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A standardised assessment scheme for conventional EEG in preterm infants

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HIGHLIGHTS

- A standardised scheme for preterm EEG assessment at different post-menstrual age is needed.
- We have developed a standard EEG assessment scheme for preterm infants.
- Good interobserver agreement is achieved using the present scheme.

ABSTRACT

Objective: To develop a standardised scheme for assessing normal and abnormal electroencephalography (EEG) features of preterm infants. To assess the interobserver agreement of this assessment scheme.
Methods: We created a standardised EEG assessment scheme for 6 different post-menstrual age (PMA) groups using 4 EEG categories. Two experts, not involved in the development of the scheme, evaluated this on 24 infants <32 weeks gestational age (GA) using random 2 hour EEG epochs. Where disagreements were found, the features were checked and modified. Finally, the two experts independently evaluated 2 hour EEG epochs from an additional 12 infants <37 weeks GA. The percentage of agreement was calculated as the ratio of agreements to the sum of agreements plus disagreements.
Results: Good agreement in all patients and EEG feature category was obtained, with a median agreement between 80% and 100% over the 4 EEG assessment categories. No difference was found in agreement rates between the normal and abnormal features ($p = 0.959$).
Conclusions: We developed a standard EEG assessment scheme for preterm infants that shows good interobserver agreement.
Significance: This will provide information to Neonatal Intensive Care Unit (NICU) staff about brain activity and maturation. We hope this will prove useful for many centres seeking to use neuromonitoring during critical care for preterm infants.

1. Introduction

Conventional EEG is a reliable tool for the assessment of neonatal brain activity and has been extensively shown to correlate with outcome (Tharp et al., 1981; Watanabe et al., 1983; Clancy et al., 1984; Radvanyi-Bouvet et al., 1987; Biagioni et al., 1996; Marret et al., 1997; Watanabe et al., 1999; Biagioni et al. 2000; Murayama et al., 2002; Le Bihannic et al., 2012; Lloyd et al., 2016).

Due to the increasing survival rates of very and extremely preterm infants, there is an urgent need to provide well-defined boundaries between normal and abnormal EEG features at different post-menstrual age (PMA) and to objectively evaluate brain activity and maturation.

Although the EEG characteristics of preterm and term infants are vastly different, the existing EEG assessment systems have been developed for mixed populations of both preterm and term infants (Watanabe et al., 1999; Holmes and Lombroso, 1993).

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These assessment schemes lack a more systematic approach of identifying specific features of the preterm EEG, which develop with PMA. This is evident in a recently developed system, named the 'standardized computer-based organised reporting of EEG' (SCORE), which provides a standard way of reporting EEG without attempting to grade the EEG (Beniczky et al., 2013;Beniczky et al., 2017). As this is a system targeting infants at all age groups, there are no specific EEG features defined for preterm infants at varying PMA. A specific EEG scoring system for very preterm infants was recently developed to predict neurodevelopmental outcome (Perivier at al., 2016). However, this score is inserted in a multimodal evaluation which includes EEG surveillance, clinical assessment at discharge and cerebral imaging for outcome assessment. This approach is similar to previous studies of preterm infants (Pisani et al., 2008; Pisani et al., 2016; Lloyd et al., 2016), in which EEG grading systems have been used together with other parameters to predict outcome (Holmes and Lombroso, 1993; Watanabe et al., 1999).

Therefore, the aim of our study was to develop a method, which was as objective as possible, to evaluate and analyse normal and abnormal EEG features in preterm infants, at different ages and to assess the interobserver agreement of this method when tested by two experts independently.

2. Materials and methods

2.1. Neurophysiological data – EEG procedures

We retrospectively used EEG data from preterm infants previously collected between April 2009 and March 2011. The NicoletOne EEG system (CareFusion Co., San Diego, USA) was used to record continuous video-EEG. EEG application was performed after consultation with the medical and nursing staff and when the infant was clinically stable. Silver-silver chloride electrodes were applied to the scalp, using a modified neonatal version of the international 10/20 system. The active electrodes were applied at positions F4, F3, C4, Cz, C3, T4, T3, O2 and O1. Reference electrodes were placed at Fz and ground electrodes were behind the left ear. Eight channels of EEG were collected at a sampling rate of 256 Hz. The method has previously been described in depth (Lloyd et al., 2015). The EEG recordings were visually analysed for quality and excluded if poor (for instance, the presence of artefacts preventing EEG interpretation).

2.2. Patients

Preterm infants less than 37 weeks GA who underwent continuous conventional EEG monitoring at the Neonatal Intensive Care Unit of Cork University Maternity Hospital in the first 3 postnatal days between April 2009 and March 2011 were retrospectively selected.

The only exclusion criterion was the presence of major congenital malformations. Ethical approval was obtained by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Ireland. Written informed parental consent was obtained.

Two groups of patients were randomly selected from a total number of 151 available preterm infants to undertake two independent phases of analysis (n=24 for Phase 1 and n=12 for Phase 2).

2.3. Literature review and manual-scheme development

A comprehensive literature review was performed to identify existing descriptions and definitions of both normal and abnormal EEG features in preterm infants. Searches were completed with PUBMed with filters that eliminated any 'non-human' study. No language restrictions were applied. We included studies from the year 1990 onwards. Authors EP and RL initially searched the literature independently. In addition, secondary sources of data (such as references used in papers) and personal libraries were also included. This was undertaken in order to ensure that all previously published preterm EEG features described in relevant papers were included in our objective assessment scheme. (Alix et al., 2015; André et al., 2010; Holmes and Lombroso, 1993; Okumura et al., 2003; Périvier et al., 2016; Selton et al., 2000; Tich et al., 2007; Tsuchida et al., 2013; Vecchierini et al., 2007; Watanabe et al., 1999). Following the literature review, an EEG assessment scheme was developed with accompanying instructions for use. The instructions provided definitions for all the EEG features at specific PMA (6 different age groups, according to the existing literature; see André et al., 2010) and guidance on how to grade specific abnormal waves and features into mild, moderate and severe grades (Supplementary Table 1). The EEG features were divided into 4 categories: (1) temporal organisation/cyclicity (sleep-wake cycles, Inter-burst Intervals -IBI-), (2) normal waves (physiological patterns/waves related to specific GA, such as, sharp theta on the occipitals of prematures/Occipital Sawtooth, slow delta waves, delta brushes), (3) abnormal waves (pathological waves related to specific GA, such as positive rolandic sharps –PRS-, positive temporal sharps –PTS-, mechanical brushes..), (4) abnormal features (asymmetry, asynchrony, pathologic voltage, excess of discontinuity, Burst Suppression pattern-, Brief Intermittent Rhythmic Discharges –BIRDs-,Periodic lateralized epileptiform discharges –PLEDs-, seizures and status epilepticus). The EEG scheme was developed to simplify and guide preterm EEG evaluation at the cot side. The scheme involves scoring 1 or 0 to note the presence or absence of the required features and grading into mild, moderate and severe for specific features (see the manual in Supplementary Table 1).

2.4. EEG analysis method

Two experts, not involved in the creation of the scheme (G.B.B., F.P.), used the EEG assessment scheme to review preterm EEGs during two separate analysis phases. For both phases of analysis, 2-h EEG epochs was reviewed for each infant; the 2-h epochs were randomly selected at 12, 24, 48, and 72 h postnatal age from each data group. The 2 experts used the EEG assessment system to interpret the EEG, while being blinded to all information except for GA, administration of morphine, phenobarbitone or other AEDs during EEG and time of EEG recording post-delivery. Following the first phase, the two experts identified any difficulties in implementing the grading scheme, disagreements were discussed and suggestions were made for further modifications to the assessment scheme. During the second analysis phase, the 2 experts reviewed the second EEG group dataset independently with the revised scheme.

3. Statistical analysis

For each infant, percentage agreement between the two examiners was calculated for each EEG category (temporal organisation/cyclicity, normal waves, abnormal waves and abnormal features). Agreement was defined as the ratio of the number of agreements to the sum of agreements plus disagreements within a category. For each feature, agreement was defined as both examiners assigning the same score to an EEG, while disagreement was defined as the two examiners assigning a different score to an EEG. Furthermore, percentage agreement was compared between the normal and abnormal features using a Wilcoxon signed-rank test. For this analysis, the mildly abnormal features were grouped with

the normal features, as previously performed in other studies (Pisani et al., 2016; Lloyd et al. 2016). The statistical analysis was performed using IBM SPSS Statistics, version 24. The statistical test was 2-tailed and a p-value < 0.05 was considered to be statistically significant. Continuous data were described using the median and interquartile range (IQR).

4. Results

4.1. EEG assessment system

An EEG assessment scheme was developed with maturation-specific features for 6 different groups of PMA (23–25, 26–27, 28–29, 30–31, 32–34, 35–36 weeks) (Fig. 1). It comprised 4 categories of EEG features, namely: (1) temporal organisation/cyclicity, (2) normal waves, (3) abnormal waves and (4) abnormal features. The normative values and definitions of each EEG feature can vary depending on the PMA group (Supplementary Table 1).

Instructions were also created with the normative values and definitions for each feature for each age group (definitive version in Supplementary Table 1). The instructions contain guidance for grading specific abnormal waves (such as immature waves and deformed waves and mechanical brushes, grading their amount in: few, moderate or several) and for abnormal features (such as low voltage and discontinuity, graded in: mild, moderate or severe).

In phase 1, the 2 experts reviewed 2-h epoch recordings from data group 1, which consisted of 24 infants (range GA: 23 + 3 – 31 + 4 weeks) at 12, 24, 48, or 72 hours after birth. In phase 2, they used a modified version of this scheme to evaluate 2-h epoch recordings from data group 2, with 12 infants (range GA: 23 + 3 – 36 + 1 weeks) at the same randomly selected time points. The demographic data of all patients are reported in Supplementary Table 2.

4.2. First–phase analysis (evaluation by two experts)

Agreements for this analysis were not calculated as the two experts discussed the issues in order to improve the standardised features to be included in the EEG assessment scheme.

Following this step, some features were modified and some new features were added in order to improve preterm EEG characterization.

Added features included normal duration of continuity after 26 weeks and amplitude of continuous activity in the different PMA (Vecchierini et al., 2007; André et al., 2010). This feature was added to all PMA groups, except for the 23–25 PMA group, due to lack of persistent continuous activity periods in this age group. Two features added to all PMA groups were the level of abnormal discontinuity and the level of abnormal voltage. In the instructions (Supplementary Table 1), a description for mild, moderate and severe discontinuity and for abnormal voltage were included, in order to correctly grade these abnormalities. Two new features that were added for all PMA groups were Status Epilepticus (Scher et al., 1993; Pavlidis et al., 2015) and Periodic Lateralized Epileptiform Discharges (PLEDS) (André et al., 2010; Pavlidis et al., 2017). Burst Suppression was removed in the younger PMA groups and only included from 30 weeks PMA and older. This decision was made as currently there is uncertainty in how to define Burst Suppression in the younger PMA, as previously suggested by some authors (Beniczky et al., 2013). Additionally, immature waves were removed from the 23 to 25 weeks PMA group, due to lack of information about a normal EEG < 23 weeks PMA. Certain features were combined together to simplify the scheme. Theta and sharp theta were combined in the normal features, while all sharp waves were grouped together. STOPS and Occipital Sawtooth waves were grouped together, as they are similar features with similar clinical relevance. The deformed waves feature was adapted also: deformed waves and mechanical brushes are independent features in the scheme. Finally, to

	23-25wks	26-27wks	28-29wks	30-31wks	32-34wks	35-36wks
Group 1 (Temporal Organisation)	Cyclicity	Cyclicity	Cyclicity	Cyclicity	Cyclicity	Cyclicity
	IBI	IBI	IBI	IBI	IBI	IBI
	Burst	Burst	Burst	Burst	Burst	Burst
		Continuity	Continuity	Continuity	Continuity	Continuity
Group 2 (Normal Waves)	STOPS/ Occipital	STOPS/ Occipital	PTT	PTT	PTT	Delta
	sawtooth	sawtooth				Brushes
	Delta	PTT	Delta Brushes	Delta Brushes	Delta Brushes	Delta
	Theta	Delta	Delta	Delta	Delta	Theta
		Theta	Theta	Theta	Theta	Frontal transient
					Frontal transient	SAD
Group 3 (Abnormal Waves)	PRS	PRS	PRS	PRS	PRS	PRS
	PTS	PTS	PTS	PTS	PTS	PTS
	Sharps	Sharps	Sharps	Sharps	Sharps	Sharps
	Deformed waves	Deformed waves	Deformed waves	Deformed waves	Deformed waves	Deformed waves
	Mechanical brushes	Mechanical brushes	Mechanical brushes	Mechanical brushes	Mechanical brushes	Mechanical brushes
		Immature Waves	Immature Waves	Immature Waves	Immature Waves	Immature Waves
Group 4 (Abnormal Features)	Asymmetry	Asymmetry	Asymmetry	Asymmetry	Asymmetry	Asymmetry
	Asynchrony	Asynchrony	Asynchrony	Asynchrony	Asynchrony	Asynchrony
	Discontinuity	Discontinuity	Discontinuity	Discontinuity	Discontinuity	Discontinuity
	Low Voltage	Low Voltage	Low Voltage	Low Voltage	Low Voltage	Low Voltage
	Isoelectric	Isoelectric	Isoelectric	Isoelectric	Isoelectric	Isoelectric
			Burst Sup	Burst Sup	Burst Sup	Burst Sup
	BIRDs	BIRDs	BIRDs	BIRDs	BIRDs	BIRDs
	PLEDs	PLEDs	PLEDs	PLEDs	PLEDs	PLEDs
	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures
	Status	Status	Status	Status	Status	Status
Medications						
Annotations						

Fig. 1. EEG assessment scheme with 6 groups of PMA and the relevant EEG features divided in 4 categories.

improve the format of the scheme and to make it more practical, two sections were included to incorporate information regarding medication and any specific comments.

All the definitions and features with instructions for assessment were included in the manual (Supplementary Table 1).

4.3. Second –phase analysis (independent evaluation by two experts)

Percentage agreement between the 2 experts showed a good agreement for all patients and for each EEG category with median percentage agreement ranging from 80% to 100% (Table 1) across the 4 categories. An agreement < 50% occurred only once, where the percentage agreement for normal waves for patient 2 was zero as there was no agreement between reviewers. Retrospective revision of the EEG and the reviewers analysis identified that this particular EEG was severely pathological, where one reviewer identified no normal waves at all in the 2 hours epoch and the other identified few normal waves in the background of the abnormal EEG trace. However both the experts showed a high agreement for the assessment of the temporal organisation/cyclicity, abnormal waves and abnormal features, showing that they both agreed on the fact that this EEG was clearly abnormal. Apart from this category, the overall agreement for this patient was good. Grouping the EEG categories into normal and abnormal groups, high-level of agreement (median 88.9% and 86.6%) between the experts was found, with no difference in agreement between the groups (p = 0.959) (Table 2).

Table 2
Percentage of agreement between observers in normal versus abnormal EEG features.

Patient	GA category	Normal	Abnormal
1	23–25	100	85.7
2		50	85.7
3	26–27	62.5	93.3
4		75	93.3
5	28–29	100	73.3
6		100	73.3
7	30–31	75	81.3
8		87.5	87.5
9	32–34	100	100
10		88.9	81.3
11	35–36	88.9	87.5
12		100	93.8
Median (IQR)		88.9 (75 to 100)	86.6 (81.3 to 93.3)
Difference: Median(IQR)		0.70 (-15.3 to 12.6)	
p-value[a]		0.959	

Percentage agreement between the two observers for normal and abnormal features in each patient. Median (IQR) were also calculated for each feature category. Wilcoxon signed-rank test was used to compare the performance of normal and abnormal features.

[a] Wilcoxon signed-rank test.

5. Discussion

We developed a tailored, age-specific, preterm EEG assessment scheme with user instructions to specifically evaluate the EEG of preterm infants at different PMA, utilizing all current knowledge about this topic.

The six different age groups were chosen according to existing literature (André et al., 2010) that suggests this subdivision following the evolution of EEG features. An approximation of 2 weeks is usually accepted in the estimation of the GA by EEG visual analysis, and this is why we think that the present subdivision is the best method to assess the developing features of the EEG in preterm infants.

The selection of what was included was carefully considered, to make the system as concise and as user friendly as possible to aid analysis at the cot side. Of course, the time required for the EEG assessment using this scheme may vary depending on the reviewer expertise and difficulty of the EEG trace. The main strength of this scheme is that it provides a defined list of all the EEG features that need to be assessed at each PMA in order to accomplish an objective review of the EEG; therefore, this scheme helps considerably in reducing reviewers' subjectivity, guiding their assessment.

This system enables qualitative assessment of the EEG. However, it also enables further quantitative analysis, if required.

Using this method, we have demonstrated that agreement between two independent experts from two different centres is high, with median agreement rates between 80% and 100% for the 4 categories of EEG features. Additionally, high median agreement of 89% was evident for normal features and 87% for abnormal features, with no significant difference in agreement between the normal and abnormal groups (p = 0.959).

Interobserver agreement in EEG data interpretation is dependent on the training and expertise of the EEG examiners (Beniczky et al., 2013). Visual analysis of EEG shows different interobserver agreement at different ages and when considering different EEG features in adults and older children (Stroink et al., 2006; Gerber et al., 2008). Specifically, epileptic discharges and abnormal background patterns have shown almost perfect – substantial agreement between examiners, whilst focal non-epileptic abnormalities have shown moderate agreement in children with new diagnosis of seizure (Stroink et al., 2006). Furthermore, in children,

Table 1
Percentage of agreement between examiners for each category of features in each patient.

Patient	GA category	Temporal organisation/cyclicity	Normal waves	Abnormal waves	Abnormal features
1	23–25	100	100	80	88.9
2		100	0	80	88.9
3	26–27	50	75	83.3	100
4		75	75	83.3	100
5	28–29	100	100	66.7	77.8
6		100	100	50	88.9
7	30–31	50	100	66.7	90
8		100	75	66.7	100
9	32–34	100	100	100	100
10		100	80	66.7	90
11	35–36	100	80	83.3	90
12		100	100	83.3	100
Median (IQR)		100 (87.5 to 100)	90 (75.0 to 100)	80 (66.7 to 83.3)	90 (88.9 to 100)

Percentage agreement between the two observers for all four feature categories in each patient. Median and inter-quartile range (IQR) were also calculated for each feature category.

it has been demonstrated that using precise definitions might improve interobserver agreement (Stroink et al., 2006). A recent study for neonatal EEG has shown variability in neonatal EEG background interpretation across electroencephalographers (Massey et al., 2019). Indeed, interrater agreement was consistently highest for voltage, seizure presence, continuity, burst voltage, suppressed background presence, delta activity presence, theta activity presence, presence of graphoelements, and overall impression. However, agreement was poor or inconsistent for all other features (Massey et al., 2019). Because of the peculiarities of neonatal EEG, we believe that the use of well-described definitions for each typical EEG feature and a shared assessment system would be beneficial in order to have an objective qualitative analysis of the neonatal EEG and a better agreement between observers for preterm EEG evaluation.

Some studies testing interobserver agreement for neonatal seizure detection in term infants have been published (Stevenson et al., 2015;Shah et al., 2008). Interobserver agreement was high when international experts on neonatal EEG reviewed multichannel EEG for seizure detection; however, lower agreement was reported in shorter or rarer seizures (Stevenson et al., 2015). In another study, the authors reported a substantial interobserver agreement when two experts in neonatal EEG reviewed 2-channel continuous EEG with aEEG for seizure detection in term infants, compared to a fair degree of agreement when only using the aEEG (Shah et al., 2008).

However, little is known about interobserver agreement in neonatal EEG interpretation in general, particularly for background activity evaluation and for its assessment in preterm infants, for whom only specific features have been studied (Murphy et al., 2015; O'Toole et al., 2017). Murphy et al. calculated interobserver agreement for burst/interburst detection and showed that moderate levels of agreement (median Kappa from 0.53 to 0.66) were achieved among 3 observers with annotations summarizing all channels (Murphy et al., 2015). Similar results were found in a more recent study, with annotations of burst/interburst on a channel-by-channel basis achieving a Kappa score agreement of 0.60 (95% CI: 0.21–0.74) (O'Toole et al., 2017).

A comprehensive glossary for neonatal EEG has previously been developed by André et al. (2010). Recently a standard computer-based system for EEG assessment and reporting has been developed, with a subsection on neonatal EEG for both term and preterm infants (Beniczky et al., 2013; Beniczky et al., 2017). Additionally, previous studies gave indications on normal and abnormal features of the EEG in preterm (Vecchierini et al., 2007; Tich et al., 2007). However, because of the increasing survival rates of very and extremely preterm infants, knowledge about the features of the EEG in this population is still growing, particularly with respect to the normal duration of interburst intervals at specific GA/PMA. We believe that this explains why the highest disagreement between raters occurred in the lower PMA groups in our study. Indeed, uncertainties about boundaries between the normal and abnormal features are still present and differences exist between EEG readers and different centres.

A tailored scheme for infants at different PMA and normative definitions for normal and abnormal features is needed in order to develop an accurate system to correctly grade the preterm EEG. Certainly, there is a huge demand to assess maturation of brain function, to effectively monitor and support brain development and to accurately assess prognosis.

Multichannel EEG is a valid tool to assess preterm neurodevelopment. EEG background activity and the presence of seizures have already been shown to be related to outcome in preterm infants (Tharp et al. 1981; Watanabe et al., 1983; Clancy et al., 1984; Radvanyi-Bouvet et al., 1987; Biagioni et al., 1996; Marret et al., 1997; Watanabe et al., 1999; Biagioni et al., 2000; Murayama et al., 2002; Le Bihannic et al., 2012; Ronen et al., 2007; Pisani et al., 2008; Pisani et al., 2012; Pisani et al., 2016; Vesoulis et al., 2014). However, its usefulness depends on the experience of the reader and the grading assessment scheme used. An objective system to evaluate EEG in preterm infants is warranted.

We believe that the approach presented in this study offers a higher possibility of achieving a consensus in the evaluation of the preterm EEG between different readers and lays the foundation for a tailored grading system for preterm EEG for prognostic purposes in this population.

A limitation of the present study is the number of subjects evaluated, thus studies with a larger sample are advisable. Future directions for the present EEG assessment system will be to implement this: (1) for grading preterm brain function in a large sample of preterm infants; (2) assessing its performance when applied to serial follow-up EEG and for the prediction of neurodevelopmental outcome; (3) validating the performances of the final developed grading system in other centres.

6. Conclusion

The present work represents the first step towards a standardized scheme for the analysis of EEG in preterm infants. This will allow a better understanding of the relationship between EEG and prognosis in this population and will possibly provide clearer descriptions of the features that EEG readers need to take into account when approaching a preterm EEG. We hope that this system, which presents high interobserver agreement, will be trialed in many different centres in the near-future allowing for a more universal way of assessing preterm EEG and the opportunity to pool larger data sets.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.09.028.

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