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Gestational Age-Specific Distribution of the Hammersmith Neonatal Neurological Examination Scores Among Low-Risk Neonates in Ghana

Harriet L.S. Lawford[a], Mercy A. Nuamah[b], Helen G. Liley[a], Anne CC Lee[c], Felix Botchway[d], Sailesh Kumar[a], IMPRINT Study Group[1], Andrew A. Adjei[d], Samudragupta Bora[a,*]

[a] Mothers, Babies and Women's Health Program, Mater Research Institute, Faculty of Medicine, The University of Queensland, South Brisbane, QLD, Australia
[b] Department of Obstetrics and Gynaecology, University of Ghana Medical School, College of Health Sciences, Korle Bu Teaching Hospital, Accra, Ghana
[c] Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[d] Department of Pathology, University of Ghana Medical School, College of Health Sciences, Korle Bu Teaching Hospital, Accra, Ghana

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ABSTRACT

Objective: To describe gestational age-specific distribution of scores for the Hammersmith Neonatal Neurological Examination (HNNE) up to 48 h after birth in a low-risk, term-born, single-center sample in Ghana.

Study design: This is a nested substudy of a larger prospective study (IMPRINT: Impact of Malaria in Pregnancy on Infant Neurodevelopment) comprising 140 low-risk, term-born neonates at Korle Bu Teaching Hospital in Accra, Ghana, between November 2018 and February 2019. The sample was stratified into three gestational age groups: early-term (37 + 0–38 + 6, weeks + days; $n = 61$), full-term (39 + 0–40 + 6, weeks + days; $n = 52$), and late/post-term (41 + 0–42 + 6, weeks + days; $n = 27$). Neonates were administered the 34-item HNNE by trained physicians. As per the original British scoring system, raw scores for the Ghanaian sample were plotted and scores > 10th centile were assigned a score of 1, 5th–10th centile 0.5, and < 5th centile 0.

Results: The range of raw scores for 16/34 HNNE items varied with gestational age. Specifically, 100% (7/7), 50% (5/10), 33% (1/3), 33% (1/3), 20% (1/5), and 14% (1/7) of items within the orientation and behavior, tone, abnormal signs/patterns, movements, tone patterns, and reflexes subdomain, respectively showed a different distribution of scores above the 10th centile across the three gestational age groups.

Conclusion: Differences in gestational age-specific results within our sample in comparison to the original British sample could be, albeit unlikely, due to misclassification of gestational age, unmeasured maternal or fetal morbidity, or perhaps more likely, variation in testing or test conditions, or some combination of these. Genetic variation in neurological development is also a possibility. Further research is warranted to determine the reasons for differences. Our findings highlight the need to determine the accuracy and reliability of standardized neurologic assessments in predicting neurodevelopmental risk for infants in low- and middle-income countries.

Neonatal neurologic assessments are helpful to understand and monitor a newborn's neurological development, inform clinical practice, and determine need for referral for early intervention [1]. The Hammersmith Neonatal Neurological Examination (HNNE) is a standardized, structured assessment of the newborn first published in 1981[2] and revised in 1998 [3]. It is a predominantly neurological assessment, which has been widely used in clinical practice to evaluate the maturity and integrity of the nervous system of extremely, very, and late preterm and term-born infants [1,4–8]. Studies have been conducted in both high- and low-resource settings, including Australia [1,9], Britain [3], Italy [7,8,10], Singapore [5], Thailand [11], Uganda [12], and Vietnam [13].

A quantitative scoring system was developed by Dubowitz et al. in 1998 and designated normative values were acquired from a sample of 224 low-risk, term-born British infants [3]. Newborns were categorized as “optimal” or “suboptimal” if their scores fell above or below the 10th centile of raw scores for the whole sample, respectively. Nine of the 34 HNNE assessment items were gestational age-dependent. This scoring system allowed for the identification of newborns at risk of concurrent neurological alterations and subsequent neurodevelopmental impairment

*Abbreviations:*HNNE, Hammersmith Neonatal Neurological Examination

* Corresponding author at: Mothers, Babies and Women's Health Program, Mater Research Institute, Raymond Terrace, South Brisbane, QLD 4101, Australia.
E-mail address: samudragupta.bora@mater.uq.edu (S. Bora).

[1] **IMPRINT Study Group** (in alphabetical order)**:** Ali Samba, Andrew A. Adjei, Anne CC Lee, Ebenezer V. Badoe, Felix Botchway, Harriet L.S. Lawford, Helen G. Liley, Mercy A. Nuamah, Richard K. Gyasi, Sailesh Kumar, Samudragupta Bora, & Samuel A. Oppong

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[1,3]. Since the HNNE scoring system was published, suboptimal scores have been associated with poor neurodevelopmental, neurosensory, and neuromotor outcomes in preterm-born infants at 2 years corrected age [9,14] and neuromotor outcomes at 11 years [15]. The HNNE has been reported to have a sensitivity and specificity of 88% and 46%, respectively to identify infants with significant brain abnormalities diagnosed by magnetic resonance imaging [16].

Prior studies have demonstrated the effects of gestational age on neurobehavior [17], hence HNNE norms have been established for preterm infants of varying gestational age at birth assessed at term [1,7,8,18], and infants of similar gestational age at birth but different assessment time points [5,10]. Generally, it is seen that the distribution of scores above the 10th centile on the HNNE is narrower for term-born infants suggesting a more mature neurological response, and wider for preterm-born infants examined at or near term reflecting that some of these infants have less mature neurological responses that manifest as lower HNNE scores [1].

However, the range and median values of the distribution of the HNNE scores in preterm-born populations in different geographical settings have been found to differ; late preterm infants from predominantly European [8], Australian [1], and Asian [5] populations exhibit dissimilar distributions of scores, evident as different distribution of scores above the 10th centile, which was used as a threshold for "optimality" in the original British sample. Furthermore, we have previously demonstrated that the distribution of HNNE scores reported in apparently low-risk, term-born neonates in several resource-limited settings also differ from that of the original British sample [19]. Specifically, the proportion of infants classified as neurologically "optimal" according to Dubowitz et al.'s British thresholds was much lower than expected in published studies from Thailand, Myanmar, Vietnam, and Uganda [11–13]. In an analysis of data from the same sample as the current study, we found that surprisingly, only 5% of low-risk, term-born neonates recruited from a single-center in Ghana were classified as neurologically optimal when scored using normative British data, despite selecting infants using very similar criteria as were used for the original study [19]. The reasons remain unknown, but could include 1) genetic differences in normal pathways of neurological maturation, 2) unmeasured confounders rendering this sample much less "low-risk" than intended, or 3) systematic differences in the test environment, administering the assessment, and interpreting the results. These possibilities have been discussed in detail elsewhere [19].

It has been recommended that a local comparison group be used where possible if an assessment is being undertaken outside of the country/region it was originally validated. Accordingly, the objective of this study was to provide gestational age-specific comparator values for low-risk, term-born Ghanaian neonates for the HNNE in the first 48 h after birth for use in studies conducted in Ghana or sub-Saharan Africa. Specifically, we aimed to describe the distribution of HNNE raw scores among Ghanaian neonates with low clinical risk and born at early-term (37 + 0–38 + 6, weeks + days), full-term (39 + 0–40 + 6, weeks + days), and late/post-term (41 + 0–42 + 6, weeks + days). We emphasize that this is to provide suitable control data for other studies in a similar population, rather than to define what is "normal".

Methods

Sample.

This is a nested substudy of a larger prospective study (IMPRINT: Impact of Malaria in Pregnancy on Infant Neurodevelopment). Between November 2018 and February 2019, pregnant women presenting during the early stages of labor to the Labour and Delivery ward at Korle Bu Teaching Hospital in Accra, Ghana, were consented, recruited, and their neonates enrolled after delivery. If the pregnancy, circumstances of delivery, and the neonate's condition at birth met the study inclusion criteria along with the availability of a study physician, their neonates were included in the study. Korle Bu Teaching Hospital is the largest public tertiary hospital in Ghana and West Africa and the third-largest hospital on the African continent. Korle Bu Teaching Hospital is the main referral hospital for southern Ghana with referrals from health centers, and from district and regional hospitals [20]. There are approximately 10,000 births per year and, as a tertiary referral center, there is a high rate of emergency deliveries for both maternal and fetal indications.

In total, 310 infants were enrolled in the IMPRINT study. The sample for this substudy comprises 140 early-term, full-term, and late/post-term neonates who met criteria for being low-risk (see inclusion criteria below). For purposes of analysis for this study, they were stratified post-enrolment into three gestational age groups: early-term (37 + 0–38 + 6, weeks + days; n = 61), full-term (39 + 0–40 + 6, weeks + days; n = 52), and late/post-term (41 + 0–42 + 6, weeks + days; n = 27). Gestational age was based on estimates from ultrasound results and/or based on the date of last menstrual period obtained from maternal medical records. Both the date of last menstrual period and ultrasound results were recorded for 94% of women, while date of last menstrual period was recorded for 98% and ultrasound estimation for 96%. Most women (39%) had their first ultrasound in the third trimester, 38% in the second trimester, 19% in the first trimester, and 4% did not receive an ultrasound but had the date of last menstrual period recorded.

The inclusion criteria were 1) ≥ 37 + 0 and ≤ 42 + 6, weeks + days gestation at birth, 2) ≥ 2500 and < 4300 g birthweight, 3) Apgar score ≥ 5 at 1 min, 4) Apgar score ≥ 7 at 5 min, 5) no admission to Neonatal Intensive Care Unit, and 6) no maternal pregnancy complications, including gestational diabetes, hypertension, preeclampsia, premature rupture of membranes, human immunodeficiency virus infection, or malaria. Table 1 describes the clinical and social characteristics of the three gestational age groups. The study protocol was approved by the institutional review board of the University of Ghana and The University of Queensland, Australia.

Measures.

A team of six trained physicians administered the HNNE to all study infants from birth to 48 h of age. Details of physician training have been described elsewhere [19]. The HNNE comprises 34 items assessing lower- and higher-order neurologic functions in six domains: tone, tone patterns, reflexes, movements, abnormal signs/patterns, and orientation and behavior. The full examination takes 10–15 min. The standardized HNNE proforma was used that includes definitions and/or pictorial representations for all 34 of the examination items. Each item consists of a column between 3 and 5 and the pictorial illustration/description most accurately representing the infant's status is circled. Each column is scored from 1–3 or 1–5 and a half-point is awarded if the response falls between two columns. These scores are referred to as raw scores. The HNNE has been reported to have robust test characteristics including an inter-rater reliability > 96% [21] and concurrent validity with neuroimaging results [16,22,23].

Data Analysis.

Data were analyzed using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) in four stages. First, maternal clinical (age, parity, and mode of delivery) and social characteristics (literacy, access to improved water, and sanitation facilities) in the three gestational age groups were compared using the Chi^2 or Fisher's exact tests and Kruskal-Wallis or one-way analysis of variance (ANOVA), based on the distribution of data. Second, the distribution of raw scores for each item was plotted and the range of raw HNNE item scores above the 10th centile and the median score for all HNNE items for each of the three gestational age groups were compared. The distribution of scores above the 10th centile was highlighted. Third, the raw scores and corresponding subdomain and total HNNE scores above the 10th centile, between the 5th and 10th centile, and below the 5th centile were determined. Scores > 10th centile were assigned a score of 1, those in the 5th–10th centile were assigned a score of 0.5, and < 5th centile were assigned a score of 0. In the original British scoring system, a score of 1 was considered "optimal", a

Table 1
Neonatal and maternal characteristics of the sample.

	Gestational Age at Birth, % [n/N]			*P*
	37–38 weeks ***N*** **= 61**	**39–40 weeks** ***N*** **= 52**	**41–42 weeks** ***N*** **= 27**	
Neonatal Clinical				
Birthweight, mean ± SD, g	3053 ± 329	3288 ± 373	3336 ± 370	< 0.001
Apgar score 1 min				
5	2 [1/61]	6 [3/52]	0 [0/27]	0.38
6	6 [4/61]	13 [7/52]	7 [2/27]	
7	25 [15/61]	25[13/52]	41 [11/27]	
8	61 [38/61]	54 [28/52]	52 [14/27]	
9	5 [3/61]	2 [1/52]	0 [0/27]	
Apgar score 5 min				
7	2 [1/61]	4 [2/52]	0 [0/27]	0.68
8	29 [18/61]	31 [16/52]	44 [12/27]	
9	66 [40/61]	63 [33/52]	56 [15/27]	
10	3 [2/61]	2 [1/52]	0 [0/27]	
Head circumference, mean ± SD, cm	34 ± 1.39	34 ± 1.49	35 ± 1.33	0.03
Maternal Clinical				
≤ 30 years of age at childbirth	30 [18/61]	57 [29/51]	67 [18/27]	0.001
Primiparous	20 [12/61]	29 [15/52]	33 [9/27]	0.32
Mode of delivery				
Spontaneous vaginal	11 [7/61]	54 [28/52]	52 [14/27]	< 0.001
Cesarean section	89 [54/61]	44 [23/52]	48 [13/27]	
Vacuum extraction/forceps	0 [0/61]	2 [1/52]	0 [0/27]	
Maternal Social				
Illiterate	15 [9/61]	20 [10/51]	44 [12/27]	0.008
No work previous 12 months	10 [6/61]	12 [6/51]	15 [4/27]	0.79
No access to improved sanitation facilities‡	27 [17/61]	51 [26/51]	59 [16/27]	0.007
No access to improved drinking water sources¥	16 [10/61]	20 [10/51]	15 [4/27]	0.84

‡ Improved sanitation facilities: flush or pour-flush to piped sewer system, septic tank, or pit latrine; ventilated improved pit latrine; pit latrine with slab; composting toilet.
¥ Improved drinking water sources: piped water into dwelling, plot, or yard; public tap/standpipe; tubewell/borehole; protected dug well; protected spring; rainwater collection.

score of 0.5 “borderline”, and a score of 0 “suboptimal”. However, we avoided using this terminology because of uncertainty about the applicability of this interpretation to this study. Finally, total HNNE scores were compared in all infants, subdivided according to several neonatal clinical variables (birthweight, mode of delivery, Apgar score at 1 and 5 min, maternal parity, and head circumference). A $P < .05$ indicated statistical significance.

Results

Gestational Age-Specific HNNE Raw Scores.

Table 2 describes the median and range of HNNE raw scores above the 10th centile among Ghanaian neonates born at early-term ($n = 61$), full-term ($n = 52$), and late/post-term ($n = 27$). The range of raw scores for 16/34 HNNE items differed with gestational age at birth. Specifically, 100% (7/7), 50% (5/10), 33% (1/3), 33% (1/3), 20% (1/5), and 14% (1/7) of items within the orientation and behavior, tone, abnormal signs/patterns, movements, tone patterns, and reflexes subdomain, respectively showed a different range of scores above the 10th centile for each of the three gestational age groups. Unexpectedly, as gestation increased, persistence of immature neurological responses was seen in raw scores for 10/16 items, whereas a shift in median values towards more mature responses was evident only for two items (arm recoil and Moro reflex).

For orientation and behavior, a wider range of scores (that included more high scores, but also some low, less neurologically mature scores) was evident for four items as gestation increased, namely auditory orientation, visual orientation, cry, and irritability. Cry scores for neonates born at late/post-term were particularly widely scattered, with 18% of neonates scoring 1 for this item, 18% scoring 2, 53% scoring 3, and 11% scoring 5. Neonates in the full-term group had a narrower range of scores relative to the higher and lower gestation groups for consolability, but for alertness 21% of full-term neonates showed no response to stimuli compared to 10% of early-term and 7% of late/post-term neonates. For eye appearances, the full-term group had a narrower range of scores, but more neonates exhibited transient eye movements relative to other gestation groups.

Among tone, a less mature response with a wider range of scores above the 10th centile was evident as gestation increased for 3/5 gestational age-specific items (leg recoil, arm recoil, and head control 2), although the median value did not increase. More neonates had a mature response for head lag as gestation increased. A narrower range of scores, although not a higher median value, was seen in full-term neonates for popliteal angle, relative to other gestational ages.

For abnormal signs/patterns, a wider range of scores above the 10th centile was evident for neonates born early-term for the startles item; more neonates in this gestation had spontaneous startles when compared to higher gestation infants, of whom > 90% had no startles, or only startles to sudden noises.

In contrast, for movements, only one item (spontaneous movements [quality]) exhibited scores that were wider for the full-term group relative to the other gestation groups.

For tone patterns, a wider range of scores in the late/post-term gestation group was seen for the neck extensor tone (sitting), suggesting a less neurologically mature response for this group.

Similarly, for reflexes, scores for the tendon reflex widened as gestation increased, with the full-term group exhibiting a lower, less neurologically mature response. It was not possible to determine the range of scores above the 10th centile for any gestation group for the placing reflex.

Gestational-Age Specific HNNE Optimality Scores.

Table 3 shows the distribution of raw scores above the 10th centile among Ghanaian neonates born at early, full, and late/post-term. Table 4 shows the reference values for the six domains of the HNNE and the total HNNE score out of a total of 34 for all infants born at 37–42 weeks gestation.

Table 2
Distribution of the percentage of HNNE raw scores among Ghanaian neonates born at early-term, full-term, and late/post-term.

HNNE Items	Sample	Raw Scores								
		1	1.5	2	2.5	3	3.5	4	4.5	5
Tone										
Posture	**37–38 weeks**	0	0	5	0	51	0	44	0	0
	39–40 weeks	0	0	4	0	65	0	31	0	0
	41–42 weeks	0	0	7	0	52	0	41	0	0
Arm recoil	**37–38 weeks**	0	0	3	0	53	0	44	0	0
	39–40 weeks	0	0	6	0	46	0	48	0	0
	41–42 weeks	4	0	11	0	30	0	56	0	0
Arm traction	**37–38 weeks**	3	0	25	0	41	3	28	0	0
	39–40 weeks	4	0	10	0	46	0	36	2	2
	41–42 weeks	0	0	30	0	37	0	33	0	0
Leg recoil	**37–38 weeks**	0	0	2	0	36	0	62	0	0
	39–40 weeks	0	0	6	0	38	0	56	0	0
	41–42 weeks	0	0	15	0	15	0	70	0	0
Leg traction	**37–38 weeks**	3	0	24	0	41	2	30	0	0
	39–40 weeks	2	0	12	0	46	0	40	0	0
	41–42 weeks	4	0	22	0	41	4	30	0	0
Popliteal angle	**37–38 weeks**	0	2	11	2	44	5	36	0	0
	39–40 weeks	2	0	8	0	48	4	38	0	0
	41–42 weeks	0	0	11	0	52	4	29	0	4
Head control 1	**37–38 weeks**	5	0	33	0	51	0	11	0	0
	39–40 weeks	4	0	29	0	48	0	19	0	0
	41–42 weeks	3	0	19	0	59	0	19	0	0
Head control 2	**37–38 weeks**	3	0	41	0	46	0	10	0	0
	39–40 weeks	10	0	27	0	50	0	13	0	0
	41–42 weeks	11	0	26	0	37	0	26	0	0
Head lag	**37–38 weeks**	11	0	41	0	43	0	5	0	0
	39–40 weeks	11	0	37	0	46	0	6	0	0
	41–42 weeks	8	0	48	0	33	0	11	0	0
Ventral suspension	**37–38 weeks**	0	0	59	0	30	0	11	0	0
	39–40 weeks	0	0	58	0	31	0	11	0	0
	41–42 weeks	0	0	56	0	26	0	19	0	0
Tone Patterns										
Flexor tone 1	**37–38 weeks**	0	0	18	0	64	0	13	0	5
	39–40 weeks	0	0	17	0	60	0	23	0	0
	41–42 weeks	0	0	21	0	57	0	18	0	4
Flexor tone 2	**37–38 weeks**	0	0	0	0	66	0	34	0	0
	39–40 weeks	0	0	0	0	73	0	27	0	0
	41–42 weeks	0	0	0	0	67	0	33	0	0
Leg extensor tone	**37–38 weeks**	0	0	33	0	51	0	16	0	0
	39–40 weeks	0	0	23	0	56	0	21	0	0
	41–42 weeks	0	0	30	0	52	0	18	0	0
Neck extensor tone (sitting)	**37–38 weeks**	0	0	6	0	79	0	15	0	0
	39–40 weeks	0	0	4	0	81	0	13	0	2
	41–42 weeks	0	0	11	0	67	0	19	0	4

(*continued on next page*)

Table 2 (*continued*)

HNNE Items	Sample	Raw Scores								
		1	1.5	2	2.5	3	3.5	4	4.5	5
Neck extensor tone (horizontal)	**37–38 weeks**	0	0	13	0	61	0	26	0	0
	39–40 weeks	0	0	21	0	50	0	29	0	0
	41–42 weeks	0	0	19	0	48	0	33	0	0
Reflexes										
Tendon	**37–38 weeks**	8	0	36	0	54	0	2	0	0
	39–40 weeks	4	0	29	0	67	0	0	0	0
	41–42 weeks	15	0	30	0	48	0	7	0	0
Suck/gag	**37–38 weeks**	0	0	25	0	75	0	0	0	0
	39–40 weeks	0	0	22	0	78	0	0	0	0
	41–42 weeks	0	0	19	0	81	0	0	0	0
Palmar grasp	**37–38 weeks**	0	0	21	0	56	2	21	0	0
	39–40 weeks	0	0	14	4	61	0	21	0	0
	41–42 weeks	0	0	15	0	59	0	22	0	4
Plantar grasp	**37–38 weeks**	2	0	32	2	64	0	0	0	0
	39–40 weeks	0	0	19	2	79	0	0	0	0
	41–42 weeks	0	0	22	0	78	0	0	0	0
Placing	**37–38 weeks**	26	2	52	0	20	0	0	0	0
	39–40 weeks	37	0	47	2	14	0	0	0	0
	41–42 weeks	19	0	44	0	37	0	0	0	0
Moro	**37–38 weeks**	0	0	2	0	51	0	47	0	0
	39–40 weeks	0	0	4	0	40	0	56	0	0
	41–42 weeks	0	0	7	0	30	0	63	0	0
Movements										
Spontaneous movements (quantity)	**37–38 weeks**	0	0	20	0	17	0	63	0	0
	39–40 weeks	0	0	14	0	17	0	69	0	0
	41–42 weeks	0	0	22	0	19	0	59	0	0
Spontaneous movements (quality)	**37–38 weeks**	0	0	2	0	26	0	70	0	2
	39–40 weeks	0	0	8	0	18	0	72	0	2
	41–42 weeks	0	0	15	0	7	0	78	0	0
Head raising in prone	**37–38 weeks**	30	0	42	0	13	0	13	0	2
	39–40 weeks	30	0	32	0	18	0	16	0	4
	41–42 weeks	30	0	30	0	15	0	18	0	7
Abnormal Signs/Patterns										
Abnormal hand/toe postures	**37–38 weeks**	0	0	43	0	44	0	13	0	0
	39–40 weeks	0	0	42	0	45	0	13	0	0
	41–42 weeks	0	0	27	0	50	0	23	0	0
Tremors	**37–38 weeks**	0	0	74	0	18	0	8	0	0
	39–40 weeks	0	0	75	0	21	0	4	0	0
	41–42 weeks	0	0	74	0	22	0	4	0	0
Startles	**37–38 weeks**	36	0	44	0	12	0	8	0	0
	39–40 weeks	49	0	43	0	6	0	2	0	0
	41–42 weeks	48	0	48	0	4	0	0	0	0
Orientation and Behavior										
Eye appearances	**37–38 weeks**	23	0	0	0	75	0	2	0	0
	39–40 weeks	18	0	0	0	82	0	0	0	0
	41–42 weeks	4	0	0	0	89	0	7	0	0

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Table 2 (*continued*)

HNNE Items	Sample	Raw Scores								
		1	1.5	2	2.5	3	3.5	4	4.5	5
Auditory orientation	**37–38 weeks**	22	0	42	0	33	0	3	0	0
	39–40 weeks	24	0	38	0	26	0	8	0	4
	41–42 weeks	15	0	41	0	29	0	11	0	4
Visual orientation	**37–38 weeks**	31	0	40	0	22	0	7	0	0
	39–40 weeks	35	0	27	0	19	0	13	0	6
	41–42 weeks	26	0	29	0	19	0	19	0	7
Alertness	**37–38 weeks**	10	0	57	0	28	0	5	0	0
	39–40 weeks	21	0	39	0	23	0	17	0	0
	41–42 weeks	7	0	56	0	11	0	26	0	0
Irritability	**37–38 weeks**	13	0	59	0	25	0	3	0	0
	39–40 weeks	27	0	51	0	16	0	6	0	0
	41–42 weeks	22	0	52	0	11	0	15	0	0
Cry	**37–38 weeks**	17	0	10	0	70	0	0	0	3
	39–40 weeks	25	0	24	0	45	0	0	0	6
	41–42 weeks	18	0	18	0	53	0	0	0	11
Consolability	**37–38 weeks**	16	0	30	0	37	0	15	0	2
	39–40 weeks	32	0	18	0	40	0	8	0	2
	41–42 weeks	19	0	41	0	22	0	11	0	7

Note: Cells with shading indicate the range of raw scores > 10th centile; cells with thick borders indicate median scores.

For tone and tone patterns, composite scores were calculated for 140 neonates. Tone scores ranged from 7 to 10; scores between 9 and 10 were seen in 92% of neonates who were consequently assigned an overall score of 1, those scoring 8.5 were assigned an overall score of 0.5 and those scoring < 8.5 assigned an overall score of 0. Tone patterns scores ranged from 3.5 to 5; a score of 5 was found for 91% of neonates who were consequently assigned an overall score of 1, those scoring 4–4.5 were assigned an overall score of 0.5, and those scoring < 4 were assigned an overall score of 0. For reflexes, composite scores were calculated for 138 neonates and ranged from 5 to 6. Scores between 5.5 and 6 were seen in 94% of neonates; therefore scores of ≥ 5.5 were assigned an overall score of 1, those scoring 5 were assigned an overall score of 0.5 and those scoring < 5 were assigned an overall score of 0. For movements, composite scores were calculated for 137 neonates and scores ranged from 2 to 3. A score of 3 was demonstrated by 91% of neonates who were consequently assigned an overall score of 1, those scoring 2–2.5 were assigned an overall score of 0.5 and those scoring < 2 were assigned an overall score of 0. For abnormal signs/patterns, composite scores were calculated for 115 neonates. Scores ranged from 1 to 3; scores between 2.5 and 3 were demonstrated by 95% of neonates who were assigned an overall score of 1, those scoring 2 were assigned a score of 0.5, and those scoring < 2 were assigned an overall score of 0. For orientation and behavior, composite scores were calculated for 129 neonates. Scores ranged from 4.5 to 7; scores between 6 and 7 were seen in 92% of neonates who were consequently assigned an overall score of 1, those scoring 5–5.5 were assigned an overall score of 0.5 and those scoring < 5 were assigned an overall score of 0.

The total HNNE score was calculated for 105 neonates. When all the 34 item scores were summed, scores ranged from 30 to 34. A score ≥ 31 was seen in 92% of Ghanaian neonates, 30.5 in 7% of neonates, and < 30.5 in 1% of neonates. There was 0.7 standard deviation difference in the total scores between the Ghanaian sample and British normative data. Table 5 presents a comparison for the Ghanaian sample of the total HNNE scores by birthweight, Apgar score at 1 and 5 min, head circumference, parity, and mode of delivery. There was no statistically significant difference for any of these comparisons.

Discussion

To the best of our knowledge, this study is novel in describing the gestational age-specific distribution of HNNE raw scores in a single-center sample of low-risk, term-born Ghanaian neonates, thereby providing a base for comparison with Ghanaian neonates at higher risk. We propose that this description will assist in the design of future studies to determine the predictive value for later neurodevelopment of the HNNE in Ghanaian infants. The results may have external validity for other countries in sub-Saharan Africa, although this is yet to be confirmed.

Our distribution and effects of increasing gestation are markedly different from those of the original British sample [3]. Firstly, 16/34 items showed gestational age-dependent differences in distribution in the Ghanaian sample compared to only 9/34 items in the original British sample. Secondly, there were noteworthy dissimilarities in the pattern of responses; across the 4 items (leg recoil, arm recoil, popliteal angle, and head lag) that were dependent on gestational age at birth for both groups, a positive linear increase in maturity of responses was seen with gestation for the British sample, whereas a less-mature response was exhibited for two items (leg recoil and arm recoil) by Ghanaian neonates born at late/post-term. It was not possible to determine the range of scores above the 10th centile for the cry item for Ghanaian neonates born at late/post-term. This discrepancy could partly be explained by the small number of late/post-term neonates in the Ghanaian sample, which accounted for only 27/140 neonates examined, relative to 45/224 in the British sample. Similarly, it was not possible to determine the range of scores above the 10th centile for any gestation group for the placing reflex, questioning the utility of this item in this population.

Methodological strengths of this substudy include sampling of low-risk, term-born neonates from a large tertiary teaching hospital that is able to diagnose and manage most common complications of pregnancy. To minimize observer and measurement bias, a team of six local physicians were recruited and trained for this study, all of whom had previous training and experience with similar neonatal assessment tools. Approximately 80% of HNNE examinations were undertaken by two of these physicians to minimize assessor bias. The inclusion criteria were very similar to those used by Dubowitz et al. to ensure that similarly low-risk infants were included. However, as discussed in detail elsewhere [19], it is possible, though not highly likely that unmeasured morbidity during pregnancy or birth accounted for some of our results.

Key limitations of this single-center sample have been described in detail elsewhere [19]. Possible inaccuracy in gestational age estimation in our Ghanaian sample deserves consideration. Over one-third of mothers in this sample had their first ultrasound in the third trimester

Table 3
Distribution of HNNE raw scores above the 10th centile, between the 5th and 10th centile, and below the 5th centile among Ghanaian neonates born at early-term, full-term, and late/post-term.

HNNE Items	37–38 weeks			39–40 weeks			41–42 weeks		
	1	0.5	0	1	0.5	0	1	0.5	0
Tone									
Posture*	3,4		< 3,5	3,4		< 3,5	3,4	2	< 2,5
Arm recoil*	3,4		< 3,5	3,4	2	< 2,5	2,3,4		< 2,5
Arm traction	2,3,4	1.5,4.5	1,5	2,3,4	1.5,4.5	1,5	2,3,4	1.5,4.5	1,5
Leg recoil*	3,4		< 3,5	3,4	2	< 2,5	2,3,4		< 2,5
Leg traction	2,3,4	1.5,4.5	1,5	2,3,4	1.5,4.5	1,5	2,3,4	1.5,4.5	1,5
Popliteal angle*	2,3,4	1.5,4.5	1,5	3,4	1.5,2,4.5	1,5	2,3,4	1.5,4.5	1,5
Head control 1	2,3,4		< 2	2,3,4		< 2	2,3,4		< 2
Head control 2*	2,3,4		< 2,5	2,3,4	1	5	1,2,3,4		5
Head lag*	1,2,3		4,5	1,2,3	4	5	2,3,4	1	5
Ventral suspension	2,3,4		< 2,5	2,3,4		< 2,5	2,3,4		< 2,5
Tone Patterns									
Flexor tone 1	2,3,4		5	2,3,4		5	2,3,4		5
Flexor tone 2	3,4		5	3,4		5	3,4		5
Leg extensor tone	2,3,4		5	2,3,4		5	2,3,4		5
Neck extensor tone (sitting)*	3,4	2	5	3,4		2,5	2,3,4		5
Neck extensor tone (horizontal)	2,3,4		5	2,3,4		5	2,3,4		5
Reflexes									
Tendon*	2,3	1	4,5	2,3		< 2,4,5	1,2,3	4	5
Suck/gag	2,3		< 2,5	2,3		< 2,5	2,3		< 2,5
Palmar grasp	2,3,4		< 2,5	2,3,4		< 2,5	2,3,4		< 2,5
Plantar grasp	2,3		< 2	2,3		< 2	2,3		< 2
Placing	1,2,3			1,2,3			1,2,3		
Moro*	3,4		< 3,5	3,4		< 3,5	3,4	2	< 2,5
Movements									
Spontaneous movements (quantity)	2,3,4		< 2,5	2,3,4		< 2,5	2,3,4		< 2,5
Spontaneous movements (quality)*	3,4		< 3,5	3,4	2	< 2,5	2,3,4		< 2,5
Head raising in prone*	1,2,3,4		5	1,2,3,4		5	1,2,3,4	5	
Abnormal Signs/Patterns									
Abnormal hand/toe postures	2,3,4		5	2,3,4		5	2,3,4		5
Tremors*	2,3	4	5	2,3		4,5	2,3		4,5
Startles*	1,2,3	4	5	1,2	3	4,5	1,2		3,4,5
Orientation and Behavior									
Eye appearances*	1,3		4,5	1,3		4,5	3,4		1,5
Auditory orientation*	< 4		4,5	< 5		5	< 5		5
Visual orientation*	< 4	4	5	< 5	5		< 5	5	
Alertness*	2,3,4	1	5	< 5		5	2,3,4	1	5
Irritability*	< 4		4,5	< 4	4	5	< 5		5
Cry*	1,2,3		5	1,2,3	5		1,2,3,5		
Consolability*	< 5		5	< 4	4	5	< 5	5	

Note: Scores > 10th centile assigned a score of 1, 5th–10th centile a score of 0.5, and < 5th centile a score of 0.
* Gestational age-specific items.

Table 4
Reference values for the six domains of the HNNE and the total HNNE score for all neonates born at 37–42 weeks gestation.

HNNE Subdomain	Score Cut-Offs		
	1	0.5	0
Tone	≥ 9	8.5	≤ 8
Tone patterns	5	4,4.5	≤ 3.5
Reflexes	≥ 5.5	5	≤ 4.5
Movements	3	2,2.5	< 2
Abnormal signs/patterns	≥ 2.5	2	< 2
Orientation and behavior	≥ 6	5,5.5	< 5
Total HNNE score	≥ 31	30.5	≤ 30

of pregnancy. Early ultrasound measurement of fetal crown-rump length, preferably < 14 weeks gestation, is more accurate than later ultrasounds which have increasing inaccuracy for each trimester [24]. Because dates in 81% of our sample were based on ultrasound scans after the 1st trimester or based on date of last menstrual period, it is possible that there was some misclassification of gestational age in our sample, with underestimation (due to fetal growth restriction) seeming more likely than overestimation. This would result in more mature neonates being misclassified into the lower gestation groups, and could have artefactually shifted the results for these groups into a more mature distribution, which would in turn tend to flatten the effects of gestation on the results. However, this does not describe our findings well. If the misclassification in gestation was random rather than skewed, the wider variation we found in our results than were reported in the British sample could be explained. Similar to our study, when the HNNE was applied to low-risk, Ugandan infants, the mean score for those born late/post-term was lower than for infants born early-term and full-term [12]. Of note, there is no description of how gestational age was estimated in the Ugandan study. A possible explanation for these results is the increased risk of placental insufficiency and spinal cord suppression in prolonged pregnancy and the risk of cerebral palsy and neurological and developmental disorders at preschool age, which has been seen to be higher in post-term infants [26,27]. If (due to misclassification of gestation) there were more high-risk, post-mature infants in our Ghanaian sample than we suspected, this might have explained the distribution of scores we saw. However, there were no differences in clinical characteristics that could reflect morbidity associated with post-maturity between the gestation groups we studied.

HNNE results in preterm-born infants assessed at term-equivalent age have been reported to differ from those of term-born infants assessed soon after birth. For example, infants born at 32–34 weeks gestation have been reported to have less mature suck/gag reflexes when

Table 5
Total HNNE score by neonatal clinical characteristics.

Clinical Characteristics	Total HNNE Score		*P*
	Mean ± SD	Range	
Birthweight			
≤ 3125 g	33.2 ± 0.95	30.5–34	0.24
> 3125 g	33.0 ± 1.26	30–34	
Apgar score 1 min			
5	33.0 ± 1.41	32–34	0.68
6	33.6 ± 0.58	32.5–34	
7	33.1 ± 1.14	30–34	
8	33.0 ± 1.16	30.5–34	
9	32.8 ± 1.04	31.5–34	
Apgar score 5 min			
7	34.0 ± 0.0	34	0.74
8	33.0 ± 1.21	30–34	
9	33.1 ± 1.08	30.5–34	
10	32.7 ± 1.26	31.5–34	
Head circumference			
≤ 34 cm	33.0 ± 1.10	30.5–34	0.45
> 34 cm	33.2 ± 1.15	30–34	
Presentation			
Cephalic	33.1 ± 1.1	30–34	0.86
Breech	33.0 ± 1.4	31–34	
Mode of delivery			
Spontaneous vaginal /vacuum extraction/ forceps	33.1 ± 1.2	30–34	0.80
Cesarean section	33.1 ± 1.1	30.5–34	
Parity			
Primiparous	32.8 ± 1.3	30.5–34	0.12
Multiparous	33.2 ± 1.0	30–34	

compared to infants born at 25–31 weeks gestation, and infants born at 28–29 weeks gestation exhibited stronger leg recoil than infants born at 30–34 weeks gestation [7]. Further, late preterm infants born at 36 weeks gestation had less mature leg recoil, quality of spontaneous movements, and startles relative to infants born at 34–35 weeks gestation [8]. These studies suggest that increasing chronological age from birth has an important maturational influence. While this particular factor would not have applied in our study in which all neonates were examined within 48 h of birth, these findings suggest that post-menstrual age is not the only determinant of neurological maturation as measured by the HNNE.

International variation in neurological development and maturity could be considered as an explanation for the gestational age-specific differences in HNNE seen in our sample. Importantly, term-born reference infants from some high-resource settings (Europe, Australia, and Singapore) also exhibit a different proportion of infants scoring in the "optimal" range as defined in the HNNE scoring system [1,5,8]. Indeed, only 68% of term-born Singaporean infants had a score ≥ 30.5 (and therefore met criteria for "optimality"), compared to 95% of British reference infants [5]. Analogously, there appears to be variation between countries in the distribution of scores for successive editions of the Bayley Scales of Infant and Toddler Development, with authors suggesting these discrepancies could be due to, among other reasons, the Flynn effect (the observed rise in intelligent quotient scores over time) [45], and over- and under-estimations of normative data [29]. Importantly, researchers have emphasized the importance of using local reference data when interpreting Bayley scores, however it is easier to propose this in a country where the distribution of scores is higher than the original reference standards than when, as in our sample it is much lower [30]. Ethnic, racial, and cultural differences in neurodevelopment are well-documented [31–34]. Poorer neurobehavior at term has been described in non-Caucasian infants, with infants scoring an average of 10 points lower on the HNNE [35]. Culture has been said to influence neurodevelopment and skill attainment; for example language skills have been correlated with caregiving and the amount of direct speech input in the early years, which are in turn related to cultural beliefs concerning child rearing and socialization [36]. However, cultural and child-rearing differences seem very unlikely to account for differences in results of the HNNE assessed within two days of birth.

Of note, a significantly higher proportion of mothers of the late/post-term group of Ghanaian neonates had no access to improved sanitation facilities and were illiterate. Pregnancies that occur in countries with limited economic, educational, and health resources are likely to be at increased risk of exposure to multiple adversities, including poorer nutrition, infectious diseases, limited access to quality antenatal care, lower socioeconomic status, *etc.*, which could individually or collectively have negative impacts on neurological maturation *in utero* [37–39]. Prenatal stresses, including malnutrition and inflammation, and maternal individual and environmental factors are also known to impact fetal neurodevelopment [40]. However, the inclusion criteria for this study should have ruled out severe maternal disease or malnutrition; indeed, most mothers had normal or near normal hemoglobin levels and the infants' mean birthweights and head circumferences were normal. If there was unmeasured maternal or fetal morbidity in our sample it seems unlikely to have been severe, and yet its influence would have to be profound.

Further, abnormal cranial ultrasound scans have been seen in healthy Ugandan infants with normal neonatal neurological examinations, including white and gray matter echogenicity, subependymal pseudocysts, and choroid plexus cysts [41]. Unfortunately, we were unable to incorporate neuroimaging into our study, so we do not know whether any of our sample of Ghanaian neonates had congenital or perinatal brain injury or abnormalities.

We are left considering it is possible that the differences in HNNE scores by gestational age in our studies could be associated with genetic differences in pathways or rates of neurological development, which might have no or minimal clinical significance for long-term neurodevelopment. This speculation could only be confirmed by studies which measure HNNE scores in infancy and perform follow-up assessments during childhood. Because of higher rates of early childhood morbidity in low-resource countries, large sample sizes and detailed assessment of potential confounding variables would be necessary.

It is also possible that our results differed substantially from the British findings because of observer bias or test conditions. It is noteworthy that very few neonates in our study were assigned "half" scores for any item, in contrast to the British study. If this reflected a bias on the part of our assessors towards "rounding down" to whole numbers, it could explain some of the difference between our overall results and the British sample, but would not so readily explain the difference in gestation-related patterns between the studies. If the HNNE is highly sensitive to characteristics of the observers or the testing time or environment, it will be important to consider this both in future research and clinical use.

While we have reported the median value of HNNE scores, as seen in prior HNNE publications, it should be noted the lack of half scores assigned to neonates in our Ghanaian sample does raise the question as to whether median is the most appropriate measure of central tendency to use. Highlighting and comparing the modal scores may be a more valuable and informative measure to report in the HNNE, though it should be noted that the median and mode raw score in this sample of Ghanaian neonates was the same for all items, except for arm recoil, head lag, startle, visual orientation, and consolability. However, if mode had been reported for arm recoil, full-term neonates would have the same mode (and a more mature score) as late/post-term neonates, early-term neonates would have the same mode (and a more mature score) as full-term neonates for head lag, full-term neonates would have a less mature mode for startle and visual orientation, and full-term neonates would have the same mode (and a more mature score) as early-term neonates for consolability.

Lastly, it must be emphasized that we do not know whether our results have external validity for other Ghanaian neonates; we

described the gestational age-dependent distribution of HNNE scores in a single, urban, tertiary hospital-based sample with over-representation of higher socioeconomic status families relative to other parts of the country and the region, and potentially more complicated pregnancies. Further research is needed using a multi-site approach to, firstly validate our results, and secondly determine the longitudinal neurological well-being of these infants.

Importantly, as Dubowtiz et al. stated in their original 1998 publication, infants scoring "suboptimally" on the HNNE are not necessarily neurologically "abnormal", but "suboptimality" identifies infants who need to be reassessed to differentiate between those with persistent as opposed to transient abnormalities [3]. As maintained by Prechtl (1980), "optimal is not synonymous with normal" and it is possible that non-optimal responses may lie within a normal range, but may still indicate the presence of an abnormal condition [42]. Indeed, while pathology can be considered stereotyped and uniform, normality is variable with both inter-individual and intra-individual variation seen [43]. Therefore it has been suggested that using the term "reduced optimality" may be clearer than "non-optimal" [42] and should be a consideration for future studies applying the HNNE scoring system. It was for this reason that we were hesitant to classify Ghanaian infants as scoring "optimally" or "suboptimally" in this sample without further understanding their long-term neurological outcomes.

Additionally, dysfunction of the nervous system at birth may not be permanent; transient neurological abnormalities are characteristic of neurological examinations in the first year of life, and are seen in term and preterm-born infants with and without prenatal and/or perinatal risk factors [44]. Transient neurological abnormalities could explain the high rate of false positives in some neurological examinations [44]. This emphasizes the importance of ensuring a high negative predictive value of neurological assessments in order to distinguish these transient abnormalities and thereby prevent unnecessary follow-up, particularly in countries where resources are limited, allowing resources to be focused on the longitudinal follow-up of clinically at-risk infants. The less mature scores for some HNNE items seen in late/post-term neonates could have occurred if this group is particularly prone to transient neurological abnormalities, however this phenomenon seems unlikely to explain the major difference from the British results for our sample as a whole.

In conclusion, our description of the gestation-related distribution of scores for the HNNE in this sample of Ghanaian neonates demonstrated substantial differences from the original British reference group, despite inclusion of only similarly healthy infants. Further research to explain the reasons for and implications of the results is needed. Normative data for well-established, easily administered tools such as the HNNE for Ghana and other similar settings is essential and is the first step to enhance its clinical utility in a setting where the need is greatest.

Conflict of interest

The authors have no potential, perceived, or real conflict of interest relevant to this study to disclose.

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