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Quantitative EEG analysis in neonatal hypoxic ischaemic encephalopathy

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HIGHLIGHTS

- We examine the ability of several quantitative EEG measures to discriminate between EEG grades of HIE.
- Quantitative EEG measures are chosen to replicate the neurophysiologist's approach when visually classifying full term neonatal EEG.
- EEG measures of amplitude and continuity of the EEG signal are the best performing measures in distinguishing between EEG/HIE grades.
- No single quantitative measure is capable of discriminating between all EEG/HIE grades.
- This study demonstrates the potential to simplify interpretation of neonatal EEG in HIE.

ABSTRACT

Objective: To test the hypothesis that quantitative EEG (qEEG) measures are associated with a grading of HIE based on the visual interpretation of neonatal EEG (EEG/HIE).
Methods: Continuous multichannel video-EEG data were recorded for up to 72 h. One-hour EEG segments from each recording were visually analysed and graded by two electroencephalographers (EEGers) blinded to clinical data. Several qEEG measures were calculated for each EEG segment. Kruskal–Wallis testing with post hoc analysis and multiple linear regression were used to assess the hypothesis.
Results: Fifty-four full-term infants with HIE were studied. The relative delta power, skewness, kurtosis, amplitude, and discontinuity were significantly different across four EEG/HIE grades ($p < 0.05$). A linear combination of these qEEG measures could predict the EEG/HIE grade assigned by the EEGers with an accuracy of 89%.
Conclusion: Quantitative analysis of background EEG activity has shown that measures based on the amplitude, frequency content and continuity of the EEG are associated with a visual interpretation of the EEG performed by experienced EEGers.
Significance: Identifying qEEG measures that can separate between EEG/HIE grades is an important first step towards creating a classifier for automated detection of EEG/HIE grades.

1. Introduction

Perinatal hypoxia ischaemia, is the third commonest cause of all neonatal deaths globally (23%), after infection (26%) and preterm birth (28%) (Lawn et al., 2005). Among survivors, it can lead to hypoxic ischaemic encephalopathy (HIE), which is the most common cause of long-term severe neurological disability in newborn infants (Vannucci, 2000). Clinical features of HIE range from mild irritability and hyperalertness to severe coma and death. The outcome depends on the severity of the encephalopathy, with mild encephalopathy having a normal outcome, moderate encephalopathy having a 20–40% risk of neurological disability and severe encephalopathy almost invariably leading to severe neurological impairment or death (Robertson and Finer, 1985; Gray et al., 1993). The recent success of several international trials of therapeutic hypothermia for newborn infants with HIE has shown that it may now be possible to limit the effects of progressive encephalopathy and improve neurodevelopmental outcome (Inder et al., 2004; Wyatt et al., 2007; Jacobs et al., 2007; Rutherford et al., 2010). If therapeutic hypothermia is to be effective, it must be initiated within the first 6 h after birth before secondary energy failure occurs in the brain following the initial hypoxic ischaemic insult (Lorek et al., 1994; Roth et al., 1997). Furthermore, as there

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are well-documented adverse effects of mild therapeutic hypothermia such as increased thrombocytopenia and hypotension requiring inotrope support (Jacobs et al., 2007), the category of affected infants that best respond to this intervention must be identified. A systematic review of randomised and quasi-randomised studies comparing the use of therapeutic hypothermia with standard care in infants with HIE has shown that cooling for term newborn infants with moderate-to-severe HIE reduces mortality and also decreases the chance of major neurodisability in survivors (Jacobs et al., 2007). Moreover, the 2010 guidelines for neonatal resuscitation advise that only newborn infants born at or near-term with evolving moderate-to-severe HIE should be offered therapeutic hypothermia (Perlman et al., 2010; Kattwinkel et al., 2010). Therefore, there is an urgent need for prompt diagnosis of the HIE severity and the initiation of appropriate treatment in the immediate postnatal period.

Grading of HIE is most commonly made by clinical assessment, but may also be made using the electroencephalogram (EEG) or amplitude integrated EEG (aEEG). For clinical grading of HIE, Levene's modification of the Sarnat staging system is widely adopted by neonatologists and is easy to assign (Sarnat and Sarnat, 1976; Evans and Levene, 1999). However, estimating the severity of injury can be difficult in the immediate postnatal period, and the worst clinical grade is often only evident at approximately 48 h after birth. This is clearly too late for the initiation of therapeutic hypothermia. Furthermore, the use of sedative or anti-epileptic medications make clinical assessment of the grade of HIE more difficult (Pressler et al., 2001). An alternative scoring system has been proposed by Thompson et al., which is easy to apply, has good positive predictive value for outcome, and correlates well with the Sarnat and Sarnat system (Thompson et al., 1997). However, the peak HIE score that has the highest positive predictive value for outcome and therefore, is the best indicator of the severity of HIE, is usually only observed on day 3 and 4, which limits its' use for early monitoring within the first 6 h after birth. Moreover, unlike the Sarnat system, this scoring system has yet to be correlated with EEG grades of HIE.

In contrast, continuous multichannel EEG and aEEG have been successfully used for the early prediction of long-term neurodevelopmental outcome in HIE (Pezzani et al., 1986; Wertheim et al., 1994; Selton and Andre, 1997; Toet et al., 1999; Pressler et al., 2001; ter Horst et al., 2004; Osredkar et al., 2005; Murray et al., 2009). Unlike in clinical assessment of HIE, the worst EEG grade of HIE is evident as early as within the first 6 h after birth (Murray et al., 2009). Moreover, continuous EEG allows precise monitoring of the evolution of the encephalopathy.

Grading of HIE using EEG is based on a visual analysis of the background activity. The background activity is usually classified by interpreting features such as the continuity of the EEG signal, interhemispheric symmetry and synchrony, amplitude, frequency content, and presence or absence of sleep-wake cycling (SWC) (Boylan et al., 2008). There is, however, no single standardised classification system available to grade neonatal EEG in HIE (EEG/HIE). Most classification schemes described in the literature are based on the amalgamation of results from a number of authors (Monod et al., 1972; Watanabe et al., 1980; Tharp et al., 1981; Lombroso, 1985). This has resulted in significant overlap between various classification systems that are currently in use. It must be noted that these studies found a highly significant correlation between EEG/HIE grade (using their own classification system) and outcome (Sarnat and Sarnat, 1976; Watanabe et al., 1980; Murray et al., 2009).

The implementation of a standardised EEG classification scheme would allow the most objective and accurate estimation of the severity of developing HIE. Neonatal EEG is, however, difficult to interpret, and neurophysiologists with the required neonatal experience are scarce. In many neonatal intensive care units (NICU), it may be possible to obtain a brief EEG recording but it may take hours or even days to get a report. The need to identify infants suitable for therapeutic hypothermia as early after birth as possible means that the interpretation of the EEG is required rapidly and often out of normal working hours. Neurophysiologists worldwide have been unable to provide a 24 h emergency service for neonatal EEG monitoring resulting in the increased use of 1 or 2 channel aEEG in the NICU for grading neonatal HIE. This has proved very useful in the hands of experienced aEEG users but non-expert users struggle to interpret the wide variety of background patterns and to differentiate noisy signals caused by excessive biological or environmental interference (Boylan et al., 2010). It is clear that some sort of objective aid for EEG interpretation would be of great benefit to the neonatologist in the NICU.

In this study, we present a method which attempts to replicate the approach used by the neurophysiologist when visually classifying full term neonatal EEG. We examine the ability of several quantitative EEG (qEEG) measures to discriminate between EEG/HIE grades. We have also used a combination of these quantitative measures to distinguish between normal/mildly abnormal, moderately abnormal, majorly abnormal, and inactive EEGs seen in full term newborn infants with HIE. Only full term newborn infants with HIE were recruited for this study. Even though preterm infants can also be subjected to asphyxia and subsequently develop HIE, the visual characteristics of the preterm EEG are very different to full term neonatal EEG and depend on the gestational age of the infant (Pressler et al., 2007; Andre et al., 2010). Thus, certain qEEG measures, for example measures of amplitude and discontinuity, might be virtually applicable to both full term and preterm EEG; however, their context of interpretation would be very different.

2. Methods

2.1. Subjects and setting

This study was performed in a large maternity service with approximately 6000 deliveries per year between May 2003 and May 2005. Following parental consent, term newborn infants with HIE were recruited to the study if they fulfilled two or more of the following criteria: Apgar score at 5 min < 5; initial capillary or arterial blood pH of <7.1; initial capillary or arterial blood lactate >7 mmol/l; or abnormal neurological signs. Initial neurological assessment of the newborn infants was performed using a standardised method – the Sarnat clinical scoring system (Sarnat and Sarnat, 1976; Evans and Levene, 1999). The study had full approval from the Clinical Ethics Committee of the Cork Teaching Hospitals and written informed parental consent was obtained for all infants studied.

2.2. EEG recording

Continuous video-EEG data were recorded using the NicoletOne™ EEG system (CareFusion Co., San Diego, USA) in the NICU. All recordings were commenced as soon as possible after birth, generally within 6 h, and continued for 24–72 h in order to monitor the progression of the developing encephalopathy.

EEG was recorded from 9 scalp electrodes positioned using the international 10–20 electrode placement system, modified for neonates (F4, C4, T4, O2, F3, C3, T3, O1, and Cz). A reference electrode was placed on the midline between Fz and Cz electrode positions. Silver-silver chloride electrodes were attached to the infant's scalp using a conductive water-soluble paste and secured using an adhesive tape. A soft net was used in some cases in order to additionally secure the electrodes. Electrode impedance was maintained below

5 kΩ at all times. EEGs were sampled at 256 Hz and stored on a computer hard disk for off-line analysis. Physiological measurements of heart rate, respiration and oxygen saturation were recorded simultaneously and stored with the EEG signal on the same disk.

2.3. Visual EEG analysis

One hour of EEG data, free of seizures and major movement artefacts (amplitude higher than 250 μV lasting for more than 3 s) were chosen from each infant's recording for visual and subsequent quantitative analyses. The EEG data were selected soon after the recording was commenced. The segments of EEG were selected so that a constant EEG/HIE grade was present for the entire hour. All patient identifiers were removed from the EEG files to facilitate blinding of the data. All one-hour EEG files were stored separately from the original recordings and then independently visually analysed by two experienced neonatal electroencephalographers (EEGers) (GBB and IK). An overall EEG/HIE grade was assigned to the background EEG activity for each recording. The inter-observer agreement between both EEGers was high ($\kappa = 0.9$). In those cases when two different grades were assigned to the same EEG file, the EEGs were subsequently reviewed, discussed by the EEGers and consensus on the EEG/HIE grade was reached. An 8-channel bipolar montage was used for visual analysis in order to minimise the impact of the reference electrode (F4-C4, F3-C3, C4-O2, C3-O1, T4-C4, C4-Cz, Cz-C3, C3-T3) (Andre et al., 2010). The visual classification system used in this study is adapted from the system used by Murray et al. which was specifically developed for full term infants with HIE (Murray et al., 2009). This classification system is summarised in Table 1. The neonatal EEG was assigned one of 4 grades corresponding to normal/mildly abnormal (EEG/HIE 1), moderately abnormal (EEG/HIE 2), majorly abnormal (EEG/HIE 3) and inactive (EEG/HIE 4) EEG. This neonatal EEG classification system has been shown to correlate with both Sarnat grade of HIE and outcome (Murray et al., 2009).

2.4. EEG segmentation

The qEEG measures were calculated on the same one hour of EEG data that was visually inspected by the EEGers. Each channel of EEG was first segmented into 64 s non-overlapping epochs. Quantitative EEG measures were then estimated on each epoch and the median value of the qEEG measure across all epochs was averaged across eight EEG channels and used in subsequent statistical analysis. A similar EEG data segmentation procedure was performed in Lofhede et al. (2010). In the case of interhemispheric measurements (interhemispheric symmetry and synchrony), the median qEEG measure was averaged across 3 bilateral electrode pairs (F3-C3/F4-C4, Cz-C3/C4-Cz and C3-01/C4-02). The segmentation process is summarised as:

Table 2
The association between visual characteristics of the neonatal EEG and qEEG measures.

Visual characteristics	Quantitative measure
Continuity of EEG signal	Skewness, kurtosis, discontinuity
Amplitude	Amplitude integrated EEG
Frequency content	Relative delta power, spectral edge frequency, and fractal dimension
Interhemispheric symmetry	Revised brain symmetry index
Interhemispheric synchrony	Linear correlation coefficient

1. Segment a single EEG channel into non-overlapping 64 s epochs.
2. Calculate a qEEG measure on each 64 s EEG epoch.
3. Take the median of the qEEG measure per channel over the hour long recording.
4. Repeat for each of the 8 channels of EEG recording (3 bilateral electrode pairs for interhemispheric measurements).
5. Average the median qEEG value over the channels of EEG recording.
6. Repeat for each qEEG measure.

One hour of multiple channel EEG recording per infant, therefore, resulted in a single value for each qEEG measure.

2.5. Quantitative EEG measures

The qEEG measures used for analysis were selected to respond to characteristics of neonatal EEG that are used by EEGers in the visual interpretation of the EEG such as; continuity, amplitude, frequency content, symmetry and synchrony (Boylan et al., 2008).

The qEEG measures calculated were: amplitude, relative delta power (RDP) (Welch, 1967), spectral edge frequency (SEF), fractal dimension (FD) (Higuchi, 1988; Kasdin, 1995), skewness, kurtosis (Peebles, 2001), discontinuity, interhemispheric symmetry (van Putten, 2007) and synchrony (Scher, 2004). Visual characteristics used for interpretation of neonatal EEG and corresponding quantitative measures used in this study are shown in Table 2. The qEEG measures are defined in Supplementary Appendix A.

2.6. Statistical analysis

The mean and standard deviation were calculated for demographic factors such as birth weight and gestational age. Median, minimum, maximum values, and interquartile range were calculated for age (in hours) at the beginning of the chosen one-hour EEG segments.

The ability of each qEEG measure to differentiate between visually analysed EEG/HIE grades was then tested using the Kruskal–Wallis test. Post hoc analysis was performed using the Mann–Whitney test due to the lack of a normal distribution in the qEEG

Table 1
Classification of EEG background activity in hypoxic ischaemic encephalopathy.

EEG/HIE grade	EEG changes	Description
1	Normal/mild abnormalities	Continuous background pattern with normal/slightly abnormal activity (mild asymmetries, mild voltage depression [30–50 μV]), presence of SWC that might be poorly defined
2	Moderate abnormalities	Discontinuous activity with IBI of ⩽10 s, disrupted SWC, clear asymmetry or asynchrony
3	Major abnormalities	IBI of 10–60 s, lack of variability, severe attenuation of background patterns [<30 μV], absence of SWC
4	Inactive	Background activity <10 μV, or severe discontinuity with IBI ⩾60 s

IBI = interburst interval, SWC = sleep wake cycle, μV = microvolt, s = second. SWC was defined as: normal if all sleep states were present in proportions observed in healthy infants (Scher et al., 2002; Korotchikova et al., 2009); poor or disrupted if SWC was still present but proportionate representation of sleep states was abnormal; absent if there were no state changes in the EEG activity (Murray et al., 2009).

Table 3
Demographic characteristics of the study group.

Demographic data	
Gestational age at birth (weeks)	40.2 (±1.4)*
Birth weight (g)	3430 (±614)*
Age at EEG recording (h)	16.2 (min – 3.7; max – 58.3; Q1 – 8.0, Q3 – 24.3)**
Gender (M/F)	32/22
Mode of delivery	
Emergency Caesarean section	20 (37.0%)
Normal vaginal delivery	12 (22.2%)
Vacuum assisted vaginal delivery	12 (22.2%)
Forceps delivery	5 (9.3%)
Vacuum and forceps delivery	5 (9.3%)
Clinical Sarnat scoring at 24 h	
Mild HIE	22 (40.7%)
Moderate HIE	20 (37.0%)
Severe HIE	12 (22.2%)

* Data are shown as mean with standard deviation.
** Data are shown as median with minimum (min), maximum (max) values and interquartile range (Q1 = 25th percentile, Q3 = 75th percentile).

measures across EEG/HIE grade. A Bonferroni correction was applied so effects are reported at a 0.0167 level of significance.

Finally, multiple linear regression was used to assess the potential of a combination of qEEG measures for predicting visually annotated EEG/HIE grade.

3. Results

3.1. Demographic characteristics of the study group

Continuous video-EEG was recorded from 54 term newborn infants with HIE. Demographic characteristics of the study group are shown in Table 3.

3.2. qEEG measures vs EEG/HIE grade

An example of an epoch of multichannel neonatal EEG for each grade of HIE is shown in Fig. 1. The corresponding qEEG values are shown in Table 4.

The summary statistics of the qEEG measures that were statistically significant across the EEG/HIE grades are shown in Table 5. RDP was lower in EEG/HIE grade 3 and 4 comparing to EEG/HIE grade 1 and 2. Skewness and kurtosis, both measures of continuity of the EEG signal, increased (with the exception of EEG/HIE grade 4) and the amplitude decreased with increasing grade of EEG/HIE. The discontinuity was lower in EEG/HIE grade 1 comparing to EEG/HIE grade 2 and 3 with the lowest value in EEG/HIE grade 4.

The results of the post hoc analysis between successive EEG/HIE grades (Mann–Whitney test) are presented in Table 6. None of the qEEG measures were significantly different between EEG/HIE grade 1 and grade 2. However, the skewness ($z = -2.623$, $p = 0.008$), kurtosis ($z = -2.932$, $p = 0.003$) and amplitude ($z = -3.755$, $p < 0.0001$) showed significant differences between EEG/HIE grade

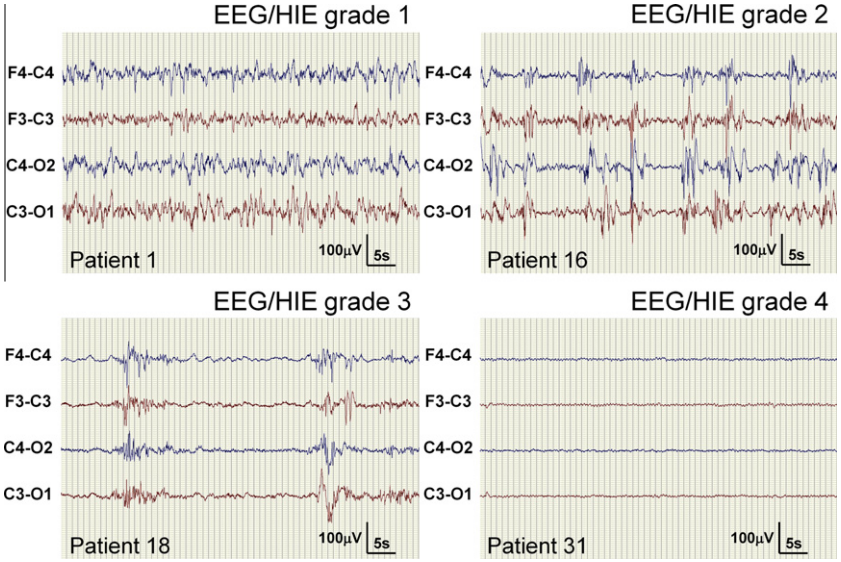

Fig. 1. Ideal examples of graded EEG recordings – approximately 60 s of recording are shown and the time and voltage scale are identical across all 4 examples. Only four EEG channels are demonstrated per patient for better visual presentation.

Table 4
Response of qEEG measures to EEG with different EEG/HIE grade. Actual values for the qEEG measures presented in this table are calculated on the one-hour recordings of which 60s examples are shown in Fig. 1.

EEG/HIE grade	Patient ID	RDP	SEF (Hz)	FD	Skewness	Kurtosis	Amplitude (μV)	Discontinuity	r-sBSI	Synchrony
1	1	0.79	4.03	1.84	0.09	3.72	11.61	4.16	0.52	0.34
2	16	0.81	4.15	1.81	0.20	7.02	10.98	7.01	0.46	0.34
3	18	0.75	4.08	1.84	0.27	10.29	5.87	4.72	0.45	0.38
4	31	0.70	4.39	1.92	0.08	2.91	1.85	0.35	0.39	0.36

RDP = relative delta power, SEF = spectral edge frequency, FD = fractal dimension, r-sBSI = revised standard brain symmetry index, synchrony = interhemispheric synchrony, Hz = Hertz and μV = microvolt.

Table 5
The results of Kruskal–Wallis analysis and summary statistics of the qEEG measures for different EEG/HIE grades (they are presented as median, 25th and 75th percentile).

qEEG measure	Kruskal–Wallis analysis	EEG/HIE grade			
		1	2	3	4
RDP	$H(3) = 10.209, p = 0.017$	0.79(0.77, 0.81)	0.80(0.73, 0.83)	0.73(0.69, 0.77)	0.71(0.61, 0.80)
Skewness	$H(3) = 17.236, p = 0.001$	0.11(0.10, 0.12)	0.13(0.10, 0.17)	0.25(0.17, 0.39)	0.13(0.09, 0.30)
Kurtosis	$H(3) = 16.739, p = 0.001$	4.29(3.82, 4.55)	4.44(4.04, 6.02)	9.01(6.43, 11.55)	5.47(3.24, 11.19)
Amplitude (μV)	$H(3) = 33.328, p < 0.0001$	11.07(9.59, 11.21)	9.20(8.32, 1.16)	5.88(5.10, 6.56)	1.91(1.71, 2.10)
Discontinuity	$H(3) = 16.519, p = 0.001$	4.13(3.75, 4.64)	4.58(3.60, 6.30)	4.58(3.14, 5.71)	0.60(0.33, 1.56)

H = test statistic, RDP = relative delta power and μV = microvolt.

Table 6
Results of Mann–Whitney tests for each qEEG measure comparing EEG/HIE 1 vs 2, 2 vs 3, and 3 vs 4.

qEEG measure	EEG/HIE grade		
	1 vs 2	2 vs 3	3 vs 4
RDP	$U = 159, r = -0.010$	$U = 51, r = -0.33$	$U = 32, r = -0.09$
SEF	$U = 134, r = -0.14$	$U = 58, r = -0.26$	$U = 28, r = -0.18$
FD	$U = 116, r = -0.23$	$U = 46, r = -0.38$	$U = 24, r = -0.26$
Skewness	$U = 106, r = -0.28$	$U = 33, r = -0.51$*	$U = 22, r = -0.31$
Kurtosis	$U = 120, r = -0.21$	$U = 27, r = -0.57$*	$U = 19, r = -0.37$
Amplitude	$U = 104, r = -0.29$	$U = 11, r = -0.73$*	$U = 0, r = -0.79$*
Discontinuity	$U = 126, r = -0.18$	$U = 72, r = -0.12$	$U = 0, r = -0.79$*
Interhemispheric symmetry	$U = 115, r = -0.24$	$U = 48, r = -0.36$	$U = 32, r = -0.09$
Interhemispheric synchrony	$U = 149, r = -0.06$	$U = 66, r = -0.18$	$U = 32, r = -0.09$

U = U-statistic and r = an effect size.
* Means a significant difference in qEEG measure between the two EEG/HIE grades at 0.0167 level of significance.

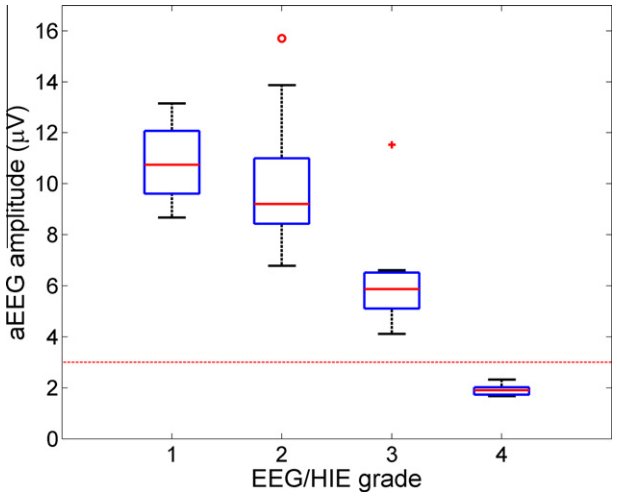

Fig. 2. The distribution of the amplitude measure with respect to visually annotated EEG/HIE grade.

2 and 3. The amplitude and discontinuity showed a significant difference between EEG/HIE grade 3 and 4 ($z = -3.372$, $p < 0.0001$).

The only qEEG measures that did not show a significant difference between EEG/HIE grades were the spectral edge frequency and fractal dimension – measures of the frequency content of the EEG, as well as the measures of interhemispheric symmetry and synchrony.

3.3. Multiple linear regression analysis

A multiple linear regression analysis (MLRA) was then performed to see if qEEG measures could be linearly combined into an equation that could predict EEG/HIE grade.

All recordings with EEG/HIE grade 4 (inactive) were excluded from this analysis as most of the qEEG measures used, with the exception of amplitude, are not useful for the analysis of isoelectric brain activity. EEG/HIE grade 4 can be differentiated from other EEG/HIE grades using amplitude alone. This is shown in Fig. 2. All six EEG recordings classified as EEG/HIE grade 4 (isoelectric) by the EEGers in our dataset were correctly identified based on the amplitude measurement alone with a cut off of 3 μV.

First, a MLRA was performed using only the measures calculated on aEEG (amplitude and discontinuity) to examine if they can predict EEG/HIE grade. The results are shown in Table 7. Amplitude integrated EEG is widely used in NICUs and is thus clinically

Table 7
The grading of EEG in HIE (grade 1–3) using a linear combination of qEEG measures derived from the aEEG (amplitude and discontinuity).

EEG/HIE grade as per EEGers	EEG/HIE grade as predicted by MLRA			Total by EEGers
	1	2	3	
1	22			22
2	6	8		14
3		2	10	12
Total by MLRA	28	10	10	48

MLRA = multiple linear regression analysis and EEGers = electroencephalographers.

Table 8
The grading of EEG in HIE (grade 1–3) using a linear combination of qEEG measures (relative delta power, skewness, kurtosis, amplitude, and discontinuity).

EEG/HIE grade as per EEGers	EEG/HIE grade as predicted by MLRA			Total by EEGers
	1	2	3	
1	22			22
2	4	9	1	14
3		1	11	12
Total by MLRA	26	10	12	48

MLRA = multiple linear regression analysis and EEGers = electroencephalographers.

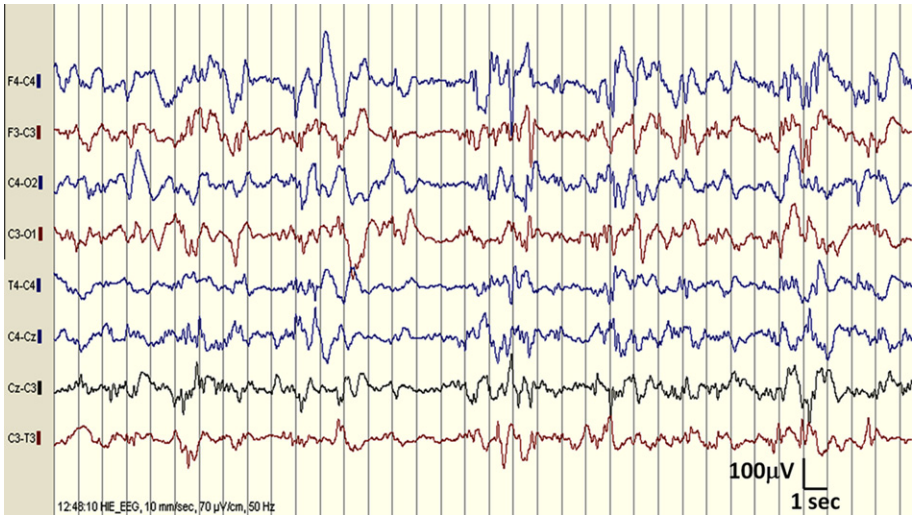

Fig. 3. A 35 s example from the EEG recording visually graded as EEG/HIE 2 by the electroencephalographers because of significantly disrupted sleep wake architecture and predicted to be a grade 1 by the multiple linear regression analysis as sleep wake cycle was not taken into account in our quantitative EEG analysis.

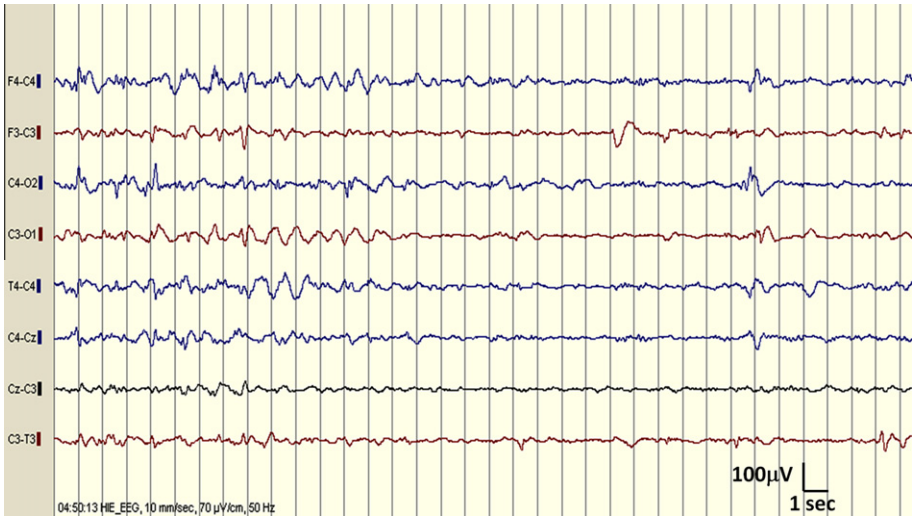

Fig. 4. A 35 s example from the EEG recording graded as EEG/HIE 3 by the electroencephalographers and predicted to be a grade 2 by the multiple linear regression analysis.

relevant. These aEEG measures were shown to have the lowest *p*-values in the Kruskal–Wallis analysis.

Second, a MLRA was used to see if a combination of the significantly different qEEG measures, according to the Kruskal–Wallis analysis (RDP, skewness, kurtosis, amplitude, and discontinuity), could be used to predict EEG/HIE grade. The results are shown in Table 8.

As demonstrated in Table 8, 87.5% (42/48) of the original EEG files (EEG/HIE grade 1–3) annotated visually were correctly predicted by the MLRA using a combination of significant qEEG measures. As all EEG/HIE grade 4 recordings were correctly identified using the amplitude measures only, the combined classification accuracy (EEG/HIE grade 1–4) using all qEEG measures is 89% (48/54).

Two EEG recordings were considered outliers in the dataset. An outlier was defined as a case that had an absolute standardised residual greater than 2. These two recordings were subsequently inspected further to determine why the qEEG analysis was incorrect.

The first recording was visually graded as EEG/HIE grade 2 by the EEGers but predicted to be a grade 1 by the MLRA. The EEGers graded this recording as EEG/HIE 2 due to low variability of the EEG signal within one hour of recording and absent SWC. The entire recording had a persistently discontinuous background EEG pattern. The qEEG analysis classified this recording differently because the RDP and amplitude calculated on this recording were high. These findings are not surprising as RDP and amplitude have been shown to be significantly higher in quiet compared to active sleep (Korotchikova et al., 2009). As SWC was not taken into account in our qEEG analysis, this recording was classified as EEG/HIE grade 1. A 35 s example taken from this EEG recording is shown in Fig. 3.

The second outlier was a recording that was assigned grade 3 by the EEGers but predicted to be a grade 2 by the MLRA. Grade 3 was given to this EEG as it had no SWC present, very low variability of the EEG signal, generally low voltage ranging from 0 to 60 μV, and suppression periods for up to 15 s. The value of the discontinuity measure calculated on this EEG was low. This might explain the different classification of this EEG recording by the MRLA. Fig. 4 contains a 35 s example from this recording.

4. Discussion

We have shown that qEEG measures are significantly different between EEG/HIE grades as determined by visual inspection of

the EEG. However, no single qEEG measure was found capable of discriminating between all grades of EEG/HIE. Therefore, we investigated a linear combination of qEEG measures and have shown that a combination of qEEG measures can accurately predict EEG/HIE grade. This is an important finding as it demonstrates the potential to simplify interpretation of the EEG signal for clinical use in the NICU, thus facilitating early recognition of HIE grade and early initiation of appropriate intervention.

The best performing measures in distinguishing between EEG/HIE grades in our study were the measures calculated on aEEG (amplitude and discontinuity). The amplitude measure was particularly useful in discriminating EEG/HIE grade 4 recordings with a clear cut off point of 3 μV (all qEEG values mentioned in this paper are calculated based on the applied bipolar montage). None of the qEEG measures used in this study were significantly different between EEG/HIE grade 1 and 2. This finding reflects the difficulties that exist in visual classification of EEG in HIE. Individual visual EEG classification systems have been shown to be most robust at the extremes. Selton and Andre found that 90% of the infants with clinical grade 3 HIE, had a severely abnormal EEG on their grading system, and 7.4% of those with grade 3 HIE had a normal EEG. At the other end of the spectrum, no infant with clinical grade 1 HIE had a severely abnormal EEG, and 35.7% had a normal EEG ($p < 0.001$) (Selton and Andre, 1997). The moderately abnormal group are less easily defined, with less definite outcomes, and it is these EEGs that most classification systems disagree on. The differing opinions regarding grading of features include such features as; diffuse delta patterns being moderately (Holmes and Lombroso, 1993; Selton and Andre, 1997) or severely abnormal (van Lieshout et al., 1995; Zeinstra et al., 2001); dysmaturity being normal (Holmes and Lombroso, 1993; Biagioni et al., 2001) or moderately abnormal (van Lieshout et al., 1995; Zeinstra et al., 2001); and asymmetry >50% being moderately (Murray et al., 2009) or severely abnormal (van Lieshout et al., 1995; Zeinstra et al., 2001).

The qEEG measures that failed to distinguish between the successive EEG/HIE grades were the measures of the frequency content of EEG as well as the measures of interhemispheric symmetry and synchrony. This suggests that the frequency content of EEG bursts is not significantly different from the frequency content of continuous EEG background across our cohort of infants with different EEG/HIE grades. The only frequency measure that showed significance in the Kruskal–Wallis analysis was the RDP. The RDP decreased with the increasing EEG/HIE grade apart from EEG/HIE grade 2. The RDP in EEG/HIE grade 2 was higher compared to EEG/HIE grade 1 (0.80 vs 0.79). However, this can be explained as the RDP is higher in quiet compared to active sleep (Korotchikova et al., 2009) and quiet sleep dominates the EEG in EEG/HIE grade 2 (Scher et al., 2002). The other qEEG measures that were not significantly different between EEG/HIE grades were the measures of interhemispheric symmetry and synchrony. While EEG recordings with pronounced interhemispheric asymmetry and asynchrony were included in the analysis, the asymmetry/asynchrony were neither present consistently throughout the recording nor in every infant's recording with a particular EEG/HIE grade. Thus, this EEG characteristic was statistically insignificant when a large cohort of infants was studied.

Previous work in the area of automated classification of the background activity of neonatal EEG has been attempted. However, the main focus of these studies was on either automated detection of SWC (Scher, 2004; Piryatinska et al., 2009; Gerla et al., 2009) or the burst-suppression pattern (Lofhede et al., 2010). The main difficulty in the development of automated EEG/HIE classification is the lack of a single accepted clearly defined, universal visual classification system, or even a predominant one, such as exists for clinical scoring of HIE such as Sarnat scoring. Most of the different visual classification systems are based upon the same EEG measures, but with slight variations in interpretation of the value of a feature which constitutes a particular grade. For this study we adapted the classification system described in Murray et al. (2009). The authors recognise that although this is a robust and validated classification system, minor variations in results would be expected if a different visual classification system was used, similar to what would be expected if a single neurophysiologist used two separate visual classification systems to grade the same EEG recording. We advocate that a consensus agreement on a universal visual EEG/HIE classification score is required, not only as the means of overcoming the error caused by the use of different visual classification systems, but also to facilitate research in general by allowing easy comparison between study populations. When such a universal classification system of EEG in HIE is developed it can be then quantified using objective measurements.

Apart from the lack of a universal visual classification system, three main limitations to our study are recognised. Firstly, the variability of the qEEG features over the hour of recording, such as that caused by SWC, was not taken into account in the current qEEG study. The analysis of EEG recordings classified alternatively by the MLRA suggests that the variability of the qEEG measures over time may be an important indicator of EEG/HIE grade. Secondly, we have only used EEG recordings that are free of seizures and high amplitude artefact associated with gross body movements. This can be overcome in future analyses by incorporating methods of automated seizure detection, removing artefacts from the EEG recording, or quarantining contaminated EEG. Thirdly, a small sample size in this study means that the predictive equation based on the qEEG features cannot be used in general to classify EEG, but it does highlight the potential of qEEG analysis for future use.

To our knowledge, this study is the first to investigate the performance of specific quantitative measures to discriminate between EEG grades of HIE. The results of our study suggest that the use of several characteristics of the EEG must be considered before an EEG/HIE grade can be accurately assigned as evidenced by the MLRA. This multiple feature approach supports the method of interpretation used by neurophysiologists i.e. many features of the EEG are considered during classification. There is an opportunity for more advanced qEEG measures coupled with alternate classifier implementations, such as machine learning, to improve automated analysis of neonatal EEG (Lofhede et al., 2010).

5. Conclusion

Quantitative analysis of the neonatal EEG can facilitate early diagnosis of severity of HIE thus improving the long-term outcome of infants. The results of this study have shown that quantitative analysis of background EEG activity using measures based on the amplitude, frequency content and continuity of the EEG is associated with a visual interpretation of the EEG performed by experienced EEGers.

The identification of the qEEG measures that are significantly different across EEG/HIE grades is an important first step in the development of automated neonatal EEG analysis techniques.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2010.12.059.

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