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Neonatal neurological examination in a resource-limited setting: What defines normal?

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ABSTRACT

Objective: To describe the results of the Hammersmith Neonatal Neurological Examination (HNNE) in a low-risk, term-born, contemporary sample in Ghana. Of particular interest was to compare these findings with the original British study that validated the HNNE, and published data from other low- and middle-income countries.

Study design: In a nested substudy of a larger prospective study (IMPRINT: Impact of Malaria in Pregnancy on Infant Neurodevelopment), 140 low-risk, term-born neonates (39.3 ± 1.4 weeks gestation) at Korle Bu Teaching Hospital in Accra, Ghana were administered the 34-item HNNE from birth to 48 h of age by trained physicians. Neonates' performance was compared with previously published normative data from the United Kingdom (1998), and published data from Thailand, Myanmar, Vietnam, and Uganda.

Results: Ghanaian neonates demonstrated lower scores on 29/34 HNNE items relative to normative data from the United Kingdom ($P < .05$), with only 5% of Ghanaian neonates in our sample classified as neurologically optimal. There were significant differences in the proportion of neonates scoring optimally per HNNE item between our Ghanaian sample, compared with published data from other settings (Thai [13/16 items], Burmese [14/16 items], Vietnamese [7/9 items], and Ugandan [22/34 items] neonates). Raw scores were markedly different between Ghanaian and British neonates, with Ghanaian neonates demonstrating lower median and wider range of scores. These differences were less prominent between Ghanaian and Ugandan neonates.

Conclusion: Our findings raise questions as to whether or not the thresholds for optimality for the HNNE based on data from the United Kingdom are applicable to Ghanaian newborns. Our study could not fully resolve whether the differences in scores were due to genetic differences in developmental pathways, the implementation of the assessment, or the characteristics of our sample. Low proportions of neonates scoring optimally from other low- and middle-income countries suggest the need for further research to determine the clinical utility of the HNNE in resource-limited settings, including the predictive value for neurodevelopment later in infancy.

Validated, structured neonatal neurologic assessments are clinical tools to identify neonates at risk of neurological abnormalities and neurodevelopmental impairments [1–4]. They can aid the interpretation of findings from neuroimaging by establishing the functional correlates of structural maturation and integrity of the central nervous system. Where resources limit the availability of neuroimaging, they may be the only feasible form of assessment. Specifically, neonatal neurologic assessments are strongly correlated with magnetic resonance imaging-identified qualitative measures of white and gray matter abnormality [5,6], white matter

Abbreviations: HNNE, Hammersmith Neonatal Neurological Examination; LMIC, Low- and Middle-Income Countries.

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fractional anisotropy [7], and cranial ultrasound results [8]. Studies have also shown predictive value to detect neuromotor and cognitive impairments in early childhood among infants born preterm [2], and among high-risk, term-born infants with hypoxic-ischemic encephalopathy, prenatal drug exposure, and cerebral palsy [9,10]. Thus, standardized neurologic assessments of the newborn serve the threefold purpose of screening for neurological abnormalities, tracking the progression of these abnormalities, and prognostic information for long-term outcomes [11].

The potential exposure to adversities during pregnancy and infancy in low- and middle-income countries (LMICs), including infectious diseases, poor nutrition, and limited access to high-quality antenatal and postnatal care, can negatively impact infant neurodevelopment. Globally, ~250 million children < 5 years, the majority residing in LMICs, are not attaining their full neurodevelopmental potential [12]. Hence, neonatal neurologic assessments are vital in these resource-limited settings to identify those in need of early intervention or support services and to provide a baseline to monitor their subsequent neurodevelopmental trajectory.

There are several challenges in incorporating standardized, structured neurologic assessments into routine neonatal care in LMICs where, due to limited access to neuroimaging, the need for them may be greatest. First, assessments can be time-consuming with most taking 20–30 min to complete [13], which may not be feasible in low-resource health systems with few health care providers. Second, formal training and specialized equipment, often available only in high-income countries, may be unaffordable [13]. Third, scoring and normative data for these assessments typically originate from high-income countries, which raises concerns over the use of assessment tools in populations other than the one in which they were developed [14]. Lastly, reliability and validity measures of these assessments in LMICs are infrequently reported, if reported at all, and thus their utility may be limited [15].

The Hammersmith Neonatal Neurological Examination (HNNE) was first published in 1981 and revised by Dubowitz et al. in 1998 [16]. It involves testing of 34 items across six subdomains (tone, tone patterns, reflexes, movements, abnormal signs/patterns, and orientation and behavior) spanning neurological and neurobehavioral components as well as the assessment of both lower-order (tone and primitive functions) and higher-order (early behavior) functions [17,18]. It requires no special equipment or formal training, the administration is quick (< 15 min), and has robust test characteristics including an inter-rater reliability > 96% [19]. The HNNE is used widely to classify neonates as either neurologically optimal (normal) or suboptimal (abnormal) during the newborn period. However, lower HNNE scores have been reported in low-risk, term-born neonates from Thailand, Myanmar [20], Vietnam [21], and Uganda [22], relative to the original normative data from the United Kingdom. Thus, the utility of the HNNE in LMICs remains unclear.

Accordingly, the objective of this study was to describe the results of the HNNE in a low-risk, term-born, contemporary sample in Ghana. The specific aims were:

1. To determine the distribution of HNNE scores and the proportion of Ghanaian neonates classified as neurologically optimal using the HNNE optimality scoring system based on previously published normative data from the United Kingdom.
2. To compare the distribution of HNNE scores and the proportion of Ghanaian neonates classified as neurologically optimal relative to previously published data from other LMICs including Thailand, Myanmar, Vietnam, and Uganda, matched on neonatal clinical characteristics.

1. Methods

1.1. Sample

This is a nested substudy of a larger single-center, hospital-based, prospective observational study (IMPRINT: Impact of Malaria in Pregnancy on Infant Neurodevelopment). The IMPRINT study aimed to compare neonatal neurological outcomes of infants exposed to malaria in pregnancy with those of unexposed infants. Participants were recruited from Korle Bu Teaching Hospital in Accra, the largest tertiary teaching hospital in Ghana, with approximately 10,000 live births annually. This hospital is the leading referral center in the region, as well as for primary and secondary health facilities in the southern part of the country with a catchment area of 50 km radius and a population of > 3 million [23]. From November 2018 to February 2019, pregnant women presenting during the early stages of labor were consented, recruited, and their neonates enrolled after birth. In total, 310 neonates were enrolled in the IMPRINT study, of whom 140 were eligible for this nested substudy (see Appendix: Study sample flow diagram). The inclusion criteria were similar to Dubowitz et al. [16]: 1) $\geq$ 37 and $\leq$ 42 weeks gestation at birth, 2) Apgar score $\geq$ 5 at 1 min, and 3) Apgar score $\geq$ 7 at 5 min. Given the context of this substudy, the following additional inclusion criteria were also applied: 4) $\geq$ 2500 and < 4300 g birthweight, 5) no admission to the Neonatal Intensive Care Unit, and 6) no evidence of maternal pregnancy complications, including gestational diabetes, human immunodeficiency virus infection, hypertension, malaria, pre-eclampsia, or premature rupture of membranes. Neonates in the original HNNE optimality scoring sample were also excluded if their cord artery pH levels were < 7.2; however, cord blood gases are not routinely measured in Ghana, so this was not applicable. Maternal and neonatal clinical data were extracted from medical records. Gestational age was based on estimates from ultrasound results and/or the date of last menstrual period obtained from maternal medical records. The study protocol was approved by the institutional review board of the University of Ghana and The University of Queensland, Australia. Written informed consent was obtained from all mothers.

1.2. Measures

Neonates were administered the HNNE once between birth and 48 h of age in the postnatal ward. The postnatal age at the time of assessment was not recorded. The examination was conducted by a team of six trained physicians with proven competency in neonatal examinations who were recruited solely for the IMPRINT study and were not engaged in other clinical responsibilities for the study duration. To minimize potential assessor bias, ~80% of examinations were undertaken by two physicians.

No formal training is required for the HNNE and there is no formal process for credentialing examiners. Over one week, physicians were trained exclusively on the HNNE using 'The neurological assessment of the preterm and full-term newborn infant (2nd ed., 1999)' [24] as a primary resource, alongside videos [25], live demonstrations, observations, and practice assessments on neonates in the postnatal ward with oversight by the first author. The training session included parallel scoring for each HNNE item, with feedback provided for administration, scoring, and interpretation of every item. Any errors in implementation of an item was corrected and the item repeated by the assessor. The examinations were not double-scored but were scored collectively by the group at the same time, with each item administration and scoring supervised by the first author. As the HNNE has a demonstrated inter-rater reliability > 96% even with inexperienced assessors [19], inter-

rater reliability was not conducted for this study. Videos were not taken of the HNNE administration for external scoring.

The standardized HNNE proforma was used [16]. To compare between samples, the pre-specified optimality score cut-offs from the original Dubowitz et al. publication were applied by the first author once all data had been collected and entered [16]. According to these cut-offs, the scores for each item are classified as optimal (> 10th centile, scored 1), borderline (5th–10th centile, scored 0.5), and suboptimal (< 5th centile, scored 0), with a maximum total score of 34. Total scores < 30.5 are considered suboptimal.

1.3. Data analysis

Data were analyzed using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Based on the distribution of data, Chi^2 or Fisher's exact tests and Kruskal-Wallis or Student's *t* tests were used to determine significant differences in neonatal and maternal clinical characteristics, and the proportions of neonates classified as optimal vs. suboptimal. A significance level of .05 was used throughout inferential analysis.

Subgroup analyses were undertaken for gestational age group. First, the proportion of Ghanaian neonates scoring optimally was calculated using the Dubowitz et al. optimality scoring system [26]. Second, the median and range of raw scores of the Ghanaian sample were compared with the original normative data generated from the United Kingdom in 1998 [26]. Third, the median and range of raw scores of the Ghanaian sample were compared with published data from three groups of low-risk, term-born neonates from LMICs. The first group was recruited in 1995–97 from Siriraj Hospital, Bangkok, which is the largest tertiary teaching hospital in Thailand. The second group was recruited in 1995–97 from the Maela refugee camp on the Thailand-Myanmar border, with three-quarters of the population from Karen/Kayin State in Myanmar (hereon referred to as Karen group). The results of the Thai and Karen neonates were published together [20]. The third group was recruited in 1999 from Hung Vuong Maternity Hospital, Ho Chi Minh City, Vietnam [21]. Lastly, the Ghanaian sample was compared with published data from a group of term-born neonates recruited in 2007 from Mulago University Hospital, a major public hospital in Kampala, Uganda [22]. The Thai, Karen, and Vietnamese neonates were examined using a shortened proforma [20], while Ugandan neonates were examined using the full proforma.

2. Results

2.1. Ghanaian sample vs. normative data from the United Kingdom

There were no significant differences in maternal demographic characteristics between the infants included in this nested substudy and the remaining infants included in the larger IMPRINT study, though significantly more excluded mothers had a history of a sexually transmitted infection ($P < .001$). In total, 140 low-risk, term-born neonates (136 Ghanaian, 2 Nigerian, 1 Ivorian, 1 Malian ethnicity) were assessed; 35 neonates were not in the correct state and could not be administered all items, therefore data for all 34 items were available for 75% (105/140) of neonates enabling computation of the total HNNE score. The Ghanaian sample had lower mean gestational age (39.3 ± 1.4 weeks) than the original British sample ($n = 224$; 40.2 weeks). Table 1 describes the neonatal and maternal clinical characteristics of the two groups. Regarding social characteristics, 22% of Ghanaian mothers were illiterate and 12% had not worked in the previous 12 months. No social characteristics of the original British sample were provided.

The total mean score of the Ghanaian sample was significantly lower than the United Kingdom sample from 1998 (25.3 ± 3.6 vs. 32.9 ± 1.8; $P < .001$). Furthermore, only 5/105 (5%) neonates scored ≥ 30.5 and were classified as neurologically optimal according to the British HNNE optimality scoring system. Table 2 shows the proportions of neonates scoring optimally for each of the 34 items. Using the pre-specified cut-offs (Table 2), significantly fewer neonates scored within the optimal category across 29/34 items ($P < .001$). However, there was no significant difference for arm recoil, popliteal angle, flexor tone 1, neck extensor tone (horizontal), and Moro reflex.

When scores were condensed into the six subdomains, the proportion of Ghanaian neonates classified as optimal were lower relative to the United Kingdom ($P < .001$). Specifically, 36%, 35%, 69%, 20%, 43%, and 22% were classified as optimal for tone, tone patterns, reflexes, movements, abnormal signs/patterns, and orientation and behavior subdomains, respectively, relative to ≥ 95% for each subdomain for the United Kingdom sample.

Supplementary Table 1 provides a comparison of the range and median scores for each of the 34 items and their corresponding subdomains. For tone, the median score was the same for leg recoil but was consistently lower for Ghanaian neonates compared with the United Kingdom for the remaining 9 items. The range of scores > 10th centile was similar in 1 item (arm recoil) and different in the remaining 9 items, with the range of scores conistently wider for Ghanaian neonates.

In terms of tone patterns, the median score was the same across both groups of neonates for all items. The range of scores > 10th centile was similar for 2 items (flexor tone 1, neck extensor tone [horizontal]) and different for the remaining 3 items.

Regarding reflexes, the median scores were similar across the Ghanaian and United Kingdom samples for 4/6 items (tendon reflex, suck/gag, palmar and plantar grasp, and Moro reflex). The median was 1 score lower for placing reflex among Ghanaian neonates. The range of scores > 10th centile was similar for tendon and Moro reflex but wider among Ghanaian neonates for the remaining 4 items.

For the 3 items assessing movements, the median score was the same for the quantity and quality of spontaneous movements but different for head raising in prone, with a lower median score for Ghanaian neonates. There were no similarities in the range of scores > 10th centile, with Ghanaian neonates demonstrating a wider range of scores.

Similar profiles were evident for the abnormal signs/patterns subdomain; median scores were the same for 2/3 items (tremors, startles) but different for abnormal hand/toe posture. The range of scores > 10th centile was different for 2/3 items (abnormal hand/toe postures, startles) and similar for tremors.

Finally, for the orientation and behavior subdomain, median scores were the same for 3/7 items (eye appearances, irritability, and cry), but were 0.5 scores lower among Ghanaian neonates for consolability, 1 score lower for auditory orientation and alertness, and 2 scores lower for visual orientation. There was no similarity in the range of scores > 10th centile for any item.

2.2. Ghanaian sample vs. published data from Thailand and Myanmar

Data for Thai and Karen neonates were extracted from McGready et al., allowing comparison of 46 Thai and 61 Karen neonates born between 38 and 40 weeks gestation with gestational age-matched Ghanaian neonates from this study ($n = 68$). Ghanaian neonates had a lower gestation than Thai (38.9 ± 0.7 vs. 39.1 ± 0.6 weeks; $P = .11$) and Karen neonates (38.9 ± 0.7 vs. 39.2 ± 0.5 weeks; $P = .006$). Ghanaian neonates were heavier at birth relative to Thai (3155 ± 372 vs. 2985 ± 395 g; $P = .02$) and Karen (3155 ± 372 vs. 2942 ± 338 g; $P < .001$) neonates.

Table 1
Neonatal and maternal clinical characteristics among samples from Ghana and the United Kingdom [16].

Characteristics	Ghana, % [n/N]	United Kingdom, % [n/N]	*P*
Neonatal Clinical			
Gestational age at birth			
37 weeks	10 [14/140]	4 [9/224]	.001
38 weeks	33 [47/140]	19 [42/224]	
39 weeks	19 [26/140]	29 [65/224]	
40 weeks	19 [26/140]	28 [63/224]	
41 weeks	13 [18/140]	16 [36/224]	
42 weeks	6 [9/140]	4 [9/224]	
Birthweight for gestational age, mean ± SD[a]			
37 weeks	3111 ± 331	2846	–
38 weeks	3035 ± 330	3186	
39 weeks	3339 ± 340	3418	
40 weeks	3238 ± 402	3449	
41 weeks	3437 ± 291	3676	
42 weeks	3136 ± 445	3775	
Apgar score 1 min			
5	3 [4/140]	–	
6	9 [13/140]	–	
7	28 [39/140]	–	
8	57 [80/140]	–	
9	3 [4/140]	–	
Apgar score 5 min			
7	2 [3/140]	–	
8	33 [46/140]	–	
9	63 [88/140]	–	
10	2 [3/140]	–	
Maternal Clinical			
Age at childbirth			
≤ 30 years	47 [65/139]	42 [94/224]	.37
Parity			
Primipara	26 [36/140]	52 [116/224]	< .001
Mode of delivery			
Spontaneous vaginal	35 [49/140]	57 [128/224]	< .001
Cesarean section	64 [90/140]	22 [49/224]	
Vacuum extraction/forceps	1 [1/140]	21 [47/224]	

[a] SD of the United Kingdom sample was not provided.

The abridged version of the HNNE was administered to Thai and Karen neonates. Using the optimality scoring system [16,20], 16/34 items were scored. Table 3 shows the proportions of neonates across these three groups scoring optimally for each item. Relative to Karen neonates, a significantly higher proportion of Ghanaian neonates scored optimally for 4/16 items (head lag, visual orientation, tremors, and alertness), whereas, more Karen neonates scored optimally for 10/16 items. A significantly higher proportion of Ghanaian neonates scored optimally for 2/16 items (arm recoil, tremors), whereas more Thai neonates scored optimally for 11/16 items. Across the three groups, there was no significant difference in the proportions of neonates scoring optimally for the popliteal angle.

2.3. Ghanaian sample vs. published data from Vietnam

Data for Vietnamese neonates were extracted from Hieu et al. [21] allowing comparison of 58 Vietnamese neonates born between 38 and 42 weeks gestation with gestational age matched Ghanaian neonates from this study ($n = 117$). Ghanaian neonates had a lower gestation than Vietnamese neonates (39.4 ± 1.1 vs. 39.9 ± 0.8 weeks; $P = .002$). Also, 62% (72/117) of Ghanaian neonates were delivered by cesarean section whereas all Vietnamese neonates had vaginal births. Birthweight (3210 ± 374 vs. 3061 ± 350 g; $P = .01$) and head circumference (34.2 ± 1.4 vs. 32.0 ± 1.3 cm; $P < .001$) were greater in Ghanaian than Vietnamese neonates. Furthermore, Ghanaian and Vietnamese mothers had a significantly different age at childbirth (31 ± 5.9 vs. 26 ± 5.4 years; $P < .001$), weight (80.4 ± 15.1 vs 56 ± 6.2 kg; $P < .001$), and height (160 ± 7.2 vs 155 ± 4.6 cm; $P < .001$), respectively.

When Vietnamese neonates were administered the abridged HNNE and scored by Hieu et al. [21] using the optimality scoring system [16], they had a lower total score, with 50% scoring > 10th centile of the United Kingdom data (equating to total score ≥22.5) [21]. Using the same 10th centile cut-off, 81% (85/105) of Ghanaian neonates were classified as neurologically optimal.

Table 4 shows the proportions of Ghanaian and Vietnamese neonates scoring optimally for 9/34 items. A significantly higher proportion of Vietnamese neonates scored optimally for head control 1, head control 2, ventral suspension, startles, and alertness, whereas, a higher proportion of Ghanaian neonates scored optimal for posture and Moro reflex. There was no significant difference for head lag or placing reflex.

2.4. Ghanaian sample vs. published data from Uganda

Data for Ugandan neonates were extracted from Hagmann et al. [22] allowing comparison of 44 Ugandan neonates born between 37 and 42 weeks gestation with gestational age matched Ghanaian neonates from this study ($n = 140$). There was no significant difference in gestation (39.3 ± 1.4 vs. 39.4 ± 1.4 weeks, $P = .68$), birthweight, or head circumference. However, a significantly higher number of Ugandan mothers were primipara, compared with Ghanaian mothers (26% vs. 44%; $P < .001$) and more Ghanaian neonates were delivered by cesarean section relative to Ugandan neonates (64% vs. 41%; $P < .001$).

In terms of the total HNNE score, Ghanaian neonates had a significantly lower score than Ugandan neonates (25.3 ± 3.6 vs.

Table 2
Proportion of neonates with optimal scores on the HNNE among samples from Ghana and the United Kingdom [16].

HNNE Items	Optimal Score	Ghana, % [n/N]	United Kingdom, % [n/N]	*P*
Tone				
Posture	4	39 [54/140]	90 [202/224]	< .001
Arm recoil	3, 4	94 [131/140]	92 [206/224]	.57
Arm traction	3, 4	76 [107/140]	99 [222/224]	< .001
Leg recoil	4	61 [86/140]	91 [204/224]	< .001
Leg traction	3, 4	78 [109/140]	96 [215/224]	< .001
Popliteal angle	3, 4	88 [123/140]	90 [202/224]	.49
Head control 1	3, 4	67 [94/140]	94 [211/224]	< .001
Head control 2	3, 4	60 [84/140]	96 [215/224]	< .001
Head lag	2.5, 3, 4	49 [68/140]	91 [204/224]	< .001
Ventral suspension	3, 4	42 [59/140]	91 [204/224]	< .001
Tone Patterns				
Flexor tone 1	2, 3, 4	97 [136/140]	99 [222/224]	.21
Flexor tone 2	3	69 [96/140]	99 [222/224]	< .001
Leg extensor tone	3, 4	71 [100/140]	92 [206/224]	< .001
Neck extensor tone (sitting)	3	77 [108/140]	94 [211/224]	< .001
Neck extensor tone (horizontal)	2, 3, 4	100 [140/140]	100 [224/224]	1.0
Reflexes				
Tendon	2, 3	90 [125/139]	99 [222/224]	< .001
Suck/gag	3	78 [107/138]	92 [206/224]	< .001
Palmar grasp	3, 4	82 [114/139]	93 [208/224]	.002
Plantar grasp	3	73 [102/139]	98 [220/224]	< .001
Placing	2, 3	71 [90/139]	99 [222/224]	< .001
Moro	3, 4	96 [135/140]	99 [222/224]	.11
Movements				
Spontaneous movements (quantity)	4	64 [89/138]	92 [206/224]	< .001
Spontaneous movements (quality)	4	72 [100/138]	93 [208/224]	< .001
Head raising in prone	3, 4	31 [42/137]	90 [202/224]	< .001
Abnormal Signs/Patterns				
Abnormal hand/toe postures	2, 3	85 [99/116]	97 [217/224]	< .001
Tremors	2, 3	94 [131/139]	100 [224/224]	< .001
Startles	2	44 [61/138]	94 [211/224]	< .001
Orientation and Behavior				
Eye appearances	2	80 [111/138]	92 [206/224]	.001
Auditory orientation	2, 3, 4	77 [105/137]	100 [224/224]	< .001
Visual orientation	3, 4	32 [41/130]	92 [206/224]	< .001
Alertness	3, 4	36 [48/133]	97 [217/224]	< .001
Irritability	2	55 [76/139]	93 [208/224]	< .001
Cry	3	57 [79/138]	92 [206/224]	< .001
Consolability	2, 3, 4	74 [103/139]	98 [220/224]	< .001

Table 3
Proportion of neonates with optimal scores on the HNNE among samples from Ghana, Myanmar, and Thailand [20].

HNNE Items	Ghana, % [n/N]	Myanmar, % [n/N]	*P**	Thailand, % [n/N]	*P***
Tone					
Posture	63 [43/68]	100 [60/60]	< .001	98 [45/46]	< .001
Arm recoil	94 [64/68]	97 [58/60]	.40	72 [33/46]	.001
Arm traction	81 [55/68]	97 [58/60]	.005	98 [41/42]	.008
Leg recoil	78 [53/68]	98 [59/60]	< .001	100 [46/46]	< .001
Leg traction	76 [52/68]	93 [56/60]	.007	96 [43/45]	.005
Popliteal angle	88 [60/68]	82 [49/60]	.21	94 [43/46]	.28
Head control 1	65 [44/68]	88 [52/59]	.002	91 [41/45]	.001
Head control 2	60 [41/68]	78 [46/59]	.03	98 [44/45]	< .001
Head lag	71 [48/68]	17 [10/60]	< .001	70 [32/46]	.53
Ventral suspension	40 [27/68]	90 [54/60]	< .001	91 [42/46]	< .001
Abnormal Signs/Patterns					
Tremors	96 [65/68]	62 [37/60]	< .001	82 [37/45]	.02
Startles	43 [29/67]	87 [52/60]	< .001	97 [31/32]	< .001
Orientation and Behavior					
Auditory orientation	76 [51/67]	100 [59/59]	< .001	98 [45/46]	.001
Visual orientation	26 [16/62]	7 [4/59]	.004	85 [33/39]	< .001
Alertness	34 [22/64]	7 [4/59]	< .001	78 [31/40]	< .001
Consolability	76 [51/67]	100 [57/57]	< .001	87 [39/45]	.13

*Ghana vs. Myanmar; **Ghana vs. Thailand.

29.7 ± 3.5; $P < .001$). This pattern persisted even after stratifying the groups by gestational age at birth (i.e., 37–38 weeks, 39–40 weeks, and 41–42 weeks). Table 5 shows the proportions of Ghanaian and Ugandan neonates scoring optimally for each item, with significant differences between the two groups evident in 22 items. A significantly higher proportion of Ugandan neonates scored optimally for 19/22 items, while a higher proportion of Ghanaian neonates scored optimal for the remaining 3 items, namely posture, neck

Table 4
Proportion of neonates with optimal scores on the HNNE among samples from Ghana and Vietnam [21].

HNNE Items	Ghana, % [n/N]	Vietnam, % [n/N]	*P*
Tone			
Posture	58 [68/117]	33 [19/58]	.001
Head control 1	65 [76/117]	83 [48/58]	.01
Head control 2	61 [71/117]	81 [47/58]	.005
Head lag	67 [78/117]	57 [33/58]	.14
Ventral suspension	44 [51/117]	76 [44/58]	< .001
Reflexes			
Placing	70 [81/116]	70 [40/57]	.56
Moro	74 [87/117]	45 [26/58]	< .001
Abnormal Signs/Patterns			
Startles	44 [51/115]	76 [44/58]	< .001
Orientation and Behavior			
Alertness	37 [41/111]	64 [34/53]	.001

extensor tone (horizontal), and the quality of spontaneous movements. There was no significant difference for 12 items (arm recoil, arm traction, leg recoil, leg traction, popliteal angle, flexor tone 1, neck extensor tone [sitting], tendon reflex, palmar grasp, suck/gag reflex, Moro reflex, and tremors).

Supplementary Table 2 provides a comparison of the range and median values of raw scores for each item in their corresponding subdoamins. For tone, median scores were the same for 3 items (posture, arm traction, and leg recoil) but differed for the remaining 7 items. The range of scores > 10th centile was similar for 5/10 items (posture, arm recoil, leg recoil, head control 1, and ventral suspension).

For tone patterns, the median score was the same for both groups for all items. The range of scores > 10th centile was similar for 1 item (neck extensor tone [sitting]) only. A wider range of scores was evident for Ghanaian neonates across 3 of the remaining 4 items.

Regarding reflexes, the median scores were similar for Ghanaian and Ugandan neonates for 3/6 items (tendon, suck/gag, and plantar grasp). The median was 1 score lower for palmar grasp and placing reflex and 0.5 scores higher for Moro reflex among Ghanaian neonates. The range of scores > 10th centile was similar for tendon and Moro reflex; however, Ghanaian neonates showed a wider range of scores for the remaining 4 items.

For the 3 items assessing movements, the median score was the same for the quantity of spontaneous movements. However, Ghanaian neonates demonstrated a higher median score for the quality of spontaneous movements and a lower median score for head raising in prone, relative to Ugandan neonates. The range of scores > 10th centile was similar for 1/3 items (quality of spontaneous movements); Ghanaian neonates had a wider range for the remaining 2 items.

Within the abnormal signs/patterns subdomain, median scores were the same for all items. The range of scores > 10th centile was different for all items between Ghanaian and Ugandan neonates.

Table 5
Proportion of neonates with optimal scores on the HNNE among samples from Ghana and Uganda [22].

HNNE Items	Optimal Score	Ghana, % [n/N]	Uganda, % [n/N]	*P*
Tone				
Posture	4	39 [54/140]	18 [8/44]	.01
Arm recoil	3, 4	94 [131/140]	98 [43/44]	.46
Arm traction	3, 4	76 [107/140]	91 [40/44]	.051
Leg recoil	4	61 [86/140]	52 [23/44]	.28
Leg traction	3, 4	78 [109/140]	84 [37/44]	.27
Popliteal angle	3, 4	88 [123/140]	93 [41/44]	.41
Head control 1	3, 4	67 [94/140]	86 [38/44]	.01
Head control 2	3, 4	60 [84/140]	91 [40/44]	< .001
Head lag	2.5, 3, 4	49 [68/140]	70 [31/44]	.01
Ventral suspension	3, 4	42 [59/140]	77 [34/44]	< .001
Tone Patterns				
Flexor tone 1	2, 3, 4	97 [136/140]	98 [43/44]	.66
Flexor tone 2	3	69 [96/140]	100 [44/44]	< .001
Leg extensor tone	3, 4	71 [100/140]	89 [39/44]	.02
Neck extensor tone (sitting)	3	77 [108/140]	84 [37/44]	.20
Neck extensor tone (horizontal)	2, 3, 4	100 [140/140]	93 [41/44]	.01
Reflexes				
Tendon	2, 3	90 [125/139]	93 [41/44]	.77
Suck/gag	3	78 [107/138]	91 [40/44]	.051
Palmar grasp	3, 4	82 [114/139]	86 [38/44]	.50
Plantar grasp	3	73 [102/139]	93 [41/44]	.006
Placing	2, 3	71 [90/139]	98 [43/44]	< .001
Moro	3, 4	96 [135/140]	91 [40/44]	.22
Movements				
Spontaneous movements (quantity)	4	64 [89/138]	82 [36/44]	.03
Spontaneous movements (quality)	4	72 [100/138]	16 [7/44]	< .001
Head raising in prone	3, 4	31 [42/137]	59 [26/44]	.001
Abnormal Signs/Patterns				
Abnormal hand/toe postures	2, 3	85 [99/116]	98 [43/44]	.03
Tremors	2, 3	94 [131/139]	98 [43/44]	.69
Startles	2	44 [61/138]	80 [35/44]	< .001
Orientation and Behavior				
Eyes appearances	2	80 [111/138]	95 [42/44]	.01
Auditory orientation	2, 3, 4	77 [105/137]	98 [43/44]	.001
Visual orientation	3, 4	32 [41/130]	75 [33/44]	< .001
Alertness	3, 4	36 [48/133]	86 [38/44]	< .001
Irritability	2	55 [76/139]	80 [35/44]	.003
Cry	3	57 [79/138]	98 [43/44]	< .001
Consolability	2, 3, 4	74 [103/139]	93 [41/44]	.006

Finally, for the orientation and behavior items, median scores were the same for 3/7 items (eye appearances, irritability, and cry). There was no similarity in the range of scores above the 10th centile for any item.

3. Discussion

This study described the results of the HNNE in a sample of low-risk, term-born Ghanaian neonates born in a tertiary care referral hospital. Neonates were scored using the HNNE optimality scoring system, published in 1998 and developed using normative data from a sample of 224 neonates born in the United Kingdom. The extent of similarities and differences in the HNNE scores in Ghana and other LMICs were also documented. The profile of HNNE scores of neonates in Ghana and published results from other resource-limited settings differed significantly from the normative British data published in 1998, both for total HNNE score and for sub-domain scores. These findings suggest that structured neurologic assessments that have been standardized in a high-income setting could overestimate the number of at-risk neonates in LMICs. Specifically, only 5% of low-risk, term-born neonates in Ghana were classified as neurologically "optimal" (normal), despite similar neonatal clinical characteristics to the normative British sample.

To our knowledge, this is one of the largest studies to date comparing HNNE results between LMICs. Methodological strengths include that the sample was drawn from a contemporary urban population in an LMIC, using inclusion criteria similar to those used for the normative British sample; the use of a well-validated, structured neurologic assessment; and the recruitment of a competent team of local physicians exclusively for this study. However, certain limitations must be acknowledged. First, this is a single-center sample from a tertiary referral care hospital, which may select for more difficult pregnancies, and thus we cannot exclude unmeasured adversities as a cause for either part or all of the differences in HNNE results seen in this study. However, efforts were made to exclude neonates with any evidence of prenatal and perinatal adversities (see Appendix) to try to select a low-risk sample. Given this is a hospital-based sample, there is potential for sampling bias as the sample may not be representative of all Ghanaian infants. Second, inter-rater variability was not measured, and systematic differences in the administration and/or interpretation of the examination between the teams in Ghana and the United Kingdom remain a possibility. McGready et al., working in Thailand, developed an abridged HNNE proforma because the administration of some test items proved difficult for paramedical staff from nonmedical backgrounds [20]. However, the physicians in this study were trained in the HNNE as well as in the Ballard Maturational Assessment and other neonatal assessments which have similar items, thus avoiding these problems. Lastly, the dates for recruitment of the British (1998), Thai (1995–97), Vietnamese (1999), and Ugandan (2007) samples span over 20 years; as antenatal and postnatal care have changed over the past 20 years, it is likely that the outcomes of neonates may have differed over time.

Systematic differences in the sample and/or examination conditions could partially account for the differences in scoring. While the measured clinical characteristics of the Ghanaian sample strongly resembled those of the original normative sample from the United Kingdom, unmeasured confounders (e.g., maternal intrapartum sedation, postpartum analgesics, neonatal feeding management, or hypoglycemia) could render our sample less "low-risk" than we intended. The Ghanaian neonates had somewhat lower Apgar scores, with only 2% scoring 10/10 at 5 min, but the clinical significance of this is uncertain. Similarly, Hagmann et al. [22] included only neonates with an Apgar score $\geq$ 8 at 5 min (compared with $\geq$ 7 in other samples), which may account for the slightly better performance in their sample. Lower Apgar scores can reflect poorer condition at birth, which could result in reduced muscle tone and excitability scores in the HNNE [27]. However, the importance of the small difference in Apgar scores is uncertain; despite being the most widely used "severity of illness" score in any age-group worldwide, there is still subjectivity in Apgar scoring. For example, it has been recognized in recent years that normal neonates can take up to 10 min to achieve acyanotic oxygen saturation levels [28]. This might have led to the routine assignment of lower sub-scores for "color" in healthy neonates in the much more recent epoch when our study was performed.

It is also plausible that the timing of assessments impacted the scoring. Due to a limited time window to assess Ghanaian neonates prior to discharge, our study infants were examined from birth to 48 h, whereas the British infants were examined from 6 to 48 h. Importantly, Thai and Karen infants were assessed between 6 h and 5 days of life [20]; it is not clear what proportion of neonates were assessed at > 48 h, making it possible that older infants were included. This could explain why these infants performed somewhat better than our sample. Birth involves substantial physiological changes for the neonate, raising the possibility that even a few hours of postnatal age difference can impact the HNNE scores, especially in the first 12–24 h after birth. In Uganda, infants assessed between 48 and 96 h of age exhibited higher mean HNNE scores, though this did not reach statistical significance [22]. In contrast, another study reports that HNNE results were similar in neonates assessed before and after 6 h of age [29]. When the HNNE was administered to neonates at 0–3 h or 3–6 h and reassessed at 48 h, the results across the three time points were the same for 23/34 items [29]. In the remaining 11 items the range of scores above the 10th centile were similar across the three time points, and thus the scores considered in the optimal range were similar regardless of the time of assessment; only median scores were seen to differ at 0–3 h for 6/11 of these items relative to neonates assessed at 3–6 h [29]. Visual orientation was the only item that showed consistent improvement with postnatal age, with median scores increasing over time, which could reflect an improvement in the visual function as exposure to light increases [29]. Visual orientation is seen to improve in full-term neonates as age increases from 48 to 72 h after birth [30]. The proportion of neonates scoring optimally for the visual orientation items was significantly poorer in Karen [20], Ugandan [22], and Ghanaian infants relative to British infants, but similar in Thai and British infants. It is possible that these differences could be reflective of postnatal age at assessment.

Another plausible reason for poorer visual responsiveness in the Ghanaian sample and the generally lower behavior subdomain scores could be the examination conditions. Neonates in Ghana were assessed in the postnatal ward of a large public hospital as it was not feasible to conduct the assessments in a separate room due to resource limitations. In contrast, the neonates in Uganda were assessed in a room adjacent to the postnatal ward, which may have resulted in relatively better testing conditions and consequently higher behavior scores. Nonetheless, it is noteworthy that the testing conditions in Ghana are typical of health care settings in LMICs. Although it does not seem the most likely explanation, if the test environment is so critical as to account for the difference between the original British results and ours, it will be important to measure the extent of differences and specify this in test instructions for the future. Furthermore, improving the precision of the assessment items within the constraints of a resource-limited setting is important to address.

Another potential explanation for the differences seen between the Ghanaian sample and the original British sample could be that the mean gestational age of the Ghanaian sample was one week lower (39.3 vs. 40.2 weeks), and the less mature infant would be

expected to have lower HNNE scores. However, in our Ghanaian sample there was no significant difference in total HNNE score when adjusted for gestational age. Additionally, gestational dating of Ghanaian neonates may have some inherent inaccuracy due to the distribution of timing of ultrasound scans. The first ultrasound took place in the first trimester for 19% (26/140), second trimester for 38% (53/140), third trimester for 39% (55/140) and was not recorded for 4% (6/140) of women. Given the high proportion of third trimester ultrasounds, which are known to be less accurate for gestational age dating than first and second trimester ultrasounds [31], it is possible that there is some misclassification of infant gestational age. While random error could explain increased scatter in HNNE results, it should not have altered the measures of central tendency. No details were given regarding the method of gestational age assessment in the Ugandan samples. The Vietnamese, Thai, and Karen studies used the Dubowitz Examination for Gestational Age, which has been shown to date 95% of pregnancies within ± 2.9 weeks [32]. However, gestational age of the original British sample may have been more accurate because in most cases it was calculated from ultrasound scans performed at 14–16 weeks gestation, though second trimester ultrasounds are still less accurate that those in the first trimester [16]. While we think it unlikely that error in gestation assessment fully accounted for our results, given the importance of gestation on HNNE scoring, achieving accurate gestational assessment should be emphasized wherever it is used.

Profiling the discrepancies in the optimality scoring of the HNNE between published data from the United Kingdom and LMICs highlighted major differences in tone items, particularly reduced truncal tone, posture, ventral suspension, head lag, and visual responsiveness. However, median scores for all items within the tone patterns subdomain were similar for neonates across Ghana, Uganda, and the United Kingdom. Tone patterns have been considered a robust marker of neonatal neurological integrity [33]. For example, increased head and leg extensor tone have been found in term-born neonates with basal ganglia lesions and preterm neonates with periventricular leukomalacia [33]. Given that nearly 70% and 85% of all low-risk, term-born Ghanaian and Ugandan neonates respectively scored optimal (normal) for all items in the tone pattern subdomain, it may be more useful to consider optimal scores in the tone patterns subdomain as a maker of neurological integrity, as opposed to relying on the predictive ability of the tone items subdomain.

McGready et al. attributed lower tone items subdomain scores to the high use of peripartum maternal sedation in their Thai sample [20]. Given that a higher proportion of the Ghanaian sample (64%) was delivered by cesarean section (which is usually done under spinal epidural at Korle Bu Teaching Hospital), as compared with the Ugandan (41%), British (22%), and Vietnamese (0%) studies, it is possible that postnatal analgesia impaired performance in tone items. Although Dubowitz et al. reported no significant difference in the mean optimality scores of neonates delivered by cesarean section, a trend towards lower scores was evident [19]. Anesthesia used for cesarean section has been associated with reduced muscle tone and sucking up to 24 h post-delivery, and reduced muscle tone, orientation, and alertness up to 6 weeks of age [34] but because of the high rates of use of regional anesthesia for operative deliveries at Korle Bu Teaching Hospital, maternal anesthesia is unlikely to account for the lower scores seen in Ghanaian neonates. While it is possible that postpartum analgesia had an unmeasured impact, when Ghanaian infants were stratified by mode of delivery, there was no difference in total HNNE score between infants delivered by cesarean vs. vaginally (25.47 ± 3.6 vs. 24.99 ± 3.6; $P = .52$). Therefore, it is unlikely that cesarean section, anesthesia, or the use of postpartum analgesia can fully explain the differences seen between our samples.

Being a tertiary referral center, rates of cesarean section have been recorded at much higher rates in Korle Bu Teaching Hospital (43% of deliveries; 70% emergency, 30% elective) compared with other hospitals in the region [35]. As the proportion of women delivering by cesarean section has been found to increase with wealth quintile [36], and as Greater Accra is the wealthiest region of Ghana, it is possible that the higher rate of cesarean section is an indirect indicator of wealth, which would suggest against unmeasured social or healthcare disadvantages as an explanation for the differences in HNNE scores we found between the Ghanaian and British samples. In our study, over a quarter (38/140) of participants had undergone a previous cesarean section, so the high cesarean section rates may also be partly explained by a hesitancy for vaginal birth after cesarean section that is common in LMICs [37]. An alternative explanation is that the high rates of cesarean section reflect a higher risk of intrapartum fetal compromise in the Ghanaian sample than in the United Kingdom, which could explain lower HNNE scores in the Ghanaian sample. However, we found a downward shift in distribution of HNNE scores, not just an excessive number of very low scores. This, as well as the normal Apgar scores of our participants and lack of difference between HNNE scores by mode of delivery in our sample, would suggest against mild asphyxia being a routine explanation for the differences between the Ghanaian and British results.

Lastly, inadequate maternal nutrition could play a role. In the study of Karen neonates, poor nutrition and particularly thiamine deficiency, which has been related to neuronal maturation in preclinical studies, was believed to play a role in the lower HNNE scores [20] and poor nutrition could have a similar impact on the Ghanaian sample. However, there were no significant associations between poor tone and long-chain fatty acid or thiamine deficiency when investigated in the Vietnamese sample [21].

Overall, we believe that due to the similarities in participant selection and study design between this study and that of Dubowitz et al., the striking differences in results are unlikely to be due to observer bias or unmeasured confounders, leaving the possibility that the discrepancies are better explained by true differences in patterns of neurological maturation. When neonates in good health who were born preterm were assessed at term-equivalent age and compared with term-born neonates, the most prominent differences were evident in tone items [33], but these do not necessarily predict any later abnormality. Other studies have reported that rates of neurologic maturation can vary across races and cultures [38–40] and a variation in maturational pathways could explain the lower scores in the tone items subdomain among Ghanaian neonates. Compared with other races, black neonates show more frequent tremors, more flexed motor movements of the legs, and more vigorous arm recoil [41], which when scored using the HNNE, are considered suboptimal responses. These differences could have a genetic basis and yet be insignificant for long-term neurological or neurodevelopmental outcomes, while still adversely impacting the predictive utility of the HNNE.

The need for neurodevelopmental assessment tools developed and validated in LMICs has been raised by a number of experts in the field. There is a limited repertoire of affordable, cross-culturally appropriate screening tools for these settings. Nevertheless, this study is not the first to highlight concerns regarding the international and cross-cultural applicability of normative data to assess infants and children. For example, when the “gold standard” Bayley Scales of Infant and Toddler Development, Third Edition was administered in Malawi using norms developed in the United States, misclassification of neurodevelopmental status among Malawian infants has been shown [14]. Similarly, when Brazilian, Greek, and Canadian infants were assessed using the Alberta Infant

Motor Scale, a tool with scoring developed from Canadian reference values, Brazilian children had significantly lower scores than other infants (42) despite the tool having previously been validated in Brazil [43]. The authors concluded that lower motor scores were a consequence of cultural differences in infant care [42]. This phenomenon of cross-cultural variation in development has been described in a variety of LMICs with regards to motor, language, and socio-emotional outcomes [44–46]. Importantly, these findings are not limited to resource-limited settings. Flemish infants also showed significantly lower motor scores compared with Canadian normative data on the Alberta Infant Motor Scale, with the authors calling for new reference values to identify at-risk infants [47].

In conclusion, the highlighted discrepancies in HNNE scores in this study are not completely unexpected as neonates across different countries are inherently maturationally, culturally, and racially/ethnically diverse, and access to and quality of health care vary. However, the differences in the proportion of neonates scoring optimally between the Ugandan and Ghanaian samples, which we would expect to be somewhat similar, warrant further investigation. Nonetheless, this study emphasizes the potential for bias if assessment tools are used in populations other than the one in which they were developed and validated [14]. Also, using tools "adapted" to resource-limited settings is of limited utility if normal ranges and predictive value have not been defined in the population of interest [48]. Finally, it is noteworthy that the majority of research concerning the validation of neurodevelopmental assessments in LMICs has focused on infants and children, as opposed to neonates. A reliable and scalable method for the detection of neonates at risk of adverse neurodevelopmental outcomes is critical to allow the development of targeted, early interventions. It is evident that more work needs to be done to understand the reasons for substantial differences in the HNNE scoring in different settings. If these differences relate to modifiable factors such as assessor training, testing environment, timing of testing, or definitions of "healthy neonates" for defining a normal range, these factors need to be well understood and routinely implemented in applying this examination. On the other hand, if genetic differences in normal neonates' pathways to nervous system maturation are most important, priority needs to be given to developing a range of population-specific test norms, and replicating studies of their predictive value, so that the urgent need for reliable screening tests of infant development can be met.

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Appendix A. Supplementary data

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