborn* (pp. 517–588). (5th ed.). Philadelphia: Saunders.