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Multimodal predictor of neurodevelopmental outcome in newborns with hypoxic-ischaemic encephalopathy

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ABSTRACT

Automated multimodal prediction of outcome in newborns with hypoxic-ischaemic encephalopathy is investigated in this work. Routine clinical measures and 1 h EEG and ECG recordings 24 h after birth were obtained from 38 newborns with different grades of HIE. Each newborn was reassessed at 24 months to establish their neurodevelopmental outcome. A set of multimodal features is extracted from the clinical, heart rate and EEG measures and is fed into a support vector machine classifier. The performance is reported with the statistically most unbiased leave-one-patient-out performance assessment routine. A subset of informative features, whose rankings are consistent across all patients, is identified. The best performance is obtained using a subset of 9 EEG, 2 h and 1 clinical feature, leading to an area under the ROC curve of 87% and accuracy of 84% which compares favourably to the EEG-based clinical outcome prediction, previously reported on the same data. The work presents a promising step towards the use of multimodal data in building an objective decision support tool for clinical prediction of neurodevelopmental outcome in newborns with hypoxic-ischaemic encephalopathy.

1. Introduction

Perinatal hypoxic-ischaemic injury remains a major cause of neurodevelopmental disability. It is thought to affect between 3 and 5 per 1000 live births [1] and accounts for 23% of all neonatal deaths worldwide. With the advent of potential neuroprotective therapies in the form of induced hypothermia, early and accurate methods of diagnosis of hypoxic-ischaemic encephalopathy (HIE) have become increasingly important [38,39]. At the same time, reliable prognostic information is vital in order to counsel parents and caregivers. It is often a major challenge facing those caring for infants with HIE [2].

To date, several different types of monitoring have been studied for outcome prediction. The prognostic value of the EEG in the prediction of long-term outcome is well documented [2–5]. A meta-analysis by Sinclair et al. [3] concluded that burst suppression, slow activity, low voltage and an isoelectric pattern are associated with a markedly increased risk of death or neurodevelopmental handicap. Ramaswamy et al. [6] reviewed biomarkers in full-term newborns with encephalopathy to determine if current biomarkers were strong enough for clinical implementation as predictors of outcome. The review concluded that no biomarker had yet been studied extensively enough to warrant routine clinical use. Laptook et al. [7] reported that Apgar scores assigned at 10 min provided useful prognostic information. However, both the American Academy of Pediatrics and the American College of Obstetrics and Gynaecology recommended that the Apgar score alone should not be used as a predictor of neurodevelopmental outcome [8]. Lingwood et al. [9] hypothesized that cerebral impedance as measured by bioimpedance spectroscopy would be increased in newborns who have suffered a hypoxic/ischaemic insult and who subsequently have a poor neurological outcome. However, on examining a set of 24 newborns it was concluded that this attribute was not suitable for discrimination of outcome. Jyoti et al. [10] developed simplified magnetic resonance grades and found these grades to be highly predictive of neurodevelopmental outcome. However, the optimal timing of an MRI examination for prognosis in newborns with HIE is the second week of life and therefore its use for early prognostication may be limited [11].

The development of automated decision support systems for monitoring in the newborn is a rapidly expanding area [44]. Both

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EEG and heart rate variability (HRV) have been incorporated in the automated detection of neonatal seizures [12,13]. Neonatal HR monitoring has also been used in the prediction of sepsis and systematic inflammatory response syndrome [14]. HRV is thought to provide information on the autonomic balance of the infant, which may be disturbed post hypoxic injury [15]. More recently, depressed HRV in neonates has been associated with moderate-to-severe abnormalities on EEG and MRI [40]. Vergales et al. [40] have also found that low HRV remained significantly associated with adverse short-term outcomes (day 4–7).

The messages from the clinical literature, both with positive and negative conclusions, show that there is no single measure that provides reliable long term prognostication. Most of the cited works though were limited to linear methods that consider a single feature at a time. A nonlinear complex relationship between these predictors has not been explored, and in fact it may improve accuracy, with each parameter providing complementary information. In this study, a multimodal combination of routine clinical markers, EEG and HR parameters is investigated together with non-linear support vector machines (SVMs) employed for neurodevelopmental outcome prediction at 24 months in newborn infants with HIE.

The paper is organized as follows: Section 2 details the clinical dataset used in the experiments, introduces the investigated features, and describes the outcome prediction system developed in the group, along with the feature selection routine. Section 3 presents and discusses obtained results. Conclusions are drawn in Section 4.

2. Methods

2.1. Database

Newborns were prospectively recruited into this study if they fulfilled two or more of the following criteria: initial capillary or arterial pH <7.1, Apgar score <5 at 5 min, initial capillary or arterial lactate >7 mmol/l (normal newborn values <4 mmol/l) or abnormal neurology/clinical seizures. Infants who met the initial criteria were examined using a standardized method of neonatal neurological assessment, the Amiel–Tison method [16]. Initial pH and base deficit (BD) were analysed on admission to the neonatal unit (usually within 30 min of birth) on a unit-based ABL300 blood gas analyser (Radiometer, Copenhagen, Denmark).

Video-EEG and ECG data were recorded synchronously for each patient using the Viasys NicOne EEG system, with a sampling rate of 256 Hz. The 10–20 system of electrode placement, modified for newborns was used with the following montage: F4-C4, C4-O2, F3-C3, C3-O1, T4-C4, C4-Cz, Cz-C3 and C3-T3. Recordings were commenced as soon as possible after birth. All recordings took place in the neonatal intensive care unit of Cork University Maternity Hospital between May 2003 and May 2005, and the study had full ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals. Newborns were not treated with therapeutic hypothermia. From these recordings, 1-hour segments of EEG and ECG that were mostly free from visual artifacts were selected for analysis at 24 h of age for each infant. Developmental follow-up was assessed using the Griffiths Scales of Mental Development at 24 months [17]. A neurological assessment of motor function was performed at the same time. An abnormal outcome was defined as a general quotient less than 87, significant motor dysfunction, or death.

In total, 38 term infants fit the criteria for this study with 21/17 found to have abnormal/normal outcomes at 24 months, respectively. Fig. 1(top) shows an example of multi-channel EEG and ECG recordings for a newborn who subsequently had a normal neurodevelopmental outcome. Fig. 1 (bottom) presents an example from a newborn with an abnormal outcome. In contrast to the continuous EEG activity in Fig. 1(top), the EEG for this patient is in a state of low voltage burst-suppression with clear asymmetry between hemispheres.

2.2. Features

Limited prior knowledge was available on what features would perform well for the considered task. A large set of features was extracted from the three modalities, EEG, ECG and clinical. It is our

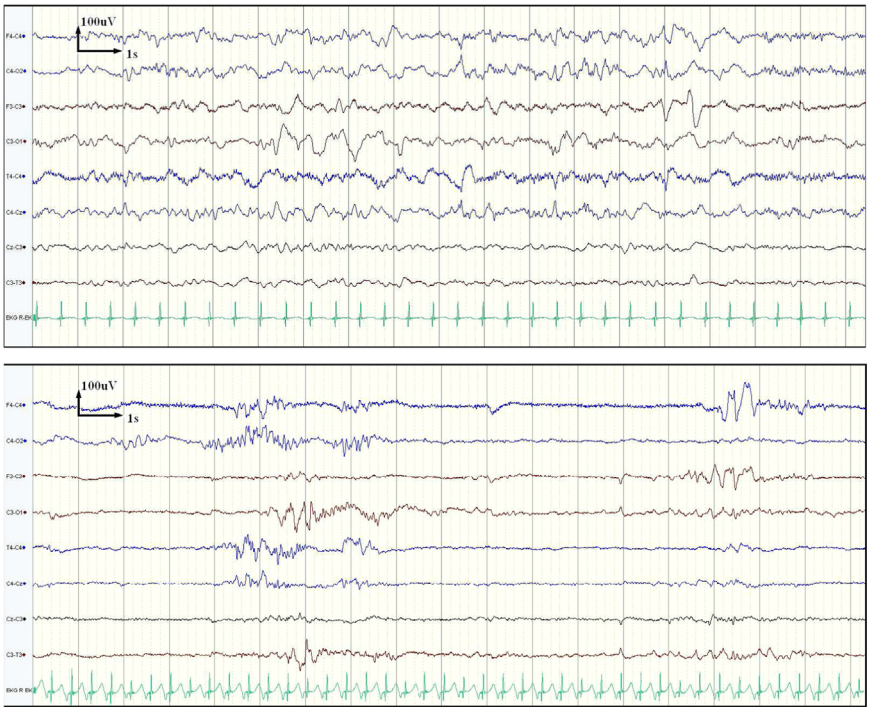

Fig. 1. Multi-channel EEG and ECG recordings from newborns who had a normal (top) and abnormal (bottom) neurodevelopmental outcome at 24 months.